BIOCHEMISTRY

Free For All

AHERN / RAJAGOPAL / TAN

1.1

Welcome

Foreword

We are happy to welcome you to our second Open Educational Resource (OER) textbook, Biochemistry Free For All. Biochemistry is a relatively young science, but its rate of growth has been truly impressive. The rapid pace of discoveries, which shows no sign of slowing, is reflected in the steady increase in the size of biochemistry textbooks. Growing faster than the size of biochemistry books have been the skyrocketing costs of higher education and the even faster rising costs of college textbooks. These unfortunate realities have created a situation where the costs of going to college are beyond the means of increasing numbers of students.

With this in mind, KGA and IR created, in 2012, a free, electronic book for introductory biochemistry, Biochemistry Free and Easy. That book was met with extraordinary enthusiasm, with over 175,000 downloads from around the world and adoption for use for several courses across the country. At OSU, we use the book for a basic course, taught over one quarter. In 2013, Oregon State University rolled out a new open textbook initiative, in partnership with OSU Libraries, OSU Press and Open Oregon State, with the mission of partnering with faculty to create open, online educational resources. Our proposal to create a biochemistry book that could be used for courses needing greater depth and breadth of coverage was chosen as one of the first projects of the Open Textbook initiative. As a result, we were able to draw on the technical expertise of several multimedia specialists for our interactive learning modules, and to hire a talented group of students to make figures, where suitable open source illustrations were not available. We also enlisted our third author, Dr. Taralyn Tan, a former student, who designed and oversaw the creation of the interactive modules.

As an OER, this book is free for anyone to use, modify, adapt, etc. for free educational purposes. It may not be used for profit-making, or where any fee is required for its use. We are providing all of the figures in this book free of cost to anyone wishing to use them for free educational purposes.

Helping students understand and enjoy biochemistry (without going broke) is our primary motivation for writing this book. We have aimed to provide a more thorough coverage of topics than in Biochemistry Free and Easy, but we do not aim to provide an encyclopedic biochemistry tome covering content that no instructor would fully cover in a single course. Neither do we aim to be the “go to” source for information on biochemistry. This is not a reference work. Consequently, we have focused on core concepts with key information. Descriptions are kept brief and to the point. Between us, we have over forty years of teaching biochemistry, and our experience is that more information does not translate to better learning. However, this does not mean that students will be shortchanged in using this book.

We have used the Foundational Concepts defined by the American Society for Biochemistry and Molecular Biology (ASBMB) and the associated learning goals as our guide in choosing and organizing the information presented.

The electronic format of Biochemistry Free For All allows us to provide multimedia to help students learn the subject. If you are not familiar with our previous efforts, you will probably see humor as another unconventional component of the structure of this book. We believe in keeping things light, fun, and informative. As certified (some might say, certifiable) biochemistry nerds and unrepentant lovers of corny jokes, we firmly believe that students can have fun while learning the subject. Toward this end, we have sprinkled each chapter with rhymes and songs that we hope will have you learning biochemistry happily. The multimedia approach also allows us to expand the content offerings in the written content by providing access to videotaped lectures, interactive learning modules; and rotatable 3-D molecules. We hope to enhance learning by creating a book that students look forward to reading and using.

We would like to express our deep appreciation for the ongoing support of Faye Chadwell, Director of the OSU Press, and Dianna Fisher, Director of OSU Extended Campus' Open Oregon State initiative. They are tireless champions of the cause of open educational resources and have been instrumental in increasing awareness and promoting the development of open educational materials at Oregon State. They also made it possible for us to avail of the skills of Victor Yee, Assistant Director of Course Development and Training for OSU ecampus; Warren Blyth, Nicholas Harper, Michael Miller and James Roberts, multimedia developers; and Rebecca Pietrowski, instructional designer. The support of Open Oregon State also gave us access to a talented pool of students, Martha Baker, Ben Carson, Penelope Irving, Pehr Jacobsen and Aleia Kim, who made many of the beautiful illustrations in the book. We also appreciate the help of Elizabeth Pendergrass, Tommy Tran, and Dmitriy Strelkov in assembling the glossary. We also appreciate the numerous people who sent us their pictures for use in assembling the cover image (which was created by Taralyn Tan). People whose images made it onto the cover include Berkman Gulenc, Clare Banister, David Shumway, Anna Pickering, Norbert Schoenberg, Margit Kjetsaa, Regina Golser, Alex McFadden, Garth Kong, Ayse Yosemin, Davis Hull, Annabelle Hull, Chelsea Parker Harp, Jennifer Shepard, Martyna Sroka, Qaim Ali Ramazan, Ingrid El-Dash, Vivian El-Dash, Wilson Ng, Daniel Watkins, Susan Thiel, Omar Ammar, and Rachel Aazzerah.

The Metabolic Melodies in the book could not have been recorded without the help of several gifted musicians. Given our non-existent musical abilities, we (and the readers of this book) are very fortunate that Liz Bacon, Heather Boren, Barbara and Neal Gladstone, Eric Hill, Tim Karplus, David Simmons and Carol Adrianne Smith were willing to help us out. We are indebted to you.

Gary Merrill and Andy Karplus, former and current heads of the Biochemistry and Biophysics department at OSU, have been steadfast supporters, throughout this project. We would also like to thank Senior Vice Provost for Academic Affairs, Becky Warner, and College of Science

Dean, Sastry Pantula, for working with the department to secure time release (for KA) to work on this project. Special thanks are due to our colleagues in the Biochemistry and Biophysics department for their friendship, collegiality and encouragement. The department, the College of Science and OSU could not have made our task any easier or more pleasant.

Finally, we would like to thank the many hundreds of students, past and present, who have inspired us to write this book. This is for you. It is a special pleasure for KA and IR to have one of you return as a co-author to help create a textbook that is truly free for all. We hope you find the book helpful in your own education.

The book is best used (currently) on iBooks (available for Macs and iPads), which allows readers to click on figures to enlarge them, watch video lectures relevant to each topic, listen to the selected songs, and link out to the internet to find more information simply by clicking on any term. Other formats, such as PDF and Kindle, allow access to all of the hyperlinks, but not all of the multimedia. If someone is interested in converting this book into a native Android format that can use all of the multimedia in the iPad version, we'd love to speak with you. If you are using the PDF version, you can download the Metabolic Melody songs at http:www.davincipress.com

We hope you find these features useful and that they help you learn biochemistry.

We would love to hear from you. Please take a few minutes after you've had a chance to use the book to tell us how the book has worked for you (email to ahernk1@gmail.com)

And join our Facebook group at https://www.facebook.com/biochemistryfreeforall/ We would really appreciate it.

Kevin Ahern
Indira Rajagopal
Taralyn Tan

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Biochemistry Free For All

This is version 1.0 of this electronic book. It is also version 1.0 of the PDF form of this book.

Disclaimer

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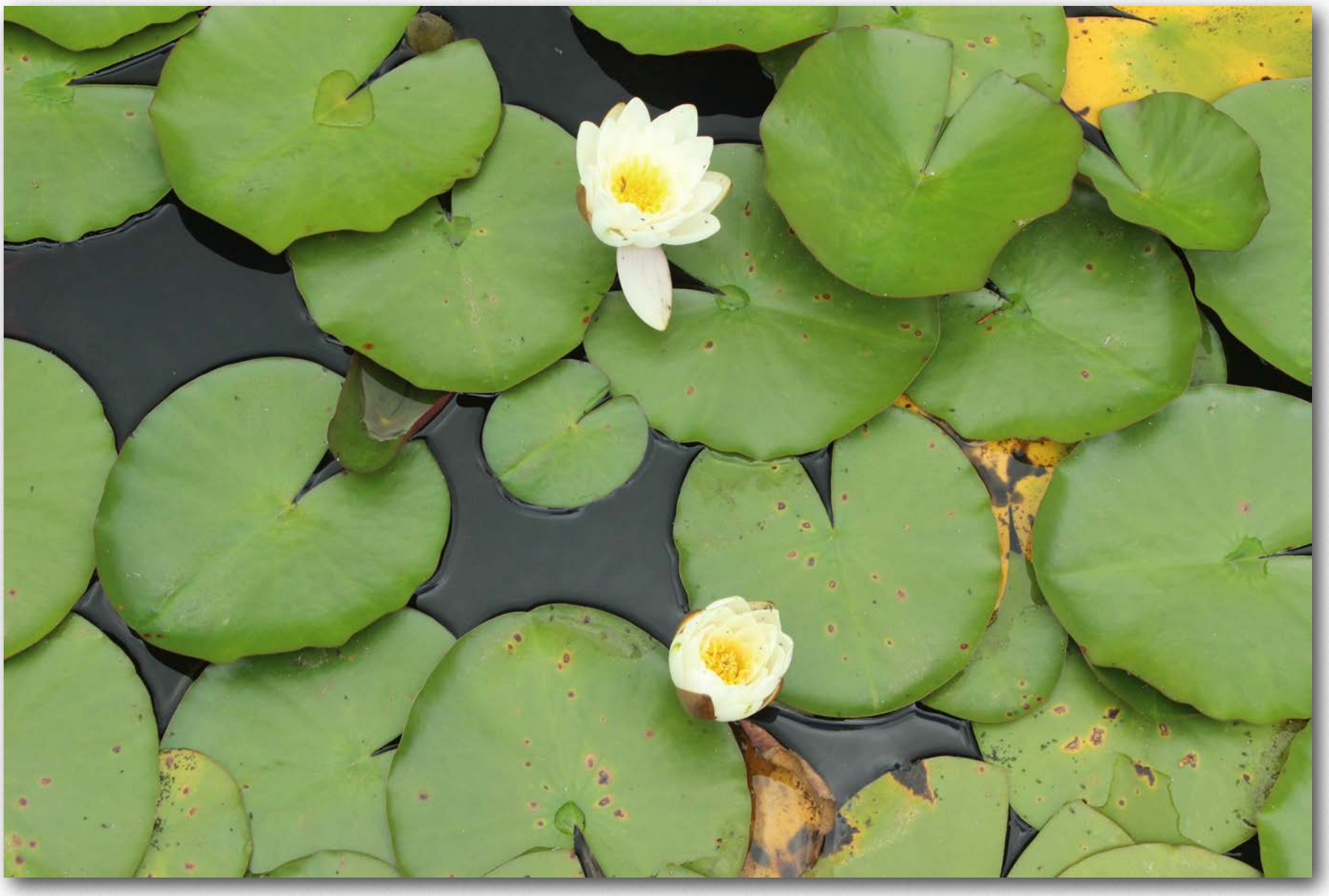
1

In the Beginning

"It is far better to grasp the universe as it really is than to persist in delusion, however satisfying and reassuring."

- Carl Sagan

Introduction: Basic Biology



The bio of biochemistry

The most obvious thing about living organisms is their astounding diversity. Estimates put the number of eukaryotic species at about 8.7 million, while bacteria account for anywhere between 10^7 and 10^9 different species. The number of species of archaea is still uncertain, but is expected to be very large.

These organisms, representing the three great domains of life, together occupy every environmental niche imaginable, from the human gut to the frozen expanses of the Antarctic, and from the rainforests of the Amazon basin to the acid waste washes of gold mines. Some organisms, like the tardigrades (Figure 1.1), or water bears, can withstand

YouTube Lectures by Kevin HERE & HERE

On these pages our aim's to extract
Knowledge out of a mountain of facts
Missing excessive data
Will not really matta
If our students can learn and relax

Figure 1.1 - Tardigrade
Wikipedia

incredibly harsh conditions - from a few degrees above absolute zero to 300°F, the vacuum of outer space, and pressures greater than those at the greatest depths of the ocean. In the memorable words of Dr. Ian Malcolm in the movie, Jurassic Park, “Life finds a way”.

Despite the differing demands of existence in these widely varied environments, all living things share some common characteristics. The most noticeable of these is that from hummingbirds to humpback whales, from fungi to frogs, and from bacteria to birch trees, all living things are made up of cells. This fact was first discovered by Robert Hooke, in 1665 (Figure 1.2), when he used a microscope to look at a slice of cork and found that it seemed to be made up of tiny chambers that he named cells. Subsequent examination of other living things revealed that they, too, were, without exception, made up of cells. Today, we know that organisms in all three domains of life – bacteria, archaea and eukaryotes, share this property – they are all made up of cells. For some, a single cell is the organism, while others are multicellular, like humans, wombats or weeping willows.

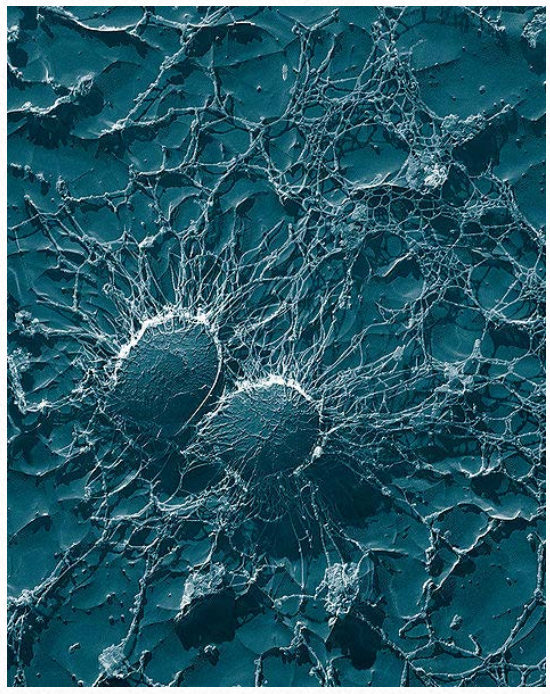


Figure 1.3 Bacterial cells
Wikipedia

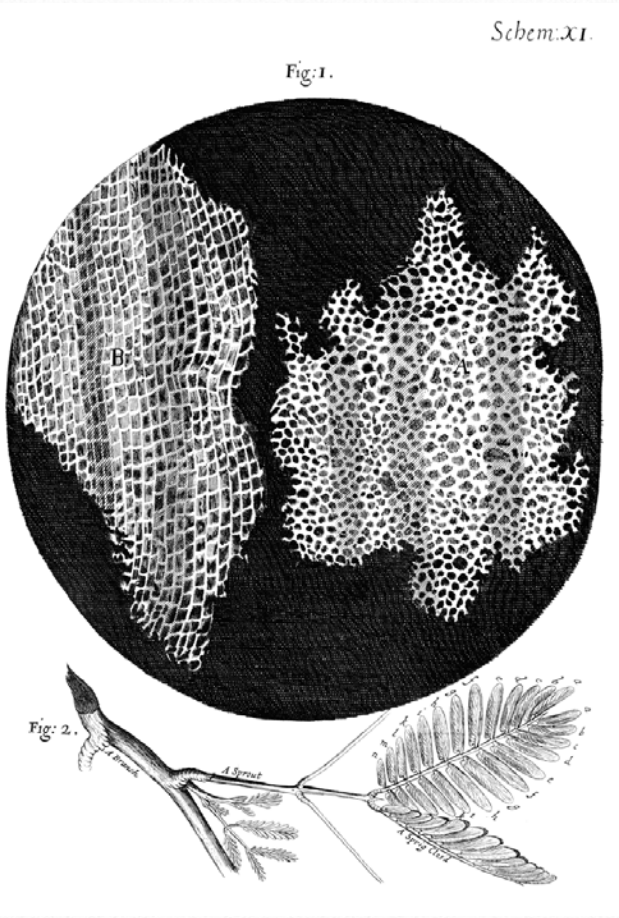


Figure 1.2 Slices of cork as seen by Hooke

The subject of this book is biochemistry, the science that explains life at the molecular level. The special characteristics of cells influence the unique chemistry of life. It is, thus fitting, to take a quick look at cells, the setting in which the molecular events of life take place.

"*There are living systems; there is no "living matter". No substance, no single molecule, extracted and isolated from a living being possess, of its own, the aforementioned paradoxical properties. They are present in living systems, only; that is to say, nowhere below the level of the cell.*" – Jacques Monod

Cells

All cells, no matter what kind, have a plasma membrane that serves as a boundary for the cell, separating it from its surroundings. They also possess a genome made up of DNA that encodes the information for making the proteins required by the cell. To translate the information in the DNA and make the proteins it encodes, all cells have the machinery for protein synthesis, namely, ribosomes and tRNAs. DNA is also the repository of information that gets copied and transmitted to the next generation, allowing living cells to reproduce.

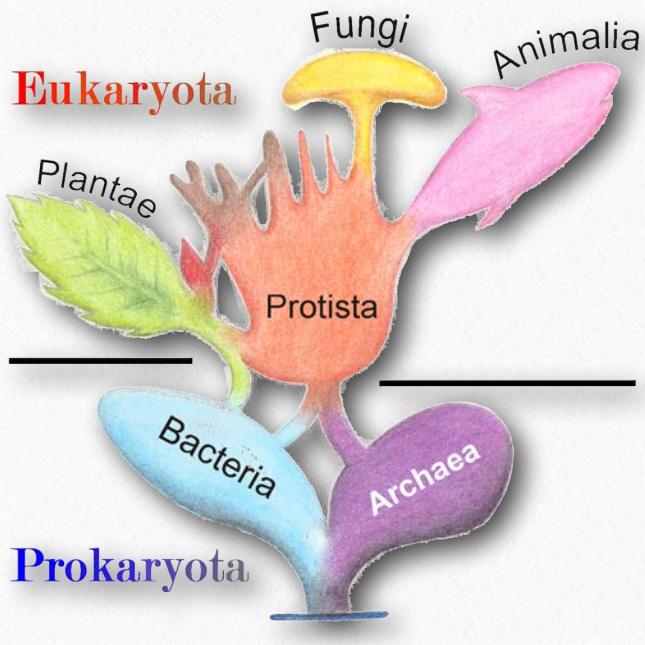


Figure 1.5 - Tree of life

Wikipedia

All cells also need to be able to obtain and use energy. The source of this energy is different in different organisms (Figure 1.4). Phototrophs are organisms that obtain metabolic energy from light, while chemotrophs get their energy from the oxidation of chemical fuels. Organisms that can capture energy from light or from chemical sources are termed autotrophs (auto=self, troph=nouris-hing). Others are heterotrophs, which use, as their energy source, the organic compounds made by other organisms. Plants, and other photosynthetic organisms are autotrophs, while animals are heterotrophs.

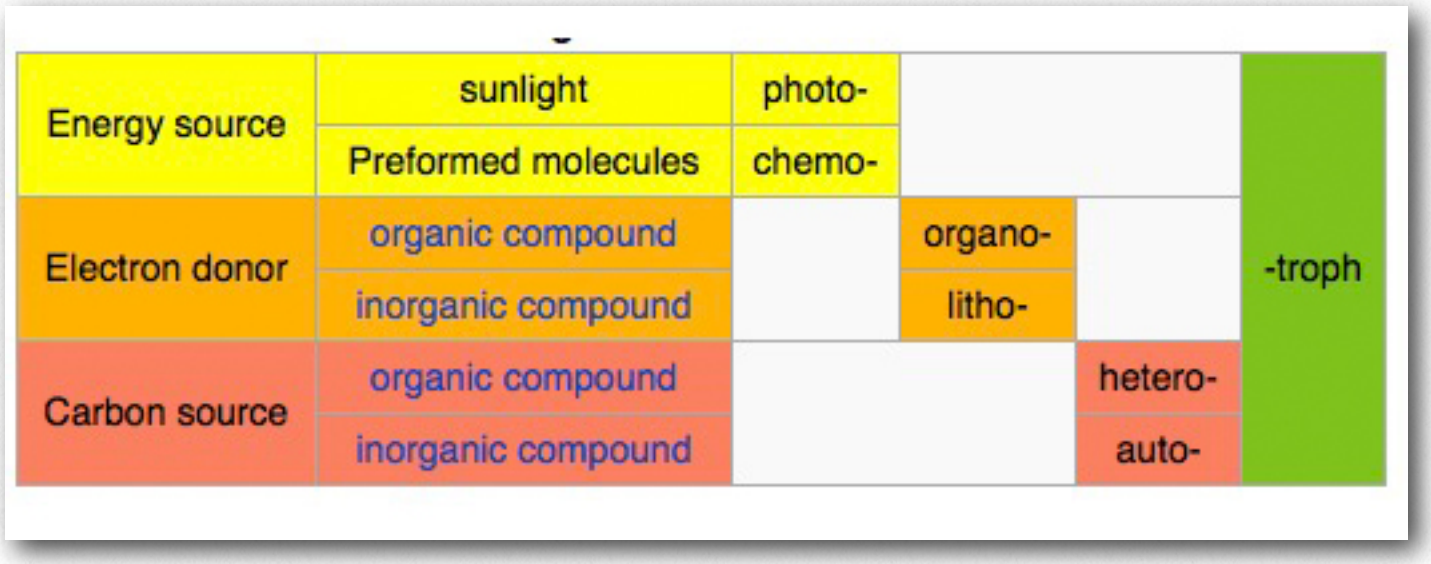


Figure 1.4 - Organization of organisms by metabolic type

Wikipedia

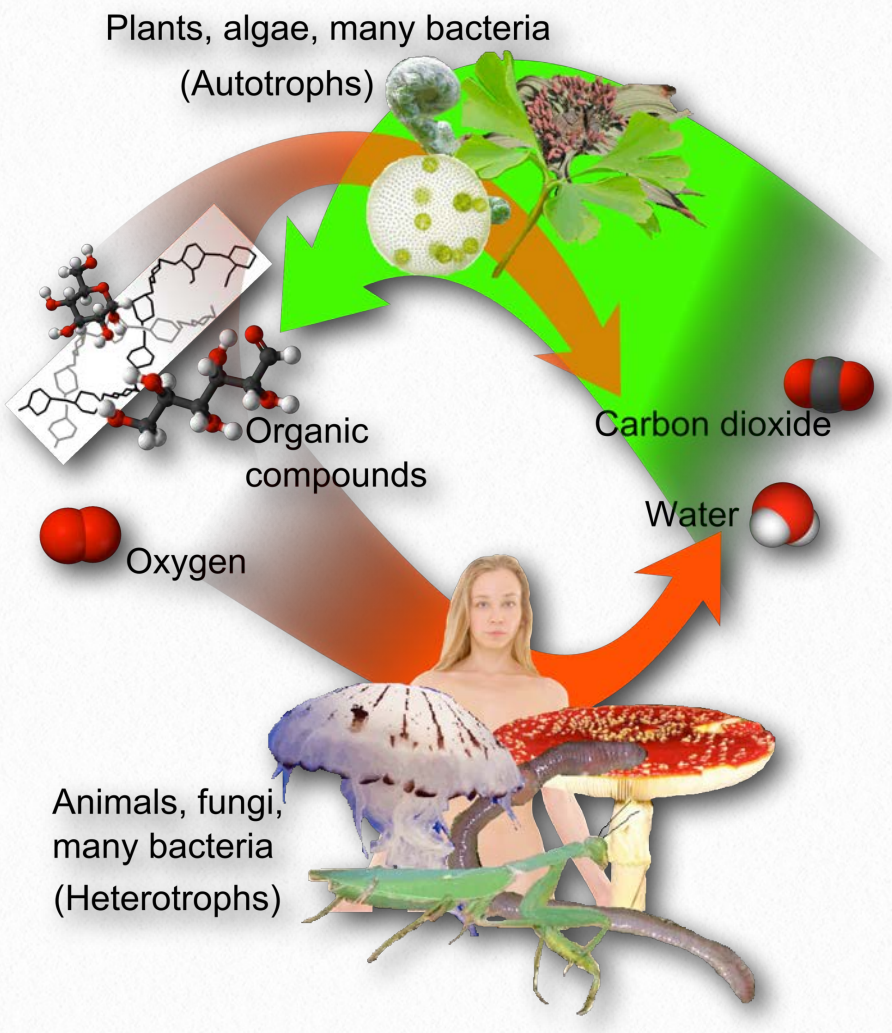


Figure 1.6 - Interplay between autotrophs and heterotrophs

Wikipedia

Cells may be aerobic (i.e., use oxygen) or anaerobic (able to live without oxygen). Some anaerobic cells are obligate anaerobes, that is, they require an environment free of oxygen.

Others are facultative anaerobes, cells that can live with, or without, oxygen.

Prokaryotic and eukaryotic cells

Organisms may be divided into two major groups, the prokaryotes and the eukaryotes. The cells of the former lack a nucleus and other organelles, while those of the latter are characterized by numerous internal, membrane-bounded compartments, including a nucleus.

Prokaryotes are unicellular and generally considerably smaller than their eukaryotic cousins, with sizes ranging from 0.5 to 5 µm in diameter. Prokaryotes typically have circular chromosomes, and may sometimes contain extra-chromosomal DNA elements (also

Table 1.1

Cellular Differences between Prokaryotes and Eukaryotes

Prokaryotes	Organelle	Eukaryotes
No definite nucleus	Nucleus	Present
Present	Cell Membrane	Present
None	Mitochondria	Present
None	Endoplasmic Reticulum	Present
None	Chloroplasts	Present in Plants

Image by Aleia Kim

usually circular) called plasmids. Although the DNA in prokaryotes is not wrapped around histones, as is the case for eukaryotes, prokaryotes have proteins associated with their DNA. The DNA-protein complexes in prokaryotes create a structure called a nucleoid, which is different from the eukaryotic nucleus in not being enclosed by a nuclear envelope (Figure 1.7). The proteins associated with the DNA in *Archaea* resemble eukaryotic histones, while those in bacteria are different from both eukaryotic and archaeal DNA packaging proteins.

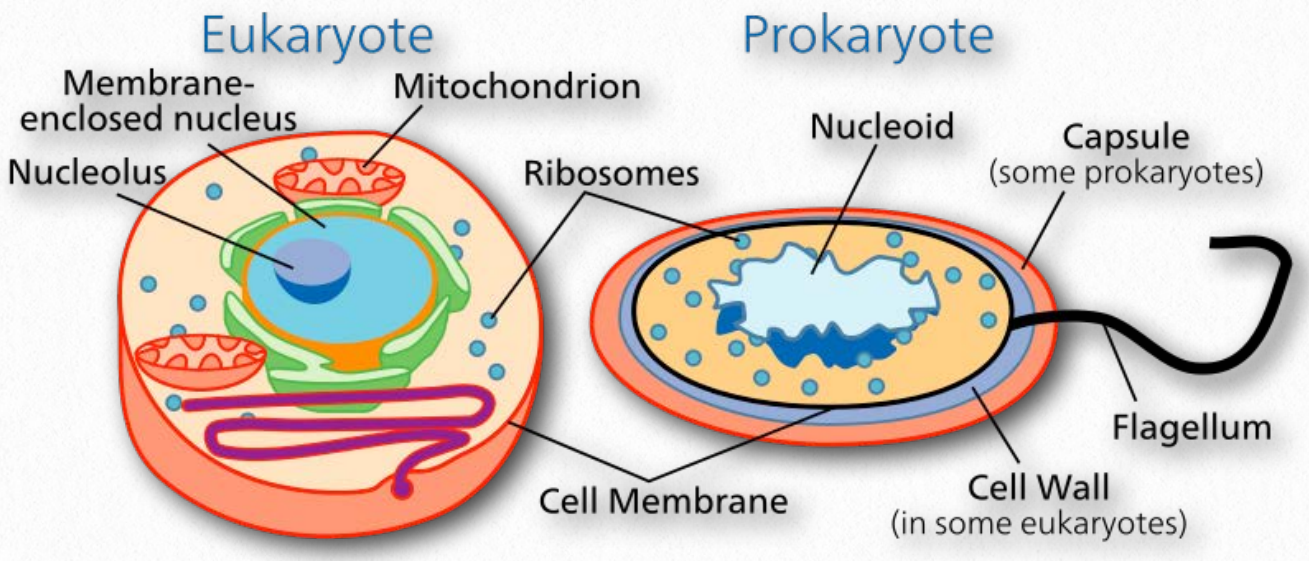


Figure 1.7 - Prokaryotic vs. eukaryotic cell structures (not to scale)

Prokaryotes may be divided into two broad categories, bacteria and archaea. These single-celled organisms are both ancient and widespread. Archaea were once thought to be a subgroup of bacteria, but have subsequently been shown to be a completely different group of organisms that are so distinct from both bacteria and eukaryotes that they now are classified in a domain of their own.

Excuse me for feeling superia
To the life forms we call the bacteria
Students know very well
There are no organelles
To be found in their tiny interia

Bacteria

Like eukaryotic cells, bacterial cells have a plasma membrane surrounding them, but in addition, they also contain an exterior cell wall, comprised of an interlocked peptidoglycan network. On their exterior surfaces, bacteria have hair-like appendages called pili that allow them to adhere to other cells. Pili play an important role in bacterial conjugation, a process in which DNA is transferred between bacterial cells. In addition, bacterial cells may have flagella that enable them to move through their surroundings.

Interestingly, bacteria can communicate, not only with members of their own species, but also with other bacterial species, using chemical signals, in a process called quorum sens-

ing. These signaling mechanisms enable bacteria to assess conditions around them (such as the size of their population). Quorum sensing plays a role in the process of infection by bacterial pathogens as well as the formation of biofilms (mats of cells that adhere to each other tightly and protect the bacteria against environmental hazards or other harmful agents).

Archaea

The first archaeans to be studied were all found in harsh environments such as salt flats and hot springs. Because of this, they were initially believed to live only in extreme environments and were described as extremophiles (Figure 1.8). We now know that archaeans can be found in every environment, moderate or extreme. Archaea have been found in the human gut, and in such huge numbers in marine plankton that it has been suggested that they may be the most abundant organisms on earth.

Figure 1.8 - Archaeans growing in acid mine waste

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While they are unicellular, and superficially resemble bacteria, archaea are in some respects more similar to eukaryotes. Their transcriptional machinery, promoter sequences and ribosomes are much more like those of eukaryotes than of prokaryotes.

Archaea are also unique among living organisms in their use of ether linkages to join the lipids used in their plasma membranes to glycerol. Not only are the ether linkages different from the ester linkages in all other forms of life, but the lipids themselves are different. In place of the fatty acids used in both bacterial and eukaryotic membranes, archaea use long isoprene-derived chains (Figure 1.9) This difference in membrane composition and structure makes archaeal membranes highly stable and may be advantageous in extreme conditions.

Archaea, like bacteria, also have a cell wall, but the cell walls do not contain peptidoglycans. Some archaea have peptidoglycan-like

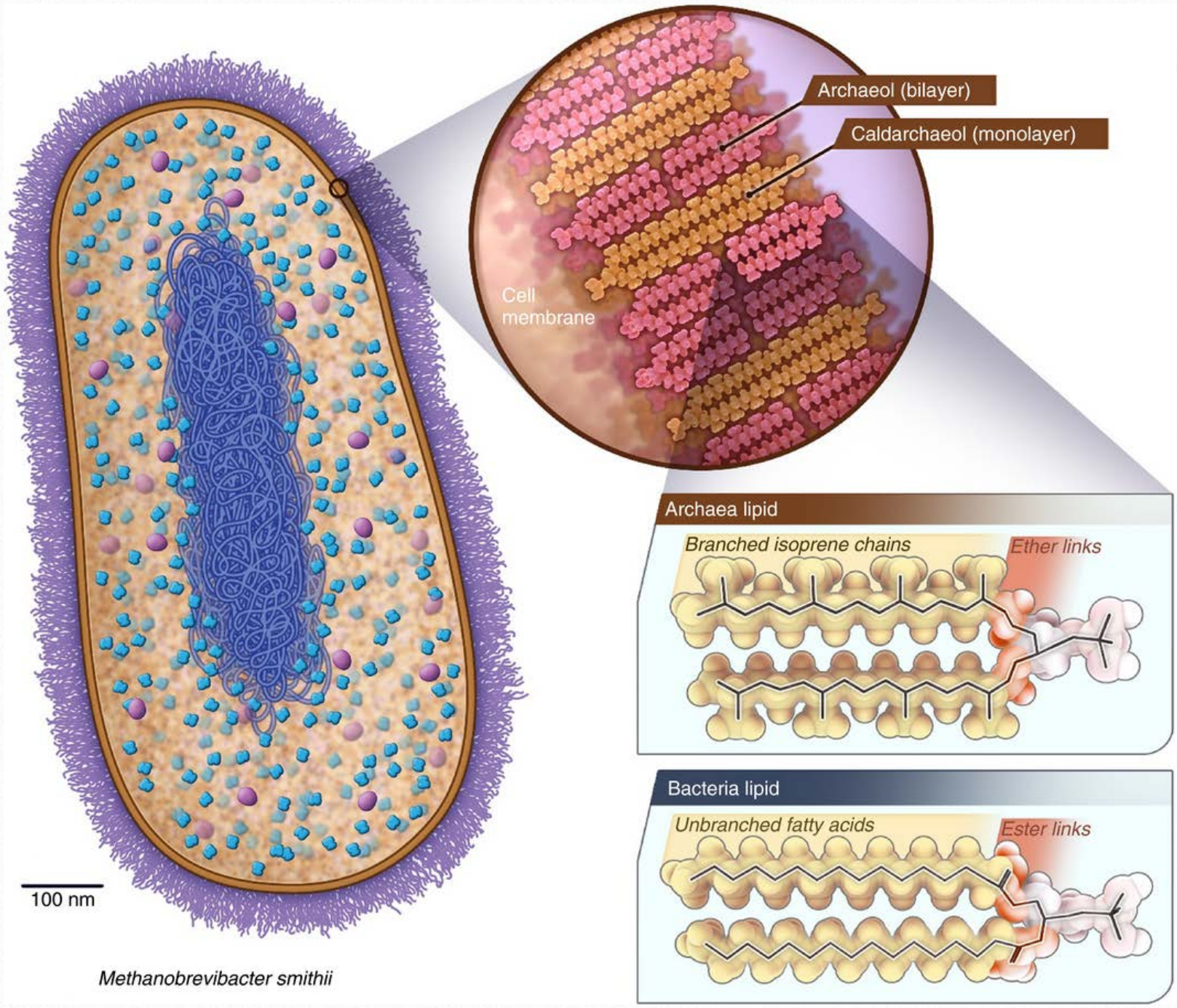

Figure 1.9 Archaeal membrane, top, showing unusual ether linkages and isoprene chains and bacterial membrane, below.

Wikipedia

molecules in their cell walls, while others build their cell walls entirely of glycoproteins and polysaccharides.

Eukaryotes

Eukaryotic cells are found in both unicellular and multicellular organizational schemes. Unicellular forms include yeast and many

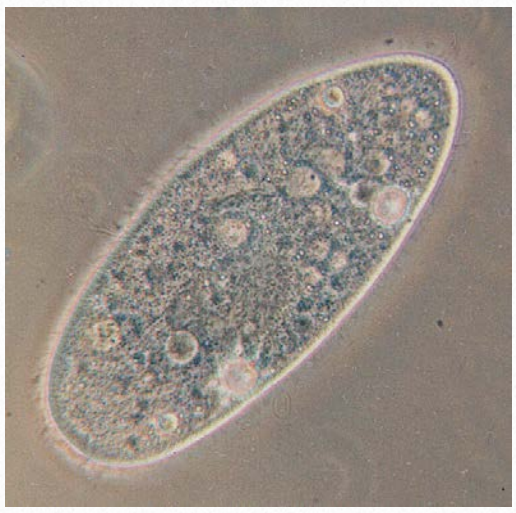

Figure 1.10 Paramecium

Wikipedia

protists, familiar to students from introductory biology labs, like *Paramecium* and *Amoeba*. Multicellular eukaryotes include plants, animals, and fungi. Eukaryotic cells are surrounded by a plasma membrane. Animal cells have no cell walls, whereas plant cells use cellu-

lose, hemicellulose, and pectins to build cell walls outside their plasma membranes. Fungal cells have cell walls that are unusual in containing the polymer, chitin, which is also found in the exoskeletons of arthropods.

Eukaryotic cells are typically much larger (typically 10-100 µm) and contain considerably more DNA than prokaryotic cells. The most distinctive feature of eukaryotic cells, however, is the presence of a variety of internal membrane-bounded structures, called organelles.

Figure 1.11 - Animal cell structure

Wikipedia

Organelles

Eukaryotic cells are characterized by internal membrane-bounded compartments, or organelles. These compartments divide up the interior of the cell into discrete parts that have specialized functions.

Organelles found in eukaryotic cells include the nucleus (houses DNA), mitochondria (electron transport system/ oxidative phosphorylation for ATP synthesis), nucleolus (ribosome synthesis and assembly), endoplasmic reticulum (lipid metabolism and targeted protein synthesis and folding), the Golgi apparatus (protein modification and secretion), peroxisomes (oxidation of very long chain fatty acids), chloroplasts (plants - photosynthesis), plastids (synthesis and storage of compounds in plants), lysosomes (animals - hydrolytic enzymes), endosomes (contain endocytosed material), and vacuoles.

The presence of multiple compartments within the cell permits reactions requiring specific conditions to be carried out in isolation from the rest of the cell. For example, the for-

mation of disulfide bonds in proteins is possible in the conditions within the endoplasmic reticulum, but would not readily occur in the different environment of the cytosol. The presence of membrane-bounded compartments also allows reactants to be more concentrated because of the smaller volume of the organelle.

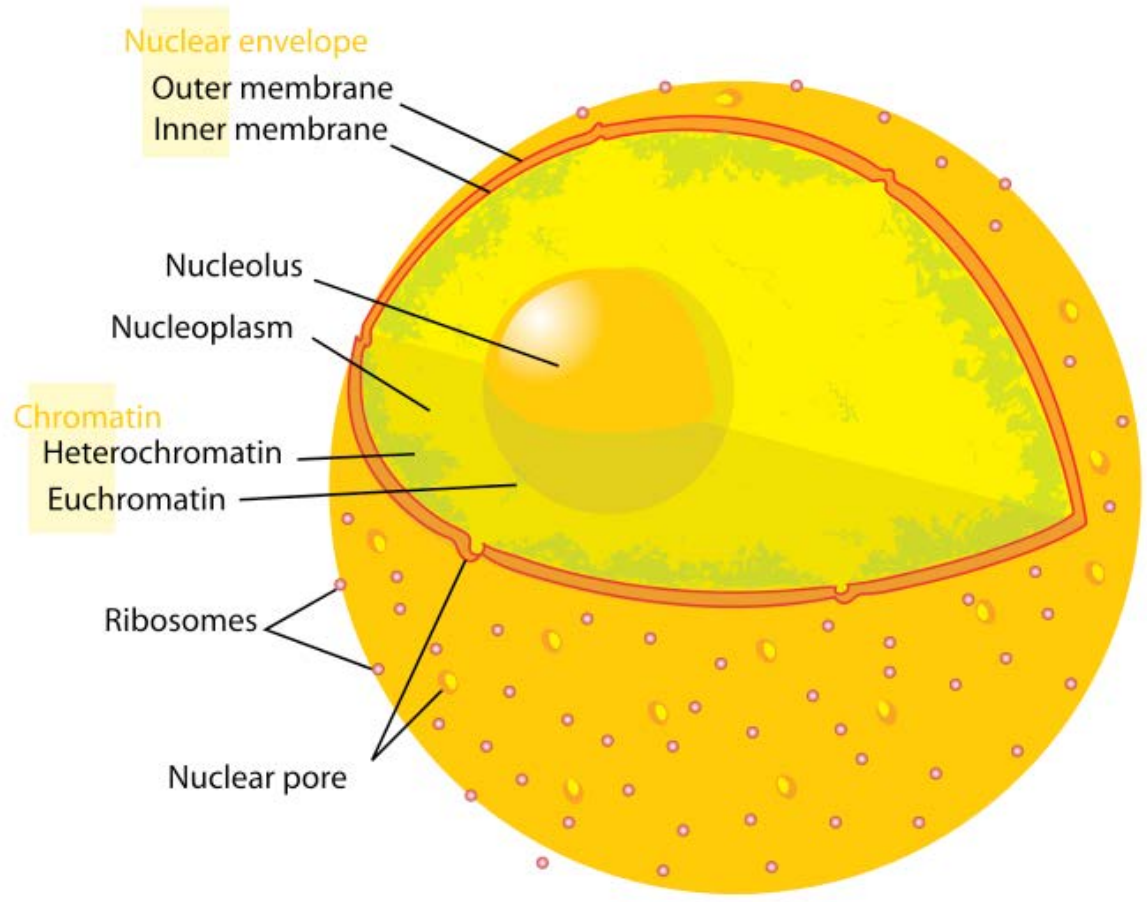

Figure 1.12 Cell nucleus

Eukaryotic DNA in a cell is divided into several linear bundles called chromosomes. Chromosomes contain the genomic DNA wrapped around cores of positively charged proteins called histones. The ends of linear eukaryotic chromosomes have telomeres, short (less than 10 bp) sequences repeated thousands of times. The role of telomeres in preventing loss of information when linear chromosomes are replicated is discussed later.

YouTube Lectures by Kevin HERE & HERE

The chromosomes in eukaryotic cells are surrounded by the nuclear envelope, a double membrane structure that encloses the nucleus (Figure 1.12). Within the nucleus, there are enzymes required for the replication and transcription of genetic information. The presence of the nuclear envelope also regulates which proteins can enter the nucleus at any given time. This, as you will see later, is an important way to control gene expression.

Mitochondria and chloroplasts have their own DNA, separate from and in addition to the nuclear DNA. This DNA is small and circular and resembles a prokaryotic chromosome. Mitochondria and chloroplasts also have their own ribosomes and tRNAs and can carry out their own protein

synthesis. This is not as odd as it seems, because these organelles are likely derived from prokaryotes that once lived as endosymbionts within ancient eukaryotic cells and eventually became integrated into their host cells.

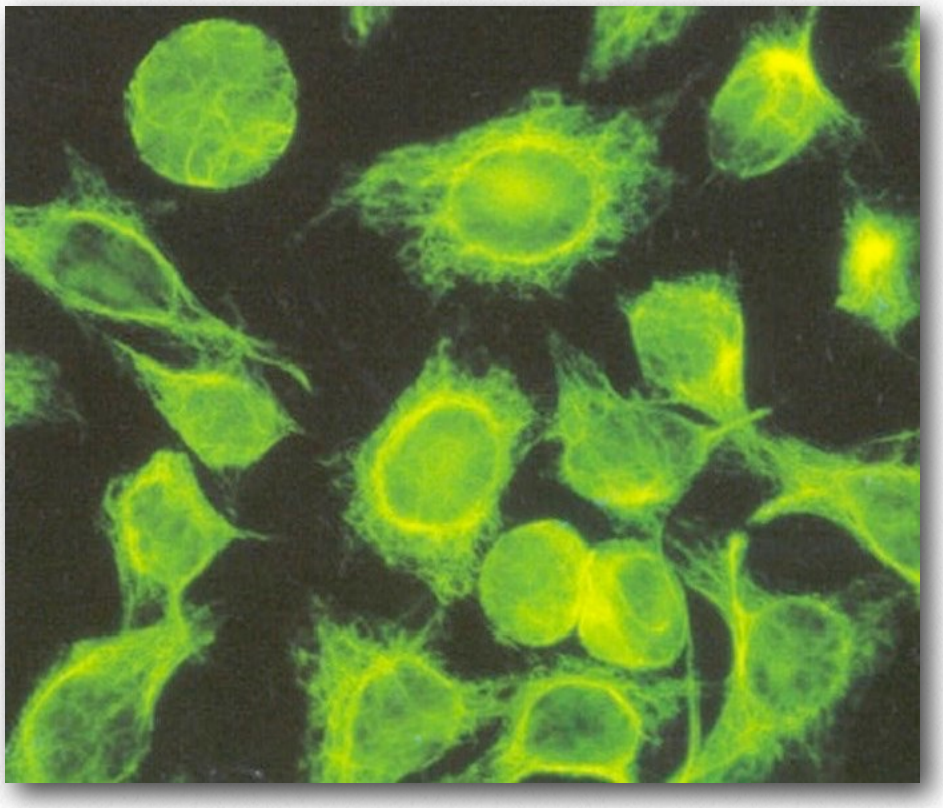

Figure 1.13 Cultured cells stained to show intermediate filaments

Wikipedia

The cytoskeleton

Another interesting feature of eukaryotic cells is the presence of an internal skeleton-like structure called a cytoskeleton. The cytoskeleton is made up of a network of interlinking protein fibers belonging to three major classes: microtubules, microfilaments, also known as actin filaments, and intermediate filaments (Figure 1.13). All eukaryotic cells have microfilaments and microtubules, but it appears that plant cells may lack intermediate filaments (It is now known that some cytoskeletal elements are present in bacteria and archaea as well, but these have been discovered relatively recently and thus, less is known about them.)

Although the word “skeleton” may suggest a rigid and fixed structure, the cytoskeleton is dynamic, with both microfilaments and microtubules disassembling and rearranging themselves on an ongoing basis, as needed. Intermediate filaments are also broken down and rebuilt, at specific times, such as during cell division. The three main classes of cytoskeletal elements are distinguished by the proteins that they are composed of, as well as the way in which those proteins assemble into the structures seen in the cell.

Intermediate filaments, for example, are made up of a variety of proteins that share a common structure, and assemble into fibers that resemble a cable made up of many individual strands of wire twisted together. This arrangement, because of its mechanical strength, makes intermediate filaments ideally suited to provide structural support to various cell structures. The nuclear envelope, for example, has a network of intermediate filaments called the nuclear lamina, just in-

side the inner membrane of the envelope in animal cells.

Microfilaments, composed of the protein actin, underlie the plasma membrane of animal cells, and give them their characteristic shapes. Remodeling of these filaments changes the shape of the cell, and is important for cell movement. In animal cells, actin also plays a role in cytokinesis, the last step in cell division, by helping to cleave the cell in two after nuclear division.

Microtubules, made up of various kinds of a protein called tubulin, also play vital roles in cell division (Figure 1.14). The spindle fibers that attach to chromosomes during metaphase, and help separate the two sets of chromosomes, are made up of microtubules. Microtubules also serve as tracks along which motor proteins, like dynein and kinesin, transport cargo to different parts of the cell.

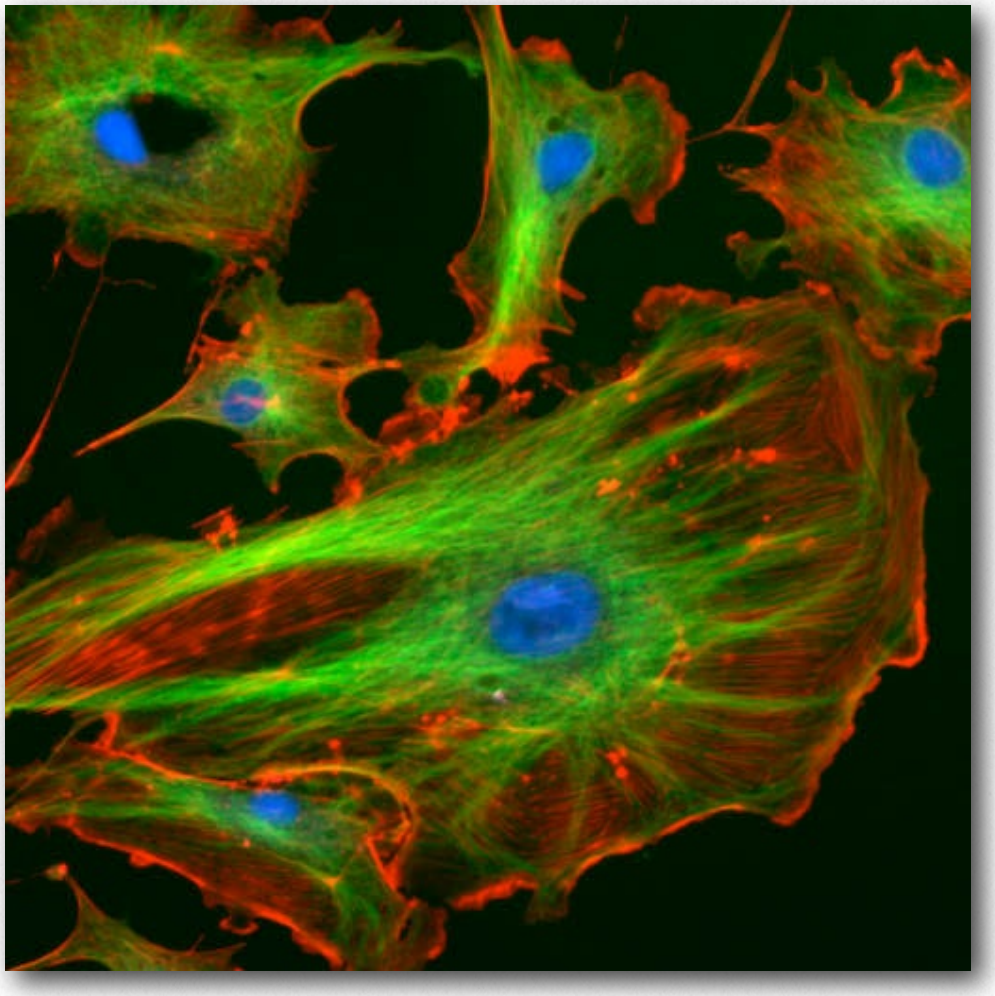

Figure 1.15 - The cytoskeleton. Actin filaments are in red, microtubules in green, nucleus in blue

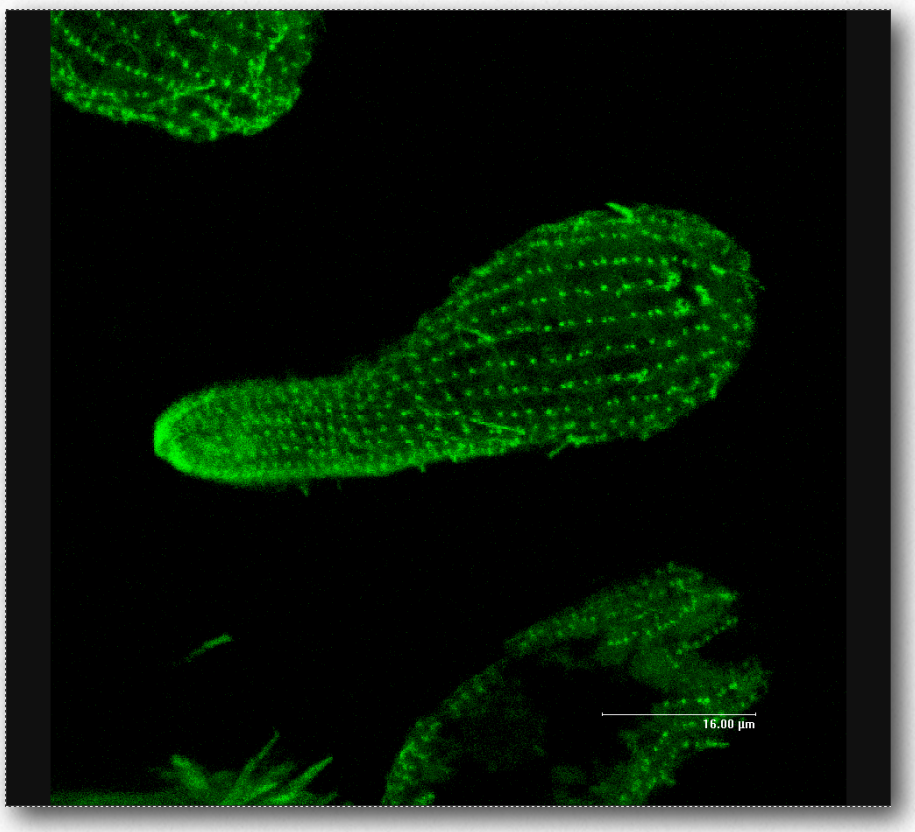

Figure 1.14 - β-tubulin in *Tetrahymena*
Wikipedia

Additional functions of the cytoskeleton include helping to organize the contents of the cell. If you ever wondered what kept organelles in an aqueous cytoplasm from floating around like beach balls in water, the answer is that organelles are anchored by attachment to the cytoskeleton. Interactions among cytoskeletal proteins and com-

ponents of the extracellular matrix are crucial in maintaining tissue structure. Membrane-associated signaling proteins are sometimes linked to components of the cytoskeleton, giving cytoskeletal proteins a role in cell signaling pathways.

Tissues

Cells in multicellular organisms are organized into tissues that play specialized roles in the body. Animals have four types of tissues in their bodies - epithelium, connective tissue, nerve tissue, and muscle tissue. The first of these, epithelial tissues line the cavities and surfaces of blood vessels and organs in the body (Figure 1.16). Epithelial cells are categorized by their shapes: squamous, columnar, and cuboidal. These can be organized in a single cell layer or in layers of two or more cells deep (referred to as stratified or layered). Glands are all comprised of epithelial cells.

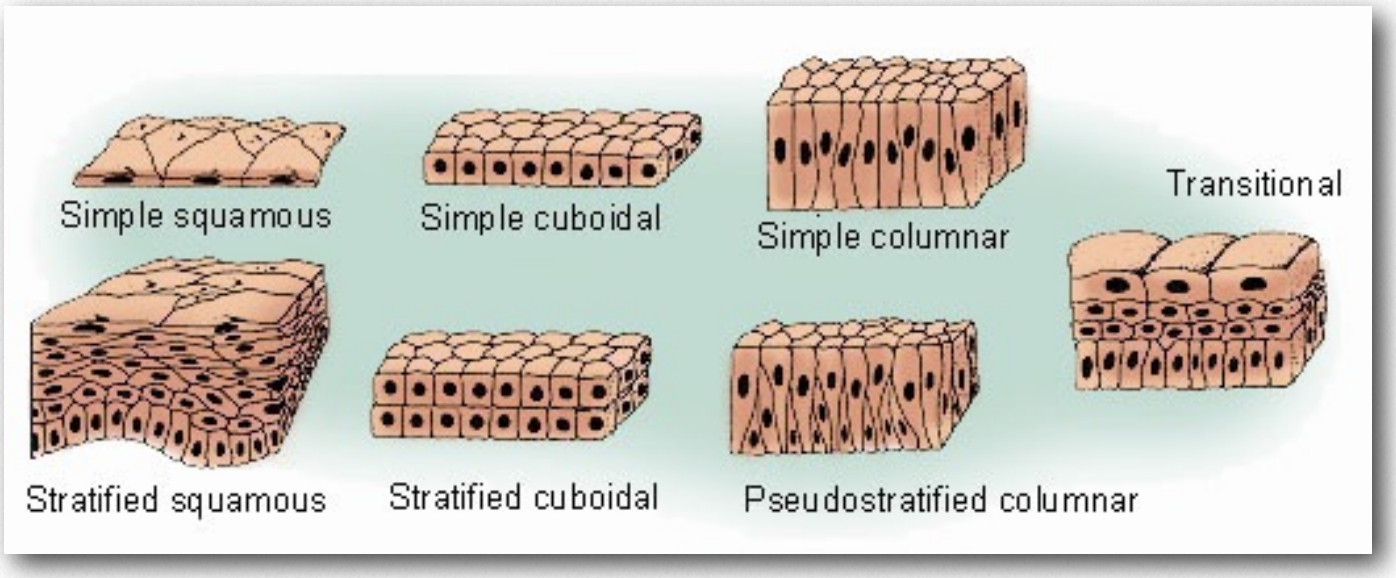

Figure 1.16 - Types of epithelial tissue

Epithelial cell functions include protection, secretion, selective absorption, transport, and sensing. Layers of epithelial cells do not contain blood vessels and must receive nutrients through the process of diffusion of materials from underlying connective tissue, through the basement membrane.

Connective tissue

Of the four animal tissues, connective tissue is the one that serves as the "glue" to hold everything together. Connective tissue fills the gaps between all the other tissues of the body, including the nervous system. In the central nervous system, for example the outer membranes, the meninges (cover of brain) and the spinal cord are composed of connective tissue. Apart from the blood and lymph, connective tissues contain three main components. They are 1) cells; 2) ground substance; and 3) fibers. Blood and lymph contain components 1 and 2, but not 3. Cell types found in connective tissue include adipocytes, fibroblasts, mast cells, macrophages, and leucocytes.

Nerve tissue

The nervous system of humans contains two main components. The brain and spinal cord comprise the central nervous system (CNS) and nerves branching from these make up the peripheral nervous system. The peripheral nervous system is responsible for regulating bodily functions and actions. In the central nervous system (CNS), the tissue types are referred to as grey matter or white matter. In the peripheral nervous system (PNS), tissue types include nerves and ganglia.

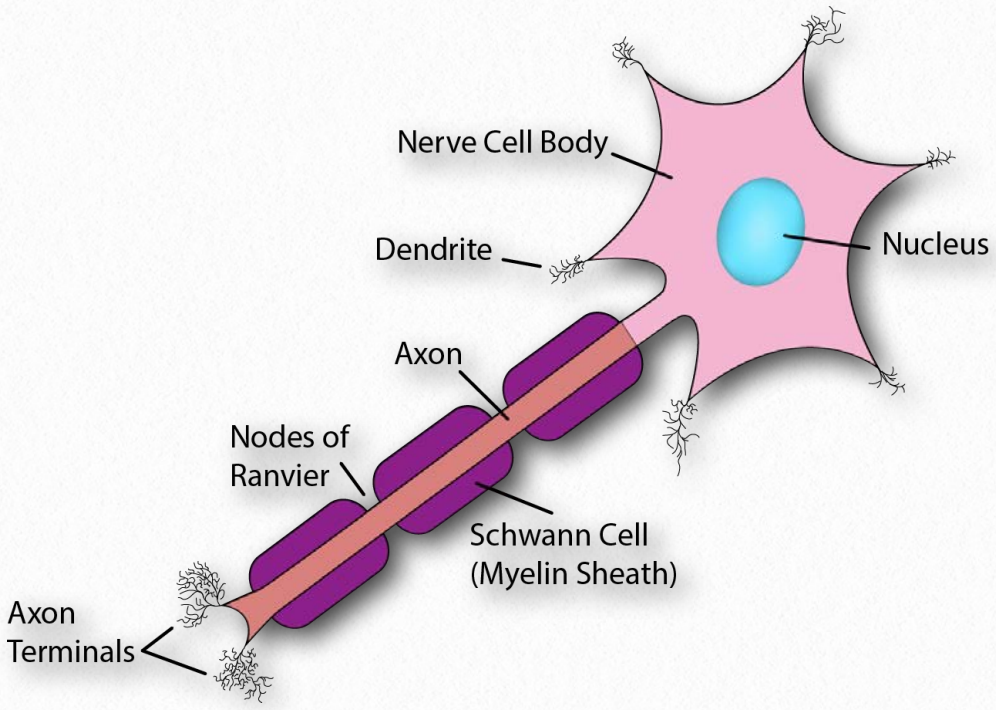

Figure 1.17 - Nerve cell anatomy

Image by Pehr Jacobson

Nerve cells are also called neurons. Neurons can transmit and receive signals. Specialized cells called glia assist in transmitting the nerve signal and also provide nutrients for the neurons. All nerve cells contain an axon (Figure 1.20) which are long fiber-like structures responsible for sending signals in the form of action potentials to adjacent cells. Nervous system functions include receiving input from senses, controlling muscles and glands, homeostasis, integration of information, and mental activity.

Muscle tissue

Muscle tissue is formed during embryonic development by a process known as myogenesis. Mammals have three types of muscle tissue - 1) skeletal/striated muscle; 2) smooth, non-striated muscle; and 3) cardiac muscle. Cardiac muscle and smooth muscle are notable for contracting involuntarily. Both can be activated through nerve stimuli from the central nervous system or by innervation from the peripheral plexus or by endocrine/hormonal activation. Striated muscles, by contrast, only contract voluntarily by (mostly) conscious action influenced by the central nervous system. Reflexive movement by striated muscles occurs non-consciously, but also arises from central nervous system stimulation.

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Biochemistry, Biochemistry

To the tune of "*Oh Christmas Tree*"

Metabolic Melodies Website HERE

Biochemistry Biochemistry
I wish that I were wiser
I feel I'm in way o'er my head
I need a new advisor

My courses really shouldn't be
Such metabolic misery
Biochemistry Biochemistry
I wish that I were wiser

Biochemistry Biochemistry
Reactions make me shiver
They're in my heart and in my lungs
They're even in my liver

I promise I would not complain
If I could store them in my brain
Biochemistry Biochemistry
I wish that I were wiser

Biochemistry Biochemistry
I'm truly in a panic
Your mechanisms murder me
I should have learned organic

For all I have to memorize
I ought to win the Nobel Prize.
Biochemistry Biochemistry
I wish that I were wiser

Recorded by Tim Karplus.
Lyrics by Kevin Ahern

Around the Nucleus

To the tune of "*Across the Universe*"
Metabolic Melodies Website HERE

DNA gets spooled like balls of yarn
Within the chromosomes
Unwinding when it's duplicated there
Around the nucleus

Primase sets down RNA
To pave the path for DNA
Across a replication fork

Complementarit-y rules (ahhhhhh)
DNA Pol-y-mer-ase
Synthesizing DNAs
RNA Pol-y-mer-ase
Making all the RNAs

Helicases split the strands
In front of replication forks
To make templates accessible
Around the nucleus

Complementary bases
Match the bonds of 'H' and hold the strands
Together till they're pulled apart
Around the nucleus
Hydrogen bonding fuels (ahhhhhhhhh)

Tiny alpha helix bands
Folding for the cells' demands
Beta sheets comprised of strands
Meeting all the cells' demands

Exons link majestically all guided
By a master plan encoded in the cell's genome
That's buried deep inside of me
Countless combinations of the codons
Bring diversity to life evolving on and on
Around the nucleus

Complexes rule the world (ahhhhhhhh)
Ribosomes and spliceosomes
Transforming the cells' genomes
Ribosomes and spliceosomes
Builders of the proteomes

YouTube video HERE

Recorded by David Simmons
Lyrics by Kevin Ahern

Biochem is Beautiful

To the tune of "*Everything is Beautiful*"
Metabolic Melodies Website HERE

Students study molecules with
All of the structures they possess
Proteins, fats and DNAs
There must be a million ways
To evaluate our knowledge for the test

Biochem is beautiful
Our professor says
From the sugar in our cells
To actions of HDLs

And molecules are dutiful
In every way
Substrates for the enzymes are
Converted e-ver-y day

There is no enzyme
That can lower Delta G
They just work all the time
On transition energy

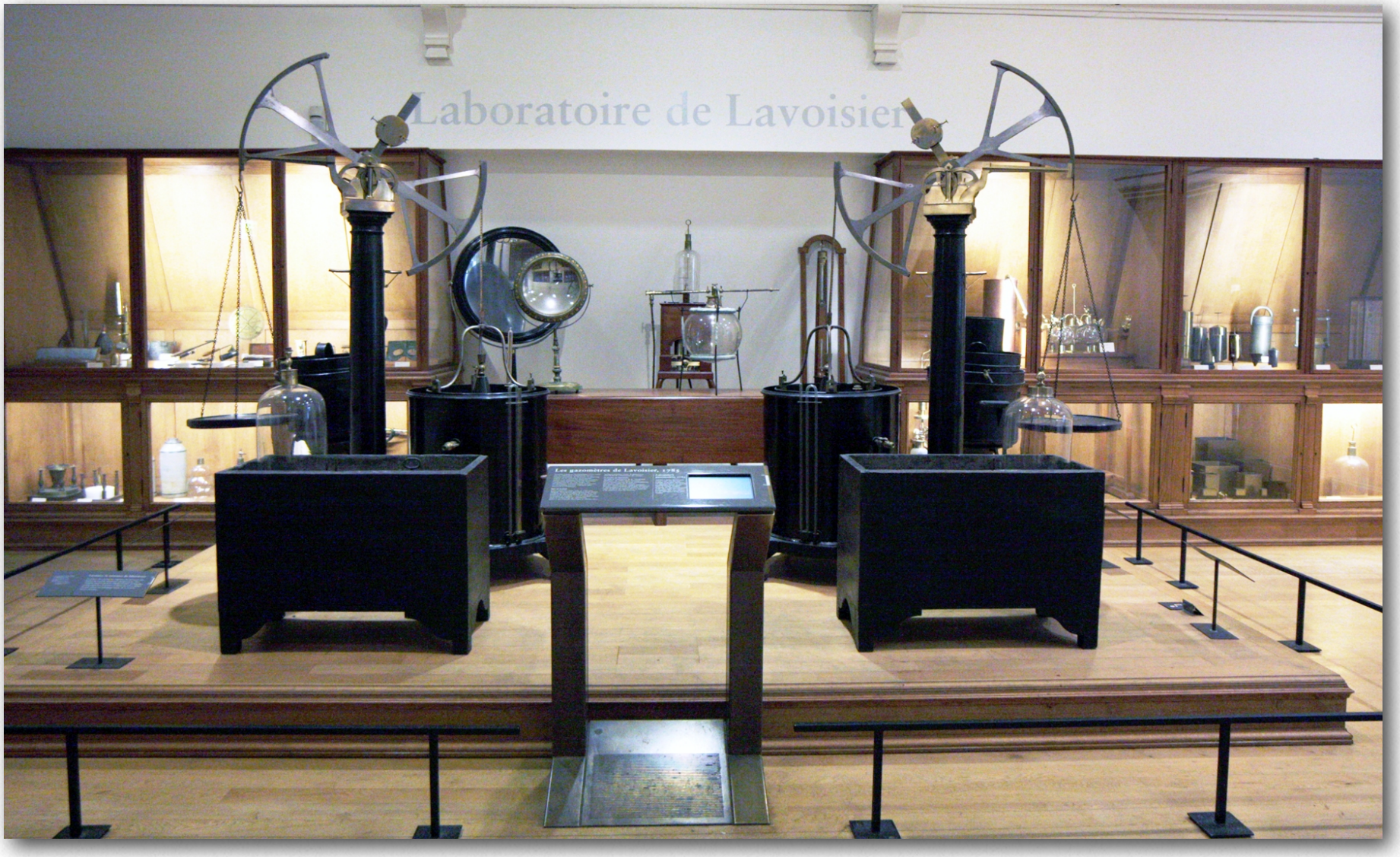
Catalysis provides to cells
Metabolic jump-startin
They all capitalize
By giving rise
To reactions 'tween the carbons

Biochem is beautiful
Saying it with zest
Would be so much easier
If I could just ace the test

Biochem is beautiful
Saying it with zest
Would be so much easier
If I could just ace the test
fade

Recorded by David Simmons
Lyrics by Kevin Ahern

Introduction: Basic Chemistry



Certain chemistry

"Organic chemistry is the chemistry of carbon compounds. Biochemistry is the chemistry of carbon compounds that crawl"

-Michael Adams.

To understand biochemistry, one must possess at least a basic understanding of organic and general chemistry. In this brief section, we will provide a rapid review of the simple concepts necessary to understand cellular chemistry. Chemistry is chemistry, whether in a cell or outside it, but biological chemistry is a particular subset of organic chemistry that often involves enormous macromolecules, and that happens in the aqueous environment of the cell.

YouTube Lectures by Kevin HERE & HERE

Figure 1.18 shows the various organic functional groups common in biochemistry. You will encounter these functional groups as you study the biosynthetic and breakdown pathways that build and recycle the

chemical compounds of which cells are made. In addition to knowing the names and structures of these groups, students need a basic understanding of covalent and ionic bonds.

Class	General Structure	Name	Functional Group
Alkenes	RCH═CHR	Double Bond	C═C
Alcohols	ROH	Hydroxyl	—OH
Ethers	ROR	Ether	—O
Amines	RNH_2		
	R_2NH		
	R_3N	Amino	—N<
Thiols	RSH	Sulfhydryl	—SH
Aldehydes	R—C(=O)—H	Carbonyl	—C(=O)—
Ketones	R—C(=O)—R	Carbonyl	—C(=O)—
Carboxylic Acids	R—C(=O)—OH	Carboxyl	—C(=O)—OH
Amides	R—C(=O)—NR_2	Amide	—C(=O)—N<
Esters	R—C(=O)—OR′	Ester	—C(=O)—OR
Phosphoric Acid Esters	R—O—P(=O)(OH)—OH	Phosphoric Ester	—O—P(=O)(OH)—OH
Phosphoric Acid Anhydrides	R—C—P(=O)(OH)—O—P(=O)(OH)—OH	Phosphoric Anhydride	—P(=O)(OH)—O—P(=O)(OH)—

Figure 1.18 - Important functional groups in biochemistry

Image by Aleia Kim

Covalent bonds, as you know, are the result of sharing of electrons between two atoms. Ionic bonds, by contrast, are formed when one atom donates an electron to another, such as in the formation of sodium chloride.

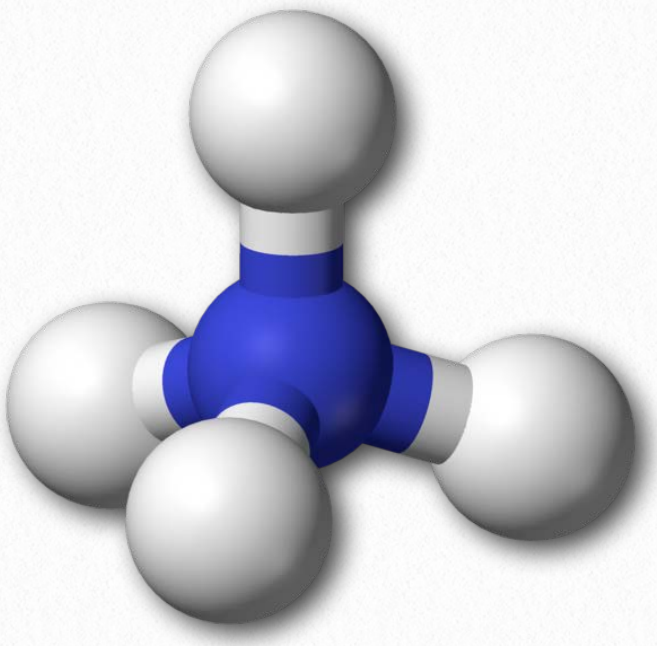


Figure 1.19 - Tetrahedral structure
Wikipedia

Single covalent bonds can rotate freely, but double bonds cannot. Single bonds around a carbon atom are arranged in a tetrahedron with bond angles of 109.5° relative to each other, with the carbon at the center (Figure 1.19). Double bonded carbons create a planar structure with bond angles typically of about 120°.

Electronegativity

Electronegativity is a measure of the affinity a nucleus has for outer shell electrons (Table 1.2). High electronegativity corresponds to high affinity. Electrons in a covalent bond are held closer to the nucleus with a greater electronegativity compared to a nucleus with lower electronegativity.

For example, in a molecule of water, with hydrogen covalently bonded to oxygen, the electrons are “pulled” toward the oxygen, which is more electronegative. Because of this, there is a slightly greater negative charge near the oxygen atom of water, compared to the hydrogen (which, correspondingly has a slightly higher positive charge). This unequal charge distribution sets up a dipole, with one side being somewhat negative and the other somewhat positive. Because of this, the molecule is described as polar.

Hydrogen bonds between water molecules are the result of the attraction of the partial positive and partial negative charges on different water molecules (Figure 1.20). Hydrogen bonds can also form between hydrogens

Table 1.2

Electronegativities of Various Atoms

Atom	Electronegativity
Oxygen	3.5
Nitrogen	3.0
Sulfur	2.6
Carbon	2.5
Phosphorous	2.2
Hydrogen	2.1

Image by Aleia Kim

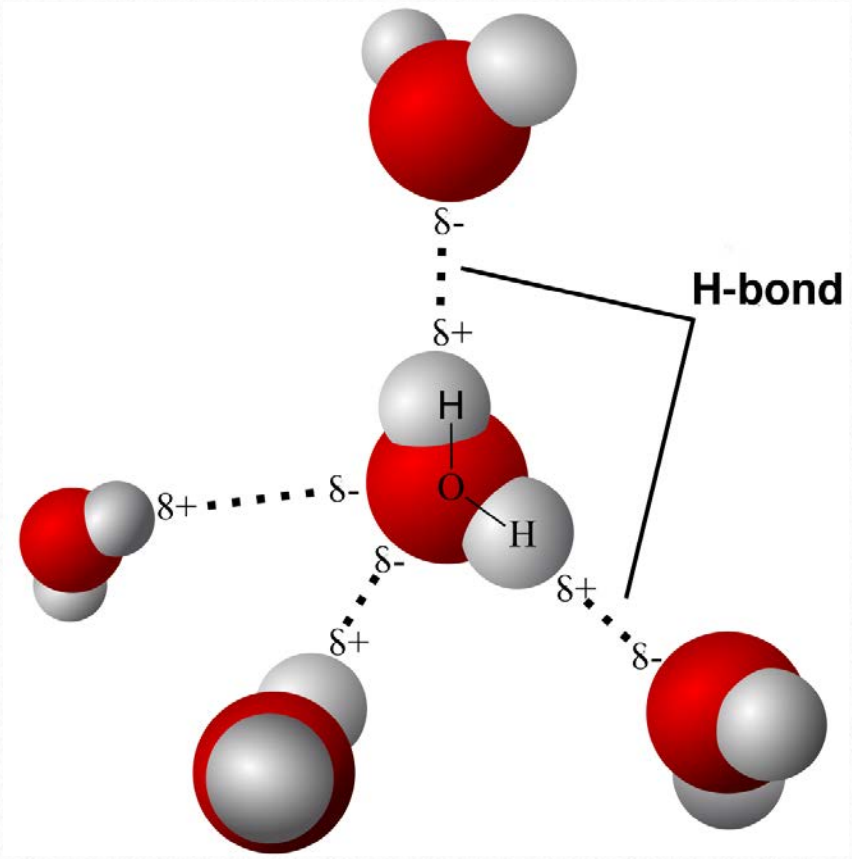


Figure 1.20 Hydrogen bonds (dotted lines) between water molecules

Wikipedia

with a partial positive charge and other strongly electronegative atoms, like nitrogen, with a partial negative charge. It is important to remember that hydrogen bonds are interactions between molecules (or parts of molecules) and are not bonds between atoms, like covalent or ionic bonds.

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Bonds between hydrogen and carbon do not form significant partial charges because the electronegativities of the two atoms are similar. Consequently, molecules containing many carbon-hydrogen bonds will not form hydrogen bonds and therefore, do not mix well with water. Such molecules are called hydrophobic. Other compounds with the ability to make hydrogen bonds are polar and can dissolve in water. They are called hydrophilic. Molecules possessing both characteristics are called amphiphilic.

Weak interactions

Hydrogen bonds are one kind of electrostatic (i.e., based on charge) interaction between dipoles. Other forms of electrostatic interactions that are important in biochemistry include weak interactions between a polar molecule and a transient dipole, or between two temporary dipoles. These temporary dipoles result from the movement of electrons in a molecule. As electrons move around, the place where they are, at a given time, becomes temporarily more negatively charged and could now attract a temporary positive charge on another molecule. Since electrons don't stay put, these dipoles are very short-lived. Thus, the attraction that depends on these dipoles fluctuates and is very weak. Weak interactions like these are sometimes called van der Waals forces. Many molecular interactions in cells depend on weak interactions. Although the individual hydrogen bonds or other dipole-dipole interactions are weak, because of their large numbers, they can result in quite strong interactions between molecules.

Oxidation/reduction

Oxidation involves loss of electrons and reduction results in gain of electrons. For

every biological oxidation, there is a corresponding reduction - one molecule loses electrons to another molecule. Oxidation reactions tend to release energy and are a source of bioenergy for chemotrophic cells.

Ionization

Ionization of biomolecules, by contrast does not involve oxidation/reduction. In ionization, a hydrogen ion (H^+) leaves behind its electron as it exits (leaving behind a negative charge) or joins a group (adding a positive charge). Biological ionizations typically involve carboxyl groups or amines, though phosphates or sulfates can also be ionized. A carboxyl group can have two ionization states - a charge of -1 corresponds to the carboxyl without its proton and a charge of zero corresponds to the charge of the carboxyl with its proton on. An amine also has two ionization states. A charge of zero corresponds to a nitrogen with three covalent bonds (usually in the form of C-NH_2) and a charge of +1 corresponds to a nitrogen making four covalent bonds (usually X-NH_3^+).

Stereochemistry

A carbon has the ability to make four single bonds (forming a tetrahedral structure) and if it bonds to four different chemical groups, their atoms can be arranged around the carbon in two different ways, giving rise to stereochemical "handedness" (Figure 1.21). Each carbon with such a property is referred to as an asymmetric center. The property of handedness *only* occurs when a carbon has four different groups bonded to it. Enzymes have very specific 3-D structures, so for biological molecules that can exist in different stereoisomeric forms, an enzyme that synthesizes it would make only one of the possible isomers. By contrast, the same molecules made chemically (not using enzymes) end up with equal amounts of both isomers, called a racemic mix.

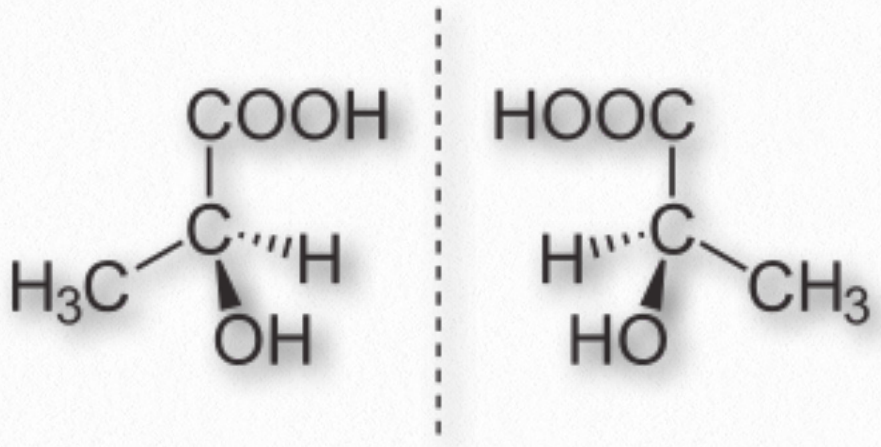

Figure 1.21 - Mirror images of lactic acid

Gibbs free energy

The Gibbs free energy calculation allows us to determine whether a reaction will be spontaneous, by taking into consideration two factors, change in enthalpy (ΔH) and change in entropy (ΔS).

The free energy content of a system is given by the Gibbs free energy (G) and is equal to the enthalpy (H) for a process minus the absolute temperature (T) times the entropy (S)

$$G = H = TS$$

For a process, the change in the Gibbs free energy ΔG is given by

$$\Delta G = \Delta H - T\Delta S$$

A ΔG that is negative corresponds to release of free energy. Reactions that release energy are exergonic, whereas those that absorb energy are called endergonic.

The biological standard Gibbs free energy change ($\Delta G°'$) corresponds to the ΔG for a process under standard conditions of temperature, pressure, and at pH = 7. For a reaction

$$aA + bB <=> cC + dD,$$

the equilibrium constant, K_{eq} is equal to

$$K_{eq} = \{[C]^c_{eq}[D]^d_{eq}]\} / \{[A]^a_{eq}[B]^b_{eq}\}$$

where a,b,c,and d are integers in the balanced equation. Large values of K_{eq} correspond to favorable reactions (more C and D produced than A and B) and small values of K_{eq} mean the opposite. At equilibrium,

$$\Delta G°' = -RT\ln K_{eq}$$

If a process has a $\Delta G = Z$ and a second process has a $\Delta G = Y$, then if the two processes are linked, ΔG and $\Delta G°'$ values for the overall reaction will be the sum of the individual ΔG and $\Delta G°'$ values.

$$\Delta G_{total} = \Delta G_1 + \Delta G_2 = Z + Y$$

$$\Delta G°'_{total} = \Delta G_1°' + \Delta G_2°'$$

Catalysis

Catalysis is an increase in the rate of a reaction induced by a substance that is, itself, unchanged by the reaction. Because catalysts remain unchanged at the end of a reaction, a single catalyst molecule can be reused for many reaction cycles. Proteins that catalyze reactions in cells are called enzymes, while ribozymes are RNA molecules that act as catalysts.

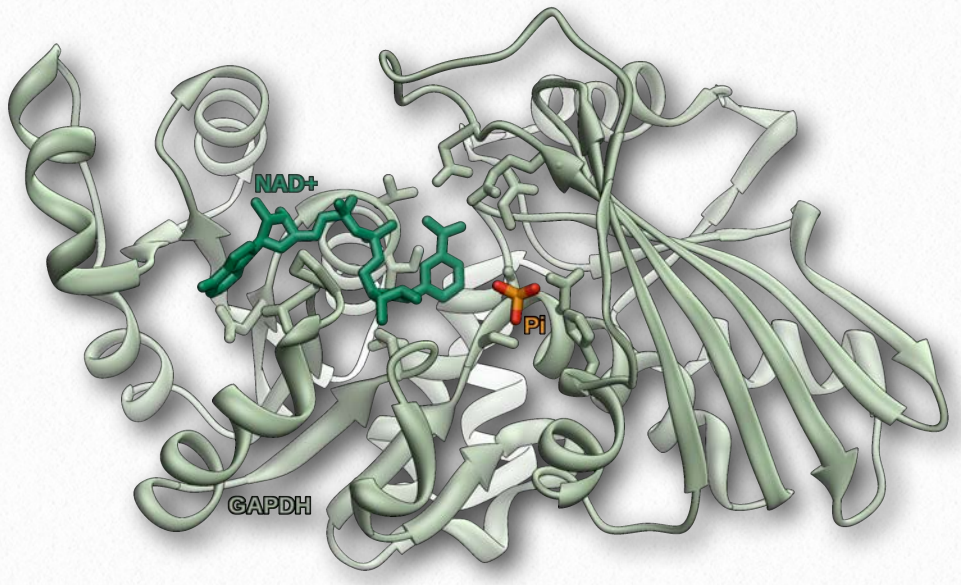

Figure 1.22 - Glyceraldehyde-3-phosphate dehydrogenase in the midst of catalysis

Wikipedia

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The Number Song

To the tune of "*Everybody Loves Somebody Sometime*"

Metabolic Melodies Website HERE

Avogadro's number is a huge one
Boltzmann's constant's rather miniscule
Values differing enormously
As we learned in school

Science numbers need to have dimensions
Size is not the most important thing
Units give the yardsticks needed
For under-STAN-ding

Bridge

It's taught in the ivory towers
By professors it's so ballyhooed
Values can have such diff'rent powers
That to know them we must have their magnitudes

One light year's a really lengthy distance
Grams define the masses high and low
The ohm can measure the resistance
If current should flow

Bridge

One set of factors you SHOULD know
The roots of seven and of three et al
Cannot be expressed as a ratio
Oh these numbers all are quite irration-al

Three point one four one five nine two six five
No end to Pi's digits it's absurd
Endlessly reminding me that I've
BEEN SO OUT-num-bered

Recording by David Simmons
Lyrics by Kevin Ahern

Elemental Learning

To the tune of "*Sentimental Journey*"

Metabolic Melodies Website HERE

Gonna do
Some elemental learning
Studying for my degree

Elevate
My supplemental earnings
With atomic chemistry

Learning ‘bout
The subatomic units
In an atom’s nucleus

Balance charge
With all of the electrons
Or an ion you’ll possess

Neutrons
They’re the chargeless bits in
Atoms
Protons sometimes wish they had ‘em
Gotta have an a-dequate supply
In nuclei

If you don’t
There’ll be a price for payin’
For the instability

‘Cuz you’ll get
The nucleus decaying
Radi-o-activity

Recording by Heather Pearson Boren and Eric Hill
Lyrics by Kevin Ahern

Introduction: Water and Buffers

Water everywhere

When it comes to water, we're literally drowning in it, as water is by far the most abundant component of every cell. To understand life, we begin the discussion with the basics of water, because everything that happens in cells, even reactions buried deep inside enzymes, away from water, is influenced by water's chemistry.

YouTube Lectures by Kevin HERE & HERE

The water molecule has wide 'V' shape (the H-O-H angle is 104°) with uneven sharing of electrons between the oxygen and the hydrogen atoms (Figure 1.23). Oxygen, with its higher electronegativity, holds electrons closer to itself than the hydrogens do. The hydrogens, as a result, are described as having a partial positive charge (typically designated as δ^+) and the oxygen has a partial negative charge (written as δ^-). Thus, water is

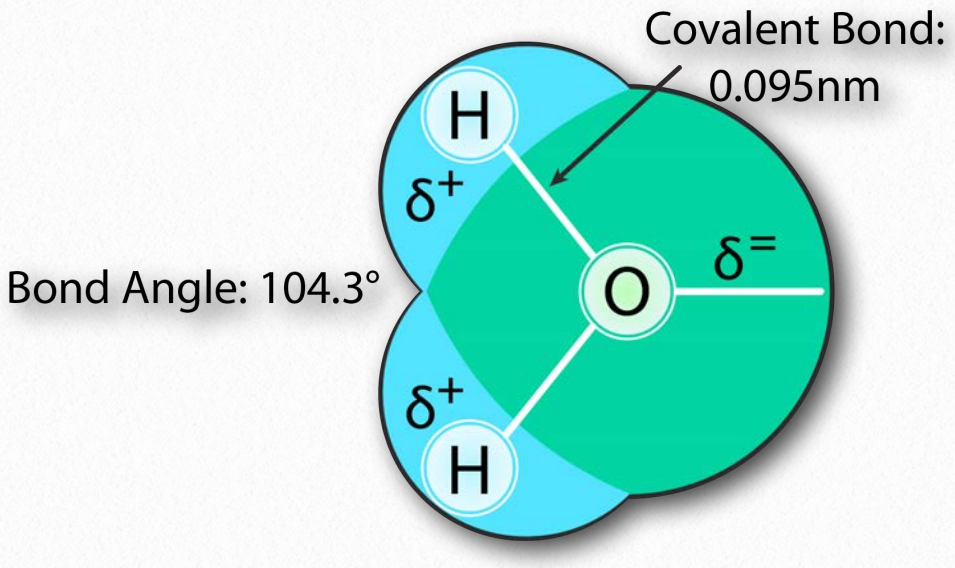

Figure 1.23 - Arrangement of atoms in water
Image by Aleia Kim

a polar molecule because charges are distributed around it unevenly, not symmetrically.

Water as a solvent

Water (Figure 1.23) is described as a solvent because of its ability to solvate (dissolve) many, but not all, molecules. Molecules that are ionic or polar dissolve readily in water, but non-polar substances dissolve poorly in water, if at all. Oil, for example, which is non-polar, separates from water when mixed with it. On the other hand, sodium chloride, which ionizes, and ethanol, which is polar, are able to form hydrogen bonds, so both dissolve in water. Ethanol's solubility in water is crucial for brewers, winemakers, and distillers – but for this property, there would be no wine, beer or spirits. As explained in an earlier section, we use the term hydrophilic to describe substances that interact well with water and dissolve in it and the term hydrophobic to refer to materials that are non-polar and do not dissolve in water. Table 1.3 illustrates some polar and non-polar substances. A third term, amphiphilic, refers to compounds that have both properties. Soaps, for example are amphiphilic, containing a long, non-polar aliphatic tail and a head that ionizes.

Solubility

The solubility of materials in water is based in free energy changes, as measured by ΔG. Re-

Table 1.3

Hydrophilic vs Hydrophobic Compounds

Hydrophobic	Hydrophilic
Nonpolar hydrocarbons (hexane)	Ionic compounds (NaCl)
Lipids (fats and cholesterol)	Polar organic compounds (alcohols, ketones or carbonyls)
	Weak acids (phosphates, amino acids)
	Sugars/carbohydrates

Image by Aleia Kim

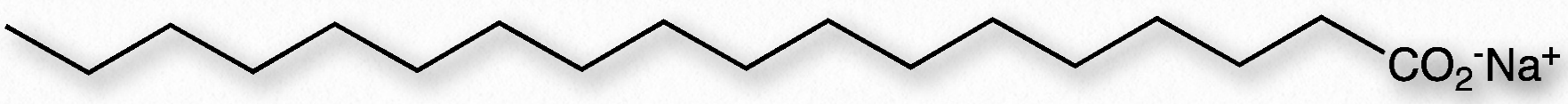

Figure 1.24 - Structure of a Soap

member, from chemistry, that H is the enthalpy (heat at constant pressure) and S is entropy. Given this,

$$\Delta G = \Delta H - T\Delta S,$$

where T is the temperature in Kelvin. For a process to be favorable, the ΔG for it must be less than zero.

From the equation, lowered ΔG values will be favored with decreases in enthalpy and/or increases in entropy. Let us first consider why non-polar materials do not dissolve in water. We could imagine a situation where the process of dissolving involves the "surrounding" of each molecule of the non-polar solute in water, just like each sodium and each chloride ion gets surrounded by water molecules as salt dissolves.

Water organization

There is a significant difference, though between surrounding a non-polar molecule with water molecules and surrounding ions (or polar compounds) with water molecules.

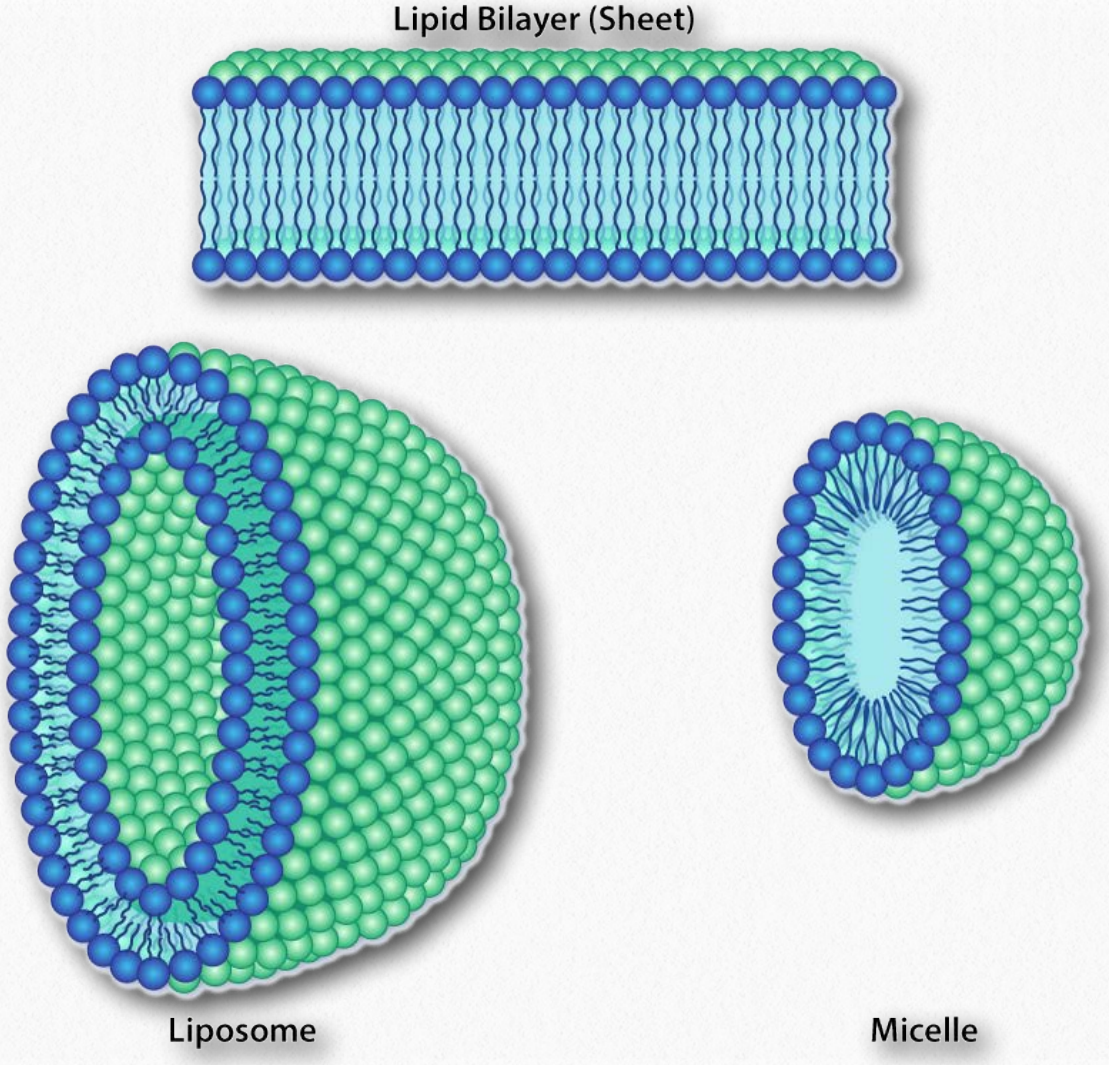

Figure 1.25 - Structures formed by amphiphilic substances in water.

Image by Aleia Kim

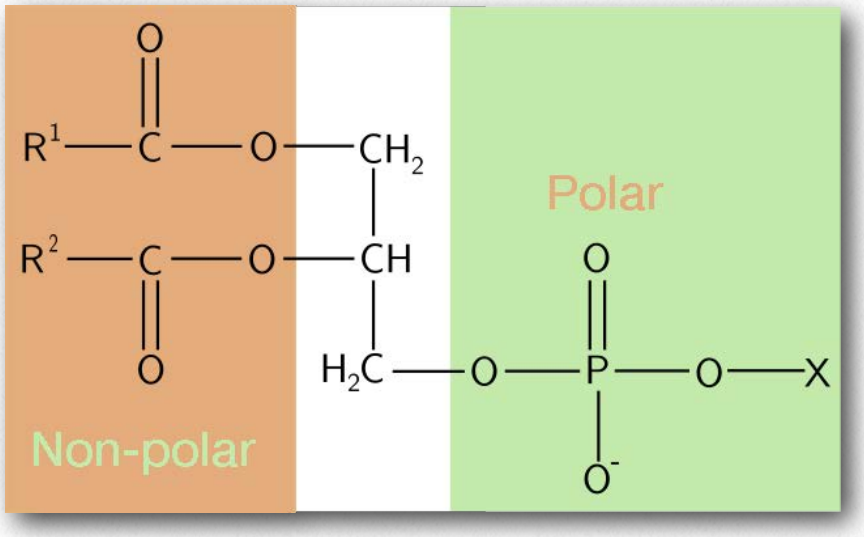

Figure 1.26 - A phospholipid - an amphiphilic substance

Since mixing a non-polar substance with water doesn't generally have any significant heat component, the ΔG is positive. This means, then, that dissolving a non-polar compound in water is not favorable and does not occur to any significant extent. Further, when the non-polar material associates with itself and not water, then the water molecules are free to mix, without being ordered, resulting in an increase of entropy. Entropy therefore drives the separation of non-polar substances from aqueous solutions.

The difference is that since non-polar molecules don't really interact with water, the water behaves very differently than it does with ions or molecules that form hydrogen bonds. In fact, around each non-polar molecule, water gets *very* organized, aligning itself regularly. As any freshman chemistry student probably remembers, entropy is a measure of disorder, so when something becomes ordered, entropy decreases, meaning the ΔS is negative, so the $T\Delta S$ term in the equation is positive (negative of a negative).

Figure 1.27 - Vinegar (black) and oil (yellow) A mix of polar and nonpolar compounds
Wikipedia

Amphiphilic substances

Next, we consider mixing of an amphiphilic substance, such as a soap, with water (Figure 1.24). The sodium ions attached to the fatty acids in soap readily come off in aqueous solution, leaving behind a negatively charged molecule at one end and a non-polar region at the other end. The ionization of the soap causes in an increase in entropy - two particles instead of one. The non-polar portion of the negatively charged soap ion is problematic - if exposed to water, it will cause

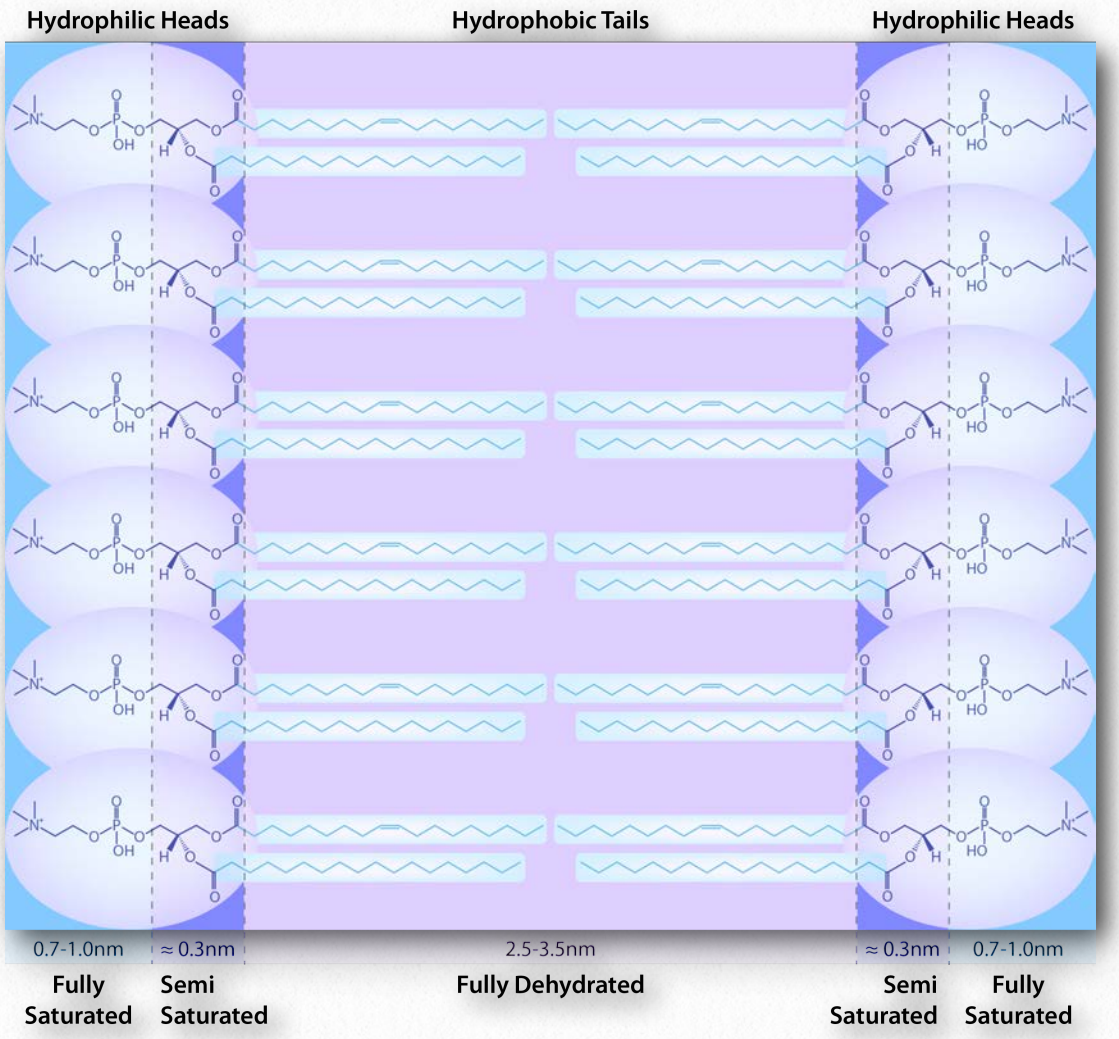

Figure 1.28 - Environment of a lipid bilayer. Water is concentrated away from the hydrophobic center, being saturated on the outside, semi-saturated near the head-tail junction and fully dehydrated in the middle.

Image by Aleia Kim

water to organize and result in a decrease of entropy and a positive ΔG.

Since we know fatty acids dissolve in water, there must be something else at play. There is. Just like the non-polar molecules in the first example associated with each other and not water, so too do the non-polar portions of the soap ions associate with each other and exclude water. The result is that the soap ions arrange themselves as micelles (Figure 1.25) with the non-polar portions on the interior of the structure away from water and the polar portions on the outside interacting with water.

The interaction of the polar heads with water returns the water to its more disordered state. This increase in disorder, or entropy, drives the formation of micelles. As will be seen in the discussion of the lipid bilayer, the same forces drive glycerophospholipids and sphingolipids to spontaneously form bilayers where the non-polar portions of the molecules interact with each other to exclude water and the polar portions arrange themselves on the outsides of the bilayer (Figure 1.28).

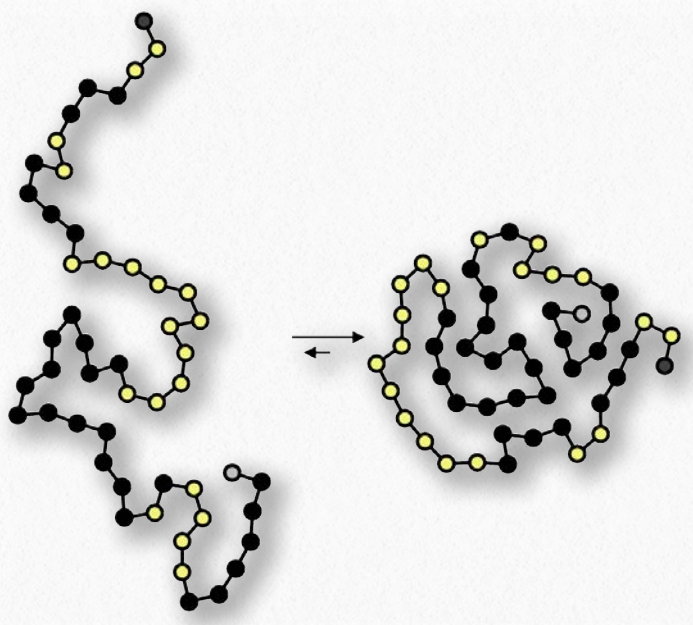

Figure 1.29 - Protein folding arranges hydrophobic amino acids (black dots) inside the protein

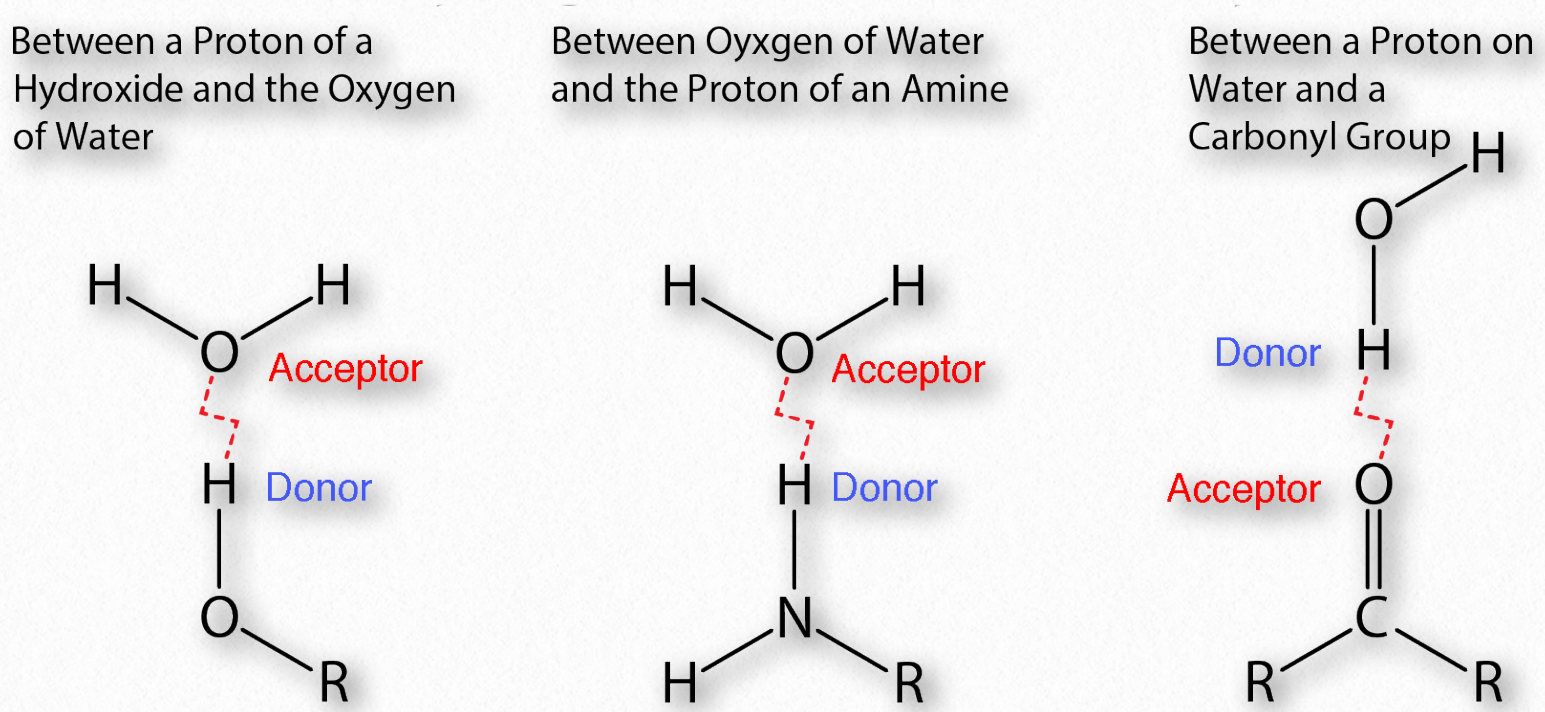

Figure 1.30 - Common hydrogen bonds in biochemistry

Image by Aleia Kim

Yet another example is seen in the folding of globular proteins in the cytoplasm. Non-polar amino acids are found in the interior portion of the protein (water excluded). Interaction of the non-polar amino acids turns out to be a driving force for the folding of proteins as they are being made in an aqueous solution.

Hydrogen bonds

The importance of hydrogen bonds in biochemistry (Figure 1.30) is hard to overstate. Linus Pauling himself said,

" . . . . *I believe that as the methods of structural chemistry are further applied to physiological problems it will be found that the significance of the hydrogen bond for physiology is greater than that of any other single structural feature.*"

In 2011, an IUPAC task group gave an evidence-based definition of hydrogen bonding that states,

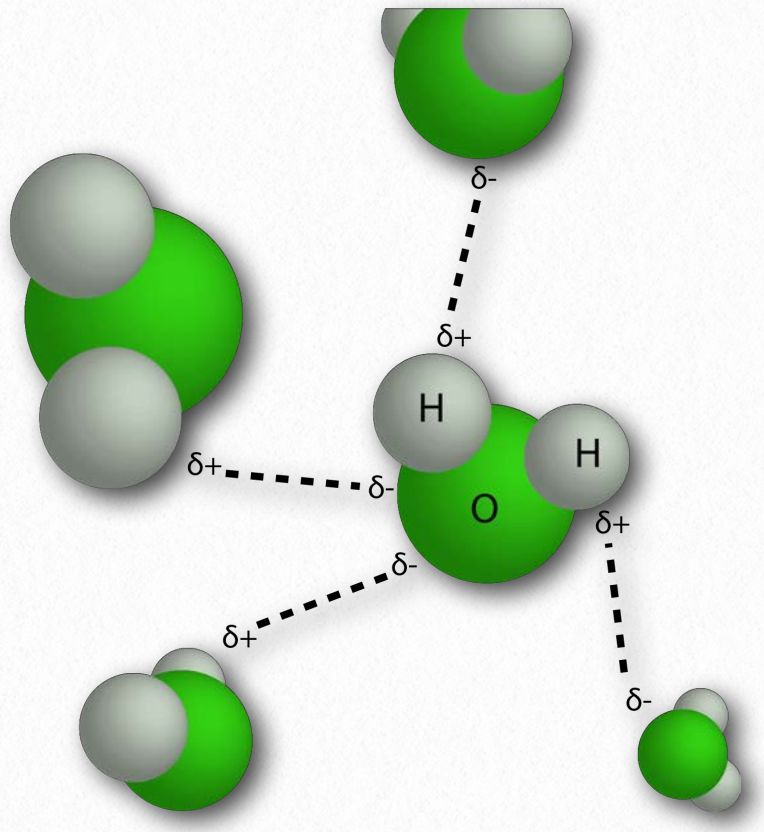

Figure 1.31 - Hydrogen bonds between water molecules

Image by Pehr Jacobson

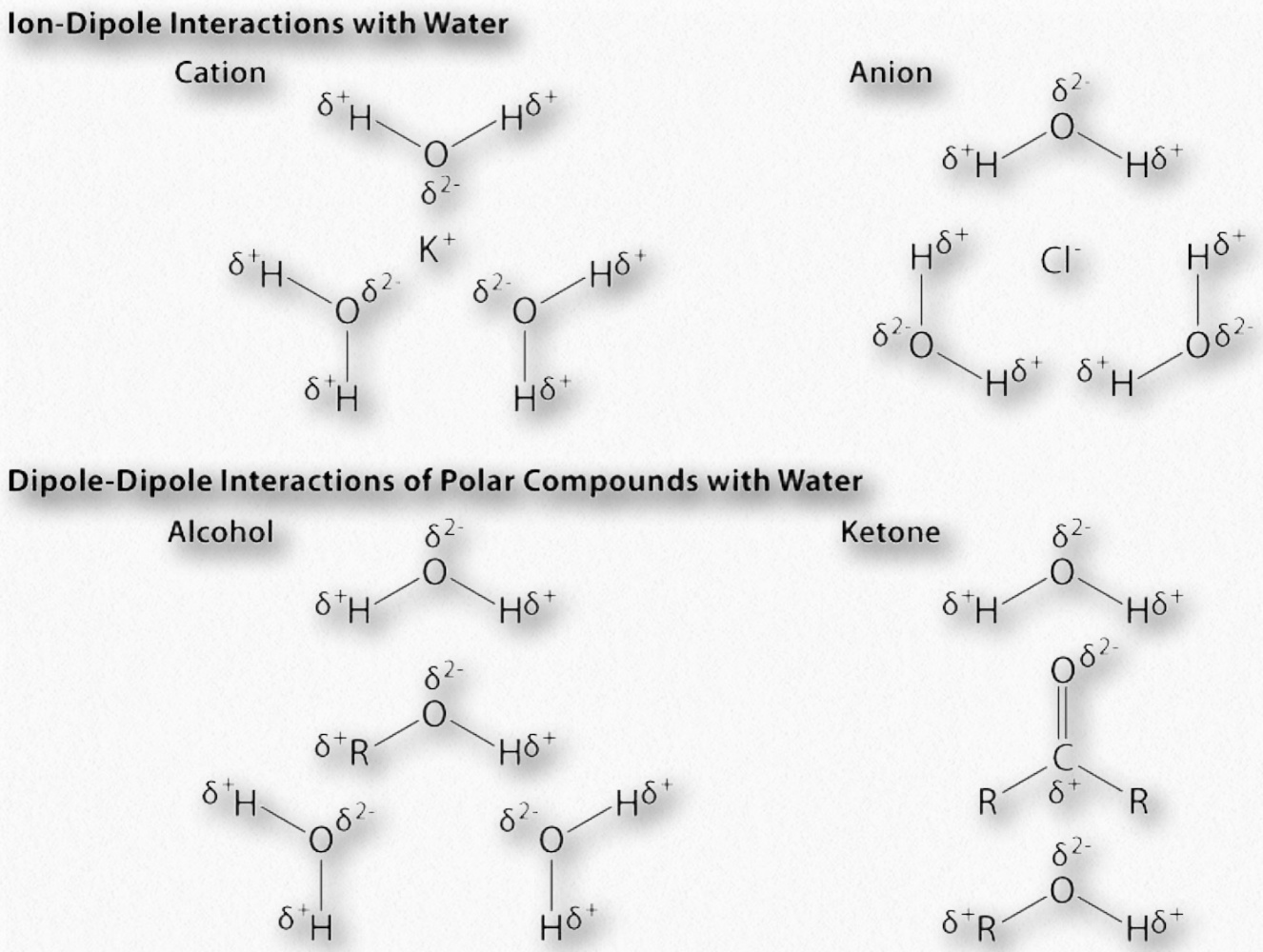

Figure 1.32 - Example dipole interactions in biochemistry
Image by Aleia Kim

"*The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.*"

YouTube Lectures by Kevin HERE & HERE

Partial charges

The difference in electronegativity between hydrogen and the molecule to which it is covalently bound give rise to partial charges as described above. These tiny charges (δ^+ and δ^-) result in formation of hydrogen bonds, which occur when the partial positive charge of a hydrogen atom is attracted to the partial negative of another molecule. In water, that means the hydrogen of one water molecule is attracted to the oxygen of another (Figure 1.31). Since water is an asymmetrical molecule, it means also that the charges are asymmetrical. Such an uneven distribution is what makes a dipole. Dipolar molecules are important for interactions with other dipolar molecules and for dissolving ionic substances (Figure 1.32).

Hydrogen bonds are not exclusive to water. In fact, they are important forces holding together macromolecules that include proteins and nucleic acids. Hydrogen bonds occur within and between macromolecules.

The complementary pairing that occurs between bases in opposite strands of DNA, for example, is based on hydrogen bonds.

Table 1.4

Bond Energies

	Type of Bond	Bond Energy (kJ/mol)
Covalent Bonds	C—H	413
	O—H	460
Noncovalent Bonds	Hydrophobic Interaction	4-12
	Hydrogen Bond	20
	Ion-dipole Interaction	20

Image by Aleia Kim

Each hydrogen bond is relatively weak (compared to a covalent bond, for example - Table 1.4), but collectively they can be quite strong.

Benefits of weak interactions

Their weakness, however, is actually quite beneficial for cells, particularly as regards nucleic acids (Figure 1.33). The strands of DNA, for example, must be separated over short stretches in the processes of replication and the synthesis of RNA. Since only a few base pairs at a time need to be separated, the energy required to do this is small and the enzymes involved in the processes can readily take them apart, as needed. Hydrogen bonds also play roles in binding of substrates to enzymes, catalysis, and protein-protein interaction, as well as other kinds of binding, such as protein-DNA, or antibody-antigen.

As noted, hydrogen bonds are weaker than covalent bonds (Table 1.4) and their strength varies from very weak (1-2 kJ/mol) to fairly strong (29 kJ/mol). Hydrogen bonds only occur over relatively short distances (2.2 to

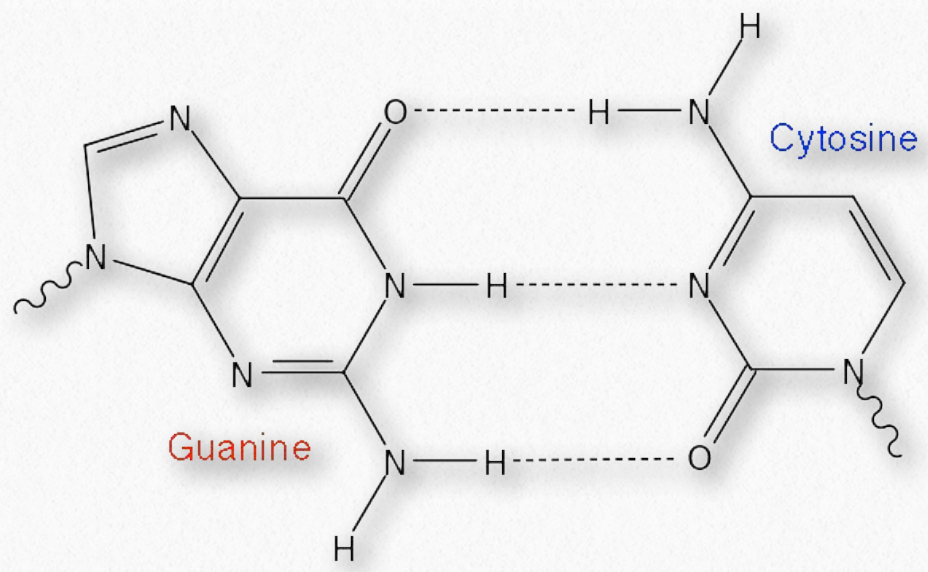

Figure 1.33 - Hydrogen bonds in a base pair of DNA

Image by Aleia Kim

4.0 Å). The farther apart the hydrogen bond distance is, the weaker the bond is.

The strength of the bond in kJ/mol represents the amount of heat that must be put into the system to break the bond - the larger the number, the greater the strength of the bond. Hydrogen bonds are readily broken using heat. The boiling of water, for example, requires breaking of H-bonds. When a biological structure, such as a protein or a DNA molecule, is stabilized by hydrogen bonds, breaking those bonds destabilizes the structure and can result in denaturation of the substance - loss of structure. It is partly for this reason that most proteins and all DNAs lose their native, or folded, structures when heated to boiling.

For DNA molecules, denaturation results in complete separation of the strands from each other. For most proteins, this means loss of

Table 1.5

Weak Acid pKa Values

Name	Chemical Structure of Acid	Chemical Structure of Salt	pKa
Acetic Acid	CH_3COOH	CH_3COO^-	4.76
Formic Acid	$HCOOH$	$HCOO^-$	3.75
Lactic Acid	$CH_3CHOHCOOH$	$CH_3CH—HCOO^-$	3.86
Pyruvic Acid	$CH_3COCOOH$	$CH_3C—COO^-$	2.50
Oxalic Acid (1)	$HOOC—COOH$	$HOOC—COO^-$	1.23
Oxalic Acid (2)	$HOOC—COO^-$	$OOC—COO^-$	4.19
Carbonic Acid (1)	H_2CO_3	HCO_3^-	6.37
Carbonic Acid (2)	HCO_3^-	CO_3^{2-}	10.20
Malic Acid (1)	$HOOC—CH_2—CHOH—COOH$	$HOOC—CH_2—CHOH—COO^-$	3.40
Malic Acid (2)	$HOOC—CH_2—CHOH—COO^-$	$^-OOC—CH_2—CHOH—COO^-$	5.26
Malonic Acid (1)	$HOOC—CH_2—COOH$	$HOOC—CH_2—COO^-$	2.83
Malonic Acid (2)	$HOOC—CH_2—COO^-$	$^-OOC—CH_2—COO^-$	5.69
Phosphoric Acid (1)	H_3PO_4	$H_2PO_4^-$	2.14
Phosphoric Acid (2)	$H_2PO_4^-$	HPO_4^{2-}	7.20
Phosphoric Acid (3)	HPO_4^{2-}	PO_4^{3-}	12.40
Succinic Acid (1)	$HOOC—CH_2—CH_2—COOH$	$HOOC—CH_2—CH_2—COO^-$	4.21
Succinic Acid (2)	$HOOC—CH_2—CH_2—COO^-$	$^-OOC—CH_2—CH_2—COO^-$	5.63

Image by Aleia Kim

their characteristic three-dimensional structure and with it, loss of the function they performed. Though a few proteins can readily reassume their original structure when the solution they are in is cooled, most can't. This is one of the reasons that we cook our food. Proteins are essential for life, so denaturation of bacterial proteins results in death of any microorganisms contaminating the food.

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The importance of buffers

Water can ionize to a slight extent (10^{-7} M) to form H^+ (proton) and OH^- (hydroxide). We measure the proton concentration of a solution with pH, which is the negative log of the proton concentration.

$$pH = -Log[H^+]$$

If the proton concentration, $[H^+]= 10^{-7}$ M, then the pH is 7. We could just as easily measure the hydroxide concentration with the pOH by the parallel equation,

$$pOH = -Log[OH^-]$$

In pure water, dissociation of a proton simultaneously creates a hydroxide, so the pOH of pure water is 7, as well. This also means that

$$pH + pOH = 14$$

Now, because protons and hydroxides can combine to form water, a large amount of one will cause there to be a small amount of the other. Why is this the case? In simple terms, if I dump 0.1 moles of H^+ into a pure water solution, the high proton concentration will react with the relatively small amount of hydroxides to create water, thus reducing hydroxide concentration. Similarly, if I dump excess hydroxide (as NaOH, for example) into pure water, the proton concentration falls for the same reason.

Acids vs bases

Chemists use the term "acid" to refer to a substance which has protons that can dissociate (come off) when dissolved in water. They use the term "base" to refer to a substance that can absorb protons when dissolved in water. Both acids and bases come in strong and weak forms. (Examples of weak acids are shown in Table 1.5.)

Strong acids, such as HCl, dissociate completely in water. If we add 0.1 moles ($6.02x10^{22}$ molecules) of HCl to a solution to make a liter, it will have 0.1 moles of H^+ and

I confess I am pleased to possess
In my buffers a strong UPS
Giving H's when needed
Grabbing same when exceeded
So my cells don't get proton distressed

Clearing Confusion - Students are often puzzled and expect that

$$[H^+] = [A^-]$$

because the dissociation equation shows one of each from HA. This is, in fact, true ONLY when HA is allowed to dissociate in pure water. Usually the HA is placed into solution that has protons and hydroxides to affect things. Those protons and /or hydroxides change the H^+ and A^- concentration unequally, since A^- can absorb some of the protons and/or HA can release H^+ when influenced by the OH^- in the solution. Therefore, one must calculate the proton concentration from the pH using the Henderson Hasselbalch equation.

$$pH = pK_a + \log([Ac^-]/[HAc])$$

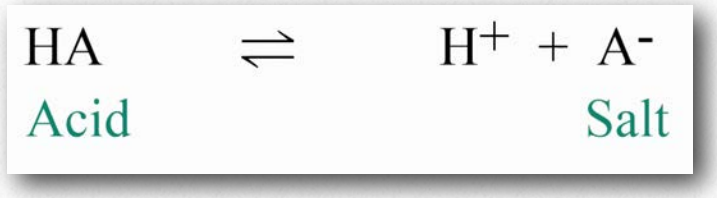

Figure 1.34 - Dissociation of a weak acid

Image by Aleia Kim

0.1 moles of Cl^- or $6.02x10^{22}$ molecules of each . There will be no remaining HCl when this happens. A strong base like NaOH also dissociates completely into Na^+ and OH^-.

Weak acids

Weak acids and bases differ from their strong counterparts. When you put one mole of acetic acid (HAc) into pure water, only a tiny percentage of the HAc molecules dissociate into H^+ and Ac^-. Clearly, weak acids are very different from strong acids. Weak bases behave similarly, except that they accept protons, rather than donate them. Since we can view everything as a form of a weak acid, we will not use the term weak base here.

You may wonder why we care about weak acids. You may never have thought much of weak acids when you were in General Chemistry. Your instructor described them as buffers and you probably dutifully memorized the fact that “buffers are substances that resist change in pH” without really learning what

Table 1.6

Salt/Acid Ratio as a Function of pK_as

pH	[Salt]/[Acid]
$pK_a + 3$	1000
$pK_a + 2$	100
$pK_a + 1$	10
pK_a	1
$pK_a - 1$	1/10
$pK_a - 2$	1/100
$pK_a - 3$	1/1000

Image by Aleia Kim

this meant. Buffers are much too important to be thought of in this way.

UPS

Weak acids are critical for life because their affinity for protons causes them to behave like a UPS. We're not referring to the UPS that is the United Parcel Service®, but instead, to the encased battery backup systems for computers called Uninterruptible Power Supplies that kick on to keep a computer running during a power failure. The battery in a laptop computer is a UPS, for example.

We can think of weak acids as Uninterruptible Proton Suppliers within certain pH ranges,

> On this chemical fact we must dwell
> H-A-C's just not like H-C-L
> It always negotiates
> Before it dissociates
> To bid every proton farewell

providing (or absorbing) protons as needed. Weak acids thus help to keep the H^+ concentration (and thus the pH) of the solution they are in relatively constant.

Consider the bicarbonate/carbonic acid system. Figure 1.35 shows what happens when H_2CO_3 dissociates. Adding hydroxide ions (by adding a strong base like NaOH) to the solution causes the H^+ ions to react with OH^- ions to make water. Consequently, the concentration of H^+ ions would go down and the pH would go up.

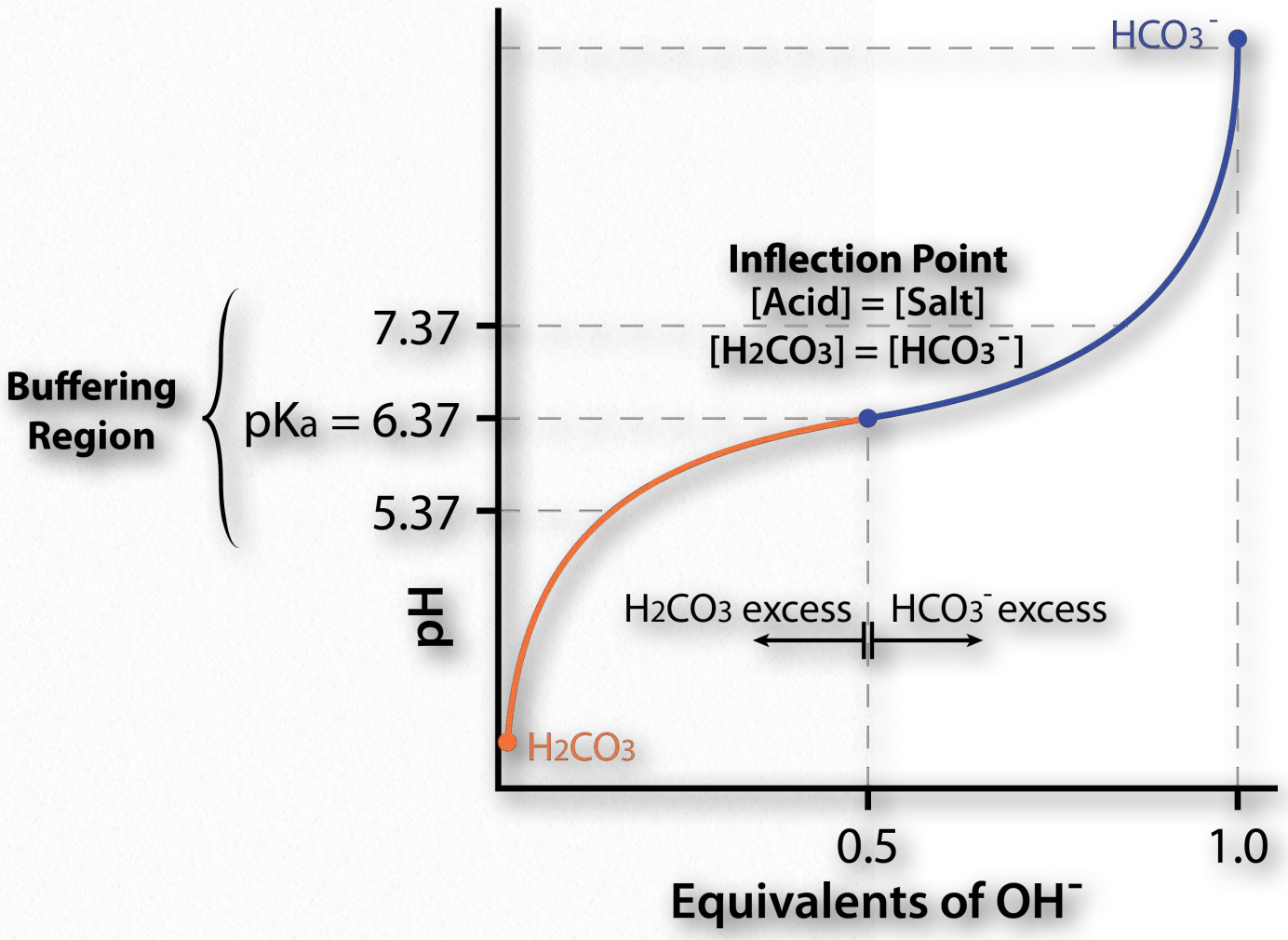

Figure 1.35 - Titration curve for carbonic acid

Image by Aleia Kim

However, in contrast to the situation with a solution of pure water, there is a backup source of H^+ available in the form of H_2CO_3. Here is where the UPS function kicks

in. As protons are taken away by the added hydroxyl ions (making water), they are partly replaced by protons from the H_2CO_3. This is why a weak acid is a buffer. It resists changes in pH by releasing protons to compensate for those "used up" in reacting with the hydroxyl ions.

Why do we care about pH? Because biological molecules can, in some cases, be exquisitely sensitive to changes in it. As the pH of a solution changes, the charges of molecules in the solution can change, as you will see. Changing charges on biological molecules, especially proteins, can drastically affect how they work and even whether they work at all.

Henderson-Hasselbalch

It is useful to be able to predict the response of the H_2CO_3 system to changes in H^+ concentration. The Henderson-Hasselbalch equation defines the relationship between pH and the ratio of HCO_3^- and H_2CO_3. It is

$$pH = pKa + \log([HCO3^-]/[H_2CO_3])$$

This simple equation defines the relationship between the pH of a solution and the ratio of $HCO3^-$ and H_2CO_3 in it. The new term, called the pK_a, is defined as

$$pK_a = -\text{Log } K_a,$$

just as

$$pH = -\text{Log } [H^+].$$

The K_a is the acid dissociation constant and is a measure of the strength of an acid. For a general acid, HA, which dissociates as

$$HA \rightleftarrows H^+ + A^-,$$

$$K_a = [H^+][A^-]/[HA]$$

Thus, the stronger the acid, the more protons that will dissociate from it when added to water and the larger the value its K_a will have. Large values of K_a translate to lower values of pK_a. As a result, the lower the pKa value is for a given acid, the stronger the weak acid is.

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Constant pK_a

Please note that pK_a is a constant for a given acid. The pK_a for carbonic acid is 6.37. By comparison, the pK_a for formic acid is 3.75. Formic acid is therefore a stronger acid than acetic acid. A stronger acid will have more protons dissociated at a given pH than a weaker acid.

Now, how does this translate into stabilizing pH? Figure 1.35 shows a titration curve. In this curve, the titration begins with the conditions at the lower left (very low pH). At this pH, the H_2CO_3 form predominates, but as more and more OH^- is added (moving to the

right), the pH goes up, the amount of $HCO3^-$ goes up and (correspondingly), the amount of H_2CO_3 goes down. Notice that the curve "flattens" near the pK_a (6.37).

Buffering region

Flattening of the curve tells us is that the pH is not changing much (not going up as fast) as it did earlier when the same amount of hydroxide was added. The system is resisting a change in pH (not stopping the change, but slowing it) in the region of about one pH unit above and one pH unit below the pK_a. Thus, the buffering region of the carbonic acid/bicarbonate buffer is from about 5.37 to 7.37. It is maximally strong at a pH of 6.37.

Now it starts to become apparent how the buffer works. HA can donate protons when extras are needed (such as when OH^- is added to the solution by the addition of NaOH). Similarly, A^- can accept protons when extra H^+ are added to the solution (adding HCl, for example). The maximum ability to donate or accept protons comes when

$$[A^-] = [HA]$$

This is consistent with the Henderson Hasselbalch equation and the titration curve. When $[A^-] = [HA]$, pH = 6.37 + Log(1). Since Log(1) = 0, pH = 6.37 = pKa for carbonic acid. Thus for any buffer, the buffer will have maximum strength and display flattening of its titration curve when $[A^-] = [HA]$ and when pH = pK_a. If a buffer has more than one pK_a (Figure 1.36), then each pK_a region will display the behavior.

Buffered vs non-buffered

To understand how well a buffer protects against changes in pH, consider the effect of adding .01 moles of HCl to 1.0 liter of pure water (no volume change) at pH 7, compared to adding it to 1.0 liter of a 1M acetate buffer at pH 4.76. Since HCl completely dissociates, in 0.01M (10^{-2} M) HCl you will have 0.01M H^+. For the pure water, the pH drops from 7.0 down to 2.0 (pH = -log(0.01M)).

By contrast, the acetate buffer's pH after adding the same amount of HCl is 4.74. Thus, the pure water solution sees its pH fall from 7 to 2 (5 pH units), whereas the buffered solution saw its pH drop from 4.76 to 4.74 (0.02 pH units). Clearly, the buffer minimizes the impact of the added protons compared to the pure water.

Buffer capacity

It is important to note that buffers have capacities limited by their concentration. Let's imagine that in the previous paragraph, we had added the 0.01 moles HCl to an acetate buffer that had a concentration of 0.01M and equal amounts of Ac^- and HAc. When we try to do the math in parallel to the previous calculation, we see that there are 0.01M protons, but only 0.005M A^- to absorb them. We could imagine that 0.005M of the protons would be

absorbed, but that would still leave 0.005M of protons unbuffered. Thus, the pH of this solution would be approximately

$$pH = -\log(0.005M) = 2.30$$

Exceeding buffer capacity dropped the pH significantly compared to adding the same amount of protons to a 1M acetate buffer. Consequently, when considering buffers, it is important to recognize that their concentration sets their limits. Another limit is the pH range in which one hopes to control proton concentration.

Multiple ionizable groups

Now, what happens if a molecule has two (or more) ionizable groups? It turns out, not surprisingly, that each group will have its own pK_a and, as a consequence, will have multiple regions of buffering.

Figure 1.36 shows the titration curve for the amino acid aspartic acid. Note that in-

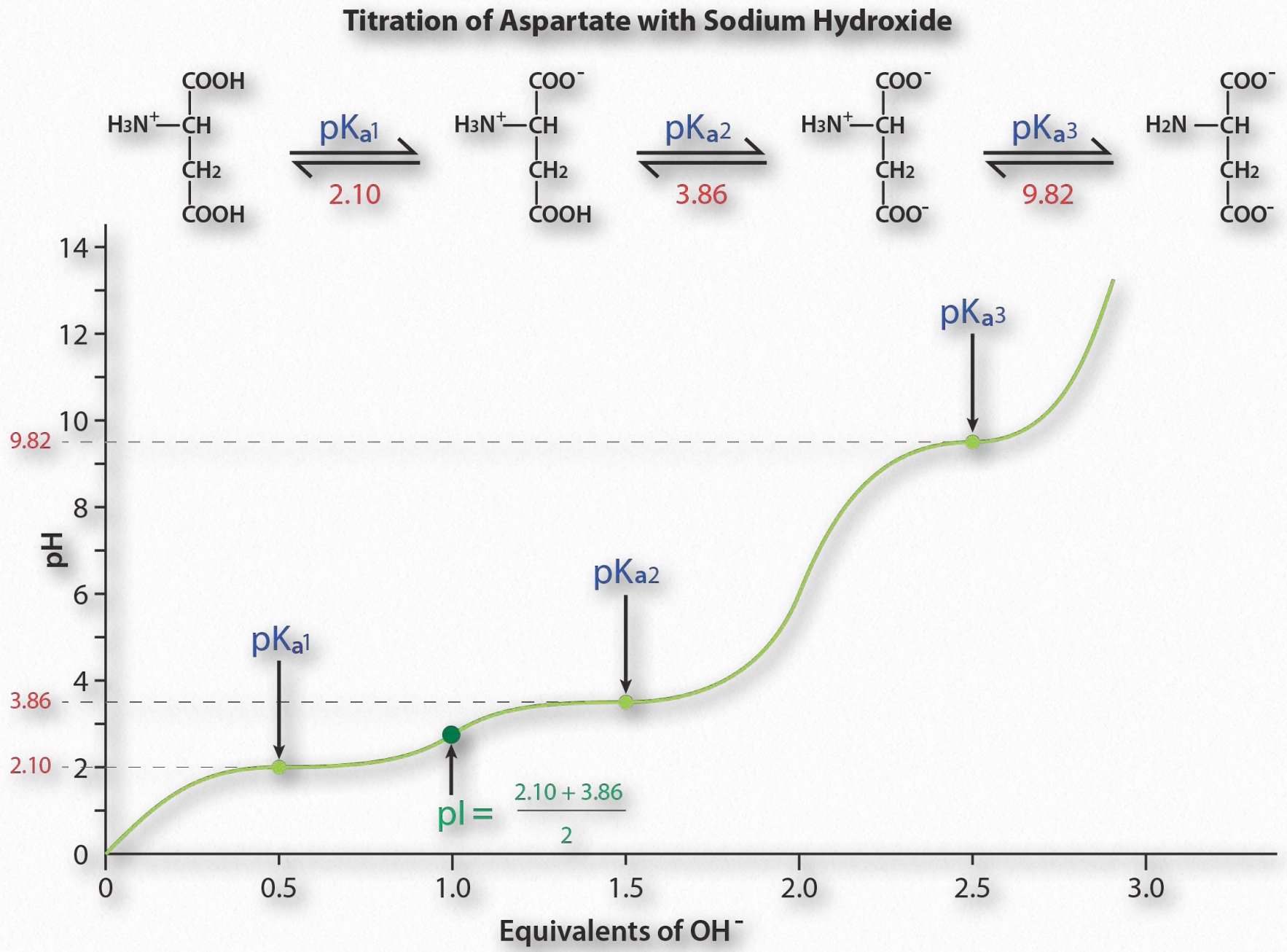

Figure 1.36 - Titration of an acidic amino acid

Image by Aleia Kim

stead of a single flattening of the curve, as was seen for acetic acid, aspartic acid's titration curve displays three such regions. These are individual buffering regions, each centered on the respective pK_a values for the carboxyl group and the amine group.

Aspartic acid has four possible charges: +1 (α-carboxyl group, α-amino group, and R-group carboxyl each has a proton), 0 (α-carboxyl group missing proton, α- amino group has a proton, R-group carboxyl has a proton), -1 (α-carboxyl group and R-group carboxyl each lack a proton, α-amino group retains a proton), -2 (α-carboxyl, R-group carboxyl, and α-amino groups all lack extra proton).

Prediction

How does one predict the charge for an amino acid at a given pH? A good rule of thumb for estimating charge is that if the pH is more than one unit below the pK_a for a group (carboxyl or amino), the proton is on. If the pH is more than one unit above the pK_a for the group, the proton is off. If the pH is NOT more than one or less than one pH unit from the pK_a, this simple assumption will not work.

Further, it is important to recognize that these rules of thumb are estimates only. The pI (pH at which the charge of a molecule is zero) is an exact value calculated as the average of the two pK_a values on either side of the zero region. It is calculated at the average of the two pKa values around the point where the charge of the molecule is zero. For aspartic acid, this corresponds to pK_{a1} and pK_{a2}.

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Henderson Hasselbalch

To the tune of "*My Country 'Tis of Thee*

Metabolic Melodies Website HERE

Henderson Hasselbalch
You put my brain in shock
Oh woe is me
The pKa's can make
Me lie in bed awake
They give me really bad headaches
Oh hear my plea

Salt - acid RA-ti-os
Help keep the pH froze
By buf-fer-ING
They show tenacity
Complete audacity
If used within capacity
To maintain things

I know when H's fly
A buffer will defy
Them actively
Those protons cannot waltz
When they get bound to salts
With this the change in pH halts
All praise to thee

Thus now that I've addressed
This topic for the test
I've got know-how
The pH I can say
Equals the pK_a
In sum with log of S o'er A
I know it now

Recorded by David Simmons
Lyrics by Kevin Ahern and Indira Rajagopal

Ode to Bicarbonate

To the tune of "*Song Sung Blue*"
Metabolic Melodies Website HERE

H-2-O
Ionizes slowly
You should know
Its behavior wholly

It presides - in cells' insides - a solvent great
But mix it with an oil and shake it up
You'll see 'em separate
See 'em separate

C-O-2
Made in oxidation
Inside you
Decarboxylation

So divine – when it combines up with the H-2-Os
Bonding together makes bicarbonates
To ease the pH woes

Bicarbonate – can conjugate and take protons out
Restoring a balance inside of the blood
Of this there is no doubt

Thus it's so
Thanks to bicarb buffer
In blood flow
You don't have to suffer

Bicarbonate – will conjugate to take the protons out
Restoring a balance inside of the blood
Of this there is no doubt

Protons stow
In the bicarb buffer
Never grow

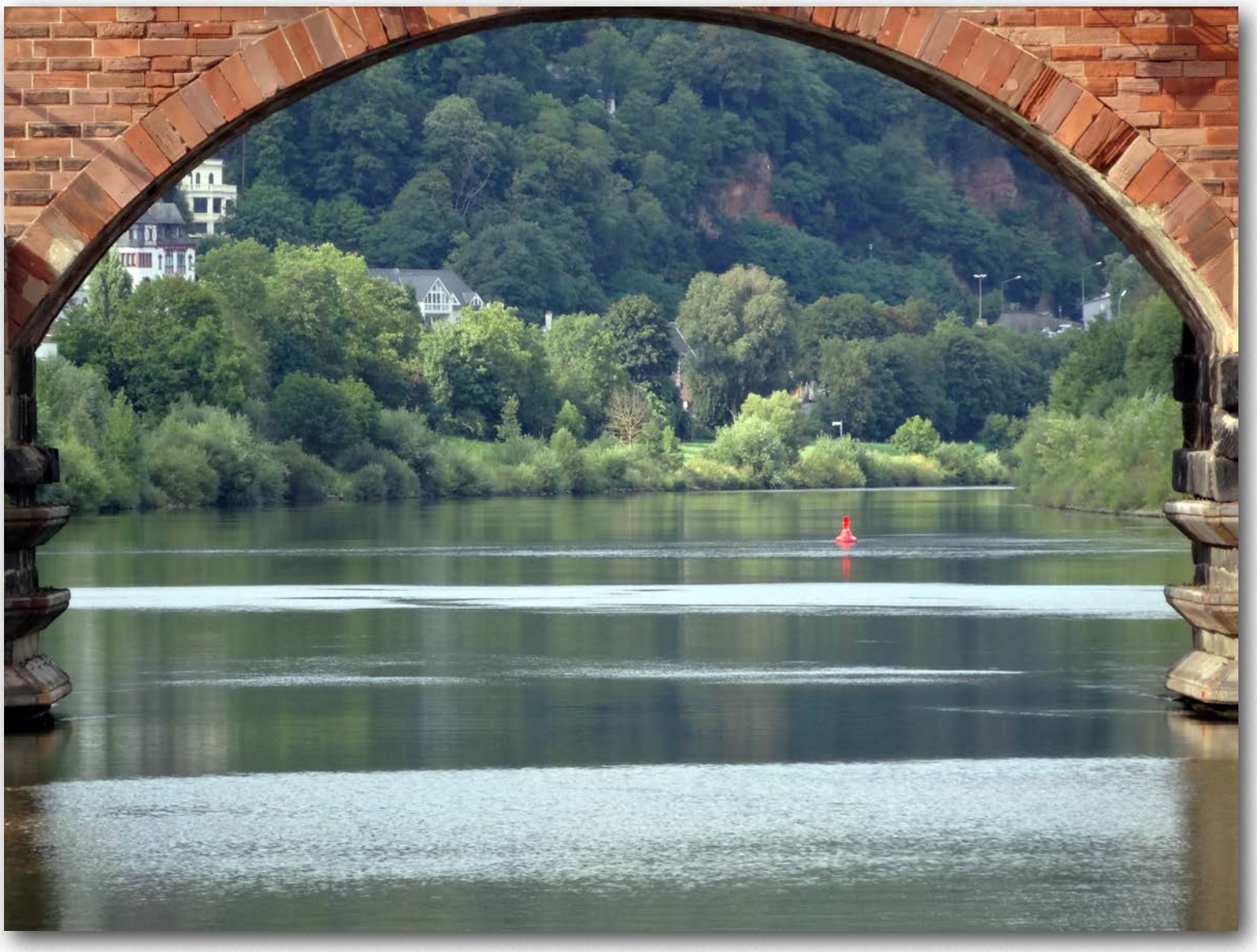
Recorded by David Simmons
Lyrics by Kevin Ahern

2

Structure & Function

"The man who does not read good books has no advantage over the man who cannot read them."

Mark Twain



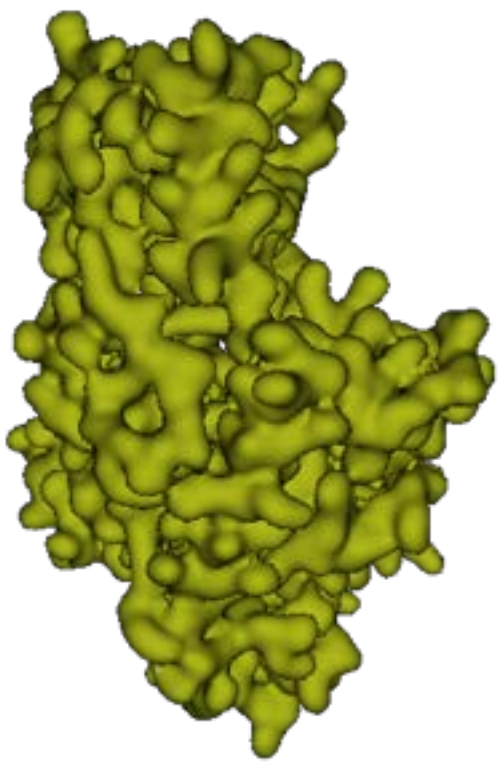
Introduction

When we study life at the molecular level, it becomes apparent that the structures of biological molecules are inseparable from their functions. The molecular interactions that underlie life are dependent on the structures of the molecules we are made of.

"*It is structure that we look for, whenever we try to understand anything. All science is built upon this search. We like to understand, and to explain, observed facts in terms of structure.*

- Linus Pauling

In this chapter, we will examine the structures of the major classes of biomolecules, with an eye to understanding how these structures relate to function.



Interactive 2.1 - The enzyme Hexokinase: as for all enzymes, the activity of hexokinase depends on its structure.

Protein Database (PDB)

Biological molecules

As noted earlier, water is the most abundant molecule in cells, and provides the aqueous environment in which cellular chemistry happens. Dissolved in this water are inorganic ions like sodium, potassium and calcium. But the distinctiveness of biochemistry derives from the vast numbers of complex, large, carbon compounds, that are made by living cells. You have probably learned that the major classes of biological molecules are proteins, nucleic acids, carbohydrates and lipids. The first three of these major groups are macromolecules that are built as long polymers made up of smaller subunits or monomers, like strings of beads. The lipids, while not chains of monomers, also have smaller subunits that are assembled in various ways to make the lipid components of cells, including membranes. The chemical properties and three dimensional conformations of these molecules determine all the molecular interactions upon which life depends. Whether building structures within cells, transferring information, or catalyzing reactions, the activities of biomolecules are governed by their structures. The properties and shapes of macromolecules, in turn, depend on the subunits of which they are built.

Building blocks

We will next examine the major groups of biological macromolecules: proteins, polysaccharides, nucleic acids, and lipids. The building blocks of the first three, respectively, are amino acids, monosaccharides (sugars), and nucleotides. Acetyl-CoA is the most common building block of lipids.

Structure & Function: Amino Acids

"It is one of the more striking generalizations of biochemistry ...that the twenty amino acids and the four bases, are, with minor reservations, the same throughout Nature."

- Francis Crick

Building blocks of protein

All of the proteins on the face of the earth are made up of the same 20 amino acids. Linked together in long chains called polypeptides, amino acids are the building blocks for the vast assortment of proteins found in all living cells.

YouTube Lectures by Kevin HERE & HERE

All amino acids have the same basic structure, which is shown in Figure 2.1. At the “center” of each amino acid is a carbon called the **α** carbon and attached to it are four groups - a hydrogen, an **α**-carboxyl group, an **α**-amine group, and an R-group, sometimes referred to as a side chain. The α carbon, carboxyl, and amino groups are common to all amino acids, so the

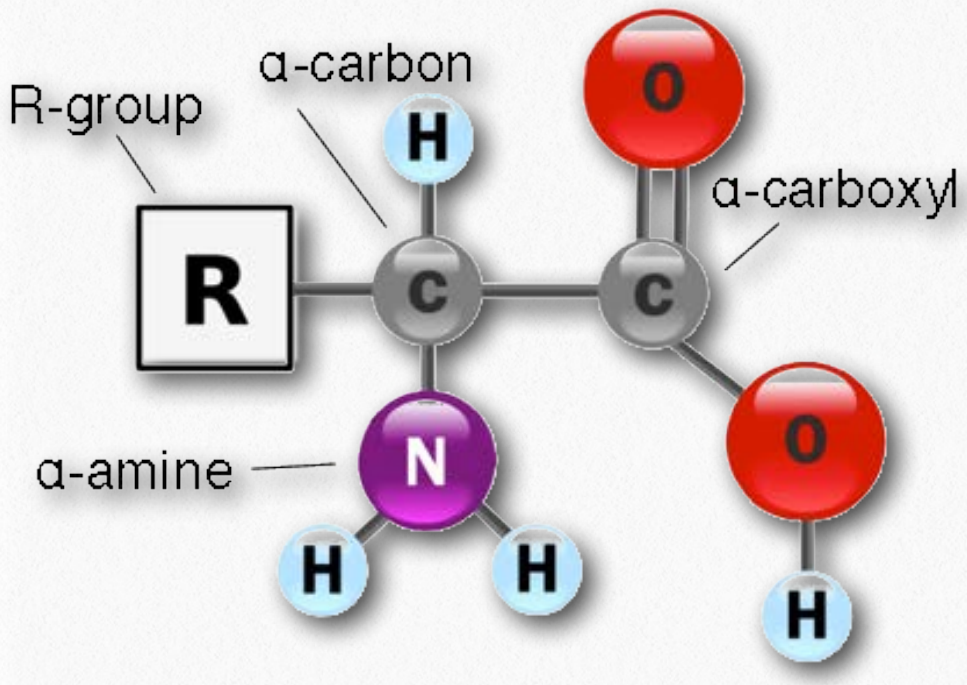


Figure 2.1 - General amino acid structure

R-group is the only unique feature in each amino acid. (A minor exception to this structure is that of proline, in which the end of the R-group is attached to the α-amine.) With the exception of glycine, which has an R-group consisting of a hydrogen atom, all of the amino acids in proteins have four different groups attached to them and consequently can exist in two mirror image forms, L and D. With only very minor exceptions, every amino acid found in cells and in proteins is in the L configuration.

There are 22 amino acids that are found in proteins and of these, only 20 are specified by the universal genetic code. The others, selenocysteine and pyrrolysine use tRNAs that are able to base pair with stop codons in the mRNA during translation. When this happens, these unusual amino acids can be incorporated into proteins. Enzymes containing selenocysteine, for example, include glutathione peroxidases, tetraiodothyronine 5' deiodinases, thioredoxin reductases, formate dehydrogenases, glycine reductases, and selenophosphate synthetase. Pyrrolysine-containing proteins are much rarer and are mostly confined to archaea.

Essential	Non-Essential
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Lysine	Aspartic acid
Methionine	Cysteine
Phenylalanine	Glutamic acid
Threonine	Glutamine
Tryptophan	Glycine
Valine	Proline
	Selenocysteine
	Serine
	Tyrosine

Table 2.1 - Essential and non-essential amino acids

Non-Polar	Carboxyl	Amine	Aromatic	Hydroxyl	Other
Alanine	Aspartic Acid	Arginine	Phenylalanine	Serine	Asparagine
Glycine	Glutamic Acid	Histidine	Tryptophan	Threonine	Cysteine
Isoleucine		Lysine	Tyrosine	Tyrosine	Glutamine
Leucine					Selenocysteine
Methionine					Pyrrolysine
Proline					
Valine					

Table 2.2 - Amino acid categories (based on R-group properties)

Essential and non-essential

Nutritionists divide amino acids into two groups - essential amino acids (must be in the diet because cells can't synthesize them) and non-essential amino acids (can be made by cells). This classification of amino acids has little to do with the structure of amino acids. Essential amino acids vary considerable from one organism to another and even differ in humans, depending on whether they are adults or children. Table 2.1 shows essential and non-essential amino acids in humans.

Some amino acids that are normally non-essential, may need to be obtained from the diet in certain cases. Individuals who do not synthesize sufficient amounts of arginine, cysteine, glutamine, proline, selenocysteine, serine, and tyrosine, due to illness, for example, may need dietary supplements containing these amino acids.

Non-protein amino acids

There are also α-amino acids found in cells that are not incorporated into proteins. Common ones include ornithine and citrulline. Both of these compounds are intermediates in the urea cycle. Ornithine is a metabolic precursor of arginine and citrulline can be produced by the breakdown of arginine. The latter reaction produces nitric oxide, an important signaling molecule. Citrulline is the metabolic byproduct. It is sometimes used as a dietary supplement to reduce muscle fatigue.

R-group chemistry

We separate the amino acids into categories based on the chemistry of their R-groups. If you compare groupings of amino acids in different textbooks, you will see different names for the categories and (sometimes) the same amino acid being categorized differently by different authors. Indeed, we categorize ty-

Amino acid	Short	Abbrev.	Side chain	Hydro-phobic	pKa	Polar	pH	Small	Tiny	Aromatic or Aliphatic	van der Waals volume
Alanine	A	Ala	$-CH_3$	X	-	-	-	X	X	-	67
Cysteine	C	Cys	$-CH_2SH$	-	8.18	-	acidic	X	X	-	86
Aspartic acid	D	Asp	$-CH_2COOH$	-	3.90	X	acidic	X	-	-	91
Glutamic acid	E	Glu	$-CH_2CH_2COOH$	-	4.07	X	acidic	-	-	-	109
Phenylalanine	F	Phe	$-CH_2C_6H_5$	X	-	-	-	-	-	Aromatic	135
Glycine	G	Gly	-H	X	-	-	-	X	X	-	48
Histidine	H	His	$-CH_2-C_3H_3N_2$	-	6.04	X	weak basic	-	-	Aromatic	118
Isoleucine	I	Ile	$-CH(CH_3)CH_2CH_3$	X	-	-	-	-	-	Aliphatic	124
Lysine	K	Lys	$-(CH_2)_4NH_2$	-	10.54	X	basic	-	-	-	135
Leucine	L	Leu	$-CH_2CH(CH_3)_2$	X	-	-	-	-	-	Aliphatic	124
Methionine	M	Met	$-CH_2CH_2SCH_3$	X	-	-	-	-	-	-	124
Asparagine	N	Asn	$-CH_2CONH_2$	-	-	X	-	X	-	-	96
Pyrrolysine	O	Pyl	$-(CH_2)_4NHCOC_4H_5NCH_3$	-	-	X	weak basic	-	-	-	
Proline	P	Pro	$-CH_2CH_2CH_2-$	X	-	-	-	X	-	-	90
Glutamine	Q	Gln	$-CH_2CH_2CONH_2$	-	-	X	weak basic	-	-	-	114
Arginine	R	Arg	$-(CH_2)_3NH-C(NH)NH_2$	-	12.48	X	strongly basic	-	-	-	148
Serine	S	Ser	$-CH_2OH$	-	5.68	X	weak acidic	X	X	-	73
Threonine	T	Thr	$-CH(OH)CH_3$	-	5.53	X	weak acidic	X	-	-	93
Selenocysteine	U	Sec	$-CH_2SeH$	-	5.73	-	acidic	X	X	-	
Valine	V	Val	$-CH(CH_3)_2$	X	-	-	-	X	-	Aliphatic	105
Tryptophan	W	Trp	$-CH_2C_8H_6N$	-	5.885	X	weak basic	-	-	Aromatic	163
Tyrosine	Y	Tyr	$-CH_2-C_6H_4OH$	-	10.46	X	weak acidic	-	-	Aromatic	141

Figure 2.2 - Amino acid side chain properties

Wikipedia

rosine both as an aromatic amino acid and as a hydroxyl amino acid. It is useful to classify amino acids based on their R-groups, because it is these side chains that give each amino acid its characteristic properties. Thus, amino acids with (chemically) similar side groups can be expected to function in similar ways, for example, during protein folding.

YouTube Lectures by Kevin HERE & HERE

Non-polar amino acids

Alanine (Ala/A) is one of the most abundant amino acids found in proteins, ranking second only to leucine in occurrence. A D-form of the amino acid is also found in bacterial cell walls. Alanine is non-essential, being readily synthesized from pyruvate. It is coded for by GCU, GCC, GCA, and GCG. Wikipedia link HERE.

Glycine (Gly/G) is the amino acid with the shortest side chain, having an R-group consistent only of a single hydrogen. As a result, glycine is the only amino acid that is not chiral. Its small side chain allows it to readily fit into both hydrophobic and hydrophilic environments.

Glycine is specified in the genetic code by GGU, GGC, GGA, and GGG. It is non-essential to humans. Wikipedia link HERE.

Isoleucine (Ile/I) is an essential amino acid encoded by AUU, AUC, and AUA. It has a hydrophobic side chain and is also chiral in its side chain. Wikipedia link HERE.

Leucine (Leu/L) is a branched-chain amino acid that is hydrophobic and essential.

Leucine is encoded by six codons: UUA,UUG, CUU, CUC, CUA, CUG. Wikipedia link HERE.

Methionine (Met/M) is an essential amino acid that is one of two sulfur-containing amino acids - cysteine is the other. Methionine is non-polar and encoded solely by the AUG codon. It is the "initiator" amino acid in protein synthesis, being the first one incorporated into protein chains. In prokaryotic cells, the first methionine in a protein is formylated. Wikipedia link HERE.

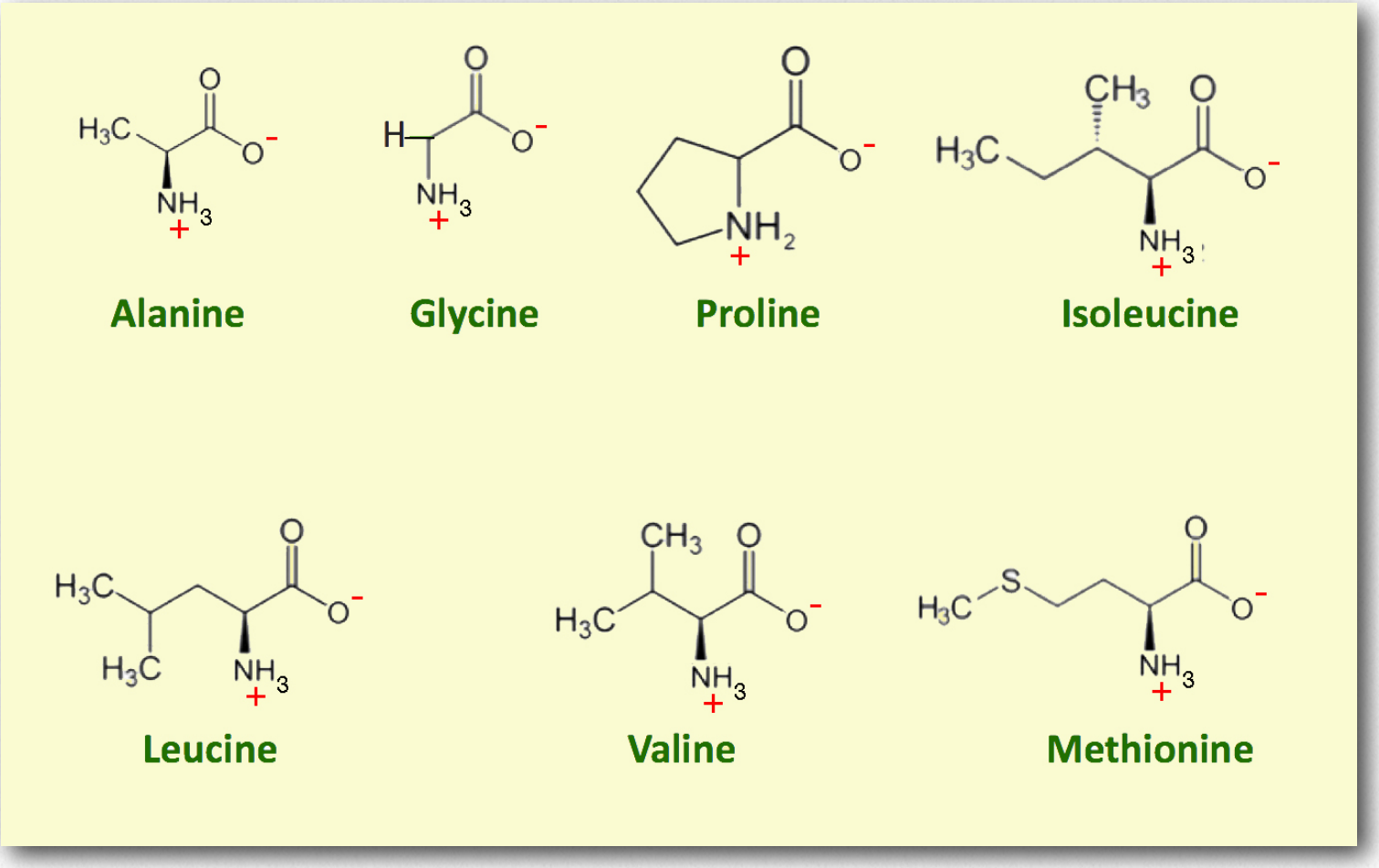


Figure 2.3 - Non-polar amino acids

Proline (Pro/P) is the only amino acid found in proteins with an R-group that joins with its own α-amino group, making a secondary amine and a ring. Proline is a non-essential amino acid and is coded by CCU, CCC, CCA, and CCG. It is the least flexible of the protein amino acids and thus gives conformational rigidity when present in

Leucine is the only dietary amino acid reported to directly stimulate protein synthesis in muscle, but caution is in order, as 1) there are conflicting studies and 2) leucine toxicity is dangerous, resulting in "the four D's": diarrhea, dermatitis, dementia and death .

a protein. Proline's presence in a protein affects its secondary structure. It is a disrupter of α-helices and β-strands. Proline is often hydroxylated in collagen (the reaction requires Vitamin C - ascorbate) and this has the effect of increasing the protein's conformational stability. Proline hydroxylation of hypoxia-inducible factor (HIF) serves as a sensor of oxygen levels and targets HIF for destruction when oxygen is plentiful. Wikipedia link HERE.

Valine (Val/V) is an essential, non-polar amino acid synthesized in plants. It is noteworthy in hemoglobin, for when it replaces glutamic acid at position number six, it causes hemoglobin to aggregate abnormally under low oxygen conditions, resulting in sickle cell disease. Valine is coded in the genetic code by GUU, GUC, GUA, and GUG. Wikipedia link HERE.

Carboxyl amino acids

Aspartic acid (Asp/D) is a non-essential amino acid with a carboxyl group in its R-group. It is readily produced by transamination of oxaloacetate. With a pK_a of 3.9, aspartic acid's side chain is negatively charged at physiological pH. Aspartic acid is specified in the genetic code by the codons GAU and GAC. Wikipedia link HERE.

Glutamic acid (Glu/E), which is coded by GAA and GAG, is a non-essential amino acid readily made by transamination of α-ketoglutarate. It is a neurotransmitter and has an R-group with a carboxyl group that readily ionizes (pK_a = 4.1) at physiological pH. Wikipedia link HERE.

Amine amino acids

Arginine (Arg/R) is an amino acid that is, in some cases, essential, but non-essential in others. Premature infants cannot synthesize arginine. In addition, surgical trauma, sepsis, and burns increase demand for arginine. Most people, however, do not need arginine supplements. Arginine's side chain contains a complex guanidinium group with a pK_a of over 12, making it positively charged at cellular pH. It is coded for by six codons - CGU, CGC, CGA, CGG, AGA, and AGG. Wikipedia link HERE.

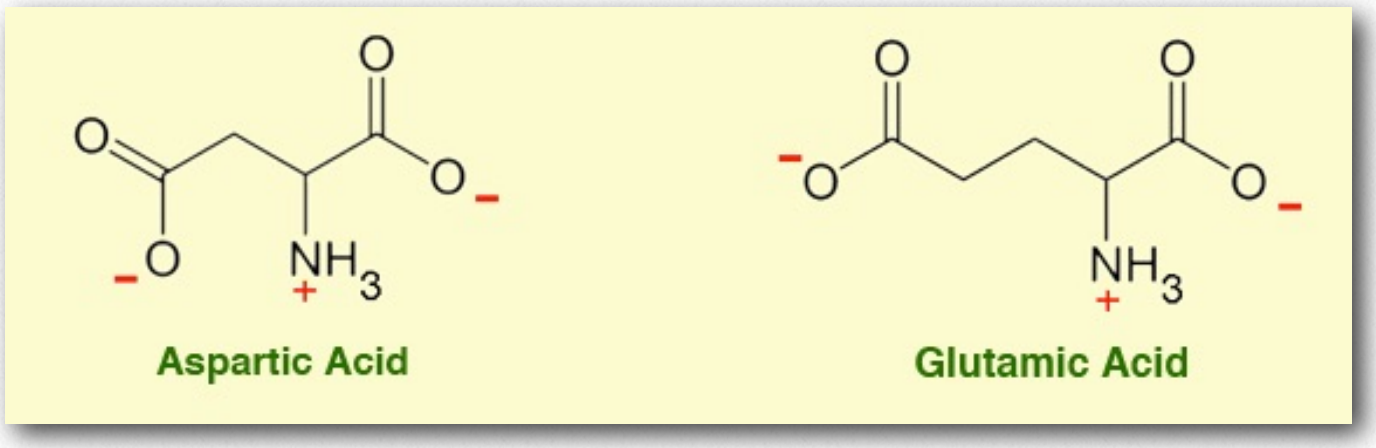


Figure 2.4 - Carboxyl amino acids

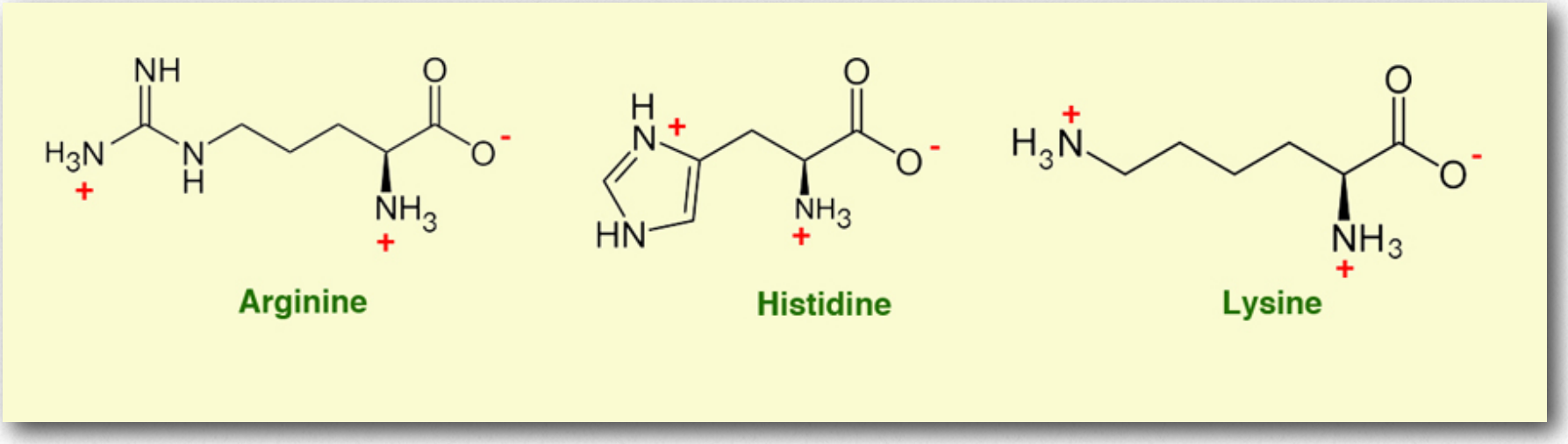


Figure 2.5 - Amine amino acids

Histidine (His/H) is the only one of the proteinaceous amino acids to contain an imidazole functional group. It is an essential amino acid in humans and other mammals. With a side chain pK_a of 6, it can easily have its charge changed by a slight change in pH. Protonation of the ring results in two NH structures which can be drawn as two equally important resonant structures. Wikipedia link HERE.

Lysine (Lys/K) is an essential amino acid encoded by AAA and AAG. It has an R-group that can readily ionize with a charge of +1 at physiological pH and can be post-translationally modified to form acetyllysine, hydroxylysine, and methyllysine. It can also be ubiquitinated, sumoylated, neddylated, biotinylated, carboxylated, and pupylated, and. O-Glycosylation of hydroxylysine is used to flag proteins for export from the cell. Lysine is often added to animal feed because it is a limiting amino acid and is necessary for optimizing growth of pigs and chickens. Wikipedia link HERE.

Aromatic amino acids

Phenylalanine (Phe/ F) is a non-polar, essential amino acid coded by UUU and UUC. It is a metabolic precursor of tyrosine. Inability to metabolize phenylalanine arises from the genetic disorder known as phenylketonuria. Phenylalanine is a component of the aspartame artificial sweetener. Wikipedia link HERE.

Tryptophan (Trp/W) is an essential amino acid containing an indole functional group. It is a metabolic precursor of serotonin, niacin, and (in plants) the auxin phytohormone. Though reputed to serve as a sleep aid, there are no clear research results indicating this. Wikipedia link HERE.

Tyrosine (Tyr/Y) is a non-essential amino acid coded by UAC and UAU. It is a target for phosphorylation in proteins by tyrosine protein kinases and plays a role

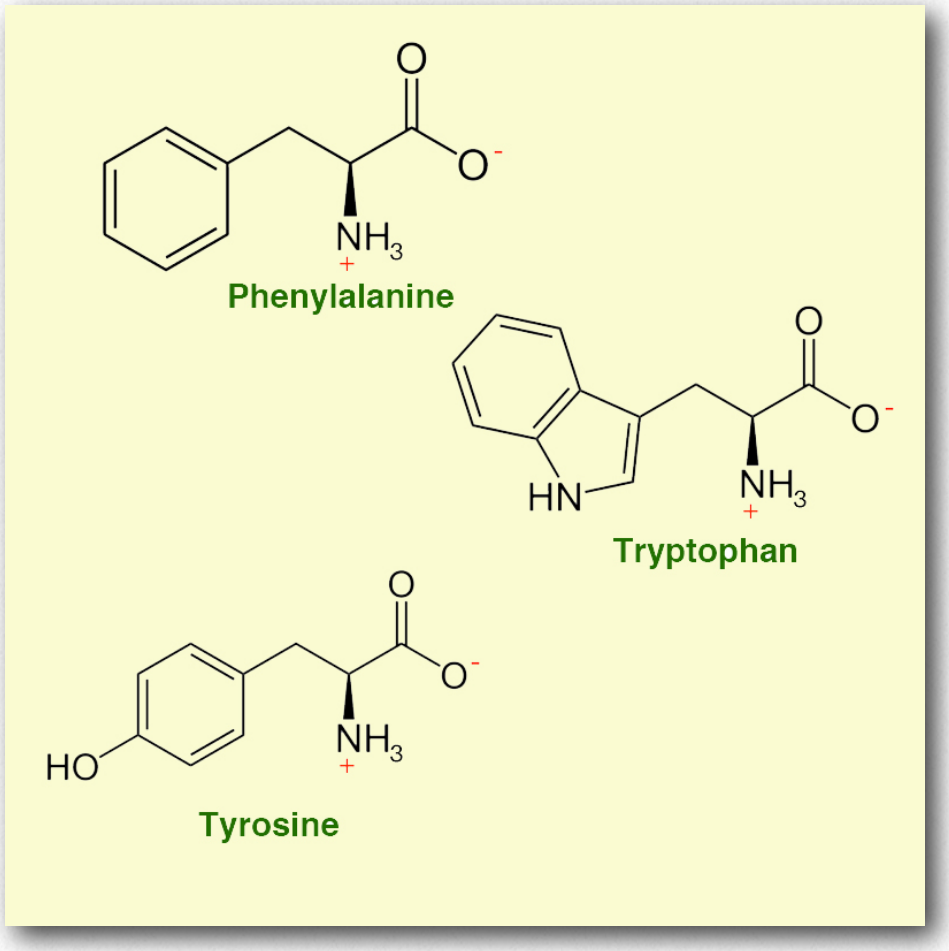


Figure 2.6 - **Aromatic amino acids**

in signaling processes. In dopaminergic cells of the brain, tyrosine hydroxylase converts tyrosine to l-dopa, an immediate precursor of dopamine. Dopamine, in turn, is a precursor of norepinephrine and epinephrine. Tyrosine is also a precursor of thyroid hormones and melanin. Wikipedia link HERE.

Hydroxyl amino acids

Serine (Ser/S) is one of three amino acids having an R-group with a hydroxyl in it (threonine and tyrosine are the others). It is coded by UCU, UCC, UCA, UGC, AGU, and AGC. Being able to hydrogen bond with water, it is classified as a polar amino acid. It is not essential for humans. Serine is precursor of many important cellular compounds, including purines, pyrimidines, sphingolipids, folate, and of the amino acids glycine, cysteine, and tryptophan. The hydroxyl group of serine in proteins is a target for phosphorylation by certain protein kinases. Serine is also a part of the catalytic triad of serine proteases. Wikipedia link HERE.

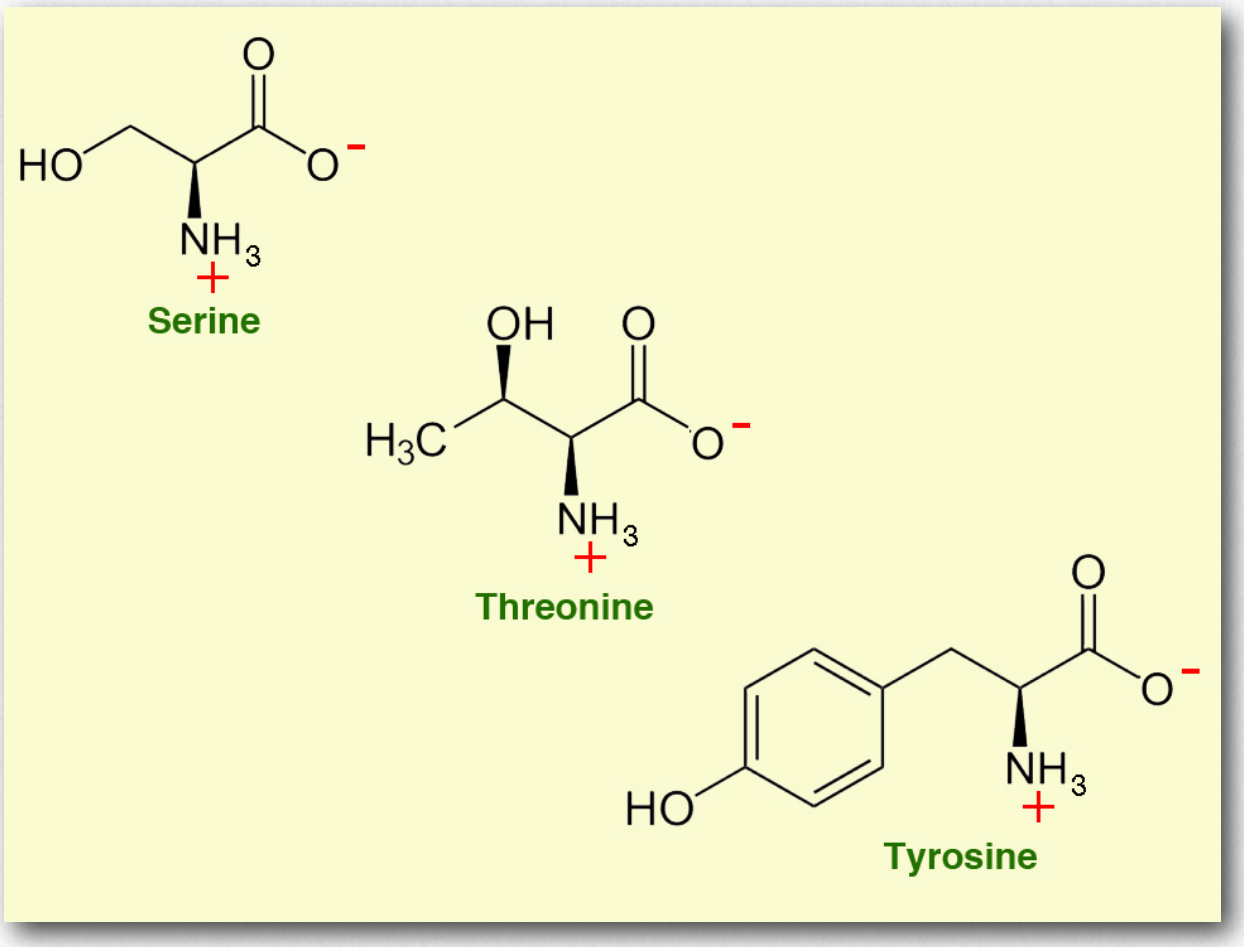


Figure 2.7 - **Hydroxyl amino acids**

Amino acid	Short	Abbrev.	Avg. mass (Da)	pI	pK_1 (α-COOH)	pK_2 (α-$^+NH_3$)
Alanine	A	Ala	89.09404	6.01	2.35	9.87
Cysteine	C	Cys	121.15404	5.05	1.92	10.70
Aspartic acid	D	Asp	133.10384	2.85	1.99	9.90
Glutamic acid	E	Glu	147.13074	3.15	2.10	9.47
Phenylalanine	F	Phe	165.19184	5.49	2.20	9.31
Glycine	G	Gly	75.06714	6.06	2.35	9.78
Histidine	H	His	155.15634	7.60	1.80	9.33
Isoleucine	I	Ile	131.17464	6.05	2.32	9.76
Lysine	K	Lys	146.18934	9.60	2.16	9.06
Leucine	L	Leu	131.17464	6.01	2.33	9.74
Methionine	M	Met	149.20784	5.74	2.13	9.28
Asparagine	N	Asn	132.11904	5.41	2.14	8.72
Pyrrolysine	O	Pyl	255.31			
Proline	P	Pro	115.13194	6.30	1.95	10.64
Glutamine	Q	Gln	146.14594	5.65	2.17	9.13
Arginine	R	Arg	174.20274	10.76	1.82	8.99
Serine	S	Ser	105.09344	5.68	2.19	9.21
Threonine	T	Thr	119.12034	5.60	2.09	9.10
Selenocysteine	U	Sec	168.053	5.47		
Valine	V	Val	117.14784	6.00	2.39	9.74
Tryptophan	W	Trp	204.22844	5.89	2.46	9.41
Tyrosine	Y	Tyr	181.19124	5.64	2.20	9.21

Figure 2.8 - Amino acid properties

Wikipedia

Threonine (Thr/T) is a polar amino acid that is essential. It is one of three amino acids bearing a hydroxyl group (serine and tyrosine are the others) and, as such, is a tar-

get for phosphorylation in proteins. It is also a target for O-glycosylation of proteins. Threonine proteases use the hydroxyl group of the amino acid in their catalysis and it is a precursor in one biosynthetic pathway for making glycine. In some applications, it is used as a pro-drug to increase brain glycine levels. Threonine is encoded in the genetic code by ACU, ACC, ACA, and ACG. Wikipedia link HERE.

Tyrosine - see HERE.

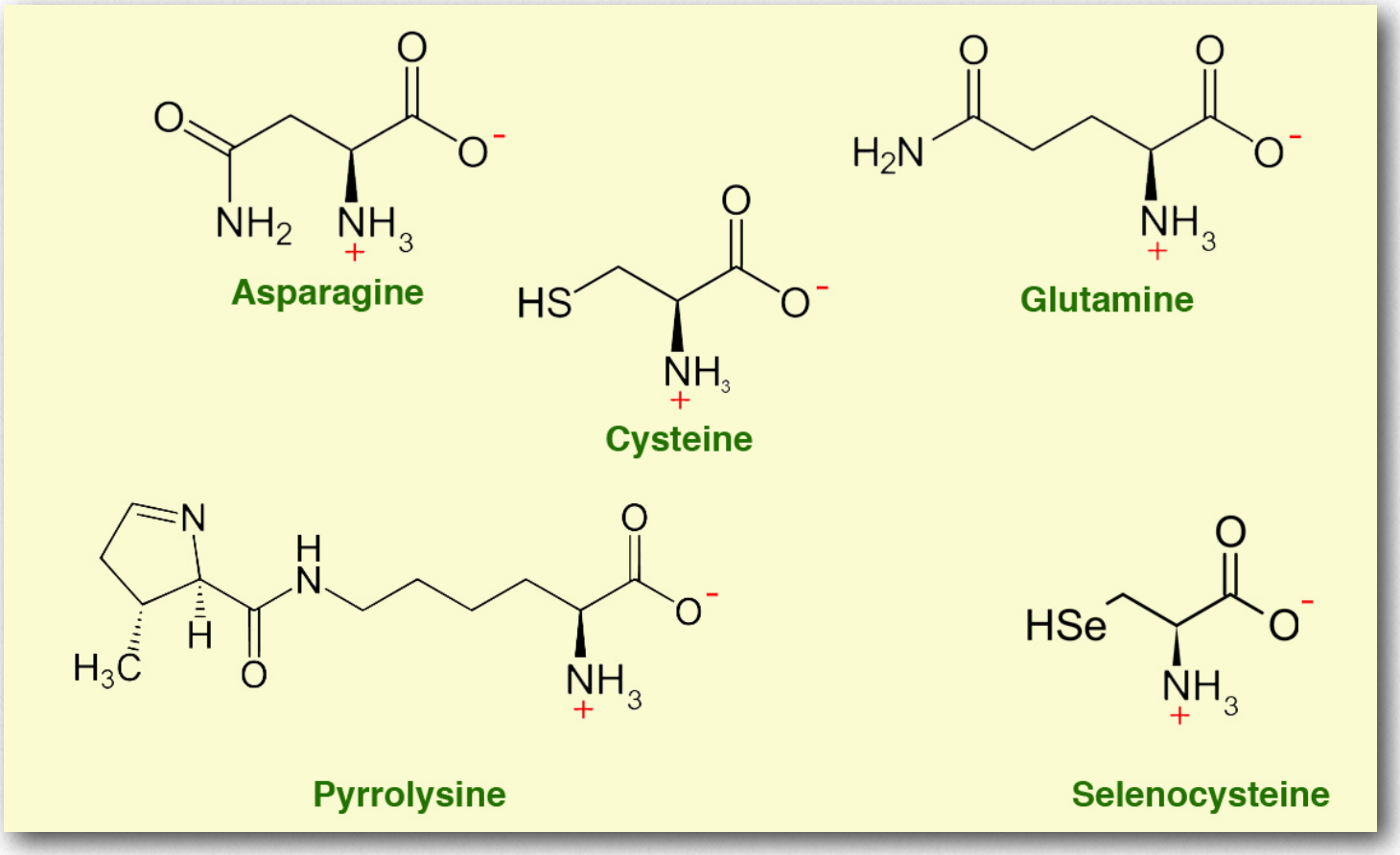


Figure 2.9 - Other amino acids

Other amino acids

Asparagine (Asn/N) is a non-essential amino acid coded by AAU and AAC. Its carboxyamide in the R-group gives it polarity. Asparagine is implicated in formation of acrylamide in foods cooked at high temperatures (deep frying) when it reacts with carbonyl groups. Asparagine can be made in the body from aspartate by an amidation reaction with an amine from glutamine. Breakdown of asparagine produces malate, which can be oxidized in the citric acid cycle. Wikipedia link HERE.

YouTube Lectures by Kevin HERE & HERE

Cysteine (Cys/C) is the only amino acid with a sulfhydryl group in its side chain. It is non-essential for most humans, but may be essential in infants, the elderly and individuals who suffer from certain metabolic diseases. Cysteine's sulfhydryl group is readily oxidized to a disulfide when reacted with another one. In addition to being found in proteins, cysteine is also a component of the tripeptide, glutathione. Cysteine is specified by the codons UGU and UGC. Wikipedia link HERE.

Glutamine (Gln/Q) is an amino acid that is not normally essential in humans, but may be in individuals undergoing intensive athletic training or with gastrointestinal disorders. It has a carboxyamide side chain which does not normally ionize under physiological pHs, but which gives polarity to the side chain. Glutamine is coded for by CAA and CAG and is readily made by amidation of glutamate. Glutamine is the most abundant amino acid in circulating blood and is one of only a few amino acids that can cross the blood-brain barrier. Wikipedia link HERE.

Selenocysteine (Sec/U) is a component of selenoproteins found in all kingdoms of life. It is a component in several enzymes, including glutathione peroxidases and thioredoxin reductases. Selenocysteine is incorporated into proteins in an unusual scheme involving the stop codon UGA. Cells grown in the absence of selenium terminate protein synthesis at UGAs. However, when selenium is present, certain mRNAs which contain a selenocysteine insertion sequence (SECIS), insert selenocysteine when UGA is encountered. The SECIS element has characteristic nucleotide sequences and secondary structure base-pairing patterns. Twenty five human proteins contain selenocysteine. Wikipedia link HERE.

Pyrrolysine (Pyl/O) is a twenty second amino acid, but is rarely found in proteins. Like selenocysteine, it is not coded for in the genetic code and must be incorporated by unusual means. This occurs at UAG stop codons. Pyrrolysine is found in methanogenic archaean organisms and at least one methane-producing bacterium. Pyrrolysine is a component of methane-producing enzymes. Wikipedia link HERE.

Ionizing groups

pK_a values for amino acid side chains are very dependent upon the chemical environment in which they are present. For example, the R-group carboxyl found in aspartic acid has a pK_a value of 3.9 when free in solution, but can be as high as 14 when in certain environments inside of proteins, though that is unusual and extreme. Each amino acid has at least one ionizable amine group (α-amine) and one ionizable carboxyl group (α-carboxyl). When these are bound in a peptide bond, they no longer ionize. Some, but not all amino acids have R-groups that can ionize. The charge of a protein then arises from the charges of the α-amine group, the α-carboxyl group. and the sum of the charges of the ionized R-groups. Titration/ionization of aspartic acid is depicted in Figure 2.10. Ionization (or deionization) within a protein's structure can have significant effect on the overall conformation of the protein and, since structure is related to function, a major impact on the activity of a protein. Most proteins have relatively narrow ranges of optimal

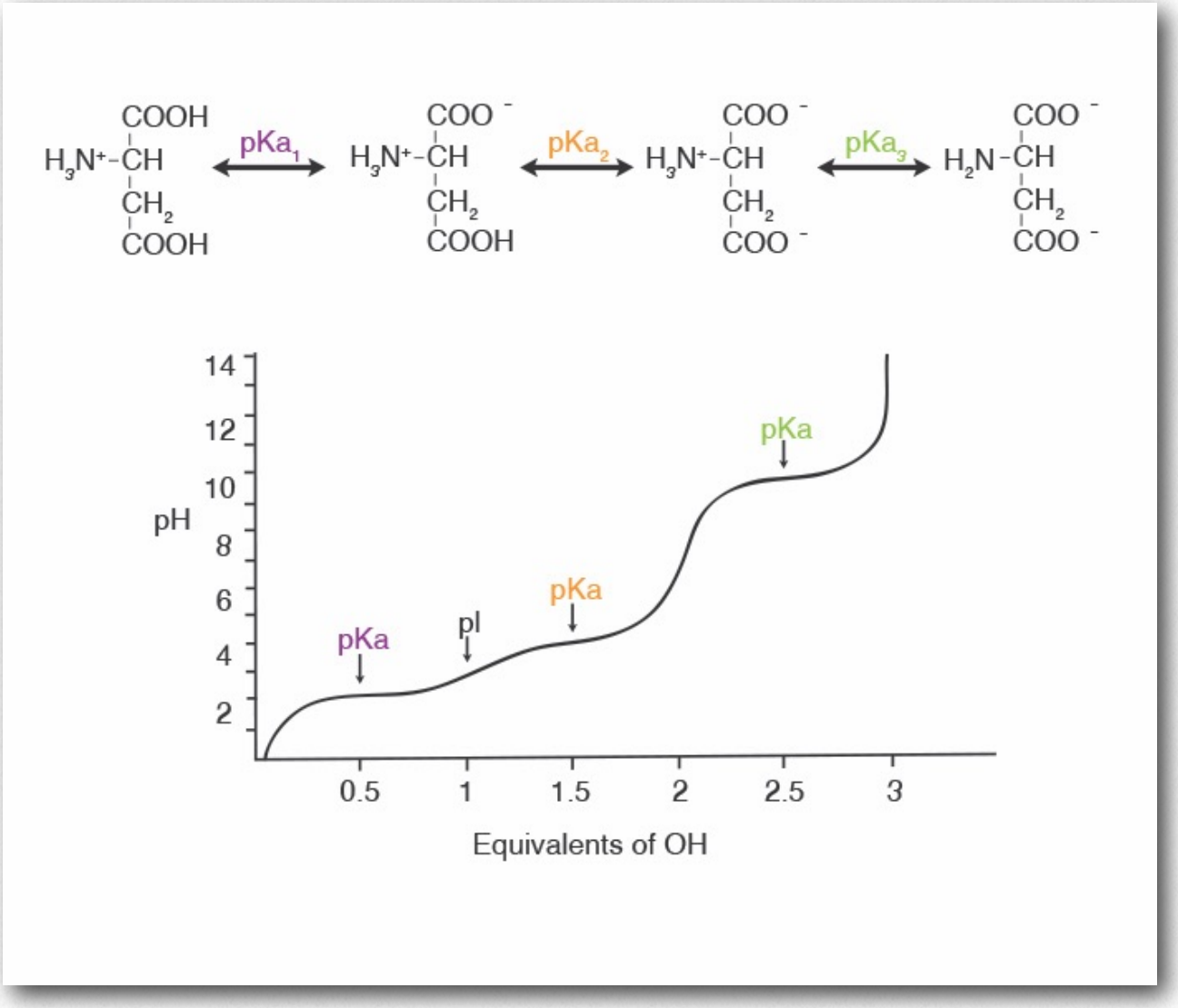


Figure 2.10 - Titration curve for aspartic acid

Image by Penelope Irving

activity that typically correspond to the environments in which they are found (Figure 2.11). It is worth noting that formation of peptide bonds between amino acids removes ionizable hydrogens from both the α-amine and α-carboxyl groups of amino acids. Thus, ionization/deionization in a protein arises only from 1) the amino terminus; 2) carboxyl terminus; 3) R-groups; or 4) other functional groups (such as sulfates or phosphates) added to amino acids post-translationally - see below.

Carnitine

Not all amino acids in a cell are found in proteins. The most common examples include ornithine (arginine metabolism), citrulline (urea cycle), and carnitine (Figure 2.12). When fatty acids destined for oxidation are moved into the mitochondrion for that purpose, they travel across the inner membrane attached to carnitine. Of the two stereoisomeric forms, the L form is the active one. The molecule is

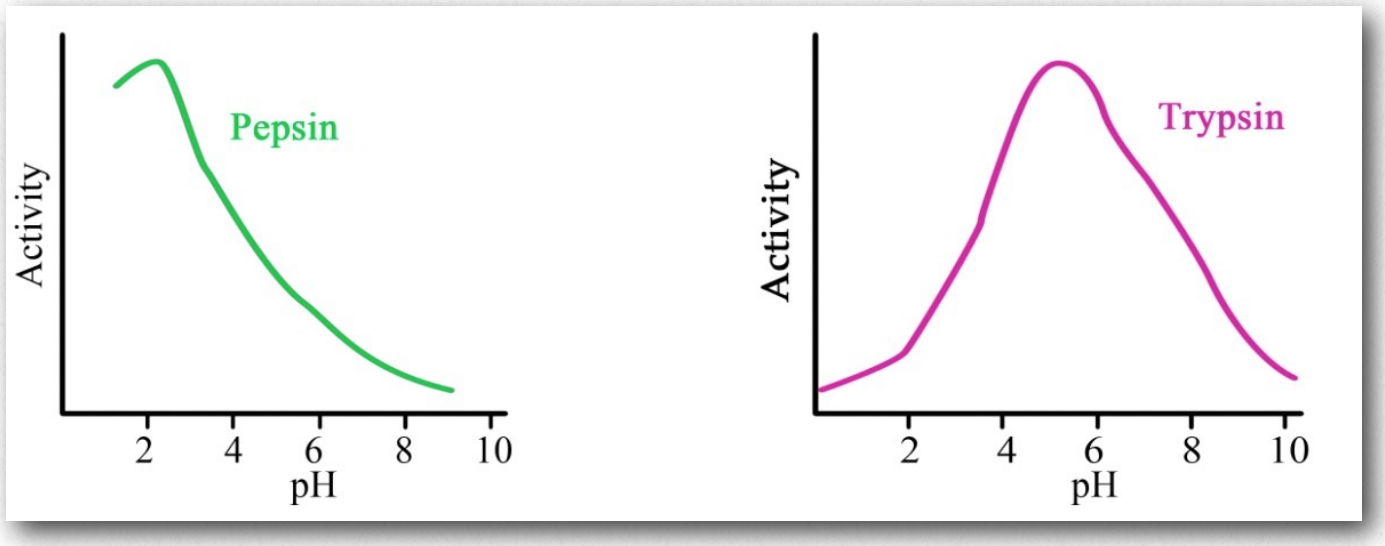


Figure 2.11 - Enzyme activity changes as pH changes

Image by Aleia Kim

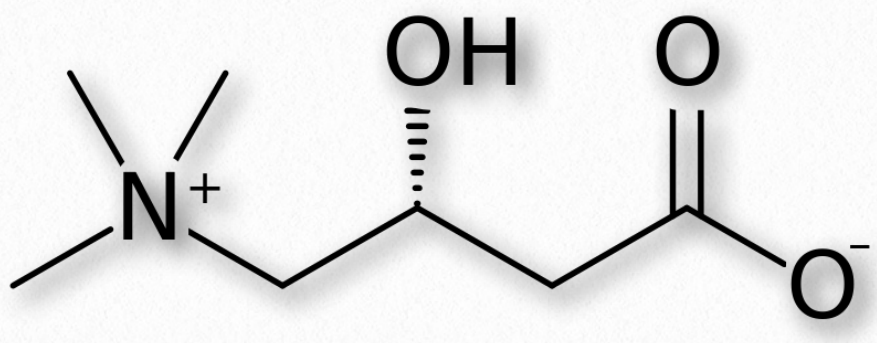


Figure 2.12 - L-Carnitine

synthesized in the liver from lysine and methionine. From exogenous sources, fatty acids must be activated upon entry into the cytoplasm by being joined to coenzyme A. The CoA portion of the molecule is replaced by carnitine in the intermembrane space of the mitochondrion in a reaction catalyzed by carnitine acyltransferase I. The resulting acylcarnitine molecule is transferred across the inner mitochondrial membrane by the carnitine-acylcarnitine translocase and then in the matrix of the mitochondrion, carnitine acyltransferase II replaces the carnitine with coenzyme A (Figure 6.88).

Catabolism of amino acids

We categorize amino acids as essential or non-essential based on whether or not an organism can synthesize them. All of the amino acids, however, can be broken down by all organisms. They are, in fact, a source of energy for cells, particularly during times of starvation or for people on diets containing very low amounts of carbohydrate. From a perspective of breakdown (catabolism), amino acids are categorized as glucogenic if they produce intermediates that can be made into glucose

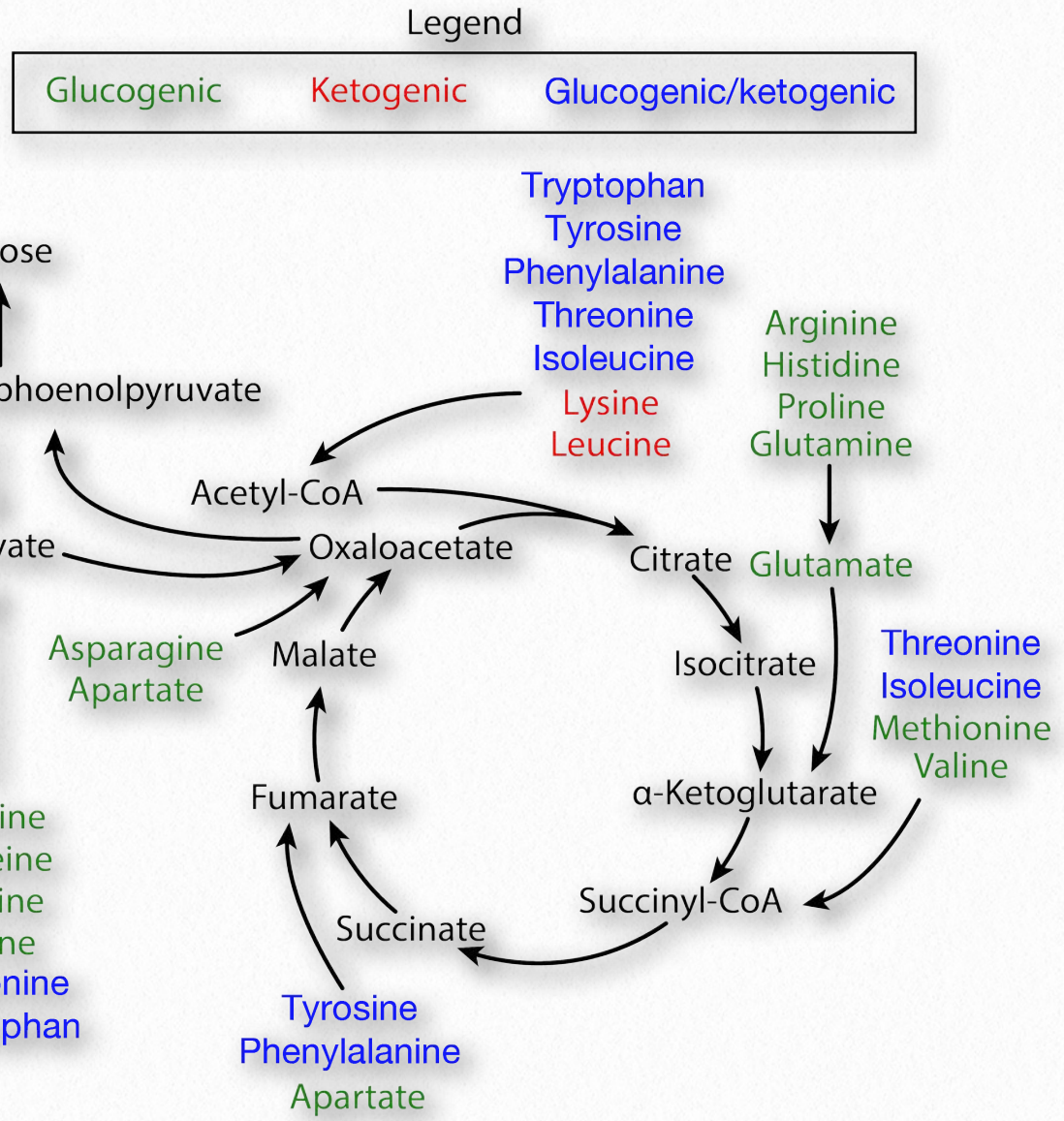


Figure 2.13 - Catabolism of amino acids. Some have more than one path.

Image by Pehr Jacobson

or ketogenic if their intermediates are made into acetyl-CoA. Figure 2.13 shows the metabolic fates of catabolism of each of the amino acids. Note that some amino acids are both glucogenic and ketogenic.

Post-translational modifications

After a protein is synthesized, amino acid side chains within it can be chemically modified, giving rise to more diversity of structure and function (Figure 2.14). Common alterations include phosphorylation of hydroxyl groups of serine, threonine, or tyrosine. Lysine, proline, and histidine can have hydroxyls added to amines in their R-groups. Other modifications to amino acids in proteins include addition of fatty acids (myristic acid or palmitic acid), isoprenoid groups, acetyl groups, methyl groups, iodine, carboxyl groups, or sulfates. These can have the effects of ionization (addition of phosphates/sulfates), deionization (addition of acetyl group to the R-group amine of lysine), or have no effect on charge at all. In addition, N-linked- and O-linked-glycoproteins have carbohydrates covalently attached to side chains of asparagine and threonine or serine, respectively.

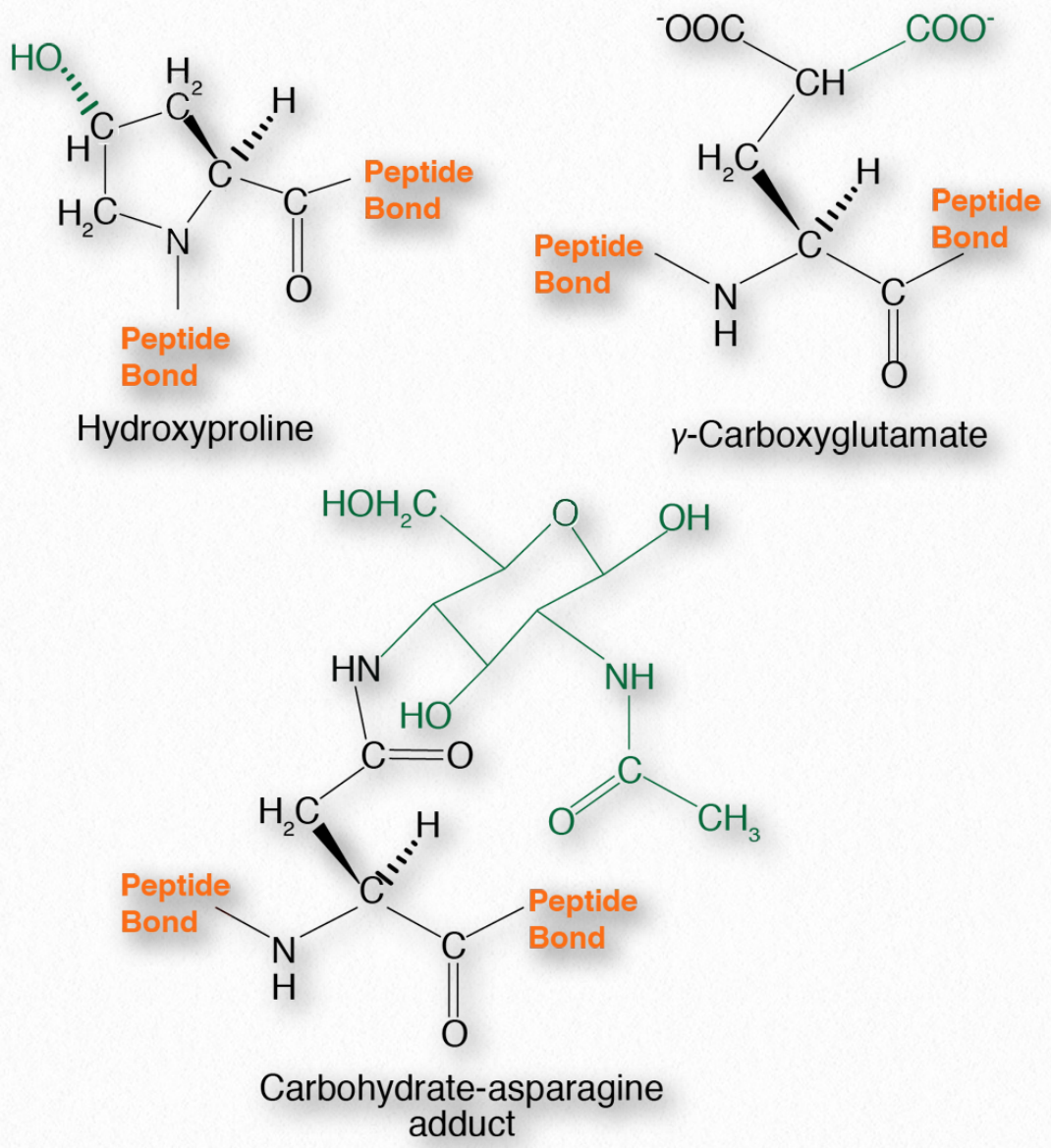


Figure 2.14 - Post-translationally modified amino acids. Modifications shown in green.

Image by Penelope Irving

Some amino acids are precursors of important compounds in the body. Examples include epinephrine, thyroid hormones, L-dopa, and dopamine (all from tyrosine), serotonin (from tryptophan), and histamine (from histidine).

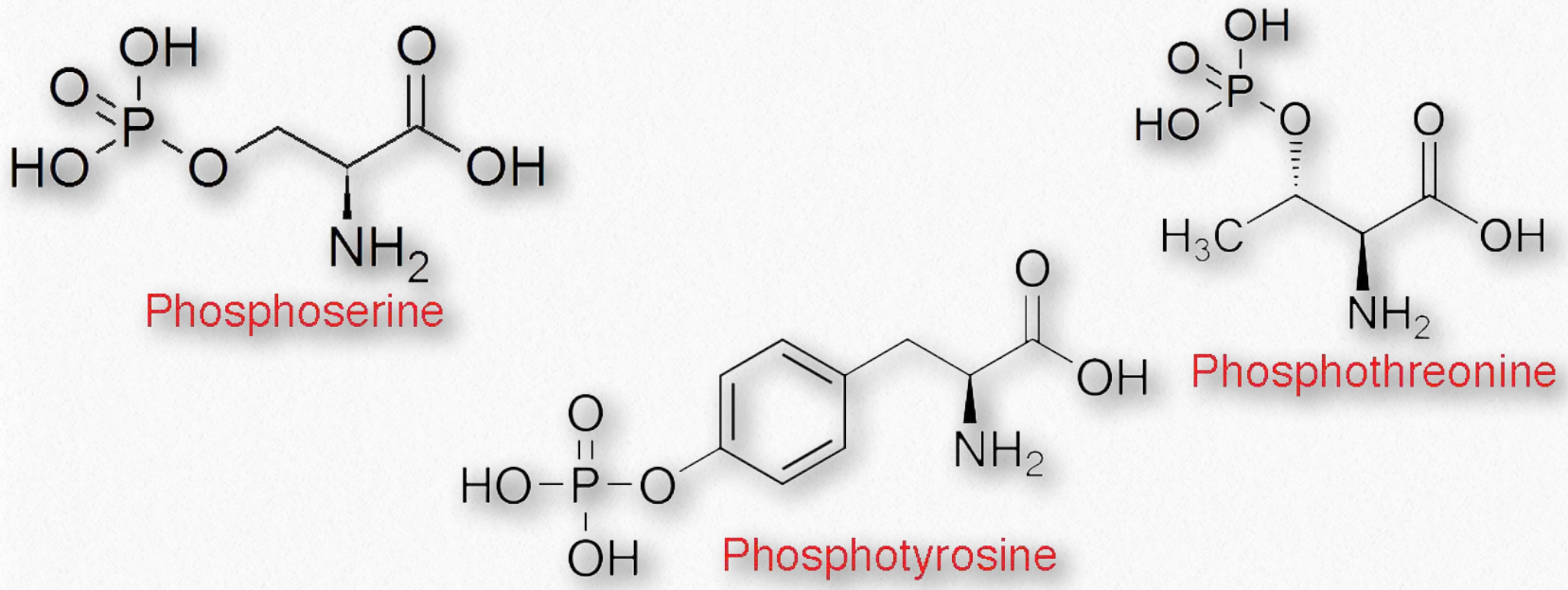


Figure 2.15 - **Phosphorylated amino acids**

Building polypeptides

Although amino acids serve other functions in cells, their most important role is as constituents of proteins. Proteins, as we noted earlier, are polymers of amino acids.

Amino acids are linked to each other by peptide bonds, in which the carboxyl group of one amino acid is joined to the amino group of the next, with the loss of a molecule of water. Additional amino acids are added in the same way, by formation of peptide bonds between the free carboxyl on the end of the growing chain and the amino group of the next amino acid in the sequence. A chain made up of just a few amino acids linked together is called an oligopeptide (oligo=few) while a typi-

YouTube Lectures by Kevin HERE & HERE

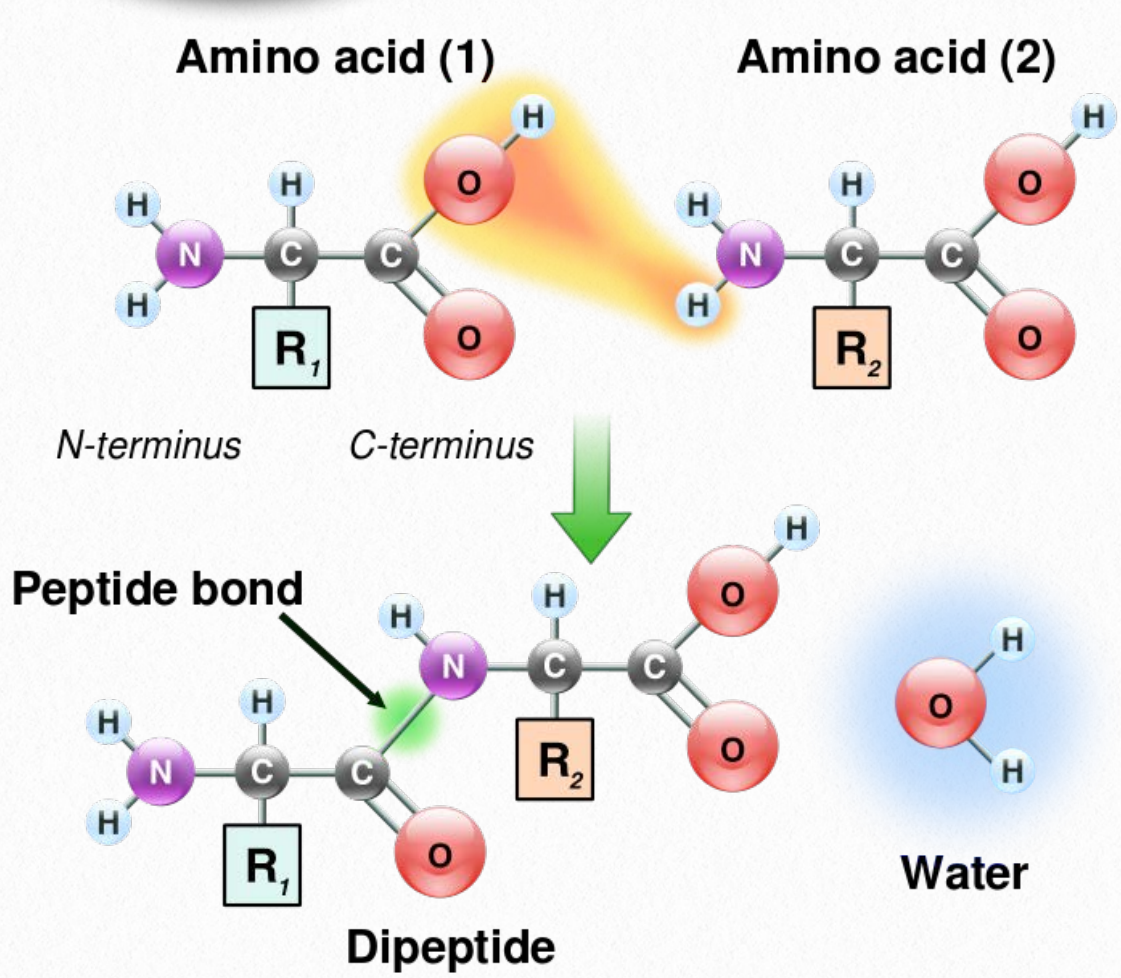


Figure 2.16 **Formation of a peptide bond**

cal protein, which is made up of many amino acids is called a polypeptide (poly=many). The end of the peptide that has a free amino group is called the N-terminus (for NH2), while the end with the free carboxyl is termed the C-terminus (for carboxyl).

As we've noted before, function is dependent on structure, and the string of amino acids must fold into a specific 3-D shape, or conformation, in order to make a functional protein. The folding of polypeptides into their functional forms is the topic of the next section.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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The Amino Alphabet Song

To the tune of "*Twinkle, Twinkle Little Star*"

Metabolic Melodies Website HERE

Lysine, arginine and his
Basic ones you should not miss
Ala, leu, val, ile, and met
Fill the aliphatic set
Proline bends and cys has 's'
Glycine's 'R' is the smallest
Then there's trp and tyr and phe
Structured aromatically

Asp and glu's side chains of R
Say to protons "au revoir"
Glutamine, asparagine
Bear carboxamide amines
Threonine and tiny ser
Have hydroxyl groups to share
These twen-TY amino A's

Recorded by David Simmons
Lyrics by Kevin Ahern

You're Cysteine

To the tune of "*You're Sixteen*"
Metabolic Melodies Website HERE

You're in every protein
That I've ever seen
There's no need to debate
You're cysteine, a building block, and you're great

You give the hair waves
It's something we crave
Makes the food on my plate
You're cysteine, a building block, and you're great

Bridge
That sulfhydryl in your chain
Can oxidize, but I don't complain
It gives support to all peptides
So proteins need to have disulfides

You're an acid it seems
And have an amine
Please don't ever mutate
You're cysteine, a building block, and you're great

Bridge
A U-G-U or U-G-C
In secret code at the cell's decree
You're in my skin and in my bone
And even in my glutathione

You're in every protein
That I've ever seen
There's no need to debate
You're cysteine, a building block, and you're great

Lyrics by Kevin Ahern

No Recording Yet For This Song

Structure & Function: Proteins I

Protein diversity

Proteins are the workhorses of the cell. Virtually everything that goes on inside of cells happens as a result of the actions of proteins. Among other things, protein enzymes catalyze the vast majority of cellular reactions, mediate signaling, give structure both to cells and to multicellular organisms, and exert control over the expression of genes. Life, as we know it, would not exist if there were no proteins. The versatility of proteins arises because of their varied structures.

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Proteins are made by linking together amino acids, with each protein having a characteristic and unique amino acid sequence.

To get a sense for the diversity of proteins that can be made using 20 different amino acids, consider that the number of different combinations possible with 20 amino acids is 20^n, where n=the number of amino acids in the chain. It becomes apparent that even a dipeptide made of just two amino acids joined together gives us $20^2 = 400$ different combinations. If we do the calculation for a

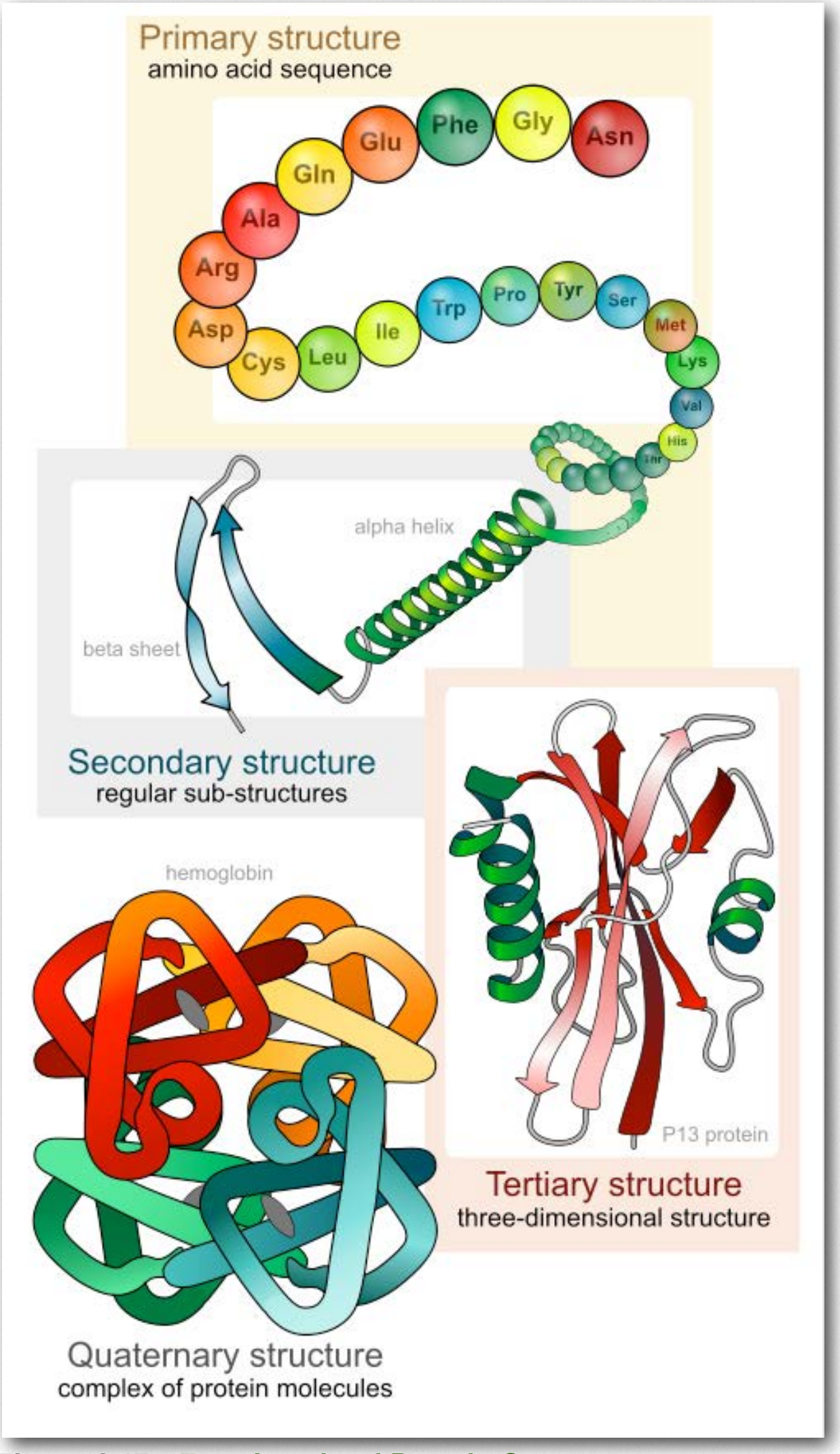

Figure 2.17 - Four Levels of Protein Structure

short peptide of 10 amino acids, we arrive at an enormous 10240000000000 combinations. Most proteins are much larger than this, making the possible number of proteins with unique amino acid sequences unimaginably huge.

Levels of structure

The significance of the unique sequence, or order, of amino acids, known as the protein's primary structure, is that it dictates the 3-D conformation the folded protein will have. This conformation, in turn, will determine the function of the protein. We shall examine protein structure at four distinct levels (Figure 2.17) - 1) how sequence of the amino acids in a protein (primary structure) gives identity and characteristics to a protein (Figure 2.18); 2) how local interactions between one part of the polypeptide backbone and another affect protein

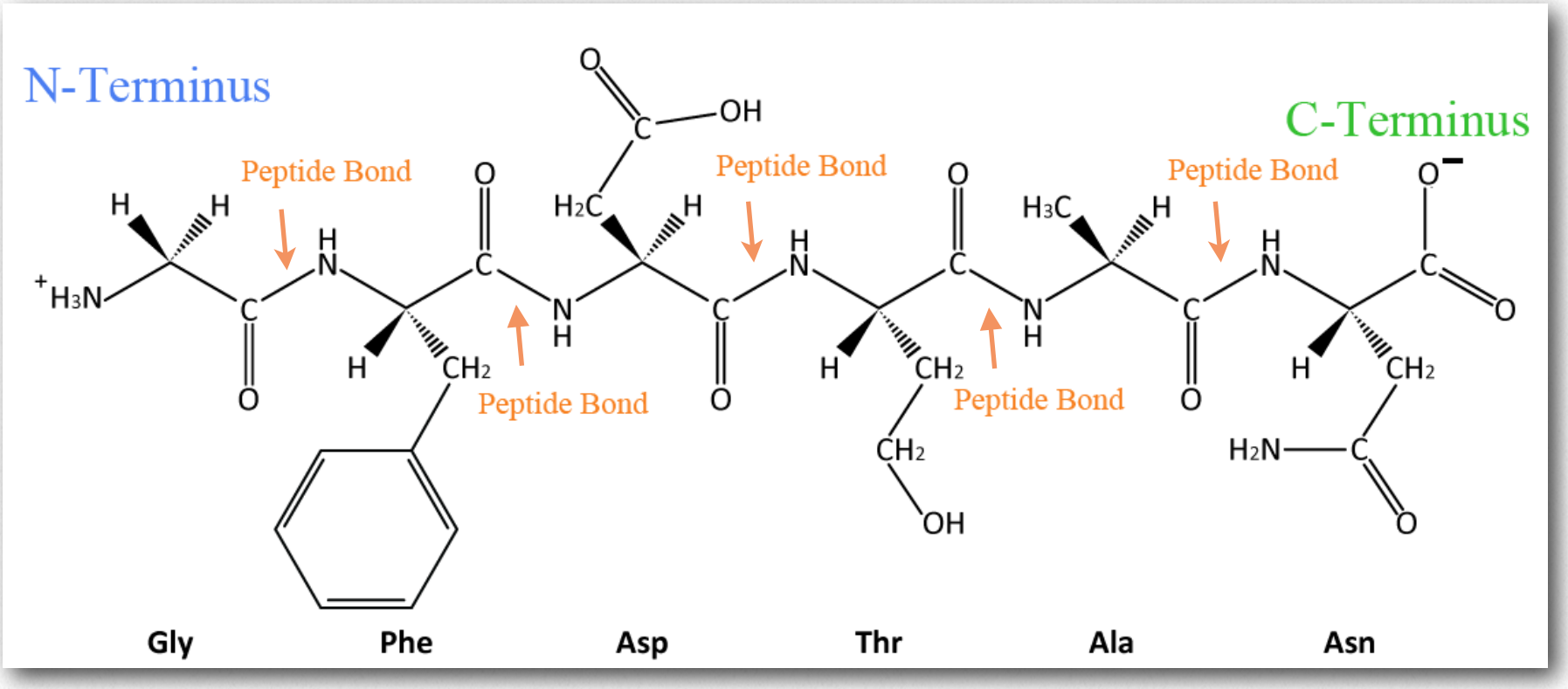

Figure 2.18 - Sequence of a simple polypeptide

Wikipedia

shape (secondary structure); 3) how the polypeptide chain of a protein can fold to allow amino acids to interact with each other that are not close in primary structure (tertiary structure); and 4) how different polypeptide chains interact with each other within a multi-subunit protein (quaternary structure). At this point, we should provide a couple of definitions. We use the term polypeptide to refer to a single polymer of amino acids. It may or may not have folded into its final, functional form. The term protein is sometimes used interchangeably with polypeptide, as in “protein synthesis”. It is generally used, however, to refer to a folded, functional molecule that may have one or more subunits (made up of individual polypeptides). Thus, when we use the term protein, we are usually referring to a functional, folded polypeptide or peptides. Structure is essential for function. If you alter the structure, you alter the function - usually, but not always, this means you lose all function. For many proteins, it is not difficult to alter the structure. Proteins are flexible, not rigidly fixed in structure. As we shall see, it is the flexibility of proteins that allows them to be amazing catalysts and allows them to adapt to, respond to, and pass on signals upon binding of other molecules or proteins. However, proteins are not infinitely flexible. There are constraints on the conformations that proteins can adopt and these constraints govern the conformations that proteins display.

Subtle changes

Even very tiny, subtle changes in protein structure can give rise to big changes in the behav-

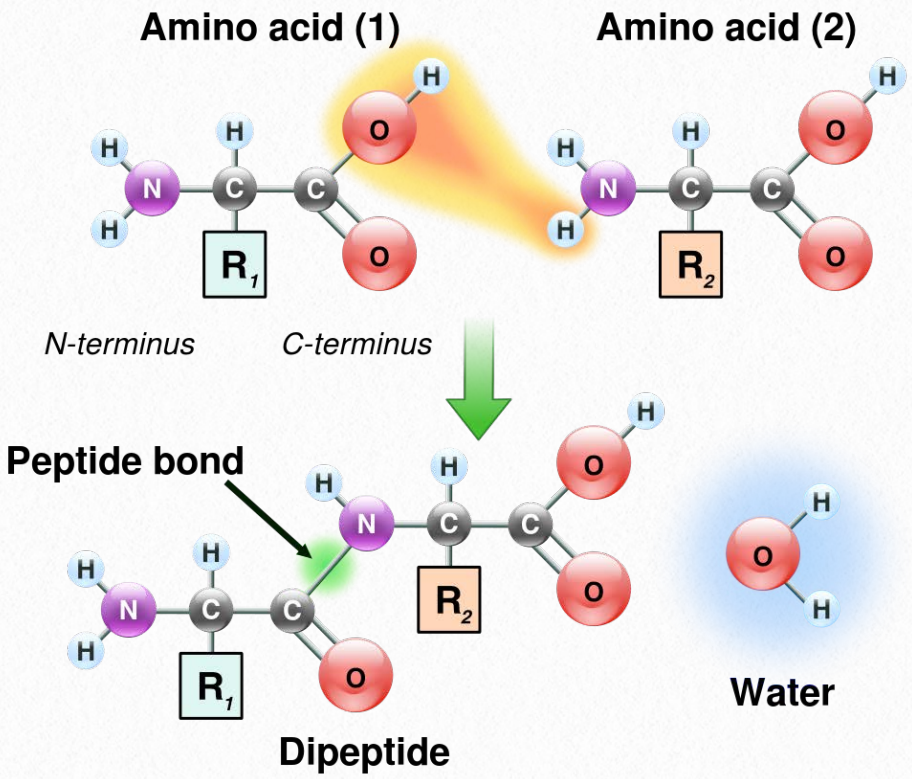

Figure 2.19 Linking of amino acids through peptide bond formation

ior of proteins. Hemoglobin, for example, undergoes an incredibly small structural change upon binding of one oxygen molecule, and that simple change causes the remainder of the protein to gain a considerably greater affinity for oxygen that the protein didn't have before the structural change.

Sequence, structure and function

As discussed earlier, the number of different amino acid sequences possible, even for short peptides, is very large . No two proteins with different amino acid sequences (primary structure) have identical overall structure.

The unique amino acid sequence of a protein is reflected in its unique folded structure. This structure, in turn, determines the protein's function. This is why mutations that alter amino acid sequence can affect the function of a protein.

Protein synthesis

Synthesis of proteins occurs in the ribosomes and proceeds by joining the carboxyl terminus of the first amino acid to the amino terminus of the next one (Figure 2.19). The end of the protein that has the free α-amino group is referred to as the amino terminus or N-terminus. The other end is called the carboxyl terminus or C-terminus , since it contains the only free α-carboxyl group. All of the other α-amino groups and α-carboxyl groups are tied up in forming peptide

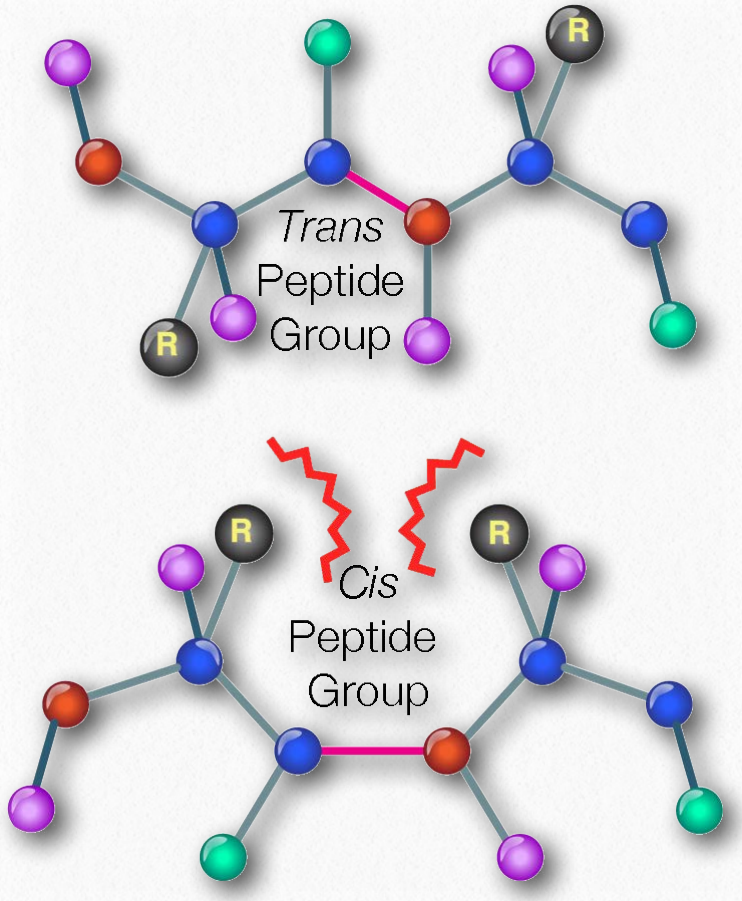

Figure 2.20 - *Cis* vs *trans* orientation of R-groups around peptide bond

Image by Aleia Kim

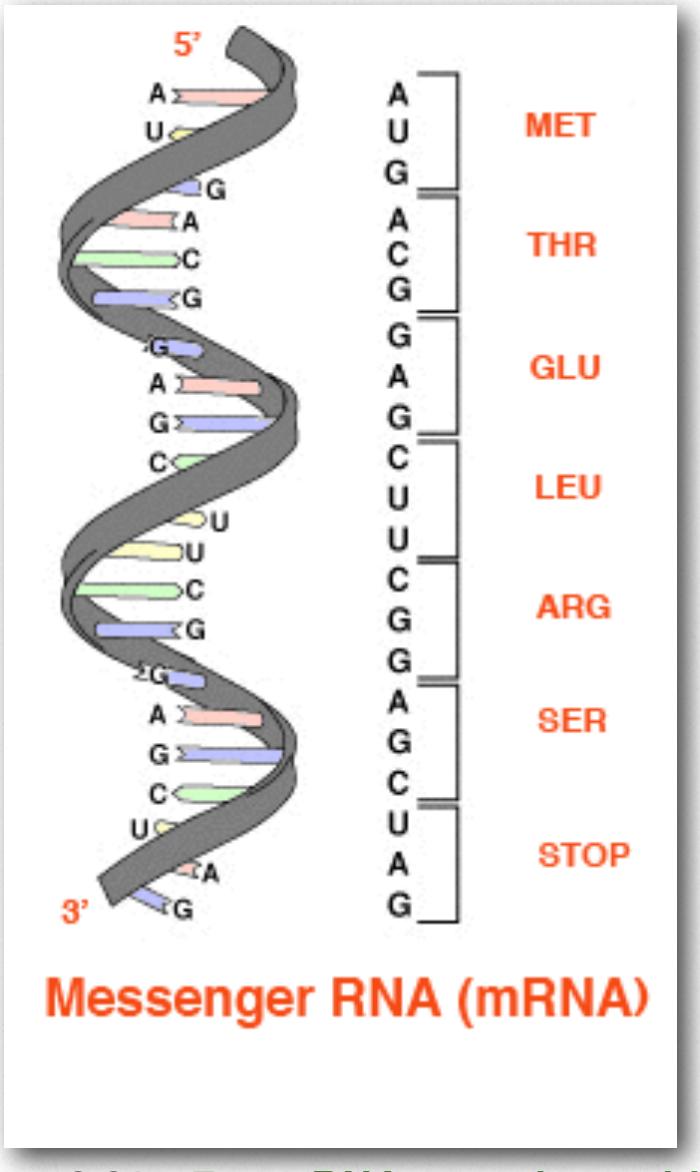

Figure 2.21 - From RNA to amino acids - the genetic code

Wikipedia

bonds that join adjacent amino acids together. Proteins are synthesized starting with the amino terminus and ending at the carboxyl terminus.

Schematically, in Figure 2.18, we can see how sequential R-groups of a protein are arranged in an alternating orientation on either side of the polypeptide chain. Organization of R-groups in this fashion is not random. Steric hindrance can occur when consecutive R-groups are oriented on the same side of a peptide backbone (Figure 2.20)

Primary structure

Primary structure is the ultimate determinant of the overall conformation of a protein. The primary structure of any protein arrived at its current state as a result of mutation and selection over evolutionary time. Primary structure of proteins is mandated by the sequence of DNA coding for it in the genome. Regions of DNA specifying proteins are known as coding regions (or genes).

The base sequences of these regions directly specify the sequence of amino acids in proteins, with a one-to-one correspondence between the codons (groups of three consecutive bases) in the DNA and the amino acids in the encoded protein. The sequence of codons in DNA, copied into messenger RNA, specifies a sequence of amino acids in a protein. (Figure 2.21). The order in which the amino acids are joined together in protein synthesis starts defining a set of interactions between amino acids even as the synthesis is occurring. That is, a polypeptide can fold even as it is being made.

The order of the R-group structures and resulting interactions are very important because early interactions affect later interactions. This is because interactions start establishing structures - secondary and tertiary. If a helical structure (secondary structure), for example, starts to form, the possibilities for interaction of a particular amino acid R-group may be different than if the helix had

not formed (Figure 2.22). R-group interactions can also cause bends in a polypeptide sequence (tertiary structure) and these bends can create (in some cases) opportunities for interactions that wouldn't have been possible without the bend or prevent (in other cases) similar interaction possibilities.

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Secondary structure

As protein synthesis progresses, interactions between amino acids close to each other begin to occur, giving rise to local patterns called secondary structure. These secondary structures include the well known **α**-helix and **β**-strands. Both were predicted by Linus Pauling, Robert Corey, and Herman Branson in 1951. Each structure has unique features.

α-helix

The **α**-helix has a coiled structure, with 3.6 amino acids per turn of the helix (5 helical turns = 18 amino acids). Helices are predominantly right handed - only in rare cases, such as in sequences with many glycines can left handed α- helices form. In the α-helix, hydrogen bonds form between C=O groups and N-H groups in the polypeptide backbone that are four amino acids distant. These hydrogen bonds are the primary forces stabilizing the α-helix.

We use the terms rise, repeat, and pitch to describe the parameters of any helix. The repeat is the number of residues in a helix before it begins to repeat itself. For an **α**-helix, the repeat

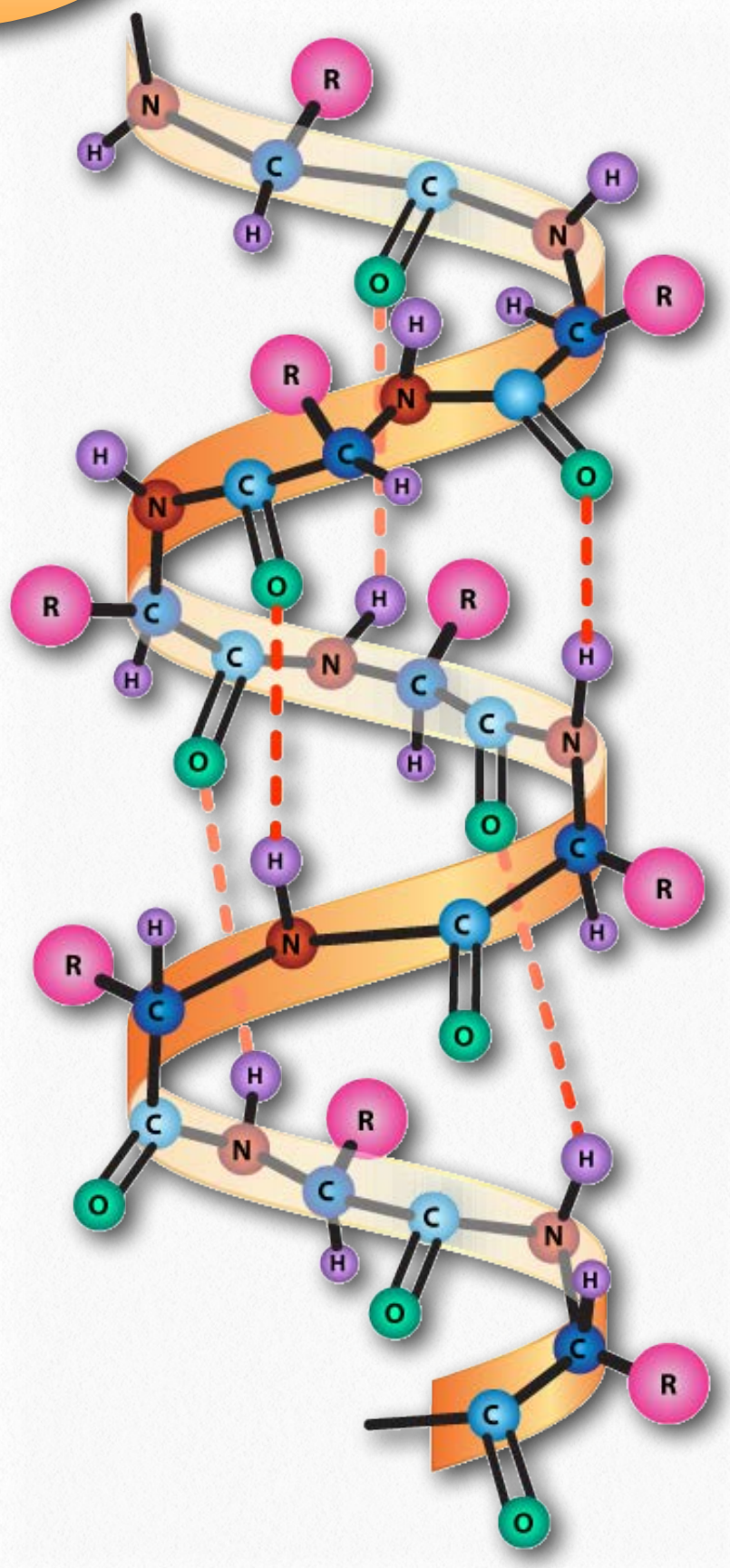

Figure 2.22 - The α-helix. Hydrogen bonds (dotted lines) between the carbonyl oxygen and the amine hydrogen stabilize the structure.

Image by Aleia Kim

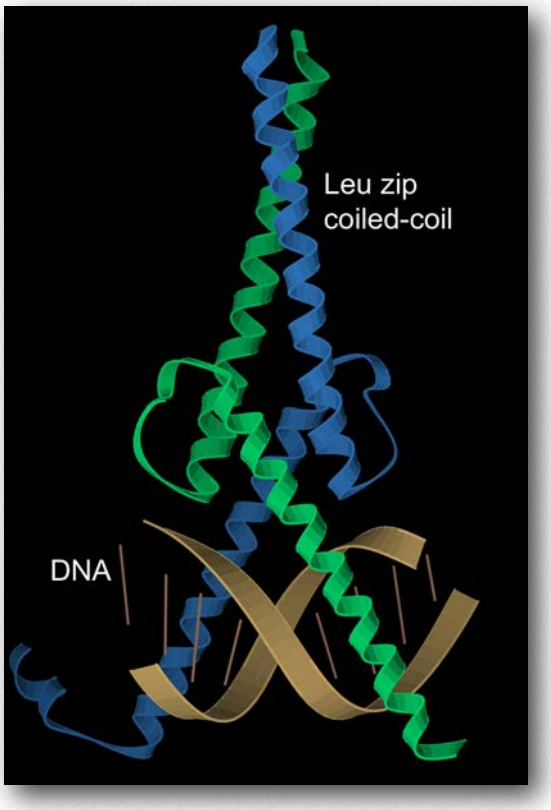

Figure 2.23 - α-helices in a protein with a leucine zipper structural domain. The α-helices are shown in blue and green and are bound to a DNA double helix in brown.

Wikipedia

Figure 2.24 - α-helix sculpture outside Linus Pauling's boyhood home

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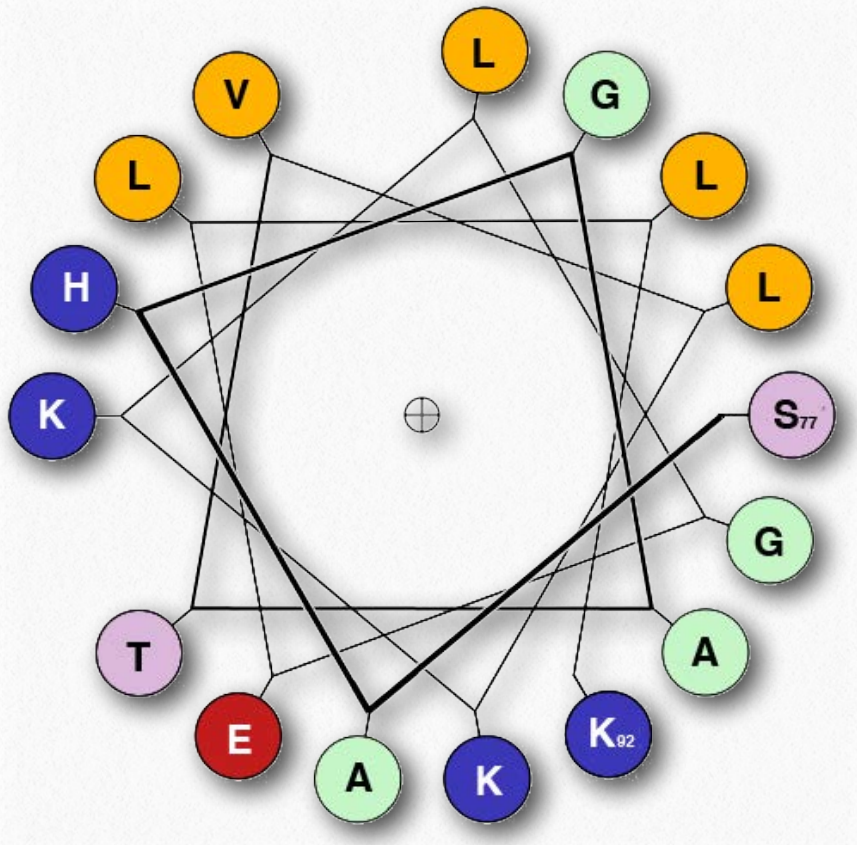

Figure 2.25 - Helical Wheel Representation of an α-Helix. The one letter genetic code is used. The helix starts at Serine #77 at the right and ends at lysine #92 in the lower right. Hydrophobic amino acids are shown in yellow and ionizing amino acids are shown in blue. Hydrophobic amino acids tend to interact with each other and not with ionizing amino acids.

Wikipedia

is 3.6 amino acids per turn of the helix. The rise is the distance the helix elevates with addition of each residue. For an α-helix, this is 0.15 nm per amino acid. The pitch is the distance between complete turns of the helix. For an α-helix, this is 0.54 nm. The stability of an **α**-helix is enhanced by the presence of the amino acid aspartate.

β strand/sheet

A helix is, of course, a three-dimensional object. A flattened form of helix in two dimen-

sions is a common description for a **β**-strand. Rather than coils, β-strands have bends and these are sometimes referred to as pleats, like the pleats in a curtain. β-strands can be organized to form elaborately organized structures, such as sheets, barrels, and other arrangements. Higher order β-strand structures are sometimes called supersecondary structures), since they involve interactions between amino acids not close in primary sequence. These structures, too, are stabilized by hydrogen bonds between carbonyl oxygen atoms and hydrogens of amine groups in the polypeptide backbone (Figure 2.28). In a higher order structure, strands can be arranged parallel (amino to carboxyl orientations the same) or anti-parallel (amino to carboxyl orientations opposite of each other (in Figure 2.27, the direction of the strand is shown by the arrowhead in the ribbon diagrams).

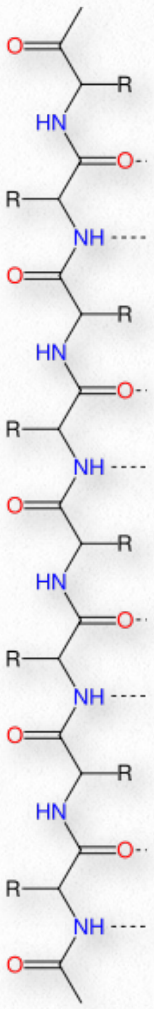

Figure 2.26 - β strand

Turns

Turns (sometimes called reverse turns) are a type of secondary structure that, as the name suggests, causes a turn in the structure of a polypeptide chain. Turns give rise to tertiary structure ultimately, causing interruptions in the secondary structures (**α**-helices and **β**-strands) and often serve as connecting regions between two regions of secondary structure in a protein. Proline and glycine play common roles in turns, providing less flexibility (starting the turn) and greater flexibility (facilitating the turn), respectively.

There are at least five types of turns, with numerous variations of each giving rise to many different turns. The five types of turns are

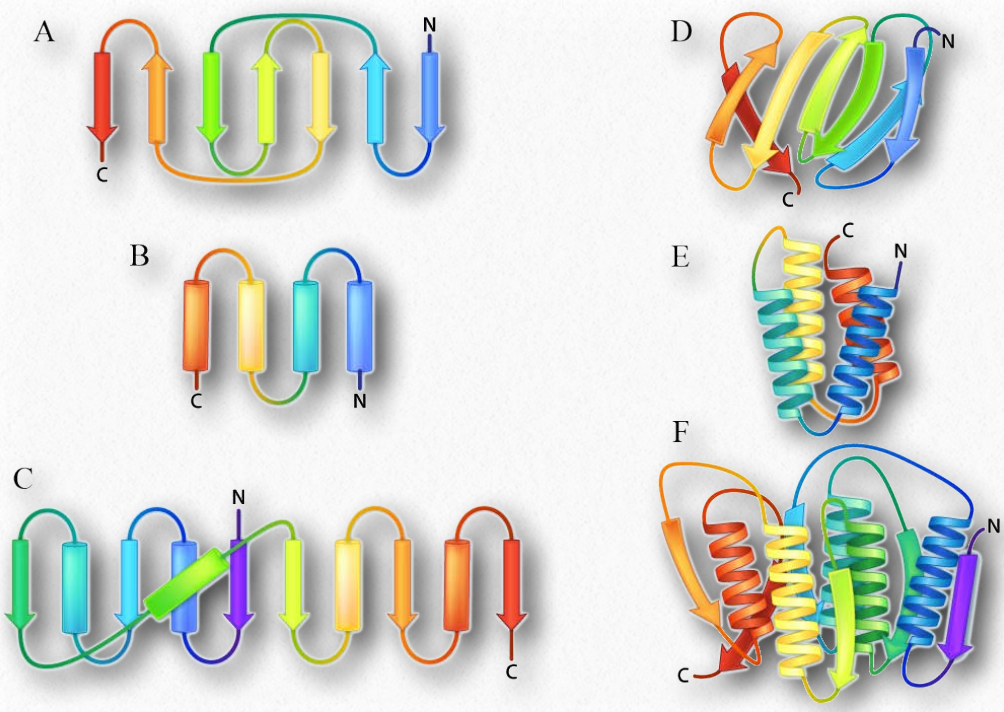

Figure 2.27 - Ribbon depictions of supersecondary β-sheets (A-D) and α-helix arrangements (E-F)

Image by Aleia Kim

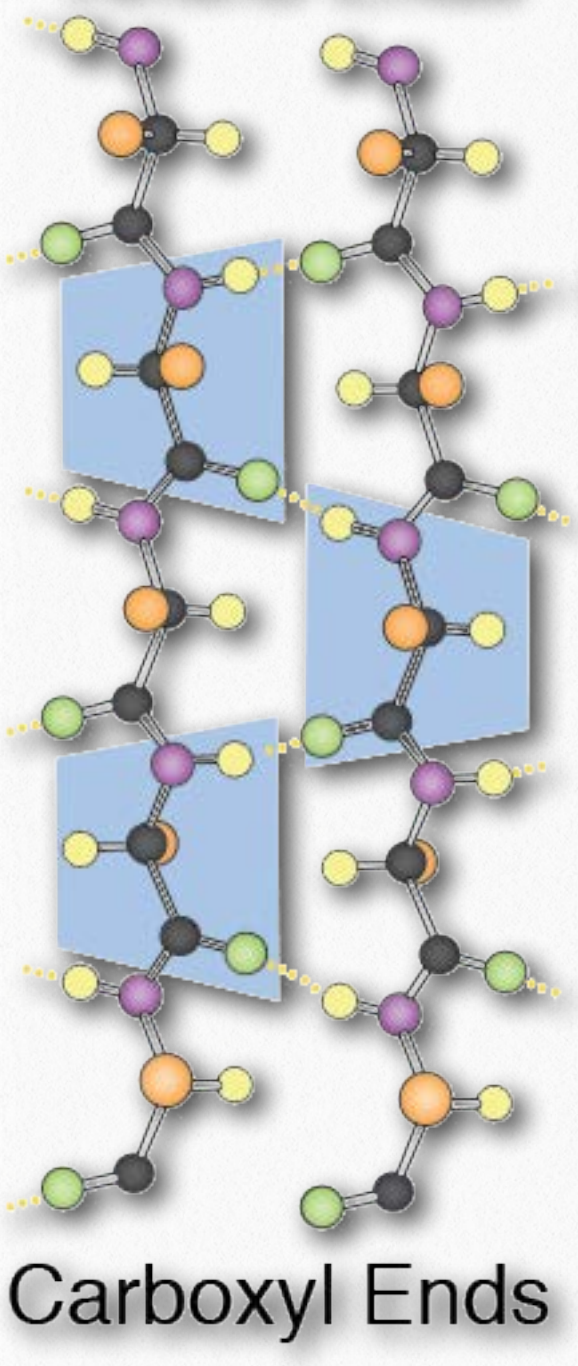

Figure 2.28 - Components of a β-sheet in a parallel arrangement. H-bonds in yellow.

Image by Aleia Kim

- **δ**-turns - end amino acids are separated by one peptide bond
- **γ**-turns - separation by two peptide bonds
- **β**-turns - separation by three peptide bonds
- **α**-turns - separation by four peptide bonds
- **π**-turns - separation by five bonds

Of these, the β-turns are the most common form and the δ-turns are theoretical, but unlikely, due to steric limitations. Figure 2.29 depicts a β-turn.

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3_{10} helices

In addition to the **α**-helix, **β**-strands, and various turns, other regular, repeating structures are seen in proteins, but occur much less commonly. The 3_{10} helix is the

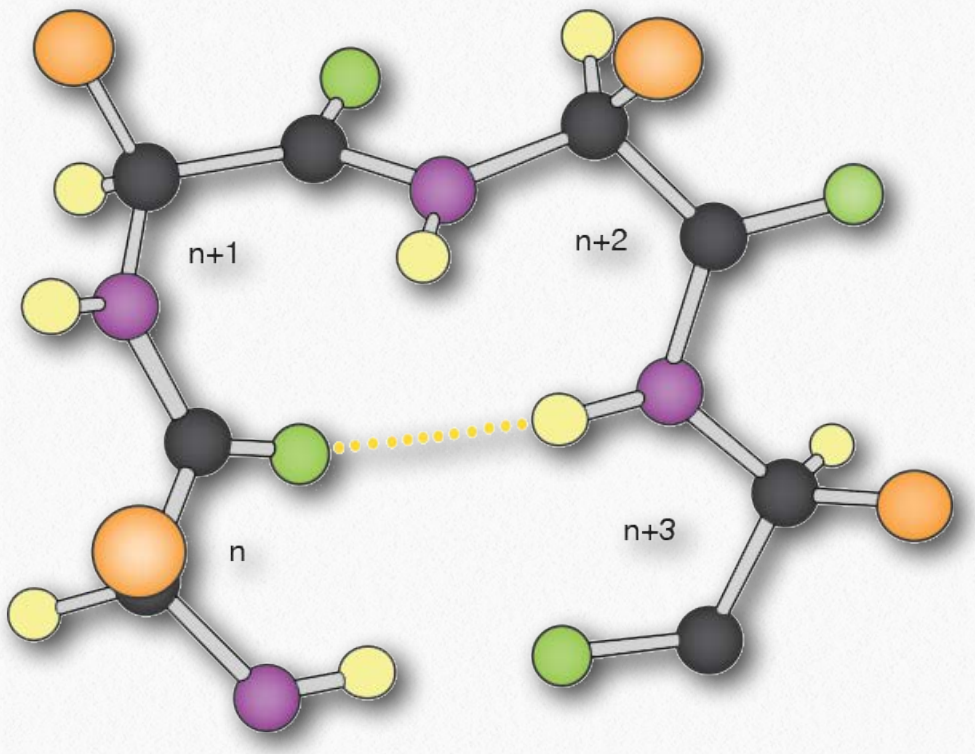


Figure 2.29 - β-turn. R-groups are shown in orange, hydrogens in yellow, carbons in charcoal, nitrogens in purple, and oxygens in green. A stabilizing hydrogen bond is indicated with the dotted line.

Image by Aleia Kim

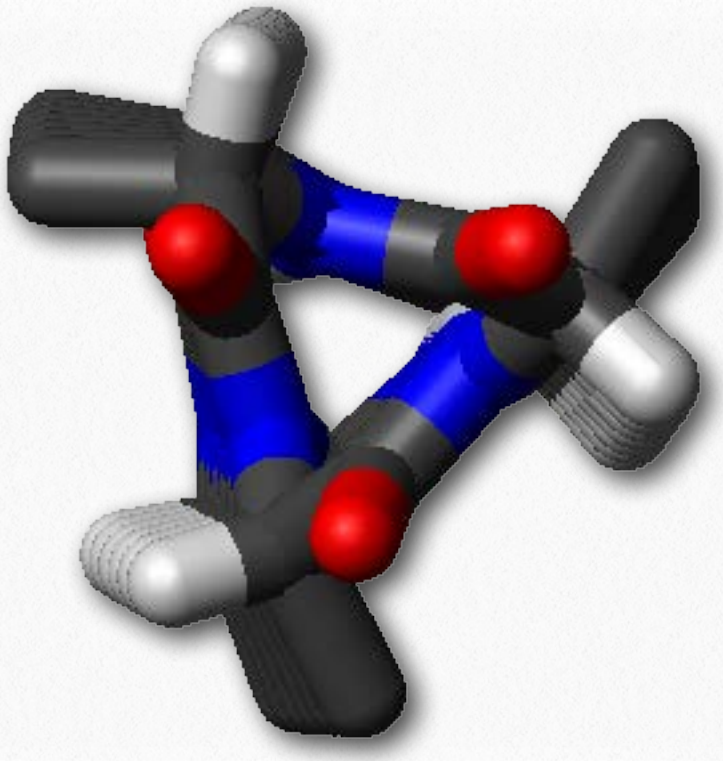


Figure 2.30 - Top view of a 3_{10} Helix. Carbonyl groups are in red and pointed upwards. Note the almost perfect 3-fold symmetry

Wikipedia

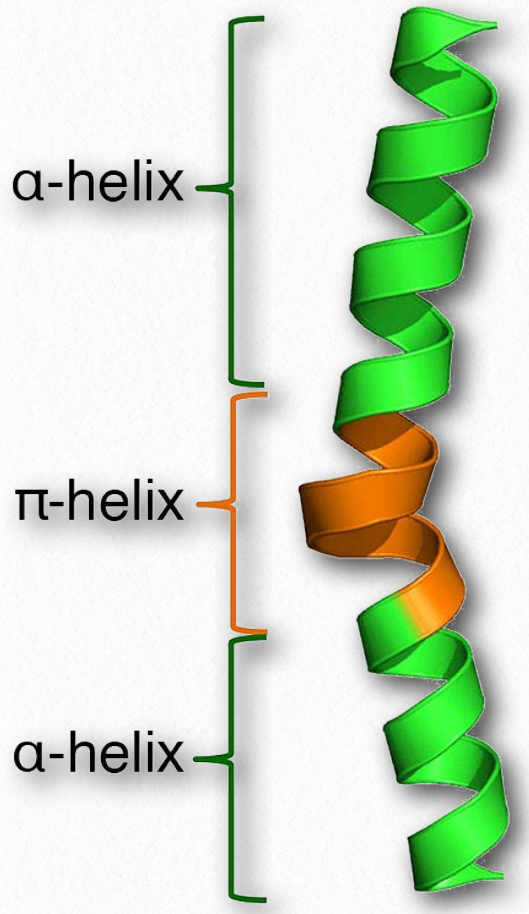


Figure 2.32 - π helix

Wikipedia

fourth most abundant secondary structure in proteins, constituting about 10-15% of all helices. The helix derives its name from the fact that it contains 10 amino acids in 3 turns. It is right-handed. Hydrogen bonds form between amino acids that are three residues apart. Most commonly, the 3_{10} helix appears at the amine or carboxyl end of an α-helix. Like the α-helix, the 3_{10} helix is stabilized by the presence of aspartate in its sequence.

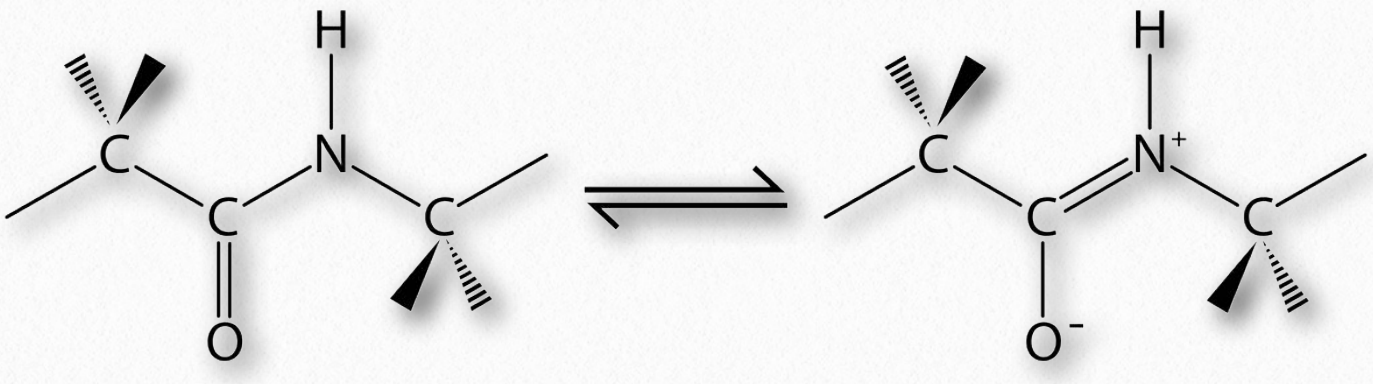


Figure 2.31 - Resonance of the peptide bond

Wikipedia

π-helices

A **π**-helix may be thought of as a special type of **α**-helix. Some sources describe it as an α-helix with an extra amino acid stuck in the middle of it (Figure 2.32). π-helices

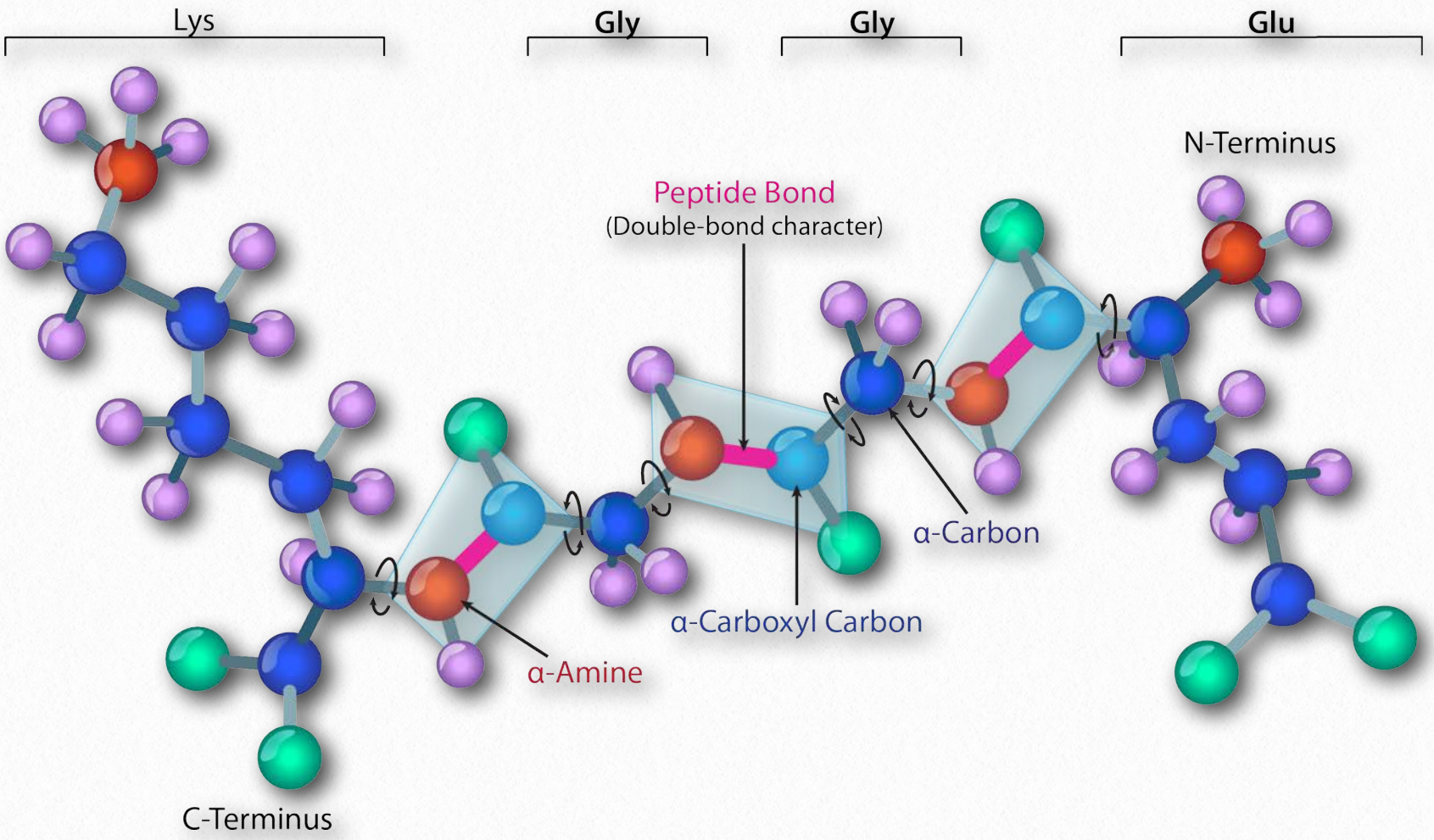


Figure 2.33 - Planes (light blue) defined by the double-bonded character of the peptide bond

Image by Aleia Kim

are not exactly rare, occurring at least once in as many as 15% of all proteins. Like the α-helix, the π-helix is right-handed, but where the α-helix has 18 amino acids in 5 turns, the π-helix has 22 amino acids in 5 turns. π-helices typically do not stretch for very long distances. Most are only about 7 amino acids long and the sequence almost always occurs in the middle of an α-helical region.

Ramachandran plots

In 1963, G.N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan described a novel way to describe protein structure. If one considers the backbone of a polypeptide chain, it consists of a repeating set of three bonds. Sequentially (in the amino to carboxyl direction) they are 1) a rotatable bond (ψ) between α-carbon and α-carboxyl preceding the peptide bond (see HERE), 2) a non-rotatable peptide bond (ω) between the α-carboxyl and α-amine groups), and 3) a rotatable bond (φ) between the α-amine and α-carbon following the peptide bond (see HERE). Note in Figures 2.33 and 2.34 that the amino to carboxyl direction is right to left.

The presence of the carbonyl oxygen on the α-carboxyl group allows the peptide bond to exist as a resonant structure, meaning that it behaves some of the time as a double

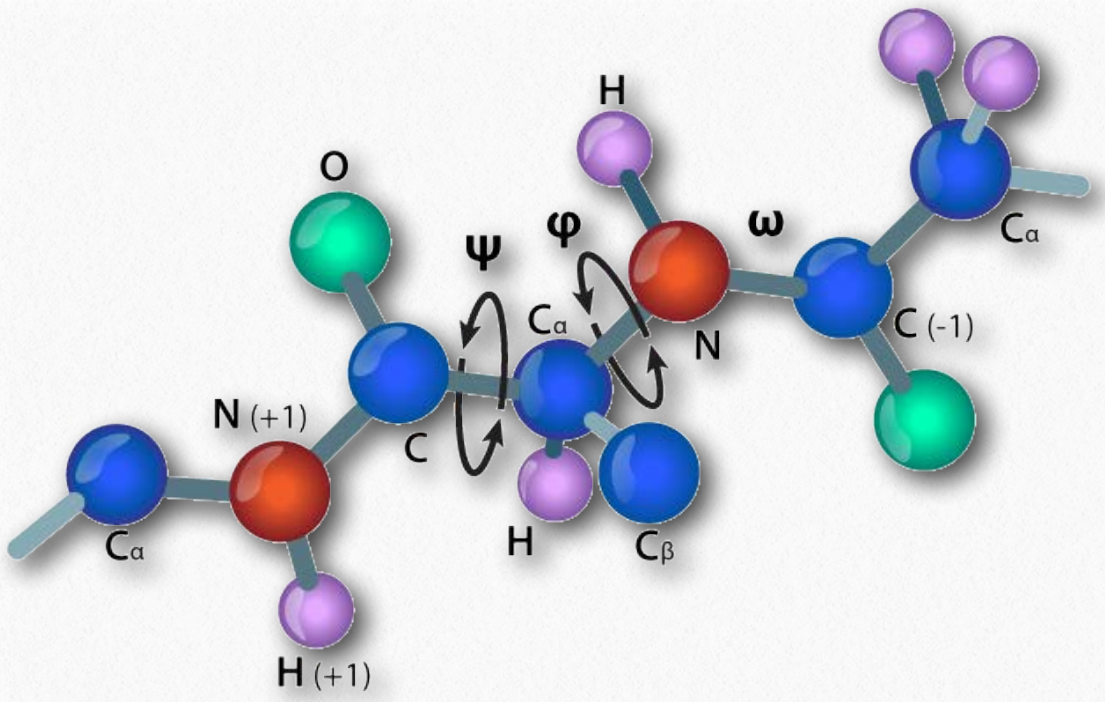


Figure 2.34 - ω, ψ, and ϕ rotational angles in a peptide
Image by Aleia Kim

bond. Double bonds cannot, of course, rotate, but the bonds on either side of it have some freedom of rotation. The φ and ψ angles are restricted to certain values, because some angles will result in steric hindrance. In addition, each type of secondary structure has a characteristic range of values for φ and ψ.

Ramachandran and colleagues made theoretical calculations of the energetic stability of all possible angles from 0° to 360° for each of the φ and ψ angles and plotted the results on a Ramachandran Plot (also called a φ-ψ plot), delineating regions of angles that were theoretically the most stable (Figure 2.35).

Three primary regions of stability were identified, corresponding to **φ-ψ** angles of β-strands (top left), right handed α-helices (bottom left), and left-handed α-helices (upper right). The plots of predicted stability are remarkably accurate when compared to φ-ψ angles of actual proteins.

Secondary structure prediction

By comparing primary structure (amino acid sequences) to known 3D protein structures, one can tally each time an amino acid is

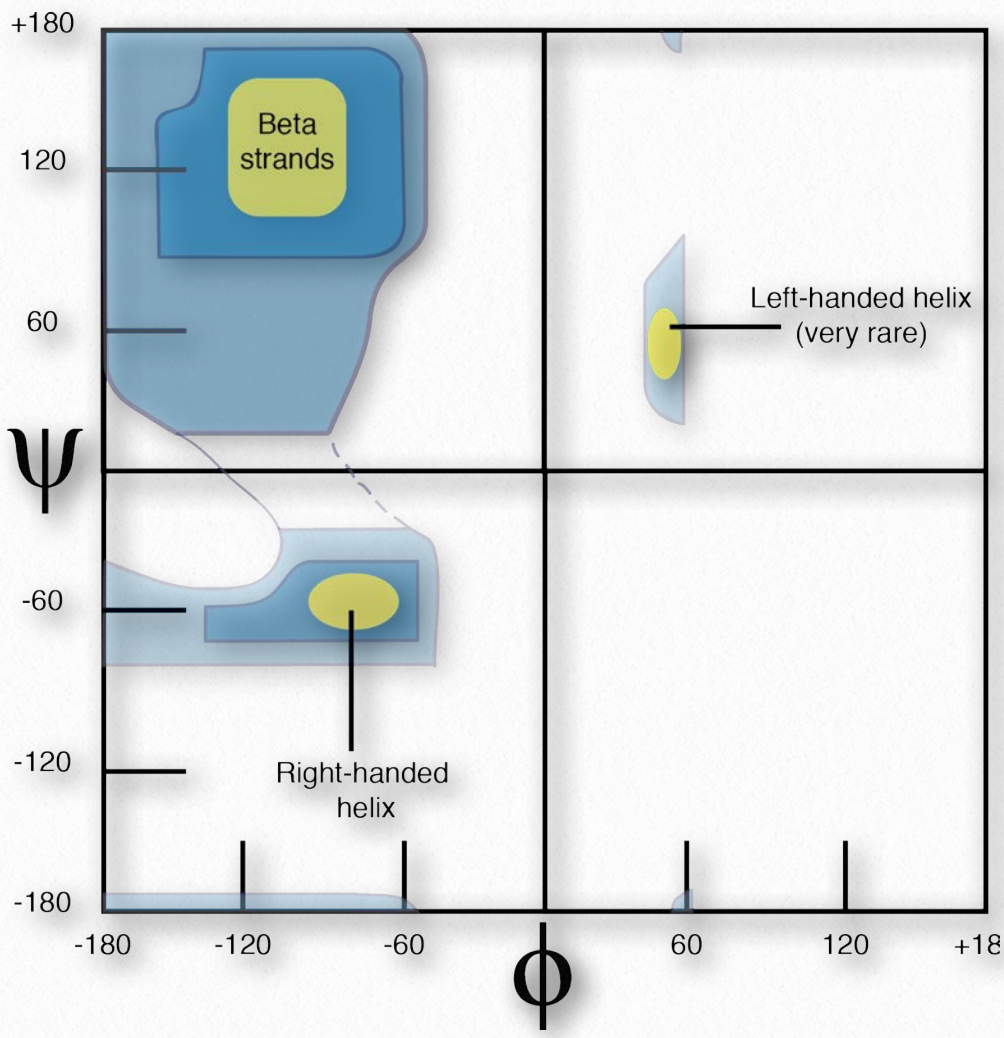


Figure 2.35 - Theoretical Ramachandran plot
Image by Penelope Irving

found in an α-helix, β-strand/sheet, or a turn. Computer analysis of thousands of these sequences allows one to assign a likelihood of any given amino acid appearing in each of these structures. Using these tendencies, one can, with up to 80% accuracy, predict regions of secondary structure in a protein based solely on amino acid sequence. This is seen in Table 2.3. Occurrence in primary sequence of three consecutive amino acids with relative tendencies higher than one is an indicator that that region of the polypeptide is in the corresponding secondary structure. An online resource for predicting secondary structures called PSIPRED is available HERE.

YouTube Lectures by Kevin HERE & HERE

Amino Acid	α helix	Reverse turn	β sheet
Ala	1.41	0.82	0.72
Arg	1.21	0.90	0.84
Asn	0.76	1.34	0.48
Asp	0.99	1.24	0.39
Cys	0.66	0.54	1.40
Gln	1.27	0.84	0.98
Glu	1.59	1.01	0.52
Gly	0.43	1.77	0.58
His	1.05	0.81	0.80
Ile	1.09	0.47	1.67
Leu	1.34	0.57	1.22
Lys	1.23	1.07	0.69
Met	1.30	0.52	1.14
Phe	1.16	0.59	1.33
Pro	0.34	1.32	0.31
Ser	0.57	1.22	0.96
Thr	0.76	0.96	1.17
Trp	1.02	0.65	1.35
Tyr	0.74	0.76	1.45
Val	0.90	0.41	1.87

Table 2.3 - Relative tendencies of each amino acid to be in a secondary structure. Higher values indicate greater tendency

Image by Penelope Irving

Hydrophobicity

The chemistry of amino acid R-groups affects the structures they are most commonly found in. Subsets of their chemical properties can give clues to structure and, sometimes, cellular location. A prime example is the hydrophobicity (water-avoiding tendencies) of some R-groups. Given the aqueous environment of the cell, such R-groups are not likely to be on the outside surface of a folded protein. However, this rule does not hold for regions of protein that may be embedded within the lipid bilayers of cellular/organelle membranes. This is because the region of such proteins that form the transmembrane domains are are buried in the hydrophobic environment in the middle of the lipid bilayer.

Amino Acid Hydropathy Scores

Amino Acid	One Letter Code	Hydropathy Score
Isoleucine	I	4.5
Valine	V	4.2
Leucine	L	3.8
Phenylalanine	F	2.8
Cysteine	C	2.5
Methionine	M	1.9
Alanine	A	1.8
Glycine	G	-0.4
Threonine	T	-0.7
Tryptophan	W	-0.9
Serine	S	-0.8
Tyrosine	Y	-1.3
Proline	P	-1.6
Histidine	H	-3.2
Glutamic acid	E	-3.5
Glutamine	Q	-3.5
Aspartic acid	D	-3.5
Asparagine	N	-3.5
Lysine	K	-3.9
Arginine	R	-4.5

Table 2.4 - Hydropathy Scores

Wikipedia

Not surprisingly, scanning primary sequences for specifically sized/spaced stretches of hydrophobic amino acids can help to identify proteins found in membranes. Table 2.4 shows hydrophobicity values for R-groups of the amino acids. In this set, the scale runs from positive values (hydrophobic) to negative values (hydrophilic). A Kyte-Doolittle Hydropathy plot for the RET protooncogene membrane protein is shown in Figure 2.36. Two regions of the protein are very hydrophobic as can be seen from the peaks near amino acids 5-10 and 630-640. Such regions might be reasonably expected to be situated either within the interior of the folded protein or to be part of transmembrane domains.

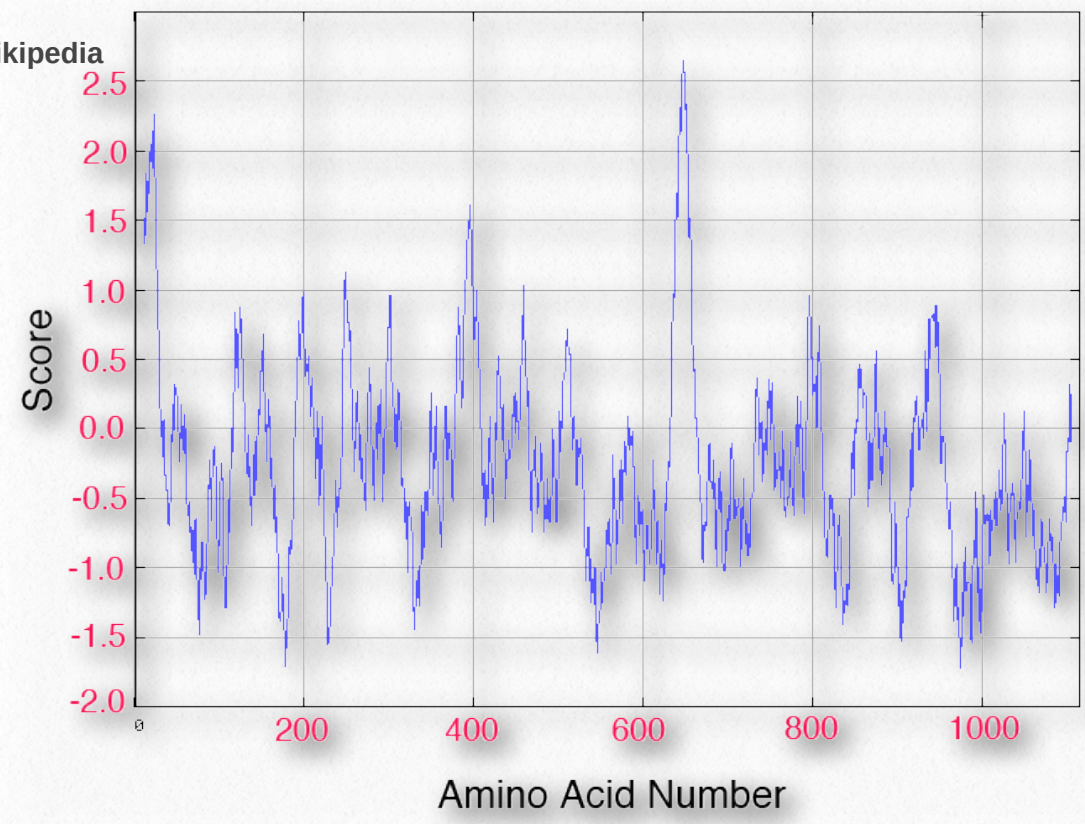


Figure 2.36 Kyte-Doolittle hydropathy plot for the RET protooncogene

Wikipedia

Random coils

Some sections of a protein assume no regular, discernible structure and are sometimes said to lack secondary structure, though they may have hydrogen bonds. Such segments are described as being in random coils and may have fluidity to their structure that results in them having multiple stable forms. Random coils are identifiable with spectroscopic methods, such as circular dichroism

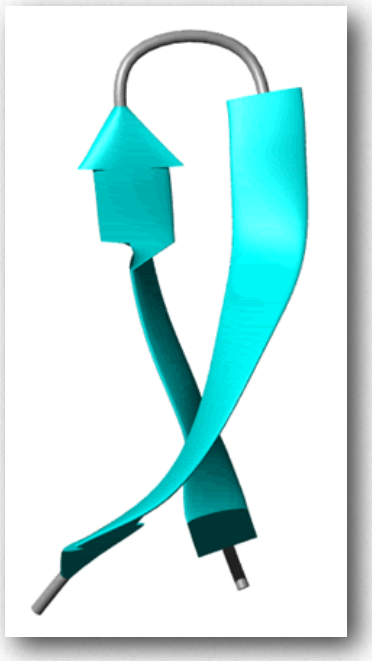


Figure 2.37 - Ribbon depiction of a β-hairpin. Shown are two β strands in turquoise interacting with each other.

and nuclear magnetic resonance (NMR) in which distinctive signals are observed. See also metamorphic proteins (HERE) and intrinsically disordered proteins (HERE).

Supersecondary structure

Another element of protein structure is harder to categorize because it incorporates elements of secondary and tertiary structure. Dubbed supersecondary structure (or structural motifs), these structures contain multiple nearby secondary structure components arranged in a specific way and that appear in multiple proteins. Since there are many ways of making secondary structures from different primary structures, so too can similar motifs arise from different primary sequences. An example of a structural motif is shown in Figure 2.37.

Tertiary structure

Proteins are distinguished from each other by the sequence of amino acids comprising them. The sequence of amino acids of a protein determines protein shape, since the chemical properties of each amino acid are forces that give rise to intermolecular interactions to begin to create secondary structures, such as α-helices and β-strands. The sequence also defines turns and random coils that play important roles in the process of protein folding.

Since shape is essential for protein function, the sequence of amino acids gives rise to all of the properties a protein has. As protein synthesis proceeds, individual components of secondary structure start to interact with each other, giving rise to folds that bring amino acids close together that are not near each other in primary structure (Figure 2.38). At the tertiary level of structure, inter-

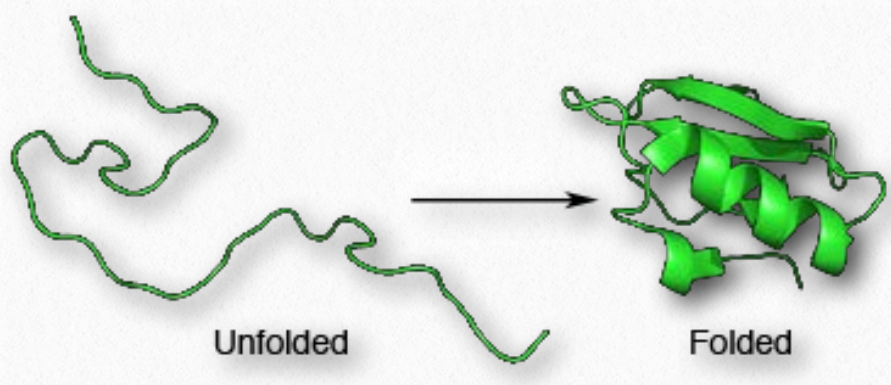


Figure 2.38 - Folding of a polypeptide chain

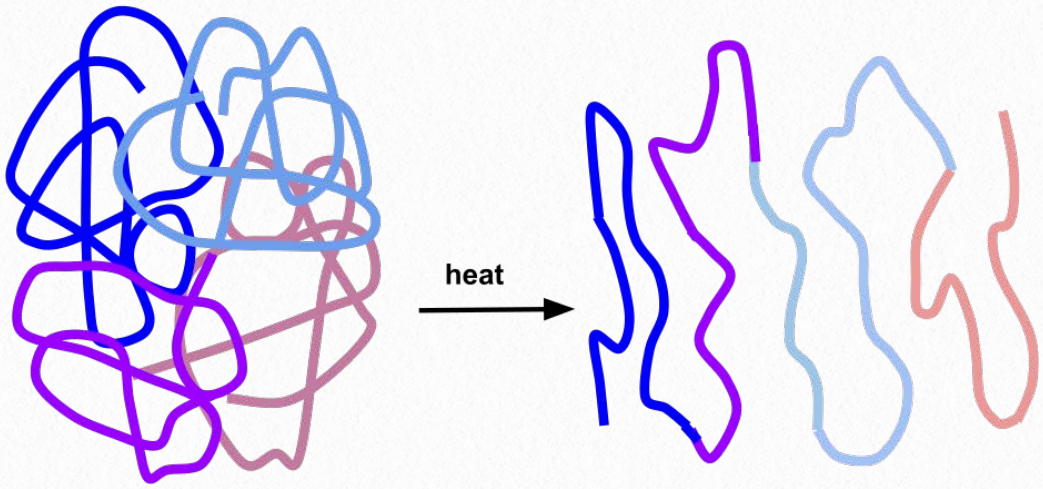


Figure 2.39 - **Unfolding (denaturation) of a protein**

Wikipedia

actions among the R-groups of the amino acids in the protein, as well as between the polypeptide backbone and amino acid side groups play a role in folding.

Globular proteins

Folding gives rise to distinct 3-D shapes in proteins that are non-fibrous. These proteins are called globular. A globular protein is stabilized by the same forces that drive its formation. These include ionic interactions, hydrogen bonding, hydrophobic forces, ionic bonds, disulfide bonds and metallic bonds. Treatments such as heat, pH changes, detergents, urea and mercaptoethanol overpower the stabilizing forces and cause a protein to unfold, losing its structure and (usually) its function (Figure 2.39). The ability of heat and detergents to denature proteins is why we cook our food and wash our hands before eating - such treatments denature the proteins in the microorganisms on our hands. Organisms that live in environments of high temperature (over 50°C) have proteins with changes in stabilizing forces - additional hydrogen bonds, additional salt bridges (ionic interactions), and compactness may all play roles in keeping these proteins from unfolding.

Protein stabilizing forces

Before considering the folding process, let us consider some of the forces that help to stabilize proteins.

Hydrogen bonds

Hydrogen bonds arise as a result of partially charged hydrogens found in covalent bonds. This occurs when the atom the hydrogen is bonded to has a greater electronegativity than hydrogen itself does, resulting in hydrogen having a partial positive charge be-

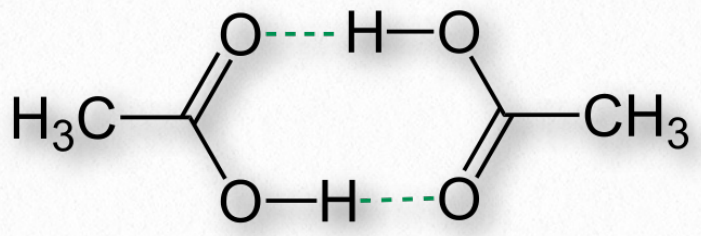


Figure 2.40 - **Hydrogen bonds (dotted lines) between two molecules of acetic acid**

cause it is not able to hold electrons close to itself (Figure 2.40).

Hydrogen partially charged in this way is attracted to atoms, such as oxygen and nitrogen that have partial negative charges, due to having greater electronegativities and thus holding electrons closer to themselves. The partially positively charged hydrogens are called donors, whereas the partially negative atoms they are attracted to are called acceptors. (See Figure 1.30).

YouTube Lectures by Kevin HERE & HERE

Individual hydrogen bonds are much weaker than a covalent bond, but collectively, they can exert strong forces. Consider liquid water, which contains enormous numbers of hydrogen bonds (Figure 2.41). These forces help water to remain liquid at room temperature. Other molecules lacking hydrogen bonds of equal or greater molecular weight than water, such as methane or carbon dioxide, are gases at the same temperature. Thus, the intermolecular interactions between water molecules help to "hold" water together and remain a liquid. Notably, only by raising the temperature of water to boiling are the forces of hydrogen bonding overcome, allowing water to become fully gaseous.

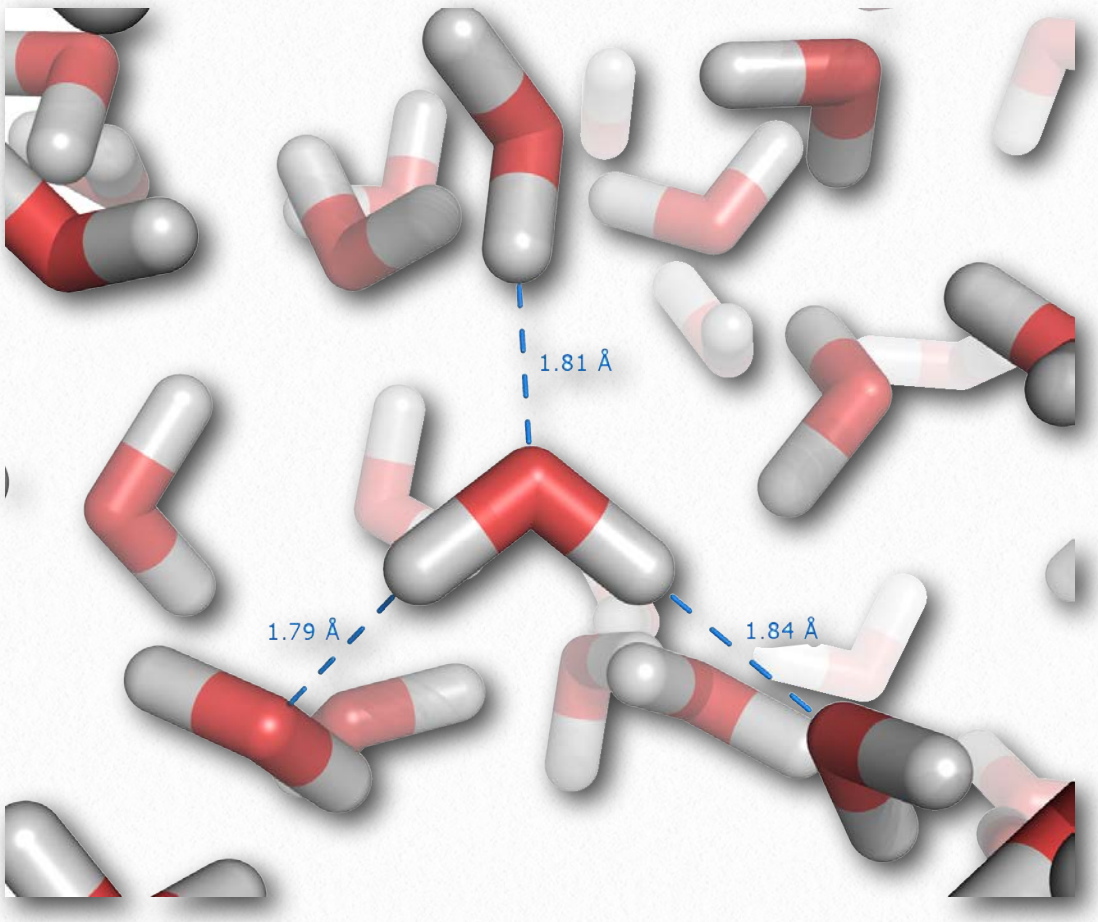


Figure 2.41 - Hydrogen bonding in liquid water
Wikipedia

Hydrogen bonds are important forces in biopolymers that include DNA, proteins, and cellulose. All of these polymers lose their native structures upon boiling. Hydrogen bonds between amino acids that are close to each other in primary structure can give rise to regular repeating structures, such as helices or pleats, in proteins (secondary structure).

Ionic interactions

Ionic interactions are important forces stabilizing protein structure that arise from ionization of R-groups in the amino acids comprising a protein. These include the carboxyl amino acids (HERE), the amine amino acids

An Ode to Protein Structure

by Kevin Ahern

The twenty wee amino A's
Define a protein many ways

Their order in a peptide chain
Determines forms that proteins gain

And when they coil, it leaves me merry
Cuz that makes structures secondary

It's tertiary, I am told
That happens when a protein folds

But folded chains are downright scary
When put together quaternary

They're nature's wonders, that's for sure
Creating problems, making cures

A fool can fashion peptide poems
But proteins come from ribosoems

(HERE), as well as the sulfhydryl of cysteine and sometimes the hydroxyl of tyrosine.

Hydrophobic forces

Hydrophobic forces stabilize protein structure as a result of interactions that favor the exclusion of water. Non-polar amino acids (commonly found in the interior of proteins) favor associating with each other and this has the effect of excluding water. The excluded water has a higher entropy than water interacting with the hydrophobic side chains. This is because water aligns itself very regularly and in a distinct pattern when interacting with hydrophobic molecules.

When water is prevented from having these kinds of interactions, it is much more disordered that it would be if it could associate with the hydrophobic regions. It is partly for this reason that hydrophobic amino acids are found in protein interiors - so they can exclude water and increase entropy.

Disulfide bonds

Disulfide bonds, which are made when two sulfhydryl side-chains of cysteine are brought into close proximity, covalently join together different protein regions and can give great strength to the overall structure (Figures 2.42 & 2.43).

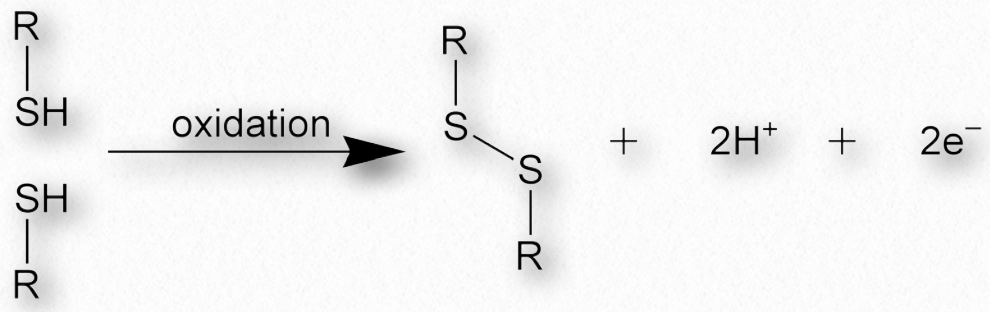


Figure 2.42 - Formation of a disulfide bond

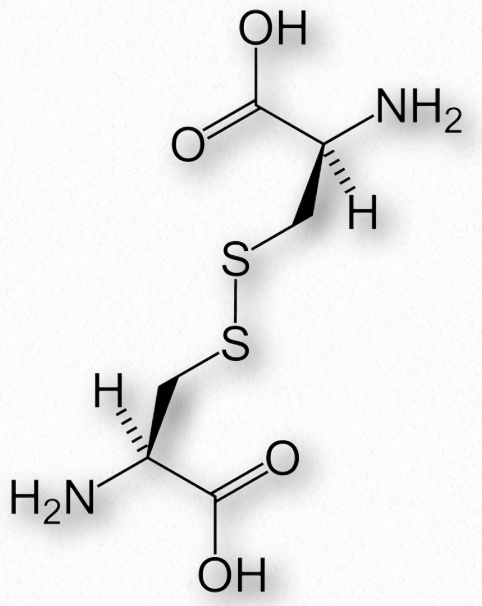


Figure 2.43 - Cystine - Two cysteines joined by a disulfide bond

These joined residues of cysteine are sometimes referred to as cystine. Disulfide bonds are the strongest of the forces stabilizing protein structure.

van der Waals forces

van der Waals forces is a term used to describe various weak interactions, including those caused by attraction between a polar molecule and a transient dipole, or between two temporary dipoles. van der Waals forces are dynamic because of the fluctuating nature of the attraction, and are generally weak in comparison to covalent bonds, but can, over very short distances, be significant.

Post-translational modifications

Post-translational modifications can result in formation of covalent bonds stabilizing proteins as well. Hydroxylation of lysine and proline in strands of collagen can result in cross-linking of these groups and the resulting covalent bonds help to strengthen and stabilize the collagen.

Folding models

Two popular models of protein folding are currently under investigation. In the first (diffusion collision model), a nucleation event begins the process, followed by secondary structure formation. Collisions between the secondary structures (as in the β-hairpin in Figure 2.37) allow for folding to begin. By contrast, in the nucleation-condensation model, the secondary and tertiary structures form together.

Folding in proteins occurs fairly rapidly (0.1 to 1000 seconds) and can occur during synthesis - the amino terminus of a protein can start to fold before the carboxyl terminus is even made, though that is not always the case.

Folding process

Protein folding is hypothesized to occur in a "folding funnel" energy landscape in which a folded protein's native state corresponds to the minimal free energy possible in conditions of the medium (usually aqueous solvent) in which the protein is dissolved. As seen in the diagram (Figure 2.44), the energy funnel has numerous local minima (dips) in which a folding protein can become trapped as it

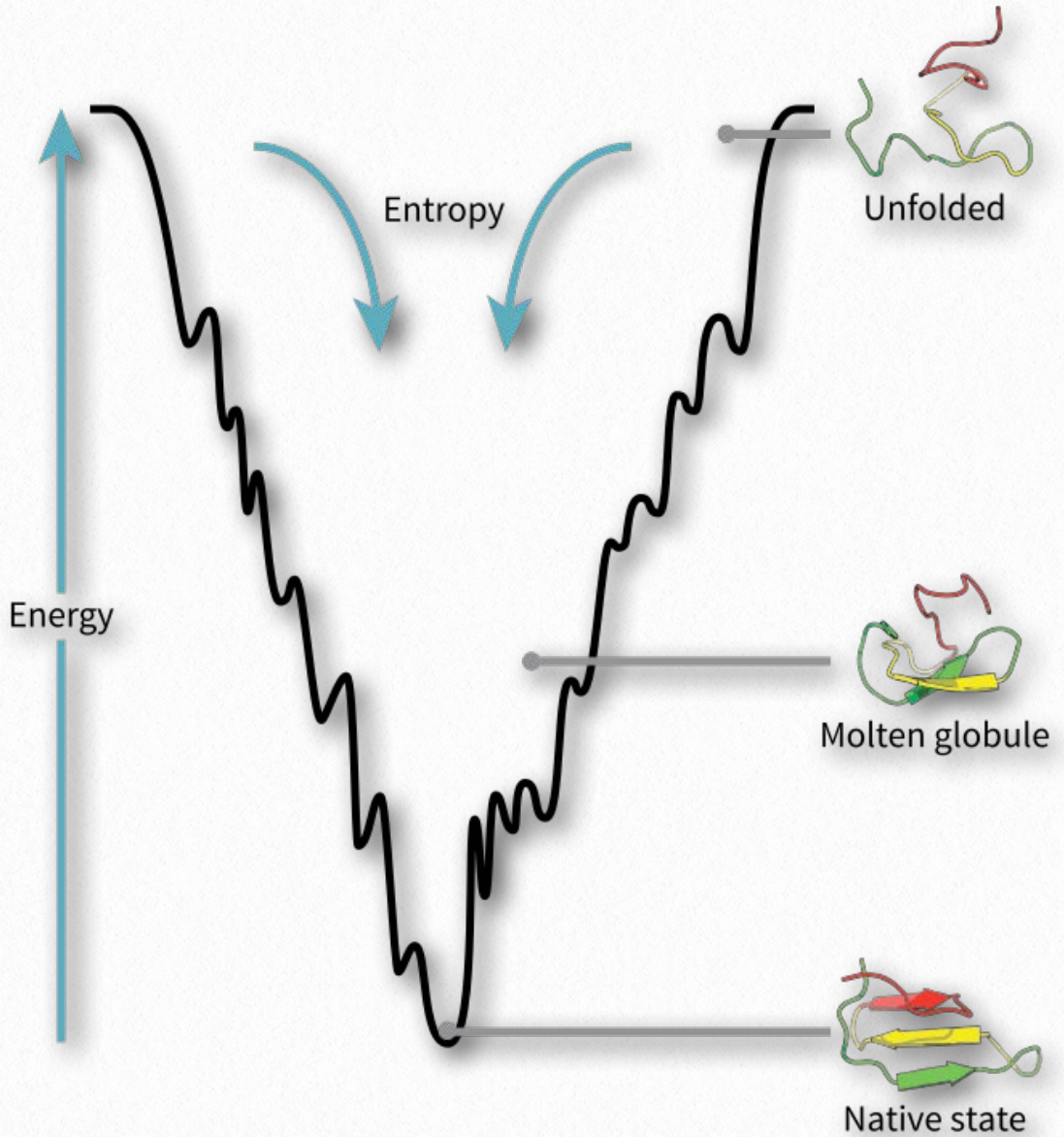


Figure 2.44 Folding funnel energy model of folding Wikipedia

Getting stuck

As the folding process proceeds towards an energy minimum (bottom of the funnel in Figure 2.44), a protein can get "stuck" in any of the local minima and not reach the final folded state. Though the folded state is, in general, more organized and therefore has reduced entropy than the unfolded state, there are two forces that overcome the entropy decrease and drive the process forward.

The first is the magnitude of the decrease in energy as shown in the graph. Since

$$\Delta G = \Delta H - T\Delta S,$$

moves down the energy plot. Other factors, such as temperature, electric/magnetic fields, and spacial considerations likely play roles.

If external forces affect local energy minima during folding, the process and end-product can be influenced. As the speed of a car going down a road will affect the safety of the journey, so too do energy considerations influence and guide the folding process, resulting in fully functional, properly folded proteins in some cases and misfolded "mistakes" in others.

a decrease in ΔH can overcome a negative ΔS to make ΔG negative and push the folding process forward. Favorable (decreased) energy conditions arise with formation of ionic bonds, hydrogen bonds, disulfide bonds, and metallic bonds during the folding process. In addition, the hydrophobic effect increases entropy by allowing hydrophobic amino acids in the interior of a folded protein to exclude water, thus countering the impact of the ordering of the protein structure by making the ΔS less negative.

Structure prediction

Computer programs are very good at predicting secondary structure solely based on amino acid sequence, but struggle with determining tertiary structure using the same information. This is partly due to the fact that secondary structures have repeating points of stabilization based on geometry and any regular secondary structure (e.g., α-helix) varies very little from one to another. Folded structures, though, have an enormous number of possible structures as shown by Levinthal's Paradox.

YouTube Lectures by Kevin HERE & HERE

Spectroscopy

Because of our inability to accurately predict tertiary structure based on amino acid sequence, proteins structures are actually determined using techniques of spectroscopy. In these approaches, proteins are subjected to varied forms of electromagnetic radiation and the ways they interact with the radiation allows researchers to determine atomic coordinates at Angstrom resolution from electron densities (see X-ray crystallography) and how nuclei spins interact (see NMR).

Levinthal's paradox

In the late 1960s, Cyrus Levinthal outlined the magnitude of the complexity of the protein folding problem. He pointed out that for a protein with 100 amino acids, it would have 99 peptide bonds and 198 considerations for φ and ψ angles. If each of these had only three conformations, that would result in 3^{198} different possible foldings or 2.95×10^{94}.

Even allowing a reasonable amount of time (one nanosecond) for each possible fold to occur, it would take longer than the age of the universe to sample all of them, meaning clearly that the process of folding is not occurring by a sequential random sampling and that attempts to determine protein structure by random sampling were doomed to fail. Levinthal, therefore, proposed that folding occurs by a sequential process that begins with a nucleation event that guides the process rapidly and is not unlike the funnel process depicted in Figure 2.44.

Diseases of protein misfolding

The proper folding of proteins is essential to their function. It follows then that

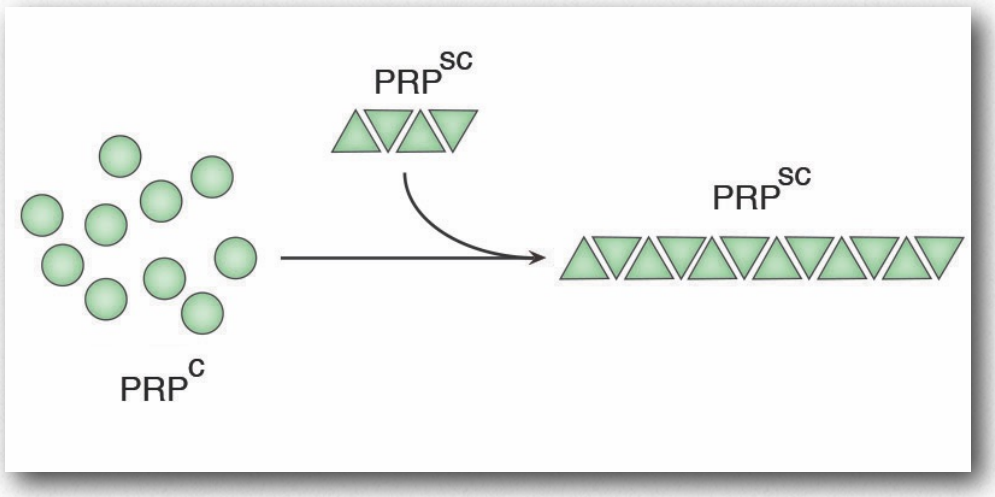


Figure 2.45 - Misfolding of the normal PRP^c protein induced by PRP^{sc}

Image by Penelope Irving

Figure 2.46 - Cows with Mad Cow Disease lose their ability to stand

misfolding of proteins (also called proteopathy) might have consequences. In some cases, this might simply result in an inactive protein. Protein misfolding also plays a role in numerous diseases, such as Mad Cow Disease, Alzheimers, Parkinson's Disease, and Creutzfeld-Jakob disease. Many, but not all, misfolding diseases affect brain tissue.

Insoluble deposits

Misfolded proteins will commonly form aggregates called amyloids that are harmful to tissues containing them because they change from being soluble to insoluble in water and form deposits. The process by which misfolding (Figure 2.45) occurs is not completely clear, but in many cases, it has been demonstrated that a "seed" protein which is misfolded can induce the same misfolding in other copies of the same protein. These seed proteins are known as prions and they act as infectious agents, resulting in the spread of disease. The list of human diseases linked to protein misfolding is long and continues to grow. A Wikipedia link is HERE.

Prions

Prions are infectious protein particles that cause transmissible spongiform encephalopathies (TSEs), the best known of which is Mad Cow disease. Other manifesta-

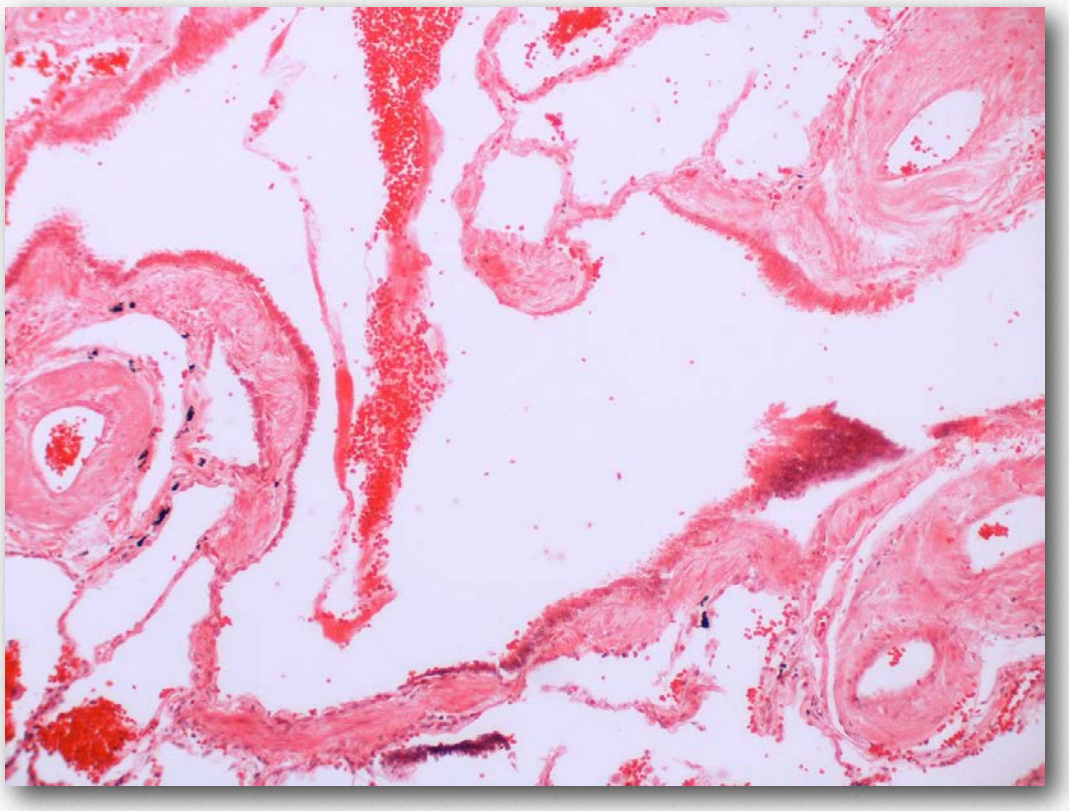


Figure 2.47 - Diffuse amyloidosis in a blood vessel (red dots)

Wikipedia

tions include the disease, scrapie, in sheep, and human diseases, such as Creutzfeldt-Jakob disease (CJD), Fatal Familial Insomnia, and kuru. The protein involved in these diseases is a membrane protein called PrP. PrP is encoded in the genome of many organisms and is found in most cells of the body. PrP^{c} is the name given to the structure of PrP that is normal and not associated with disease. PrP^{Sc} is the name given to a misfolded form of the same protein, that is associated with the development of disease symptoms (Figure 2.45).

I think that if I chanced to be on
A protein making up a prion
I'd twist it and for goodness sakes
Stop it from making fold mistakes

Misfolded

The misfolded PrP^{Sc} is associated with the TSE diseases and acts as an infectious particle. A third form of PrP, called PrP^{res} can be found in TSEs, but is not infectious. The 'res' of PrP^{res} indicates it is protease resistant. It is worth noting that all three forms of PrP have the same amino acid sequence and differ from each other only in the ways in which the polypeptide chains are folded. The most dangerously misfolded form of PrP is PrP^{Sc}, because of its ability to act like an infectious agent - a seed protein that can induce misfolding of PrP^{c}, thus converting it into PrP^{Sc}.

Function

The function of PrP^{c} is unknown. Mice lacking the PrP gene do not have major abnormalities. They do appear to exhibit problems with long term memory, suggesting a function for PrP^{c}. Stanley Prusiner, who discovered prions and coined the term, received the Nobel Prize in Medicine in 1997 for his work.

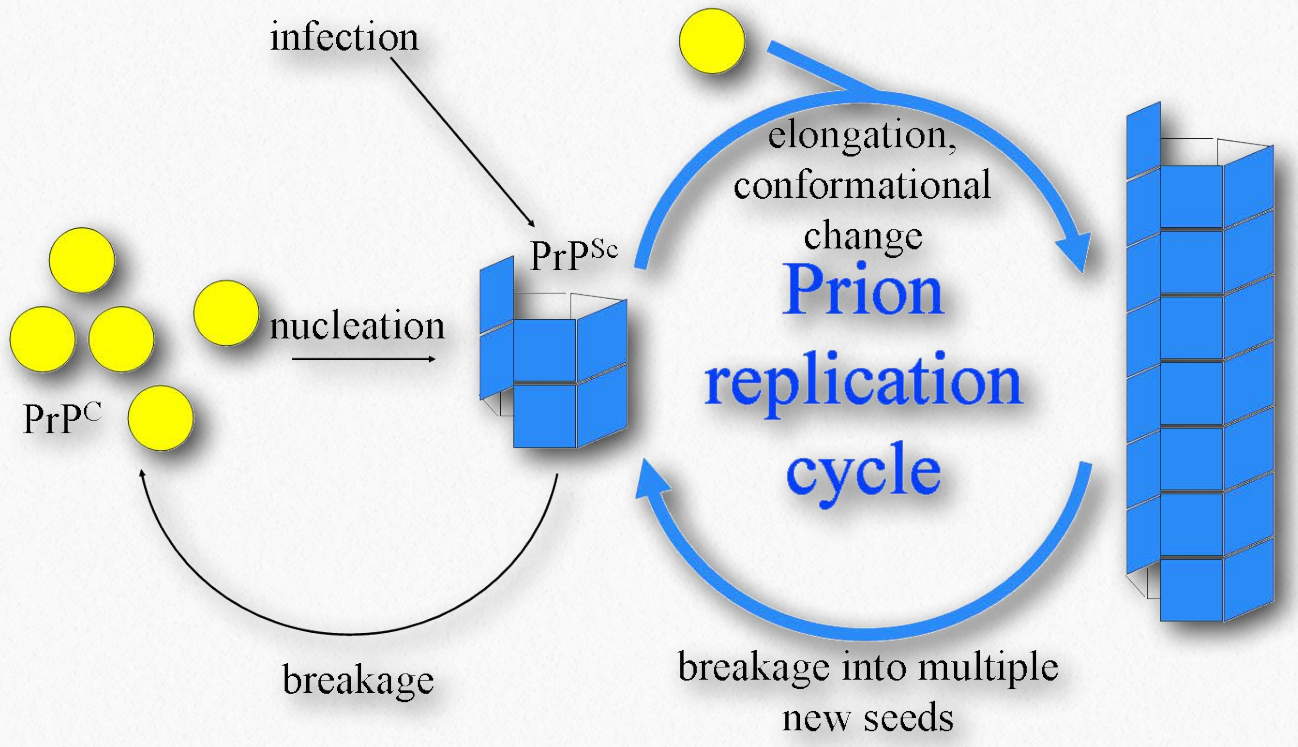


Figure 2.48 - One model of prion propagation

Wikipedia

Amyloids

Amyloids are a collection of improperly folded protein aggregates that are found in the human body. As a consequence of their misfolding, they are insoluble and contribute to some twenty human diseases including important neurological ones involving prions. Diseases include (affected protein in parentheses) - Alzheimer's disease (Amyloid β), Parkinson's disease (α-synuclein), Huntington's disease (huntingtin), rheumatoid arthritis (serum amyloid A), fatal familial insomnia (PrP^{Sc}), and others.

Amino acid sequence plays a role in amyloidogenesis. Glutamine-rich polypeptides are common in yeast and human prions. Trinucleotide repeats are important in Huntington's disease. Where sequence is not a factor, hydrophobic association between β-sheets can play a role.

Amyloid β

Amyloid β refers to collections of small proteins (36-43 amino acids) that appear to play a role in Alzheimer's disease. (Tau protein is the other factor.) They are, in fact, the main components of amyloid plaques found in the brains of patients suffering from the disease and arise from proteolytic cleavage of a larger amyloid precursor glycoprotein called Amyloid Precursor Protein, an integral membrane protein of nerve cells whose function is not known. Two proteases, β-secretase and γ-secretase perform this function. Amyloid β proteins are improperly folded and appear to induce other proteins to misfold and thus precipitate and form the amyloid characteristic of the disease. The plaques are toxic to nerve cells and give rise to the dementia characteristic of the disease.

It is thought that aggregation of amyloid β proteins during misfolding leads to generation of reactive oxygen species and that this is the means by which neurons are damaged. It is not known what the actual function of amyloid β is. Autosomal dominant mutations in the protein lead to early onset of the disease, but this occurs in no more than 10% of the cases. Strategies for treating the disease in-

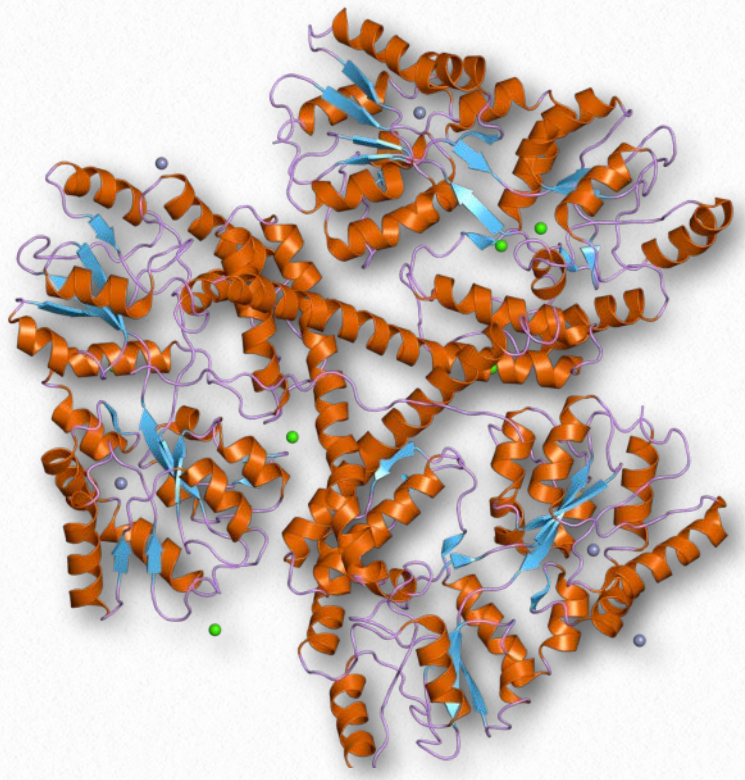


Figure 2.49 - Huntingtin

clude inhibition of the secretases that generate the peptide fragments from the amyloid precursor protein.

Huntingtin

Huntingtin is the central gene in Huntington's disease. The protein made from it is glutamine rich, with 6-35 such residues in its wild-type form. In Huntington's disease, this gene is mutated, increasing the number of glutamines in the mutant protein to between 36 and 250. The size of the protein varies with the number of glutamines in the mutant protein, but the wild-type protein has over 3100 amino acids and a molecular weight of about 350,000 Da. Its precise function is not known, but huntingtin is found in nerve cells, with the highest level in the brain. It is thought to possibly play roles in transport, signaling, and protection against apoptosis. Huntingtin is also required for early embryonic development. Within the cell, huntingtin is found localized primarily with microtubules and vesicles.

Trinucleotide repeat

The huntingtin gene contains many copies of the sequence CAG (called trinucleotide repeats), which code for the many glutamines in the protein. Huntington's disease arises when extra copies of the CAG sequence are generated when the DNA of the gene is being copied. Expansion of repeated sequences can occur due to slipping of the polymerase relative to the DNA template during replication. As a result, multiple additional copies of the trinucleotide repeat may be made, resulting in proteins with variable numbers of glutamine residues. Up to 35 repeats can be tolerated without problem. The number of repeats can expand over the course of a person's lifetime, however, by the same mechanism. Individuals with 36-40 repeats begin to show signs of the disease and if there are over 40, the disease will be present.

YouTube Lectures by Kevin HERE & HERE

Molecular chaperones

The importance of the proper folding of proteins is highlighted by the diseases associated with misfolded proteins, so it is no surprise, then, that cells expend energy to facilitate the proper folding of proteins. Cells use two classes of proteins known as molecular chaperones, to facilitate such folding in cells. Molecular chaperones are of two kinds, the chaperones, and the chaperonins. An example of the first category is the Hsp70 class of proteins. Hsp stands for "heat shock protein", based on the fact that these proteins were first observed in large amounts in cells that had been briefly subjected to high temperatures. Hsps function to assist cells in stresses arising from heat shock and exposure to oxidizing conditions or toxic heavy metals, such as cadmium and mercury. However, they also play an important role in

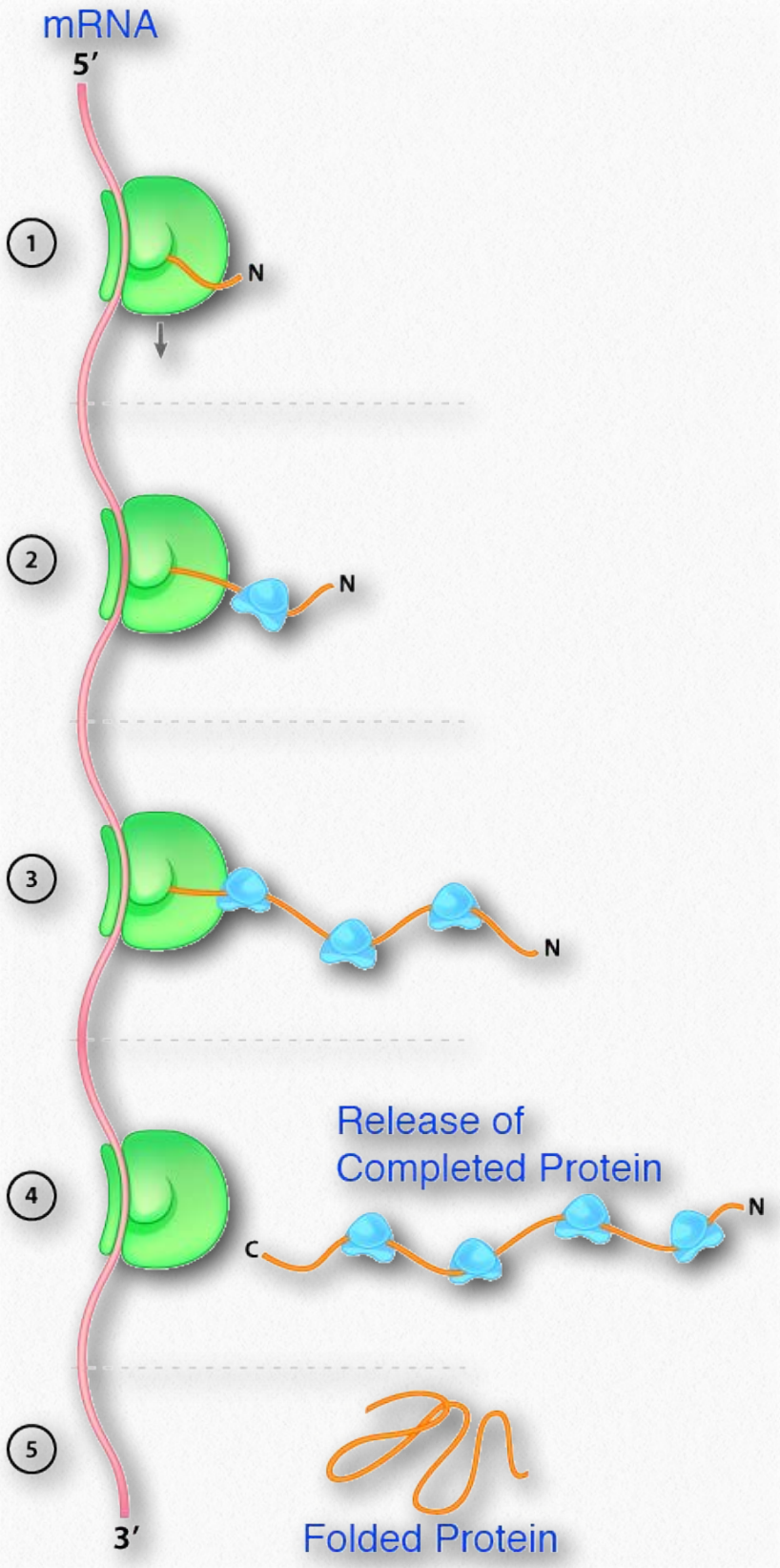


Figure 2.50 - Action of Hsp70 (blue) to facilitate proper folding of a protein (orange)

Image by Aleia Kim

normal conditions, where they assist in the proper folding of polypeptides by preventing aberrant interactions that could lead to misfolding or aggregation.

The Hsp70 proteins are found in almost all cells and use ATP hydrolysis to stimulate structural changes in the shape of the chaperone to accommodate binding of substrate proteins. The binding domain of Hsp70s contains a β-barrel structure which wraps around the polypeptide chain of the substrate and has affinity for hydrophobic side chains of amino acids. As shown in Figure 2.50, Hsp70 binds to polypeptides as they emerge from ribosomes during protein synthesis. Binding of substrate stimulates ATP hydrolysis and this is facilitated by another heat shock protein known as Hsp40. The hydrolysis of ATP causes the Hsp70 to taken on a closed conformation that helps shield exposed hydrophobic residues and prevent aggregation or local misfolding.

After protein synthesis is complete, ADP is released and replaced by ATP and this results in release of the substrate protein, which then allows the full length polypeptide to fold correctly.

In heat shock

In times of heat shock or oxidative stress, Hsp70 proteins bind to unfolded hydrophobic regions of proteins to similarly prevent them from aggregating and allowing them to properly refold. When proteins are damaged, Hsp70 recruits enzymes that ubiquitinate the damaged protein to target them for destruction in proteasomes. Thus, the Hsp70 proteins play an important role in ensuring

not only that proteins are properly folded, but that damaged or nonfunctional proteins are removed by degradation in the proteasome.

Chaperonins

A second class of proteins involved in assisting other proteins to fold properly are known as chaperonins. There are two primary categories of chaperonins - Class I (found in bacteria, chloroplasts, and mitochondria) and Class II (found in the cytosol of eukaryotes and archaebacteria). The best studied chaperonins are the GroEL/GroES complex proteins found in bacteria (Figure 2.51).

GroEL/GroES may not be able to undo aggregated proteins, but by facilitating proper folding, it provides competition for misfolding as a process and can reduce or eliminate problems arising from improper folding. GroEL is a double-ring 14mer with a hydrophobic region that can facilitate folding of substrates 15-60 kDa in size. GroES is a single-ring heptamer that binds to GroEL in the presence of ATP and functions as a cover over GroEL. Hydrolysis of ATP by chaperonins induce large conformational changes that affect binding of substrate proteins and their folding. It is not known exactly how chaperonins fold proteins. Passive models postulate the chaperonin complex functioning inertly by preventing unfavorable intermolecular interactions or placing restrictions on spaces available for folding to occur. Active models propose that structural changes in the chaperonin complex induce structural changes in the substrate protein.

Protein breakdown

Another protein complex that has an important function in the lifetime dynamics of proteins is the proteasome (Figure 2.52). Proteasomes, which are found in all eukaryotes and archaeans, as well as some bacteria, function to break down unneeded or damaged proteins by proteolytic degradation. Proteasomes help to regulate the concentration of some proteins and degrade ones that are misfolded.

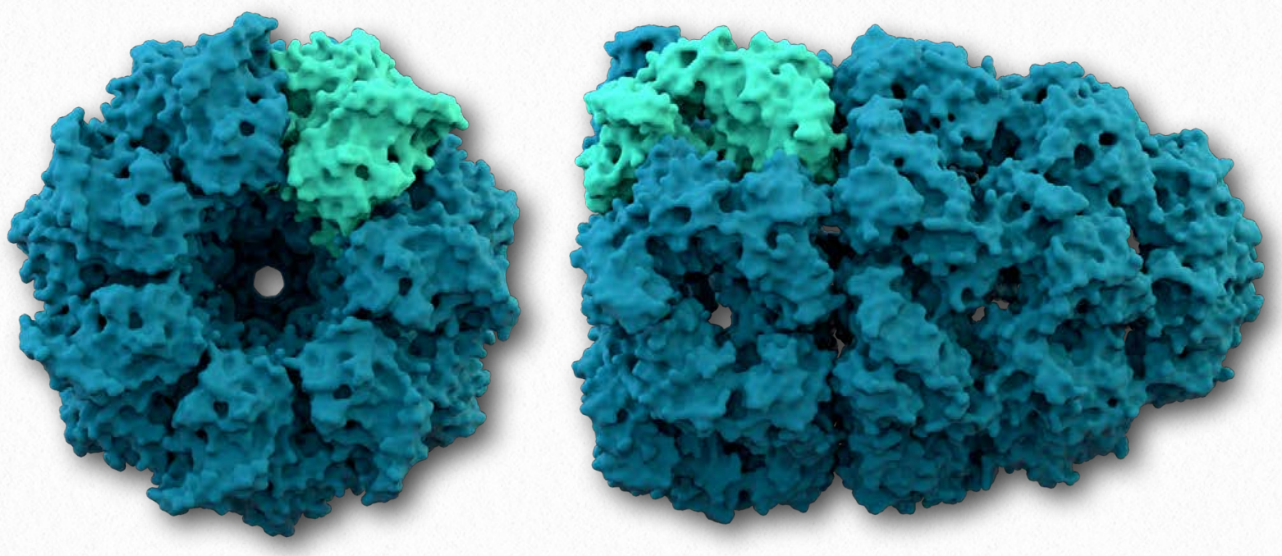


Figure 2.51 - View from bottom of GroEL (left) and GroEL/GroES complex (right)

Wikipedia

The proteasomal degradation pathway plays

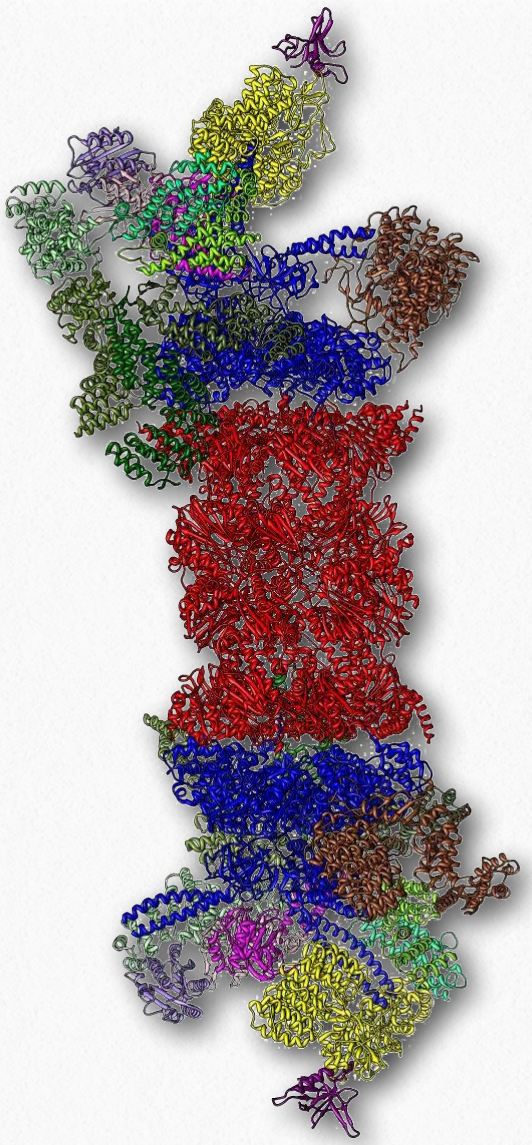


Figure 2.52 - 26S proteasome. Active site shown in red

Wikipedia

an important role in cellular processes that include progression through the cell cycle, modulation of gene expression, and response to oxidative stresses.

Degradation in the proteasome yields short peptides seven to eight amino acids in length. Threonine proteases play important roles. Breakdown of these peptides yields individual amino acids, thus facilitating their recycling in cells. Proteins are targeted for degradation in eukaryotic proteasomes by attachment to multiple copies of a small protein called ubiquitin (8.5 kDa - 76 amino acids). The enzyme catalyzing the reaction is known as ubiquitin ligase. The resulting polyubiquitin chain is bound by the proteasome and degradation begins. Ubiquitin was named due to it ubiquitously being found in eukaryotic cells.

Ubiquitin

Ubiquitin (Figure 2.53) is a small (8.5 kDa) multi-functional protein found in eukaryotic cells. It is commonly added to target proteins by action of ubiquitin ligase enzymes (E3 in Figure 2.54). One (ubiquitination)

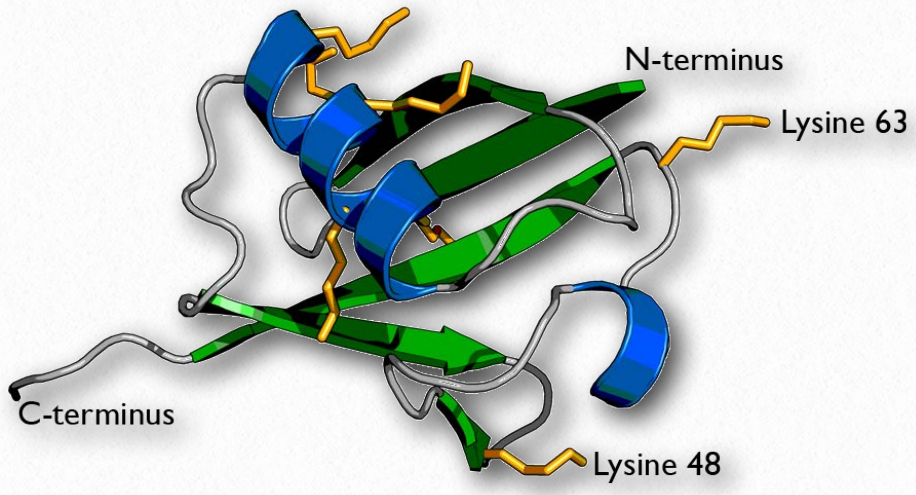


Figure 2.53 - Ubiquitin (lysine side chains shown in yellow)

Wikipedia

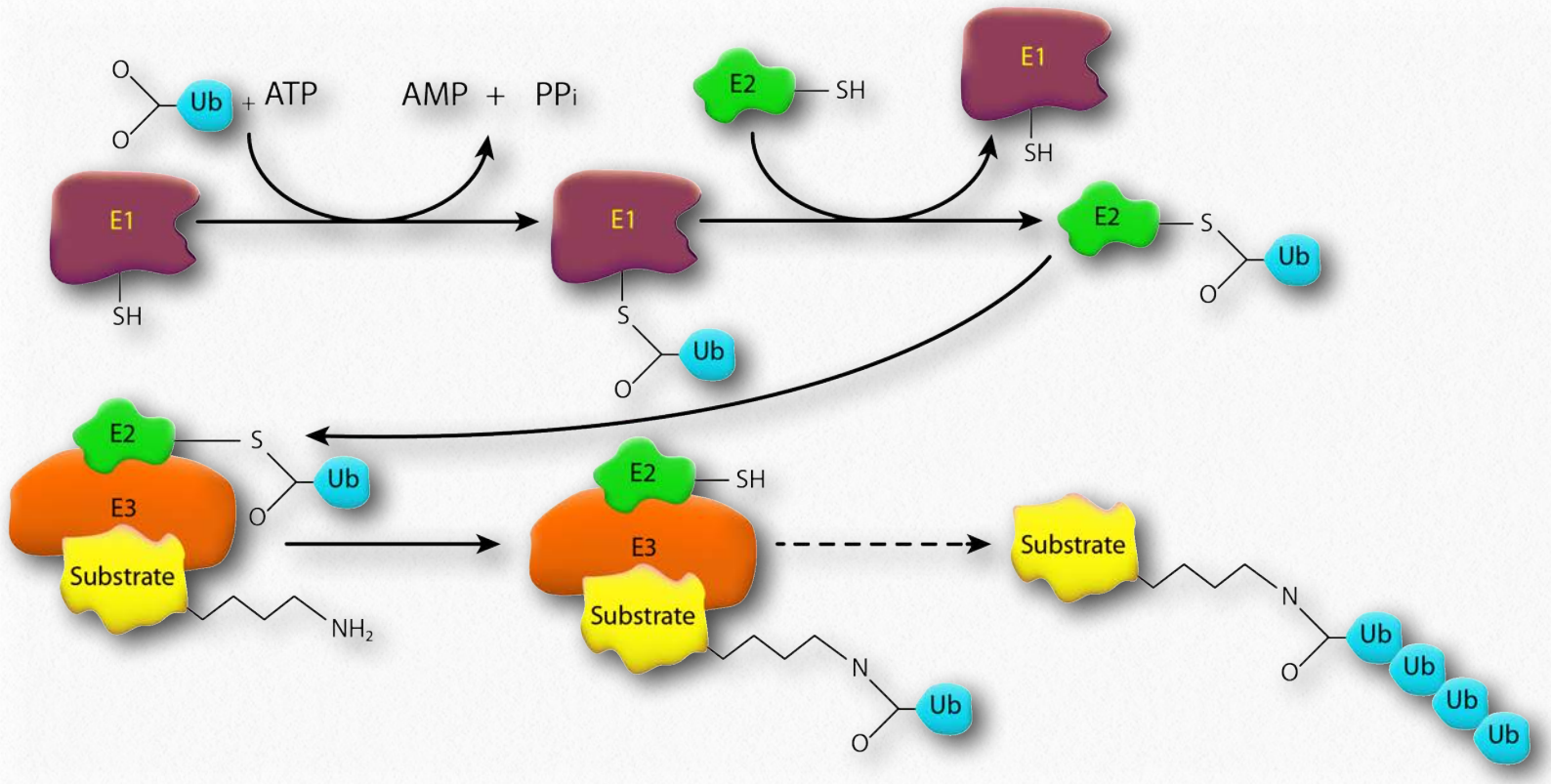


Figure 2.54 - Pathway for ubiquitination of a target substrate protein

Image by Pehr Jacobson

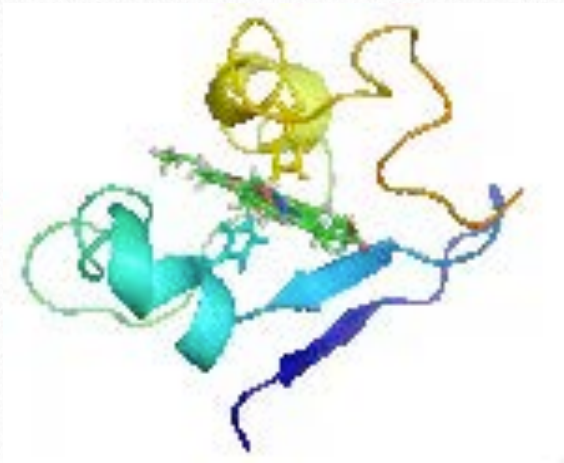
or many (polyubiquitination) ubiquitin molecules may be added. Attachment of the ubiquitin is through the side chain of one of seven different lysine residues in ubiquitin. The addition of ubiquitin to proteins has many effects, the best known of which is targeting the protein for degradation in the proteasome. Proteasomal targeting is seen when polyubiquitination occurs at lysines #29 and 48. Polyubiquitination or monoubiquitination at other lysines can result in altered cellular location and changed protein-protein interactions. The latter may alter affect inflammation, endocytic trafficking, translation and DNA repair.

Ubiquitin ligase malfunction

Parkin is a Parkinson's disease-related protein that, when mutated, is linked to an inherited form of the disease called autosomal recessive juvenile Parkinson's disease. The function of the protein is not known, but it is a component of the E3 ubiquitin ligase system responsible for transferring ubiquitin from the E2 protein to a lysine side chain on the target protein. It is thought that mutations in parkin lead to proteasomal dysfunction and a consequent inability to break down proteins harmful to dopaminergic neurons. This results in the death or malfunction of these neurons, resulting in Parkinson's disease.

Intrinsically disordered proteins

As is evident from the many examples described elsewhere in the book, the 3-D structure of proteins is important for their function. But, increasingly, it is becoming evident that not all proteins fold into a stable structure. Studies on the so-called intrinsically disordered proteins (IDPs) in the past cou-



Movie 2.1 - Dynamic movement of cytochrome C in solution

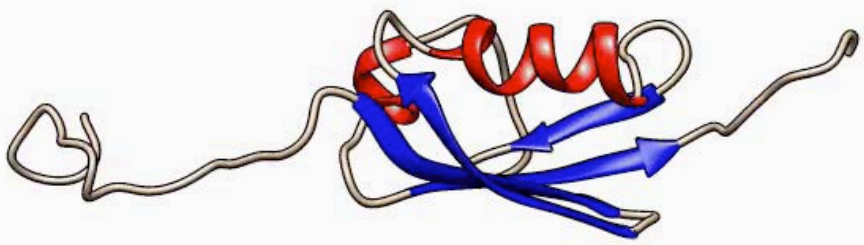
Wikipedia

ple of decades has shown that many proteins are biologically active, even though they fail to fold into stable structures. Yet other proteins exhibit regions that remain unfolded (IDP regions) even as the rest of the polypeptide folds into a structured form.

YouTube Lectures by Kevin HERE & HERE

Intrinsically disordered proteins and disordered regions within proteins have, in fact, been known for many years, but were regarded as an anomaly. It is only recently, with the realization that IDPs and IDP regions are widespread among eukaryotic proteins, that it has been recognized that the observed disorder is a "feature, not a bug".

Comparison of IDPs shows that they share sequence characteristics that appear to favor their disordered state. That is, just as some amino acid sequences may favor the folding of a polypeptide into a particular structure, the amino acid sequences of IDPs favor their remaining unfolded. IDP regions are seen to be low in hydrophobic residues and unusually rich in polar residues and proline. The presence of a large number of charged amino acids in the IDPs can inhibit folding through charge repulsion, while the lack of hydrophobic residues makes it difficult to form a stable hydrophobic core, and proline discourages the formation of helical structures. The observed differences between amino acid sequences in IDPs and structured proteins have been used to design algorithms to



Movie 2.2 SUMO-1, a protein with intrinsically disordered sections

Wikipedia

predict whether a given amino acid sequence will be disordered.

What is the significance of intrinsically disordered proteins or regions? The fact that this property is encoded in their amino acid sequences suggests that their disorder may be linked to their function. The flexible, mobile nature of some IDP regions may play a crucial role in their function, permitting a transition to a folded structure upon binding a protein partner or undergoing post-translational modification. Studies on several well-known proteins with IDP regions suggest some answers. IDP regions may enhance the ability of proteins like the lac repressor to translocate along the DNA to search for specific binding sites. The flexibility of IDPs can also be an asset in protein-protein interactions, especially for proteins that are known to interact with many different protein partners. For example, p53 has IDP regions that may allow the protein to interact with a variety of functional partners. Comparison of the known functions of proteins with predictions of disorder in these

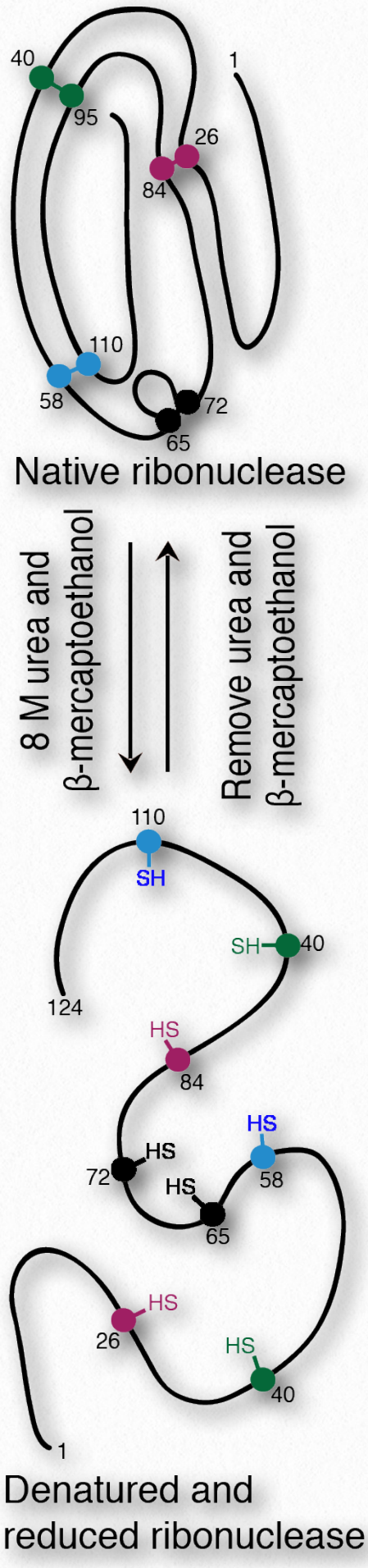


Figure 2.55 - Denaturation and renaturation of ribonuclease

Wikipedia

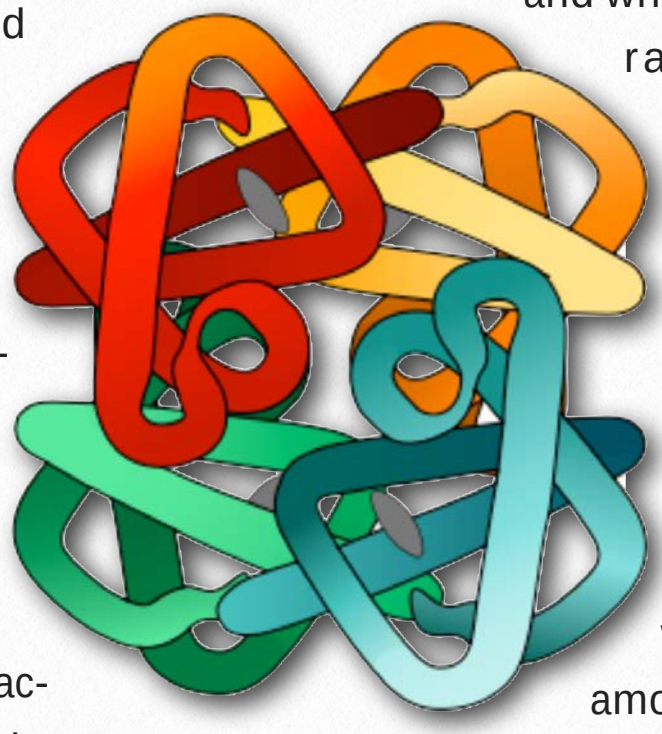
proteins suggests that IDPs and IDP regions may disproportionately function in signaling and regulation, while more structured proteins skew towards roles in catalysis and transport. Interestingly, many of the proteins found in both ribosomes and spliceosomes are predicted to have IDP regions that may play a part in correct assembly of these complexes. Even though IDPs have not been studied intensively for very long, what little is known of them suggests that they play an important and underestimated role in cells.

Metamorphic proteins.

Another group of proteins that have recently changed our thinking about protein structure and function are the so-called metamorphic proteins. These proteins are capable of forming more than one stable, folded state starting with a single amino acid sequence. Although it is true that multiple folded conformations are not ruled out

There are not very many ways
Inactivating RNase
It's stable when it's hot or cold
Because disulfides tightly hold
If you desire to make it stall
Use hot mercaptoethanol

by the laws of physics and chemistry, metamorphic proteins are a relatively new discovery. It was known, of course, that prion proteins were capable of folding into alternative structures, but metamorphic proteins appear to be able to toggle back and forth between two stable structures. While in some cases, the metamorphic protein undergoes this switch in response to binding another molecule, some proteins that can accomplish this transition on their own. An interesting example is the signaling molecule, lymphotactin. Lymphotactin has two biological functions that are carried out by its two conformers- a monomeric form that binds the lymphotactin receptor and a dimeric form that binds heparin. It is possible that this sort of switching is more widespread than has been thought.



Refolding denatured proteins

All information for protein folding is contained in the amino acid sequence of the protein. It may seem curious then that most proteins do not fold into their proper, fully active form after they have been denatured and the denaturant is removed. A few do, in fact. One good example is bovine ribonuclease (Figure 2.55). Its catalytic activity is very resistant to heat and urea and attempts to denature it don't work very well. However, if one treats the enzyme with β-mercaptoethanol (which breaks disulfide bonds) prior to urea treatment and/or heating, activity is lost, indicating that the covalent disulfide bonds help stabilize the overall enzyme structure and when they are broken, denaturation can readily occur. When the mixture cools back down to room temperature, over time some enzyme activity reappears, indicating that ribonuclease re-folded under the new conditions.

Interestingly, renaturation will occur maximally if a tiny amount of β-mercaptoethanol is left in the solution during the process. The reason for this is because β-mercaptoethanol permits reduction (and breaking) of accidental, incorrect disulfide bonds during the folding process. Without it, these disulfide bonds will prevent proper folds from forming.

Irreversible denaturation

Most enzymes, however, do not behave like bovine ribonuclease. Once denatured, their activity cannot be recovered to any significant

extent. This may seem to contradict the idea of folding information being inherent to the sequence of amino acids in the protein. It does not.

Most enzymes don't refold properly after denaturation for two reasons. First, normal folding may occur as proteins are being made. Interactions among amino acids early in the synthesis are not "confused" by interactions with amino acids later in the synthesis because those amino acids aren't present as the process starts.

Chaperonins' role

In other cases, the folding process of some proteins in the cell relied upon action of chaperonin proteins (see HERE). In the absence of chaperonins, interactions that might result in misfolding occur, thus preventing proper folding. Thus, early folding and the assistance of chaperonins eliminate some potential "wrong-folding" interactions that can occur if the entire sequence was present when folding started.

Quaternary structure

A fourth level of protein structure is that of quaternary structure. It refers to structures that arise as a result of interactions between multiple polypeptides. The units can be identical multiple copies or can be different polypeptide chains. Adult hemoglobin is a good example of a protein with quaternary structure, being composed of two identical chains called α and two identical chains called β.

Though the α-chains are very similar to the β-chains, they are not identical. Both of the α- and the β-chains are also related to the single polypeptide chain in the related protein called myoglobin. Both myoglobin and hemoglobin have similarity in binding oxygen, but their behavior towards the molecule differ significantly. Notably, hemoglobin's multiple subunits (with quaternary structure) compared to myoglobin's single subunit (with no quaternary structure) give rise to these differences. (See HERE).

References

1. https://en.wikipedia.org/wiki/Van_der_Waals_force

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

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O Little Protein Molecule

To the tune of "*O Little Town of Bethlehem*"

Metabolic Melodies Website HERE

Oh little protein molecule
You're lovely and serene
With twenty zwitterions like
Cysteine and alanine

Your secondary structure
Has pitches and repeats
Arranged in alpha helices
And beta pleated sheets

The Ramachandran plots are
Predictions made to try
To tell the structures you can have
For angles phi and psi

And tertiary structure
Gives polypeptides zing
Because of magic that occurs
In protein fol-ding

A folded enzyme's active
And starts to catalyze
When activators bind into
The allosteric sites

Some other mechanisms
Control the enzyme rates
By regulating synthesis
And placement of phosphates

And all the regulation
That's found inside of cells
Reminds the students learning it
Of pathways straight from hell

Recording by Tim Karplus
Lyrics by Kevin Ahern

My Old Enzymes

To the tune of "*Auld Lang Syne*"

Metabolic Melodies Website HERE

Whene'er my proteins go kaput
If they are past their prime.
The cells will act to soon replace
All of my old enzymes

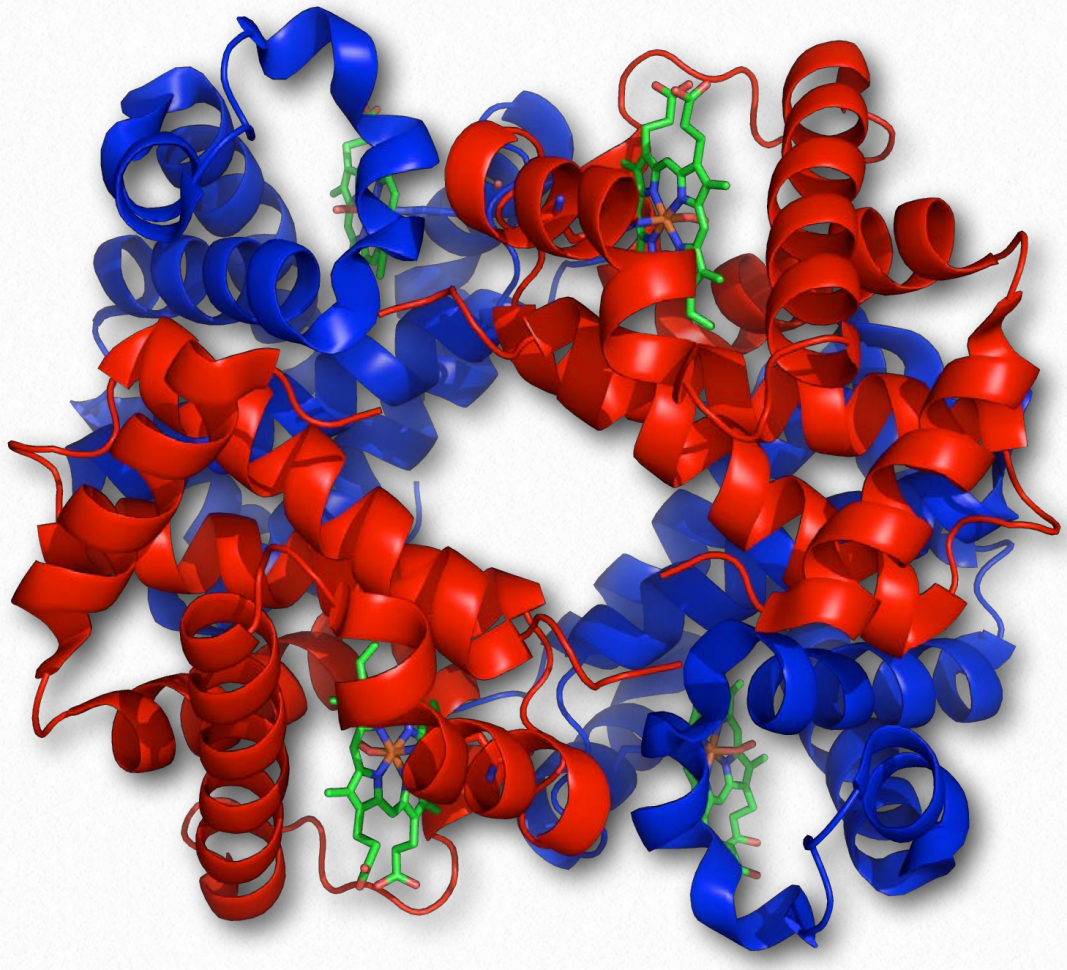
They know which ones to break apart
Ubiquitin's the sign
A marker for pro-TE-a-somes
To find the old enzymes

These soon get bound and then cut up
In pieces less than nine
More chopping yields the single ones
Building blocks from old enzymes

So in a way the cell knows well
Of father time it's true
Amino acids when reused
Turn old enzymes to new

Recording by David Simmons
Lyrics by Kevin Ahern

Structure and Function: Proteins II



Hemoglobin

Wikipedia

Structure and function

In this section, we hope to bring to life the connection between structure and function of proteins. So far, we have described notable features of the four elements (primary, secondary, tertiary, and quaternary) of protein structure and discussed example proteins/motifs exhibiting them. In this section, we will examine from a functional perspective a few proteins/domains whose function relies on secondary, tertiary, or quaternary structure.

YouTube Lectures by Kevin
HERE & HERE

It is, of course a bit of a narrow focus to ascribe protein function to any one component of structure, but our hope is by presenting these examples, we can bring to life the way in which a protein's secondary, tertiary, and quarternary structure lead to the functions it has.

Fibrous proteins - secondary structure

Proteins whose cellular or extracellular roles have a strong structural component are com-

posed primarily of primary and second structure, with little folding of the chains. Thus, they have very little tertiary structure and are fibrous in nature. Proteins exhibiting these traits are commonly insoluble in water and are referred to as fibrous proteins (also called scleroproteins). The examples described in this category are found exclusively in animals where they serve roles in flesh, connective tissues and hardened external structures, such as hair. They also contain the three common fibrous protein structures **α**-helices (keratins), **β**-strands/sheets (fibroin & elastin) and triple helices (collagen). The fibrous proteins have some commonality of amino acid sequence. Each possesses an abundance of repeating sequences of amino acids with small, non-reactive side groups. Many contain short repeats of sequences, often with glycine.

Keratins

The keratins are a family of related animal proteins that take numerous forms. α-keratins are structural components of the outer layer of human skin and are integral to hair, nails, claws, feathers, beaks, scales, and hooves. Keratins provide strength to tissues, such as

We wouldn't be too popular
If keratins were globular
Our nails and hair would be as knots
Their structures folded up like clots
No strength they'd have and oh by gosh
They'd rearrange with every wash

Figure 2.56 - The horns of an impala are composed of keratin

Wikipedia

the tongue, and over 50 different keratins are encoded in the human genome. At a cellular level, keratins comprise the intermediate filaments of the cytoskeleton. α-keratins primarily contain **α**-helices, but can also have **β**-strand/sheet structures. Individual α-helices are often intertwined to form coils of coiled structures and these strands can also be further joined together by disul-

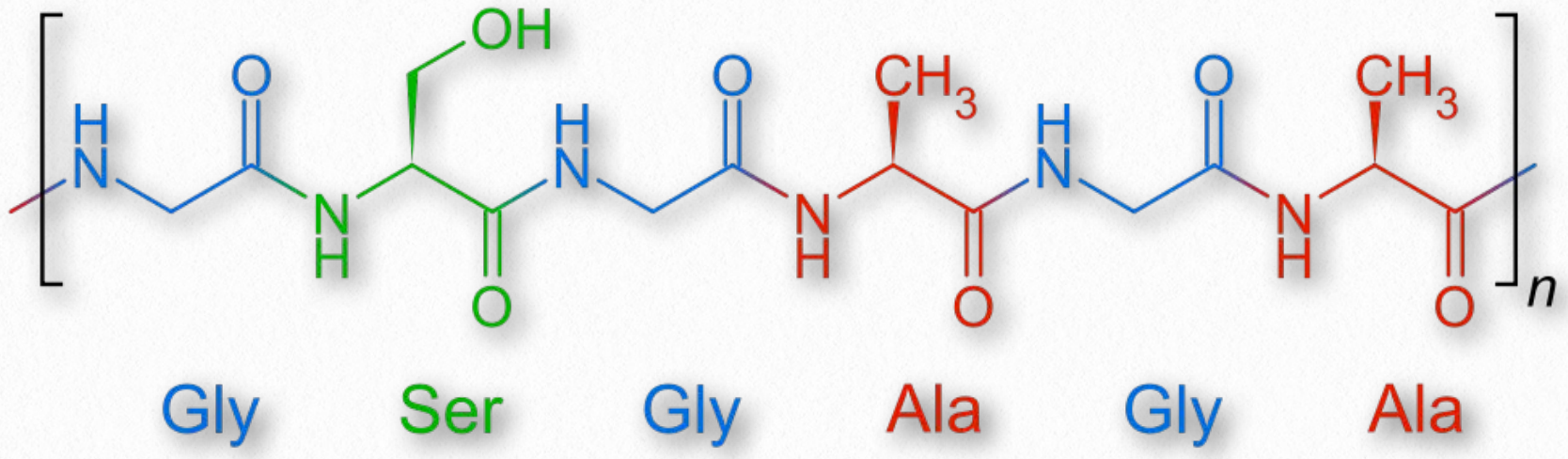


Figure 2.57 - The repeating amino acid sequence of fibroin

fide bonds, increasing structural strength considerably. This is particularly relevant for α-keratin in hair, which contains about 14% cysteine. The odor of burned hair and that of the chemicals used to curl/uncurl hair (breaking/re-making disulfide bonds) arise from their sulfurous components. β-keratins are comprised of β-sheets, as their name implies. Wikipedia link HERE.

Fibroin

An insoluble fibrous protein that is a component of the silk of spiders and the larvae of moths and other insects, fibroin is comprised of anti-parallel **β**-strands tightly packed together to form β-sheets. The primary structure of fibroin is a short repeating sequence with glycine at every other residue (Figure 2.57). The small R-groups of the glycine and alanine in the repeating sequence allows for the tight packing characteristic of the fibers of silk. Wikipedia link HERE

Figure 2.58 - Weaving of a silk sari

Wikipedia

Elastin

As suggested by its name, elastin is a protein with elastic characteristics that functions in many tissues of the body to allow them to resume their shapes after expanding or contracting. The protein is rich in glycine and proline and can comprise over 50% of the weight of dry, defatted arteries. Elastin is made by linking tropoelastin proteins together through lysine residues to make a durable complex cross-linked by desmos-

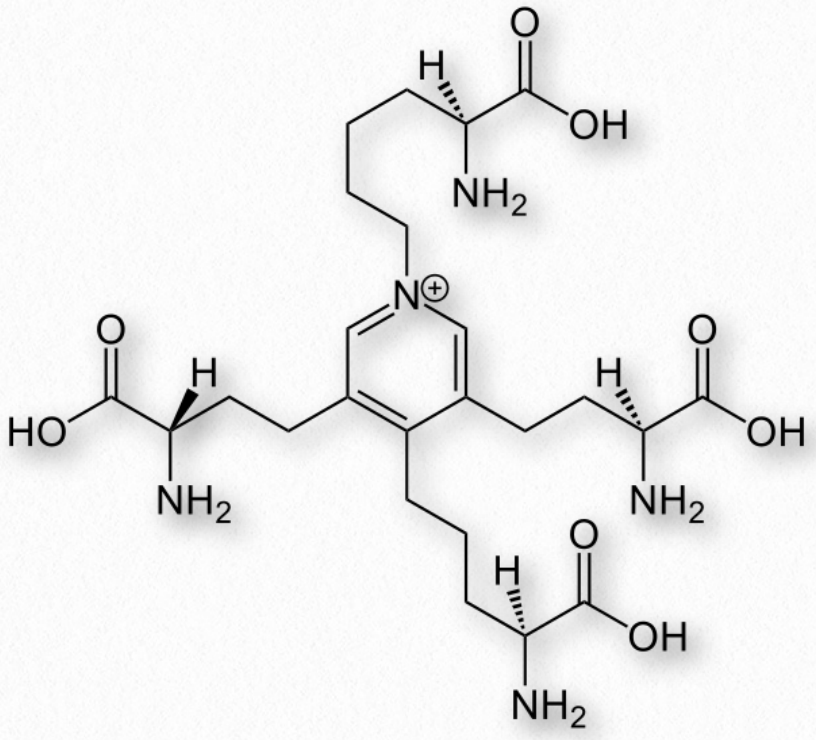


Figure 2.59 - Desmosine

Wikipedia

ine. In arteries, elastin helps with pressure wave propagation for facilitating blood flow. Wikipedia link HERE.

Collagen

Collagen is the most abundant protein in mammals, occupying up to a third of the total mass. There are at least 16 types of collagen. Its fibers are a major component of tendons and they are also found abundantly in skin. Collagen is also prominent in cornea, cartilage, bone, blood vessels and the gut.

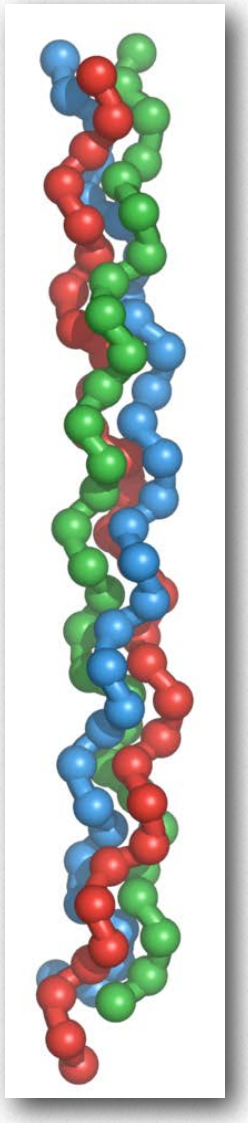


Figure 2.60 - Collagen's triple helix

Wikipedia

Collagen's structure is an example of a helix of helices, being composed of three left-handed helical chains that each are coiled together in a right-handed fashion to make the collagen fiber (Figure 2.60). Each helix

Gly-Pro-Met-Gly-Pro-Ser-Gly-Pro-Arg

Gly-Leu-Hpr-Gly-Pro-Hpr-Gly-Ala-Hpr

Gly-Pro-Gln-Gly-Phe-Gln-Gly-Pro-Hpr

Gly-Glu-Hpr-Gly-Glu-Hpr-Gly-Ala-Ser

Gly-Pro-Met-Gly-Pro-Arg-Gly-Pro-Hpr

Gly-Pro-Hpr-Gly-Lys-Asn-Gly-Asp-Asp

Hpr = Hydroxyproline

Figure 2.61 - Repeating sequences in collagen

is stretched out more than an α-helix, giving it an extended appearance. On the inside of the triple helical structure, only residues of glycine are found, since the side chains of other amino acids are too bulky. Collagen chains have the repeating structure glycine-m-n where m is often proline and n is often hydroxyproline (Figure 2.61).

Collagen is synthesized in a pre-procollagen form. Processing of the pre-procollagen in the endoplasmic reticulum results in glycosylation, removal of the 'pre'

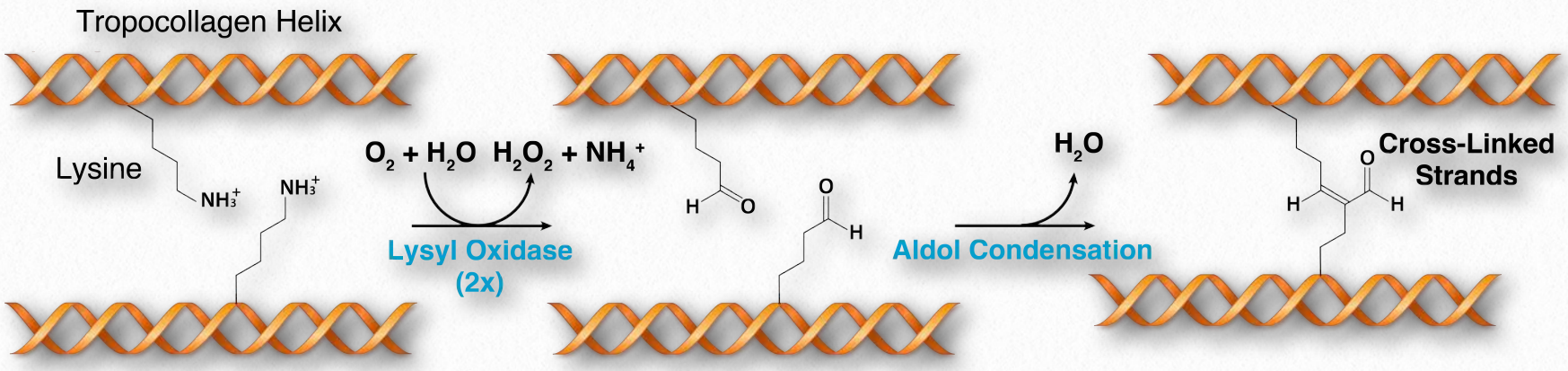


Figure 2.62 - Oxidation and cross-linking of lysine residues in tropocollagen. Only two strands of the triple helix are shown for simplicity

Image by Aleia Kim

sequence, and hydroxylation of lysine and proline residues (see below). The hydroxides can form covalent cross-links with each other, strengthening the collagen fibers. As pro-collagen is exported out of the cell, proteases trim it, resulting in a final form of collagen called tropocollagen.

Hydroxylation reactions

Hydroxylation of proline and lysine side chains occurs post-translationally in a reaction catalyzed by prolyl-4-hydroxylase and lysyl-hydroxylase (lysyl oxidase), respectively. The reaction requires vitamin C.

Since hydroxylation of these residues is essential for formation of stable triple helices at body temperature, vitamin C deficiency results in weak, unstable collagen and, consequently, weakened connective tissues. It is the cause of the disease known as scurvy. Hydrolyzed collagen is used to make gelatin, which is important in the food industry. collagens. Wikipedia link HERE

YouTube Lectures by Kevin HERE & HERE

Lamins

Lamins are fibrous proteins that provide structure in the cell nucleus and play a role in transcription regulation. They are similar to proteins making up the intermediate filaments, but have extra amino acids in one coil of the protein. Lamins help to form the nuclear lamin in the interior of the nuclear envelope and play important roles in assembling and disassembling the latter in the process of mitosis. They also help to position nuclear pores. In the process of mitosis, disassembly of the nuclear envelope is promoted by phosphorylation of lamins by a protein called mitosis promoting factor and assembly is favored by reversing the reaction (dephosphorylation).

Structural domains - tertiary structure

Every globular protein relies on its tertiary structure to perform its function, so rather than trying to find representative pro-

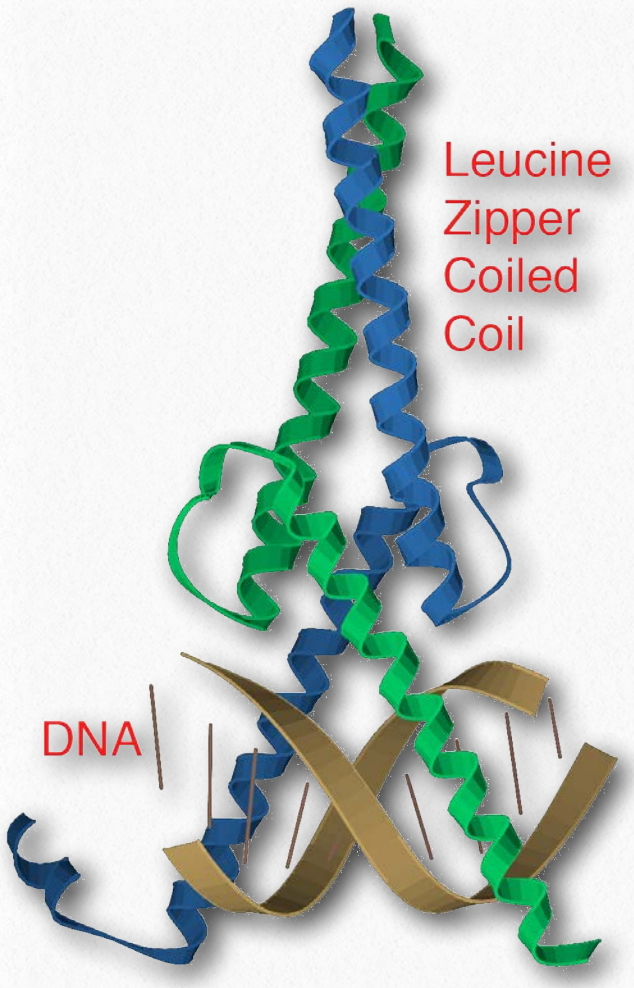


Figure 2.63 - Leucine zipper bound to DNA

Wikipedia

teins for tertiary structure (an almost impossible task!), we focus here on a few elements of tertiary structure that are common to many proteins. These are the structural domains and they differ from the structural motifs of supersecondary structure by being larger (25-500 amino acids), having a conserved amino acid sequence, and a history of evolving and functioning independently of the protein chains they are found in. Structural domains are fundamental units of tertiary structure and are found in more than one protein. A structural domain is self-stabilizing and often folds independently of the rest of the protein chain.

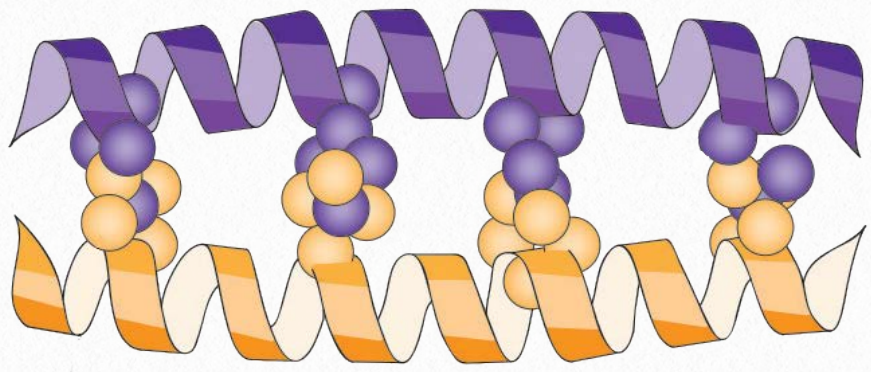


Figure 2.64 - Leucine zipper structure. Leucines are indicated by orange and purple balls.

Image by Penelope Irving

Leucine zipper

A common feature of many eukaryotic DNA binding proteins, leucine zippers are characterized by a repeating set of leucine residues in a protein that interact like a zipper to favor dimerization. Another part of the domain has amino acids (commonly arginine and lysine) that allow it to interact with the DNA double helix (Figure 2.63). Transcription factors that contain leucine zippers include Jun-B, CREB, and AP-1 fos/jun.

Zinc fingers

The shortest structural domains are the zinc fingers, which get their name from the fact that one or more coordinated zinc ions stabilize their finger-like structure. Despite their name, some zinc fingers do not bind zinc. There are many structural domains classified as zinc fingers and these are grouped into different families. Zinc fingers were first identified as components of DNA binding tran-

scription factors, but others are now known to bind RNA, protein, and even lipid structures. Cysteine and histidine side chains commonly play roles in coordinating the zinc.

Src SH_2 domain

The Src oncoprotein contains a conserved SH_2 structural domain that recognizes and binds phosphorylated tyrosine side chains in other proteins (Figure 2.65). Phosphorylation is a fundamental activity in signaling and phosphorylation of tyrosine and interaction between proteins carrying signals is critically needed for cellular communication. The SH_2 domain is found in over 100 human proteins.

Helix-turn-helix domain

Helix-turn-helix is a common domain found in DNA binding proteins, consisting

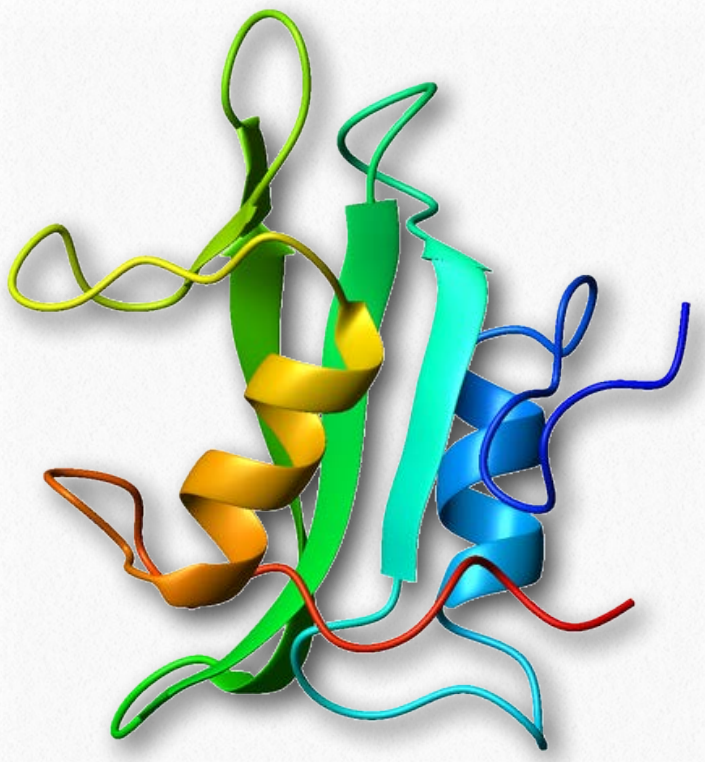


Figure 2.65 - SH_2 Domain

Wikipedia

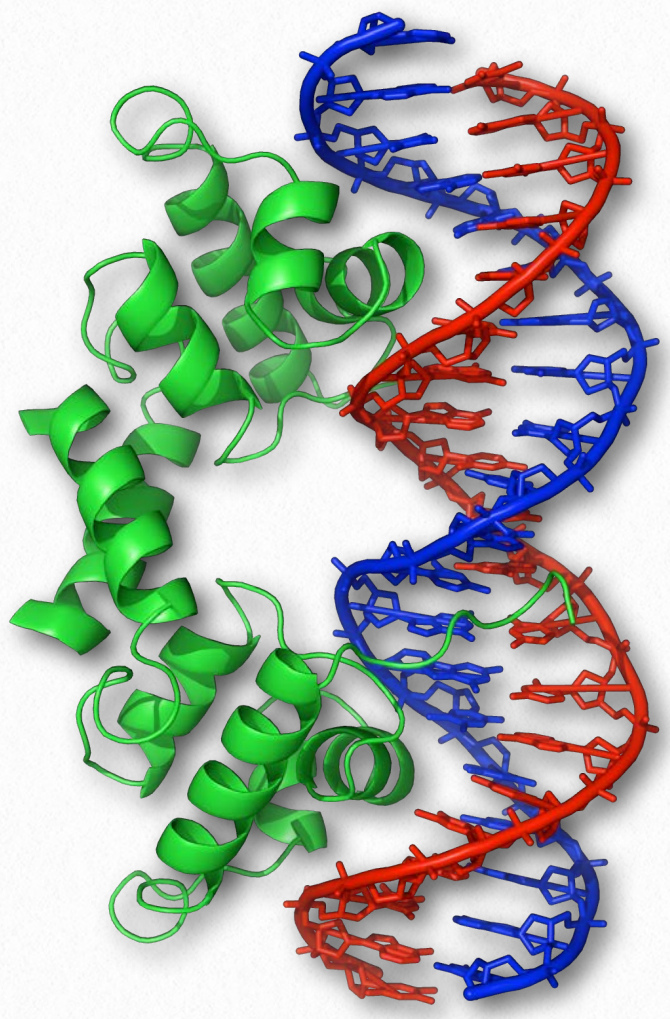


Figure 2.66 - Helix-Turn-Helix Domain of a Protein Bound to DNA

Wikipedia

of two α-helices separated by a small number of amino acids. As seen in Figure 2.66, the helix parts of the structural domain interact with the bases in the major groove of DNA. Individual α-helices in a protein are part of a helix-turn-helix structure, where the turn separates the individual helices.

Pleckstrin homology domain

Pleckstrin Homology (PH) domains are protein domains with important functions in the process of signaling. This arises partly from the affinity for binding phosphorylated inositides, such as PIP2 and PIP3, found in

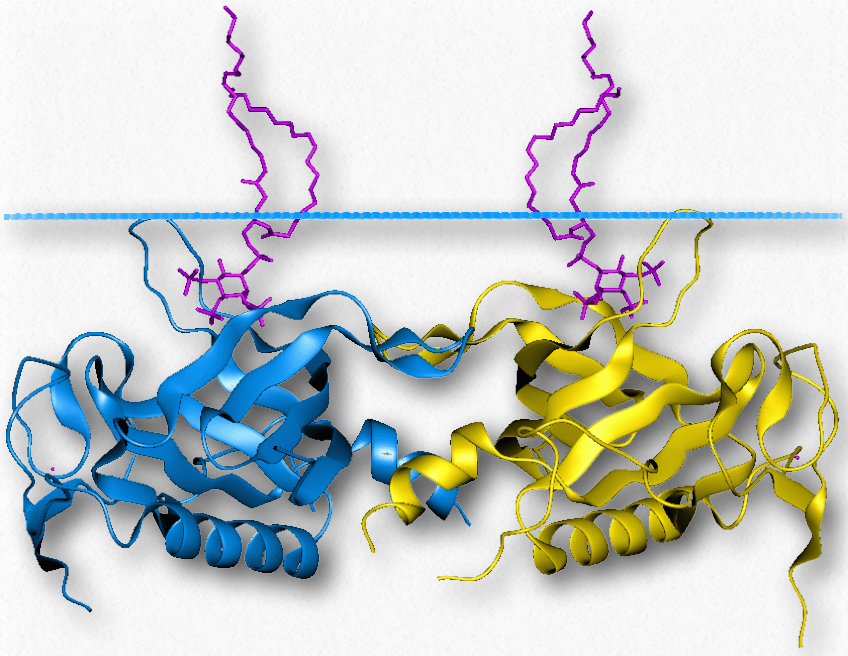


Figure 2.67 - Pleckstrin homology domain of Btk tyrosine protein kinase. The protein is embedded in a membrane (above blue line)

Wikipedia

biological membranes. PH domains can also bind to G-proteins and protein kinase C. The domain spans about 120 amino acids and is found in numerous signaling proteins. These include Akt/Rac Serine/Threonine Protein Kinases, Btk/Itk/Tec tyrosine protein kinases, insulin receptor substrate (IRS-1), Phosphatidylinositol-specific phospholipase C, and several yeast proteins involved in cell cycle regulation.

Structural globular proteins

Enzymes catalyze reactions and proteins such as hemoglobin perform important specialized functions. Evolutionary selection has reduced and eliminated waste so that we can be sure every protein in a cell has a function, even though in some cases we may not know what it is. Sometimes the structure of the pro-

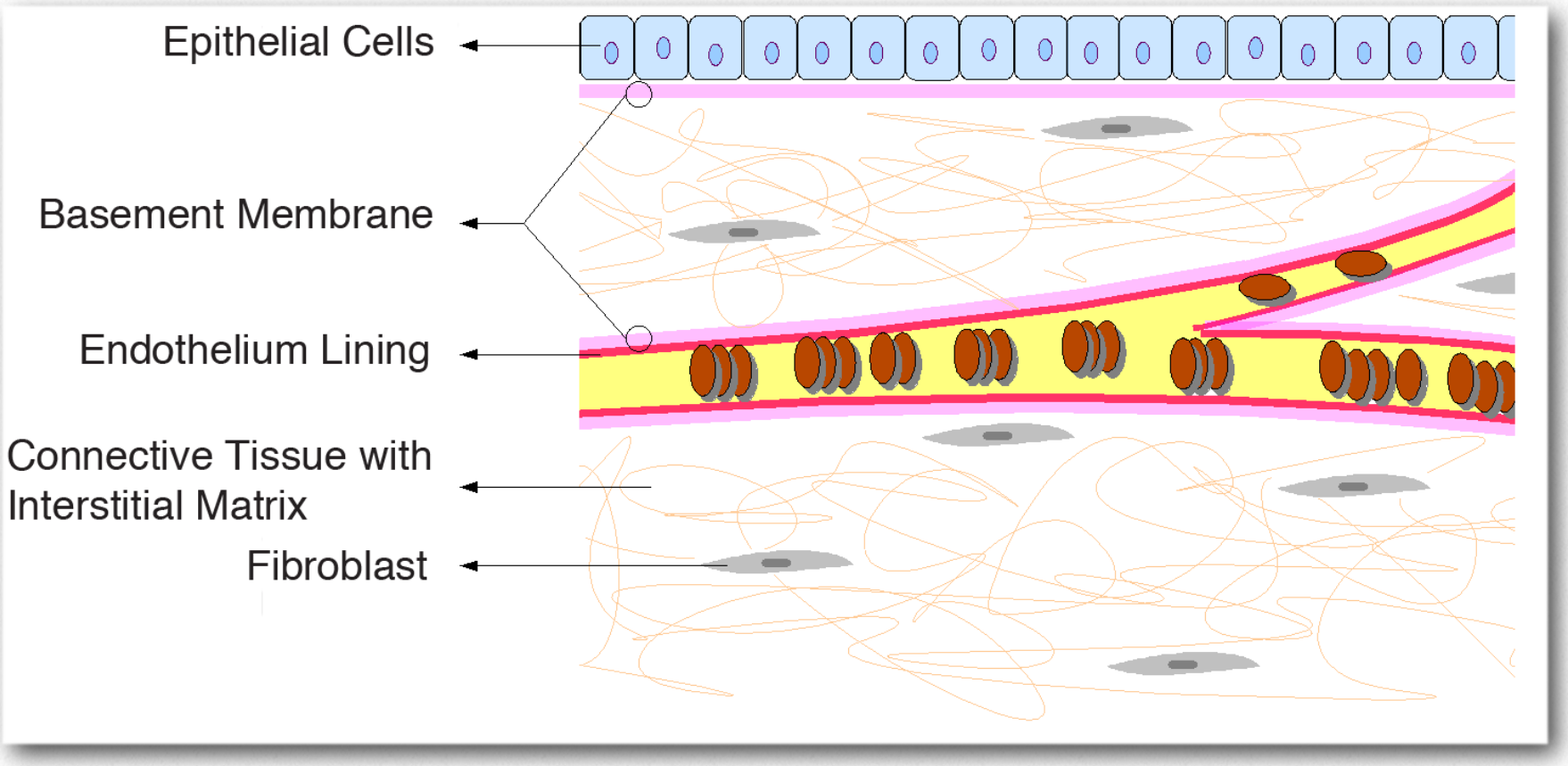


Figure 2.68 - Relationship of basement membrane to epithelium, endothelium, and connective tissue

tein *is* its primary function because the structure provides stability, organization, connections other important properties. It is with this in mind that we present the following proteins.

Basement membrane

The basement membrane is a layered extracellular matrix of tissue comprised of protein fibers (type IV collagen) and glycosaminoglycans that separates the epithelium from other tissues (Figure 2.68). More importantly, the basement membrane acts like a glue to hold tissues together. The skin, for example, is anchored to the rest of the body by the basement membrane. Basement membranes provide an interface of interaction between cells and the environment around them, thus facilitating signaling processes. They play roles in differentiation during embryogenesis and also in maintenance of function in adult organisms.

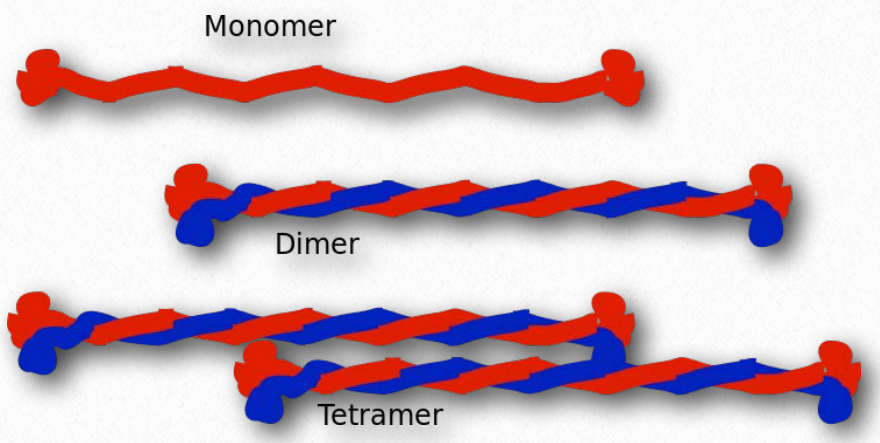


Figure 2.69 - Assembly of intermediate filaments

Actin

Actin is the most abundant globular protein found in most types of eukaryotic cells, comprising as much as 20% of the weight of muscle cells. Similar proteins have been identified in bacteria (MreB) and archaeons (Ta0583). Actin is a monomeric subunit able to polymerize readily into two different types of filaments. Microfilaments are major component of the cytoskeleton and are acted on by myosin in the contraction of muscle cells (See HERE). Actin will be discussed in more detail in the next section HERE.

Intermediate Filaments

Intermediate filaments are a part of the cytoskeleton in many animal cells and are comprised of over 70 different proteins. They are called intermediate because their size (average diameter = 10 nm) is between that of the microfilaments (7 nm) and the microtubules (25 nm).

The intermediate filament components include fibrous proteins, such as the keratins and the lamins, which are nuclear, as well as cytoplasmic forms. Intermediate filaments give flexibility to cells because of their own physical properties. They can, for example, be stretched to several times of their original length.

Six types

There are six different types of intermediate filaments. Type I and II are acidic or basic

and attract each other to make larger filaments. They include epithelial keratins and trichocytic keratins (hair components). Type III proteins include four structural proteins - desmin, GFAP (glial fibrillary acidic protein), peripherin, and vimentin. Type IV also is a grouping of three proteins and one multiprotein structure (neurofilaments). The three proteins are α-internexin, synemin, and syncoilin. Type V intermediate filaments encompass the lamins, which give structure to the nucleus. Phosphorylation of lamins leads to their disassembly and this is important in the process of mitosis. The Type VI category includes only a single protein known as nestin.

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Vimentin

Vimentin (Figure 2.70) is the most widely distributed protein of the intermediate filaments. It is expressed in fibroblasts, leukocytes, and blood vessel endothelial cells. The protein has a significant role maintaining the position of organelles in the cytoplasm, with attachments to the nucleus, mitochondria, and endoplasmic reticulum (Figure 2.70).

Vimentin provides elasticity to cells and resilience that does not arise from the microtubules or microfilaments. Wounded mice that lack the vimentin gene survive, but take longer to heal

Tubulin

A third type of filament found in cells is that of the microbutules. Comprised of a polymer of two units of a globular protein called tubulin, microtubules provide "rails" for motor proteins to move organelles and other "cargo" from one part of a cell to another. Microtubules and tubulin are discussed in more detail HERE.

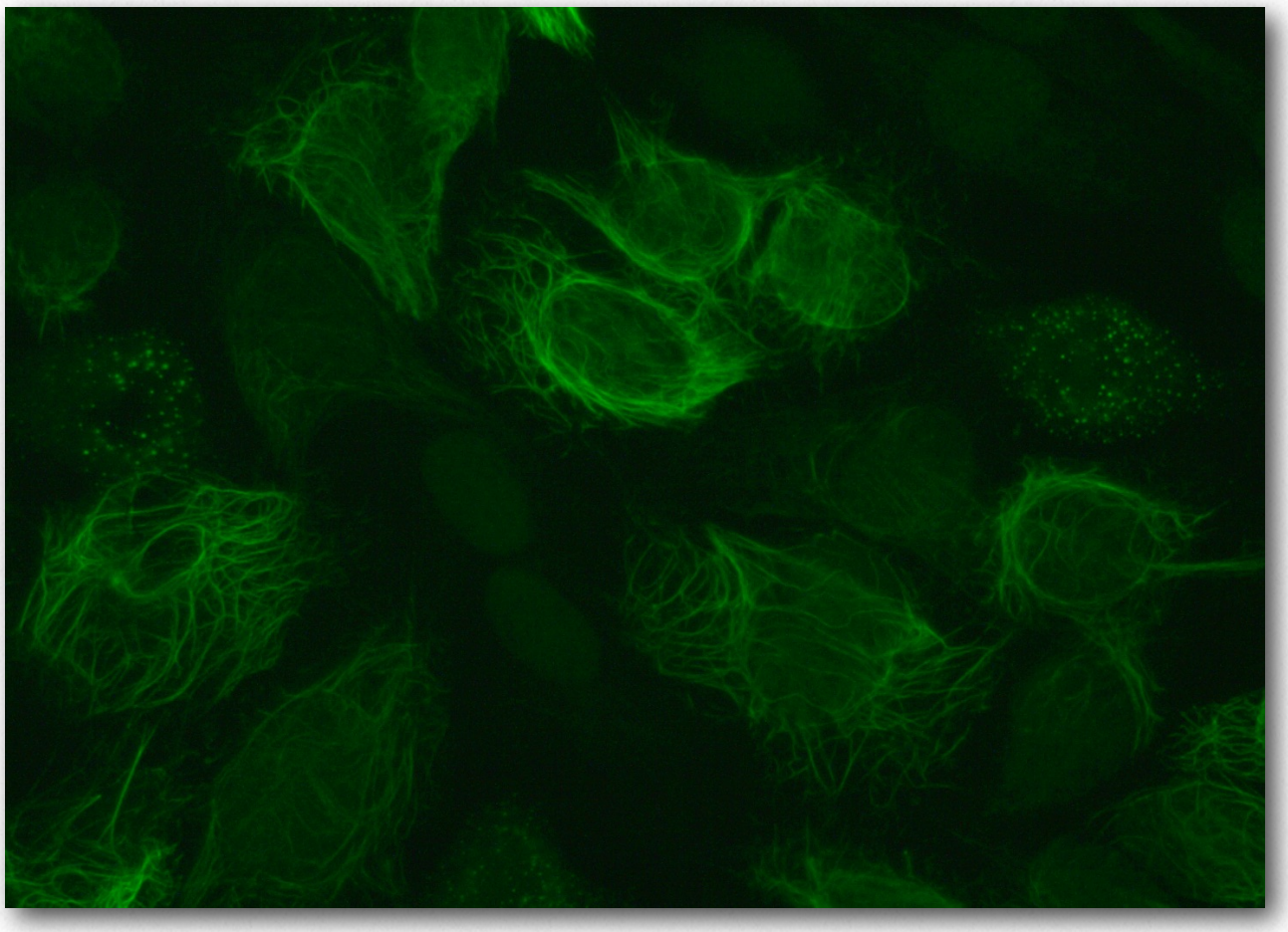

Figure 2.70 - Vimentin in cells

Wikipedia

wounds than wild type mice. Vimentin also controls the movement of cholesterol from lysosomes to the site of esterification. The result is a reduction in the amount of cholesterol stored inside of cells and has implications for adrenal cells, which must have esters of cholesterol.

Mucin

Mucins are a group of proteins found in animal epithelial tissue that have many glycosyl residues on them and typically are of high molecular weight (1 to 10 million Da). They are gel-like in their character and are often used for lubrication. Mucus is comprised of mucins.

In addition to lubrication, mucins also help to control mineralization, such as bone formation in vertebrate organisms and calcification in echinoderms. They also play roles in the immune system by helping to bind pathogens. Mucins are commonly secreted onto mucosal surfaces (nostrils, eyes, mouth, ears, stomach, genitals, anus) or into fluids, such as saliva. Because of their extensive mucosylation, mucins hold a considerable amount of water (giving them the "slimy" feel) and are resistant to proteolysis.

Vinculin

Vinculin (Figure 2.72) is a membrane cytoskeletal protein found in the focal adhesion structures of mammalian cells. It is found at cell-cell and cell-matrix junctions and interacts with integrins, talin, paxillins and F-actin. Vinculin is thought to assist (along with other proteins) in anchoring actin microfilaments to the membrane (Figure 2.71). Binding of vinculin to actin and to talin is regulating by polyphosphoinositides and can be inhibited by acidic phospholipids.

Syndecans

Syndecans are transmembrane proteins that make a single pass with a long amino acid chain (24-25 residues) through plasma membranes and facilitate G protein-coupled receptors' interaction with

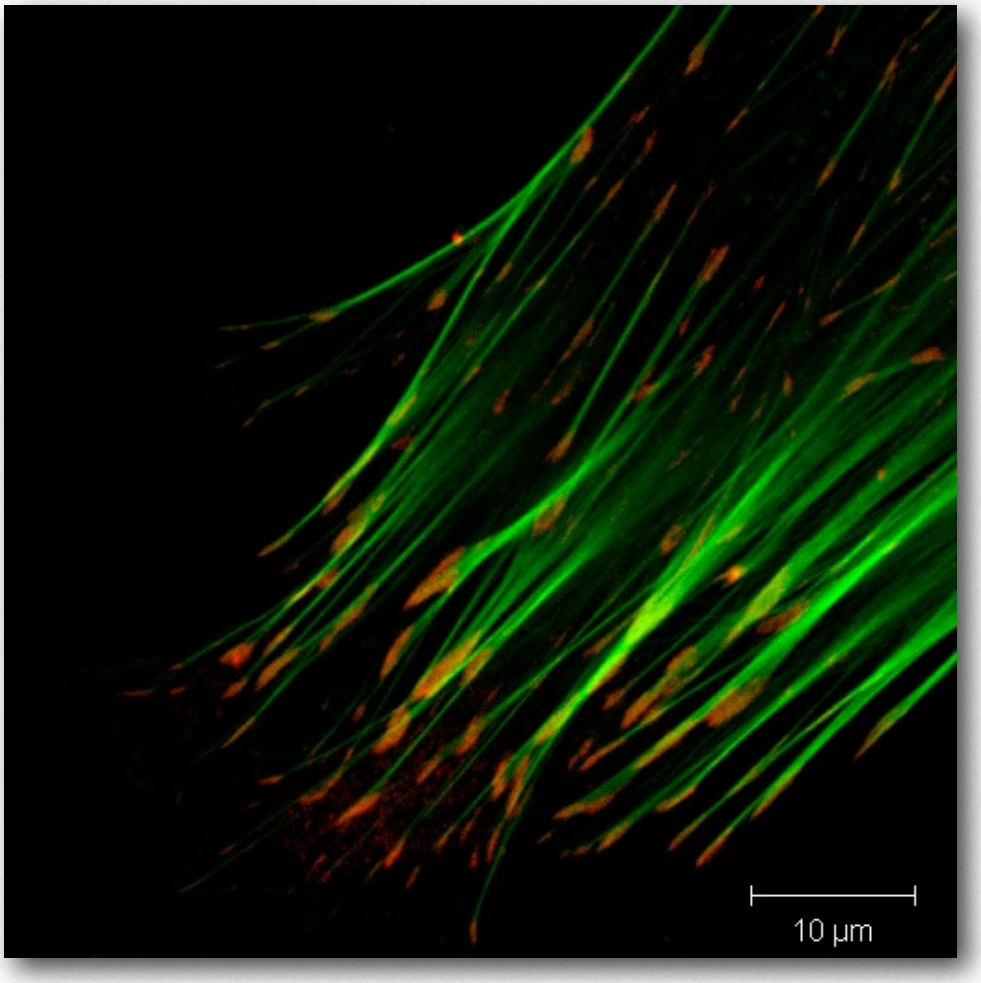

Figure 2.71 - Actin filaments (green) attached to vinculin in focal adhesion (red)

Wikipedia

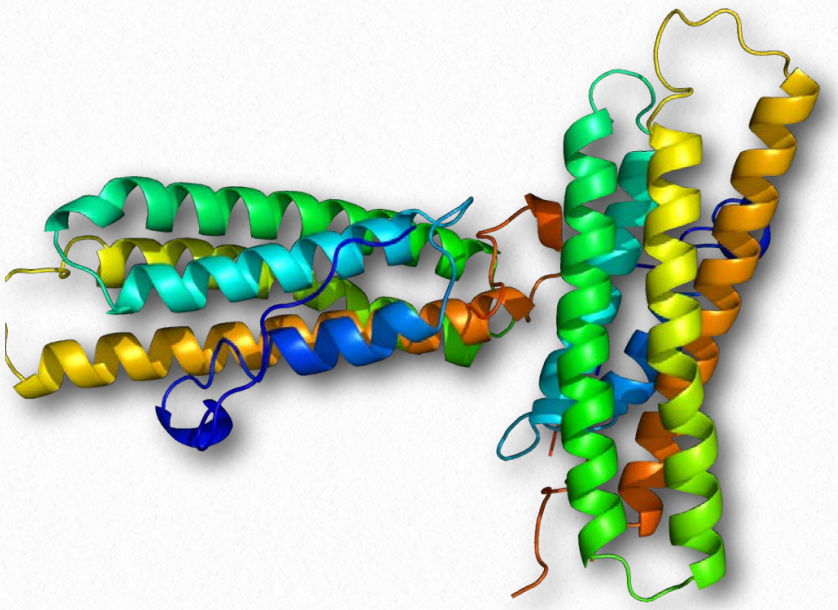

Figure 2.72 - Vinculin

ligands, such as growth factors, fibronectin, collagens (I, III, and IV) and antithrombin-1. Syndecans typically have 3-5 heparan sulfate and chondroitin sulfate chains attached to them.

Heparan sulfate can be cleaved at the site of a wound and stimulate action of fibroblast growth factor in the healing process. The role of syndecans in cell-cell adhesion is shown in mutant cells lacking syndecan I that do not adhere well to each other. Syndecan 4 is also known to adhere to integrin. Syndecans can also inhibit the spread of tumors by the ability of the syndecan 1 ectodomain to suppress growth of tumor cells without affecting normal epithelial cells.

Defensin

Defensins (Figure 2.73) are a group of small cationic proteins (rich in cysteine residues) that serve as host defense peptides in vertebrate and invertebrate organisms. They protect against infection by various bacteria, fungi, and viruses. Defensins contain between 18 and 45 amino acids with (typically) about 6-8 cysteine residues. In the immune system, defensins help to kill bacteria engulfed by phagocytosis by epithelial cells and neutrophils. They kill

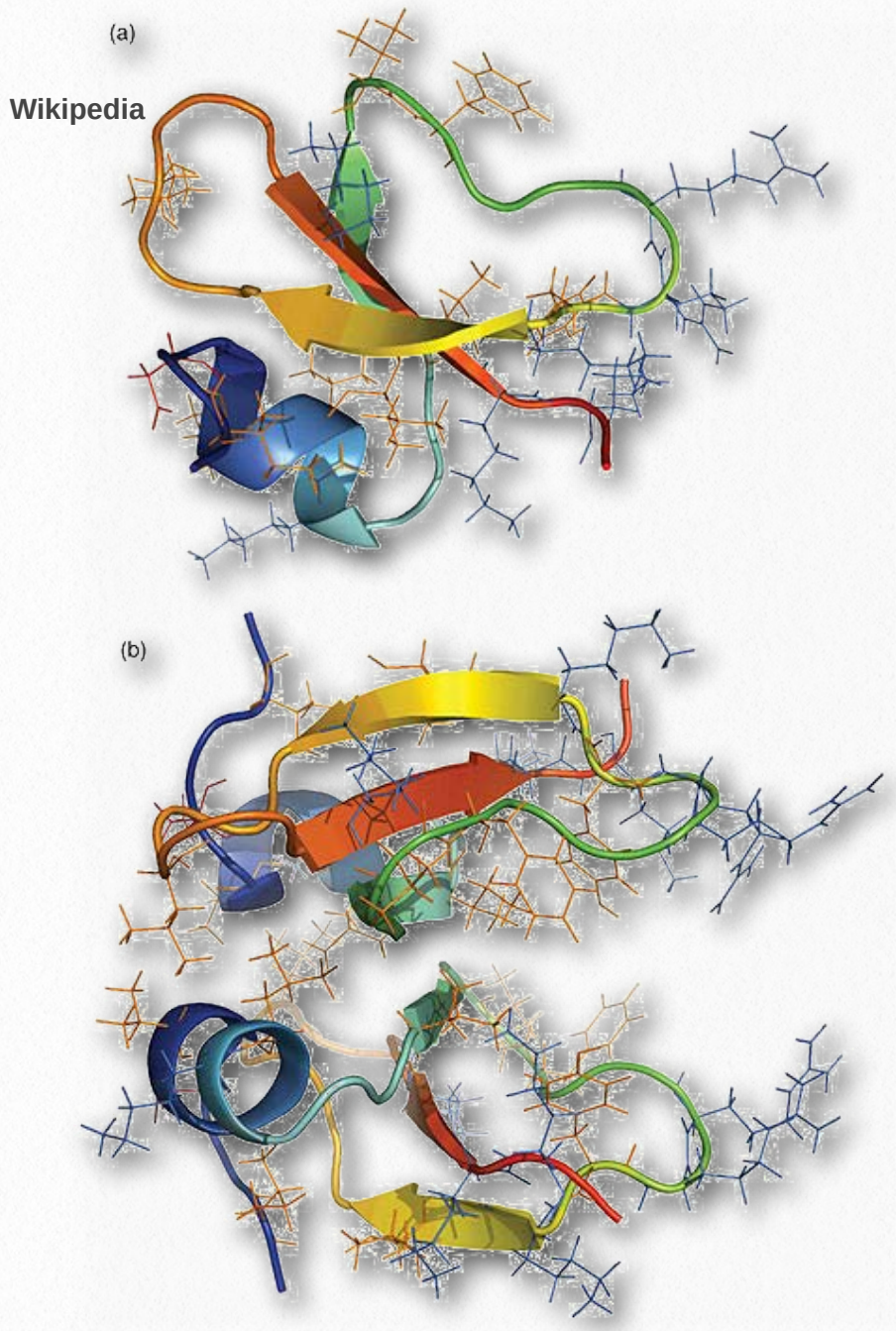

Figure 2.73 - Defensin monomer (top) and dimer (bottom) - Cationic residues in blue, hydrophobic residues in orange, and anionic residues in red

Wikipedia

bacteria by acting like ionophores - binding the membrane and opening pore-like structures to release ions and nutrients from the cells.

Focal adhesions

In the cell, focal adhesions are structures containing multiple proteins that mechanically link cytoskeletal structures (actin bundles) with the extracellular matrix. They are dynamic, with proteins bringing and leaving with signals regarding the cell cycle, cell motility, and more almost constantly. Focal adhesions serve as anchors and as a signaling hub at cellular locations where integrins bind molecules and where membrane clustering events occur. Over 100 different proteins are found in focal adhesions.

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Focal adhesions communicate important messages to cells, acting as sensors to update information about the status of the extracellular matrix, which, in turn, adjusts/affects their actions. In sedentary cells, they are stabler than in cells in motion because when cells move, focal adhesion contacts are established at the "front" and removed at the rear as motion progresses. This can be very important in white blood cells' ability to find tissue damage.

Ankyrin

Ankyrins (Figure 2.74) are a family of membrane adaptor proteins serving as "anchors" to interconnect integral membrane proteins to the spectrin-actin membrane cytoskeleton. Ankyrins are anchored to the plasma membrane by covalently linked palmitoyl-CoA. They bind to the β subunit of spectrin and at least a dozen groups of integral membrane proteins. The ankyrin proteins contain four functional domains: an N-terminal region with 24 tandem ankyrin repeats, a central spectrin-binding do-

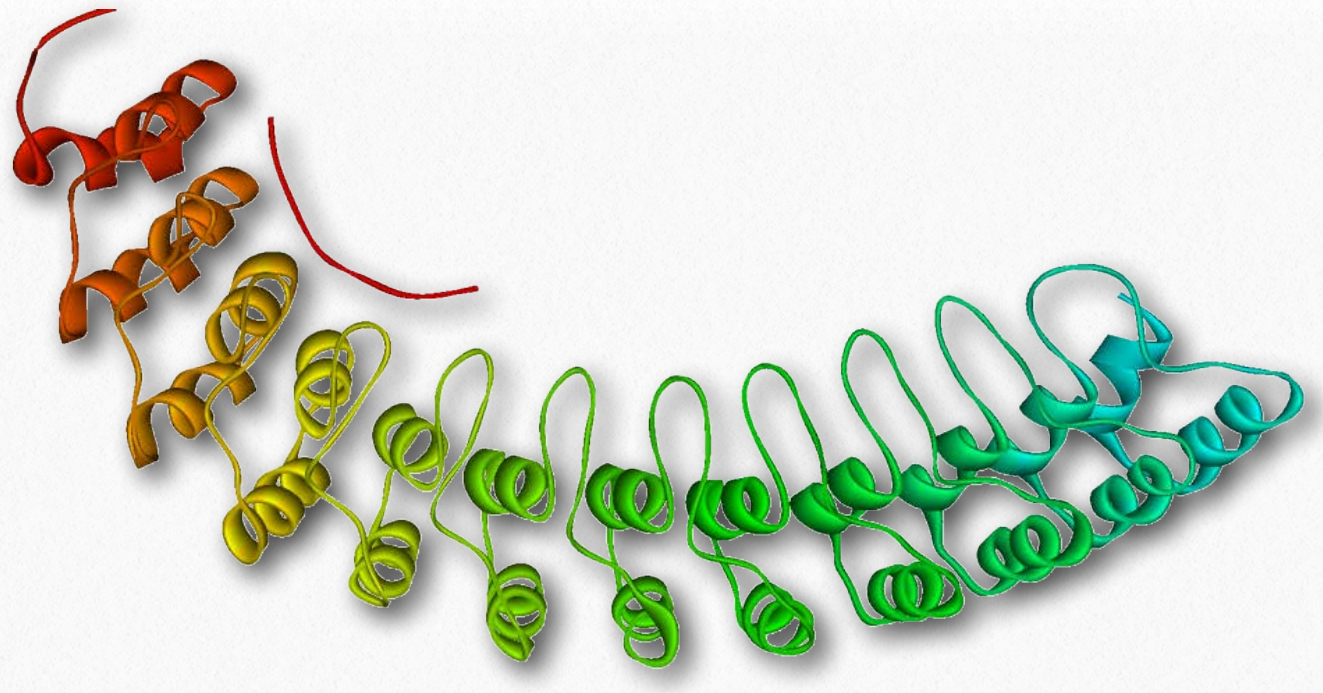

Figure 2.74 - Ankyrin's membrane-binding domain

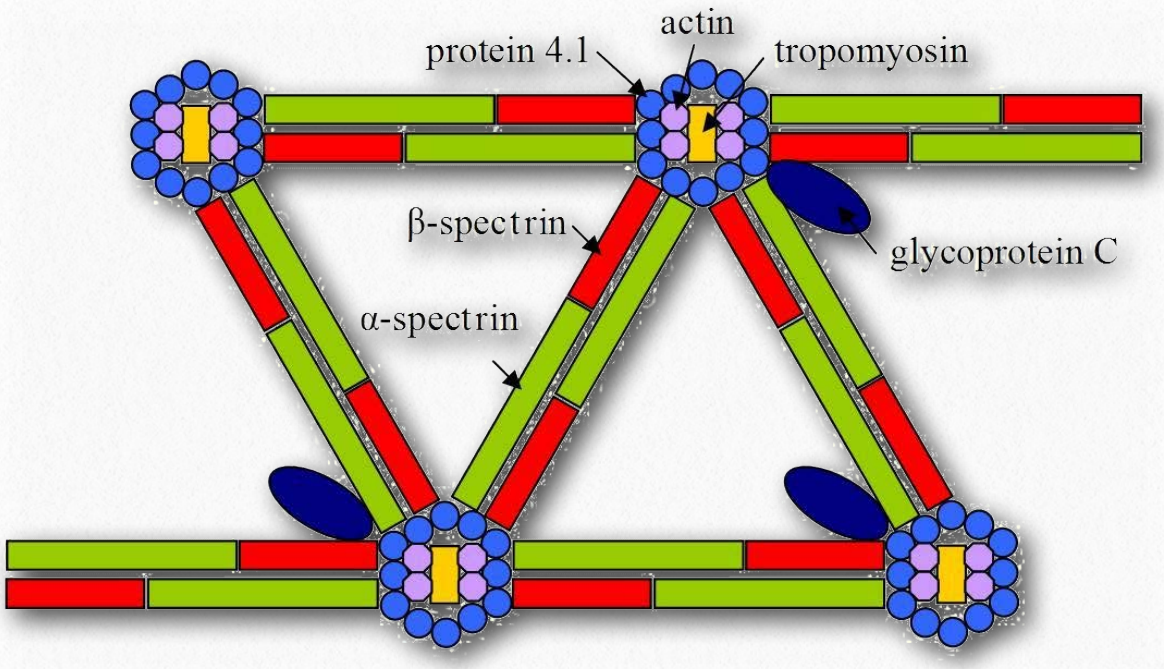

Figure 2.75 - Spectrin and other proteins in the cytoskeleton

Wikipedia

main, a “death domain” interacting with apoptotic proteins, and a C-terminal regulatory domain that is highly varied significantly among different ankyrins.

Spectrin

Spectrin (Figures 2.75 & 2.76) is a protein of the cellular cytoskeleton that plays an important role in maintaining its structure and the integrity of the plasma membrane. In animals, spectrin gives red blood cells their shape. Spectrin is located inside the inner layer of the eukaryotic plasma membrane where it forms a network of pentagonal or hexagonal arrangements.

Spectrin fibers collect together at junctional complexes of actin and is also attached to ankyrin for stability, as well as numerous integral membrane proteins, such as glycophorin.

Integrins

In multicellular organisms, cells need connections, both to each other and to the extracellular matrix. Facilitating these attachments at the cellular

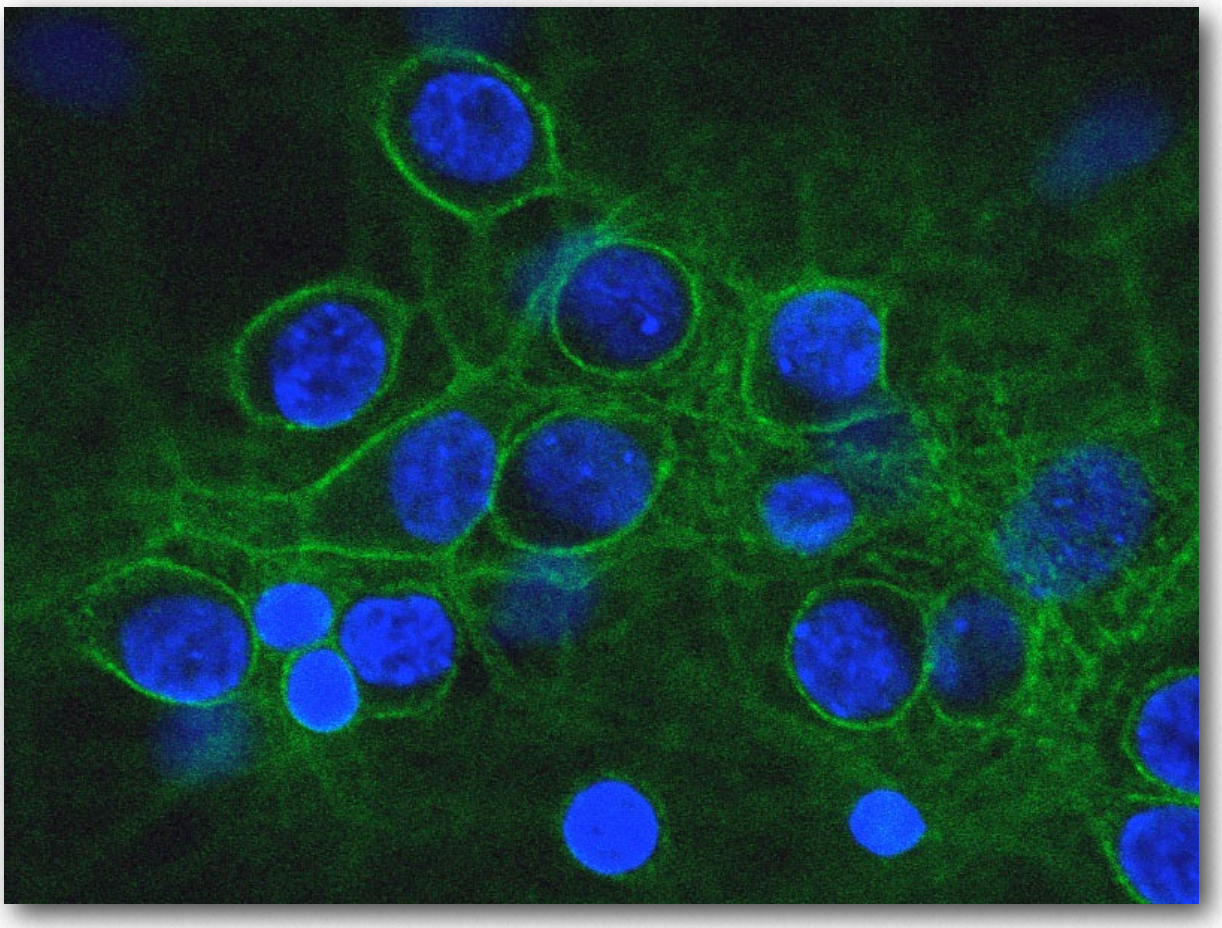

Figure 2.76 - Spectrin (green) and nuclei (Blue)

Wikipedia

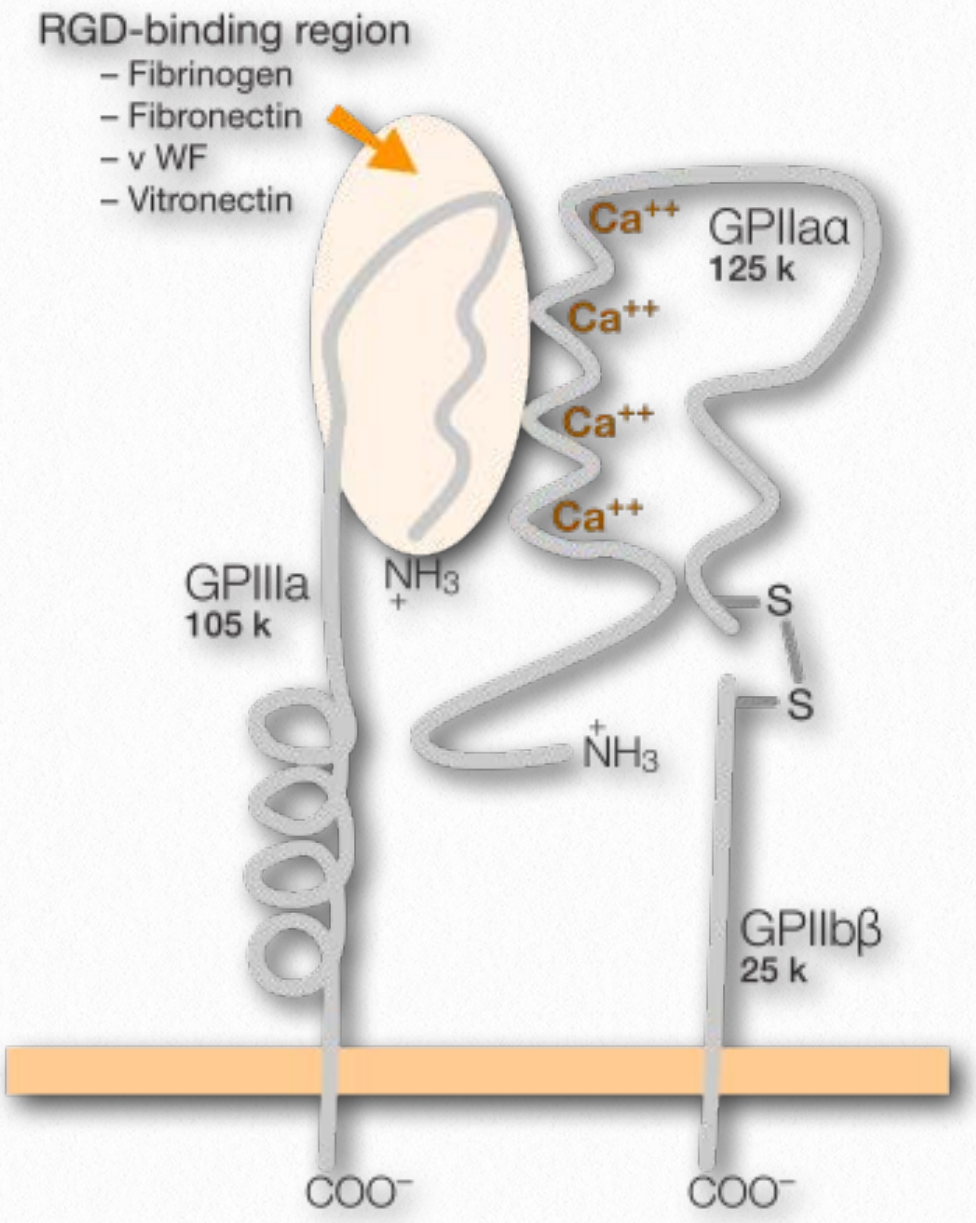

Figure 2.77 - Integrin and its binding site (on top left)

Wikipedia

end are transmembrane proteins known as integrins (Figure 2.77). Integrins are found in all metazoan cells. Ligands for the integrins include collagen, fibronectin, laminin, and vitronectin. Integrins function not only in attachment, but also in communication, cell migration, virus linkages (adenovirus, for example), and blood clotting. Integrins are able to sense chemical and mechanical signals about the extracellular matrix and move that information to intracellular domains as part of the process of signal transduction. Inside the cells, responses to the signals affect cell shape, regulation of the cell cycle, movement, or changes in other cell receptors in the membrane. The process is dynamic and allows for rapid responses as may be necessary, for example in the process of blood clotting, where the integrin known as GPIbIIIa (on the surface of blood platelets) attaches to fibrin in a clot as it develops.

Integrins work along with other receptors, including immunoglobulins, other cell adhesion molecules, cadherins, selectins, and syndecans. In mammals the proteins have a large number of subunits - 18 α- and 8 β-chains. They are a bridge between its links outside the cell to the extracellular matrix (ECM) and its links inside the cell to the cytoskeleton. Integrins play central role in formation and stability of focal adhesions. These are large molecular complexes arising from clustering of integrin-ECM connections. In the process of cellular movement, integrins at the “front” of the cell (in the direction of the movement), make new attachments to substrate and release connections to

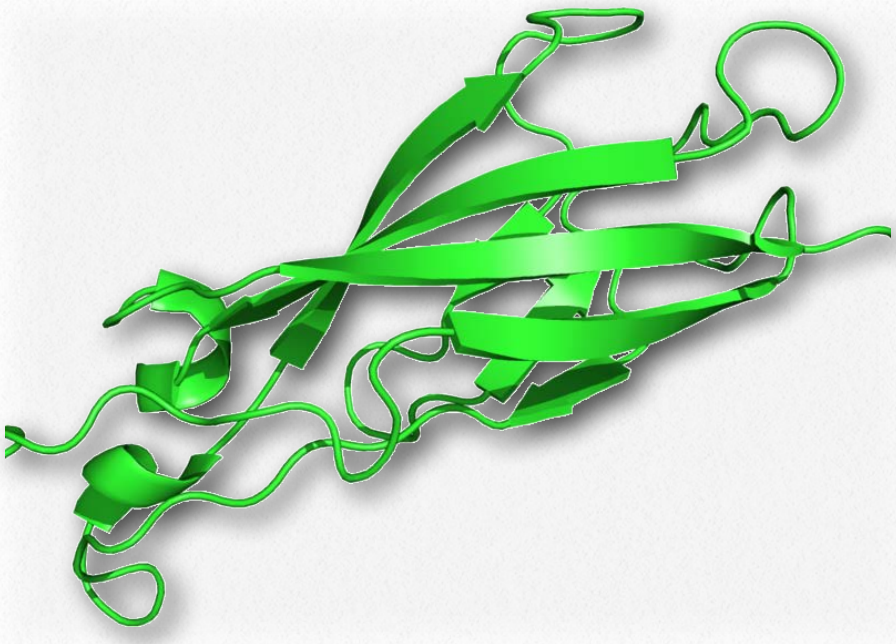

Figure 2.78 - Extracellular ectodomain of a cadherin

substrate in the back of the cell. These latter integrins are then endocytosed and reused.

Integrins also help to modulate signal transduction through tyrosine kinase receptors in the cell membrane by regulating movement of adapters to the plasma membrane. β1c integrin, for example, recruits the Shp2 phosphatase to the insulin growth factor receptor to cause it to become dephosphorylated, thus turning off the signal it communicates. Integrins can also help to recruit signaling molecules inside of the cell to activated tyrosine kinases to help them to communicate their signals.

Cadherins

Cadherins (Figure 2.78) constitute a type-1 class of transmembrane proteins playing important roles in cell adhesion. They require calcium ions to function, forming adherens junctions that hold tissues together (See Figure 2.69). Cells of a specific cadherin type will preferentially cluster with each other in preference to associating with cells containing a different cadherin type. Caderins are both receptors and places for ligands to attach. They assist in the proper positioning of cells in development, separation of different tissue layers, and cell migration.

Selectins

Selectins (Figure 2.79) are cell adhesion glycoproteins that bind to sugar molecules. As such, they are a type of lectin - proteins that bind sugar polymers (see HERE also). All selectins have an N-terminal calcium-dependent lectin domain, a single transmembrane domain, and an intracellular cytoplasmic tail.

There are three different types of selectins, 1) E-selectin (endothelial); 2) L (lymphocytic; and 3) P (platelets and endothelial cells. Selectins function in lymphocyte homing (adhesion of blood lymphocytes to cells in lymphoid organs), in inflammation processes, and in cancer metastasis. Near the site of inflammation, P-selectin on the surface of blood capillary cells interacts with glycoproteins on leukocyte cell surfaces. This has the effect of slowing the movement of the leukocyte. At the target site of inflammation, E- selectin on the endothelial cells of the blood vessel and L-selectin on the surface of the leukocyte bind to their respective carbohydrates, stopping the leukocyte movement. The leuko-

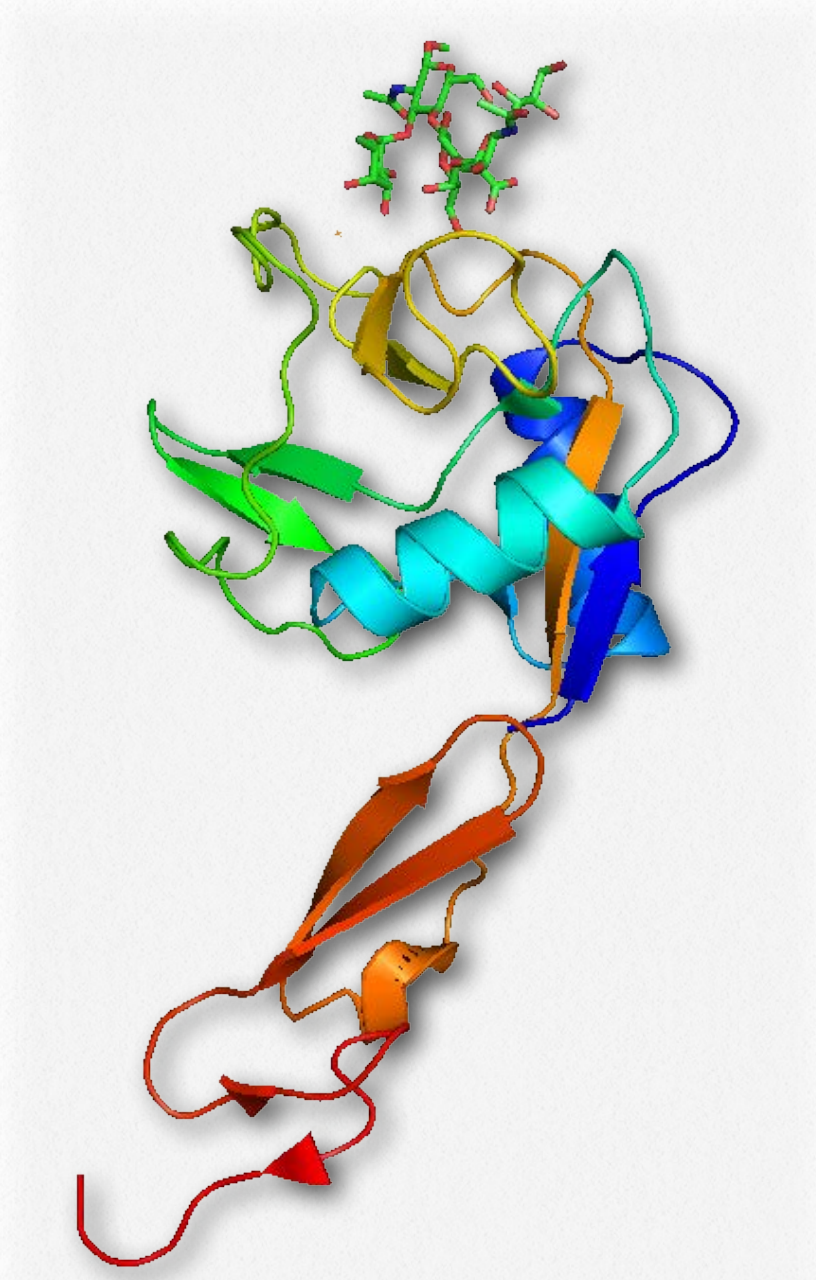

Figure 2.79 - Selectin bound to a sugar
Wikipedia

cyte then crosses the wall of the capillary and begins the immune response. Selectins are involved in the inflammatory processes of asthma, psoriasis, multiple scleroris, and rheumatoid arthritis.

Laminins

Laminins are extracellular matrix glycoproteins that a major components of the basal lamina and affect cell differentiation, migration, and adhesion. They are secreted into the extracellular matrix where they are incorporated and are essential for tissue maintenance and survival. When laminins are defective, muscles may not form properly and give rise to muscular dystrophy.

Laminins are associated with fibronectin, entactin, and perlecan proteins in type IV collagen networks and bind to integrin receptors in the plasma membrane. As a consequence, laminins contribute to cellular attachment, differentiation, shape, and movement. The proteins are trimeric in structure, having one α-chain, a β-chain, and a γ-chain. Fifteen combinations of different chains are known.

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Vitronectin

Vitronectin is a glycoprotein (75kDa) found in blood serum (platelets), the extracellular matrix, and in bone. It promotes the process of cell adhesion and spreading and binds to several protease inhibitors (serpins). It is secreted from cells and is believed to play roles in blood clotting and the malignancy of tumors. One domain of vitronectin binds to plasminogen activator inhibitor and acts to stabilize it. Another domain of the protein binds to cellular integrin proteins, such as the vitronectin receptor that anchors cells to the extracellular matrix.

Catenins

Catenins are a family of proteins interacting with cadherin proteins in cell adhesion (Figure 2.69). Four main types of catenins are known, α-, β-, γ-, and δ-catenin. Catenins play roles in cellular organization before development occurs and help to regulate cellular growth. α-catenin and β-catenin are found at adherens junctions with cadherin and help cells to maintain epithelial layers. Cadherins are connected to actin filaments of the cytoskeleton and catenins play the critical role. Catenins are important for the process whereby cellular division is inhibited when cells come in contact with each other (contact inhibition). When catenin genes are mutated, cadherin cell adhesions can disappear and tumorigenesis may result. Catenins have been found to be associated with colorectal and numerous other forms of cancer.

Glycophorins

All of the membrane proteins described so far are notable for the connections they make to other proteins and cellular structures. Some membrane proteins, though, are designed to reduce cellular connections to proteins of other cells. This is particularly important for blood cells where "stickiness" is undesirable except where clotting is concerned.

Glycophorins (Figure 2.80) are membrane-spanning sialoglycoproteins of red blood cells. They are heavily glycosylated (60%).and rich in sialic acid, giving the cells a very hydrophilic (and negatively charged) coat, which enables them to circulate in the bloodstream without adhering to other cells or the vessel walls.

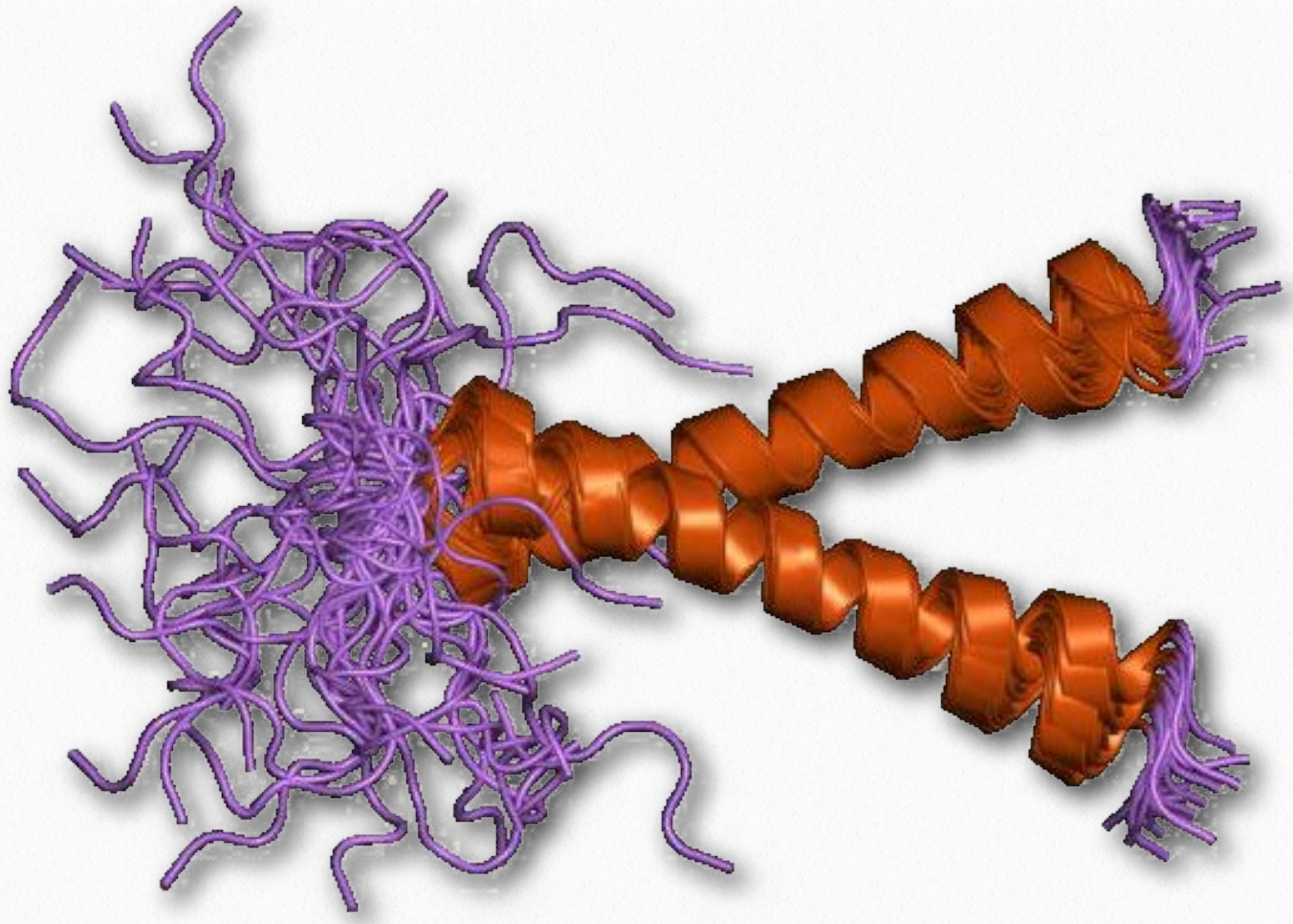


Figure 2.80 - Glycophorin a

Five glycophorins have been identified - four (A,B,C,and D) from isolated membranes and a fifth form (E) from coding in the human genome. The proteins are abundant, forming about 2% of the total membrane proteins in these cells. Glycophorins have important roles in regulating RBC membrane mechanical properties and shape. Because some glycophorins can be expressed in various non-erythroid tissues (particularly Glycophorin C), the importance of their interactions with the membrane skeleton may have a considerable biological significance.

Cooperativity and allosterism - quaternary structure

Quaternary structure, of course describes the interactions of individual subunits of a multi-subunit protein (Figure 2.81). The result of these interactions can give rise to important biological phenomena, such as cooperative binding of substrates to a protein and allosteric effects on the action of an enzyme.

Allosteric effects can occur by a series of mechanisms, but a common feature is that binding of an effector to an enzyme subunit causes (or locks) the enzyme in either a T-state (less activity) or an R-state (more activity). Effectors can be enzyme substrates (homotropic effectors) or non-substrates (heterotropic effectors). Allosterism will be covered in more depth in the Catalysis chapter HERE.

We begin our consideration of quaternary structure with a discussion of cooperativity, how it arises in the multi-subunit protein hemoglobin and how its properties contrast with those of the related, single subunit protein myoglobin.

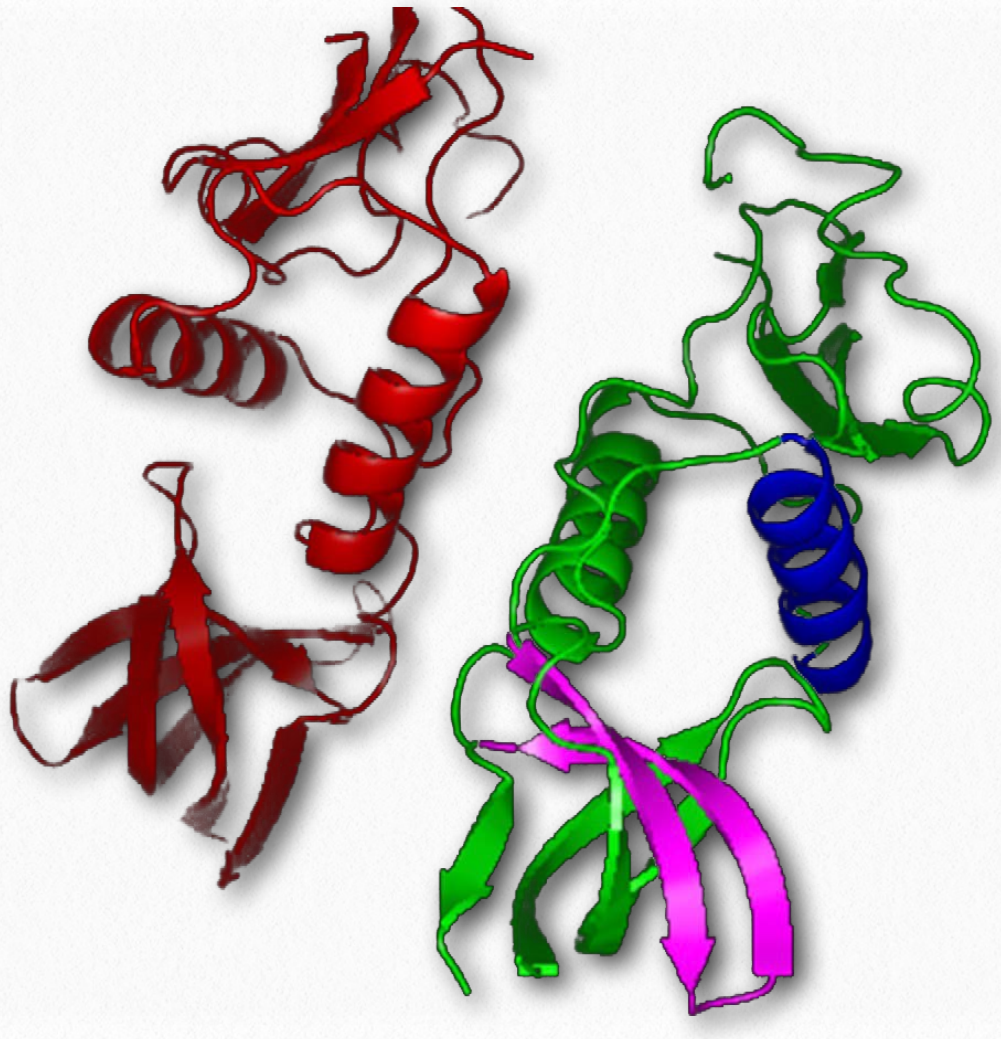


Figure 2.81 - Two polypeptide units of a protein interact in quaternary structure

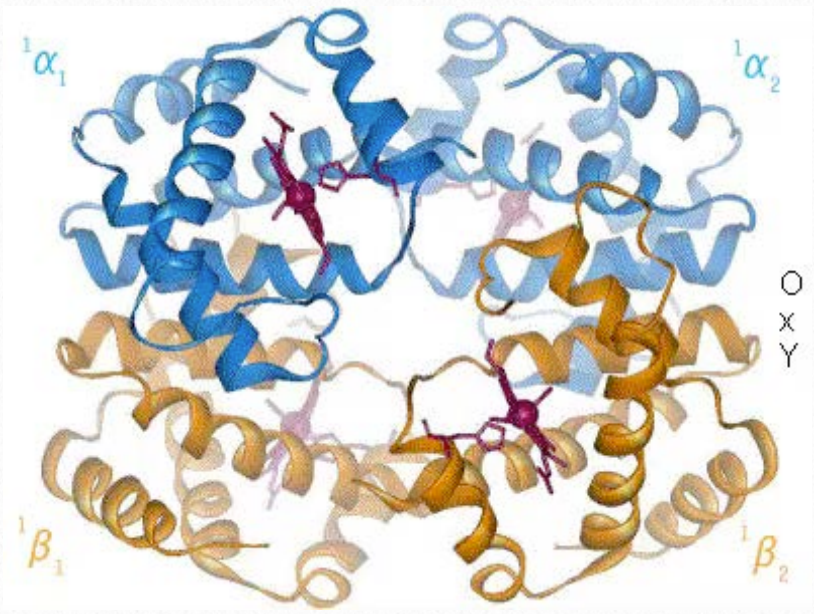
Wikipedia

Cooperativity

Cooperativity is defined as the phenomenon where binding of one ligand molecule by a protein favors the binding of additional molecules of the same type. Hemoglobin, for example, exhibits cooperativity when the binding of an oxygen molecule by the iron of the heme group in one of the four subunits causes a slight conformation change in the subunit. This happens because the heme iron is attached to a histidine side chain and binding of oxygen 'lifts' the iron along with the histidine ring (also known as the imidazole ring).

Since each hemoglobin subunit interacts with and influences the other subunits, they too are induced to change shape slightly when the first subunit binds to oxygen (a transition described as going from the T-state to the R-state). These shape changes favor each of the remaining subunits binding oxygen, as well. This is very important in the lungs where oxygen is picked up by hemoglobin, because the binding of the first oxygen molecule facilitates the rapid uptake of more oxygen molecules. In the tissues, where the oxygen concentration is lower, the oxygen leaves hemoglobin and the proteins flips from the R-state back to the T-state.

My blood has a proclivity
For co-op-ER-a-TIV-it-y
It's 'cause when in the lung environs
Ox-y-GEN binds to the irons
And changes hemoglobin's fate
Out of a T to an R-State



Movie 2.3 - Hemoglobin's structural changes on binding oxygen

Wikipedia

CO_2 transport

Cooperativity is only one of many fascinating structural aspects of hemoglobin that help the body to receive oxygen where it is needed and pick it up where it is abundant. Hemoglobin also assists in the transport of the product of cellular respiration (carbon dioxide) from the tissues producing it to the lungs where it is exhaled. Like the binding of oxygen to hemoglobin, binding of other molecules to hemoglobin affects its affinity for oxygen. The effect is particularly pronounced when comparing the oxygen binding characteristics of hemoglobin's four subunits with the oxygen binding of the related protein myoglobin's single subunit (Figure 2.83).

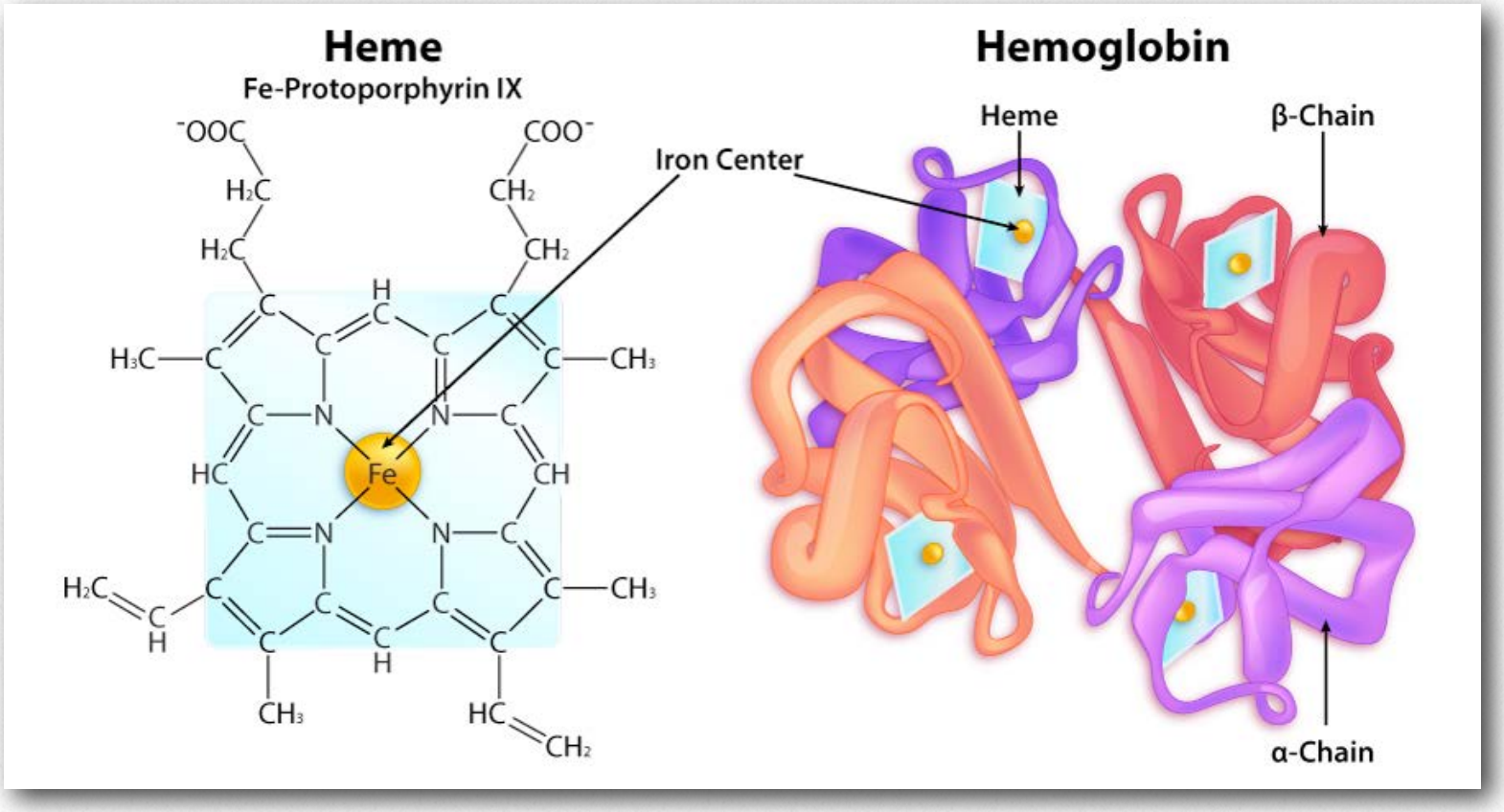


Figure 2.82 - Heme structure within hemoglobin

Image by Aleia Kim

Different oxygen binding

Like hemoglobin, myoglobin contains an iron in a heme group that binds to oxygen. The structure of the globin protein in myoglobin is very similar to the structure of the globins in hemoglobin and hemoglobin is thought to have evolved from myoglobin in evolutionary history. As seen in Figure 2.83, the binding curve of hemoglobin for oxygen is S-shaped (sigmoidal), whereas the binding curve for myoglobin is hyperbolic. What this tells us is that hemoglobin's affinity for oxygen is low at a low concentration oxygen, but

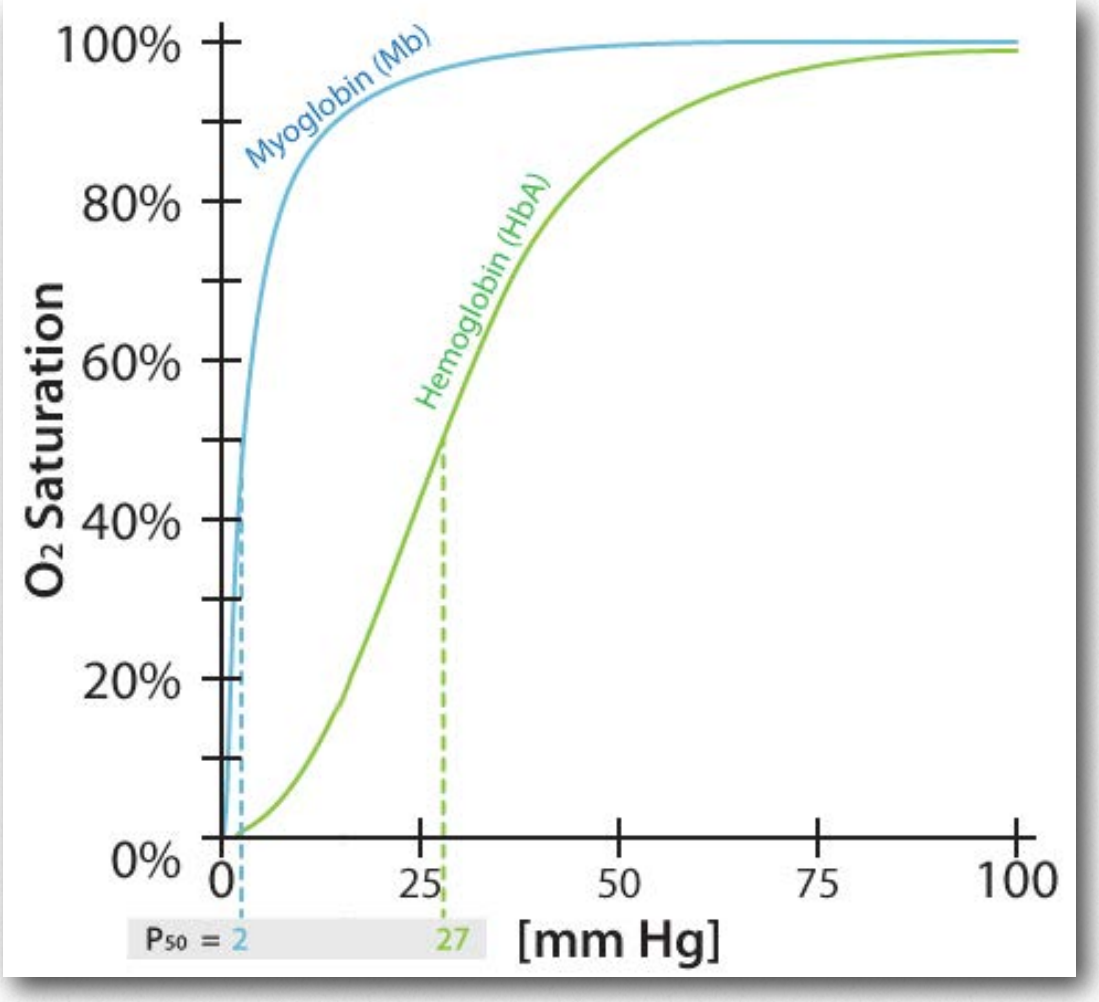


Figure 2.83 - Oxygen binding affinities for myoglobin and hemoglobin

Figure by Aleia Kim

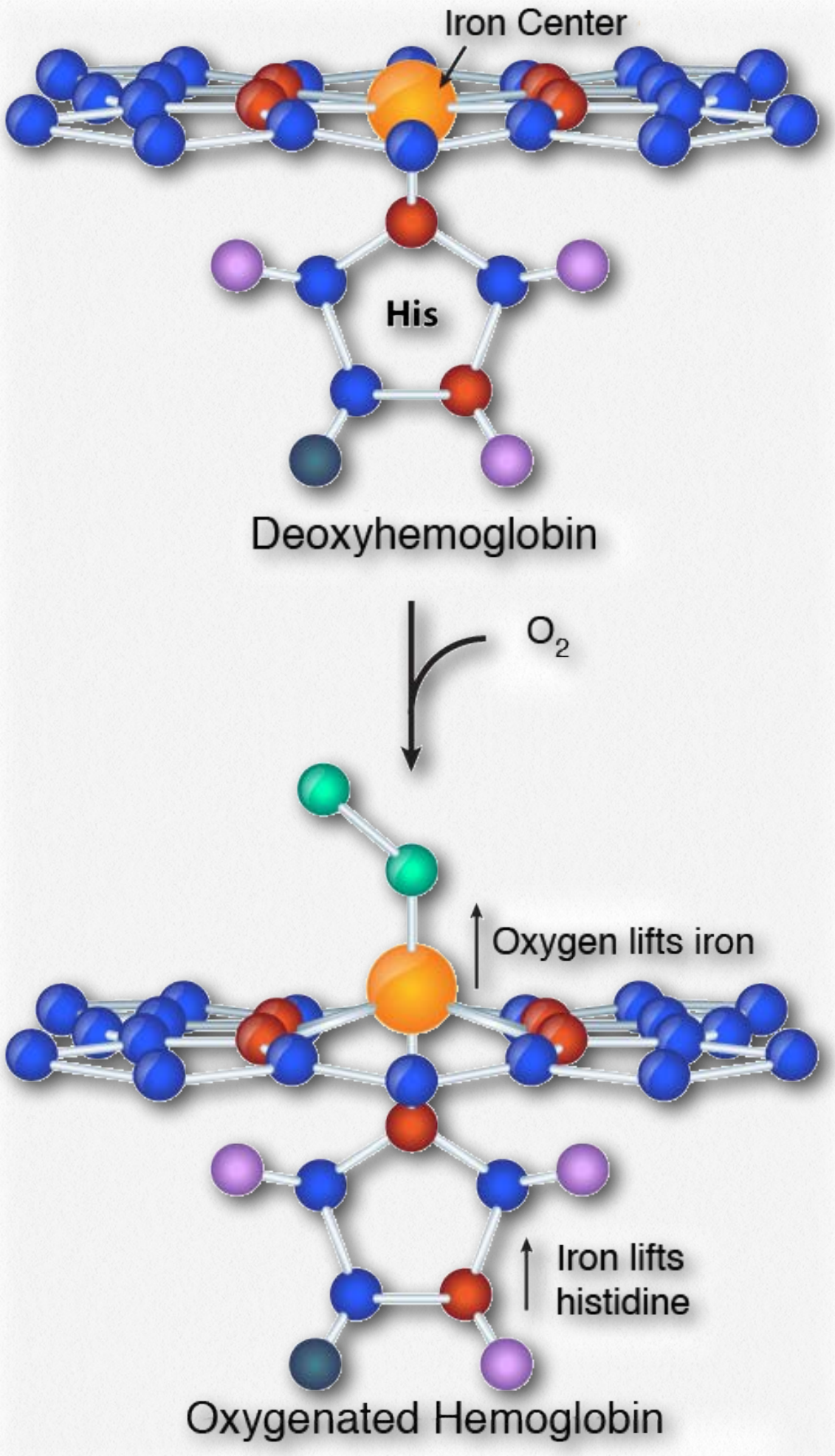


Figure 2.84 - Binding of oxygen at the heme center of hemoglobin

Image by Aleia Kim

increases as the oxygen concentration increases. Since myoglobin very quickly saturates with oxygen, even under low oxygen concentrations, it says that its affinity for oxygen is high and doesn't change.

Because myoglobin has only a single subunit, binding of oxygen by that subunit can't affect any other subunits, since there are no other subunits to affect. Consequently,

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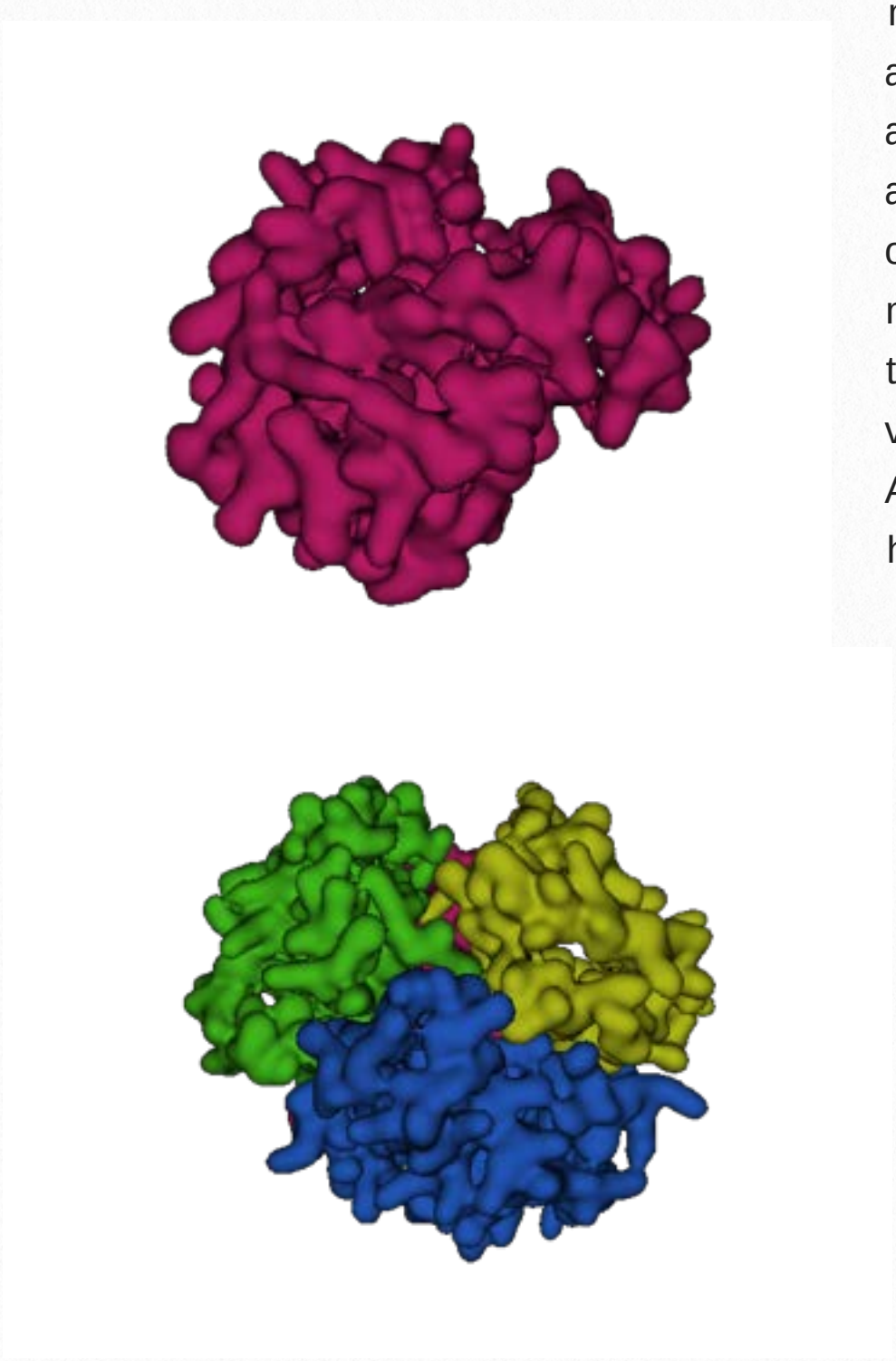
cooperativity requires more than one subunit. Therefore, hemoglobin can exhibit cooperativity, but myoglobin can't. It is worth noting that simply having multiple subunits does not mean cooperativity will exist. Hemoglobin is one protein that exhibits the characteristic, but many multisubunit proteins do not.

Storage vs. delivery

The lack of ability of



Interactive 2.2 - **Hemoglobin in the presence (top) and absence (bottom) of oxygen**

myoglobin to adjust its affinity for oxygen according to the oxygen concentration (low affinity at low oxygen concentration, such as in tissues and high affinity at high oxygen concentration, such as in the lungs) means it is better suited for storing oxygen than for delivering it according to the varying oxygen needs of and animal body. As we shall see, besides cooperativity, hemoglobin has other structural features that allow it to deliver oxygen precisely where it is needed most in the body.

Bohr effect

The Bohr Effect was first described over 100 years ago by Christian Bohr, father of the famous physicist, Niels Bohr. Shown graphically (Figures 2.86, 2.87, and 2.88), the observed effect is that hemoglobin's affinity for oxygen decreases as the pH decreases and as the concentration of carbon dioxide increases. Binding of the protons and carbon dioxide by amino

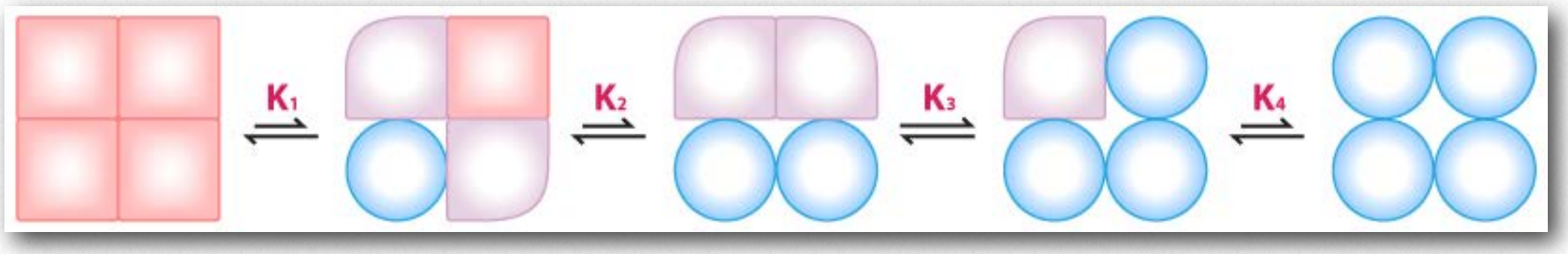


Figure 2.85 - Sequential model of binding. The sequential model is one way to explain hemoglobin's cooperativity. Squares represent no oxygen bound. Circles represent subunits bound with oxygen and rounded subunits correspond to units whose affinity for oxygen increases by interacting with a subunit that has bound oxygen.

Image by Aleia Kim

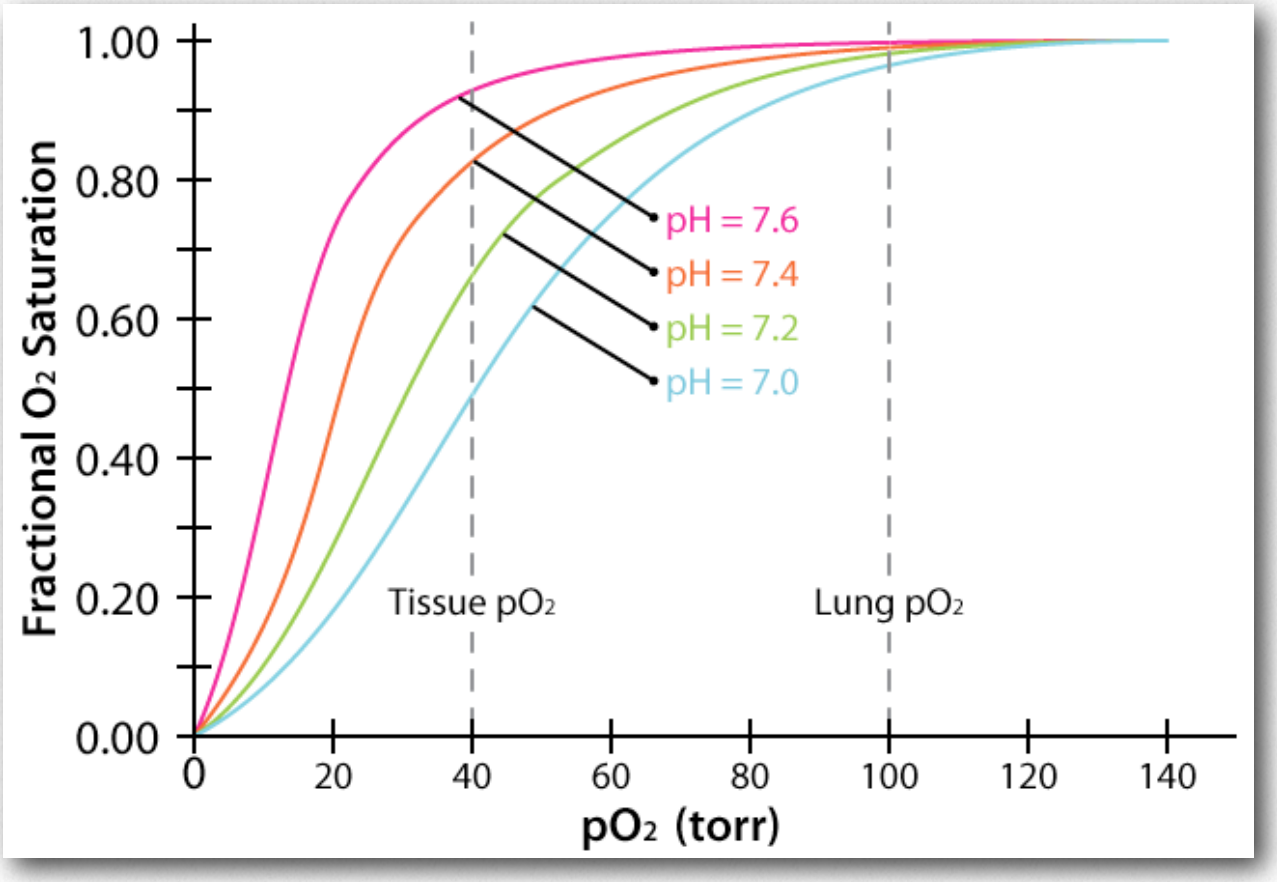


Figure 2.86 - The Bohr effect with respect to pH changes

Image by Aleia Kim

acid side chains in the globin proteins helps to facilitate structural changes in them. Most commonly, the amino acid affected by protons is histidine #146 of the β strands. When this happens, the ionized histidine can form an ionic bond with the side chain of aspartic acid #94, which has the effect of stabilizing the T-state (reduced oxygen binding state) and releasing oxygen. Other histidines and the amine of the amino terminal amino acids in the α-chains are also binding sites for protons.

2,3-BPG

Another molecule favoring the release of oxygen by hemoglobin is 2,3-bisphosphoglycerate (also called 2,3-BPG or just BPG - Figure 2.89). Like protons and carbon dioxide, 2,3-BPG is produced by actively respiring tissues, as a byproduct of glucose metabolism. The 2,3-BPG mole-

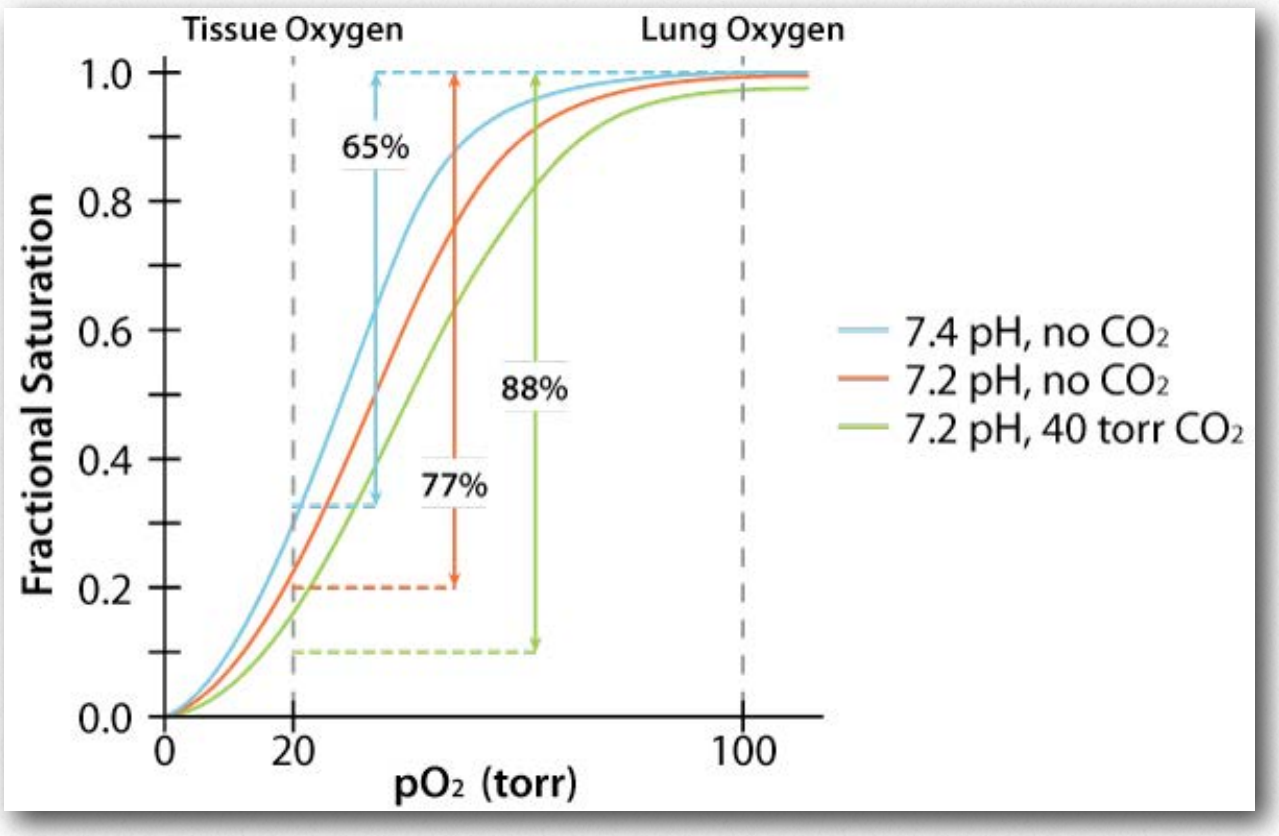


Figure 2.87 - Binding affinity of hemoglobin for oxygen under different conditions

Image by Aleia Kim

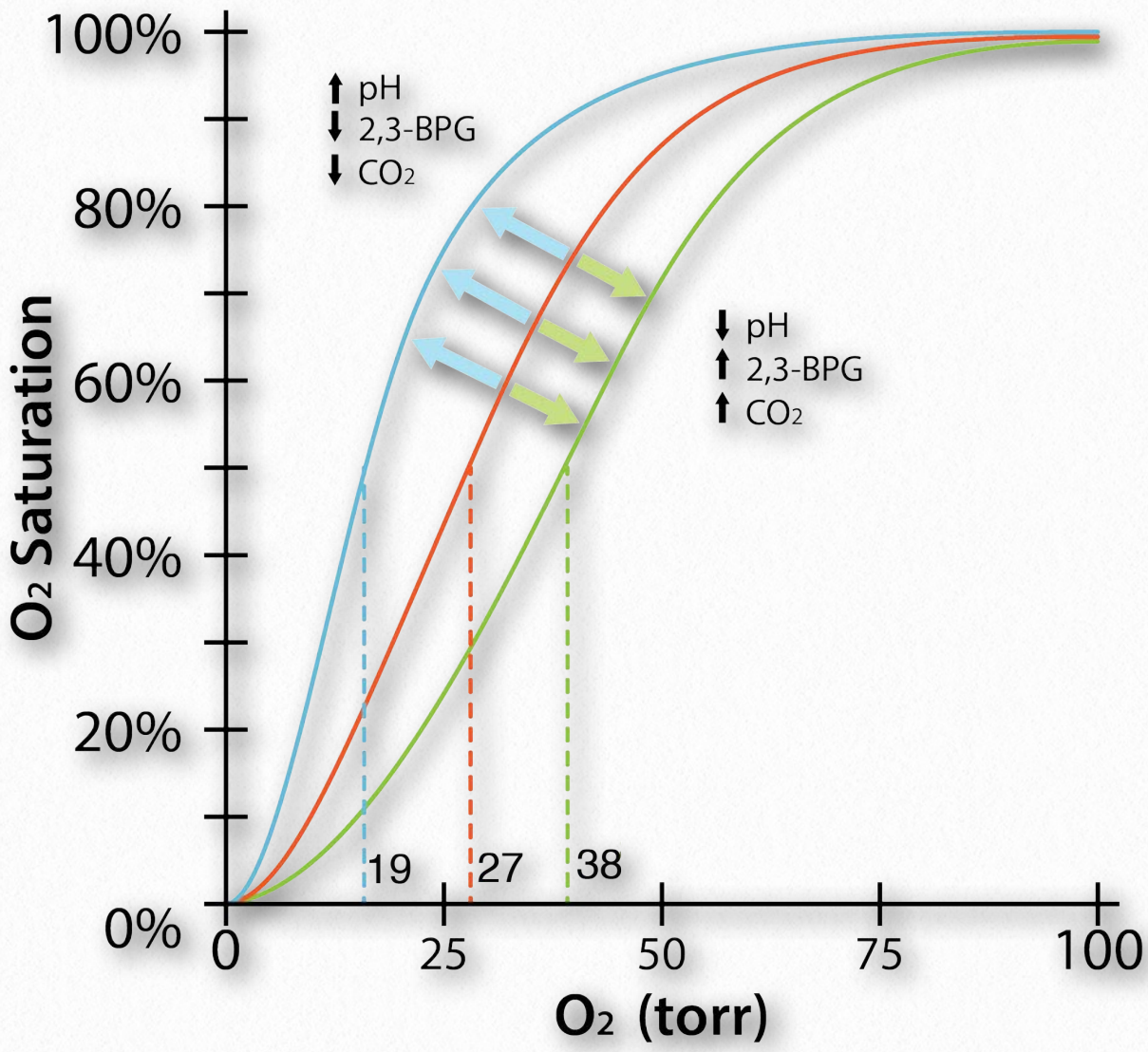


Figure 2.88 - The Bohr effect physiologically - oxygen binding curves for resting muscle (blue), active muscle (green) and reference muscle (orange) with respect to pH, 2,3-BPG, and CO_2

Image by Aleia Kim

cule fits into the 'hole of the donut' of adult hemoglobin (Figure 2.89). Such binding of 2,3-BPG favors the T-state (tight - low oxygen binding) of hemoglobin, which has a reduced affinity for oxygen. In the absence of 2,3-BPG, hemoglobin can more easily exist in the R-state (relaxed - higher oxygen binding), which has a high affinity for oxygen.

Smokers

Notably, the blood of smokers is higher in the concentration of 2,3-BPG than non-smokers, so more of their hemoglobin remains in the T-state and thus the oxygen carrying capacity of smokers is lower than non-smokers.

Another reason why smokers' oxygen carrying capacity is lower than that of non-smokers is that cigarette smoke contains carbon monoxide and this molecule, which has almost identical dimensions to molecular oxygen, effectively outcompetes with oxygen for binding to the iron atom of heme (Figure 2.90). Part of carbon monoxide's toxicity is due to its ability to bind hemoglobin and prevent oxygen from binding.

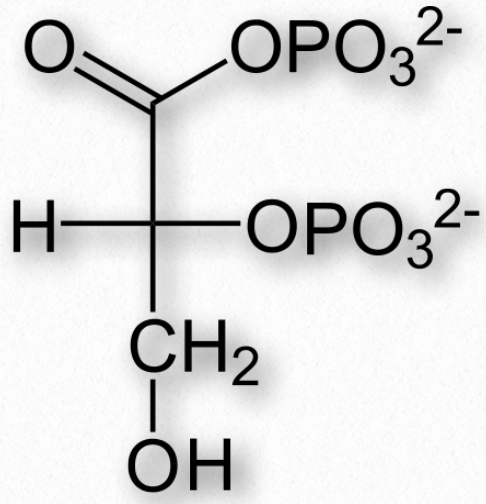


Figure 2.89 - The structure of 2,3 bisphosphoglycerate (2,3-BPG)

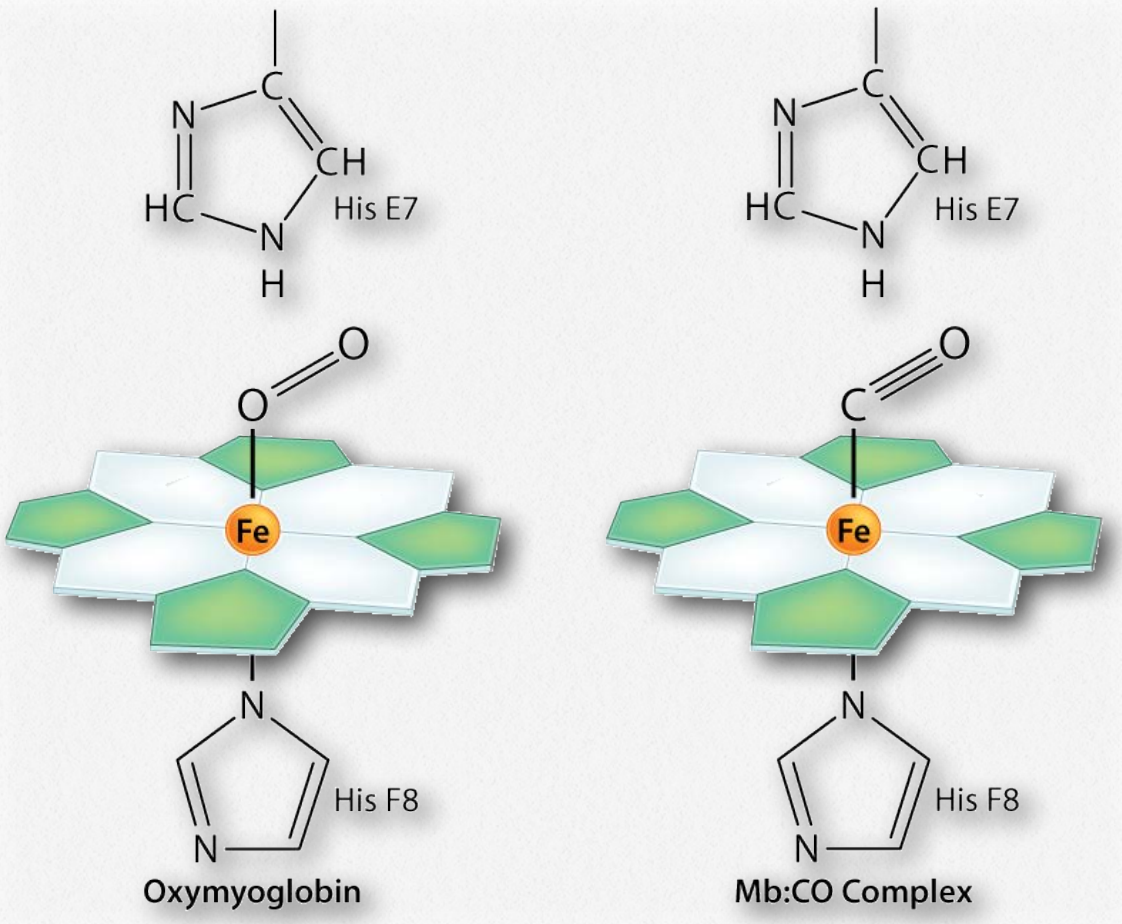


Figure 2.90 - Binding of oxygen (left) and carbon monoxide (right) by a heme group of hemoglobin

Image by Aleia Kim

back to the lungs by hemoglobin. The remainder travel as part of the bicarbonate buffering system or as dissolved CO_2. In the lungs, the process reverses itself. The lungs have a higher pH than respiring tissues, so protons are released from hemoglobin and CO_2 too is freed to be exhaled.

Carbon dioxide

Carbon dioxide binds to form a carbamate when binding the α-amine of each globin chain. The process of forming this structure releases a proton, which helps to further enhance the Bohr effect. Physiologically, the binding of CO_2 and H^+ has significance because actively respiring tissues (such as contracting muscles) require oxygen and release protons and carbon dioxide. The higher the concentration of protons and carbon dioxide, the more oxygen is released to feed the tissues that need it most.

About 40% of the released protons and about 20% of the carbon dioxide are carried

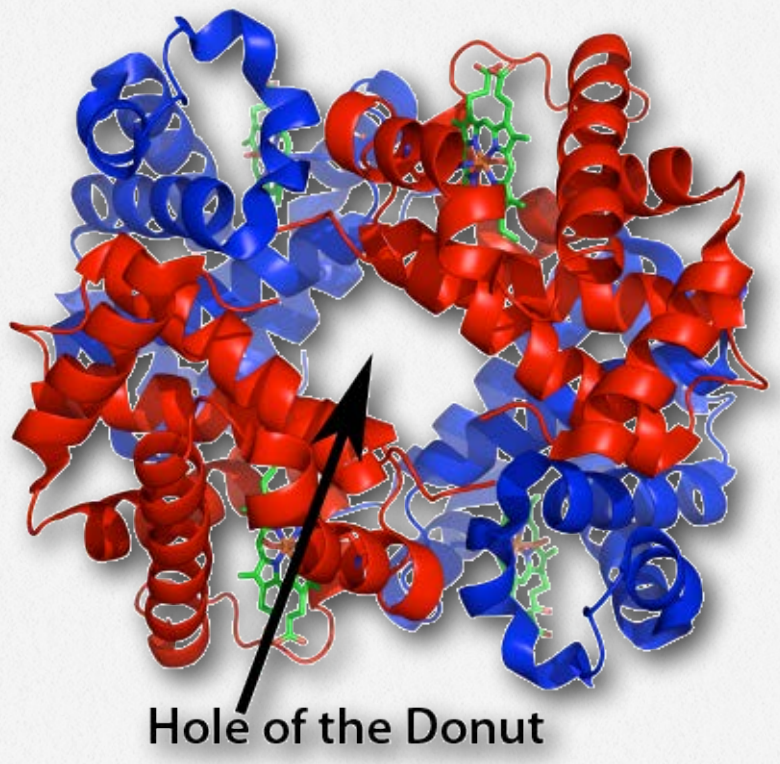


Figure 2.91 - Hemoglobin's hole of the donut for binding 2,3-BPG

Wikipedia

Fetal hemoglobin

Adult hemoglobin releases oxygen when it binds 2,3-

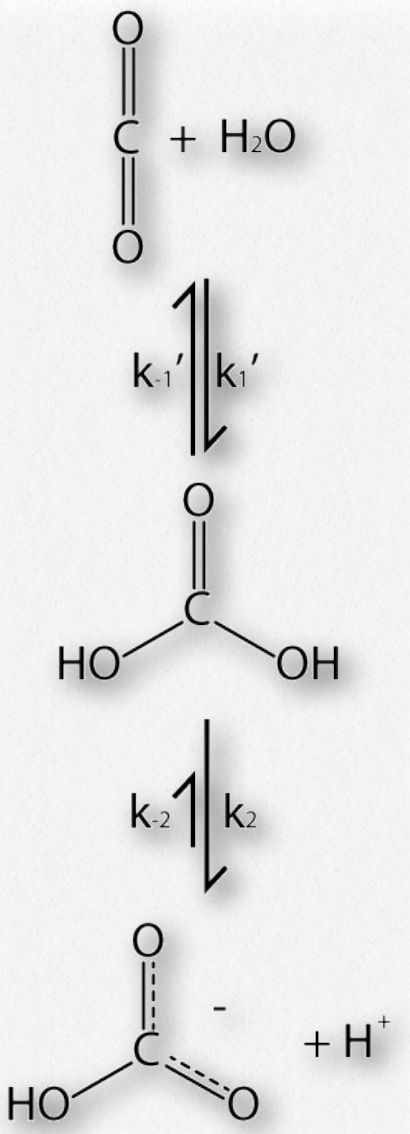


Figure 2.92 - Formation of bicarbonate from CO_2 in blood

BPG. This is in contrast to fetal hemoglobin, which has a slightly different configuration ($\alpha_2\gamma_2$) than adult hemoglobin ($\alpha_2\beta_2$). Fetal hemoglobin has a greater affinity for oxygen than maternal hemoglobin, allowing the fetus to obtain oxygen effectively from the mother's blood. Part of the reason for fetal hemoglobin's greater affinity for oxygen is that it doesn't bind 2,3-BPG. Consequently, fetal hemoglobin remains in the R-state much more than adult hemoglobin and because of this, fetal hemoglobin has greater affinity for oxygen than adult hemoglobin and can take oxygen away from adult hemoglobin. Thus, the fetus can get oxygen from the mother.

Sickle cell disease

Mutations to the globin genes coding for hemoglobin can sometimes have deleterious consequences. Sickle cell disease (also called sickle cell anemia) is a genetically transmitted disease that arises from such mutations. There are different forms of the disease. It is a recessive trait, meaning that to be afflicted with it, an individual must inherit two copies of the mutated gene.

The predominant form of hemoglobin in adults is hemoglobin A, designated HbA (two α chains and two β chains). The mutant form is known as HbS. The most common mutation is an A to T mutation in the middle of the codon for the seventh amino acid (some

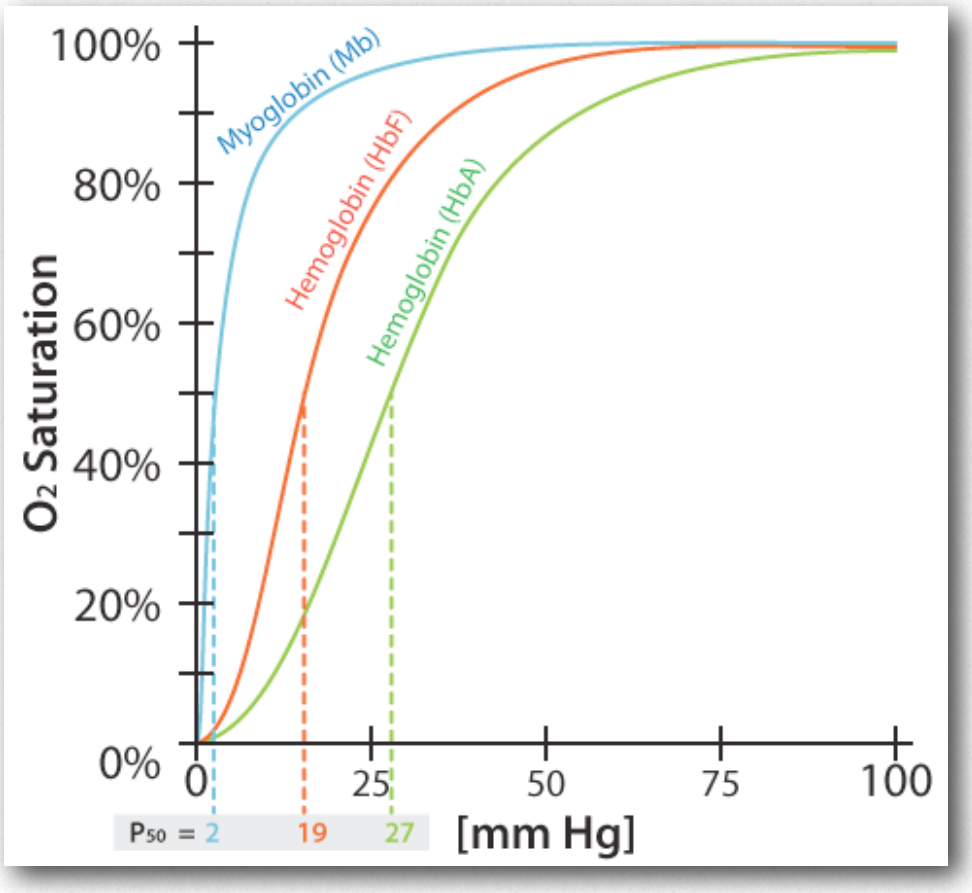


Figure 2.93 - Comparison of oxygen binding of myoglobin (blue), fetal hemoglobin (orange), and adult hemoglobin (green)

Image by Aleia Kim

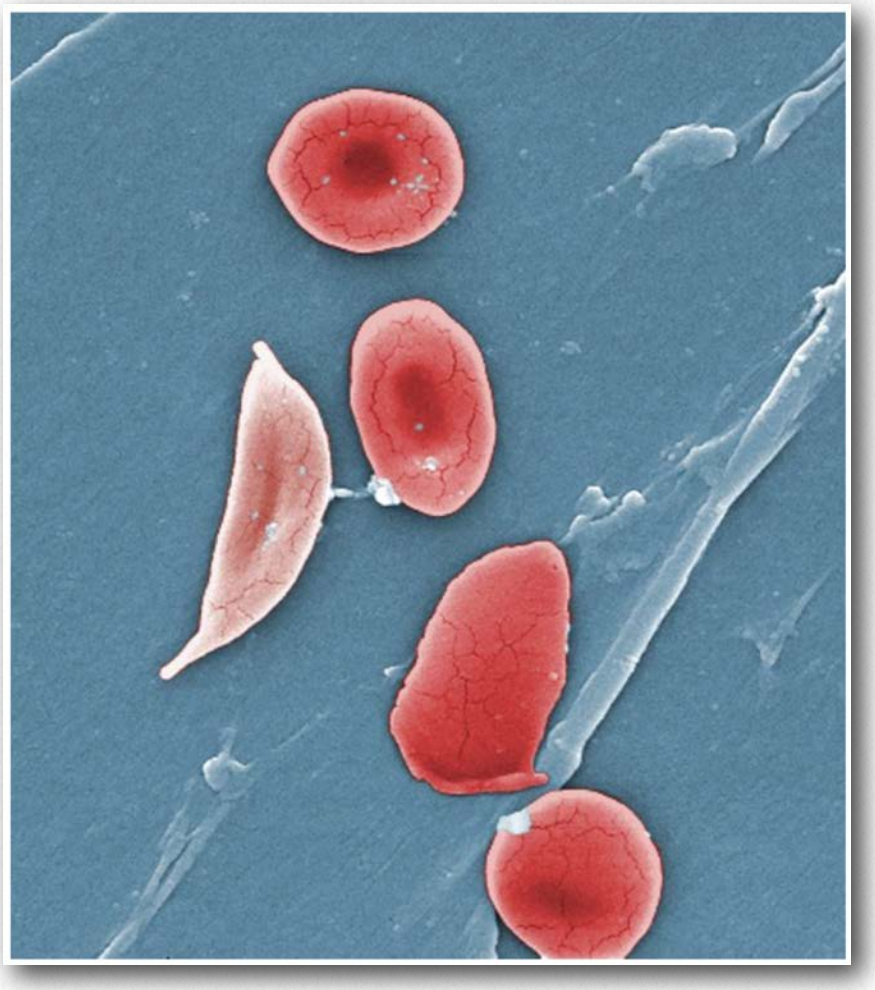


Figure 2.94 - Four normal red blood cells (right) and one sickled red blood cell (left)

Wikipedia

counting schemes call it the sixth amino acid) of the β-chain. This results in conversion of a GAG codon to GTG and thus changes the amino acid specified at that position from a glutamic acid to a valine. This minor change places a small hydrophobic patch of amino acids on the surface of the β-globin chains.

Polymerization

Under conditions of low oxygen, these hydrophobic patches will associate with each other to make long polymers of hemoglobin molecules. The result is that the red blood cells containing them will change shape from being rounded to forming the shape of a sickle (Figure 2.94). Rounded red blood cells readily make it through tiny capillaries, but sickle-shaped cells do not.

Worse, they block the flow of other blood cells. Tissues where these blockages occur are already low in oxygen, so stopping the flow of blood through them causes them to go quickly anaerobic, causing pain and, in some cases, death of tissue. In severe circumstances,

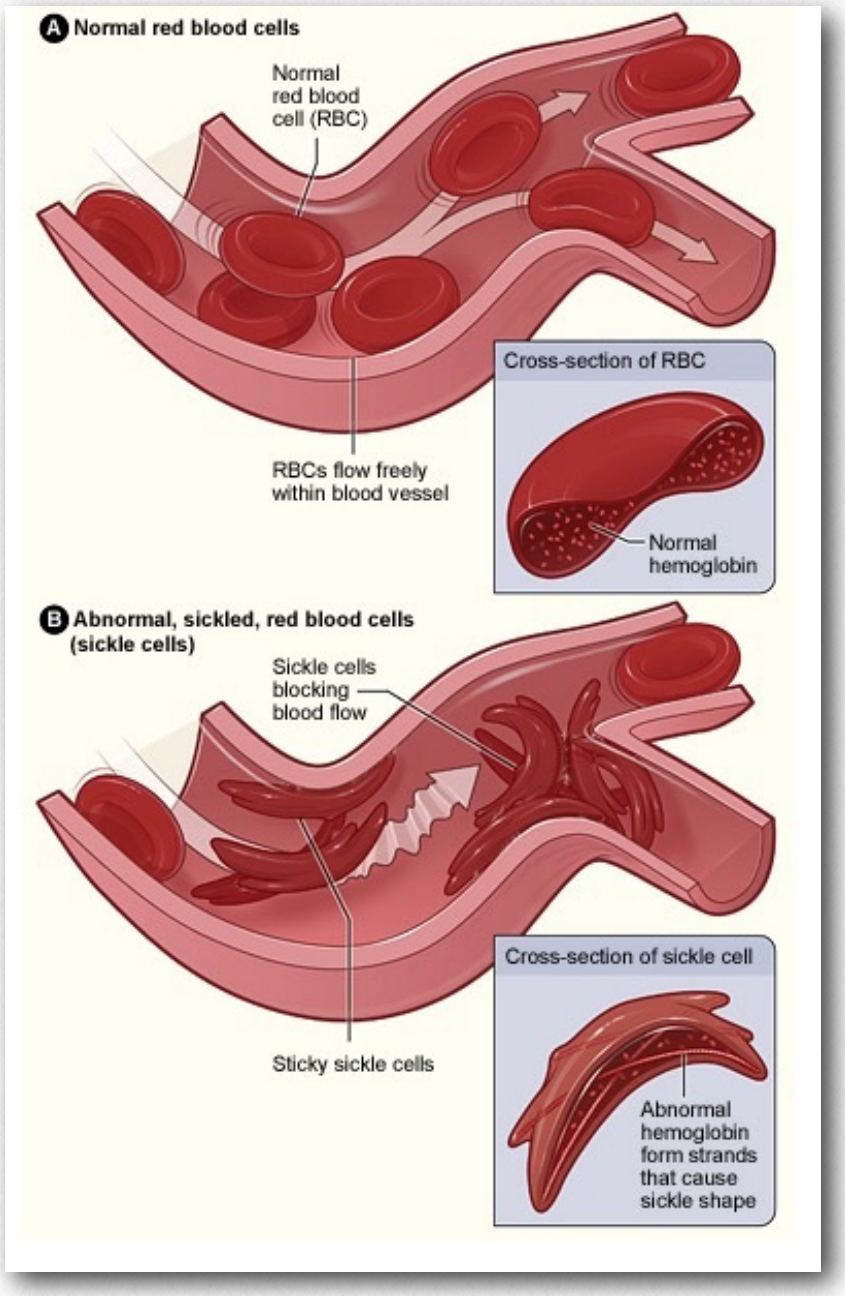


Figure 2.95 - Movement of blood in capillaries. Top - normal red blood cells. Bottom - sickled red blood cells

death may result. The disease is referred to as an anemia because the sickling of the red blood cells targets them for removal by the blood monitoring system of the body, so a person with the disease has chronically reduced numbers of red blood cells.

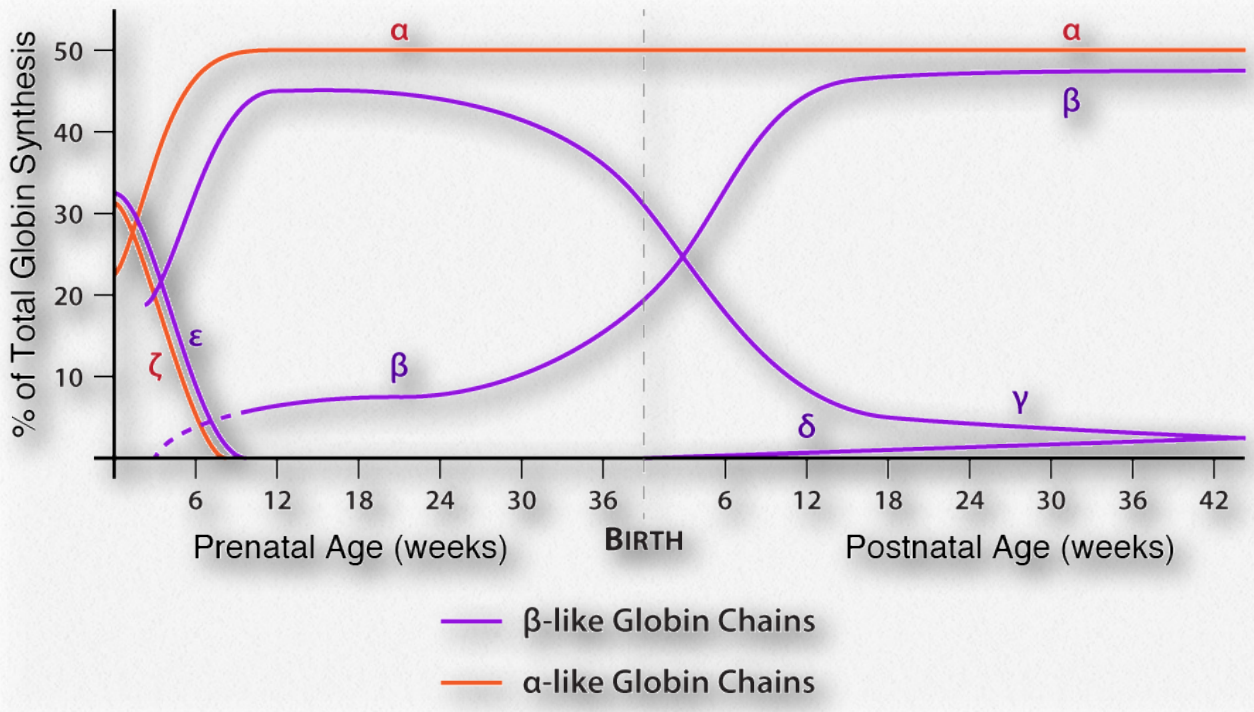


Figure 2.96 - Pattern of expression of six different globins of hemoglobin - α,β,γ,ε,δ, and ζ

Image by Aleia Kim

Heterozygote advantage

Interestingly, there appears to be a selective advantage to people who are heterozygous for the disease in areas where malaria is prominent. Heterozygotes do not suffer obvious ill effects of the disease, but their red blood cells appear to be more susceptible to rupture when infected. As a consequence, the parasite gets less of a chance to reproduce and the infected person has a greater chance of survival.

The protective effect of the mutant gene, though, does not extend to people who suffer the full blown disease (homozygotes for the mutant gene). Treatments for the disease include transfusion, pain management, and avoidance of heavy exertion. The drug hydroxyurea has been linked to reduction in number and severity of attacks, as well as an increase in survival time[1,2]. It appears to work by reactivating expression of the fetal hemoglobin gene, which typically is not synthesized to any significant extent normally after about 6 weeks of age.

Oxygen binding

Animals have needs for oxygen that differ from all other organisms. Oxygen, of course, is the terminal electron acceptor in animals and is necessary for electron transport to work. When electron transport is functioning, ATP generation by cells is many times more efficient than when it is absent. Since abundant ATP is essential for muscular contraction and animals move around a lot - to catch prey, to exercise, to escape danger, etc., hav-

ing an abundant supply of oxygen is important.

This is particularly a concern deep inside tissues where diffusion of oxygen alone (as occurs in insects) does not deliver sufficient quantities necessary for long term survival. The issue is not a problem for plants since, for the most part, their motions are largely related to growth and thus don't have rapidly changing needs/demands for oxygen that animals have. Unicellular organisms have a variety of mechanisms for obtaining oxygen and surviving without it. Two other important oxygen binding proteins besides hemoglobin are myoglobin and hemocyanin.

YouTube Lectures by Kevin HERE & HERE

Myoglobin

Myoglobin is the primary oxygen-storage protein found in animal muscle tissues. In contrast to hemoglobin, which circulates throughout the body, myoglobin protein is only found in muscle tissue and appears in the blood only after injury. Like hemoglobin, myoglobin binds oxygen at a prosthetic heme group it contains.

The red color of meat arises from the heme of myoglobin and the browning of meat by cooking it comes from oxidation of the ferrous (Fe^{++}) ion of myoglobin's heme to the ferric (Fe^{+++}) ion via oxidation in the cooking process. As meat sits in our atmosphere (an oxygen-rich environment), oxidation of Fe^{++} to Fe^{+++} occurs, leaving the brown color noted above. If meat is stored in a carbon monoxide (CO) environment, CO binds to the heme group and reduces the amount of oxidation, keeping meat looking red for a longer period of time.

High affinity

Myoglobin (Figure 2.97) displays higher affinity for oxygen at low oxygen concentrations than hemoglobin and is therefore able to absorb oxygen delivered by hemoglobin under these conditions. Myoglobin's high affinity for oxygen makes it better suited for oxygen storage than delivery. The protein exists as a single subunit of globin (in contrast to hemoglobin, which contains four subunits) and is related to the

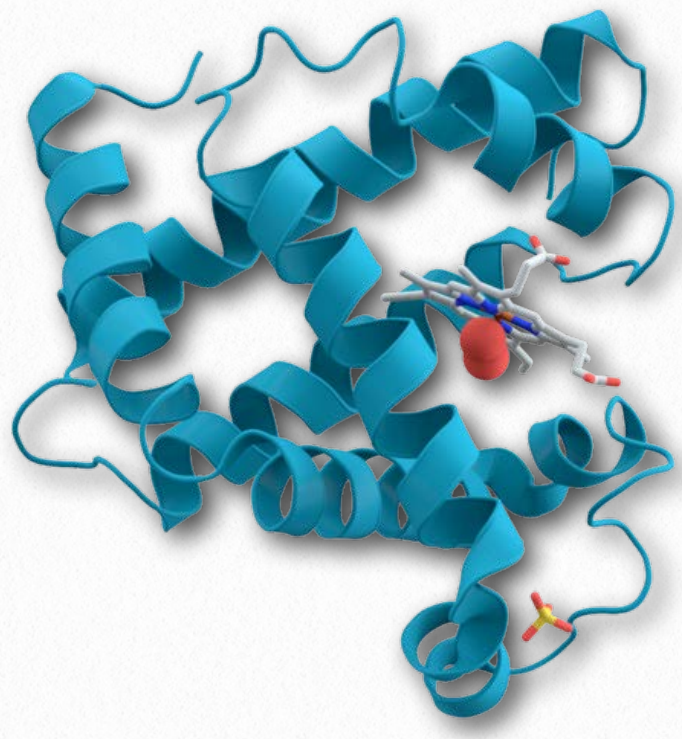


Figure 2.97 - Myoglobin bound to oxygen

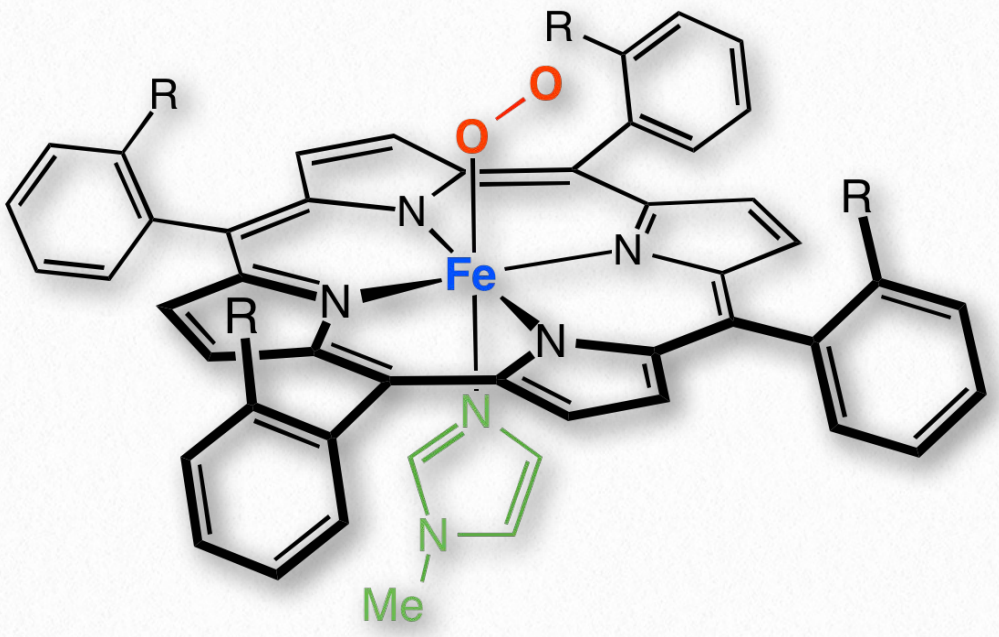


Figure 2.98 - Oxygen bound at heme of myoglobin

Wikipedia

subunits found in hemoglobin. Mammals that dive deeply in the ocean, such as whales and seals, have muscles with particularly high abundance of myoglobin. When oxygen concentration in muscles falls to low levels, myoglobin releases its oxygen, thus functioning as an oxygen “battery” that delivers oxygen fuel when needed and holding onto it under all other conditions. Myoglobin holds the distinction of being the first protein for which the 3D structure was determined by X-ray crystallography by John Kendrew in 1958, an achievement for which he later won the Nobel Prize.

Hemocyanin

Hemocyanin is the protein transporting oxygen in the bodies of molluscs and arthropods. It is a copper-containing protein found not within blood cells of these organisms, but rather is suspended in the circulating hemolymph they possess. The oxygen binding site of hemocyanin contains a pair of copper(I) cations directly coordinated to the protein by the imidazole rings of six histidine side chains.

Most, but not all hemocyanins bind oxygen non-cooperatively and are less efficient than hemoglobin at transporting oxygen. Notably, the hemocyanins of horseshoe crabs and some other arthropods do, in fact, bind oxygen cooperatively. Hemocyanin contains many subunit proteins, each with two copper atoms that can bind one oxygen molecule (O_2). Subunit proteins have atomic masses of about 75 kilodaltons (kDa). These may be arranged in dimers or hexamers depending on species.

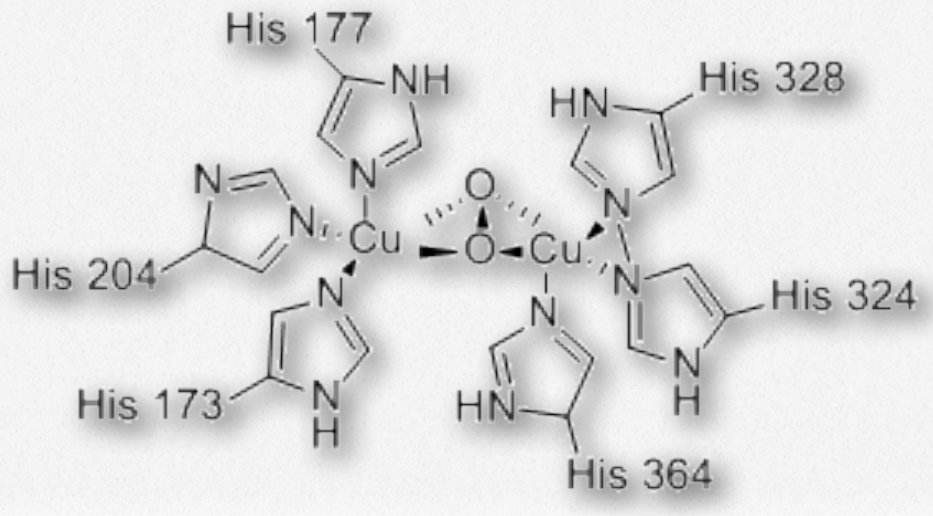


Figure 2.99 - Oxygen binding in hemocyanin

Wikipedia

Figure 2.100 - Hemocyanin (purple) in a red rock crab

Wikipedia

Superstructures comprised of dimer or hexamer complexes are arranged in chains or clusters and have molecular weights of over 1500 kDa.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Hemoglobin's Moving Around

To the tune of "*Santa Claus is Coming to Town*"

Metabolic Melodies Website HERE

Oh isn't it great?
What proteins can do
Especially ones that bind to O2
Hemoglobin's moving around

Inside of the lungs
It picks up the bait
And changes itself from T to R state
Hemoglobin's moving around

The proto-porphyrin system
Its iron makes such a scene
Arising when an O2 binds
Pulling up on histidine

The binding occurs
Cooperatively
Thanks to changes qua-ter-nar-y
Hemoglobin's moving around

It exits the lungs
Engorged with O2
In search of a working body tissue
Hemoglobin's moving around

The proton concentration
Is high and has a role
Between the alpha betas
It finds imidazole

To empty their loads
The globins decree
"We need to bind 2,3BPG"
Hemoglobin's moving around

The stage is thus set
For grabbing a few
Cellular dumps of CO2
Hemoglobin's moving around

And then inside the lungs it
Discovers ox-y-gen
And dumps the CO2 off
To start all o'er agin

So see how this works
You better expect
To have to describe the Bohr effect
Hemoglobin's moving around

YouTube Video HERE

Recording by Tim Karplus
Lyrics by Kevin Ahern

The Bloody Things

To the tune of "*Coke ® It's The Real Thing*"

Metabolic Melodies Website **HERE**

I'm gonna put some oxygens
beside my porphyrin rings
To nudge the irons up a notch
and yank on histidines
The globins' shapes will change a bit,
oh what a sight to see
The way they bind to oxygen
co-op-er-AH-tive-ly

And as I exit from the lungs
to swim in the bloodstream
Metabolizing cells they all
express their needs to me
To them I give up oxygen
and change from R to T
While my amines, they hang onto
the protons readily

But that's not all the tricks I know,
there's more that's up my sleeve
Like gaps between sub-U-nits that
hold 2,3-BPG
When near met-a-bo-LI-zing cells,
I bind things that diffuse
The protons and bicarbonates
from lowly cee oh twos

CHORUS
That's the way it is
When your cells are at play
Go say hip hip hooray
For the bloody things

Recording by David Simmons
Lyrics by Kevin Ahern

Heme

To the tune of "*Jean*"

Metabolic Melodies Website HERE

Heme, heme, colored supreme
Deepest red I've ever seen
When my oxygen's low
Hemoglobin will know
Give up your oxygen, heme

Heme, heme porphyrin ring
Bonded to five histidines
When an oxygen binds
To your iron it climbs
Tugging its histidine, heme

Then the globin arranges itself a new way
And the three other units tell their hemes OK
They can go on a bindin' - oh-two they're findin'

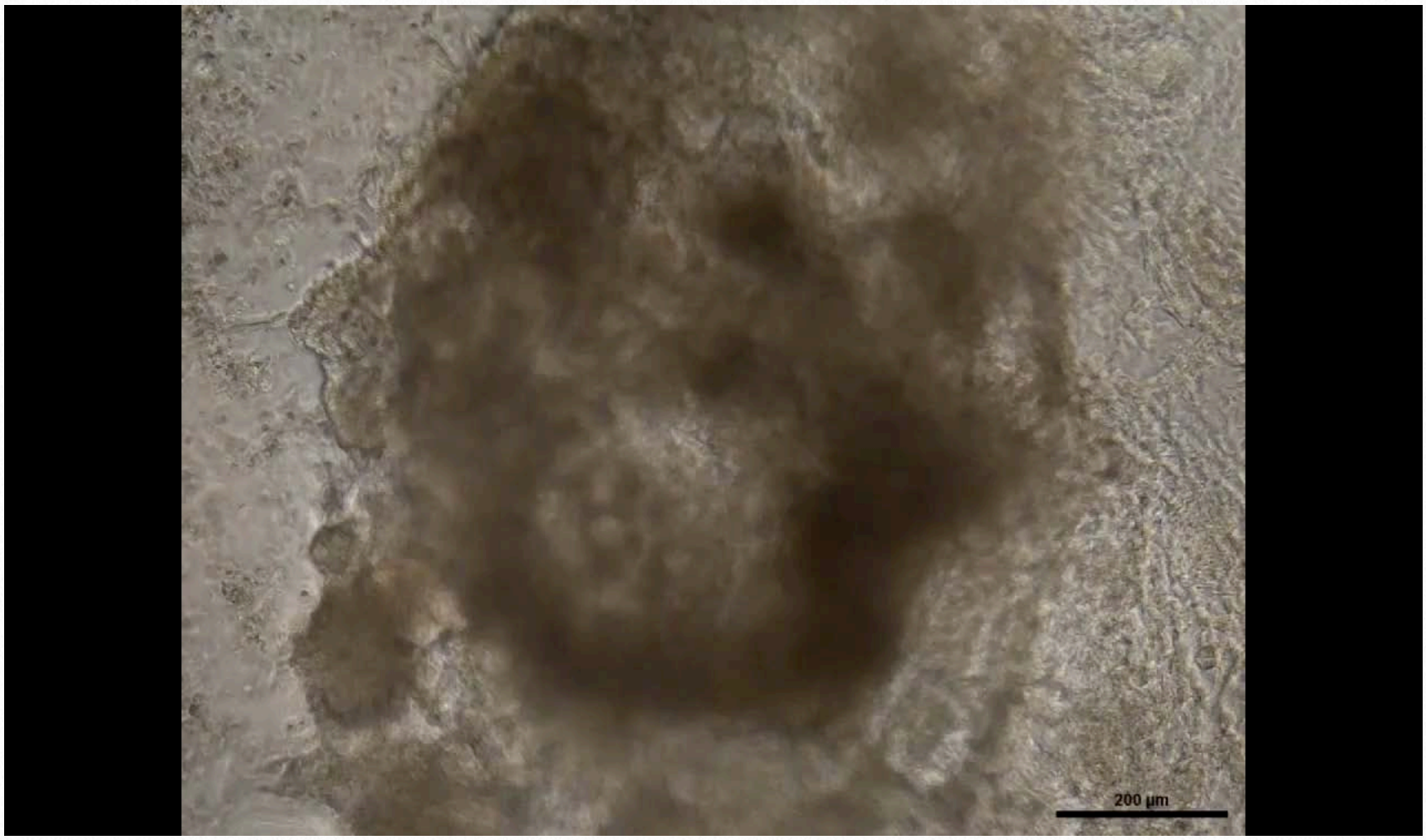
Then heme, heme leaving the lungs
Travels inside the bloodstream
When it finds a tissue
That is lacking oh-two
It gives what it needs, bloody heme

Heme, you keep me alive
Binding coop'ratively
Go release what I need
Christian Bohr has decreed
Tissues adore you, lovely heme

Lyrics by Kevin Ahern

No Recording Yet For This Song

Structure and Function: Protein Function II



To this point, the proteins we have discussed have not been catalysts (enzymes). The majority of proteins in cells, however, catalyze reactions. In this section we begin our discussion of a subclass of proteins that catalyze reactions releasing energy and convert it into mechanical force. These operate at the cellular and organismal level and are known as motor proteins. Motor proteins rely on globular structural proteins, so it is important that we describe how these cellular "railways" are assembled before discussing the motor proteins themselves. There are two relevant fibrous structures serving as rails for motor proteins. They are 1) microfilaments (composed of an actin polymer) and 2) microtubules (composed of a polymer of tubulin.

YouTube Lectures by Kevin
HERE & HERE

Actin

The monomeric unit of actin is called G-actin (globular actin) and the polymer is known as F-actin (filamentous actin). Filaments of F-actin comprise the smallest filaments of cells

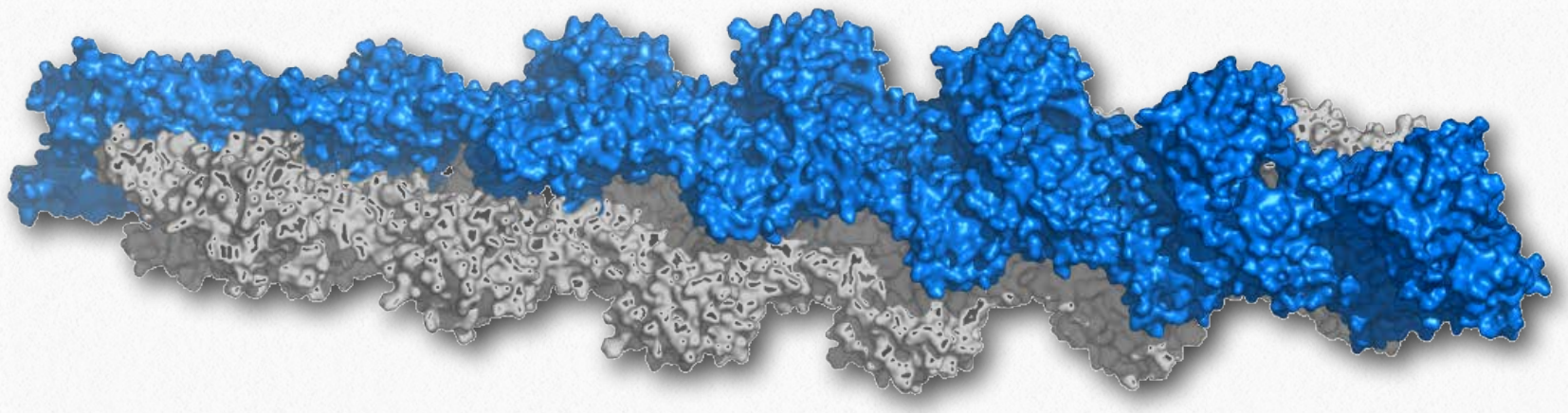


Figure 2.101 - Model of actin filaments

Wikipedia

known as microfilaments (Figure 2.101). Actin is essential for muscular contraction and also has diverse roles in cellular signaling and maintenance of cell junctions. In conjunction with other proteins, actin has numerous interactions with the cell membrane. The β- and γ-forms of actin are components of the cytoskeleton and facilitate motility inside of cells. α-actin is important in muscle tissues, where it is used by myosin in the mechanical process of contraction (See HERE).

Monomeric and polymeric forms of actin play roles in cellular activities relating to motion. Two parallel F-actin strands can pair with each other and create a double helical structure with 2.17 subunits per turn of the helix. Helical F-actin in muscles contains tropomyosin, which covers the actin binding sites for myosin in resting muscles to prevent contraction. Other proteins bound to actin muscle filaments include the troponins (I, T, and C).

Actin cellular action

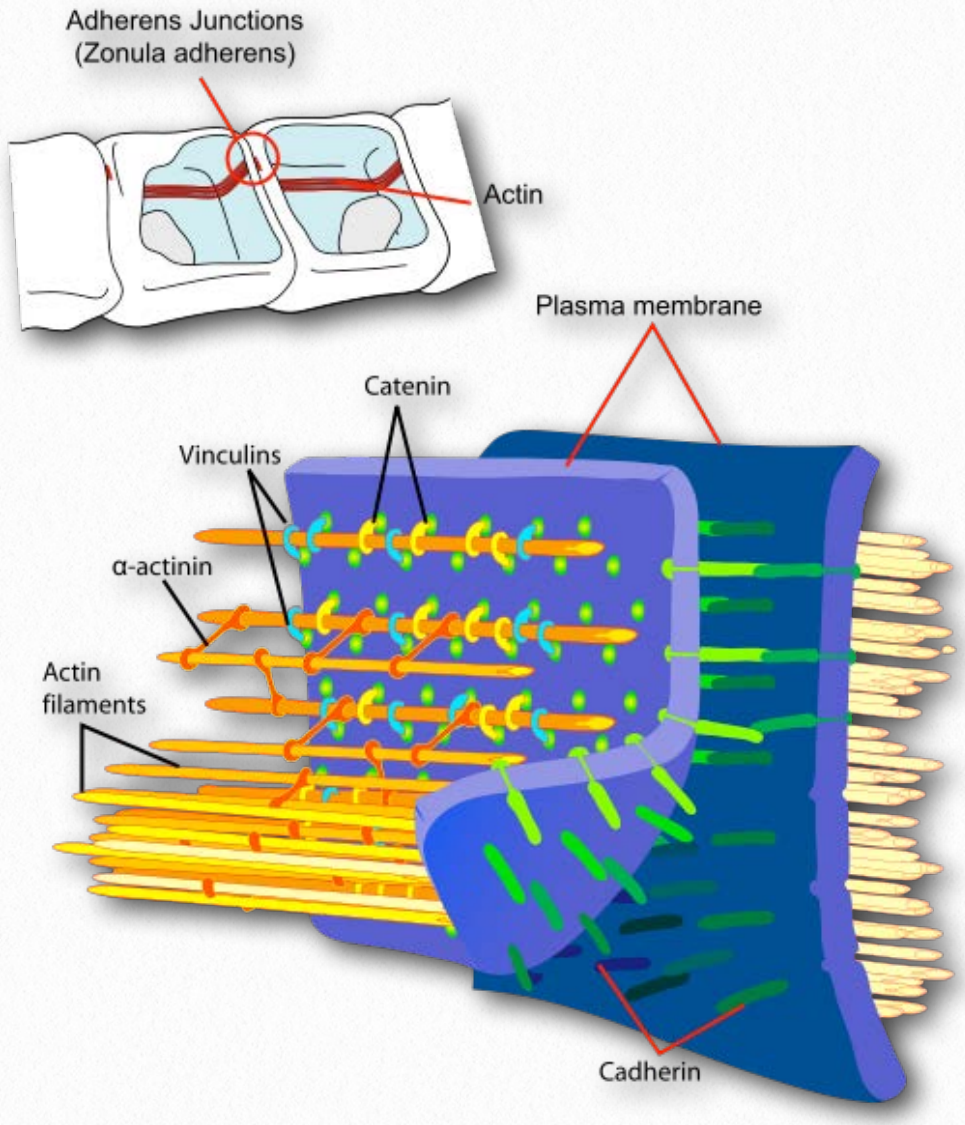


Figure 2.102 - Attachment of actin at the cell membrane complex known as the adherens junction

Wikipedia

Examples of actin action at the cellular level include cell motility, cytokinesis, intracellular transport of vesicles and organelles, and cell shape. Each actin monomer is bound to a molecule of ATP or ADP and the presence of one of these is essential for proper G-actin functioning.

The role of ATP

In the monomer, actin is more commonly bound to ATP, whereas in the filaments, it is typically bound to ADP. Actin is an inefficient ATPase, breaking the molecule down slowly, but the catalysis speeds up as much as 40,000 fold when the monomer begins to polymerize. Actin also has a binding site for divalent cations - either calcium or magnesium.

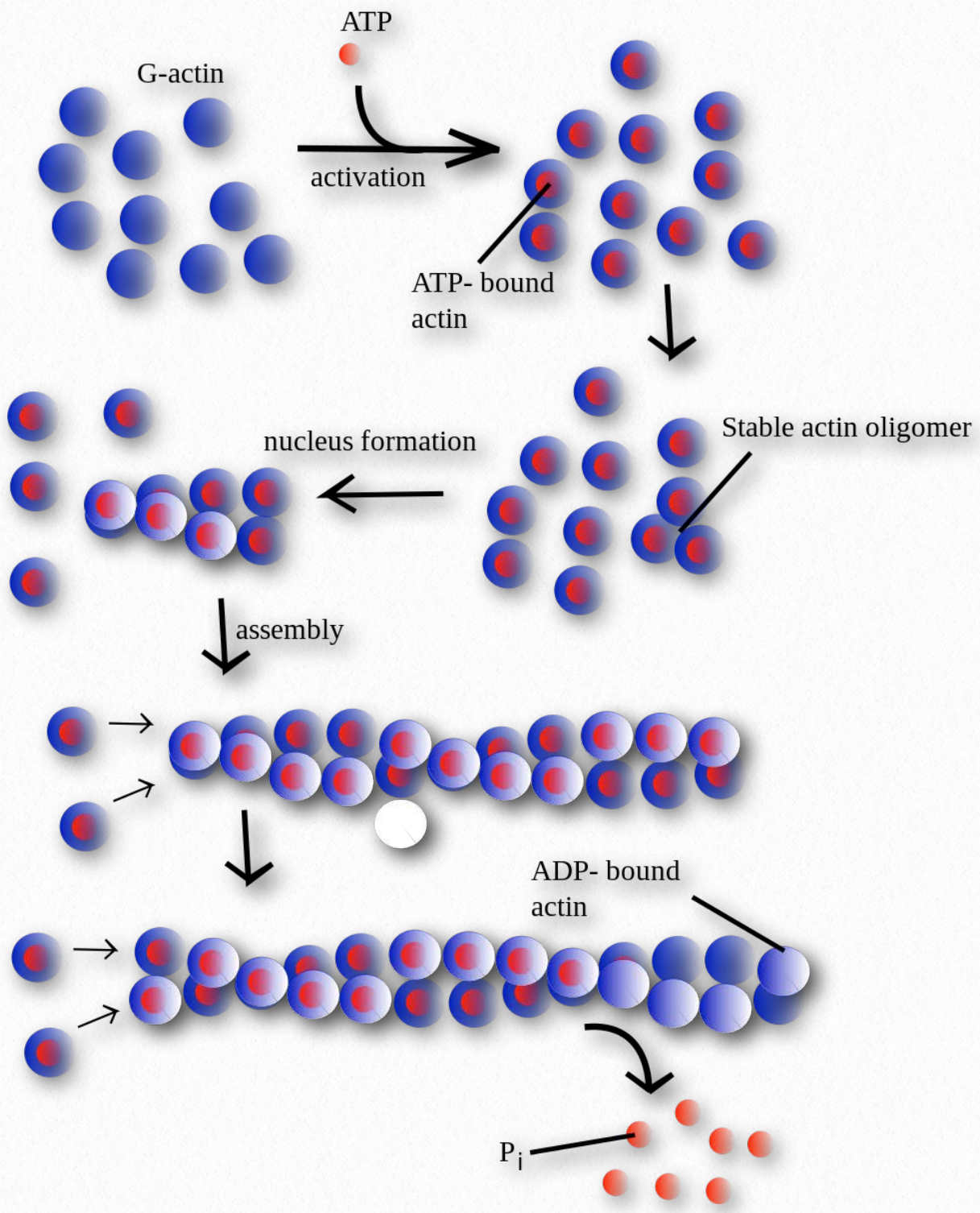


Figure 2.103 - Polymerization of G-actin monomers into F-actin polymers

Wikipedia

F-Actin binds to structural proteins at the adherens junction (Figure 2.102). These include α-actinin, vinculin (provides a membrane connection and connections to the catenins and cadherin).

Polymerization

Polymerization of actin begins with a nucleating event (Figure 2.103). One factor known to affect the process is known as the Arp 2/3 complex. It does this by mimicking an actin dimer, starting an autocatalytic process of actin assembly. The Arp 2/3 complex plays

roles both in the initiation of polymerization of new actin filaments as well as the formation of branches in the filaments.

Two proteins play roles in modulating polymer growth. Thymosin functions on the end of actin filaments to control growth. Profilin works on G-actin monomers exchanging ADP for ATP, promoting addition of monomers to a growing chain.

F-actin filaments are held together by relatively weak bonds compared to the covalent bonds of the monomers of nucleic acids, thus allowing for easier disassembly when desired.

Actin's amino acid sequence is optimized, having diverged only a relatively small amount (20%) between algae and humans. Mutations in the actin gene result in muscular diseases and/or deafness.

Tubulin

Tubulin proteins are the monomeric building blocks of eukaryotic microtubules (Figure 2.104 & 2.105). Bacterial (TubZ) and archaeon (FtsZ) equivalents are known. The α-tubulin and β-tubulin proteins polymerize to make microtubule structures in the cytoplasm of cells. Microtubules are major components of the cytoskeleton of eukaryotic cells, providing structural support, transport within the cell, and functions necessary for segregation of DNAs during cell division.

Dimerization of the α-tubulin and β-tubulin proteins is necessary for polymerization and requires that the subunits bind to GTP. Microtubules only grow in one direction. β-tubulin is found on the plus end of the tubule (growth end = plus end) and α-tubulin is exposed on the other end (non-growth end = minus end). Dimers of α-tubulin/β-tubulin are incorporated into growing microtubules in this orientation. If a dimer is bound to GDP

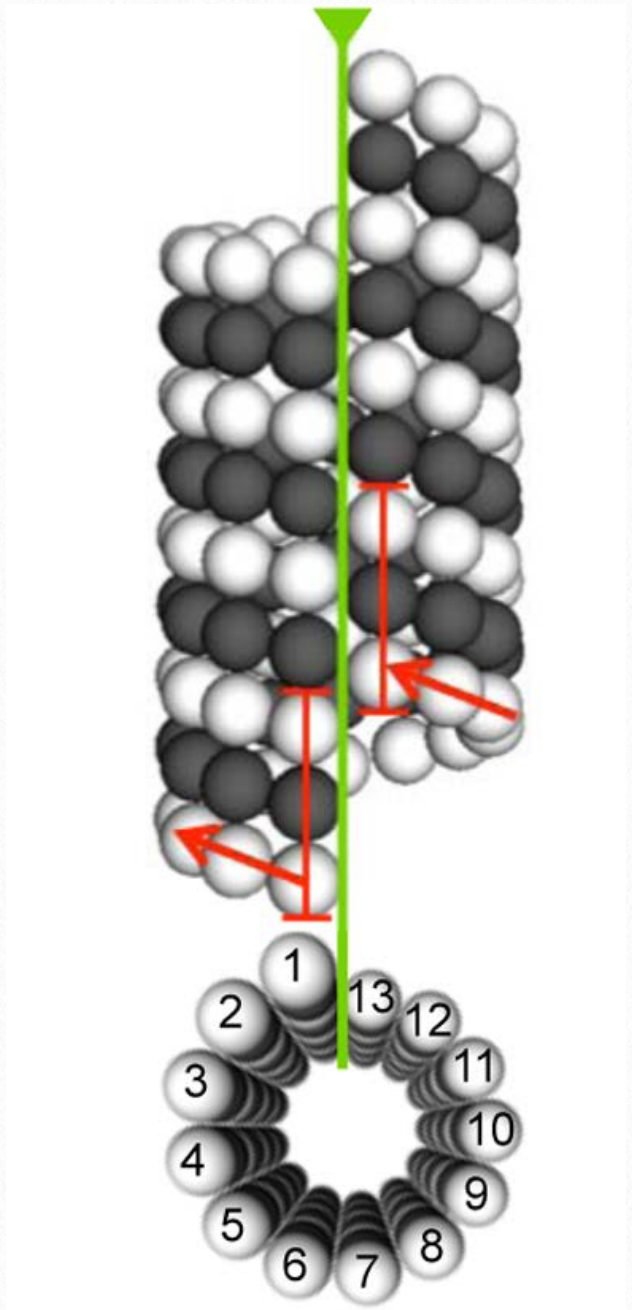


Figure 2.104 **Microtubule structure**

Wikipedia

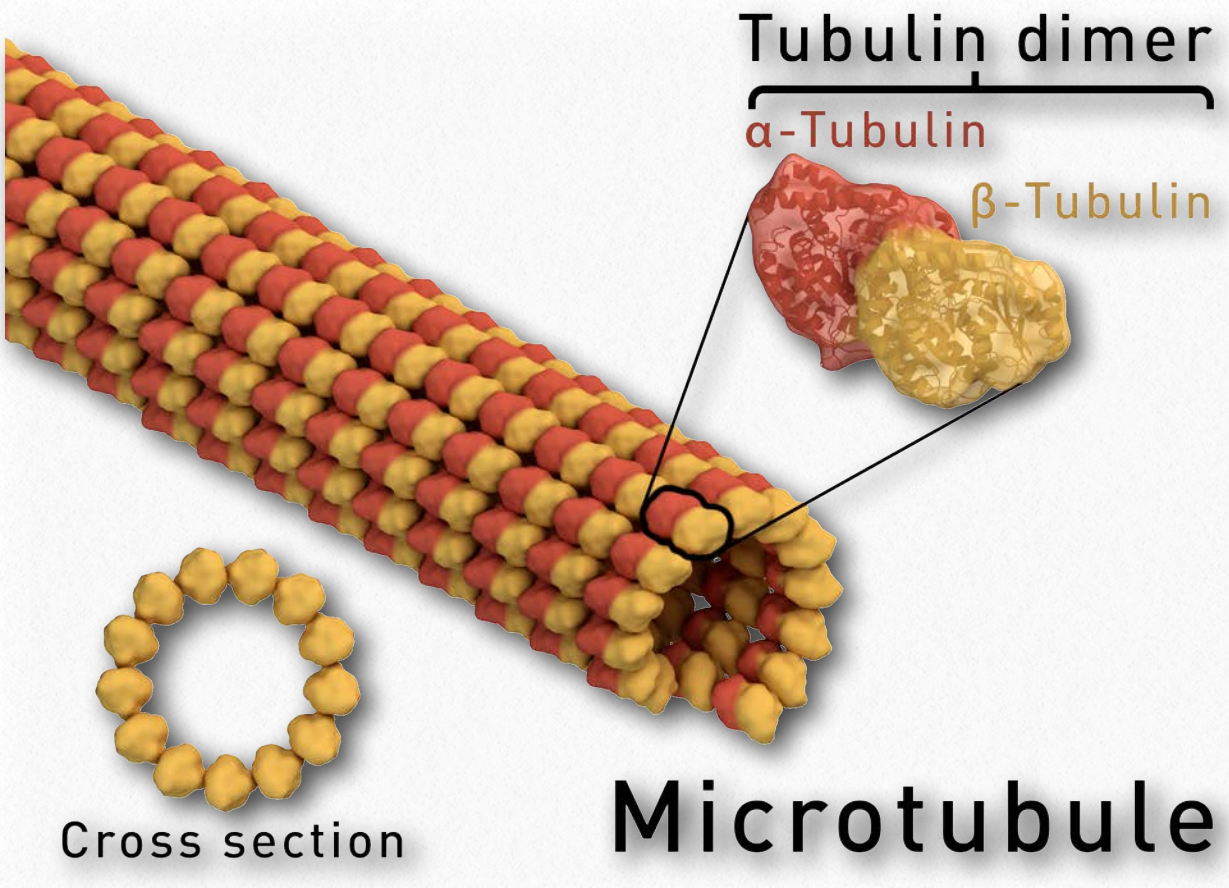


Figure 2.105 - Microtubule anatomy

Wikipedia

instead of GTP, it tends to be unstable and fall apart, whereas those bound to GTP stably assemble into microtubules.

Microtubules

Microtubules, along with microfilaments and intermediate filaments (see HERE) constitute the cytoskeleton of cells. Found in the cytoplasm, they are found in eukaryotic cells, as well as some bacteria. Microtubules help to give cells structure. They comprise the inner structure of flagella and cilia and provide rail-like surfaces for the transport of materials within cells.

Polymerization of α-tubulin and β-tubulin to form microtubules occurs after a nucleating event. Individual units get arranged in microtubule organizing centers (MTOCs), an exam-

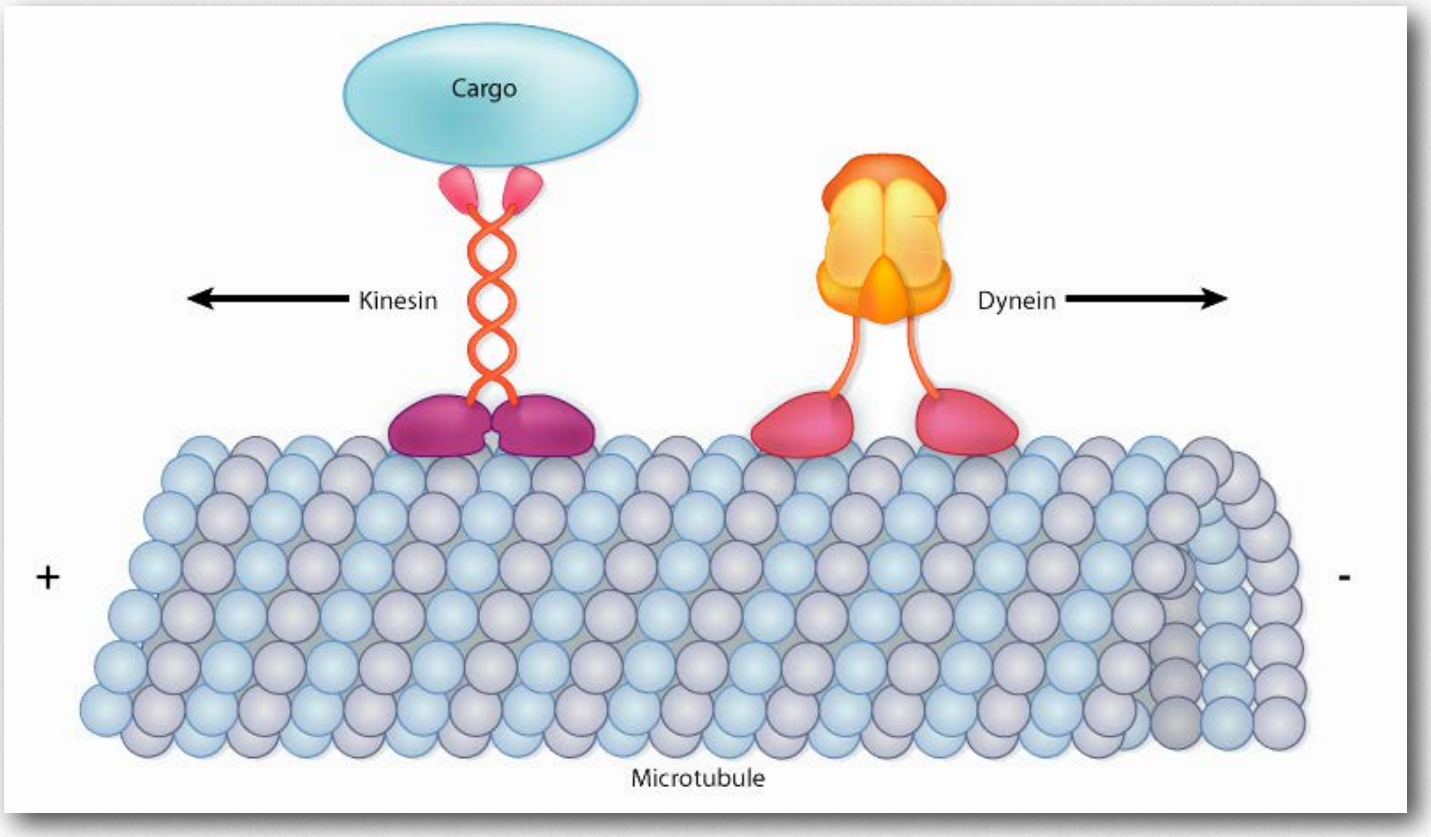


Figure 2.106 - Kinesin and dynein "walk" along microtubules, but move in opposite directions

Image by Aleia Kim

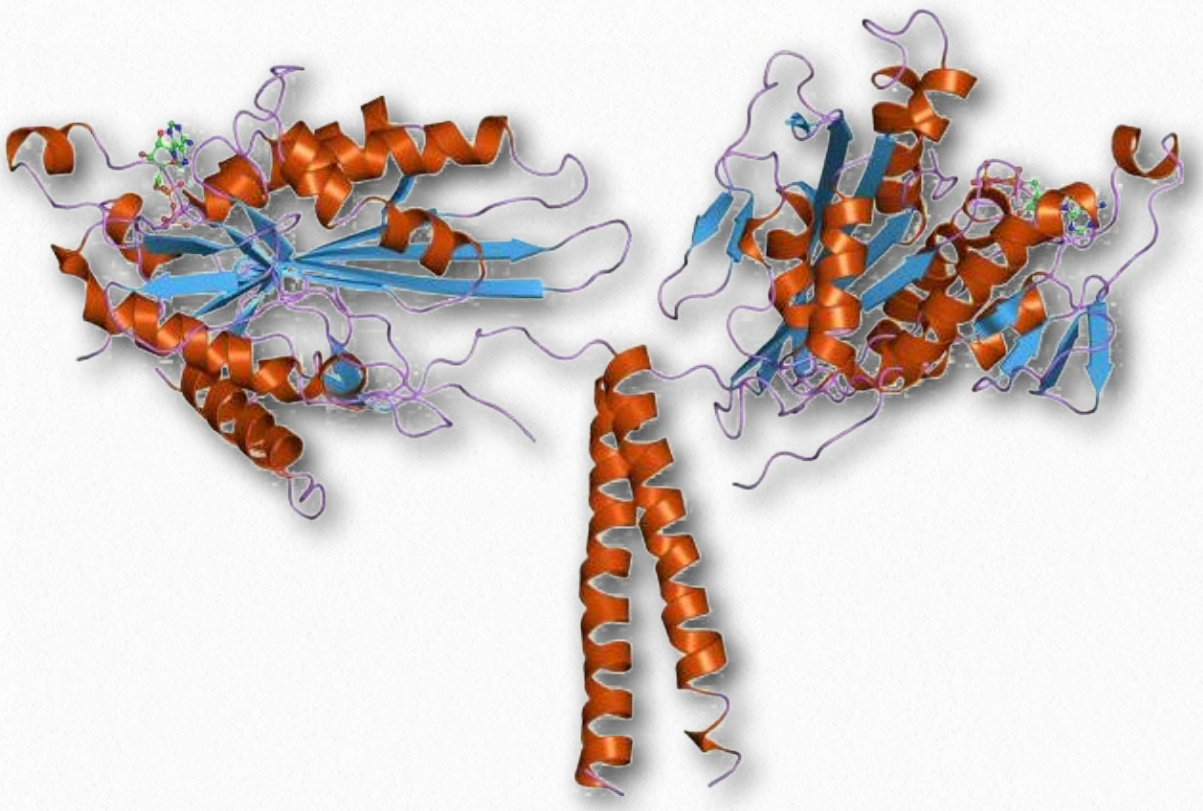


Figure 2.107 - Kinesin. "Feet" are at the top.

ple of which is the centrosome. Centrosomes are focal points of connection of microtubules. Basal bodies of cilia and flagella also help to organize microtubules.

Motor proteins

From the transport of materials within a cell to the process of cytokinesis where one cell splits into two in mitosis, a cell has needs for motion at the molecular level. Secretory vesicles and organelles must be transported. Chromosomes must be separated in mitosis and meiosis.

The proteins dynein and kinesin (Figure 2.106) are necessary for intracellular movement. These motor proteins facilitate the movement of materials inside of cells along microtubule "rails". These motor proteins are able to move along a portion of the cytoskeleton by converting chemical energy into motion with the hydrolysis of ATP. An exception is flagellar rotation, which uses energy provided from a gradient created by a proton pump.

Kinesins and dyneins

As noted, kinesins and dyneins navigate in cells on microtubule tracks (Figure 2.108 & Movie

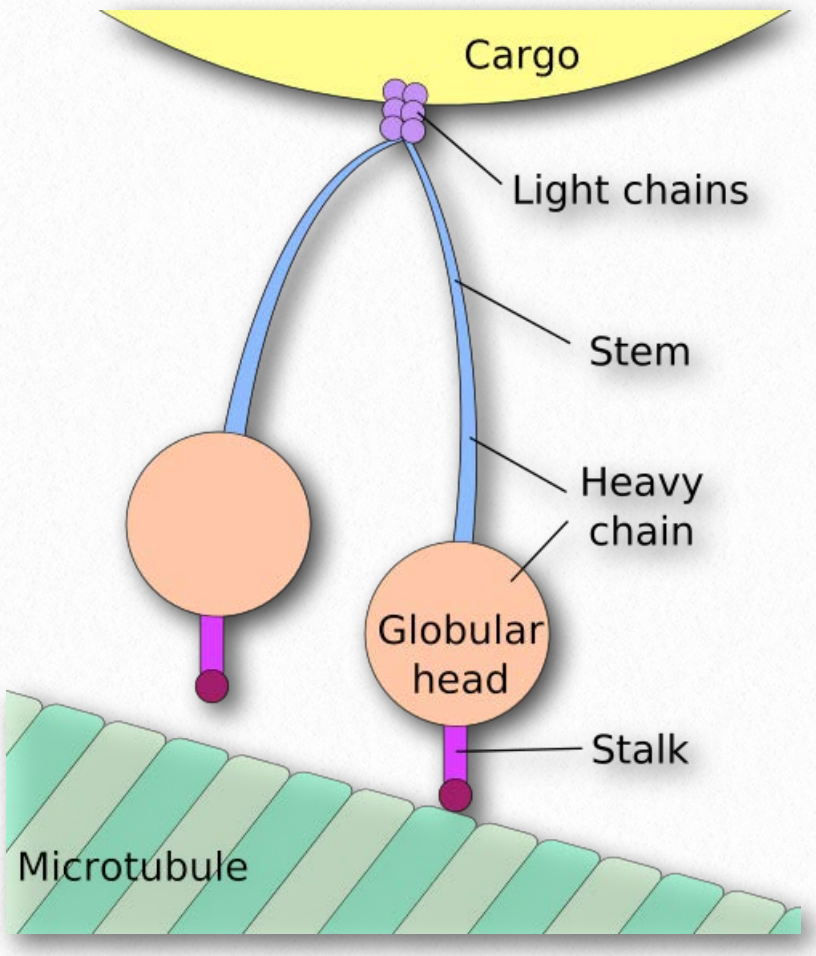
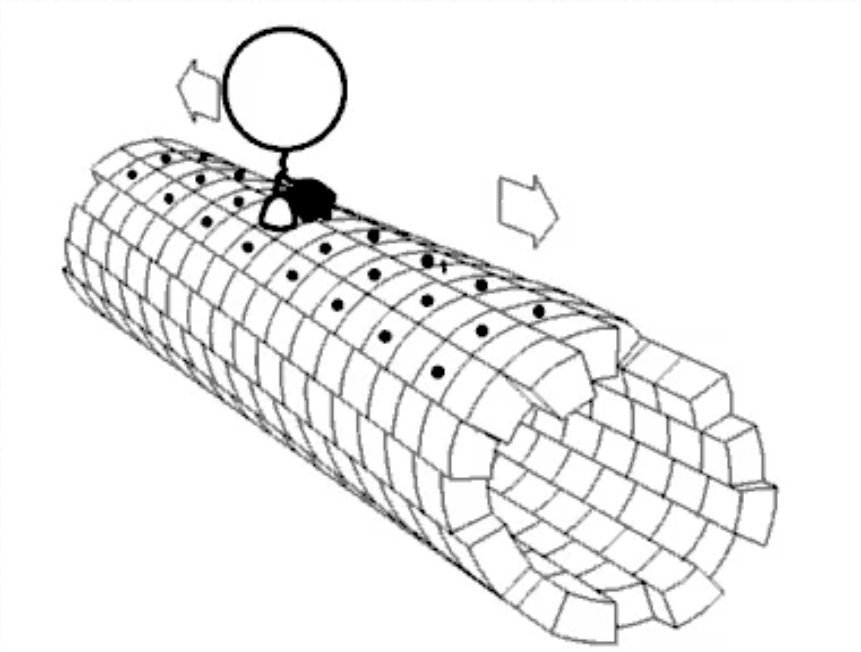


Figure 2.108 - Nomenclature of dynein. The "feet" of Figure 2.105 are the stalk and globular head of the structure here.
Wikipedia



Movie 2.4 The motor protein kinesin walking down a microtubule

Wikipedia

2.4). Most kinesins move in the direction of the synthesis of the microtubule (+ end movement), which is generally away from the cell center and the opposite direction of movement of dyneins, which are said to do retrograde transport toward the cell center. Both proteins provide movement functions necessary for the processes of mitosis and meiosis. These include spindle formation, chromosome separation, and shuttling of organelles, such as the mitochondria, Golgi apparatuses, and vesicles.

Kinesins are comprised of two heavy chains and two light chains. The head motor domains of heavy chains (in the feet) use energy of ATP hydrolysis to do mechanical work for the movement along the microtubules. There are at least fourteen distinct kinesin families and probably many related ones in addition.

Dyneins are placed into two groups - cytoplasmic and axonemal (also called ciliary or flagellar dyneins - Figure 2.109). Dyneins are more complex in structure than kinesins with many small polypeptide units. Notably, plants do not have dynein motor proteins, but do contain kinesins.

Myosin

An important group of motor proteins in the cell is the myosins. Like kinesins and dyneins, myosins use energy from hydrolysis of ATP for movement. In this case, the movement is mostly not along microtubules, but rather along microfilaments comprised of a polymer of actin (F-actin). Movement of myosin on actin is best known as the driving force for muscular contraction. Myosins

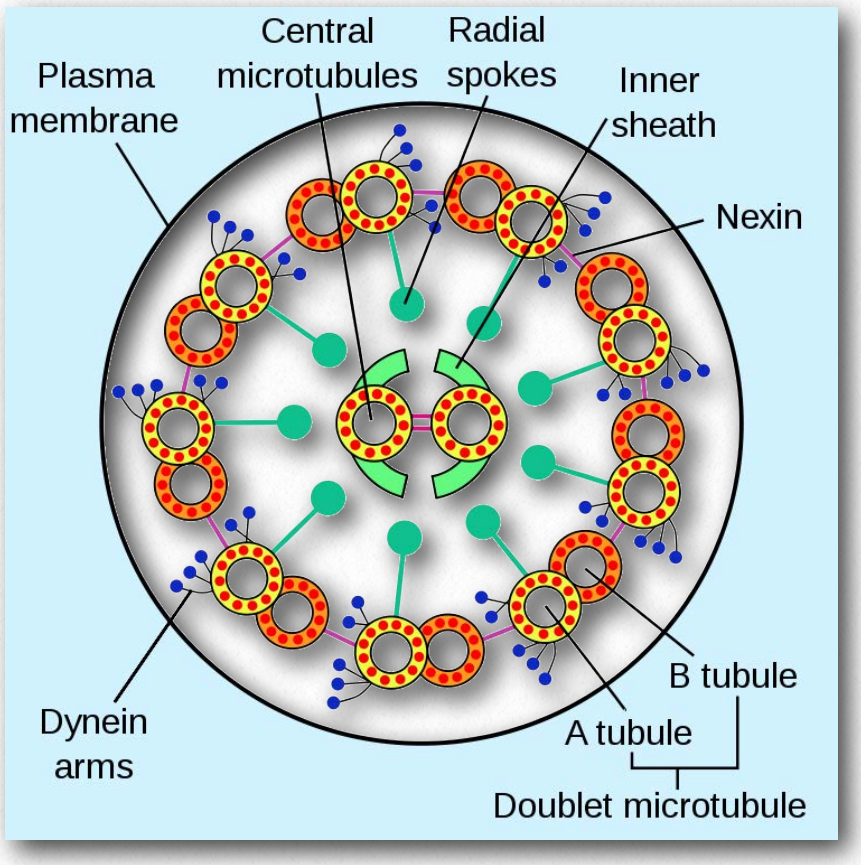


Figure 2.109 - Dynein in an axoneme

Wikipedia

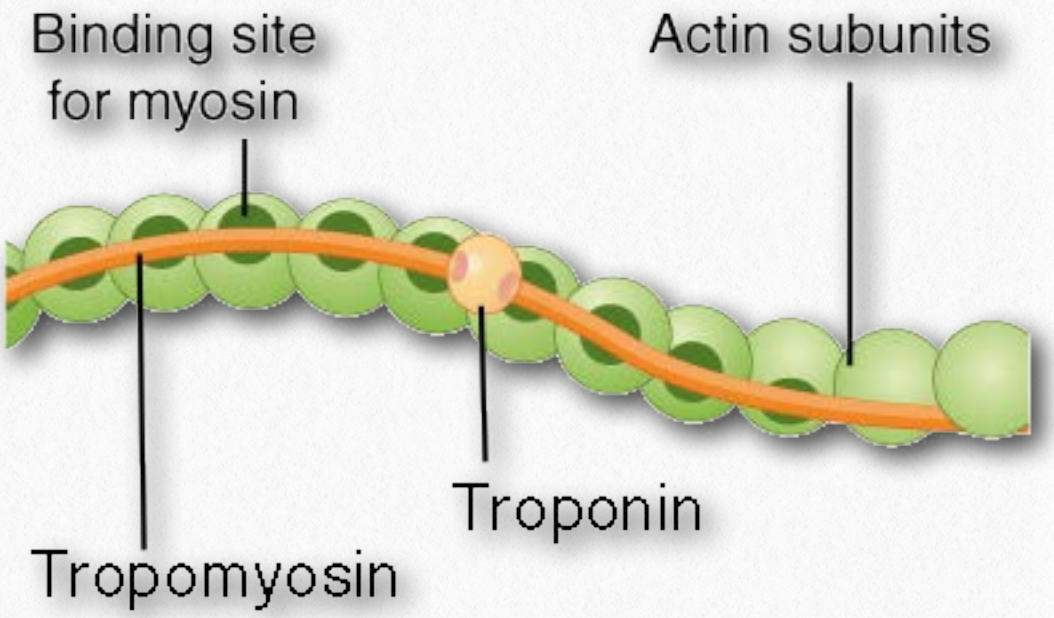


Figure 2.110 - Actin filament anatomy

Wikipedia

are a huge family of proteins, all of which bind to actin and all of which involve motion. Eighteen different classes of myosin proteins are known. Myosin II is the form responsible for generating muscle contraction. It is an elongated protein formed from two heavy chains with motor heads and two light chains. Each myosin motor head binds actin and has an ATP binding site. The myosin heads bind and hydrolyze ATP. This hydrolysis produces the energy necessary for myosin to walk toward the plus end of an actin filament.

YouTube Lectures by Kevin HERE & HERE

Non-muscle myosin IIs provide contraction needed to power the action of cytokinesis. Other myosin proteins are involved in movement of non-muscle cells. Myosin I is involved in intracellular organization. Myosin V performs vesicle and organelle transport. Myosin XI provides movement along cellular microfilament networks to facilitate organelle and cytoplasmic streaming in a particular direction.

Structure

Myosins have six subunits, two heavy chains and four light chains. Myosin proteins have domains frequently described as a head and a tail (Figure 2.111). Some also describe an intermediate hinge region as a neck. The head portion of myosin is the part that binds to actin. It uses energy from ATP hydrolysis to move along the actin filaments. In muscles, myosin proteins form aggregated structures referred to as thick filaments. Movements are directional.

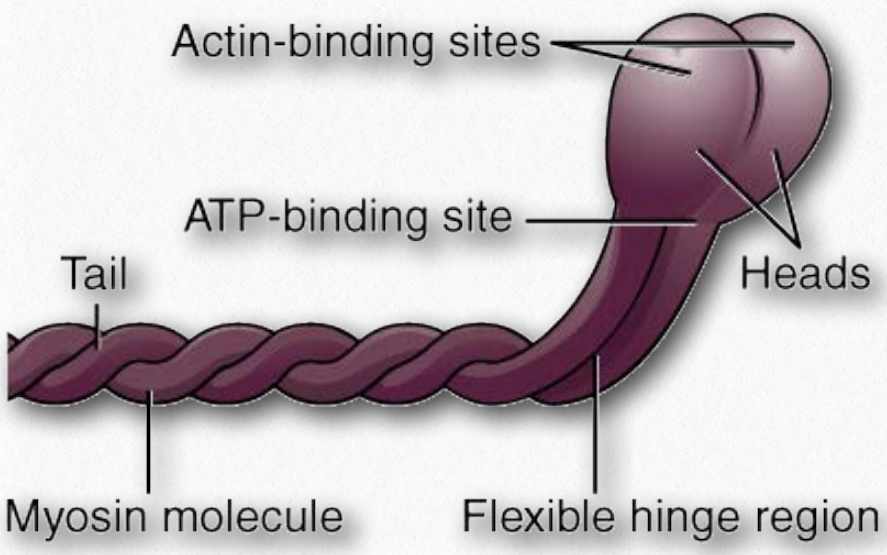


Figure 2.111 - Myosin protein anatomy

Wikipedia

Structural considerations of muscular contraction

Before we discuss the steps in the process of muscular contraction, it is important to describe anatomical aspects of muscles and nomenclature.

There are three types of muscle tissue - skeletal (striated), smooth, and (in vertebrates) cardiac. We shall concern ourselves mostly here with skeletal muscle tissue. Muscles may be activated by the central nervous system or, in the case of smooth and cardiac muscles, may contract involuntarily. Skeletal muscles may be slow twitch or fast twitch.

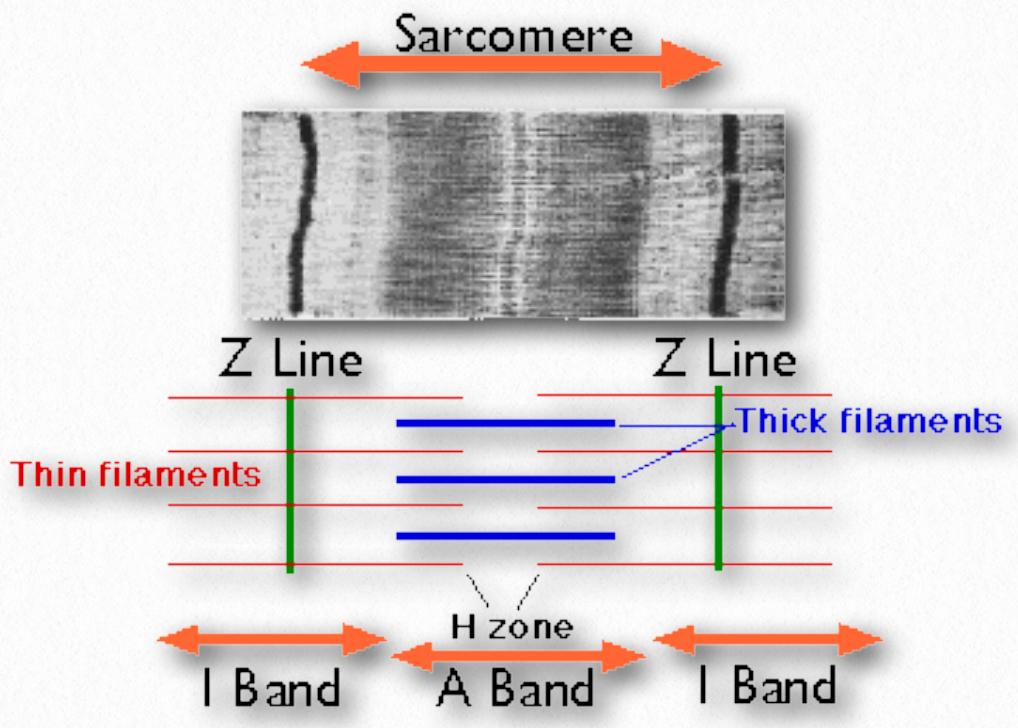


Figure 2.112 - Structural components of muscle. Wikipedia

Sarcomeres

Sarcomeres are described as the basic units comprising striated muscles and are comprised of thick (myosin) and thin (actin) filaments and a protein called titin. The filaments slide past each other in muscular contraction and then backwards in muscular relaxation. They are not found in smooth muscles.

Under the microscope, a sarcomere is the region between two Z-lines of striated muscle tissue (Figure 2.112). The Z-line is the distinct, narrow, dark region in the middle of an I-band. Within the sarcomere is an entire A-band with its central H-zone. Within the H-zone are located tails of myosin fibers, with the head pointed outwards from there projecting all the way to the I-band. The outside of the A-band is the darkest and it gets lighter moving towards the center.

Within the I-band are located thin filaments that are not occupied with thick myosin filaments. The A-band contains intact thick filaments overlaying thin filaments except in the central H zone, which contains only thick filaments. In the center of the H-zone is a line, known as the M-line. It contains connecting elements of the cellular cytoskeleton.

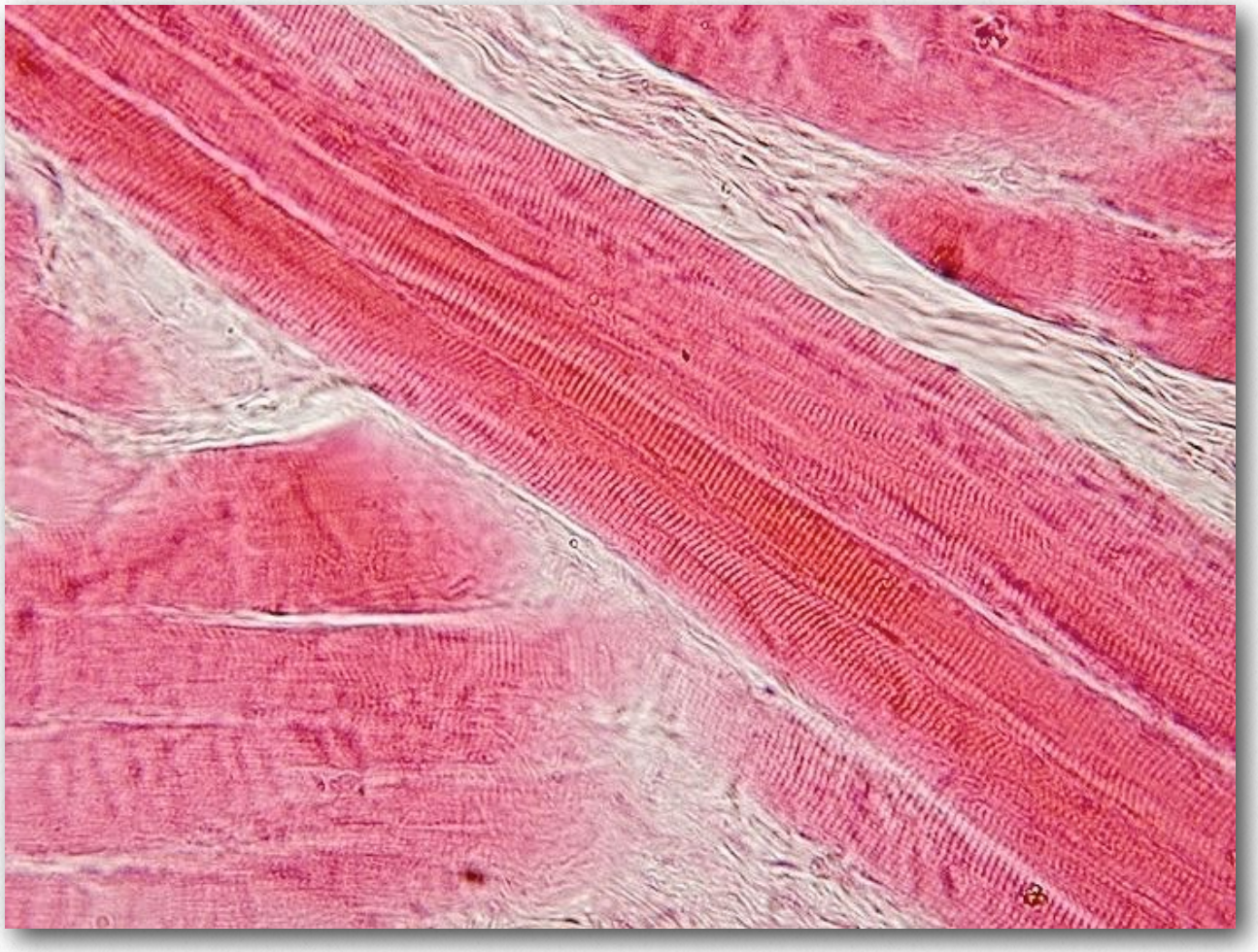


Figure 2.113 - **Skeletal muscle longitudinal section.**

Wikipedia

In muscular contraction, myosin heads walk along pulling their tails over the actin thin filaments, using energy from hydrolysis of ATP and pulling them towards the center of the sarcomere.

Sarcolemma

The sarcolemma (also known as the myolemma) is to muscle cells what the plasma membrane is to other eukaryotic cells - a barrier between inside and outside. It contains a lipid bilayer and a glycocalyx on the outside of it. The glyocalyx contains polysaccharides and connects with the basement membrane. The basement membrane serves a s scaffolding to connect muscle fibers to. This connection is made by transmembrane proteins bridging the actin cytoskeleton on the inside of the cell with the basement membrane on the outside. On the ends of the muscle fibers, each sarcolemma fuses with a tendon fiber and these, in turn, adhere to bones.

Sarcoplasmic reticulum

The sarcoplasmic reticulum (Figure 2.114) is a name for the structure found within muscle cells that is similar to the smooth endoplasmic reticulum found in other cells. It contains a specialized set of proteins to meet needs unique to muscle cells. The organelle largely serves as a calcium “battery,” releasing stored calcium to initiate muscular contraction when stimulated and taking up calcium when signaled at the end of the contraction cycle. It accomplishes these tasks using calcium ion channels for release of the ion and specific calcium ion pumps to take it up.

Movement direction

All myosins but myosin VI move towards the + end (the growing end) of the microfila-

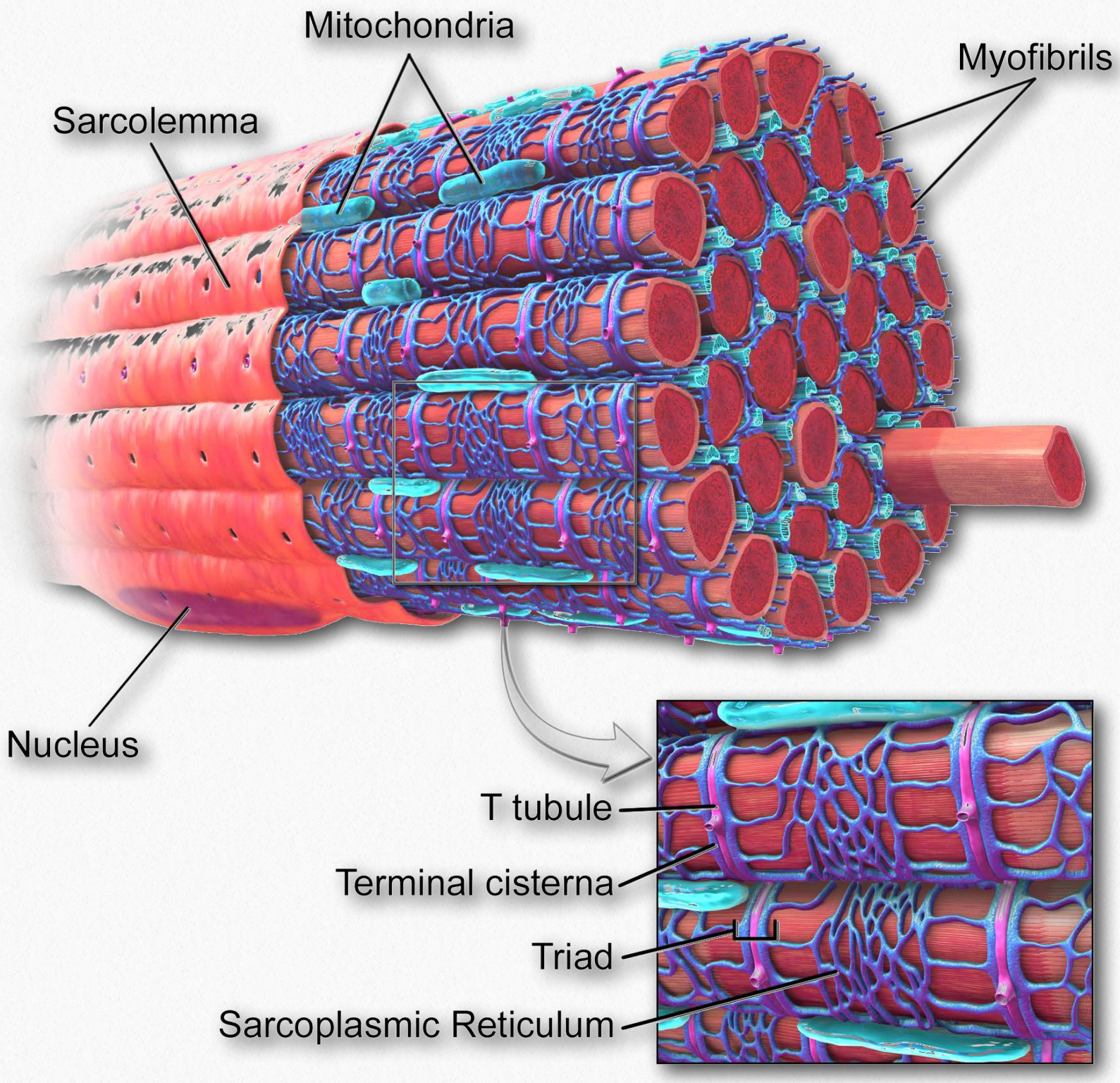


Figure 2.114 - Anatomy of a muscle fiber

Wikipedia

ment. The neck portion serves to link the head and the tail. It also a binding site for myosin light chain proteins that form part of a macromolecular complex with regulatory functions. The tail is the point of attachment of molecules or other "cargo" being moved. It can also connect with other myosin subunits and may have a role to play in controlling movement.

Muscular contraction

The sliding filament model has been proposed to describe the process of muscular tension/contraction. In this process a repeating set of actions slide a thin actin filament over a thick myosin filament as a means of creating tension/ shortening of the muscle fiber.

Steps in the process occur as follows:

A. A signal from the central nervous system (action potential) arrives at a motor neuron, which it transmits towards the neuromuscular junction (see more on the neurotransmission part of the process HERE)

B. At the end of the axon, the nerve signal stimulates the opening of calcium channels at the axon terminus causing calcium to flow into the terminal.

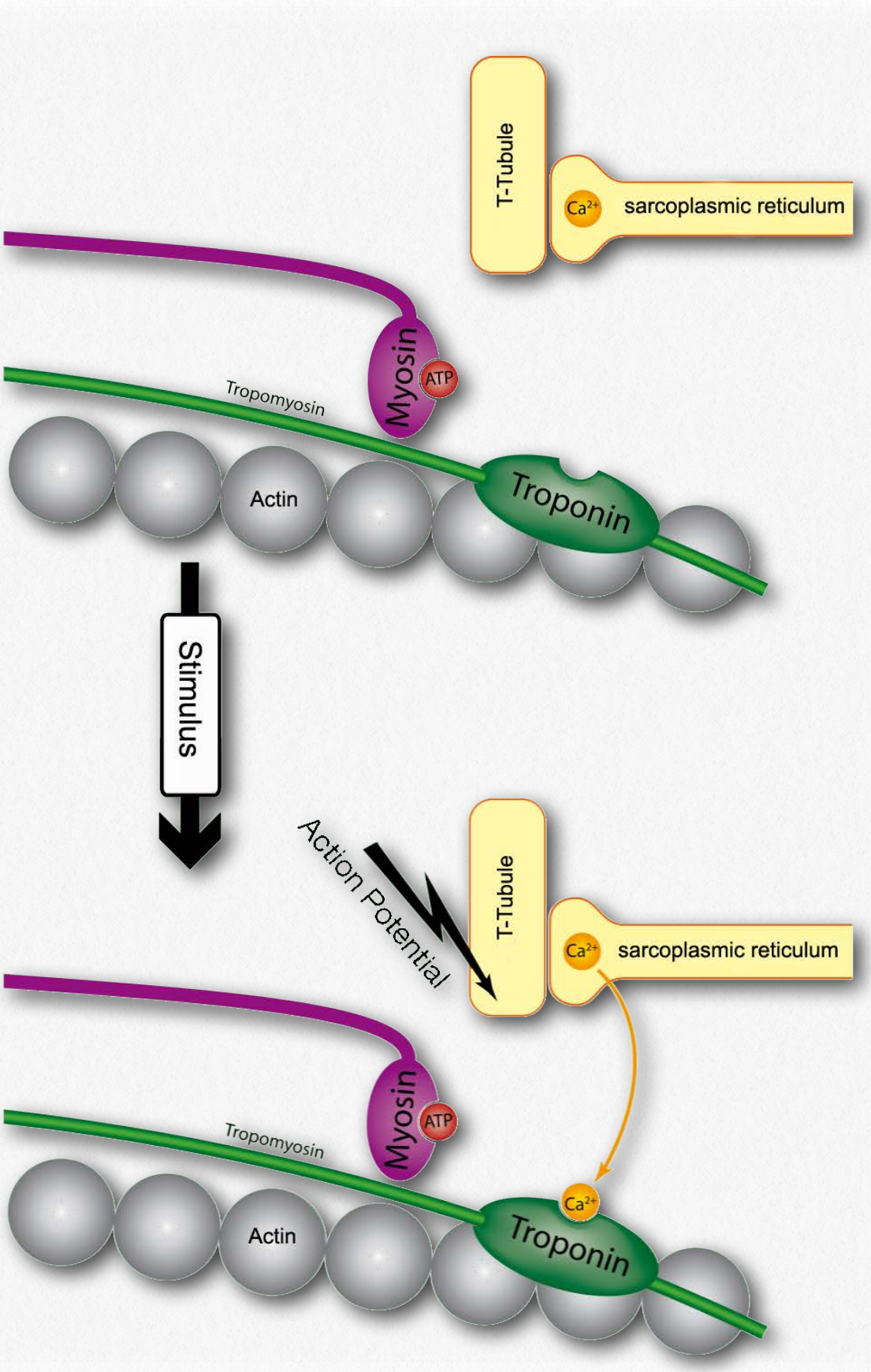


Figure 2.115 - 1. Activation of a muscle cell by release of calcium (step H)

Wikipedia

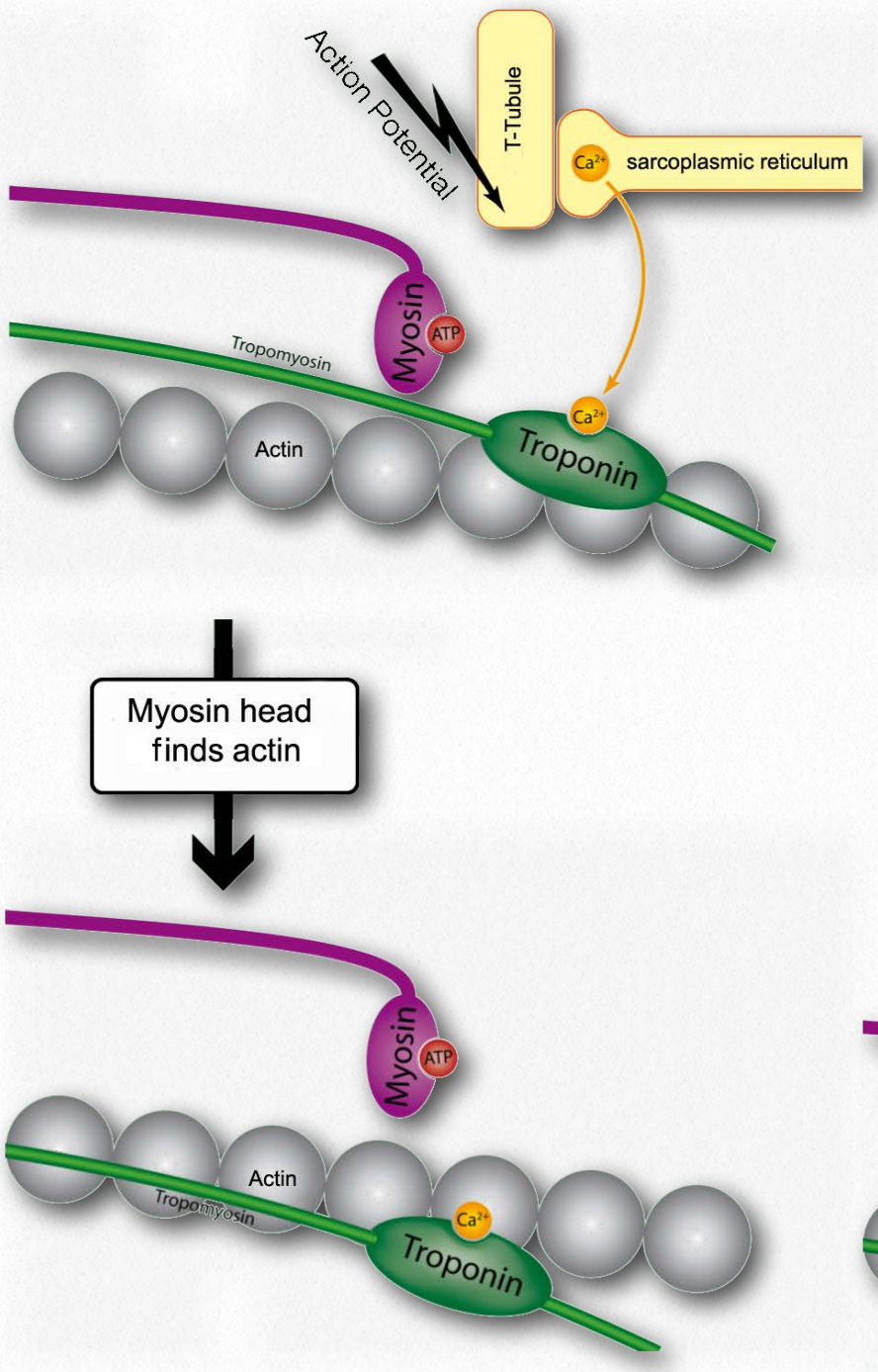


Figure 2.116 - 2. Calcium binding by troponin allows myosin to access actin sites (I).

Wikipedia

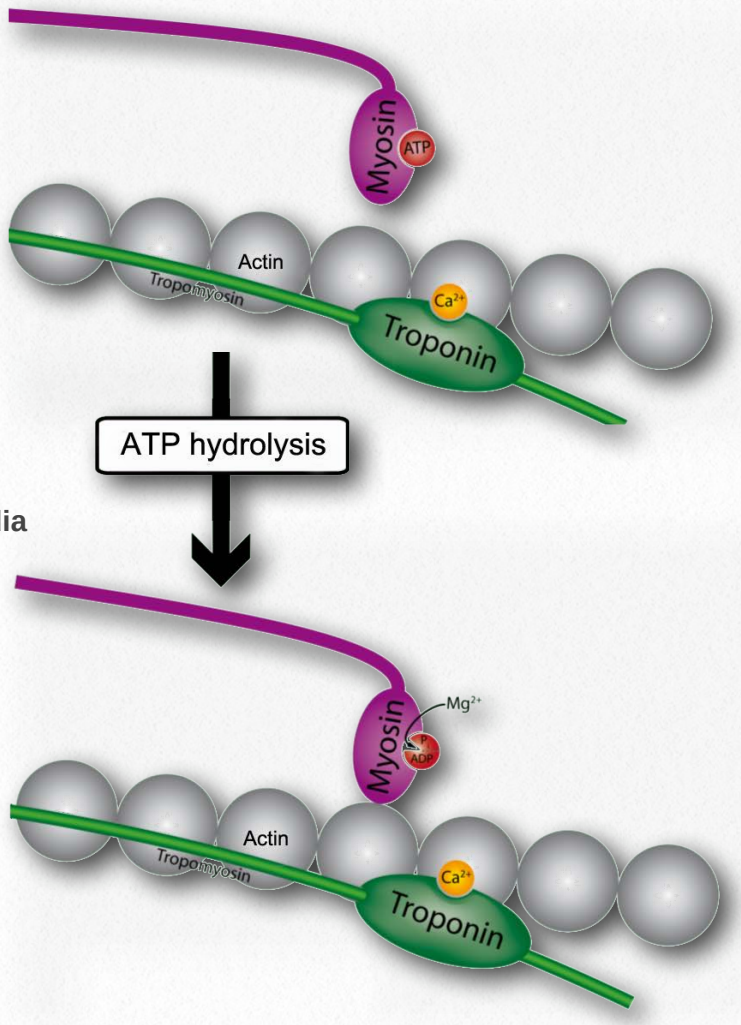


Figure 2.117 - 3. ATP cleavage by myosin allows actin attachment (J)

Wikipedia

apse and then binds to nicotinic acetylcholine receptors on the neuromuscular junction, activating them.

E. Activation of the receptor stimulates opening gates of sodium and potassium channels, allowing sodium to move into the cell and potassium to exit. The polarity of the membrane of the muscle cell (called a sarcolemma - Figure 2.111) changes rapidly (called the end plate potential).

F. Change in the end plate potential results in opening of voltage sensitive ion channels specific for sodium or potassium only to

C. Movement of calcium into the axon of the nerve causes acetylcholine (a neurotransmitter) in synaptic vesicles to fuse with the plasma membrane. This causes the acetylcholine to be expelled into the synaptic cleft between the axon and the adjacent skeletal muscle fiber.

D. Acetylcholine diffuses across the syn-

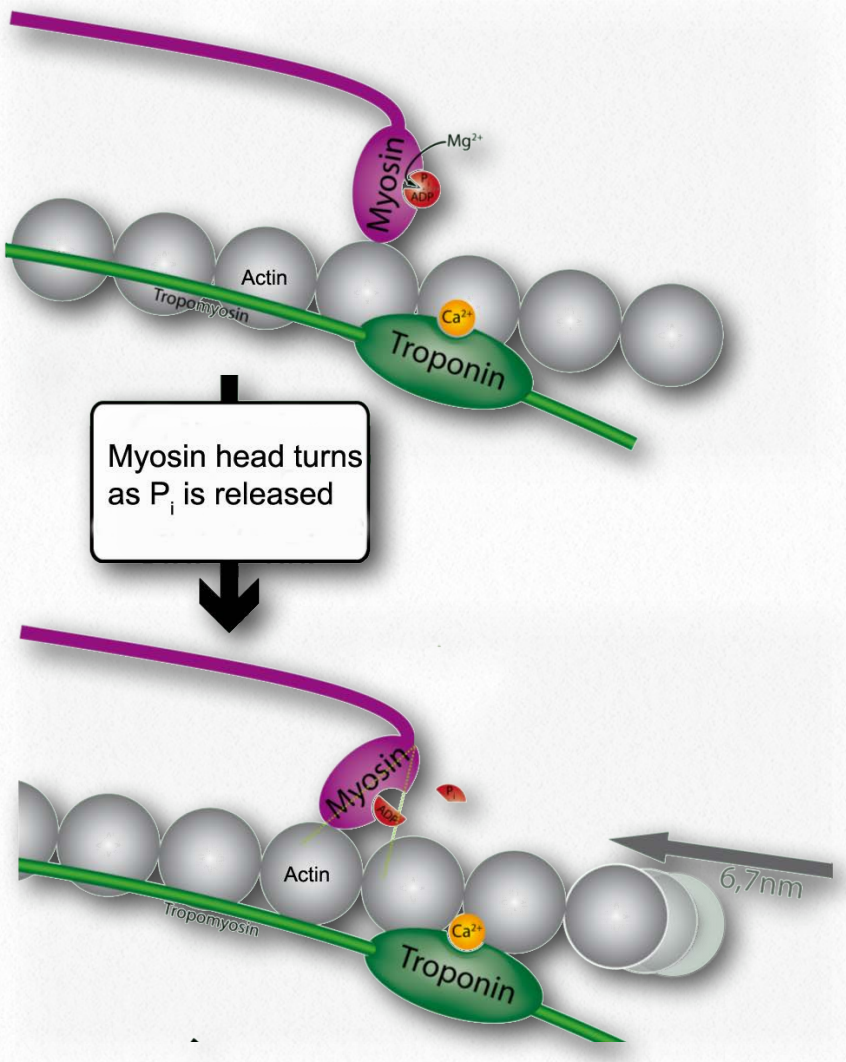


Figure 2.118 - 4. Release of P_i causes myosin hinge to bend. Thin filament pulled left (K).

Wikipedia

open, creating an action potential (voltage change) that spreads throughout the cell in all directions.

G. The spreading action potential depolarizes the inner muscle fiber and opens calcium channels on the sarcoplasmic reticulum (Figure 2.115).

H. Calcium released from the sarcoplasmic reticulum binds to troponin on the actin filaments (Figure 2.115).

I. Troponin alters the structure of the tropomyosin to which is it bound. This causes tropomyosin to move slightly, allowing access to myosin binding sites on the microfilament (also called thin filament) that it was covering (Figure 2.116).

J. Myosin (bound to ATP) cleaves the ATP to ADP and P_i, which it holds onto in its head region and then attaches itself to the exposed binding sites on the thin filaments causing inorganic phosphate to be released from the myosin followed by ADP (Figure 2.117).

K. Release of ADP and P_i is tightly coupled to

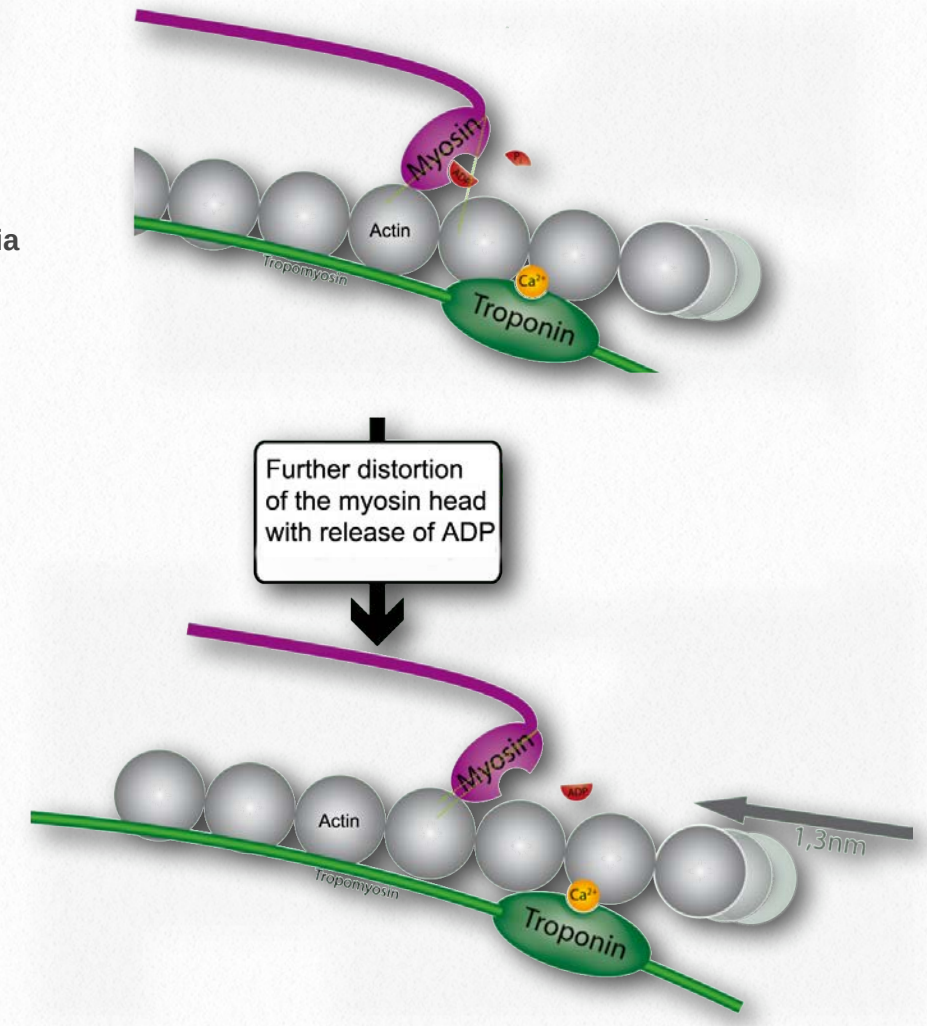


Figure 2.119 - 5. Release of ADP favors further bending of hinge and movement of thin filament leftward (K).

Wikipedia

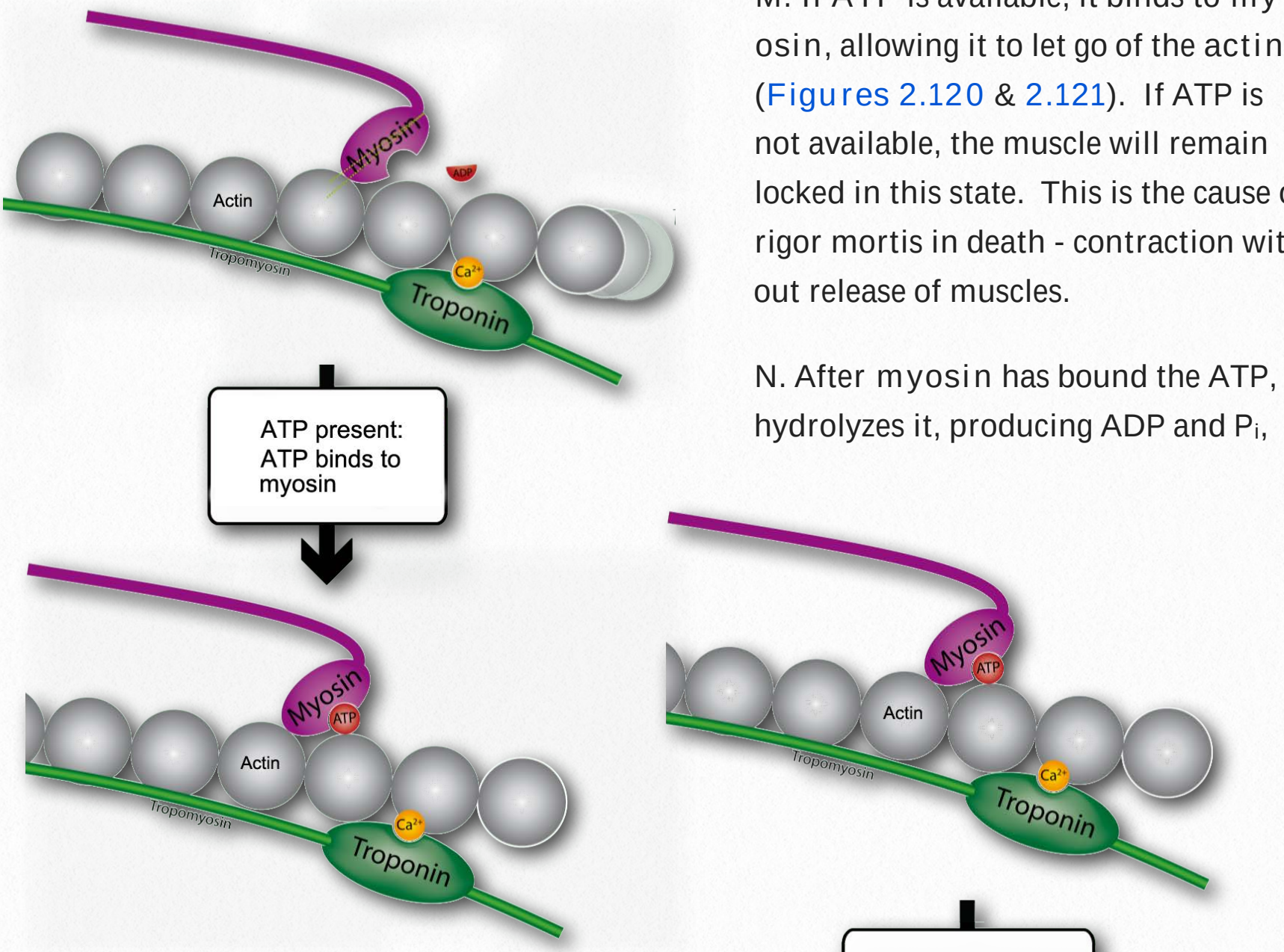


Figure 2.120 - When ATP is present, it binds to myosin (M).

Wikipedia

M. If ATP is available, it binds to myosin, allowing it to let go of the actin (Figures 2.120 & 2.121). If ATP is not available, the muscle will remain locked in this state. This is the cause of rigor mortis in death - contraction without release of muscles.

N. After myosin has bound the ATP, it hydrolyzes it, producing ADP and P_i,

a bending of the myosin hinge, resulting in what is called the power stroke. This causes the thin filament to move relative to the thick fibers of myosin (Figures 2.118 & 2.119).

L. Such movement of the thin filaments causes the Z lines to be pulled closer to each other. This results in shortening of the sarcomere as a whole (Figure 2.122) and narrowing of the I band and the H zones (Figure 2.123).

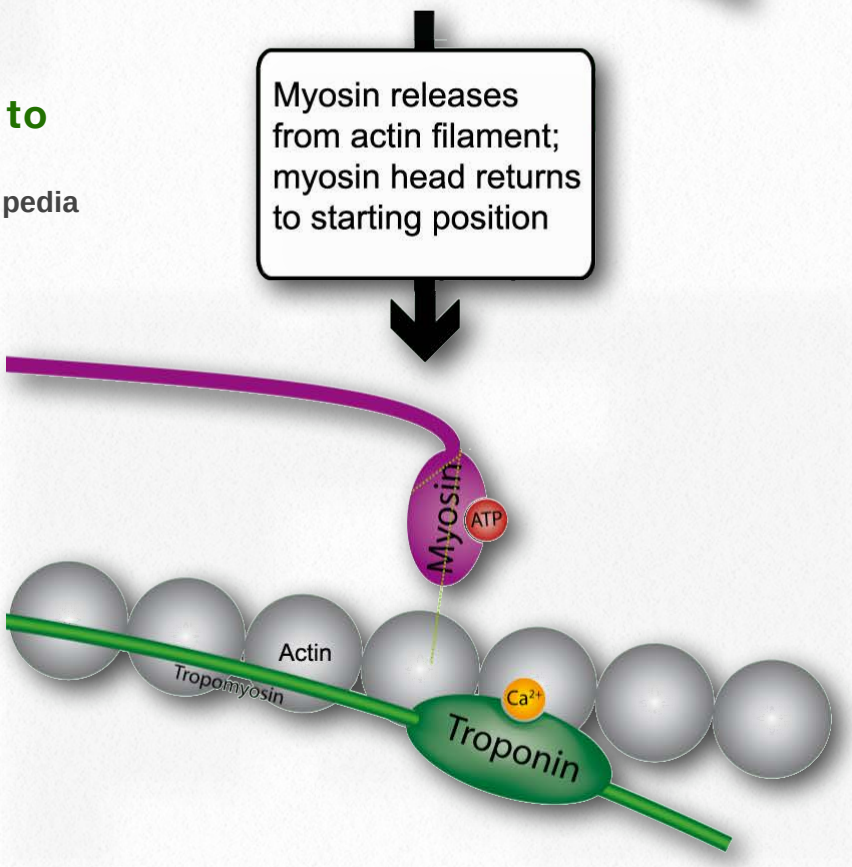


Figure 2.121 - Binding of ATP favors release of myosin from actin site (N)

Wikipedia

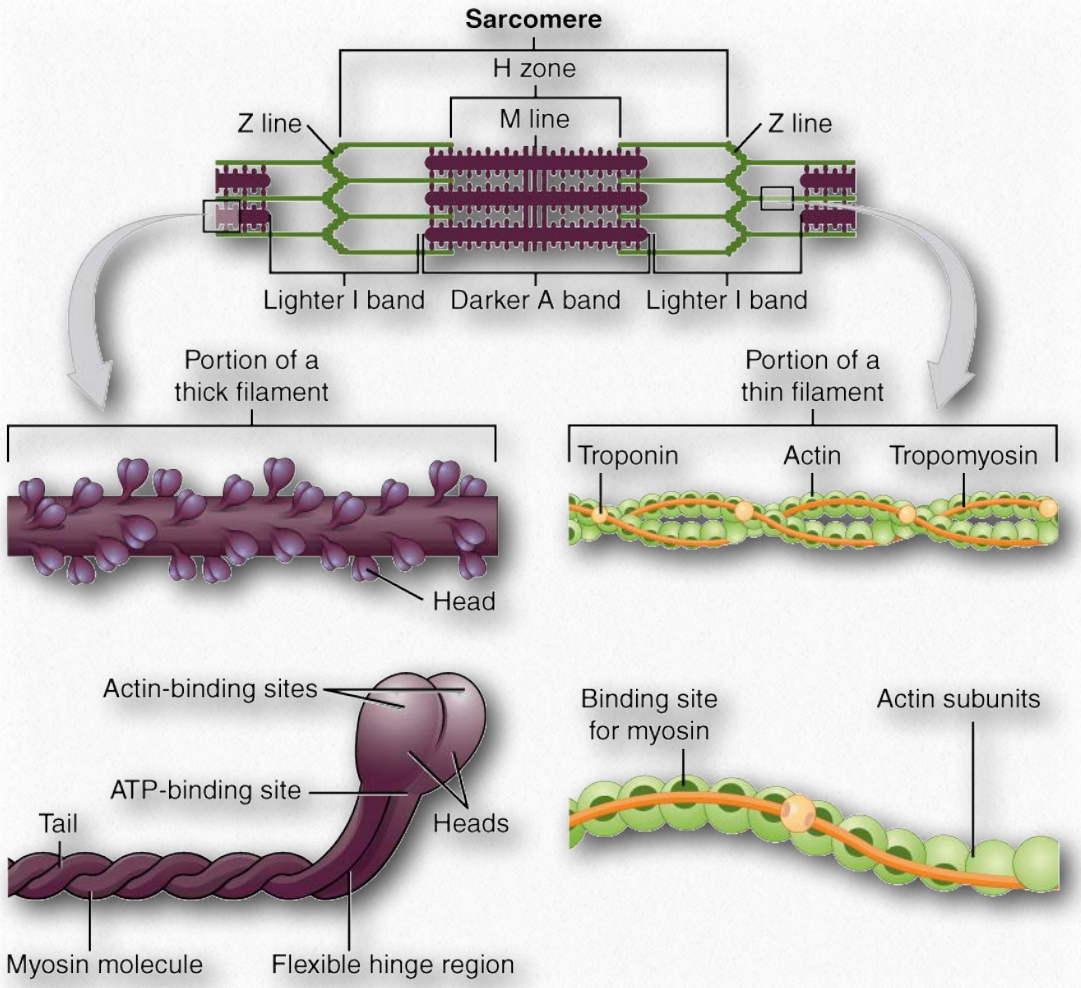


Figure 2.122 - Sarcomere Anatomy

Wikipedia

which are held by the head. Hydrolysis of ATP resets the hinge region to its original state, unbending it. This unbent state is also referred to as the cocked position.

O. If tropomyosin is still permitting access to binding sites on actin, the process repeats so long as ATP is available and calcium remains at a high enough concentration to permit it to bond to troponin.

Relaxation of the muscle tension occurs as the action potential in the muscle cell dissipates. This happens because all of the following things happen 1) the nerve signal stops; 2) the neurotransmitter is degraded by the enzyme acetylcholinesterase; and 3) the calcium concentration declines because it is taken up by the sarcoplasmic reticulum.

It should be noted that the sarcoplasmic reticulum is always taking

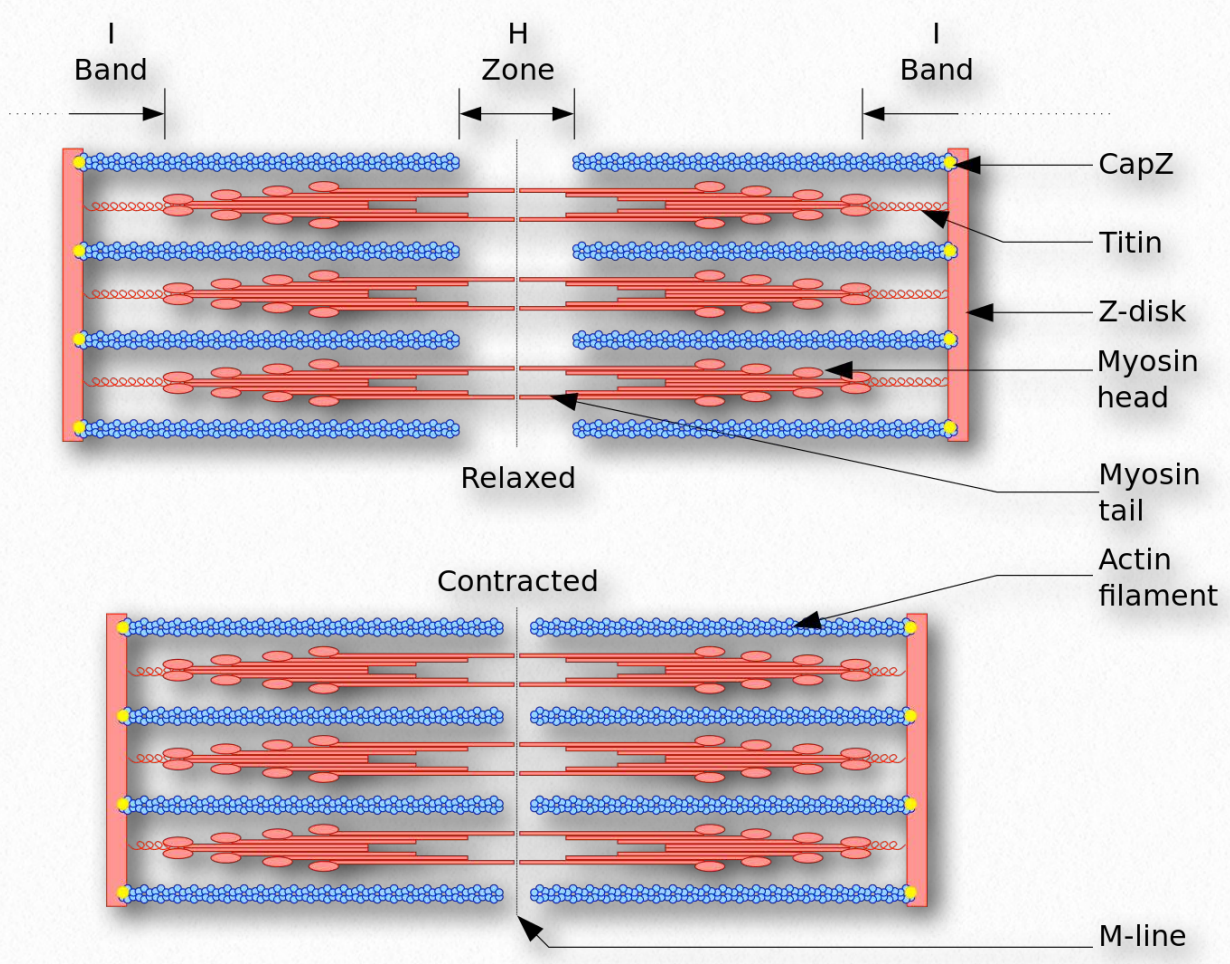


Figure 2.123 - The Sliding Filament Model of Muscular Contraction

Wikipedia

up calcium. Only when its calcium gates are opened by the action potential is it unable to reduce cellular calcium concentration. As the action potential decreases, then the calcium gates close and the sarcoplasmic reticulum "catches up" and cellular calcium concentrations fall. At that point troponin releases calcium, tropomyosin goes back to covering myosin binding sites on actin, myosin loses its attachment to actin and the thin filaments slide back to their original positions relative to the myosin thick filaments.

Tropomyosin

Tropomyosins are proteins that interact with actin thin filaments to help regulate their roles in movement, both in muscle cells and non-muscle cells (Figure 2.124). Tropomyosins interact to form head-to-toe dimers and perch along the α-helical groove of an actin filament. The isoforms of tropomyosin that are in muscle cells control interactions between myosin and the actin filament within the sarcomere and help to regulate contraction of the muscle. In other cells, non-muscle tropomyosins help to regulate the cytoskeleton's functions.

The interactions of tropomyosin with the cytoskeleton are considerably more complicated than what occurs in muscle cells. Muscle cells have five tropomyosin isoforms, but in the cytoskeleton of non-muscle cells, there are over 40 tropomyosins.

Troponin

The troponins involved in muscular contraction are actually a complex of three proteins known as troponin I, troponin C, and tro-

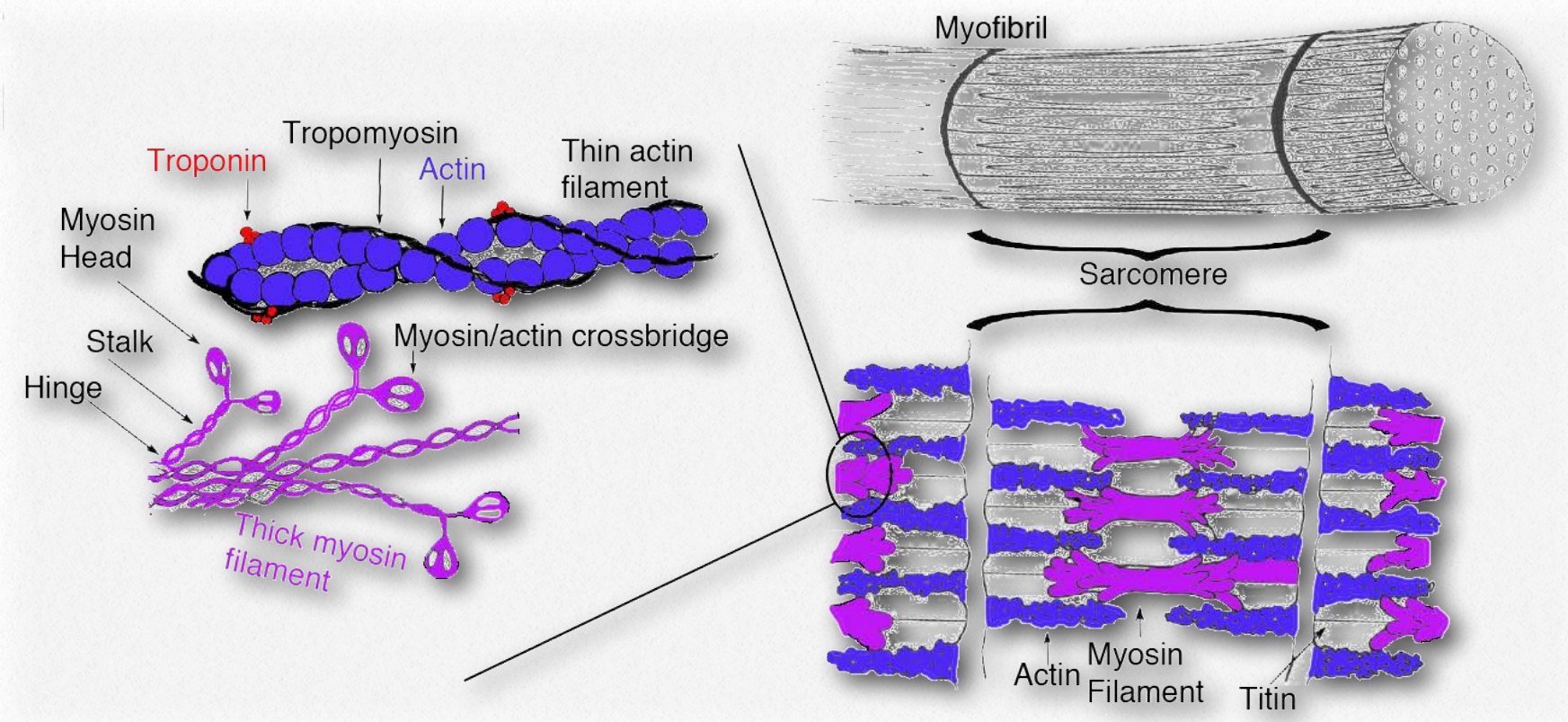


Figure 2.124 - Tropomyosin and troponin in muscle anatomy

Wikipedia

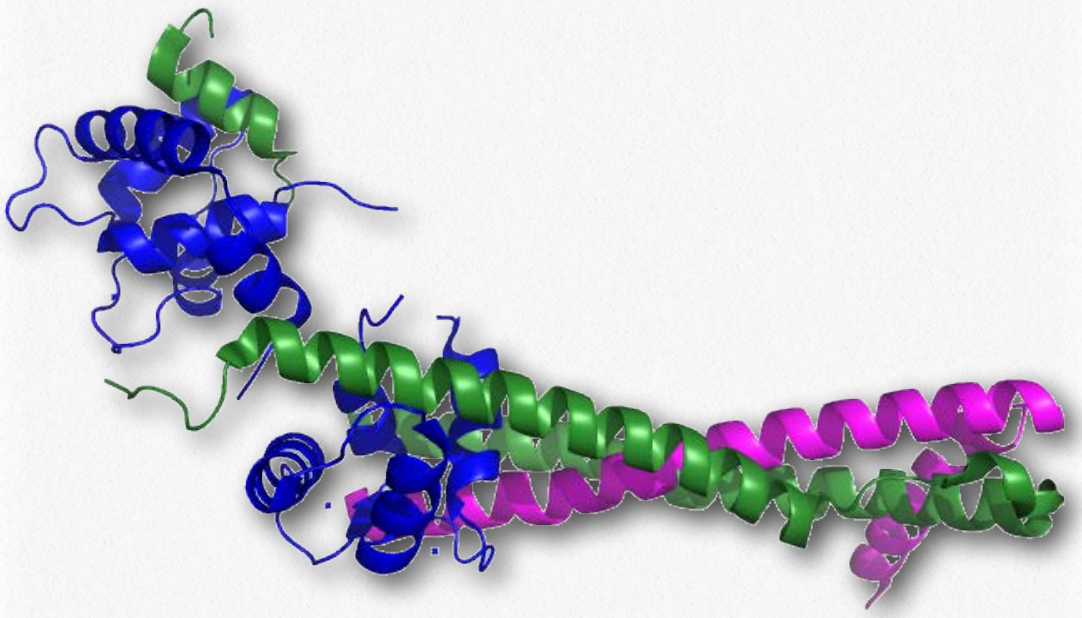


Figure 2.125 - Troponin complex of muscle. Blue = troponin C, magenta = troponin T , green = troponin I

ponin T (Figure 2.125). They associate with each other and with tropomyosin on actin filaments to help regulate the process of muscular contraction. Troponin I prevents binding of myosin's head to actin and thus prevents the most important step in contraction. Troponin C is a unit that binds to calcium ions. Troponin T is responsible for binding all three proteins to tropomyosin. Troponins in the bloodstream are indicative of heart disorders. Elevation of troponins in the blood occurs after a myocardial infarction and can remain high for up to two weeks.

Actinin

Actinin is a skeletal muscle protein that attaches filaments of actin to Z-lines of skeletal muscle cells. In smooth muscle cells, it also connects actin to dense bodies.

Titin

Titin (also known as connectin) is the molecular equivalent of a spring that provides striated muscle cells with elasticity. It is the third most abundant protein in muscle cells. The protein is enormous, with 244 folded individual protein domains spread across 363 exons (largest known number), with the largest known exon (17,106 base pairs long), and it is the largest protein known (27,000 to 33,000 amino acids, depending on splicing).

Unstructured sequences

The folded protein domains are linked together by unstructured sequences. The unstructured regions of the protein allow for unfolding when stretching occurs and refolding upon relaxation. Titin connects the M and Z lines in the sarcomere (Figure 2.123). Tension created in titin serves to limit the range of motion of the sarcomere, giving rise to what is called passive stiffness.

YouTube Lectures by Kevin HERE & HERE

Skeletal and cardiac muscles have slight amino acid sequence variations in their ti-

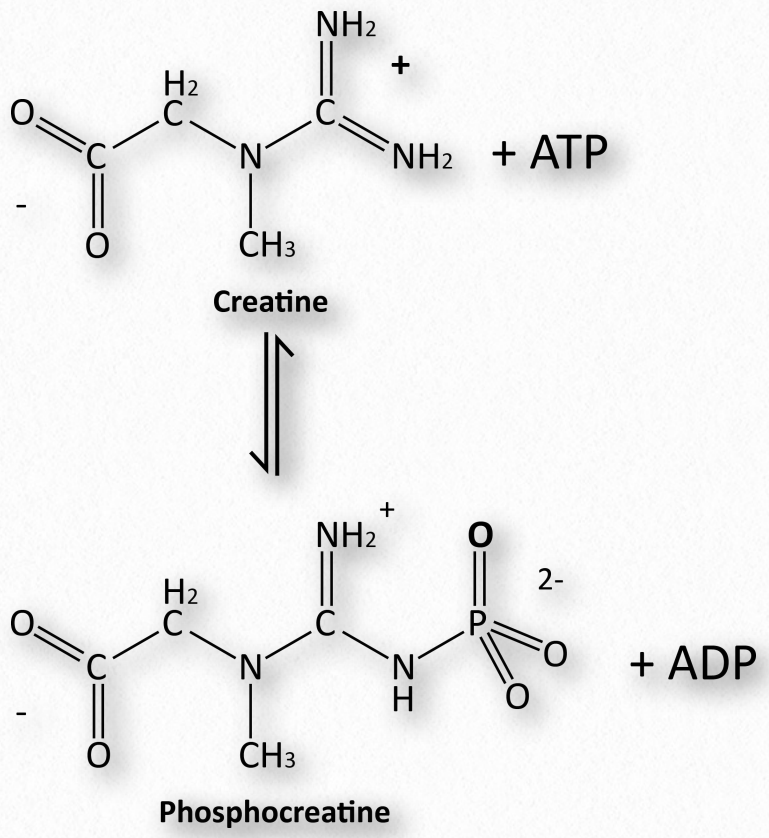


Figure 2.126 - Phosphorylation of creatine (phosphocreatine) - making of a creatine phosphate battery

Image by Aleia Kim

tin proteins and these appear to relate to differences in the mechanical characteristics of each muscle.

Energy backup for muscle energy

Myoglobin was described as a molecular batter for oxygen. Muscle cells have a better of their own for ATP. The is important for animals, but not for plants because a plant's need for energy is different than an animal's. Plants do not need to access energy sources as rapidly as animals do, nor do they have to maintain a constant internal temperature. Plants can neither flee predators, nor chase prey. These needs of animals are much more immediate and require that energy stores be accessible on demand.

Muscles, of course, enable the motion of animals and the energy required for muscle contraction is ATP. To have stores of energy readily available, muscles have, in addition to ATP, creatine phosphate for energy and glycogen for quick release of glucose to make more energy. The synthesis of creatine phosphate is a prime example of the effects of concentration on the synthesis of high energy molecules. For example, creatine phosphate has an energy of hydrolysis of -43.1 kJ/mol whereas ATP has an energy of hydrolysis of -30.5 kJ/mol. Creatine phosphate, however, is made from creatine and ATP in the reaction shown in Figure 2.126. How is this possible?

The $\Delta G^{\circ\prime}$ of this reaction is +12.6 kJ/mol, reflecting the energies noted above. In a resting muscle cell, ATP is abundant and ADP is low, driving the reaction downward, creating creatine phosphate. When muscular contraction commences, ATP levels fall and ADP levels climb. The above reaction then reverses and proceeds to synthesize ATP immediately. Thus, creatine phosphate acts like a battery, storing energy when ATP levels are high and releasing it almost instantaneously to create ATP when its levels fall.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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The Muscle Energy Song

To the tune of "*I Will*"

Metabolic Melodies Website HERE

For running and for jumping
You need some energy
Chemically the body stores it
In the form of ATP

If backup should be needed
Reserves are there in wait
Muscles brimming with supplies of
Tiny creatine phosphate

Ready whenever you are ever
Wanting to exercise
Steady as ever when whatever
Energy needs arise

The action is exacting
For leaping in the air
Myofibrils all contracted
Using energy extracted

From reactions that react in me
Using A-T-P
You see

Recorded by David Simmons
Lyrics by Kevin Ahern

Structure and Function: Nucleic Acids

Information molecules

The nucleic acids, DNA and RNA, may be thought of as the information molecules of the cell. In this section, we will examine the structures of DNA and RNA, and how these structures are related to the functions these molecules perform.

We will begin with DNA, which is the hereditary information in every cell, that is copied and passed on from generation to generation. The race to elucidate the structure of DNA was one of the greatest stories of 20th century science. Discovered in 1869 by Friedrich Miescher, DNA was identified as the genetic material in experiments in the 1940s led by Oswald Avery, Colin MacLeod, and Maclyn McCarty. X-ray diffraction work of Rosalind Franklin and the observations of Erwin Chargaff were combined by James Watson and Francis Crick to form a model of DNA that we are familiar with today. Their famous paper, in the April 25, 1953 issue of Nature, opened the modern era of molecular biology. Arguably, that one-page paper has had more scientific impact per word than any other research arti-

cle ever published. Today, every high school biology student is familiar with the double helical structure of DNA and knows that G pairs with C and A with T.

> It's taught in school of DNA
> The race for structure underway
> Gave rise to competition huge
> Along with data subterfuge
> In view of this we should extend
> New authorship to make amends
> A fairer order could be picked
> Franklin, Wilkins, Watson, Crick

The double helix, made up of a pair of DNA strands, has at its core, bases joined by hydrogen bonds to form base pairs - adenine always paired with thymine, and guanine invariably paired with cytosine. Two hydrogen bonds are formed between adenine and thymine, but three hydrogen bonds hold together guanine and cytosine (Figure 2.127).

The complementary structure immediately suggested to Watson and Crick how DNA might be (and in fact, is) replicated and it further explains how information is DNA is transmitted to RNA for the synthesis of proteins. In addition to the hydrogen bonds between bases of each strand, the double helix is held together by hydrophobic interactions of the

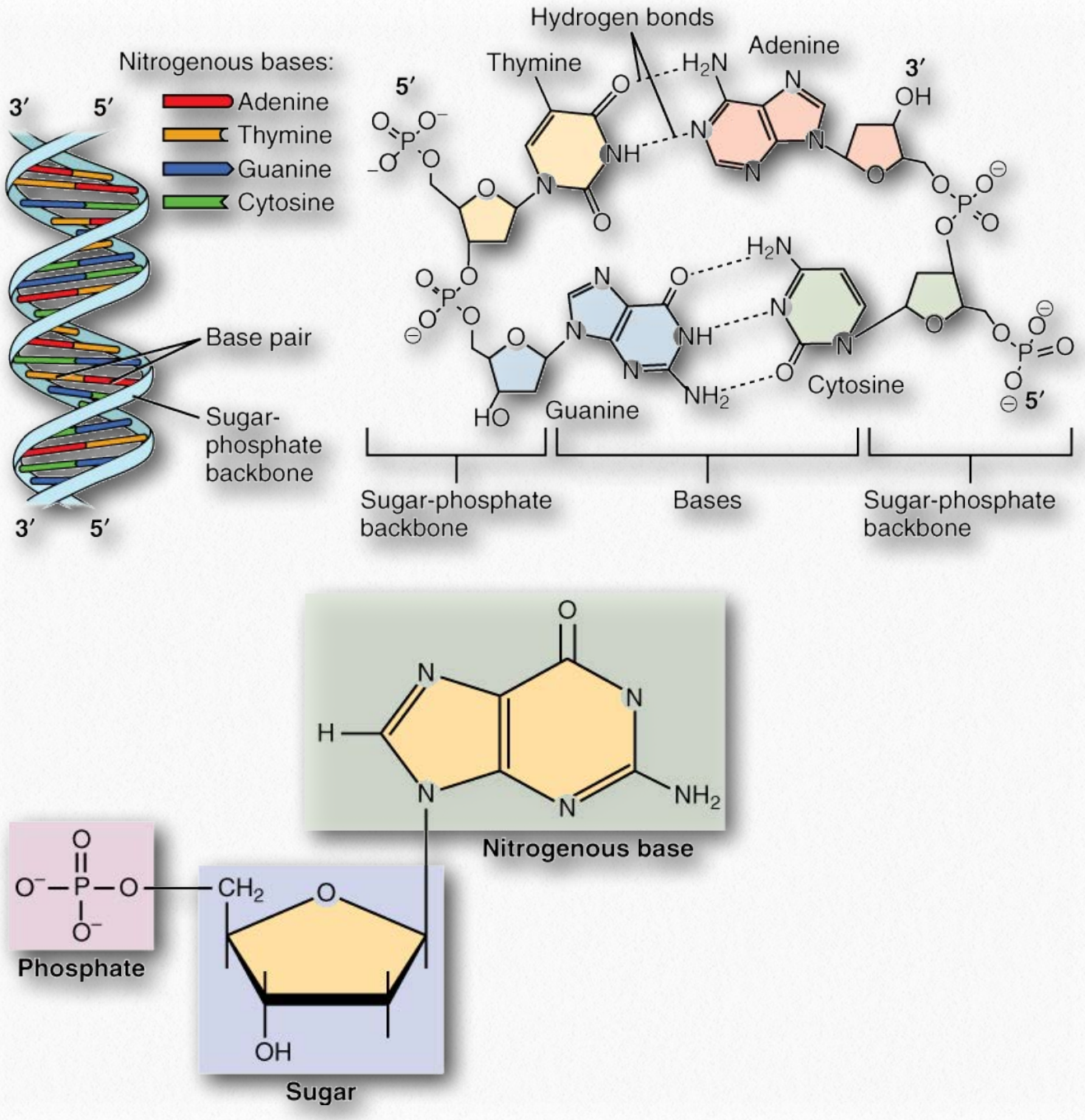

Figure 2.127 - A DNA duplex with base pairs, a closeup of base pairing, and a closeup of a nucleotide

Wikipedia

stacked, non-polar bases. Crucially, the sequence of the bases in DNA carry the information for making proteins. Read in groups of three, the sequence of the bases directly specifies the sequence of the amino acids in the encoded protein.

Structure

A DNA strand is a polymer of nucleoside monophosphates held together by phosphodiester bonds. Two such paired strands make up the DNA molecule, which is then twisted into a helix. In the most common B-form, the DNA helix has a repeat of 10.5 base pairs per turn, with sugars and phosphate forming the covalent phosphodiester "backbone" of the molecule and the adenine, guanine, cytosine, and thymine bases oriented in the middle where they form the now familiar base pairs that look like the rungs of a ladder.

Building blocks

The term nucleotide refers to the building blocks of both DNA (deoxyribonucleoside triphosphates, dNTPs) and RNA (ribonucleoside triphosphates, NTPs). In order to discuss this important group of molecules, it is necessary to define some terms.

Nucleotides contain three primary structural components. These are a nitrogenous base, a pentose sugar, and at least one phosphate. Molecules that contain only a sugar and a nitrogenous base (no phosphate) are called nucleosides. The nitrogenous bases found in nucleic acids include adenine and guanine (called purines) and cytosine, uracil, or thymine (called pyrimidines).

There are two sugars found in nucleotides - deoxyribose and ribose (Figure 2.128). By convention, the carbons on these sugars are labeled 1' to 5'. (This is to distinguish the carbons on the sugars from those on the

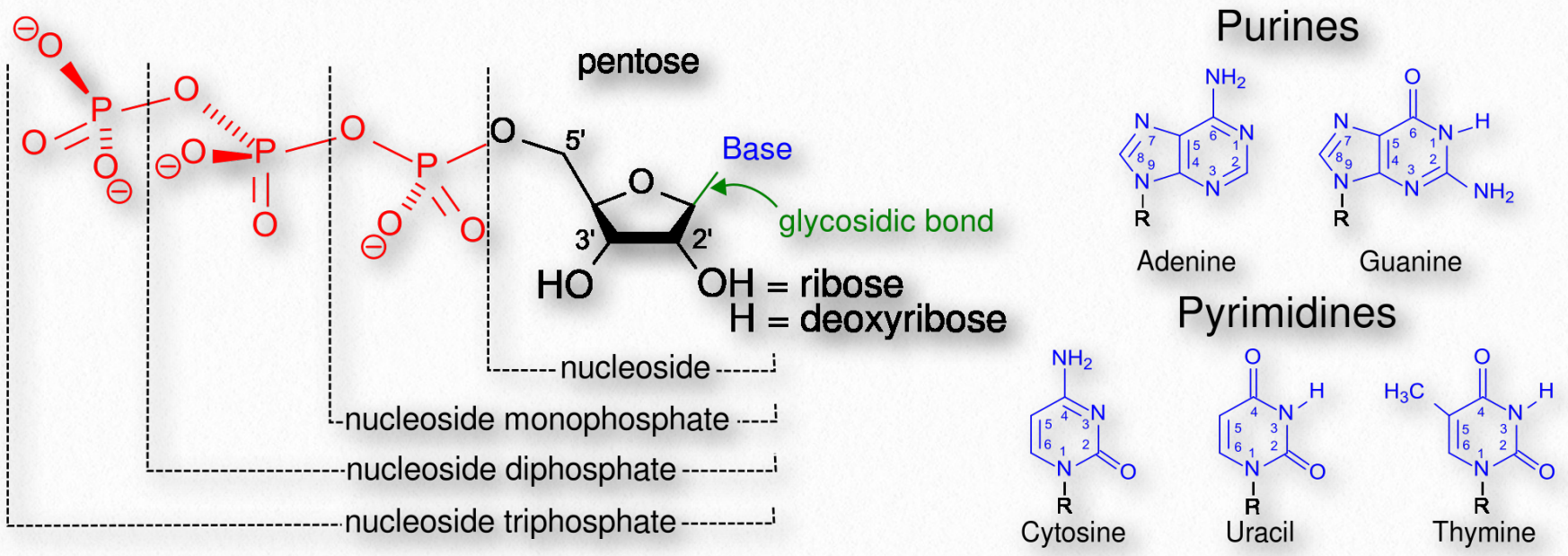

Figure 2.128 - Nucleotides, nucleosides, and bases

bases, which have their carbons simply labeled as 1, 2, 3, etc.) Deoxyribose differs from ribose at the 2' position, with ribose having an OH group, where deoxyribose has H.

Nucleotides containing deoxyribose are called deoxyribonucleotides and are the forms found in DNA. Nucleotides containing ribose are called ribonucleotides and are found in RNA. Both DNA and RNA contain nucleotides with adenine, guanine, and cytosine, but with very minor exceptions, RNA contains uracil nucleotides, whereas DNA contains thymine nucleotides. When a base is attached to a sugar, the product, a nucleoside, gains a new name.

uracil-containing = uridine (attached to ribose) / deoxyuridine (attached to deoxyribose)

thymine-containing - ribothymidine (attached to ribose) / thymidine (attached to deoxyribose)

cytosine-containing = cytidine (attached to ribose - Figure 2.129) / deoxycytidine (attached to deoxyribose)

guanine-containing = guanosine (attached to ribose) / deoxyguanosine (attached to deoxyribose)

adenine-containing = adenosine (attached to ribose) / deoxyadenosine (attached to deoxyribose)

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Of these, deoxyuridine and ribothymidine are the least common. The addition of one or more phosphates to a nucleoside makes it a nucleotide. Nucleotides are often referred to as nucleoside phosphates, for this reason. The number of phosphates in the nucleotide is indicated by the appropriate prefixes (mono, di or tri).

Figure 2.129 Cytidine

Thus, cytidine, for example, refers to a nucleoside (no phosphate), but cytidine monophosphate refers to a nucleotide (with one phosphate). Addition of second and third phosphates to a nucleoside monophosphate requires energy, due to the repulsion of negatively charged phosphates and this chemical energy is the basis of the high energy triphosphate nucleotides (such as ATP) that fuel cells.

Ribonucleotides as energy sources

Though ATP is the most common and best known cellular energy source, each of the four ribonucleotides plays important roles in providing energy. GTP, for example, is the energy source for protein synthesis (translation) as well as for a handful of metabolic reactions. A bond between UDP and glucose

makes UDP-glucose, the building block for making glycogen. CDP is similarly linked to several different molecular building blocks important for glycerophospholipid synthesis (such as CDP-diacylglycerol).

The bulk of ATP made in cells is not from directly coupled biochemical metabolism, but rather by the combined processes of electron transport and oxidative phosphorylation in mitochondria and/or photophosphorylation that occurs in the chloroplasts of photosynthetic organisms. Triphosphate energy in ATP is transferred to the other nucleosides/nucleotides by action of enzymes called kinases. For example, nucleoside diphosphokinase (NDPK) catalyzes the following reaction

$$ATP + NDP \rightleftarrows ADP + NTP$$

where 'N' of "NDP" and "NTP corresponds to any base. Other kinases can put single phosphates onto nucleosides or onto nucleoside monophosphates using energy from ATP.

Deoxyribonucleotides

Individual deoxyribonucleotides are derived from corresponding ribonucleoside diphosphates *via* catalysis by the enzyme known as ribonucleotide reductase (RNR). The deoxyribonucleoside diphosphates are then converted to the corresponding triphosphates (dNTPs) by the addition of a phosphate group. Synthesis of nucleotides

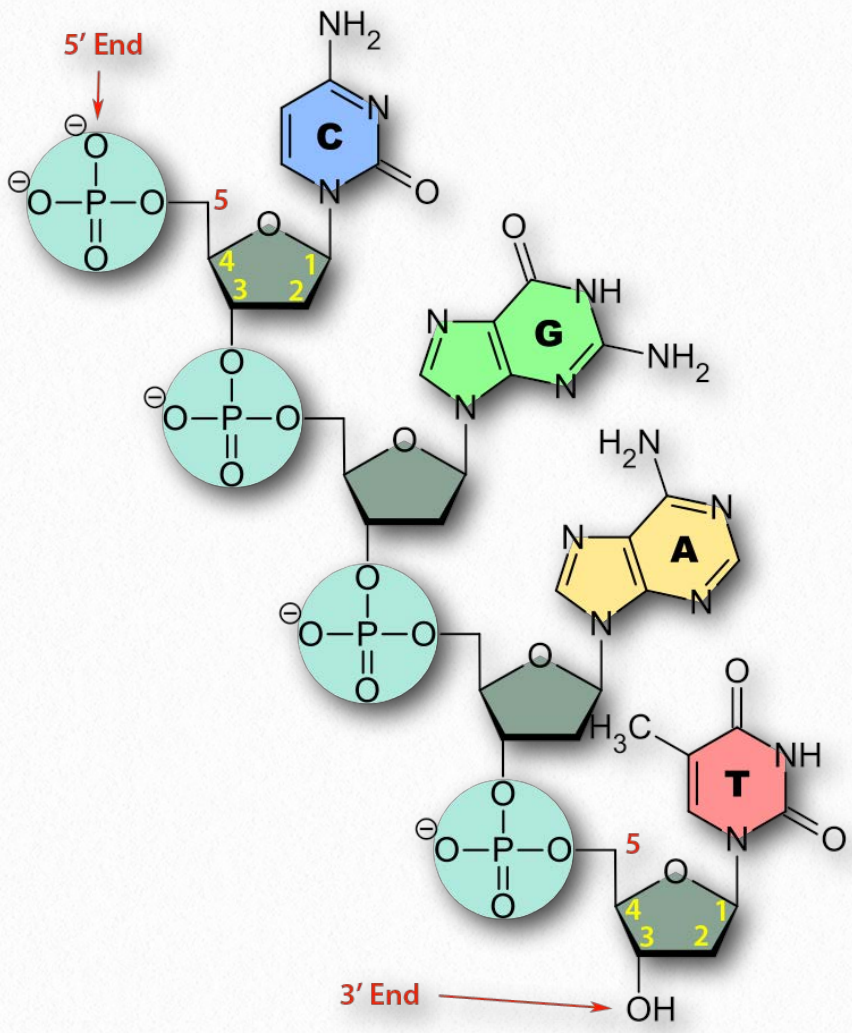


Figure 2.130 - 5'-3' Polarity of a DNA strand

containing thymine is distinct from synthesis of all of the other nucleotides and will be discussed later.

Building DNA strands

Each DNA strand is built from dNTPs by the formation of a phosphodiester bond, catalyzed by DNA polymerase, between the 3'OH of one nucleotide and the 5' phosphate of the next. The result of this directional growth of the strand is that the one end of the strand has a free 5' phosphate and the other a free 3' hydroxyl group (Figure 2.130). These are designated as the 5' and 3' ends of the strand.

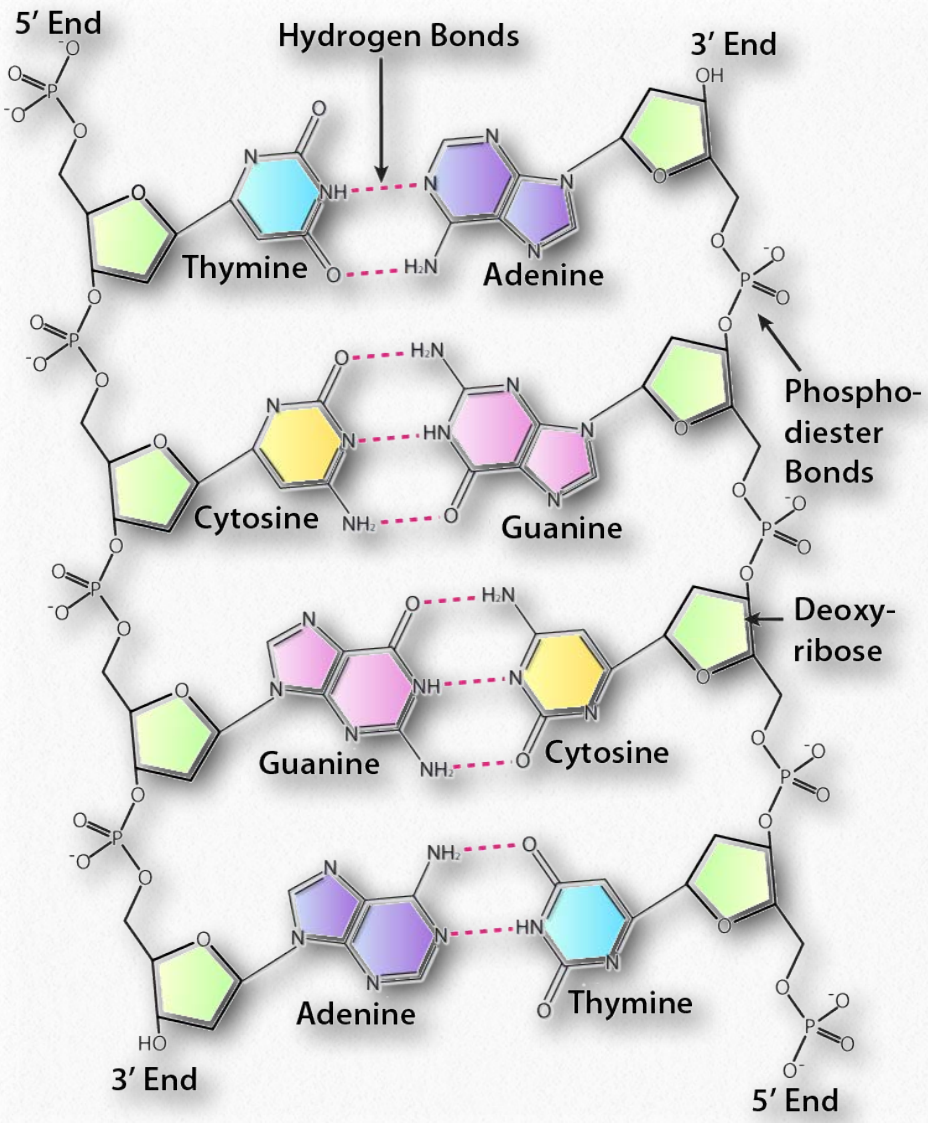


Figure 2.131 - Anti-parallel orientation of a DNA duplex, phosphodiester backbone, and base pairing

Image by Aleia Kim

Figure 2.131 shows two strands of DNA (left and right). The strand on the left, from 5' to 3' reads T-C-G-A, whereas the strand on the right, reading from 5' to 3' is T-C-G-A. The strands in a double-stranded DNA are arranged in an anti-parallel fashion with the 5' end of one strand across from the 3' end of the other.

Hydrogen bonds

Hydrogen bonds between the base pairs hold a nucleic acid duplex together, with two hydrogen bonds per A-T pair (or per A-U pair in RNA) and three hydrogen bonds per G-C pair. The B-form of DNA has a prominent major groove and a minor groove tracing the path of the helix (Figure 2.132). Proteins, such as transcription factors bind in these grooves and access the hydrogen bonds of the base pairs to "read" the sequence therein.

Other forms of DNA besides the B-form (Movie 2.5) are known (Figure 2.133). One of these, the A-form, was identified by Rosalind Franklin in the same issue of Nature as Watson and Crick's paper. Though the A-form structure is a relatively minor form of DNA and resembles

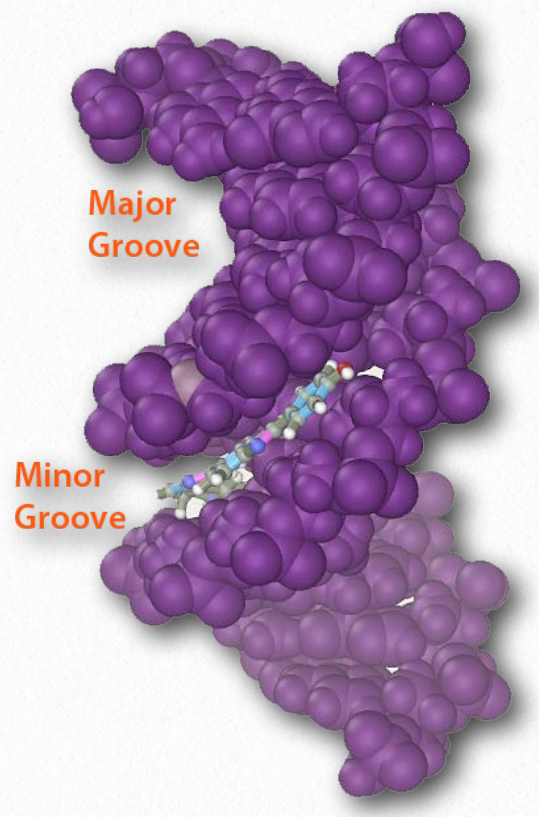
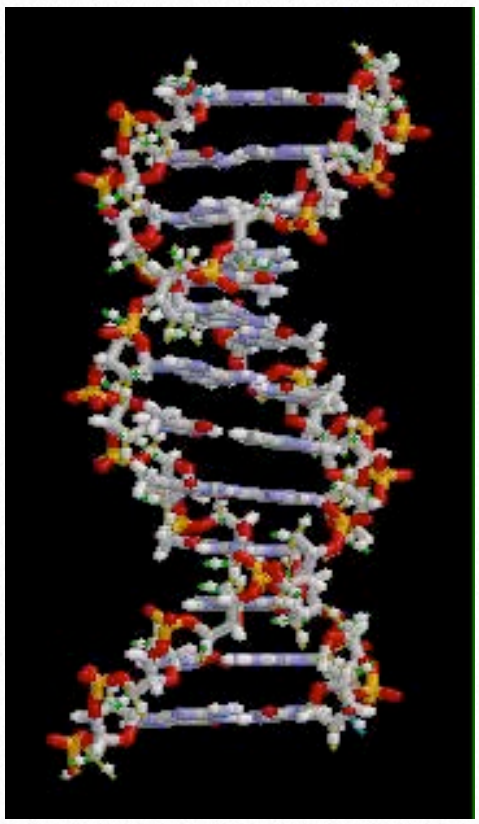


Figure 2.132 - Major and minor grooves of DNA. The minor groove has been bound by a dye

Wikipedia



Movie 2.5 - B-form DNA duplex rotating in space

Wikipedia

the B-form, it turns out to be important in the duplex form of RNA and in RNA-DNA hybrids. Both the A form and the B-form of DNA have the helix oriented in what is termed the right-handed form.

Z-DNA

The A-form and the B-form stand in contrast to another form of DNA, known as the Z-form. Z-DNA, as it is known, has the same base-pairing rules as the B and A forms, but instead has the helices twisted in the opposite direction, making a left-handed helix (Figure 2.133). The Z-form has a sort of zig-zag shape, giving rise to the name Z-DNA.

In addition, the helix is rather stretched out compared to the A- and B-forms. Why are there different topological forms of DNA? The answer relates to both superhelical tension and sequence bias. Sequence bias means that certain sequences tend to favor the "flipping" of B-form DNA into other forms. Z-DNA forms are favored by long stretches of alternating Gs and Cs. Superhelical tension is discussed below.

Superhelicity

Short stretches of linear DNA duplexes exist in the B-form and have 10.5 base pairs per turn. Double helices of DNA in the cell can vary in the number of base pairs per turn they

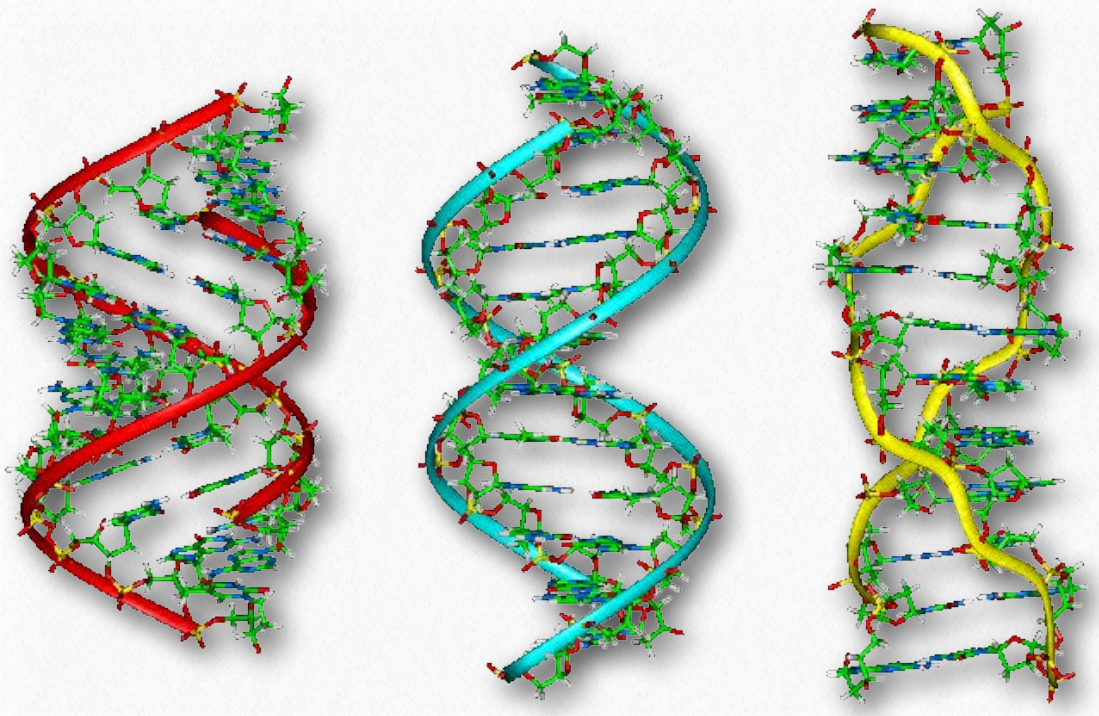


Figure 2.133 - From left to right, the A-, B-, and Z-forms of DNA

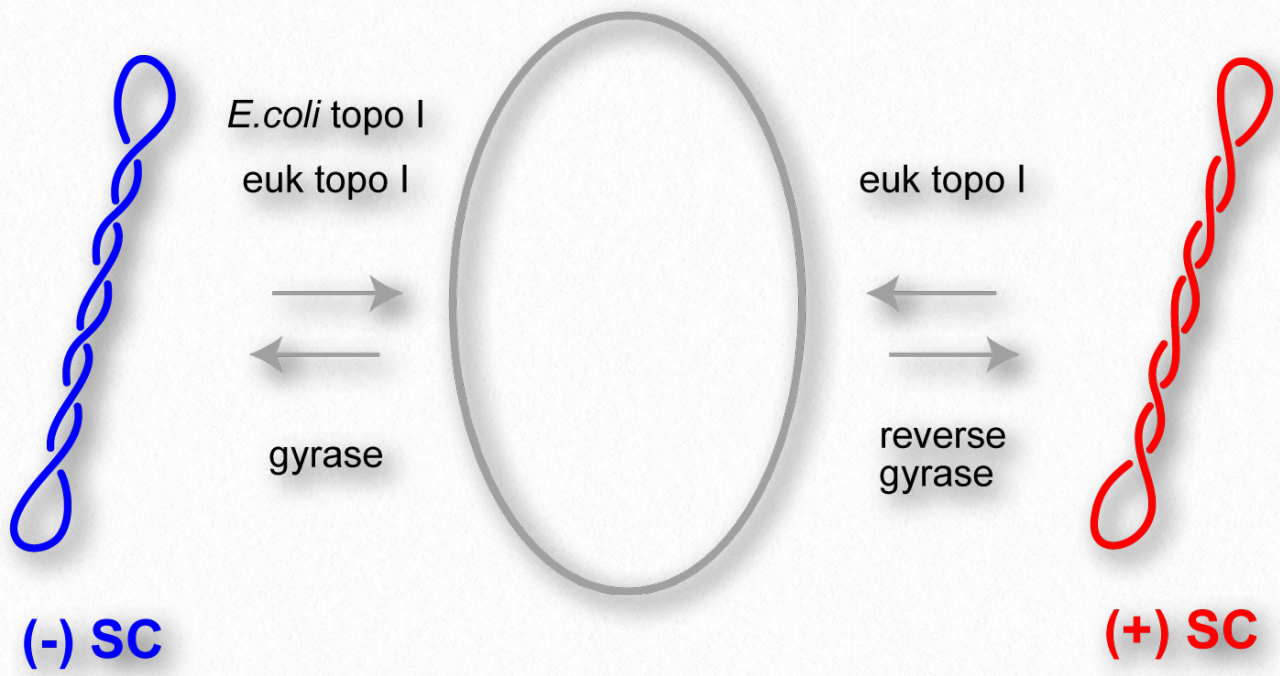


Figure 2.134 - Negatively supercoiled, relaxed circular, and positively supercoiled DNA interconverted by topoisomerase enzymes

Wikipedia

contain. There are several reasons for this. For example, during DNA replication, strands of DNA at the site of replication get unwound at the rate of 6000 rpm by an enzyme called helicase. The effect of such local unwinding at one place in a DNA has the effect increasing the winding ahead of it. Unrelieved, such 'tension' in a DNA duplex can result in structural obstacles to replication.

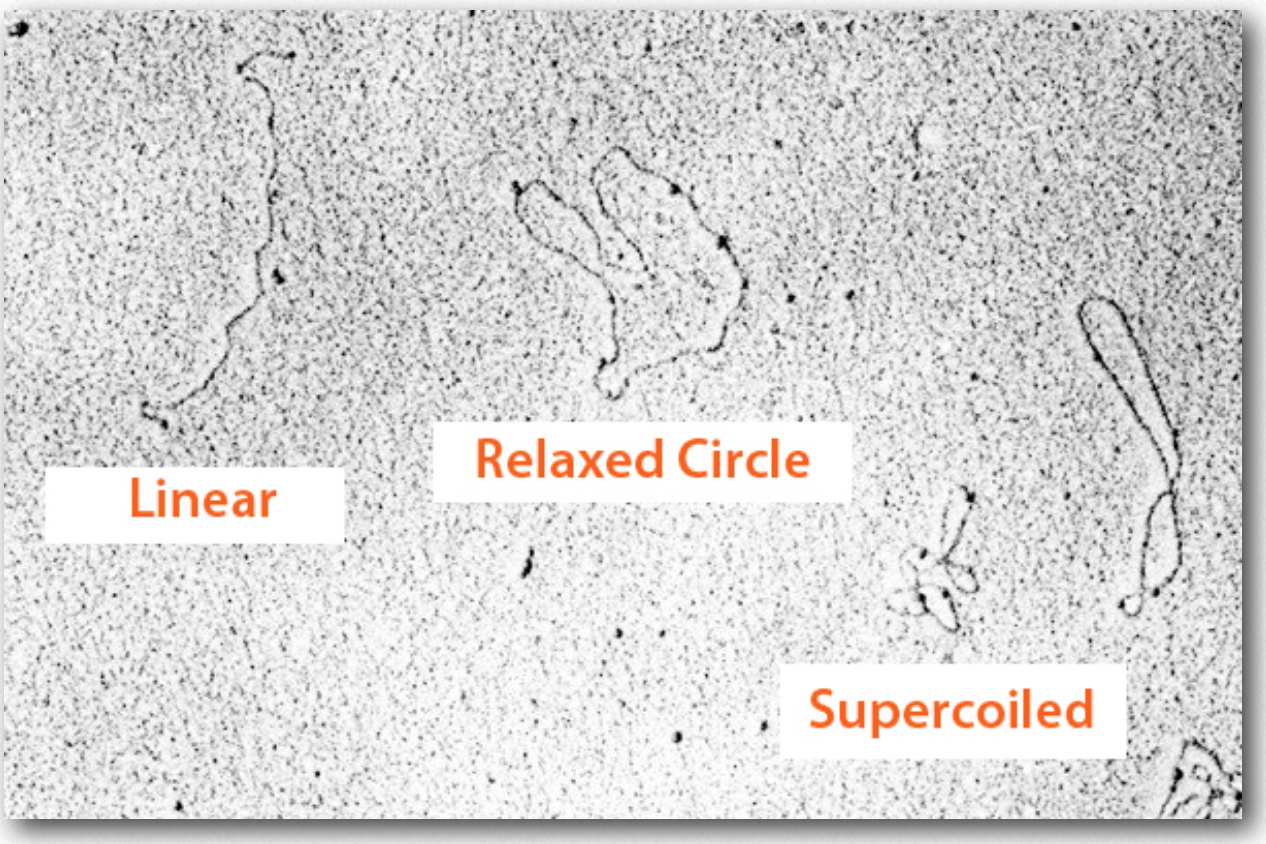


Figure 2.135 - Three topological forms of DNA

Wikipedia

Such adjustments can occur in three ways. First, tension can provide the energy for 'flipping' DNA structure. Z-DNA can arise as a means of relieving the tension. Second, DNA can 'supercoil' to relieve the tension (Figures 2.134 & 2.135). In this method, the duplex crosses over itself repeatedly, much like a rubber band will coil up if one holds one section in place and twists another part of it. Third, enzymes called topoisomerases can act to relieve or, in some cases, increase

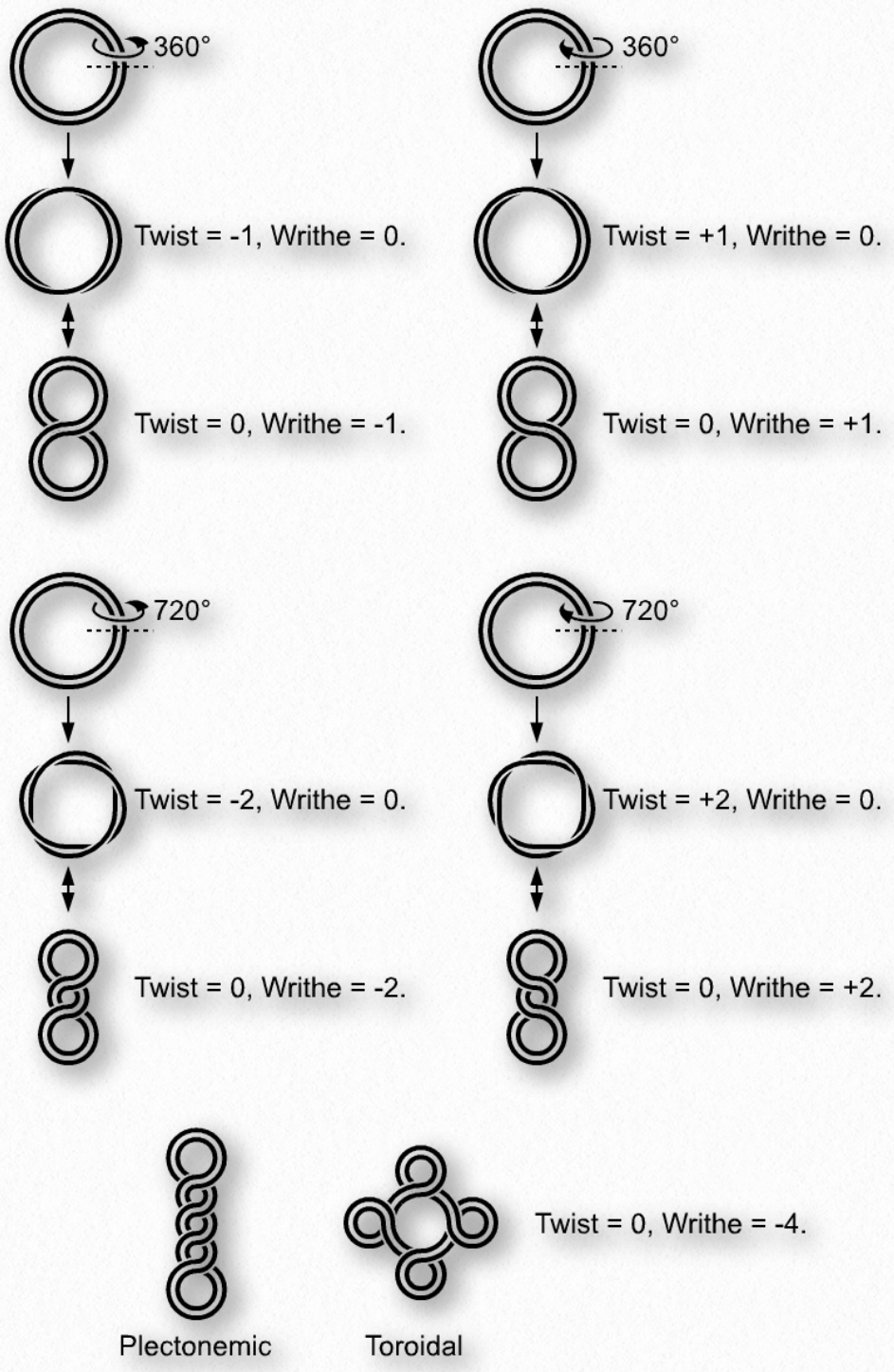


Figure 2.136 - Twists and writhes - DNA duplex coiling omitted for simplicity

Wikipedia

the tension by adding or removing twists in the DNA.

Topological isomers

As noted, so-called "relaxed" DNA has 10.5 base pairs per turn. Each turn corresponds to one twist of the DNA. Using enzymes, it is possible to change the number of base pairs per turn. In either the case of increasing or decreasing the twists per turn, tension is introduced into the DNA structure. If the tension cannot be relieved, the DNA duplex will act to relieve the strain, as noted. This is most easily visualized for circular DNA, though long linear DNA (such as found in eukaryotic chromosomes) or DNAs constrained in other ways will exhibit the same behavior.

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Parameters

To understand topologies, we introduce the concepts of 'writhe' and 'linking number'. First, imagine either opening a closed circle of DNA and either removing one twist or adding one twist and then re-forming the circle. Since the strands have no free ends, they cannot relieve the induced tension by re-adding or removing the twists at their ends, respectively. Instead, the tension is relieved by "superhelices" that form with crossing of the double strands over each other (figure 8 structures in Figure 2.136). Though it is not apparent to visualize, each crossing of the double strands in this way allows twists to be increased or decreased correspondingly. Thus, superhelicity allows the double helix to re-assume 10.5 base pairs per turn by adding or subtracting twists as necessary and replacing them with writhes.

We write the equation L = T + W where T is the number of twists in a DNA, W is the number of writhes, and L is the linking number. The linking number is therefore the sum of the twists and writhes. Interestingly, inside of cells, DNAs typically are in a supercoiled form. Supercoiling affects the size of the DNA (compacts it) and also the expression of genes within the DNA, some having enhanced expression and some having reduced expression when supercoiling is present. Enzymes called topoisomerases alter the superhelical density of DNAs and play roles in DNA replication, transcription, and control of gene expression. They work by making cuts in one strand (Type I topoisomerases) or both strands (Type II topoisomerases) and then add or subtract twists as appropriate to the target DNA. After that process is complete, the topoisomerase re-ligates the nick/cut it had made in the DNA in the first step.

Topoisomerases may be the targets of antibiotics. The family of antibiotics known as fluoroquinolones work by interfering with the action of bacterial type II topoisomerases. Ciprofloxacin also preferentially targets bacterial type II topoisomerases. Other topoisomerase inhibitors target eukaryotic topoisomerases and are used in anti-cancer treatments.

RNA

The structure of RNA (Figure 2.137) is very similar to that of a single strand of DNA. Built of ribonucleotides, joined together by the same sort of phosphodiester bonds as in DNA, RNA uses uracil in place of thymine. In cells, RNA is assembled by RNA polymerases, which copy a DNA template in the much same way that DNA polymerases replicate a parental strand. During the synthesis of RNA, uracil is used across from an adenine in the DNA template. The building of messenger RNAs by copying a DNA template is a crucial step in the transfer of the information in DNA to a form that directs the synthesis of protein. Additionally, ribosomal and transfer RNAs serve important roles in "reading" the information in the

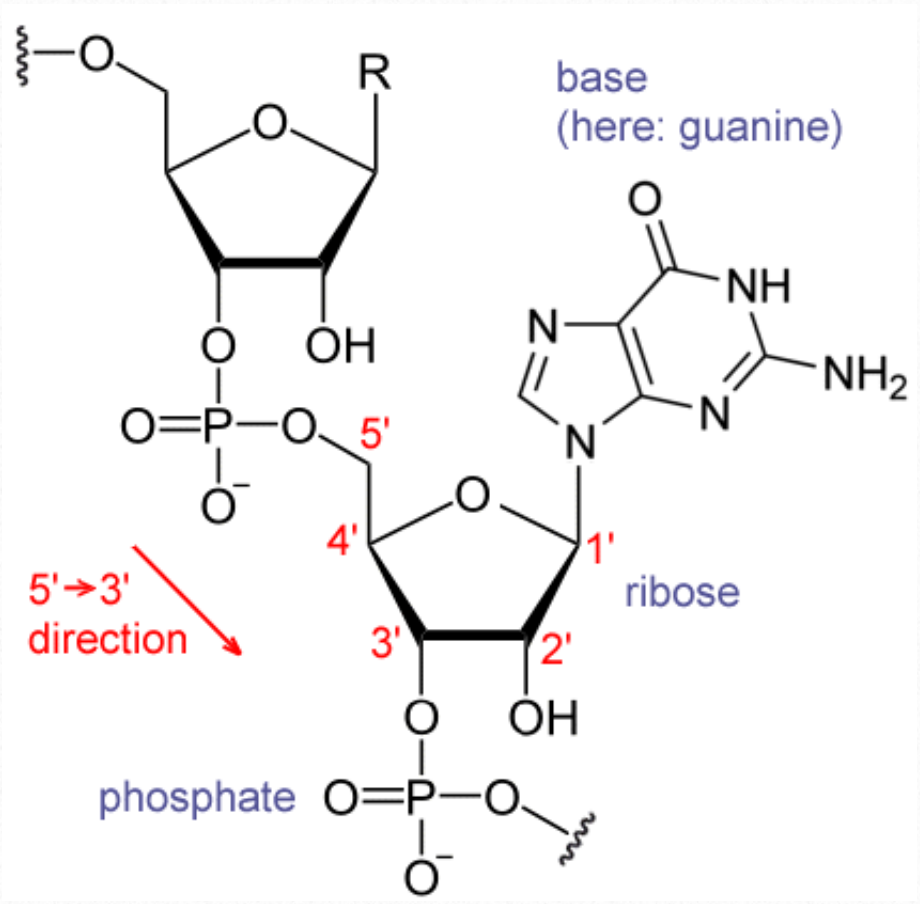

Figure 2.137 A section of an RNA molecule
Wikipedia

mRNA codons and in polypeptide synthesis. RNAs are also known to play important roles in the regulation of gene expression.

RNA world

The discovery, in 1990, that RNAs could play a role in catalysis, a function once thought to be solely the domain of proteins, was followed by the discovery of many more so-called ribozymes- RNAs that functioned as enzymes. This suggested the answer to a long-standing chicken or egg puzzle - if DNA encodes proteins, but the replication of DNA requires proteins, how did a replicating system come into being? This problem could be solved if the first replicator was RNA, a molecule that can both encode information and carry out catalysis. This idea, called the "RNA world" hypothesis, suggests that DNA as genetic material and proteins as catalysts arose later, and eventually prevailed because of the advantages they offer. The lack of a 2'OH on deoxyribose makes DNA more stable than RNA. The double-stranded structure of DNA also provides an elegant way to easily replicate it. RNA catalysts, however, remain, as remnants of that early world. In fact, the formation of peptide bonds, essential for the synthesis of proteins, is catalyzed by RNA.

Secondary structure

With respect to structure, RNAs are more varied than their DNA cousin. Created by copying regions of DNA, cellular RNAs are synthesized as single strands, but they often have self-complementary regions leading to "foldbacks" containing duplex regions. These are most easily visualized in the ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs) (Figure 2.138), though other RNAs, including

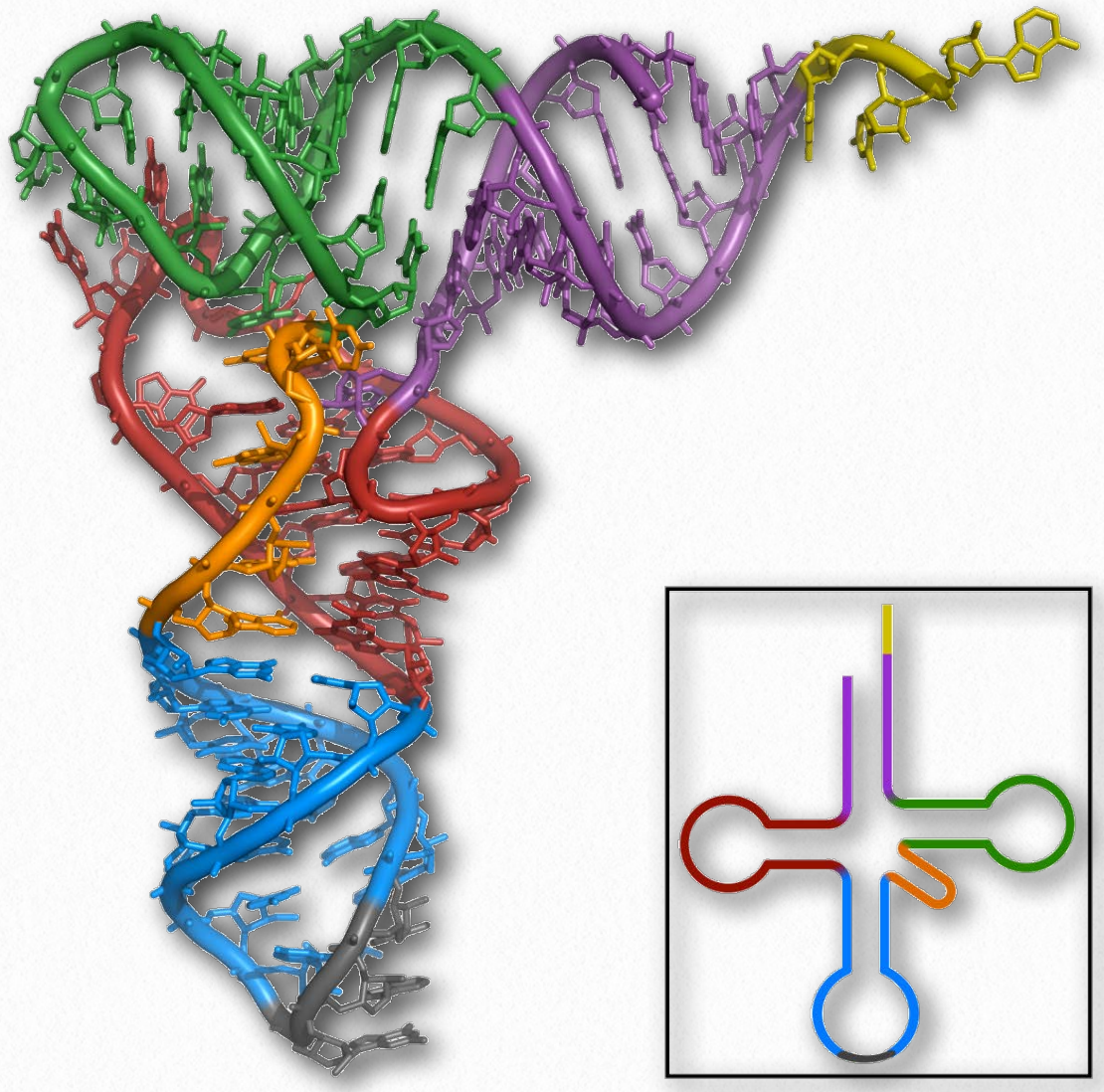

Figure 2.138 - tRNA Images - 3D projection (left) and 2D projection (inset)

Wikipedia

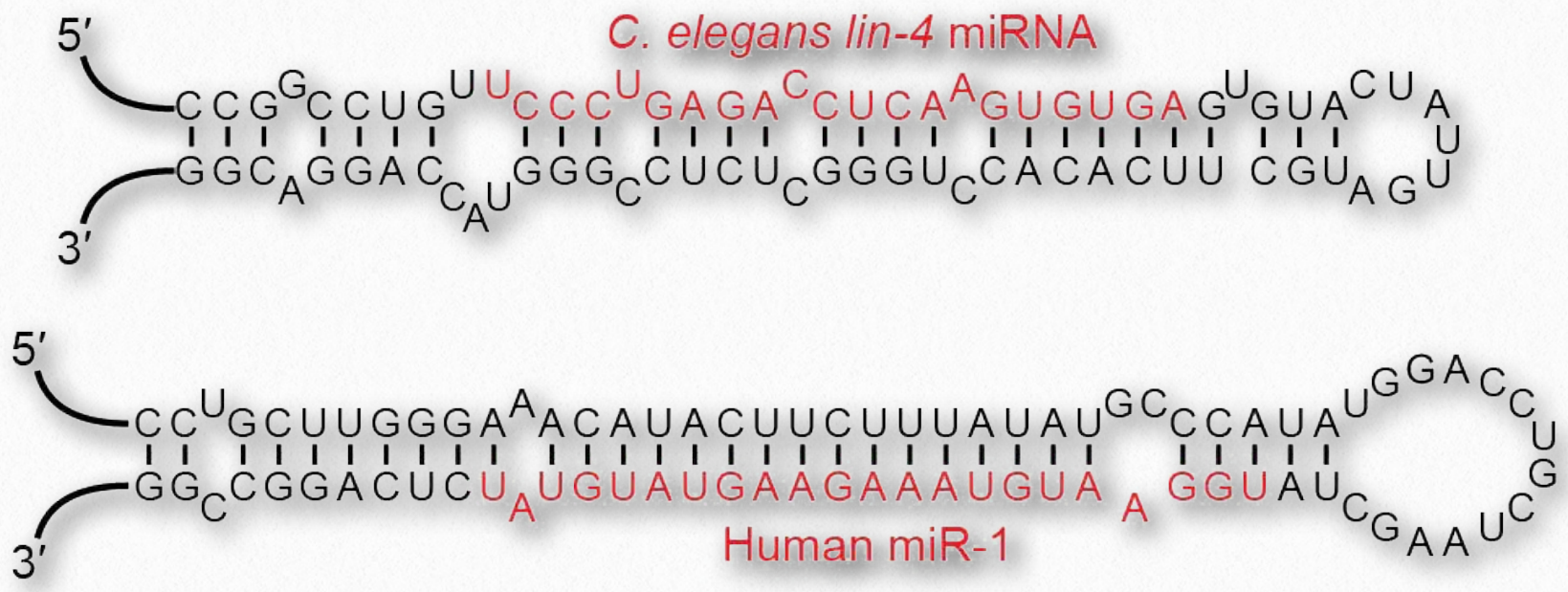

Figure 2.139 - MicroRNA stem loops.

Wikipedia

messenger RNAs (mRNAs), small nuclear RNAs (snRNAs), microRNAs (Figure 2.139), and small interfering RNAs (siRNAs) may each have double helical regions as well.

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Base pairing

Base pairing in RNA is slightly different than DNA. This is due to the presence of the base uracil in RNA in place of thymine in DNA. Like thymine, uracil forms base pairs with adenine, but unlike thymine, uracil can, to a limited extent, also base pair with guanine, giving rise to many more possibilities for pairing within a single strand of RNA.

These additional base pairing possibilities mean that RNA has many ways it can fold upon itself that single-stranded DNA cannot. Folding, of course, is critical for protein function, and we now know that, like proteins, some RNAs in their folded form can catalyze reactions just like enzymes. Such RNAs are referred to as ribozymes. It is for this reason scientists think that RNA was the first genetic material, because it could not only carry information, but also catalyze reactions. Such a scheme might allow certain RNAs to make copies of themselves, which would, in turn, make more copies of themselves, providing a positive selection.

Stability

RNA is less chemically stable than DNA. The presence of the 2' hydroxyl on ribose makes RNA much more prone to hydrolysis than DNA, which has a hydrogen instead of a hydroxyl. Further, RNA has uracil instead of thymine. It turns out that cytosine is the

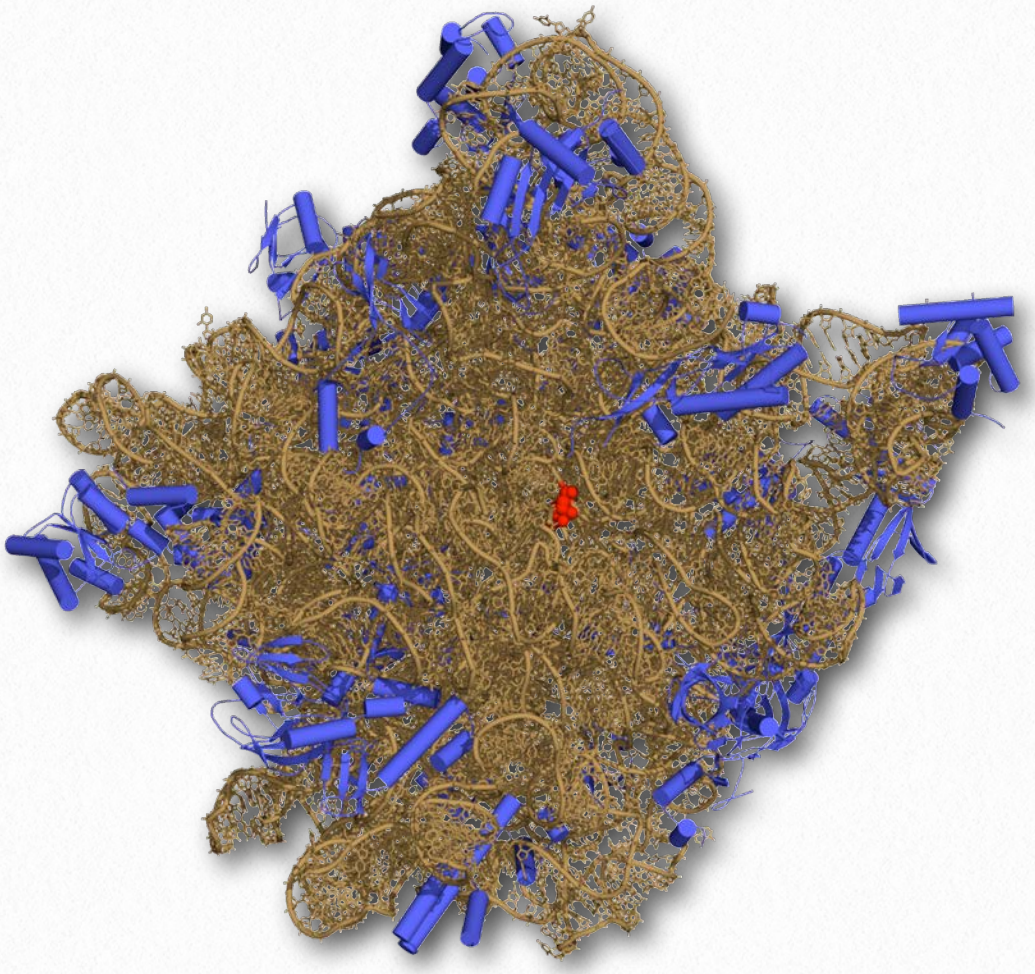

Figure 2.140 - Structure of the 50S ribosomal subunit. rRNA shown in brown. Active site in red
Wikipedia

least chemically stable base in nucleic acids. It can spontaneously deaminate and in turn is converted to a uracil. This reaction occurs in both DNA and RNA, but since DNA normally has thymine instead of uracil, the presence of uracil in DNA indicates that deamination of cytosine has occurred and that the uracil needs to be replaced with a cytosine. Such an event occurring in RNA would be essentially undetectable, since uracil is a normal component of RNA. Mutations in RNA have much fewer consequences than mutations in DNA because they are not passed between cells in division.

Catalysis

RNA structure, like protein structure, has importance, in some cases, for catalytic function. Like random coils in proteins that give rise to tertiary structure, single-stranded regions of RNA that link duplex regions give these molecules a tertiary structure, as well. Catalytic RNAs, called ribozymes, catalyze important cellular reactions, including the formation of peptide bonds in ribosomes (Figure 2.114). DNA, which is usually present in cells in strictly duplex forms (no tertiary structure, per se), is not known to be involved in catalysis.

RNA structures are important for reasons other than catalysis. The 3D arrangement of tRNAs is necessary for enzymes that attach amino acids to them to do so properly. Further, small RNAs called siRNAs found in the nucleus of cells appear to play roles in both gene regulation and in cellular defenses against viruses. The key to the mechanisms of these actions is the formation of short fold-back RNA structures that are recognized by cellular proteins and then chopped into smaller units. One strand is copied and used to base pair with specific mRNAs to prevent the synthesis of proteins from them.

Denaturing nucleic acids

Like proteins, nucleic acids can be denatured. Forces holding duplexes together include hydrogen bonds between the bases of each strand that, like the hydrogen bonds in proteins, can be broken with heat or urea. (Another important stabilizing force for DNA arises from the stacking interactions between the bases in a strand.) Single strands absorb light at 260 nm more strongly than double strands. This is known as the hyperchromic effect (Figure 2.141)and is a consequence of the disruption of interactions among the stacked bases. The changes in absorbance allow one to easily follow the course of DNA denaturation. Denatured duplexes can readily renature when the temperature is lowered below the "melting temperature" or T_m, the temperature at which half of the DNA strands are in duplex form. Under such conditions, the two strands can re-form hydrogen bonds between the complementary sequences, returning the duplex to its original state. For DNA, strand separation and re-hybridization are important for the technique known as the polymerase chain reaction (PCR). Strand separation of DNA duplexes is accomplished in the method by heating them to boiling. Hybridization is an important aspect of the method that requires single stranded primers to "find" matching sequences on the template DNA and form a duplex. Considerations for efficient hybridization (also called annealing) include temperature, salt concentration, strand concentration, and magnesium ion levels (for more on PCR, see HERE).

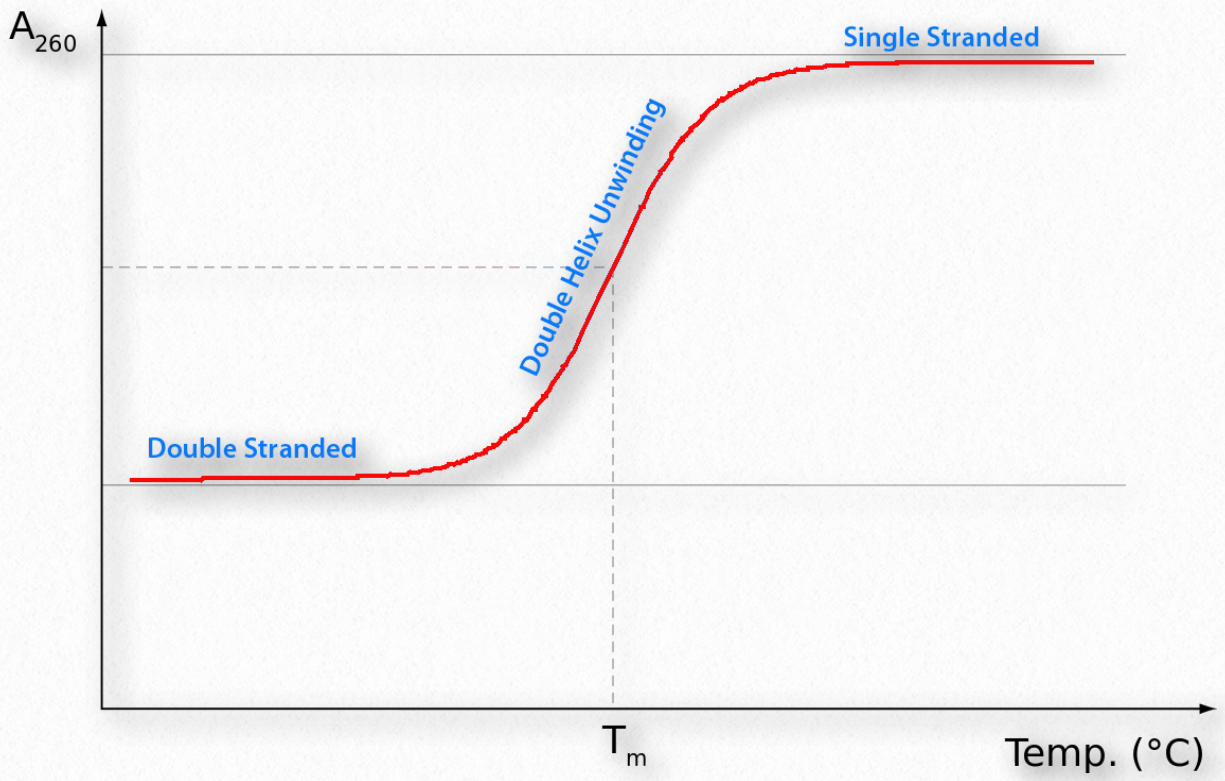

Figure 2.141 - The hyperchromic effect

Wikipedia

DNA packaging

DNA is easily the largest macromolecule in a cell. The single chromosome in small bacterial cells, for example, can have a molecular weight of over 1 billion Daltons. If one were to take all of the DNA of human chromosomes from a single cell and lay them end to end, they would be over 7 feet

long. Such an enormous molecule demands careful packaging to fit within the confines of a nucleus (eukaryotes) or a tiny cell (bacteria). The chromatin system of eukaryotes is the best known, but bacteria, too, have a system for compacting DNA.

Bacteria

In bacteria, there is no nucleus for the DNA. Instead, DNA is contained in a structure

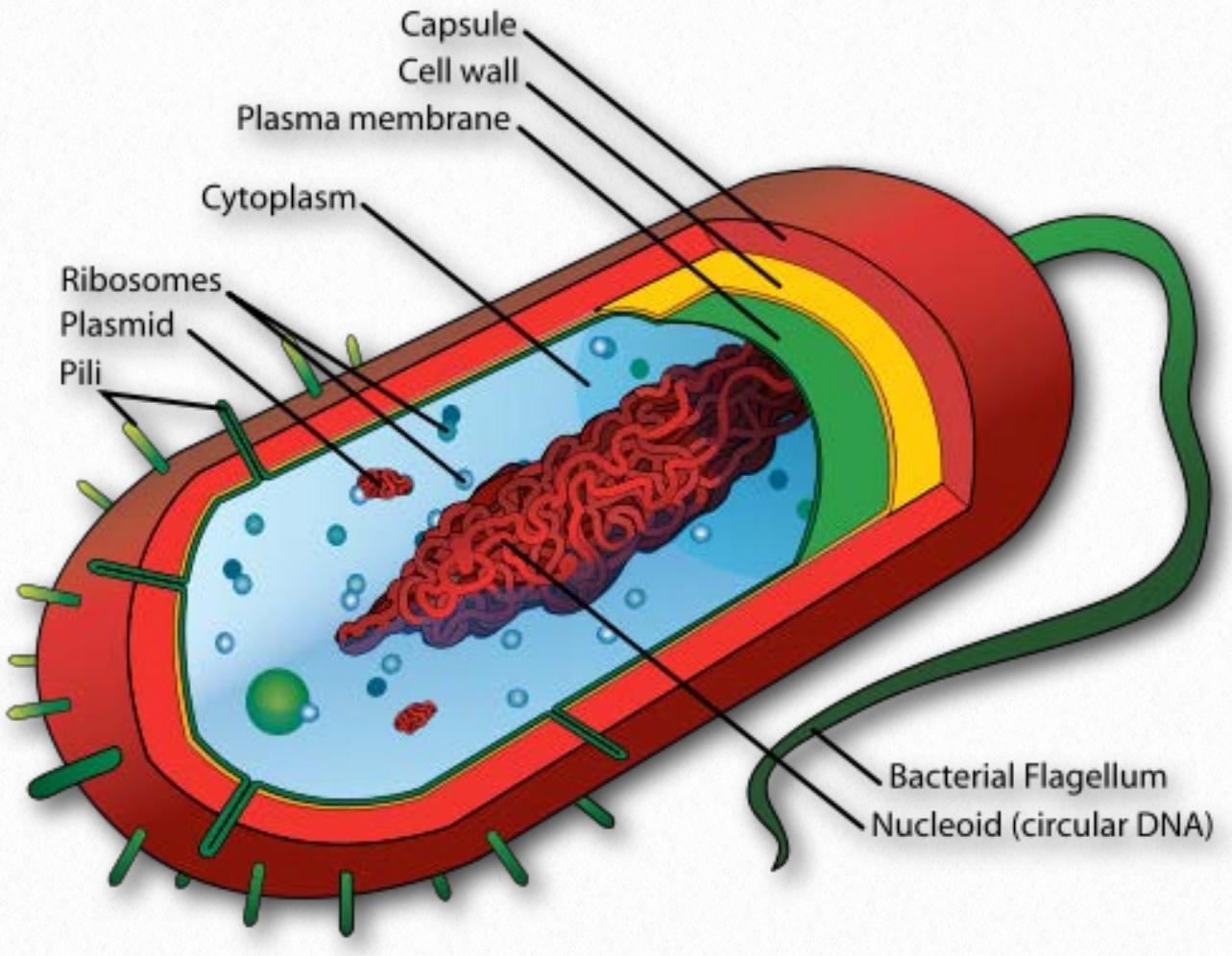

Figure 2.142 - Anatomy of a bacterial cell.

called a nucleoid (Figure 2.142). It contains about 60% DNA with much of the remainder comprised of RNAs and transcription factors. Bacteria do not have histone proteins that DNA wrap around, but they do have proteins that help organize the DNA in the cell - mostly by making looping structures.

These proteins are known as Nucleoid Associated Proteins and include ones named HU, H-NS, Fis, CbpA, and Dps. Of these, HU most resembles eukaryotic histone H2B and binds to DNA non-specifically. The proteins associate with the DNA and can also cluster, which may be the origin of the loops. It is likely these proteins play a role in helping to regulate transcription and respond to DNA damage. They may also be involved in recombination.

Eukaryotes

The method eukaryotes use for compacting DNA in the nucleus is considerably different, and with good reason - eukaryotic DNAs are typically much larger than prokaryotic DNAs, but must fit into a nucleus that is not much bigger than a prokaryotic cell. Human DNA, for example, is about 1000 times longer than *c* DNA.

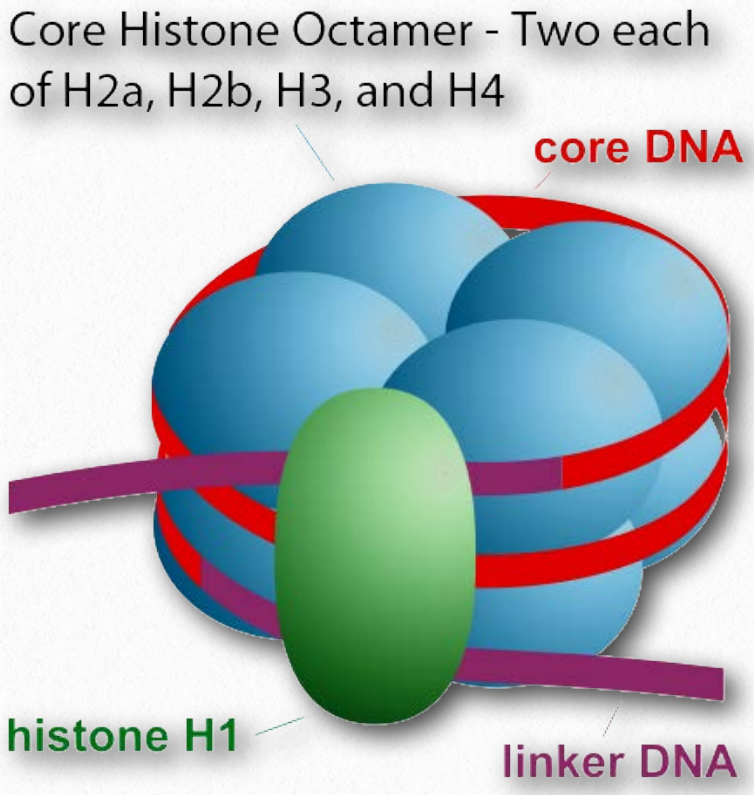

Figure 2.143 - Structure of a nucleosome

Wikipedia

Octamer

The core of 8 proteins is called an octamer. The stretch of DNA wrapped around the octamer totals about 147 base pairs and makes 1 2/3 turns around it. This complex is referred to as a core particle (Figure 2.144). A linker region of about 50-80 base pairs separate core particles. The term nucleosome then refers to a a core particle plus a linker region (Figure 2.143). Histone H1 sits near the junction of the incoming DNA and the histone core. It is often referred to as the linker histone. In the absence of H1, non-condensed nucleosomes resemble "beads on a string" when viewed in an electron microscope.

The strategy employed in eukaryotic cells is that of spooling - DNA is coiled around positively charged proteins called histones. These proteins, whose sequence is very similar in cells as diverse as yeast and humans, come in four types, dubbed H1, H2a, H2b, H3, and H4. A sixth type, referred to as H5 is actually an isoform of H1 and is rare. Two each of H2a, H2b, H3, and H4 are found in the core structure of what is called the fundamental unit of chromatin - the nucleosome (Figure 2.143).

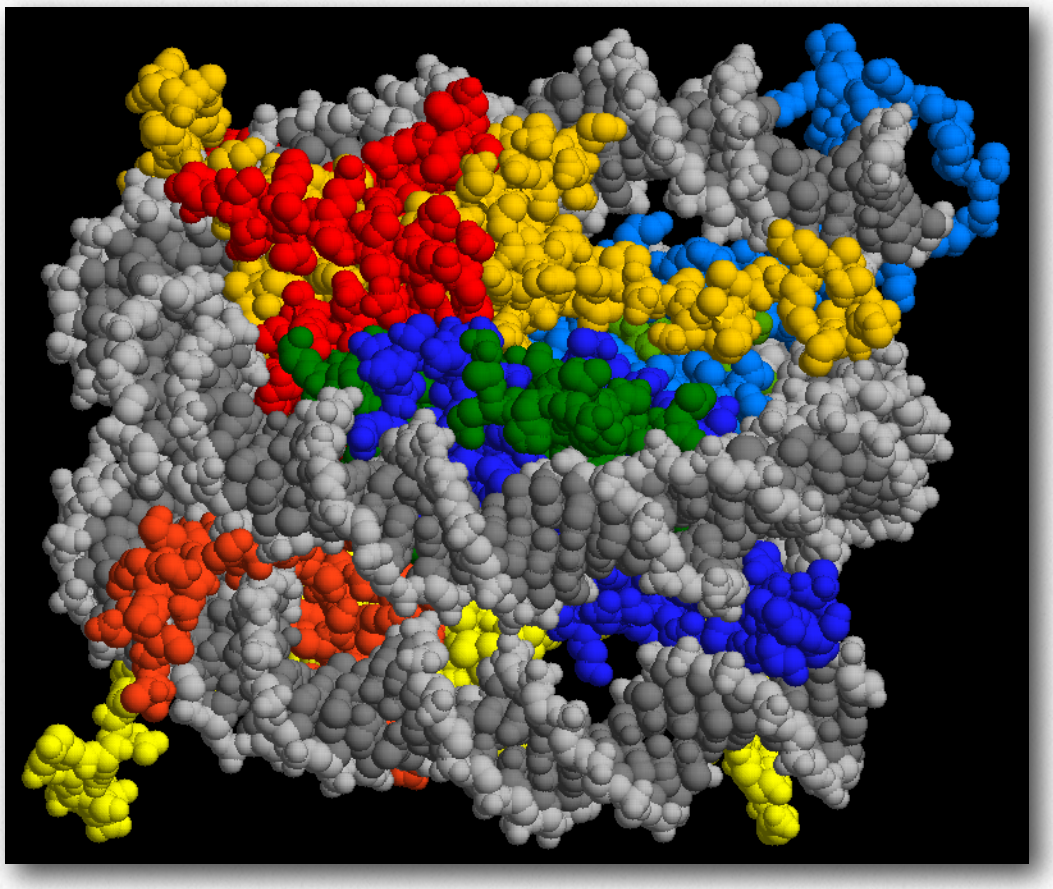

Figure 2.144 - Detailed core particle structure - DNA in gray, histones in red, yellow, green, blue

Wikipedia

MARTKQTARKSTGGKAPRKQLASKAA
RKSAPSTGGVKKPHRYKPGTVALREIR
RFQKSTELLIRKLPFQRLVREIAQDFKT
DLRFQSSAIGALQESVEAYLVSLFEDT
NLASIHAKRVTIQKKDIKLARRLRGERS

Figure 2.145 - Amino acid sequence (1-letter code) of histone H3 of *S. cerevisiae*. Arginines (R) and lysines (K) shown in red.

Histones

Histone proteins are similar in structure and are rich in basic amino acids, such as lysine and arginine (Figure 2.145). These amino acids are positively charged at physiological pH, with enables them to form tight ionic bonds with the negatively charged phosphate backbone of DNA.

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For DNA, compression comes at different levels (Figure 2.146). The first level is at the nucleosomal level. Nucleosomes are stacked and coiled into higher order structures. 10 nm fibers are the simplest higher order structure (beads on a string) and they grow in complexity. 30 nm fibers consist of stacked nucleosomes and they are packed tightly. Higher level packing produces the metaphase chromosome found in meiosis and mitosis.

The chromatin complex is a logistical concern for the processes of DNA replication and (particularly) gene expression where specific regions of DNA must be transcribed. Altering chromatin structure is therefore an essential function for transcriptional activation in eukaryotes. One strategy involves adding acetyl groups to the positively charged lysine side chains to "loosen their grip" on the negatively charged DNA, thus allowing greater access of proteins involved in activating transcription to gain access to the DNA. The mechanisms involved in eukaryotic gene expression are

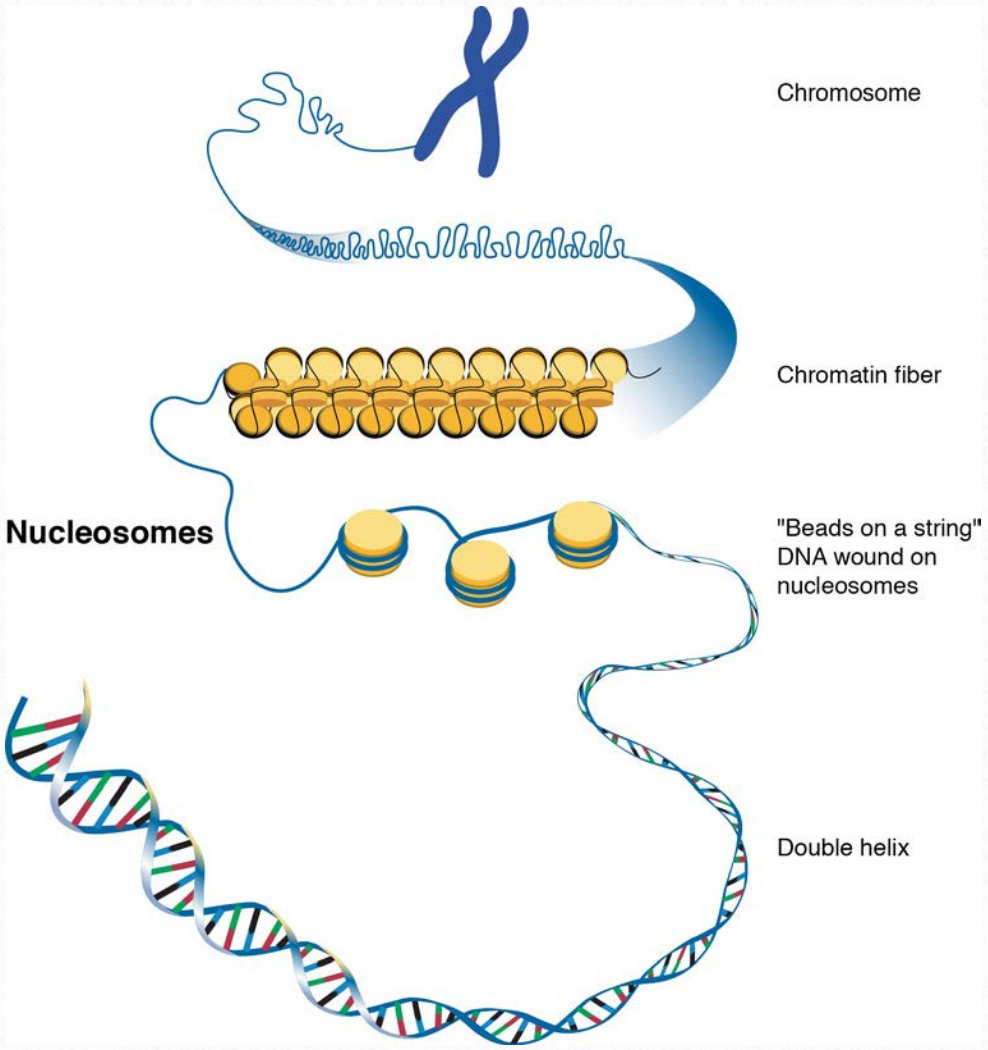

Figure 2.146 Packaging of DNA into a chromosome

discussed in more detail HERE.

Ames test

The Ames test (Figure 2.147) is an analytical method that allows one to determine whether a compound causes mutations in DNA (is mutagenic) or not. The test is named for Dr. Bruce Ames, a UC Berkeley emeritus professor who was instrumental in creating it. In the procedure, a single base pair of a selectable marker of an organism is mutated in a plasmid to render it non-functional. In the example, a strain of *Salmonella* is created that lacks the ability to grow in the absence of histidine. Without histidine, the organism will not grow, but if that one base in the plasmid's histidine gene gets changed back to its original base, a functional gene will be made and the organism will be able to grow without histidine.

A culture of the bacterium lacking the functional gene is grown with the supply of histidine it requires. It is split into two vials. To one of the vials, a compound that one wants to test the mutagenicity of is added. To the other vial, nothing is added. The bacteria in each vial are spread onto plates lacking histidine. In the absence of mutation, no bacteria will grow. The more colonies of bacteria that grow, the more mutation happened. Note that even the vial without the possible mutagenic compound will have a few colonies grow, as a result of mutations unlinked to the potential mutagen.

Mutation happens in all cells at a low level. If the plate with the cells from the vial with the compound has more colonies than the cells from the control vial (no compound), then that would be evidence that the compound causes more mutations than would normally occur and it is therefore a mutagen. On the

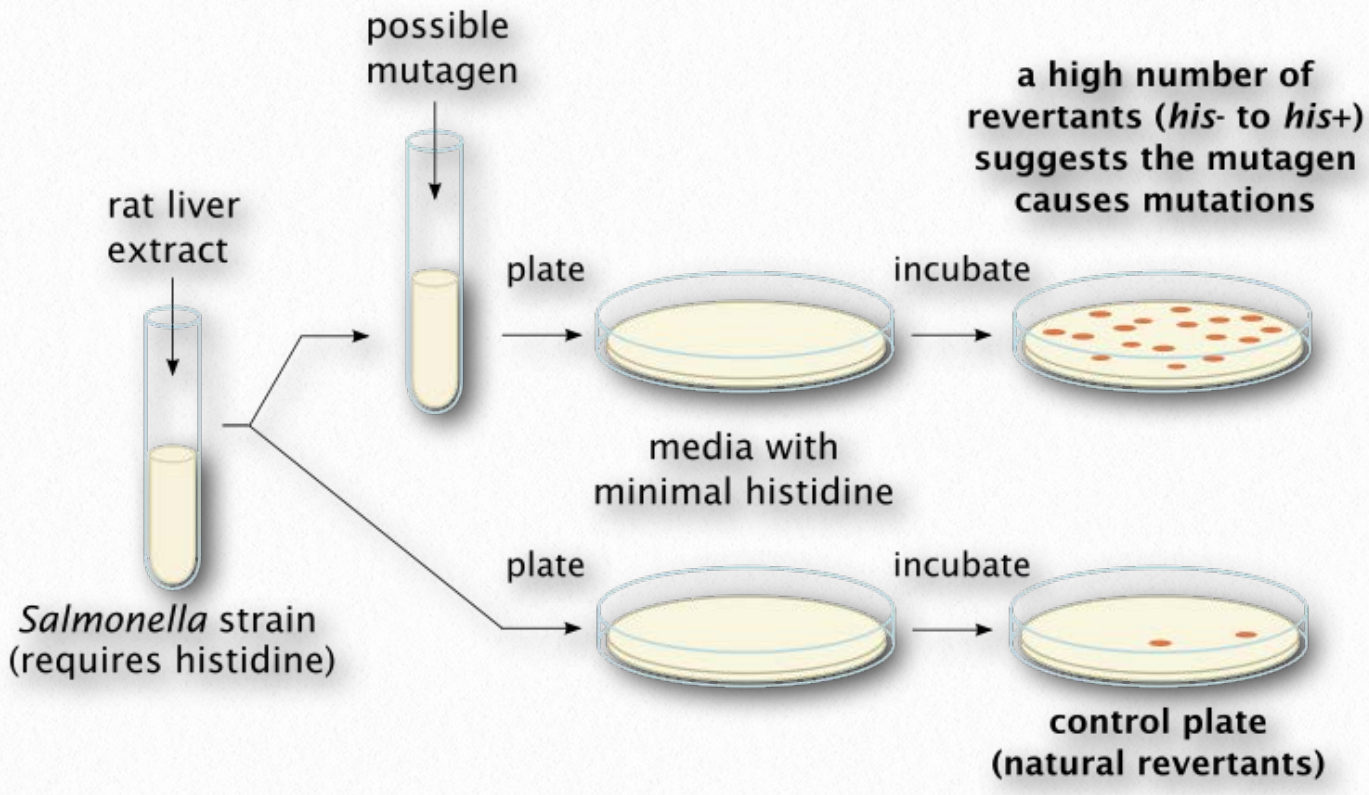

Figure 2.147 - The Ames test

Wikipedia

other hand, if there was no significant difference in the number of colonies on each plate, then that would suggest it is not mutagenic. The test is not perfect - it identifies about 90% of known mutagens - but its simplicity and inexpensive design make it an excellent choice for an initial screen of a compound.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

Click HERE for Penelope Irving's Web Page

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Histones

To the tune of "*Meet the Flintstones*"

Metabolic Melodies Website HERE

Histones, tiny histones
Wrap up eukaryotic DNA

Using lysine side chains
They arrange a chromatin array

With them - DNAs of seven feet
Fit in - side the nucleus so sweet

When you use the histones
You have to deal with condensation

And its ablation
Inside your chromosomes

Recording by David Simmons
Lyrics by Kevin Ahern

B-DNA

To the tune of "*Y-M-C-A*"

Metabolic Melodies Website HERE

Phosphates
Are in nucleotides
I say phosphates
Cover bases inside
I say phosphates
Span the 5 and 3 primes
There's no need - to - be - real - mixed - up

Bases
Carry info you see
I say bases
Are all complement'ry
I say bases
Like A,T,G and C
They have got - to - be – all - paired - up

It's fun to play with some B-DNA
It's got a boatload of G-C-T-A
It's got everything
A polymerase needs
When you melt all the A's and T's

It's fun to play with some B-DNA
It's got a boatload of G-C-T-A
You can make RNAs
With a po-ly-mer-ase
Just by pairing up U's with A's

Proteins
Full of amino A's
I say proteins
Come from mRNAs
I say proteins
Require tRNAs
There is more – you - need - to – trans-late

Codons
Like our friend U-A-C
I say codons
Come in clusters of three
I say codons
Have one base wobble –ee
Now you can - go - forth - and - tran-slate

It's fun to play with some B-DNA
It's got a boatload of G-C-T-A
With those hydrogen Bs
And right-hand he-li-ces
Anti-par-a-llel fives and threes

It's fun to play with some B-DNA
It's got a boatload of G-C-T-A
With those hydrogen Bs
And right-hand he-li-ces
Anti-par-a-llel fives and threes

Recording by Tim Karplus
Lyrics by Kevin Ahern

Major Groovy

To the tune of "*Feelin' Groovy*"

Metabolic Melodies Website HERE

The DNA forms
A and B
Have bases
Complementary
Despite the similarities
They differ in their
Major groovies
Nanananananana major groovies

Transcription factors
With their bindin'
Cause DNA to
Start unwindin'
Holding it
Aggressively
By forming bonds
In major groovies
Nanananananana major groovies

For proteins, the key
To sequence I-D
Is hydrogen bonding, each base pair unique
Purine, pyrimidine patterns discrete
In DNA's most
Major groovy

Recording by David Simmons
Lyrics by Kevin Ahern

Structure & Function: Carbohydrates

Introduction

Carbohydrates are a third major group of biomolecules. This diverse group is commonly described as sugars, or saccharides, from the Greek word for sugar. The simplest carbohydrates are called monosaccharides, or simple sugars. An example is glucose. Monosaccharides can be joined to make larger molecules. Disaccharides contain two monosaccharides. Sucrose is a disaccharide, containing both fructose and glucose. Polysaccharides are chains of many sugar subunits. Examples include glycogen and cellulose, both of which are polymers of glucose (but with different configurations).

YouTube Lectures by Kevin HERE & HERE

Carbohydrates are literally “hydrates of carbon.” This designation derives from the generalized formula of simple monosaccharides, which can be written in the form of $C_x(H_2O)_x$, where x is a digit typically between 3 and 8. Not all sugars have this formula, however. Deoxyribose, the sugar found in every nucleo-

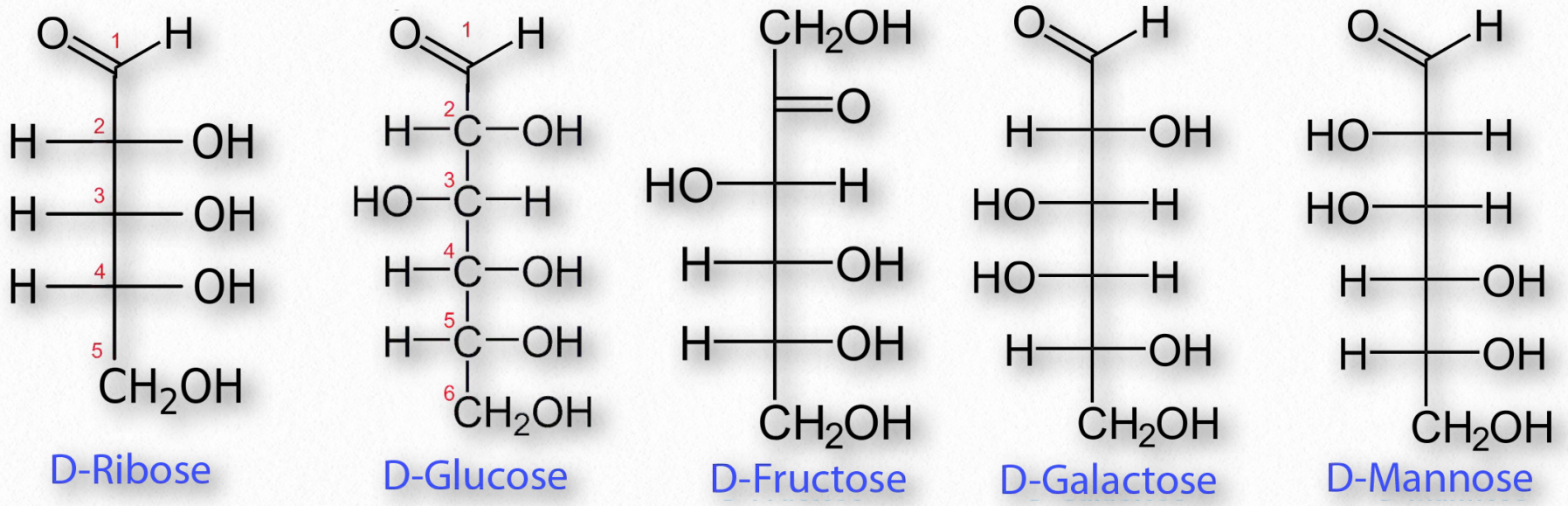


Figure 2.148 - Common sugar structures

tide in a DNA molecule lacks one oxygen and thus has the formula $C_5H_{10}O_4$.

Carbohydrates are important in cells as energy sources (glucose, glycogen, amylose), as markers of cellular identity (oligosaccharides on the surface of cells of multicellular organisms), as structural components (cellulose in plants), and as constituents of nucleotides (ribose in RNA, deoxyribose in DNA).

The building blocks of carbohydrates are simple sugars and it is here we begin our description.

Monosaccharides

The most common monosaccharides include glucose, fructose, galactose, ribose, and mannose. Of these sugars, all but one (fructose) exists as an aldehyde. Fructose and other less well known sugars are ketones. Figure 2.148 shows the structure of these sugars. Some discussion of nomenclature is appropriate.

By convention, the letters 'ose' at the end of a biochemical name flags a molecule as a sugar. Thus, there are glucose, galactose, sucrose, and many other '-oses'. Other descriptive nomenclature involves use of a prefix that tells how many carbons the sugar contains. For example, glucose, which contains six carbons, is described as a hexose. The following list shows the prefixes for numbers of carbons in a sugar:

- **Tri- = 3**
- **Tetr- = 4**
- **Pent- = 5**
- **Hex- =6**
- **Hept- = 7**
- **Oct- = 8**

Other prefixes identify whether the sugar contains an aldehyde group (aldo-) or a ketone (keto-) group. Prefixes may be combined. Glucose, which is a 6-carbon sugar with an aldehyde group, can be described as an aldo-

hexose. The list that follows gives the common sugars and their descriptors.

- **Ribose = aldo-pentose**
- **Glucose = aldo-hexose**
- **Galactose = aldo-hexose**
- **Mannose = aldo-hexose**
- **Fructose = keto-hexose**

Diastereomers

Sugars may have multiple asymmetric carbons and thus differ from each other in the configuration of hydroxyl groups on asymmetric carbons. Two sugars having the same chemical form (aldoses, for example) and the same number of carbons, but that differ only in the stereochemical orientations of their carbons are referred to as diastereomers (Figure 2.149). For example, glucose, galactose, and mannose all have the formula of $C_6H_{12}O_6$, but are chemically distinct from each other in the orientation of hydroxyl groups around the carbons within them.

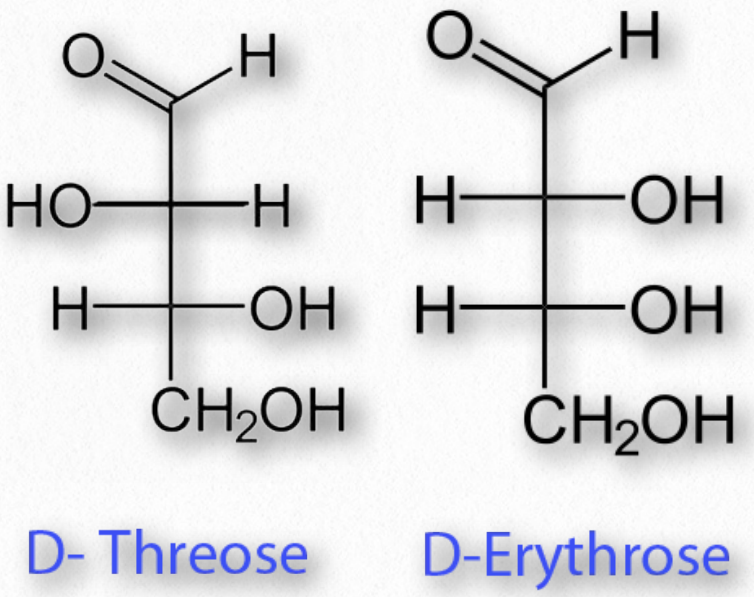


Figure 2.149 - Diastereomers

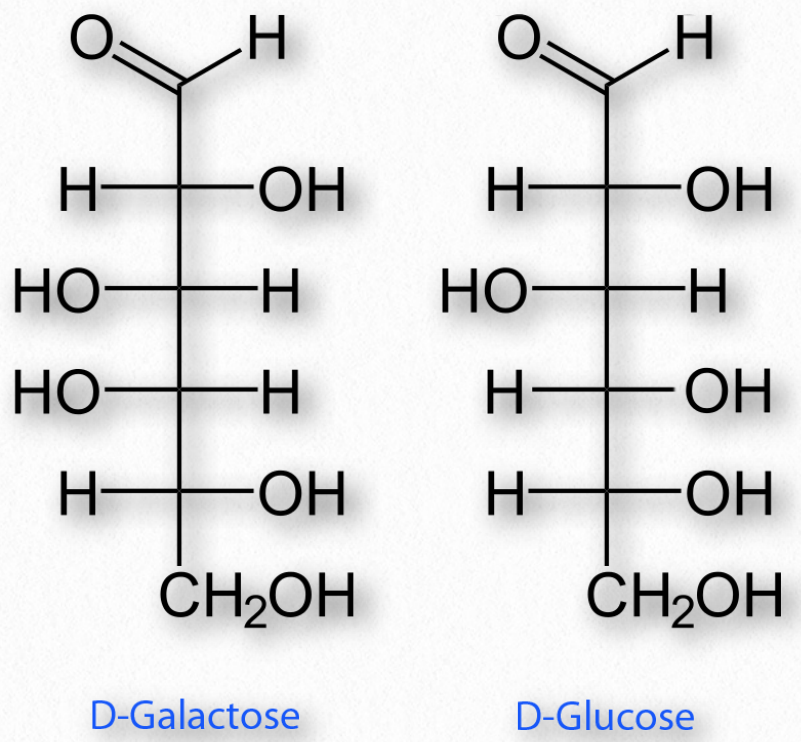


Figure 2.150 - Epimers - D-Galactose and D-Glucose differ only in the configuration of carbon #4

Enantiomers and epimers

If two sugars are identical except for having one hydroxyl configured differently (such as

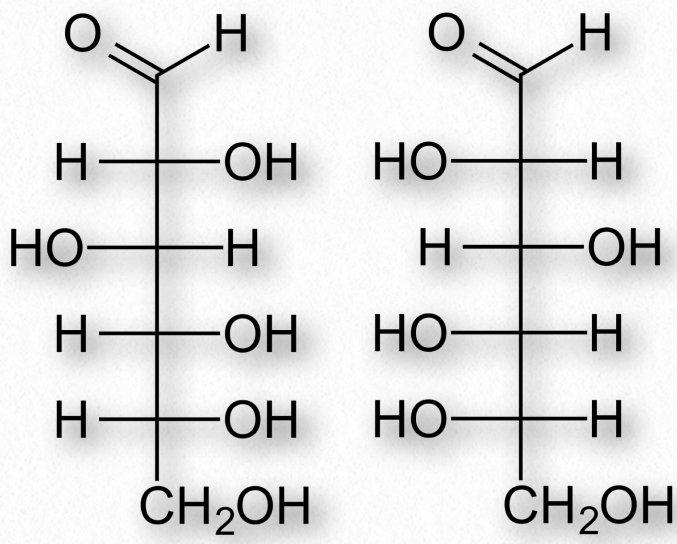


Figure 2.151 - Enantiomers - D-Glucose (left) and L-Glucose (right) are mirror images

ror
im-

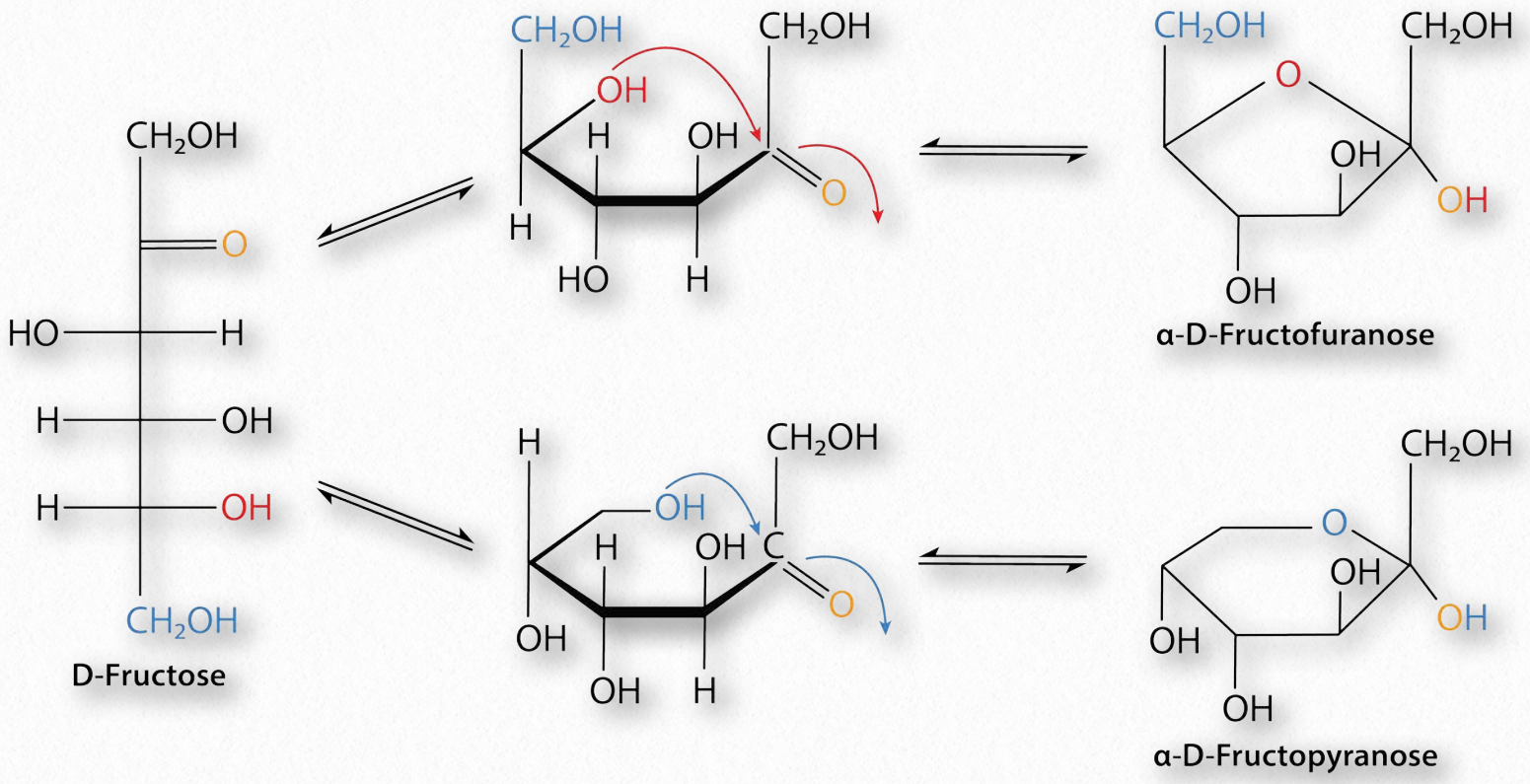
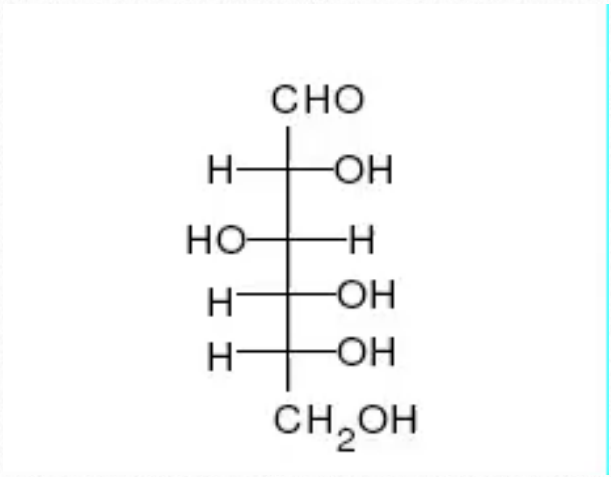


Figure 2.152 - Conversion of D-fructose between furanose (top right), linear (left), and pyranose (bottom right) forms

Image by Pehr Jacobson

glucose and galactose - Figure 2.150), they are diastereomers known as epimers. If the configuration of all of the hydroxyls of one sugar is exactly the opposite of their configuration in another sugar, the two sugars are mirror images of each other (Figure 2.151). Mirages of sugars are known as enantiomers. Please note that due to the way sugars are named, L-glucose is the mirror image of D-glucose.



Movie 2.6 - Conversion of glucose from a straight chain form to a ring form

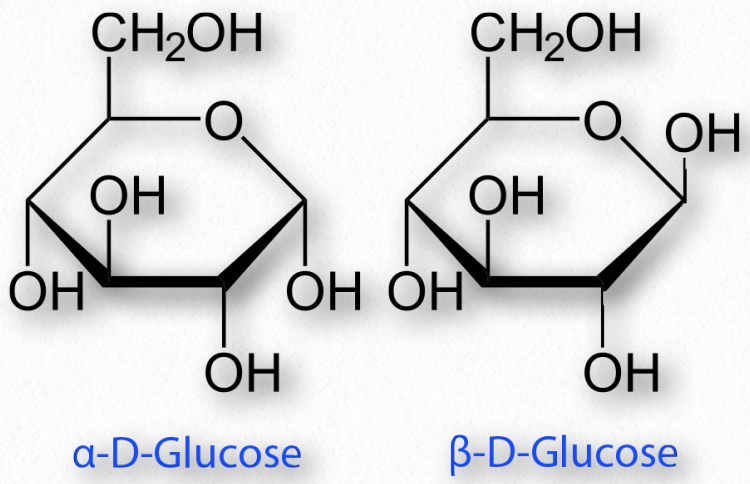


Figure 2.153 - Anomers - α-D-Glucose and β-D-Glucose differ only in the configuration of the anomeric carbon #1

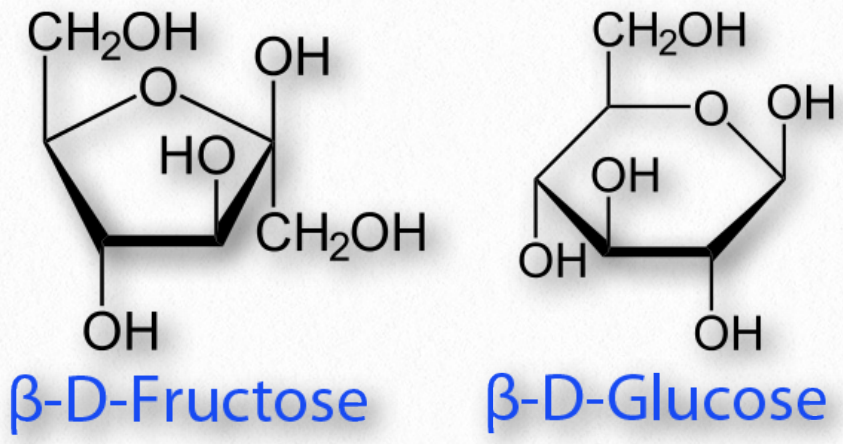


Figure 2.154 - A furanose (left) and a pyranose (right)

Sugars with five and six carbons can readily cyclize (Figure 2.152, Movie 2.6) and when they do, a new asymmetric carbon is created that didn't exist in the same sugars when they were in the straight chain form. This carbon has a special name - it is called the anomeric carbon and (like the other asymmetric carbons in sugars) it can have the hydroxyl in two different positions. These positions are referred to as α and β . Sugars, such as α-D-glucose and β-D-glucose that differ only in the configuration of the anomeric carbon are referred to as anomers (Figure 2.153).

Sugars cyclizing to form rings with five atoms in them (see fructose in Figure 2.128) are referred to as furanoses (named for furan) and those forming rings with six atoms, such as glucose in the same figure, are called pyranoses (named for pyran). The carbonyl carbon beomces the anomeric carbon in the ring by binding to the oxygen of a hydroxyl elsewhere in the chain. α- and β- forms of a given sugar can readily "flip" between each form in solution, so long as the anomeric hydroxyl is free. Most pentoses and hexoses can form both furanose and pyranose structures (Figure 2.152).

Linking the anomeric hydroxyl to another group will create a glycoside and glycosides will remain locked in whichever α- or β- configuration they were in when the anomeric hydroxyl was altered.

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Boat/chair conformations

Orbitals of carbon prefer to be in tetrahedral conformations and this means that the bonds between carbons in a ring do not lie flat. Indeed, rings "pucker" to try to accommodate this tendency, giving rise to different 3D forms for any given sugar. Some of these

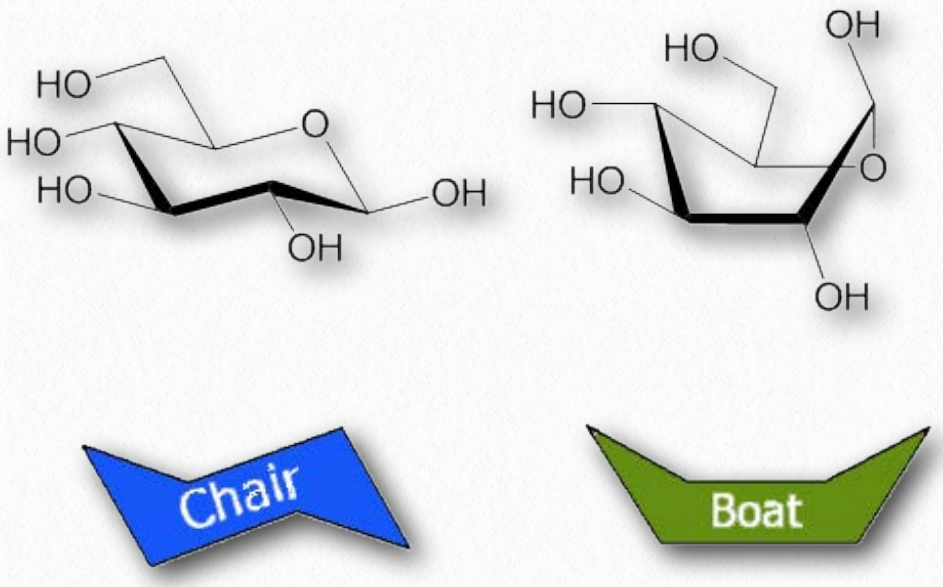

Figure 2.155 - Chair and boat forms of glucose

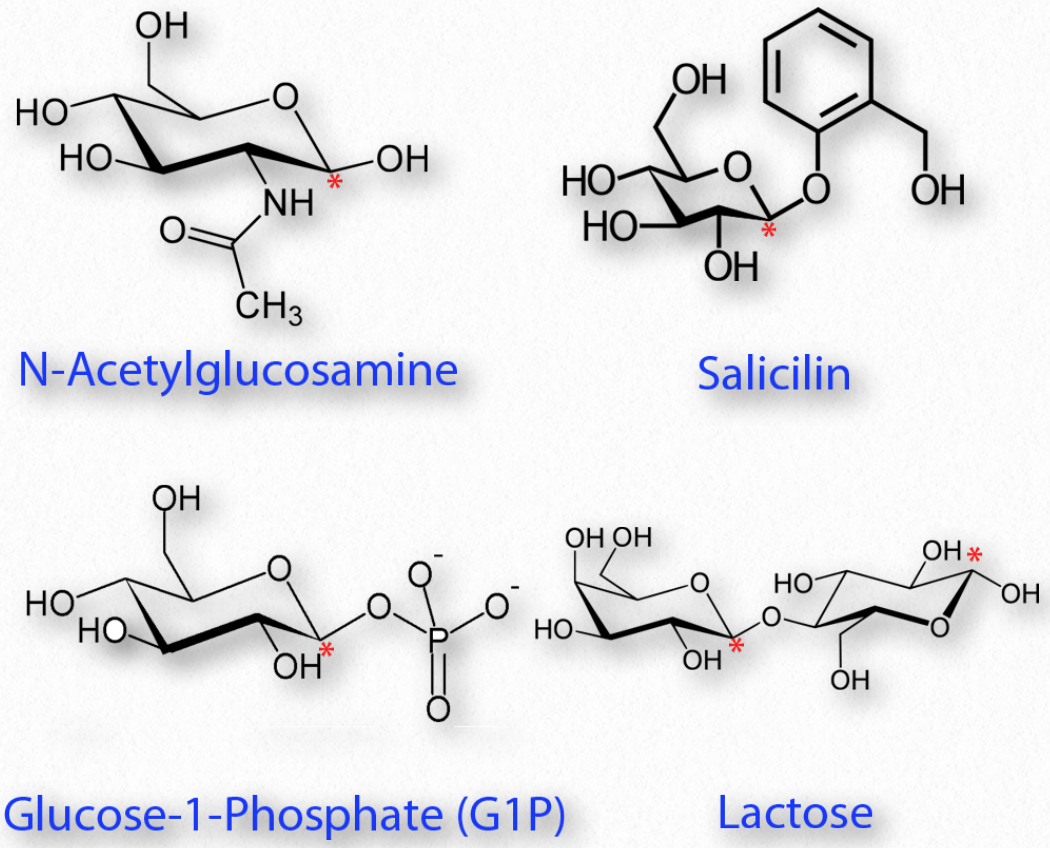

Figure 2.156 - Modified sugars. Locations of glycosidic carbon indicated with red asterisks. All are glycosides except N-acetylglucosamine

forms resemble boat structures, which others resemble chairs or envelopes (Figure 2.155). The stablest (and thus most abundant) of these forms have all of the hydoxyls in the equatorial positions, resulting in less steric hindrance.

Modified monosaccharides

Many modifications can occur on sugar residues (Figure 2.156). Common ones include oxidation, reduction, phosphorylation, and substitution of an amine or an acetylamine for a hydroxyl. The ones that affect the anomeric hydroxyl group make glycosides (Figure 2.157), whereas modifications that don't affect the anomeric hydroxyl, (glucose-6-phosphate, for example), do not.

Oxidation/reduction

The last considerations for simple sugars relative to their structure are their chemical reactivity and modification. Sugars that are readily oxidized are called 'reducing sugars' because their oxidation causes other reacting molecules to be reduced. A test for reducing sugars is known as Benedict's test. In it, sugars are mixed and heated with an alkaline solution containing Cu^{++}. Reducing sugars will donate an elec-

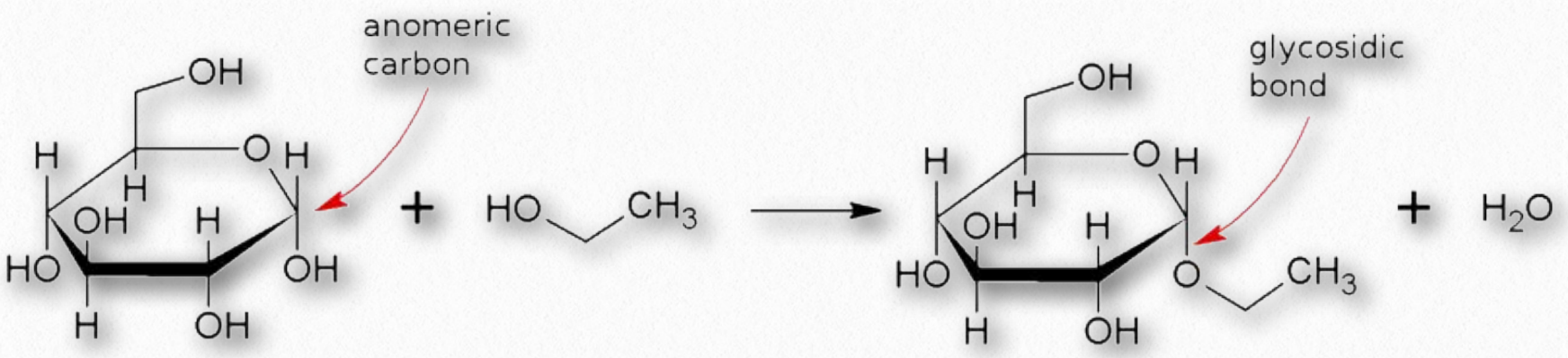

Figure 2.157 - Formation of a glycosidic bond

Figure 2.158 - A positive Benedict's test starting at left and moving right

Wikipedia

tron to Cu^{++}, converting it to Cu^{+}, which will produce cuprous oxide Cu_2O, as an orange precipitate (Figure 2.158). Since Cu^{++} solution is blue, the change of color provides an easy visual indication of a reducing sugar.

The aldehyde group of aldoses is very susceptible to oxidation, whereas ketoses are less so, but can easily be oxidized if, like fructose, they contain an α-hydroxyl and can tautomerize to an aldose. Most monosaccharides are reducing sugars. This includes all of the common ones galactose, glucose, fructose, ribose, xylose, and mannose. Some disaccharides, such as lactose and maltose are reducing sugars since they have at least one anomeric carbon free, allowing that part of the sugar to linearize and yield

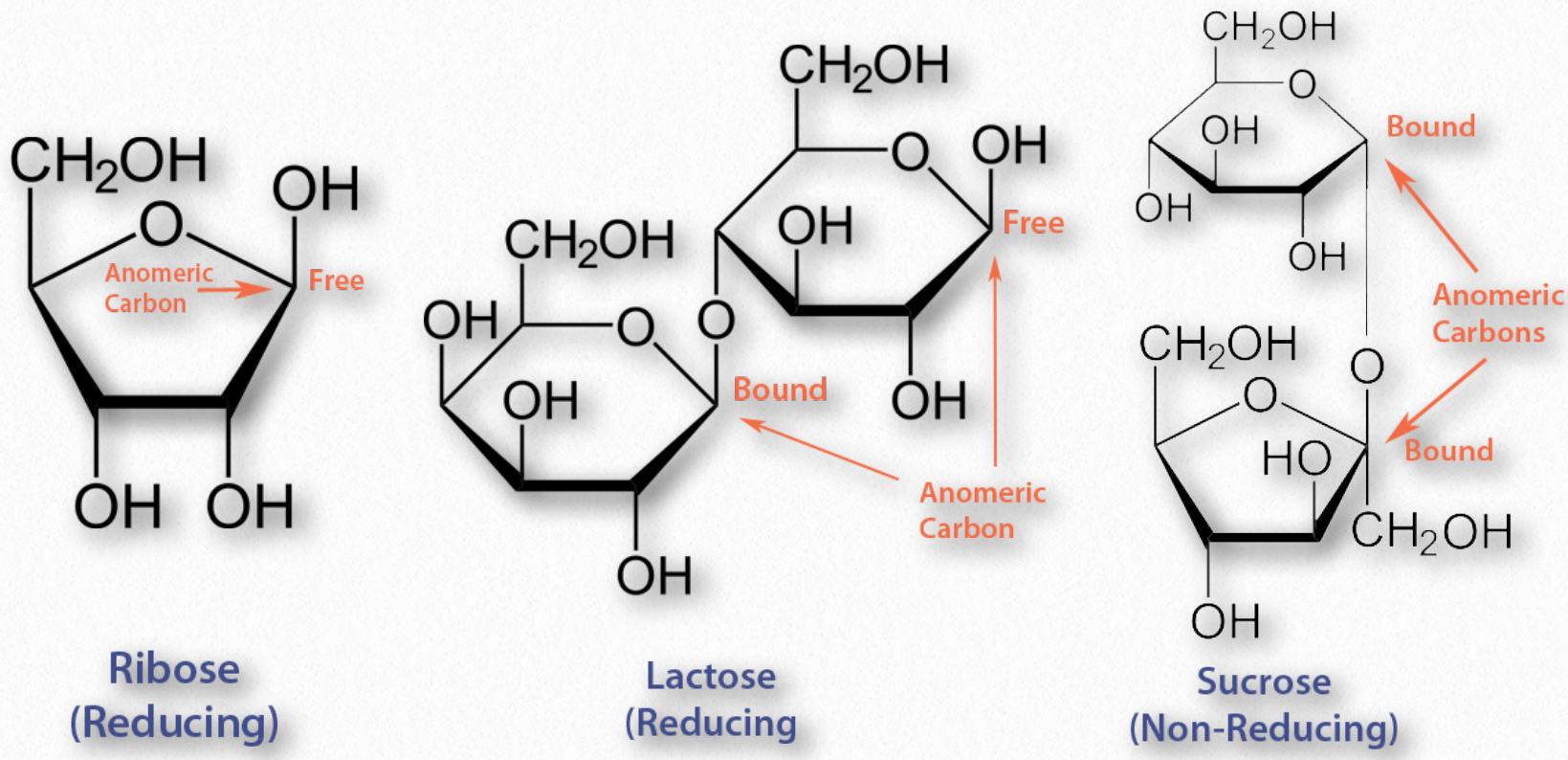

Figure 2.159 - Reducing and non-reducing sugars

an aldose. Sucrose, on the other hand has no anomeric carbons free - both are involved in a glycosidic linkage, so they cannot linearize and thus it is not a reducing sugar.

Oxidation and reduction of sugars can occur in cells. As we will see, phosphorylation of sugars occurs routinely during metabolism.

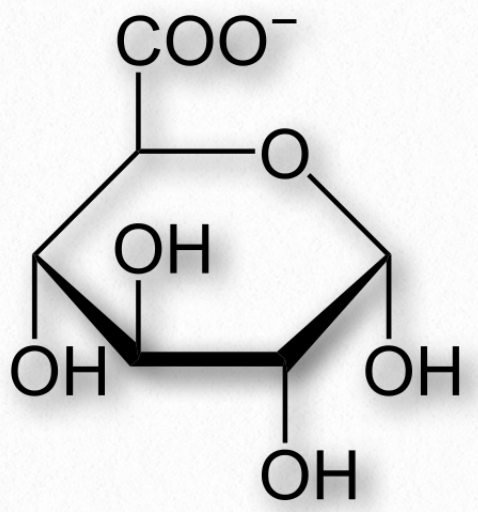

Figure 2.160 - Glucuronic acid

Glucuronic acid

One oxidation product of glucose is glucuronic acid, a six carbon molecule where the CH_2OH on carbon six is oxidized to a carboxylic acid (Figure 2.160). Related oxidized sugars include galacturonic acid and mannuronic acid. Glucuronic acid is commonly conjugated to other molecules in the liver/bile by UDP-glucuronyltransferase enzymes to make the molecules more water soluble for excretion, since the carboxyl group of glucoronic acid ionizes readily at physiological pH. The reactions are usually done starting with glucuronic acid linked to UDP (UDP-Glucuronic Acid). In addition, glucuronic acid is made from a UDP-glucose precursor. Glucuronic acid is a common constituent of glycosaminoglycans, proteoglycans, and glycoglycerolipids. Glucuronic acid is found in heparin, dermatan sulfate, chondroitin sulfate, hyaluronic acid, and keratan sulfate. Glucuronic acid is also a precursor of ascorbic acid (Vitamin C) in organisms that synthesize this compound.

Sugar alcohols

Reduction of aldoses or ketoses by hydrogenation produces the corresponding sugar alcohols. The compounds are widely used as thickeners of food or as artificial sweeteners, due to their ability to stimulate sweet receptors on the tongue. Common sugar alcohols (sugar progenitor in parentheses) include glycerol (glyceraldehyde), xylitol (xylose), sorbitol (Figure 2.161 - from glucose), galactitol (galactose), arabitol (arabinose), and ribitol (ribose). Most of these compounds have a sweetness of between 0.4 and 1.0 times as sweet as sucrose, but provide considerably fewer calories per weight. Xylitol is the sweetest of them with a sweetness equal to

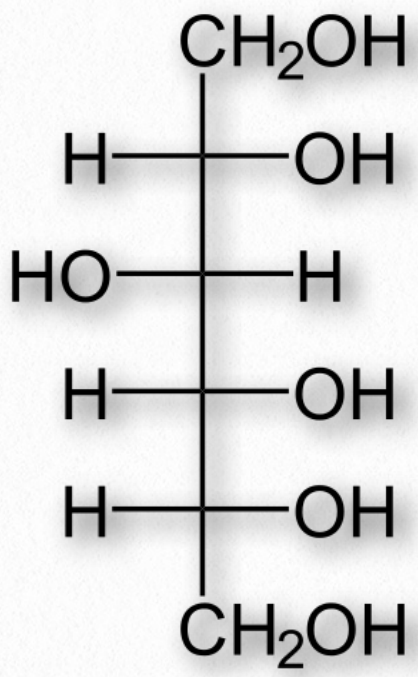

Figure 2.161 - Sorbitol (also called glucitol)

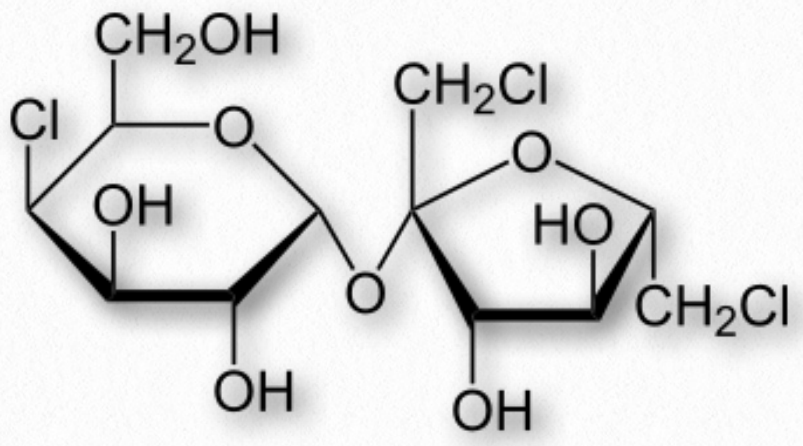

Figure 2.162 - Structure of sucralose

that of sucrose. Sugar alcohols are used sometimes to mask the aftertaste of other artificial sweeteners. Many of them also produce a cooling sensation upon dissolving, due to that being an endothermic process for them, resulting in a pleasant mouth sensation. Last, they are poorly absorbed by intestines, and so have a low glycemic index.

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Artificial sweeteners

Artificial sweeteners are compounds that stimulate taste receptors for sweetness, but are metabolized for energy inefficiently at best. Such compounds frequently are many times sweeter than table sugar (sucrose) on a weight/weight basis and are referred to as "intensely sweet." Most of the artificial sweeteners are not carbohydrates, but rather are able to stimulate the same sweet receptors that sugar does. Seven such compounds are approved for use in the U.S. - stevia, aspartame, sucralose, neotame, acesulfame potassium, saccharin,

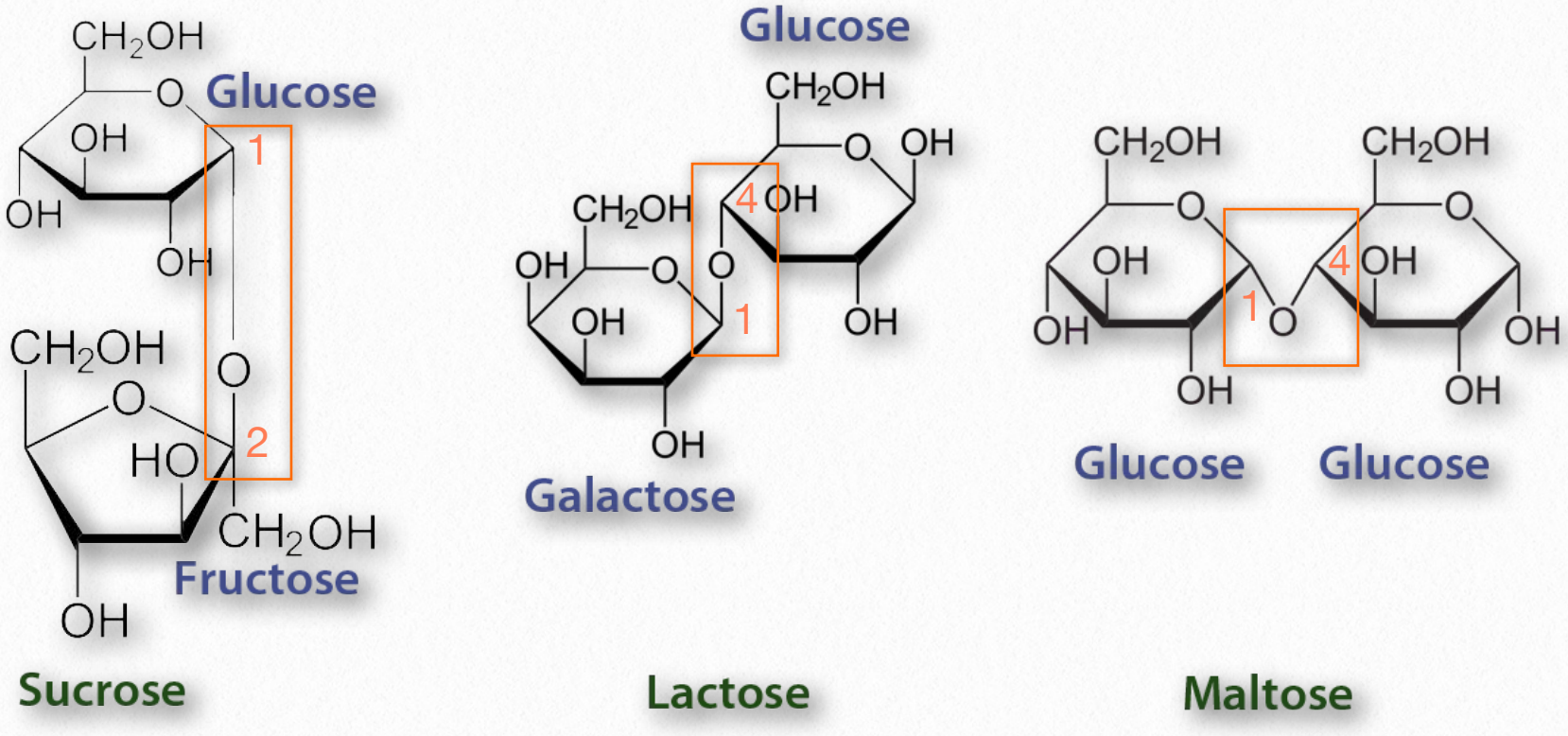

Figure 2.163 - Common disaccharides - glycosidic bonds in rectangles

and advantame. The sugar alcohol known as sorbitol is also sometimes used as an artificial sweetener.

Disaccharides

Disaccharides (Figure 2.163) are made up of two monosaccharides. The most common ones include sucrose (glucose and fructose), lactose (galactose and glucose), and maltose (glucose and glucose). All of the common disaccharides contain at least one glycosidic bond (see HERE). We name the disaccharides according to which carbons are linked to each other and the how the anomeric carbon of the glycosidic bond is configured. Lactose, for example, is described as β-D-galactopyranosyl-(1→4)-D-glucose, or more succinctly as having an α-1,4 glycosidic bond.

Oligosaccharides

As their name implies, oligosaccharides (Figure 2.164) are comprised of a few (typically 3 to 9) sugar residues. These often, but not always contain modified sugars. Unlike all of the other saccharides, oligosaccharides are not typically found unattached to other cellular structures. Instead, oligosaccharides are found bound, for example, to sphingolipids (making cerebrosides or gangliosides) or proteins (making glycoproteins).

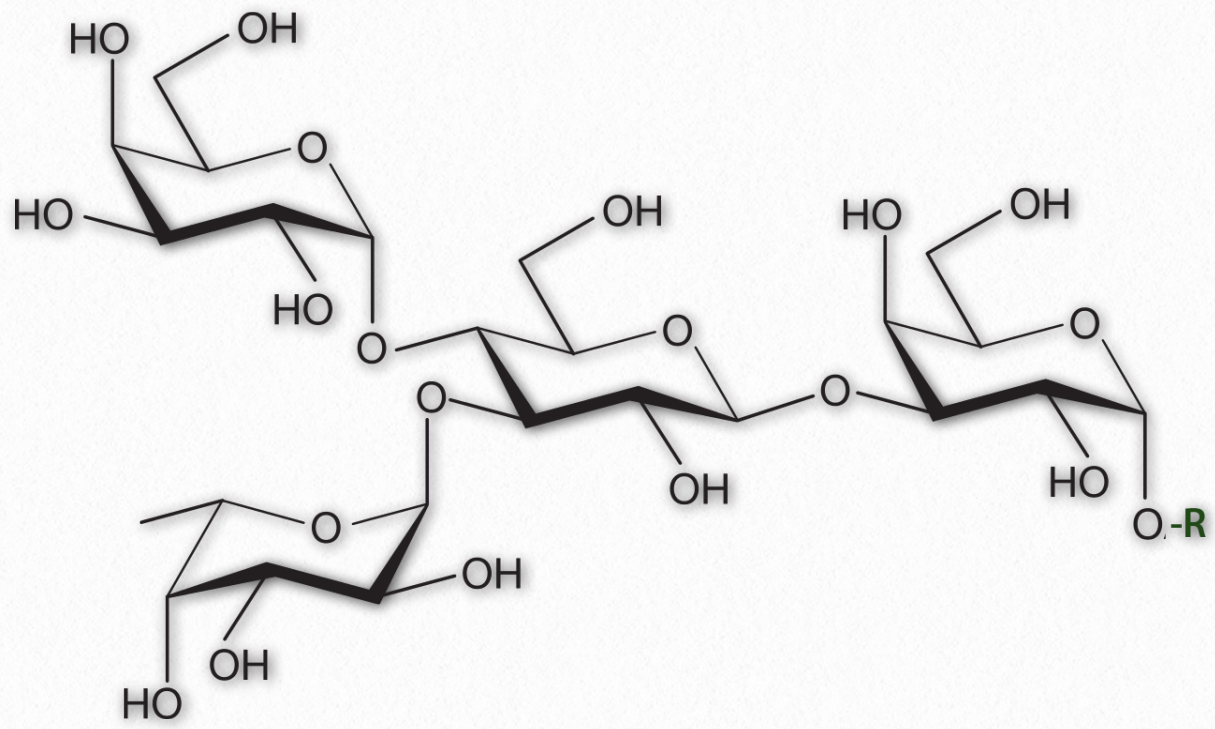

Figure 2.164 - A Branched oligosaccharide attached to an R-Group

Oligosaccharides in membrane glycoproteins play important roles in cellular identity/recognition. The patterns of oligosaccharides displayed on the extracellular face of the plasma membrane acts as a sort of barcode that identifies specific cell types. The immune system recognizes these identity tags in the body. “Foreign” oligosaccharide structures trigger the immune system to attack them. While this provides a very good defense against invading cells of an organism, it

also can pose significant problems when organs are transplanted from one individual into another, with rejection of donated organs, in some cases.

Organelle targeting

The oligosaccharides that are attached to proteins may also determine their cellular destinations. Improper glycosylation or errors in subsequent sugar modification patterns can result in the failure of proteins to reach the correct cellular compartment.

For example, inclusion cell disease (also called I-cell disease) arises from a defective phosphotransferase in the Golgi apparatus. This enzyme normally catalyzes the addition of a phosphate to a mannose sugar attached to a protein destined for the lysosome. In the absence of a functioning enzyme, the unphosphorylated glycoprotein never makes it to the lysosome and is instead exported out of the cell where it accumulates in the blood and

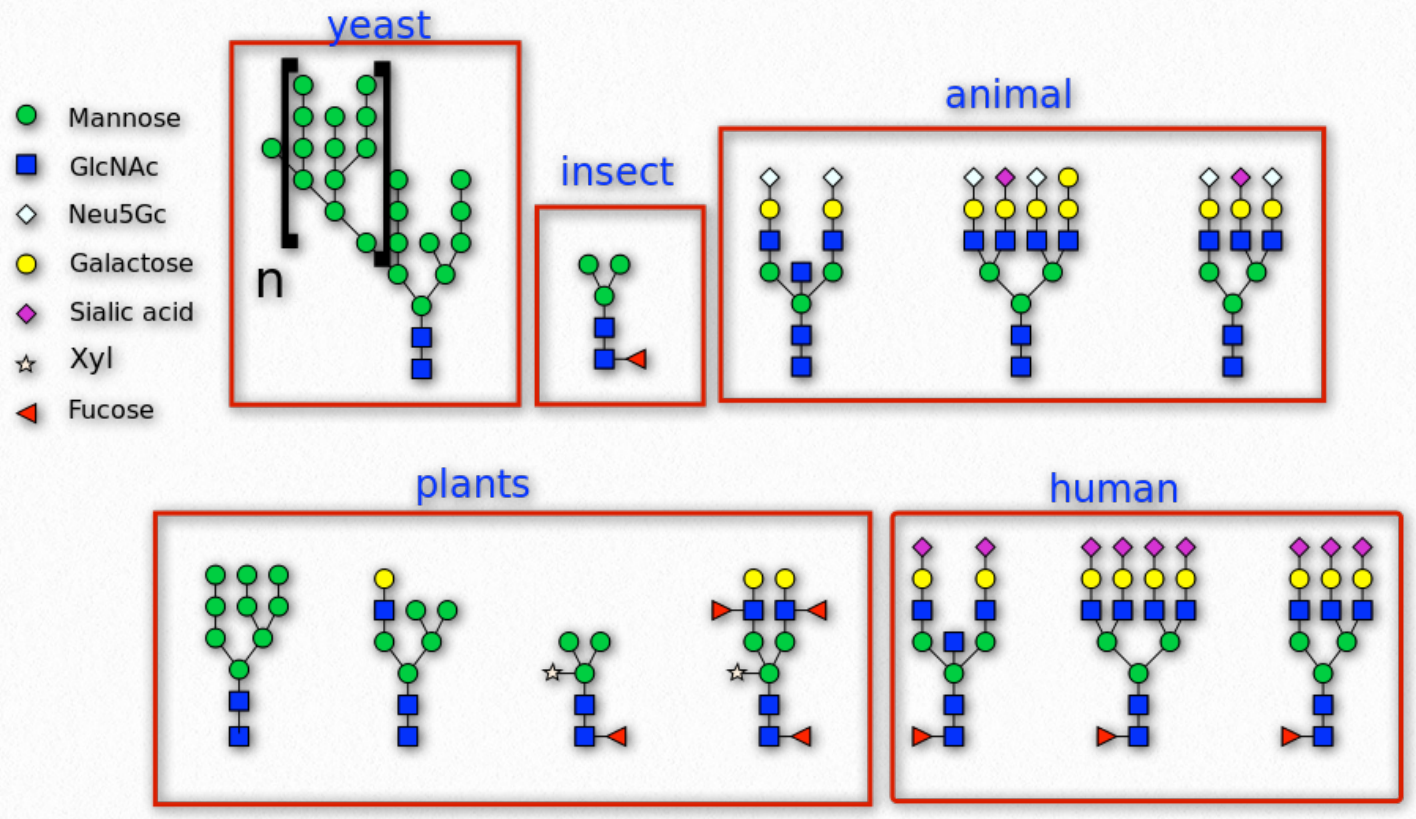

Figure 2.165 - N-linked glycosylation in various organisms

Wikipedia

is excreted in the urine. Individuals with I-cell disease suffer developmental delays, abnormal skeletal development, and restricted joint movement.

Glycosylation

Sugars are commonly attached to proteins in a process called glycosylation. Typically the attachment is to a hydroxyl or other functional group. The majority of proteins synthesized in the endoplasmic reticulum are glycosylated. Five classes of glycosylated products (called glycans if multiple carbohydrates are attached via glycosidic bonds) are known. They include:

• N-linked glycans (Figure 2.165) - carbohydrate attached to N group of asparagine or arginine side chain

• O-linked glycans - carbohydrate attached to OH of serine, threonine, tyrosine, hydroxyproline, hydroxylysine, or lipids.

• Phosphoglycans - attachment to a phosphoserine

• Glypiation - linkage of a phosphatidyl inositol to link proteins to lipids via glycan linkages

• C-linked glycans - sugar attached to a carbon on a tryptophan side chain.

YouTube Lectures by Kevin HERE & HERE

Glycosylation has several molecular/cellular functions. Some proteins require glycosylation to fold properly or to be stable. Glycosylated proteins on the plasma membrane serve as cellular identifiers. Blood types, for example, arise from differential glycosylation of a blood cell membrane protein. Glycosylation can also play an important role in cell-cell adhesion - important in the immune system.

N-linked glycosylation

N-linked protein glycosylation is one of five different types of protein glycosylation and it is the most common type of such alteration. The process 1) occurs in the endoplasmic reticulum, 2) involves "building" a part of the glycosyl chain on a molecule called dolichol pyrophosphate before transfer to the amide nitrogen of a target protein's asparagine, and 3) has a common "core" structure of carbohydrate residues linked to the proteins.

The process occurs commonly in eukaryotic cells, in some archaean cells, and rarely in bacteria. The structure of glycans varies a bit by protein and it also varies by the cell and by the organism. Bonds between the sugars of the glycan are glycosidic (involve anomeric carbon) and usually occur between carbons one and four. The consensus sequence of the protein attachment site is the asparagine in the sequence Asn-X-Ser/Thr where X is any amino acid except proline.

Steps

The process of making an N-linked protein occurs in three steps. It begins with synthesis of a pre-oligosaccharide on the terminal phosphate of dolichol pyrophosphate. Dolichol is a lipid molecule comprised of multiple isoprene units. The pre-oligosaccharide is assembled as follows:

a. Two molecules of UDP-N-acetylglucosamine donate N-acetylglucosamines to the pyrophosphate.

b. Five molecules of GDP-mannose donate mannose to the N-acetylglucosamines

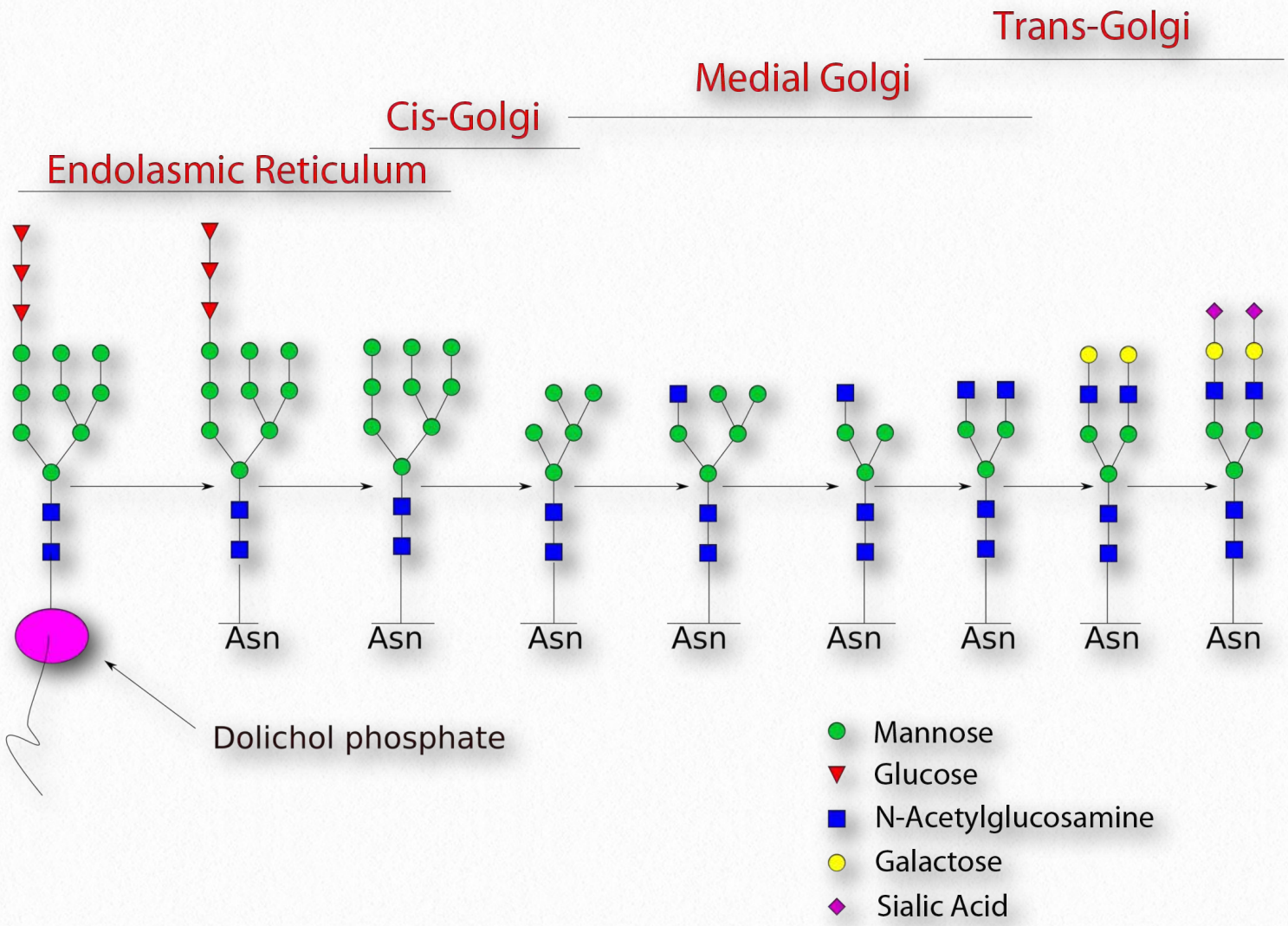

Figure 2.166 - Processing path for N-linked glycosylation

Wikipedia

At this point, the dolichol-sugar complex flips with respect to the endoplasmic reticulum membrane (catalyzed by an enzyme known as flippase), moving the sugar from facing the cytoplasm to facing the inside of the ER lumen. This completes Phase I of the modification. In Phase II, four more mannoses and three glucoses are added to the sugars on the end of the dolichol complex, creating the finished intermediate (Dolichol - GlcNAc2 – Man9-Glc3), which is then transferred to the amide nitrogen on asparagine of the target protein.

Last alterations

The remaining alterations occur to the glycan unit on the protein. First, the protein folds and then the three glucoses are removed. If the protein cannot fold properly, it cannot leave the ER and the glucoses remain intact. A properly folded protein is transferred to the cis-Golgi where various glycan modifications can occur, giving rise to three

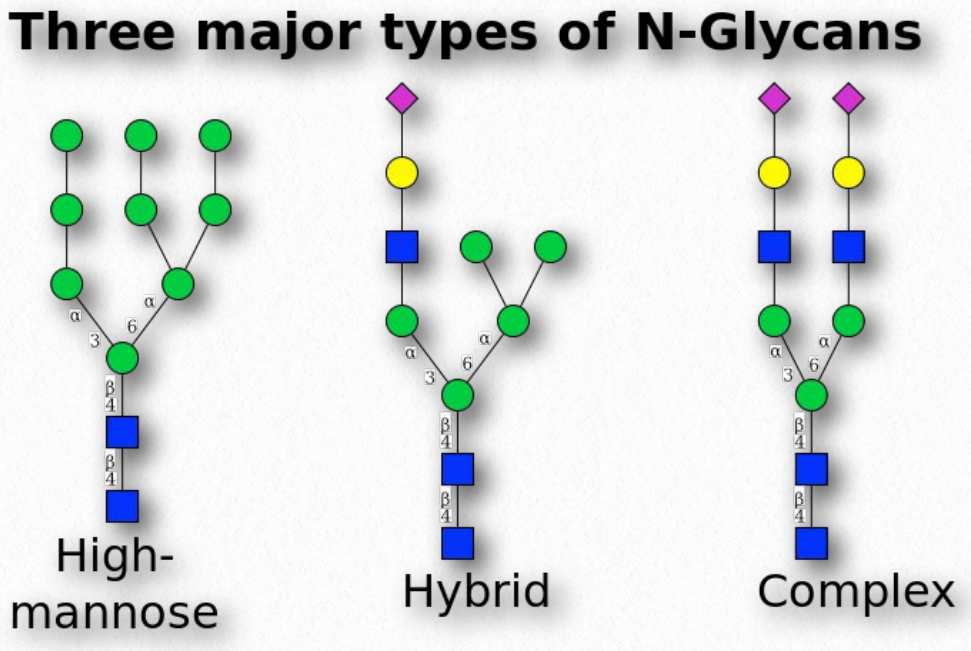

Figure 2.167 - Major N-glycan types - green = mannose, blue = N-acetylglucosamine, red = glucose
Wikipedia

major glycan types (Figure 2.167) - 1) high mannose, 2) hybrid glycans, and 3) complex glycans.

N-glycans on cell surfaces play roles in the immune system. The immunoglobulin types (IgG, IgA, IgE, IgD, and IgM) have distinct glycosylation patterns that confer unique functions by affecting their affinities for immune receptors. Glycans also are important in self/non-self identity is tissue rejection and autoimmune diseases.

O-Linked protein glycosylation

O-linked glycosylation is one of five types of glycosylation that occurs to proteins in all kingdoms of biology. The process is initiated primarily in the Golgi apparatus of eukaryotic cells, though a few such linkages start in the endoplasmic reticulum. The modification occurs on the oxygen of the hydroxyl group of serine, threonine, or tyrosine residues, but there is no clear sequence pattern directing the process. Amino acids that become hydroxylated through post-translational modification can also be involved in O-linkages (see below).

O-linked glycosylation commonly starts with attachment of a sugar, such as N-acetylgalactosamine to a serine or threonine side chain. Other sugars are then attached to this initial one. These include sialic acid, galactose, and others. The synthesis of proteoglycans occurs via this route

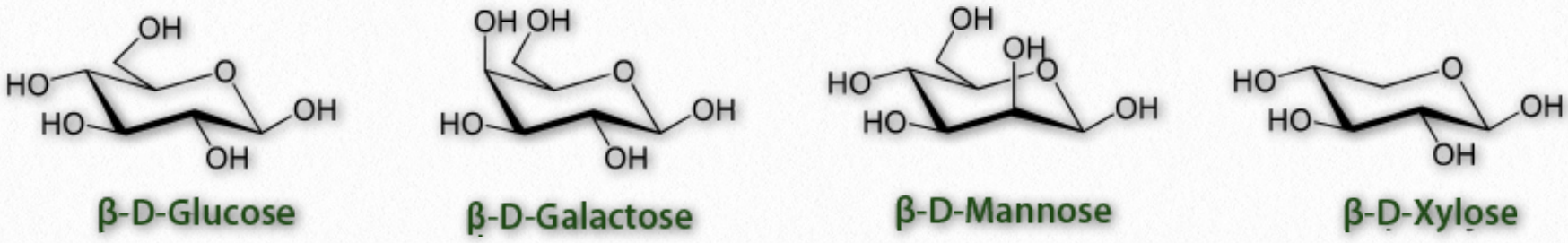

Figure 2.168 - Simple sugars common in glycosylation

when a xylose residue of a glycosaminoglycan is attached to a serine via an O-linkage. Mucins are membrane or secreted glycoproteins that have many O-linked oligosaccharide chains and are present in most bodily secretions.

Other sugars

Other sugars attached to proteins via O-linkages include fucose, glucose, N-acetylglucosamine, and mannose. Collagen is an important fibrous protein whose lysine residues are commonly hydroxylated in post-translational modification. Hydroxyls can be linked via their O-groups to galactose followed by attachment of glucose residues to the galactose. Such modifications are essential for proper functioning of collagen. Interestingly, hydroxyproline is also formed in collagen, but it is not a target for glycosylation.

C-linked glycosylation

C-linked glycosylation is the rarest and least understood protein glycosylation. It commonly occurs as a link between a mannose residue and a tryptophan side chain. The protein amino acid sequence where this occurs is typically Trp-X-X-Trp, where X is any amino acid and the first Trp is the location of the mannosylation. Thrombospondin proteins are the most commonly C-linked proteins.

Phospho-linked glycosylation

Attachment of a sugar residue to a phosphoserine occurs in phospho-linked glycosylation of proteins. Linkages to fucose, mannose, N-acetylglucosamine, and xylose are known.

Glypiation

In glypiation, a protein becomes linked to glycosylphosphatidylinositol (GPI) as a means of anchoring it to a cell membrane. The linkage occurs at the carboxyl terminus of the protein through one or more phosphoethanolamine linkers, which are, in turn, linked to mannose residues that are attached to GPI embedded in the membrane.

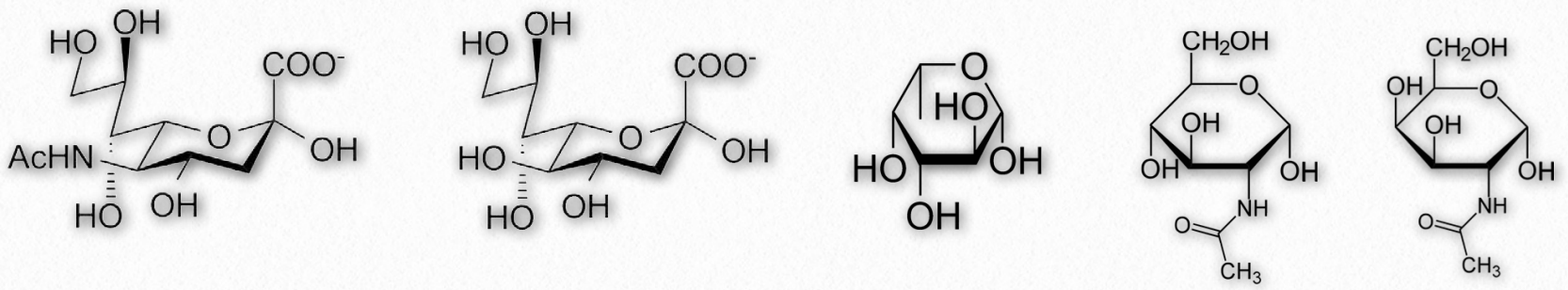

Figure 2.169 - Common modified sugars in glycosylated proteins - from left - two sialic acids (N-acetylneuraminic acid and 2-keto-3-deoxynonic acid), α-L-fucose, N-acetylglucosamine, and N-acetylgalactosamine

Glycoproteins

Glycoproteins are a very diverse collection of saccharide-containing proteins with many functions. Attachment of the saccharide to the protein is known as glycosylation. Secreted extracellular proteins and membrane proteins with exposed extracellular regions are often glycosylated. Saccharides attached to these may be short (oligosaccharides) or very large (polysaccharides). Glycoproteins play important roles in the immune system in antibodies and as components of the major histocompatibility complex (MHC). They are important for interactions between sperms and eggs, in connective tissues and are abundant in egg whites and blood plasma. Two glycoproteins (gp41 and gp120) are part of the HIV viral coat and are important in the infection process. Some hormones, such as erythropoietin, human chorionic gonadotropin, follicle-stimulating hormone and luteinizing hormone are also glycoproteins.

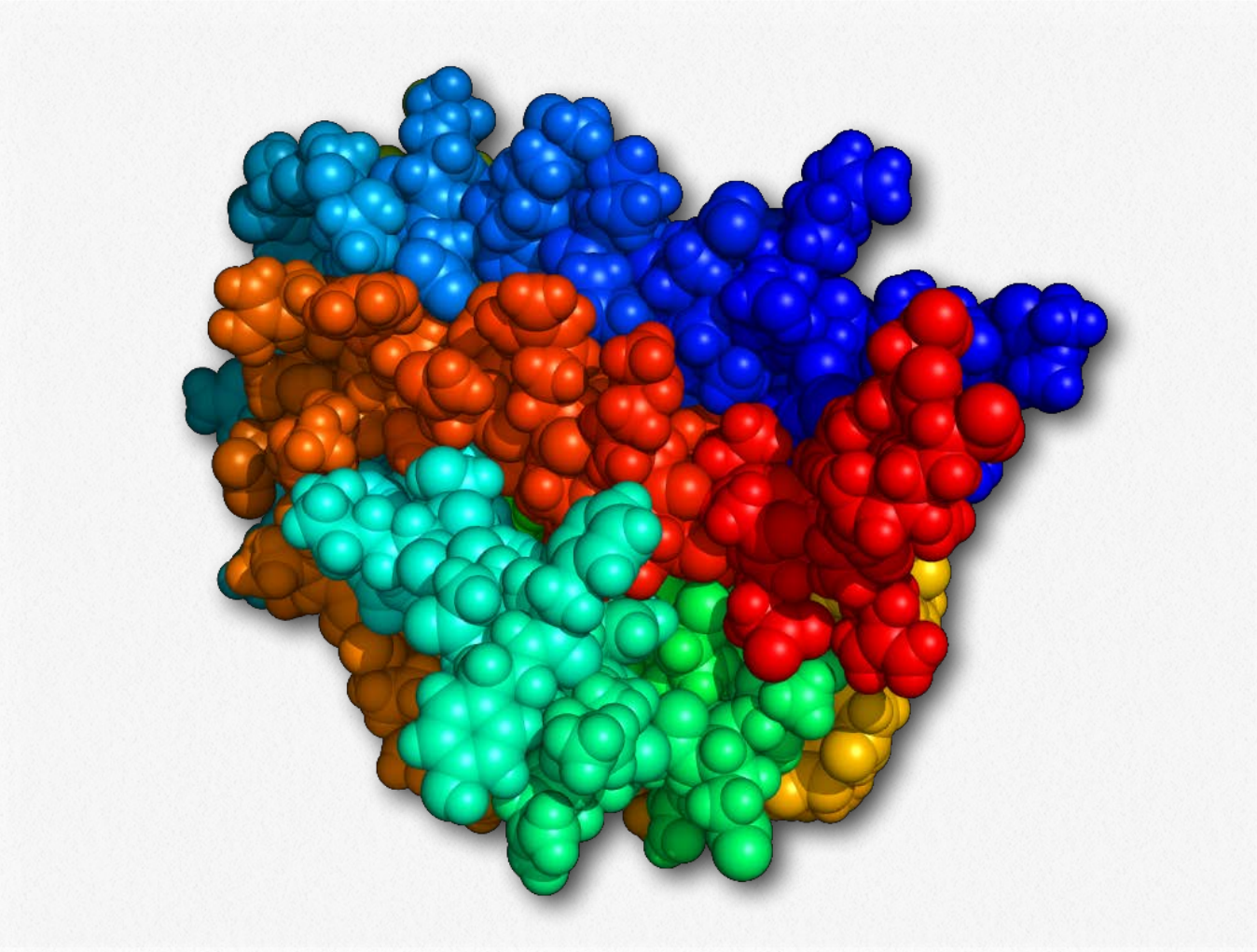

Figure 2.170 - Erythropoietin
Wikipedia

Glycation

Glycation is a chemical process (non-enzymatic) that occurs when a protein or lipid covalently binds to a sugar, such as glucose or fructose. Glycation differs from glycosylation in that the latter process is controlled by enzymes and results in specific attachment of specific sugars to biomolecules. Glycation, by contrast, is driven by two properties of monosaccharides 1) their chemistry and 2) their concentration. Glycations may be endogenous (occurring in an organism) or exogenous (occurring external to an organism).

Exogenous glycation arises most commonly as a result of cooking of food and this results in

attachment of sugars to lipids and/or proteins to form advanced glycation endproducts (AGEs). At temperatures above 120°C, AGE production occurs readily and contributes to the taste and the appearance of the food we eat.

Cooking

Browning of food, for example, is a product of glycation and is enhanced as the sugar content of a food increases. Browning of french fries is often enhanced, for example, by adding sugar to them. The formation of a crust of bread or the toasting of bread are other examples. These glycations are products of the Maillard reaction in which a reactive sugar carbonyl group combines with a nucleophilic amine of an amino acid. The process is favored in an alkaline environment, when amines are less protonated. The formation of the harder shell of a pretzel, for example, results from addition of lye to the exterior. At higher temperatures, though, a carcinogen known as acrylamide can be formed by reactions involving asparagine.

YouTube Lectures by Kevin HERE & HERE

Endogenous glycation, on the other hand, arises with a frequency that is proportional to the concentration of free sugar in the body. These occur most frequently with fructose, galactose, and glucose in that decreasing order and are detected in the bloodstream. Both proteins and lipids can be glycated and the accumulation of endogenous advanced glycation endproducts (AGEs) is associated with Type 2 diabetes, as well as in increases in cardiovascular disease (damage to endothelium, cartilage, and fibrinogen), peripheral neuropathy (attack of myelin sheath), and deafness (loss of myelin sheath).

The formation of AGEs increases oxidative stress, but is also thought to be exacerbated by it. Increased oxidative stress, in turn causes additional harm. Damage to collagen in blood cells causes them to stiffen and weaken and is a factor in hardening of the arteries and formation of aneurysms, respectively. One indicator of diabetes is increased glycation of hemoglobin in red blood cells, since circulating sugar concentration are high in the blood of diabetics. Hemoglobin glycation is measured in testing for blood glucose control in diabetic patients.

Homopolymer	Monomeric Unit
Glycogen	Glucose
Cellulose	Glucose
Amylose	Glucose
Callose	Glucose
Chitin	N-acetylglucosamine
Xylan	Xylose
Mannan	Mannose
Chrysolaminarin	Glucose

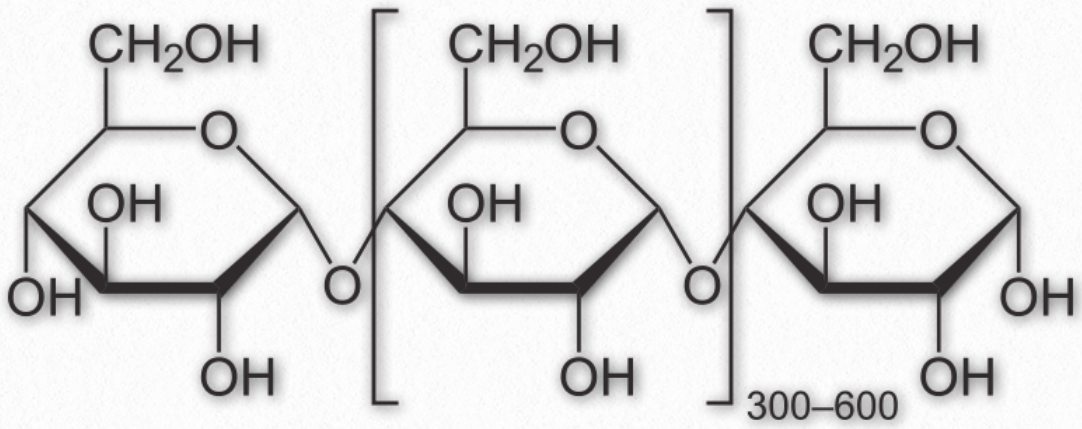

Figure 2.171 - Repeating unit of amylose

Nutritional polysaccharides

This group of polysaccharides is used exclusively for storage of sugar residues. They are easily easily broken down by the organism making them, allowing for rapid release of sugar to meet rapidly changing energy needs.

Polysaccharides

Long polymers of sugar residues are called polysaccharides and can be up to many thousands of units long. Polysaccharides are found free (not attached to other molecules) or bound to other cellular structures such as proteins. Some polysaccharides are homopolymers (contain only one kind of sugar),Others are heteropolymers (glycosaminoglycans, hemicellulose). Polysaccharides function in energy storage (nutritional polysaccharides, such as glycogen, amylose, amylopectin, e.g.), structure enhancement (chitin, cellulose, e.g.), and lubrication (hyaluronic acid, e.g.). These individual categories of polysaccharides are discussed below.

Amylose

Amylose has the simplest structure of any of the nutritional polysaccharides, being made up solely of glucose polymers linked only by α-1,4 bonds (Figures 2.171 & 2.172). (Note that the term 'starch' is actually a mixture of amylose and amylopectin). Amylose is insoluble in water and is harder to digest than amylopectin (see below). The complexing of amylopectin with amylose facilitates its water

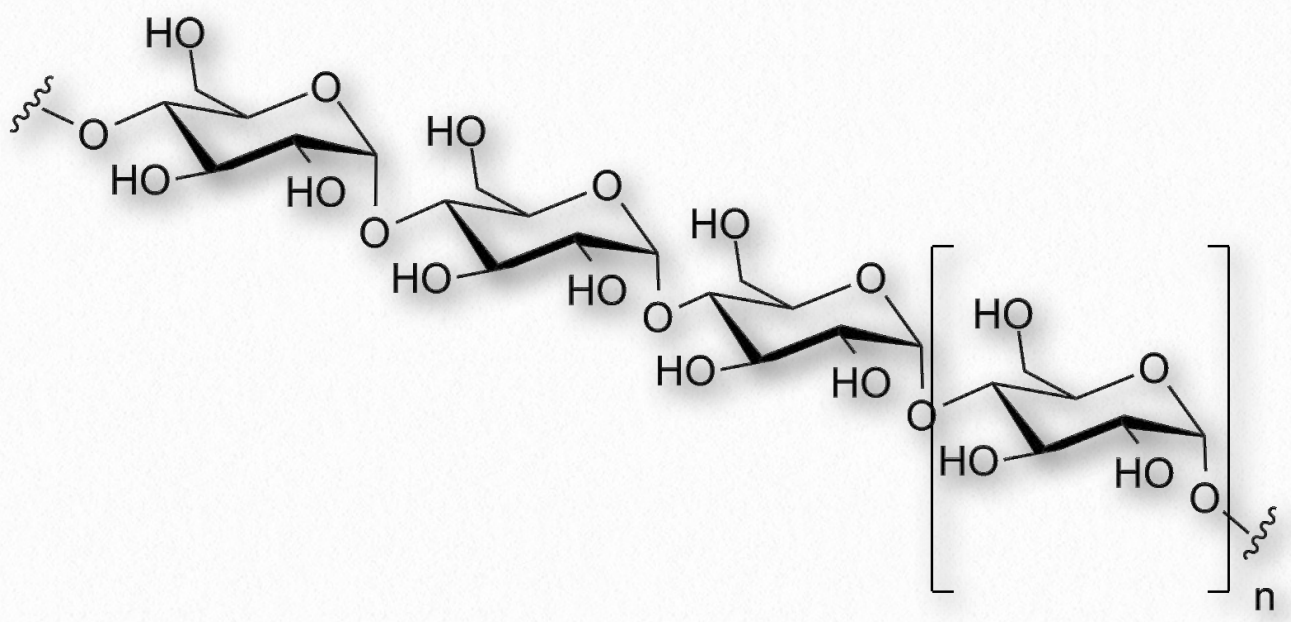

Figure 2.172 - Another view of amylose

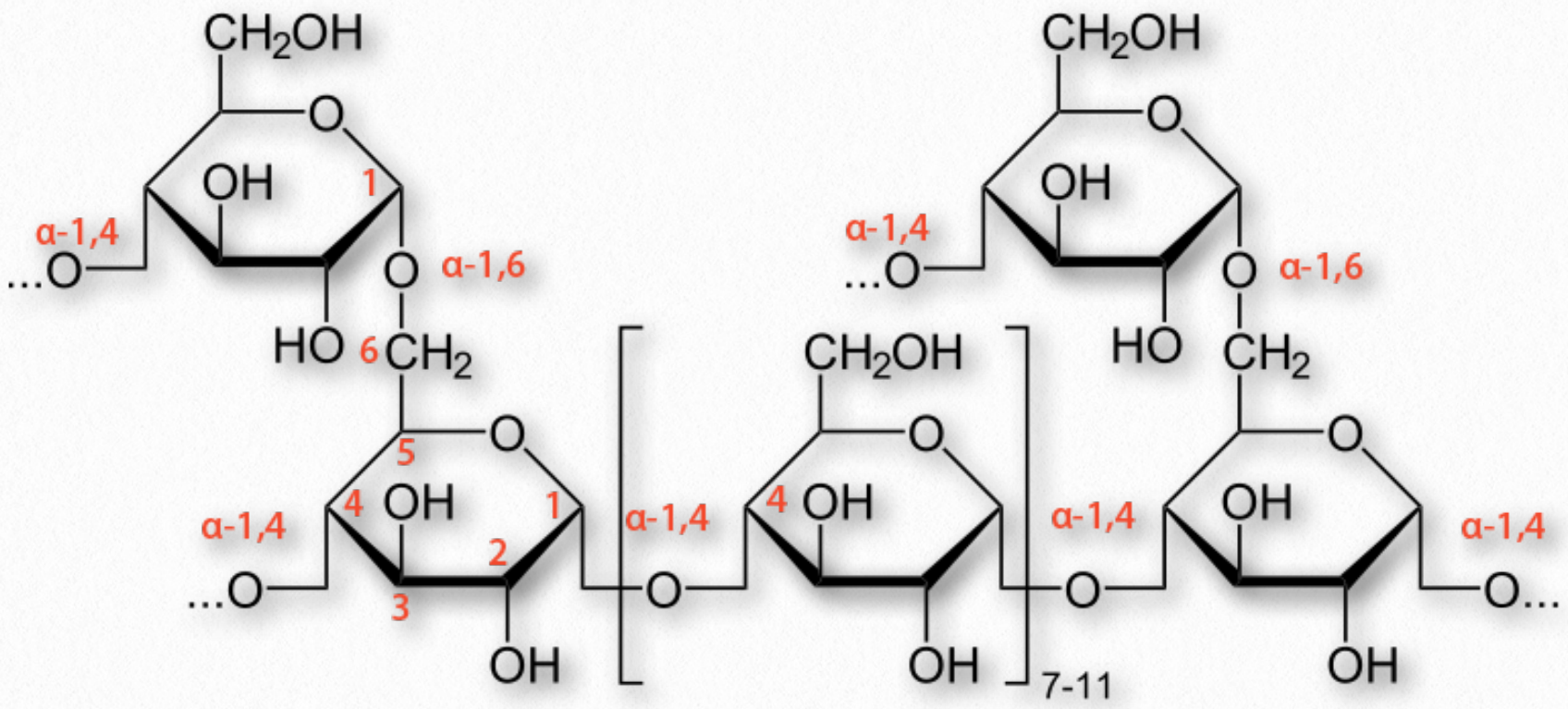

Figure 2.173 - Structure of glycogen

solubility and its digestion. Amylose is produced in plants for energy storage and since plants don't have rapidly changing demands for glucose (no muscular contraction, for example), its compact structure and slow breakdown characteristics are consistent with plants' needs.

Amylopectin and glycogen

More complicated homopolymers of glucose are possessed by amylopectin in plants and glycogen (Figure 2.173) in animals. Both compounds contain long glucose chains with α-1,4 bonds like amylose, but unlike amylose, these long chains have branches of α-1,6 bonds. Amylopectin is the less-branched of the two, having such bonds about every 25-30 residues, whereas glycogen has branches about every 8-12 residues. Branching plays important roles in increasing water solubility and in providing more "ends" to the polymer. In animals, glycogen is broken down starting at the ends, so more ends means more glucose can be released quickly. Again, plants, which have a lower need for quick release of glucose than animals get by with less branching and fewer ends.

Structural polysaccharides

An additional function of polysaccharides in cells relates to structure. Cellulose, which is a polymer of glucose with exclusive β-1,4 linkages between the units (Figure 2.174) is an important structural component of plants and fungi cells. Notably, most non-ruminant animals are unable to digest this polymer, as they lack the enzyme known as cellulase.

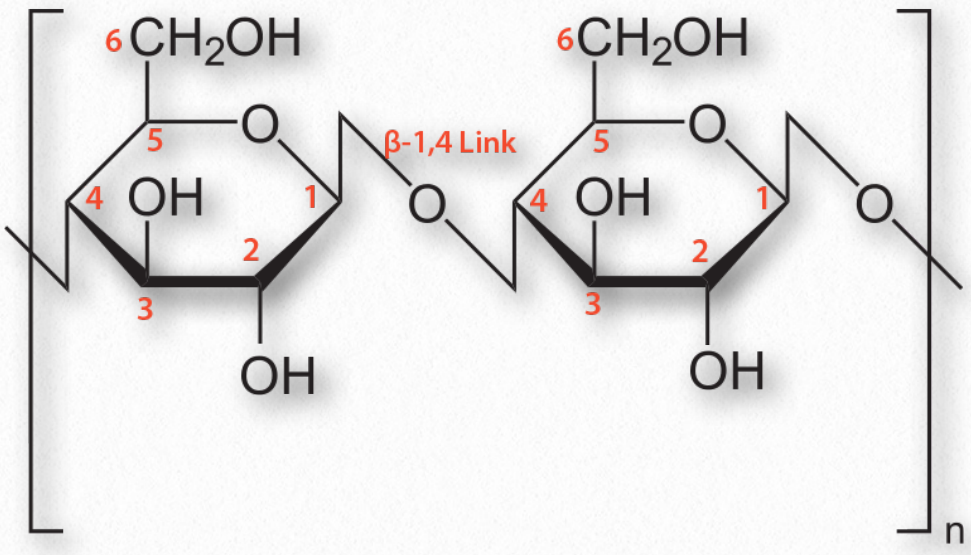

Figure 2.174 - Cellulose with β-1,4 links between glucose sugars

Ruminants, such as cattle, however, contain in their rumen a bacterium that possesses this enzyme and allows them to obtain glucose energy from plants. Another group of polysaccharides found in plant cell walls is the hemicelluloses. This class of molecules encompasses several branched heteropolymers of (mostly) D-pentose sugars along with a few hexoses and L-sugars as well. Hemicelluloses are shorter than cellulose (500-3000 sugars versus 7000-15,000 sugars).

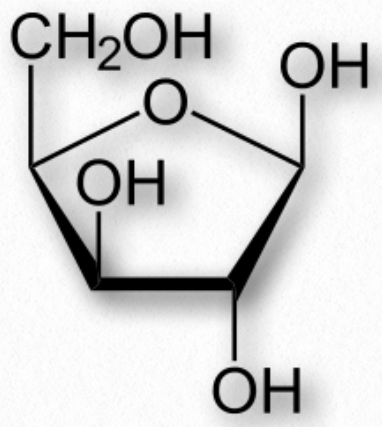

Figure 2.175 Xylose

Monomer sugars of polysaccharides besides glucose include xylose, mannose, galactose, rhamnose, and arabinose. Xylose is usually present in the greatest amount (Figure 2.175).

Chitin

Chitin (Figure 2.176) is another structural polysaccharide, being comprised of N-acetylglucosamine units joined by β-1,4 linkages. It is a primary component of the cell walls of fungi and is also prominent in the exoskeletons of arthropods and insects, as well as the beaks and internal shells of cephalopods (Figure 2.177). Chitin's structure was solved by Albert Hofmann in 1929. It is like cellulose except for the acetylamine group replacing the hydroxyl on position 2. This change allows hydrogen bonding to occur between adjacent polymers, thus providing greater strength.

Pectins

Another group of structural polysaccharides is the pectins (Figure 2.178). These com-

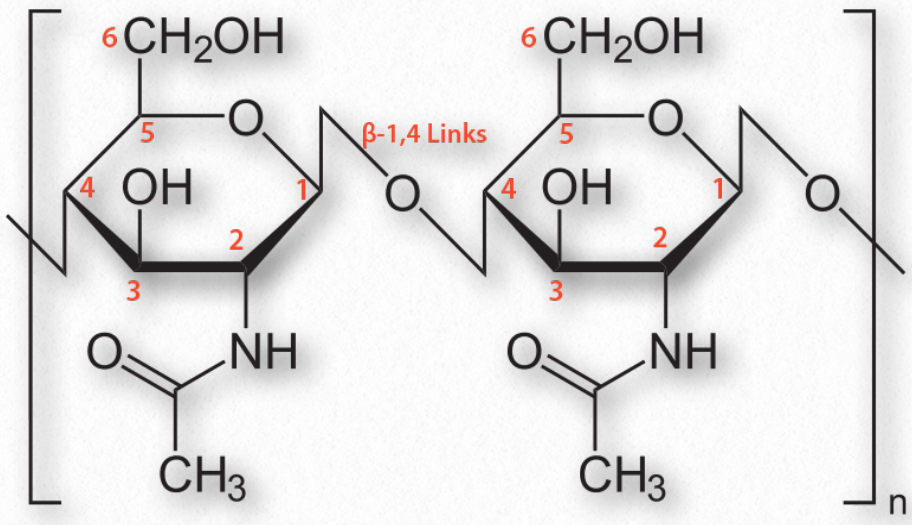

Figure 2.176 - Chitin with β-1,4 links between N-acetylglucosamine sugars

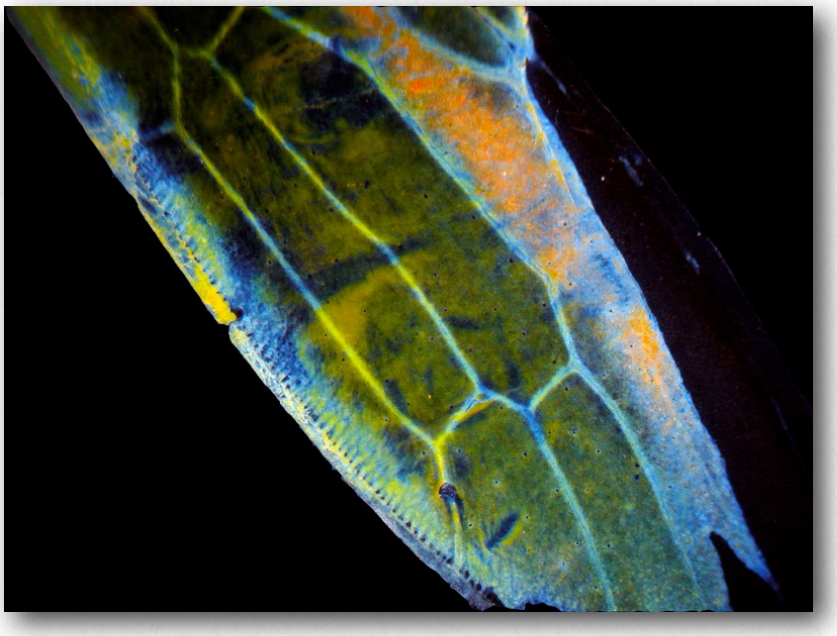

Figure 2.177 - Chitin in the wing of a sap beetle

Wikipedia

pounds are present in most primary plant cell walls and are abundant in non-woody parts of terrestrial plants. They are rich in galacturonic acid (α-1,4 links with no branches - Figure 2.179) and are used commercially as a gelling agent in jams/jellies, as well as a stabilizer in fruit juices and milk drinks. Pectin consumption may result in reduced blood cholesterol levels due to its tendency to 1) bind cholesterol and 2) to increase viscosity in the intestinal tract, thus reducing absorption of cholesterol from food. Pectins also trap carbohydrates in the digestive system and reduce their rate of absorption.

Figure 2.178 - A powdered form of pectin

Lectins

Lectins are not carbohydrates, but proteins that specifically bind to carbohydrate molecules found in animals and plants (where they are known as phytohemagglutinins) and are each highly specific for certain sugars. They function in cellular and molecular recognition, as well as cell adhesion. One lectin recognizes hydrolytic enzymes containing mannose-6-phosphate and targets them to be delivered to lysosomes. In the innate immune system, a mannose binding lectin helps defend against invading microbes. Other lectins have roles in inflammation and autoimmune disorders.

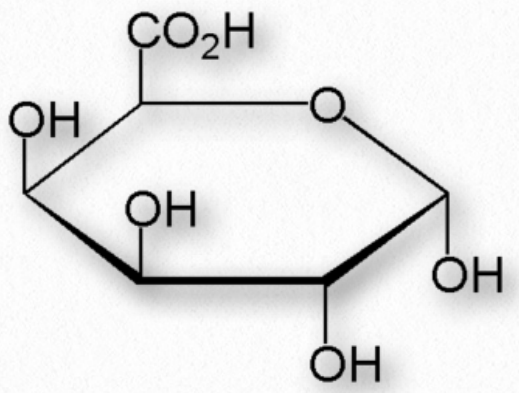

Figure 2.179 - α-D-Galacturonic acid - An important component of pectin polymers

Some viruses and bacteria use lectins to recognize and bind specific carbohydrate residues on the surface of target cells. Flu virus, for example, carries a lectin known as hemagglutinin (Figure 2.180) that binds to sialic acid and is essential for entrance of the virus into the target cell. After binding, the viral particle enters by endocytosis after the hemagglutinin has been cleaved by a protease.

After replication of the virus inside of the cell, hemagglutinin and and a viral enzyme known as neuraminidase cluster in the cell membrane. Viral RNA and associated viral proteins cluster near this membrane site and new viruses bud off in a portion of the cell's membrane after the hemagglutinin-sialic acid link to the infected cell is released by the neuraminidase cutting the bond between the sialic acid and the rest of the cell surface carbohydrate. Drugs, such as tamiflu, that interfere with neuraminidase work by preventing release of the viral particle. Unreleased particles will tend to aggregate and not function.

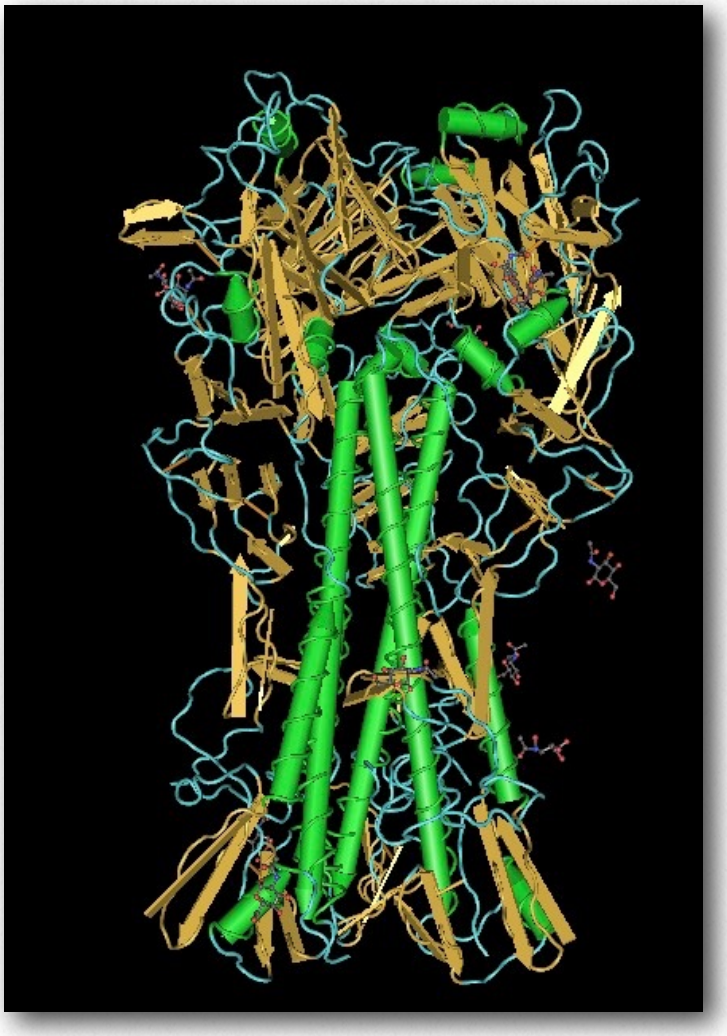

Figure 2.180 - Hemagglutinin

Some viral glycoproteins from hepatitis C virus may attach to lectins on the surface of liver cells in their infectious cycle. The bacterium *Helicobacter pylori* uses a cell surface lectin to bind oligosaccharides on epithelial cells lining the stomach. One lectin known as ricin is a very powerful toxin. It is produced in the endosperm of seeds of the castor oil plant and is of concern as a bioterrorism weapon as a result of its acute toxicity when inhaled or ingested.

Lectins were discovered originally in plants and have been most studied in legumes, but lectins are now known to be widely dispersed in nature. In the immune system, a mannan binding lectin (MBL) helps mediate the first defenses against microorganisms. Other immune system lectins are thought to modulate inflammatory processes and probably play a role in self/non-self recognition that is at the root of rejection of transplanted organs.

YouTube Lectures by Kevin HERE & HERE

Biofuels

In an era of diminishing energy sources, interest in using fuels made by biological processes is growing. Biofuels are made by biological systems and are commonly metabolic products of plants, yeast, and/or bacteria. A common output product is ethanol (used in gasoline) or methane (natural gas) and a common starting material is cellulose

from plant metabolism. In biofuel production with these materials, plant material containing cellulose is digested a) enzymatically (by the enzyme cellulase); b) chemically (with strong acids); or c) biologically (yeast/bacteria) to yield the glucose sugars comprising it. Fermentation of those sugars by yeasts/bacteria can yield ethanol while alternative metabolism by other bacteria can yield methane.

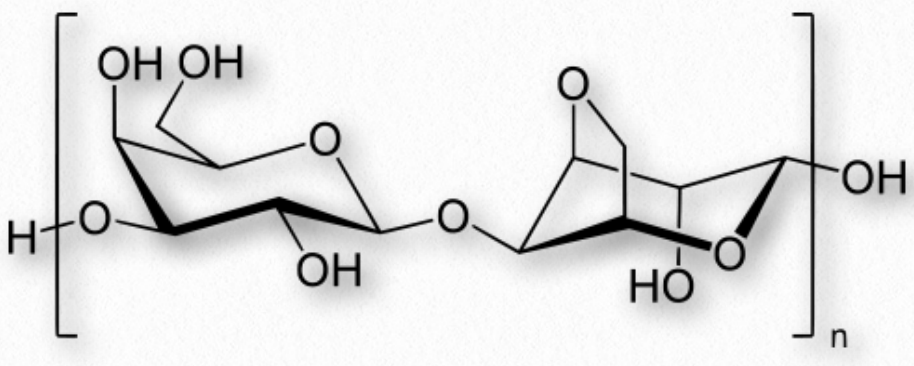

Figure 2.182 - Repeating unit of agarose - 3,6-anhydro-L-galactopyranose

Agar/agarose

A polysaccharide product that has numerous uses in laboratories is agar/agarose. Agarose is a polysaccharide polymer of D-galactose and 3,6-anhydro-L-galactopyranose that is extracted from seaweed and has a repeating structure shown in Figure 2.182. Addition of agaropectin creates the material known as agar. Both substances make gel-like structures when boiled in water and then cooled. Agar is commonly used to make plates for culturing microorganisms (Figure 2.183) and agarose is the common support of agarose gels (Figure 2.184) used to separate DNA fragments in electrophoresis.

Figure 2.183 - Agar plates for culturing bacteria

Figure 2.181 Biofuel-powered bus

Glycosaminoglycans

Another variation on the polysaccharide theme is found in

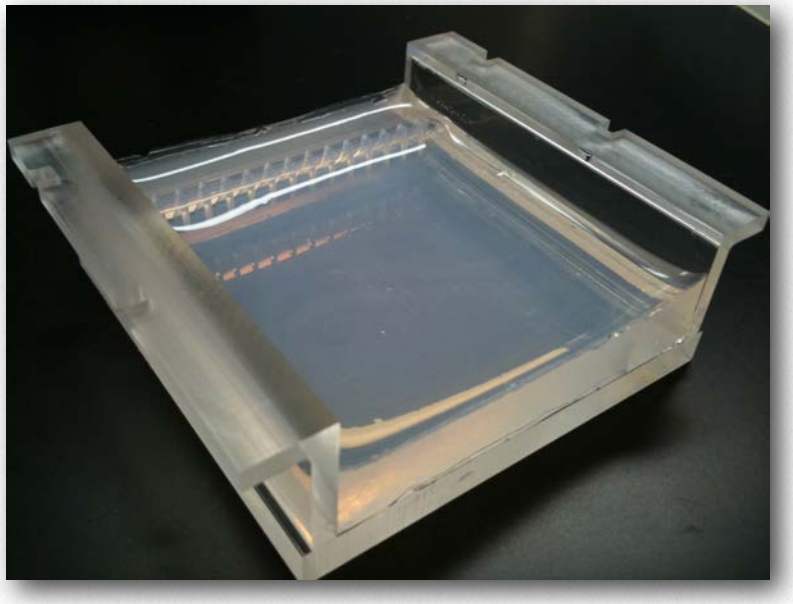

Figure 2.184 - Agarose gel

Wikipedia

polymers known as the glycosaminoglycans. Previously known as mucopolysaccharides, glycosaminoglycans are polymers of unbranched repeating disaccharides. The repeating units of the disaccharide core of the molecules typically have an amino sugar (N-acetylglucosamine or N-acetylgalactosamine) and a uronic sugar (glucuronic acid or iduronic acid) or galactose. Glycosaminoglycans vary considerably in molecular mass, disaccharide structure, and sulfation. The presence of uronic acid residues and sulfates in glycosaminoglycans causes them to be polyanionic. As such, they are capable of binding many cations including sodium, potassium, and calcium. Glycosaminoglycans are organized in four groups - those found in connective tissue (linked to collagen) and they also act as lubricants for joints (hyaluronic acid in synovial fluid), as anti-clotting agents (heparin) and as components of mucus where they help to protect against infection.

Chondroitin sulfate

Chondroitin sulfate (Figure 2.185) is a glycosaminoglycan found in cartilage with a repeating disaccharide structure of

- a modified glucuronic acid and
- a modified N-acetylgalactosamine. At least one of the sugars of the disaccharide will have a covalently bound sulfate on it, giving the polymer a polyanionic character.

Chondroitin sulfate chains will typically have over 100 individual sugars and the chemical composition of each one can vary. It is a structural component of cartilage and

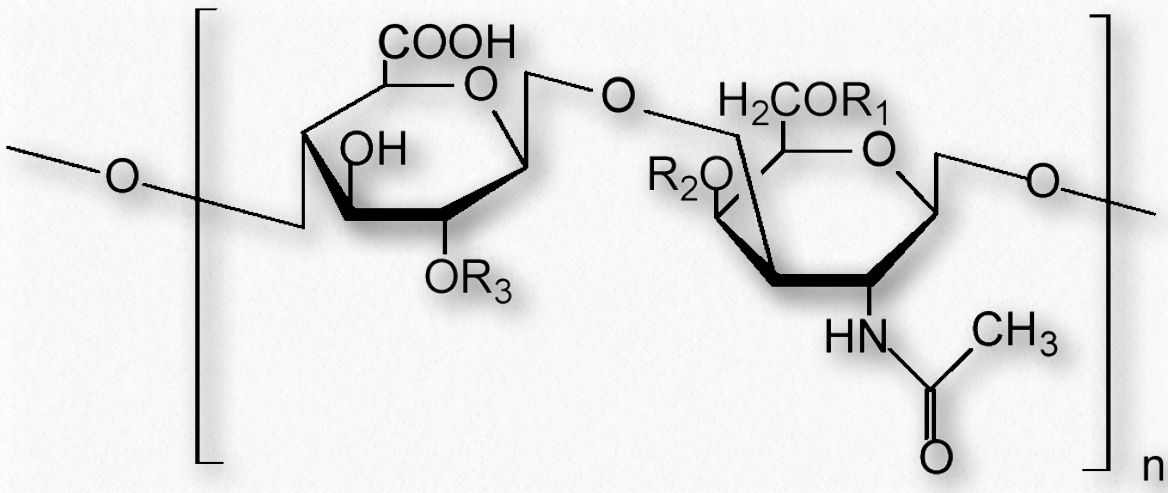

Figure 2.185 - Repeating disaccharide in chondroitin sulfate

helps to give it the ability to resist compression.

Chondroitin sulfate is used as a dietary supplement to treat joint pain and osteoarthritis, though its ability to provide relief is not clear. In cells, the compound is a component of the extracellular matrix. It can be linked to proteins through serine residues to form proteoglycans, such as aggrecan, versican, brevican, and neurocan. These substances are prominent in the extracellular matrix of the brain. In the form of aggrecan, chondroitin sulfate is a major component of cartilage. Loss of chondroitin sulfate from cartilage is an issue in osteoarthritis.

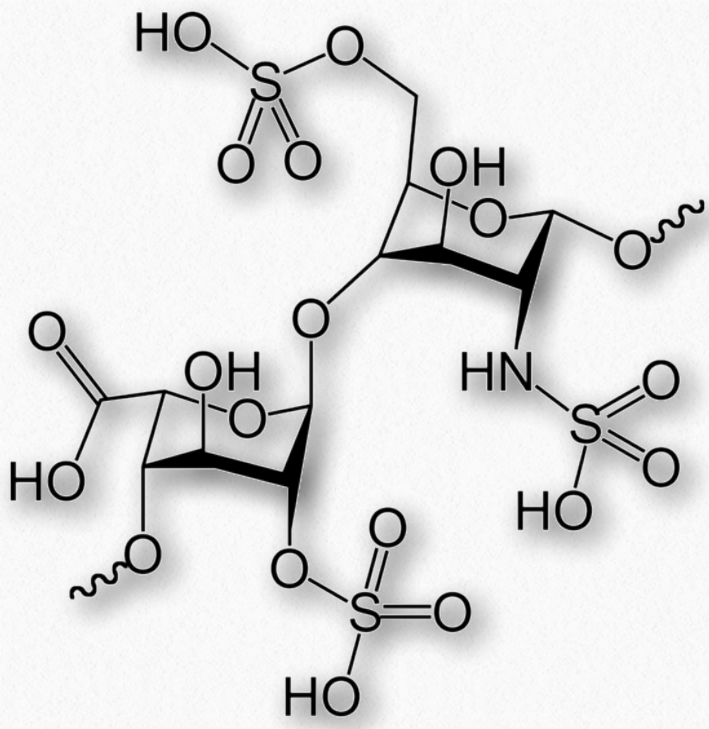

Figure 2.186 - Repeating sulfated disaccharide in heparin

Heparin

Heparin (Figures 2.186 & 2.187) is a modified polysaccharide whose biological function is unclear, but whose ability to prevent clotting of blood is used for medical purposes. Heparin does not dissolve blood clots. Rather, it acts to prevent conversion of fibrinogen to fibrin (see HERE).

Whether or not heparin is actually used by the body for its anticoagulation property is uncertain. It is stored in the secretory granules of mast cells and released at the point of injury and it has been proposed it is a protection against bacteria and other foreign materials.

Heparin has abundant sulfates and is, in fact, the molecule with the highest negative charge density known. Its size varies from 3 kDa to 30 kDa, with an average of about 15 kDa. The repeating disaccharide of 2-O-sulfated iduronic acid and 6-O-sulfated, N-

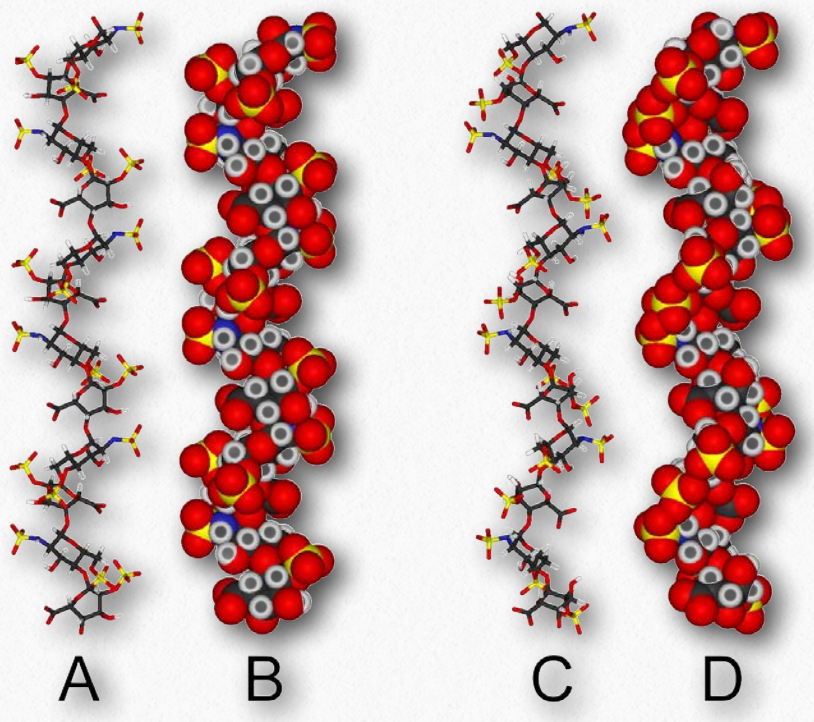

Figure 2.187 - Two structures for heparin

sulfated glucosamine, occupies about 85% of the molecule. Copper salts of heparin help stimulate the synthesis of blood vessels (angiogenic).

Hyaluronic acid

Hyaluronic acid (also known as hyaluronan or hyaluronate) is a glycosaminoglycan found in connective, epithelial, and nerve tissues. It is an unusual glycosaminoglycan (Figure 2.188), lacking sulfate, is made by hyaluronan synthases on the inner face of the plasma membrane and has a molecular weight in the millions. An average adult body contains about 15 grams of HA, one third of which is replaced every day. The repeating unit in hyaluronic acid is a disaccharide structure of D-glucuronic acid joined to D-N-acetylglucosamine. The compound, which can have upwards of 25,000 units of the disaccharide, is delivered directly into the extracellular matrix by enzymes from its plasma membrane site of synthesis.It is an important component of the extracellular matrix, where it assists in cell proliferation and migration. The polymer provides an open hydrated matrix to facilitate general cell migration whereas directed cell migration occurs *via* the interaction between hyaluronic acid and specific cell surface receptors. HA interaction with the receptor RHAMM (Receptor for Hyaluronan Mediated Motility) has been shown to be involved in wound repair as well as tumor progression.

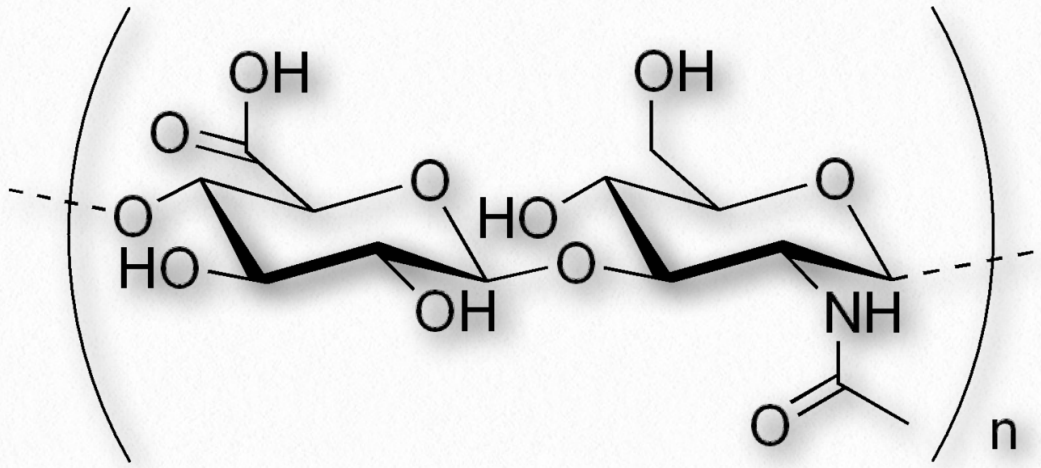

Figure 2.188 - Repeating disaccharide of hyaluronic acid

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Synovial Fluid

The function of hyaluronic acid has traditionally been described as providing lubrication in synovial fluid (the lubricating material in animal joints - Figure 2.189). Along with the proteoglycan called lubricin, hyaluronic acid turns water into lubricating material. Hyaluronic acid is present as a coat around each cell of articular cartilage and forms complexes with proteoglycans that absorb water, giving resilience (resistance to compression) to cartilage. Aging causes a decrease in size of hyaluronans, but an increase in concentration.

Function in skin

Hyaluronic acid is a major component of skin and has functions in tissue repair. With exposure to excess UVB radiation, cells in the

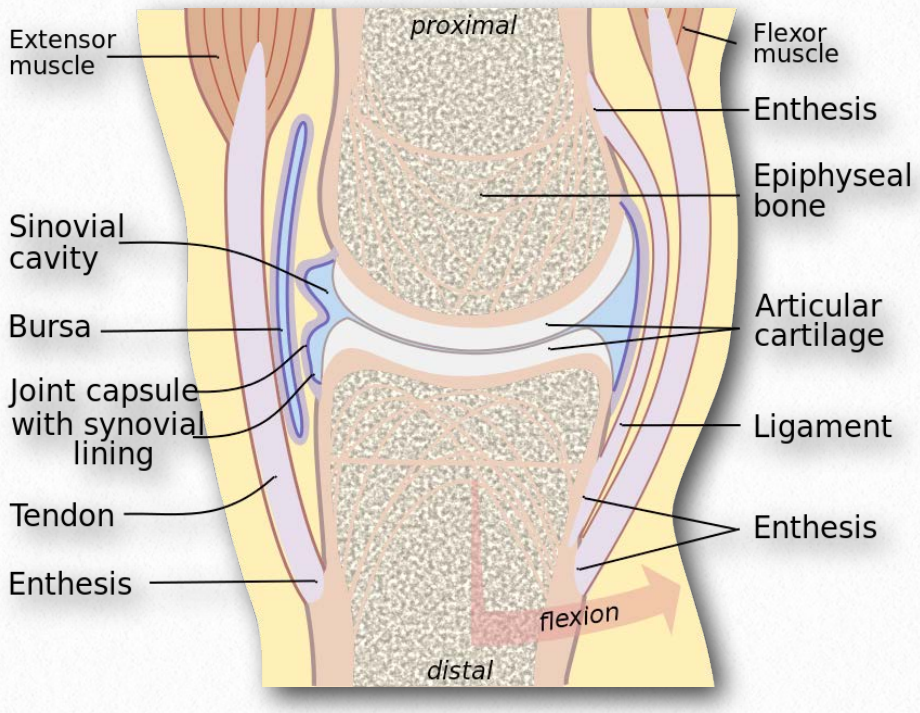

Figure 2.189 - Synovial fluid in joint lubrication

Wikipedia

dermis produce less hyaluronan and increase its degradation.

For some cancers the plasma level of hyaluronic acid correlates with malignancy. Hyaluronic acid levels have been used as a marker for prostate and breast cancer and to follow disease progression. The compound can to used to induce healing after cataract surgery. Hyaluronic acid is also abundant in the granulation tissue matrix that replaces a fibrin clot during the healing of wounds. In wound healing, it is thought that large polymers of hyaluronic acid appear early and they physically make room for white blood cells to mediate an immune response.

Breakdown

Breakdown of hyaluronic acid is catalyzed by enzymes known as hyaluronidases. Humans have seven types of such enzymes, some of which act as tumor suppressors. Smaller hyaluronan fragments can induce inflammatory response in macrophages and dendritic cells after tissue damage. They can also perform pro-angiogenic functions.

Proteoglycans

Glycosaminoglycans are commonly found attached to proteins and these are referred to as proteoglycans. Linkage between the protein and the glycosaminoglycan is made through a serine side-chain. Proteoglycans are made by glycosylation of target proteins in the Golgi apparatus.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

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Hark the Sucrose

To the tune of "*Hark the Herald*"
Metabolic Melodies Website HERE

Carbohydrates all should sing
Glory to the Haworth ring

Anomeric carbons hide
When they're in a glycoside

Glucopyranose is there
In the boat or in the chair

Alpha, beta, D and L
Di-astere-omer hell

Alpha, beta, D and L
Di-astere-omer hell

Recording by Tim Karplus
Lyrics by Kevin Ahern

Hyaluronic Acid

To the tune of "*Rudolph the Red-Nosed Reindeer*"

Metabolic Melodies Website HERE

Hyaluronic Acid
Acting almost magically
Placed just beneath the kneecap
Lubricating the debris

Better than joint replacement
Simple as 1-2-3
If it can stop the aching
You will get to keep your knee

When the pain is getting bad
Try not to be sad
Just go out and have a talk
With your orthopedic doc

Beg him to use the needle
To not do so would be a crime
Hyaluronic acid
Workin' where the sun don't shine

Recording by David Simmons
Lyrics by Kevin Ahern

Structural Lullaby

To the tune of "*Brahms' Lullaby*"

Metabolic Melodies Website HERE

In your sleep
You can keep
Learning more about sugars
Fischer schemes
Haworth rings
D & L and everything

Hydroxides
Can't collide
Fav'ring chair over boat form
Spatial guides
Coincide
With the wav structures form

Recording by David Simmons
Lyrics by Kevin Ahern

Structure & Function: Lipids and Membranes

Lipids

Lipids are a diverse group of molecules that all share the characteristic that at least a portion of them is hydrophobic. Lipids play many roles in cells, including serving as energy storage (fats/oils), constituents of membranes (glycerophospholipids, sphingolipids, cholesterol), hormones (steroids), vitamins (fat soluble), oxygen/electron carriers (heme), among others. For lipids that are very hydrophobic, such as fats/oils, movement and storage in the aqueous environment of the body requires special structures. Other, amphipathic lipids, such as glycerophospholipids and sphingolipids spontaneously organize themselves into lipid bilayers when placed in water. Interestingly, major parts of many lipids can be derived from acetyl-CoA.

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Fatty acids

The most ubiquitous lipids in cells are the fatty acids. Found in fats, glycerophospholipids, sphingolipids and serving as as

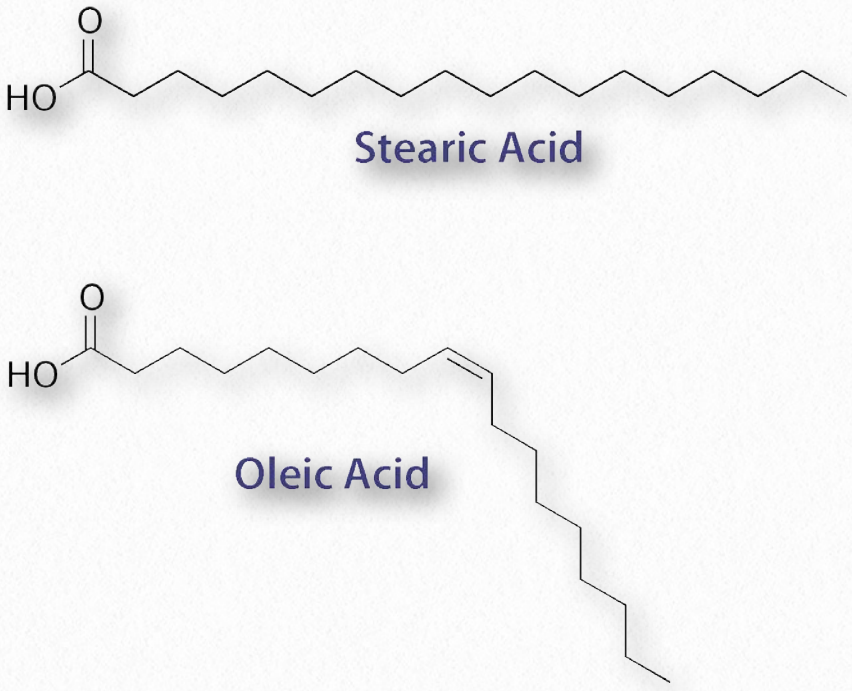

Figure 2.190 - Saturated fatty acid (stearic acid) and unsaturated fatty acid (oleic acid)

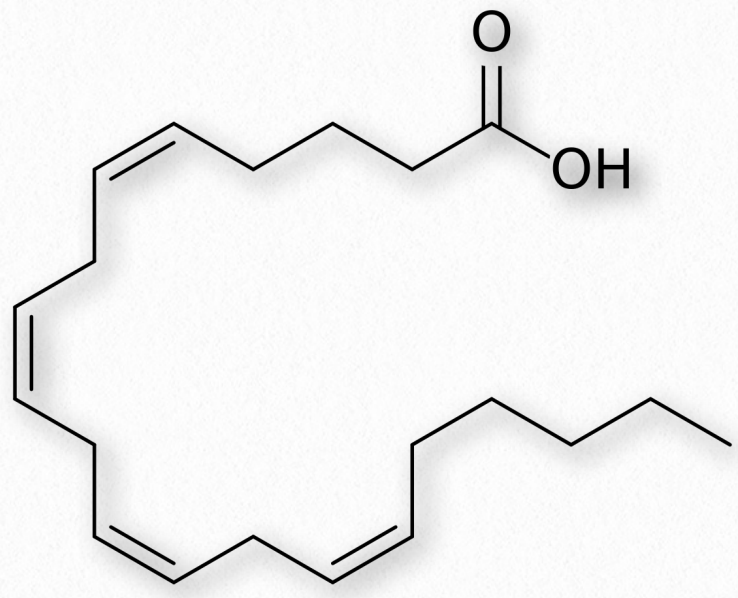

Figure 2.191 - Arachidonic acid - A polyunsaturated fatty acid

Wikipedia

membrane anchors for proteins and other biomolecules, fatty acids are important for energy storage, membrane structure, and as precursors of most classes of lipids. Fatty acids, as can be seen from Figure 2.190 are characterized by a polar head group and a long hydrocarbon tail. Fatty acids with hydrocarbon tails that lack any double bonds are described as saturated, while those with one or more double bonds in their tails are known as unsaturated fatty acids. The effect of double bonds on the fatty acid tail is to introduce a kink, or bend, in the tail, as shown for oleic acid. Stearic acid, a saturated fatty acid, by contrast has a straight hydrocarbon tail. Figures 2.190-2.194 show the most common saturated and unsaturated fatty acids. Fatty acids with unsaturated tails have a lower melting temperature than those with satu-

Common name	Chemical structure	
Caprylic acid	$CH_3(CH_2)_6COOH$	8
Capric acid	$CH_3(CH_2)_8COOH$	10
Lauric acid	$CH_3(CH_2)_{10}COOH$	12
Myristic acid	$CH_3(CH_2)_{12}COOH$	14
Palmitic acid	$CH_3(CH_2)_{14}COOH$	16
Stearic acid	$CH_3(CH_2)_{16}COOH$	18
Arachidic acid	$CH_3(CH_2)_{18}COOH$	20
Behenic acid	$CH_3(CH_2)_{20}COOH$	22
Lignoceric acid	$CH_3(CH_2)_{22}COOH$	24
Cerotic acid	$CH_3(CH_2)_{24}COOH$	26

Figure 2.192 - Saturated fatty acids. Number of carbons in right column

Wikipedia

Name	Double Bond Info	
Myristoleic acid	*cis*-Δ^9	14:1
Palmitoleic acid	*cis*-Δ^9	16:1
Sapienic acid	*cis*-Δ^6	16:1
Oleic acid	*cis*-Δ^9	18:1
Elaidic acid	*trans*-Δ^9	18:1
Vaccenic acid	*trans*-Δ^{11}	18:1
Linoleic acid	*cis*,*cis*-Δ^9,Δ^{12}	18:2
Linoelaidic acid	*trans*,*trans*-Δ^9,Δ^{12}	18:2
α-Linolenic acid	*cis*,*cis*,*cis*-Δ^9,Δ^{12},Δ^{15}	18:3
Arachidonic acid	*cis*,*cis*,*cis*,*cis*-$\Delta^5\Delta^8$,Δ^{11},Δ^{14}	20:4
Eicosapentaenoic acid	*cis*,*cis*,*cis*,*cis*,*cis*-Δ^5,Δ^8,Δ^{11},Δ^{14},Δ^{17}	20:5
Erucic acid	*cis*-Δ^{13}	22:1
Docosahexaenoic acid	*cis*,*cis*,*cis*,*cis*,*cis*,*cis*-Δ^4,Δ^7,Δ^{10},Δ^{13},Δ^{16},Δ^{19}	22:6

Figure 2.193 - Unsaturated fatty acids. Right column Indicates number of carbons and double bonds

Wikipedia

Biochemically, the double bonds found in fatty acids are predominantly in the *cis* configuration. So-called *trans* fats arise as a chemical by-product of partial hydrogenation of vegetable oil. In humans, consumption of *trans* fat raises low density lipoprotein (LDL) levels and lowers high density lipoprotein (HDL) levels. Each is thought to contribute to the risk of developing coronary artery disease. The most

rated tails of the same length. Shorter tails also decrease melting temperature. These properties carry over to the fats/oils containing them.

Fatty acids with more than one double bond are called polyunsaturated. Plants are excellent sources of unsaturated and polyunsaturated fatty acids. The position of the double bond(s) in fatty acids has important considerations both for their synthesis and for their actions in the body.

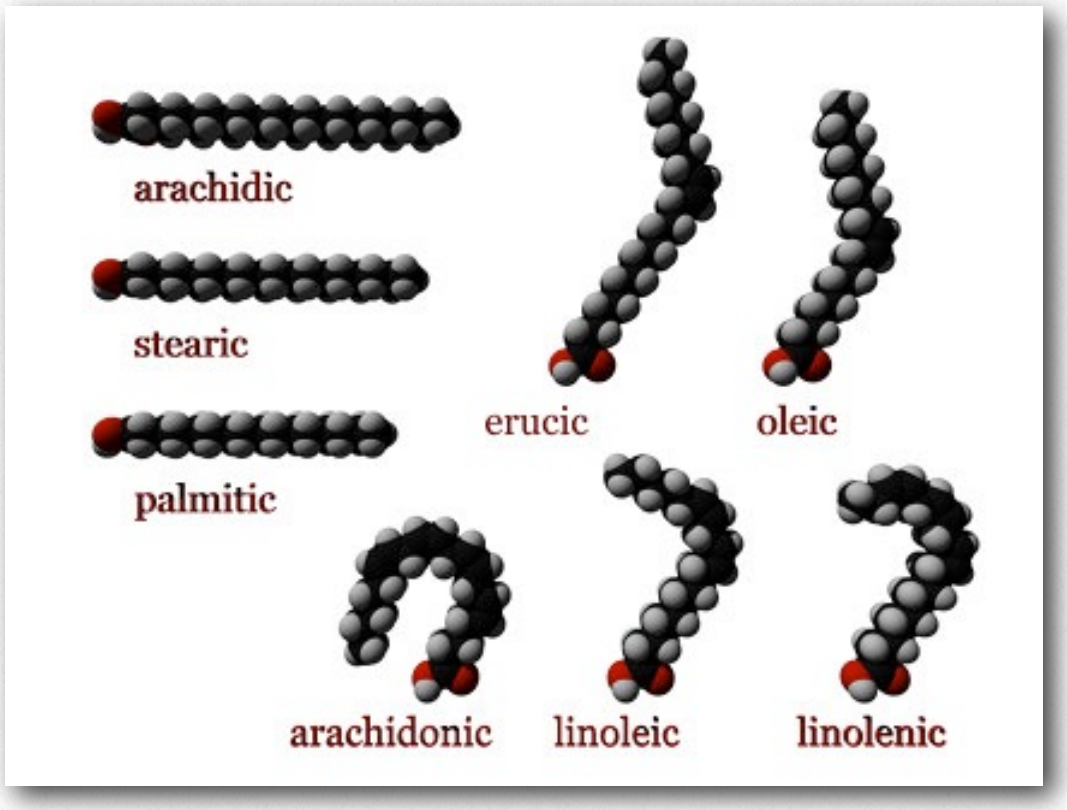

Figure 2.194 - Fatty acid models. Carboxyl end labeled in red

Wikipedia

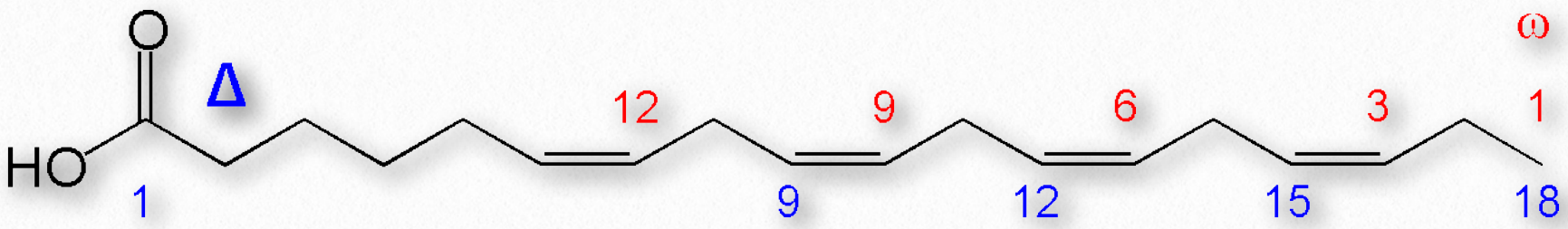

Figure 2.195 - Δ and ω numbering systems for fatty acids

Image by Pehr Jacobson

common fatty acids in our body include palmitate, stearate, oleate, linolenate, linoleate, and arachidonate. Two notable shorter fatty acids are nonanoic (9 carbons) and decanoic acid (10 carbons), both of which appear to have anti-seizure effects. Decanoic acid directly inhibits excitatory neurotransmission in the brain and may contribute to the anticonvulsant effect of the ketogenic diet.

Numbering

Figure 2.195 shows two different systems for locating double bonds in a fatty acid. The ω system counts carbons starting with the methyl end (shown in red) while the Δ system counts from the carboxyl end (shown in blue). For example, an ω-3 (omega 3) fatty acid would have a double bond at the third carbon from the methyl end. In the Δ system, a fatty acid that has a *cis* double bond at carbon 6, counting from the carboxyl end, would be written as cis-Δ^6.

Fatty acids are described as essential fatty acids if they must be in the diet (can't be synthesized by the organism) and non-essential fatty acids if the organism can synthesize them. Humans and other animals lack the desaturase enzymes necessary to make double bonds at positions greater than Δ-9, so fatty acids with double bonds beyond this position must be obtained in the diet. Linoleic acid and linolenic acid, both fall in this category. Related unsaturated fatty acids can be made from these fatty acids, so the presence of linoleic and linolenic acids in the diet eliminates the need to have all unsaturated fatty acids in the diet.

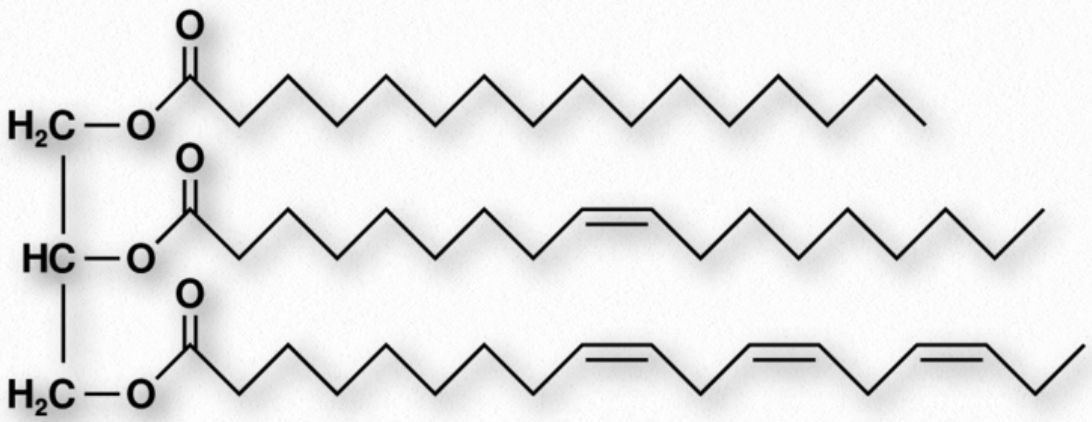

Figure 2.196 - Structure of a fat/oil

Both linoleic and linolenic acid contain 18 carbons, but linoleic acid is an ω-6 fatty acid, whereas linolenic acid is an ω-3 fatty acid. Notably, ω-6 fatty acids tend to be pro-inflammatory, whereas ω-3 fatty acids are lesser so.

Fats/oils

Fats and oils are the primary energy storage forms of animals and are also known as triacylglycerols and triglycerides, since they consist of a glycerol molecule linked via ester bonds to three fatty acids (Figure 2.196). Fats and oils have the same basic structure. We give the name fat to those compounds that are solid at room temperature and the name oil to those that are liquid at room temperature. Note that biological oils are not the same as petroleum oils.

Increasing the number of unsaturated fatty acids (and the amount of unsaturation in a given fatty acid) in a fat decreases the melting temperature of it. Organisms like fish, which live in cool environments, have fats with more unsaturation and this is why fish oil contains polyunsaturated fatty acids.

Adipocytes

Fats are stored in the body in specialized cells known as adipocytes. Enzymes known as lipases release fatty acids from fats by hydrolysis reactions (Figure 2.197). Triacylglycercol lipase (pancreatic - Figure 2.198) is able to cleave the first two fatty ac-

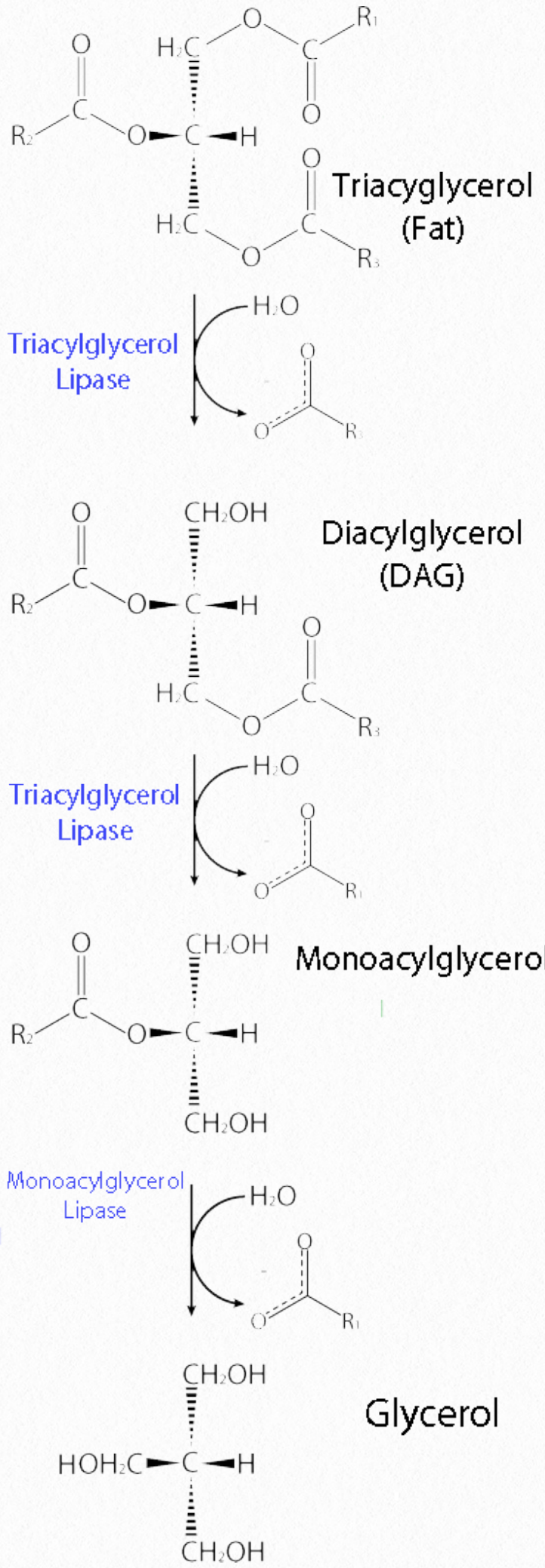

Figure 2.197 - Lipase action on a fat
Image by Aleia Kim

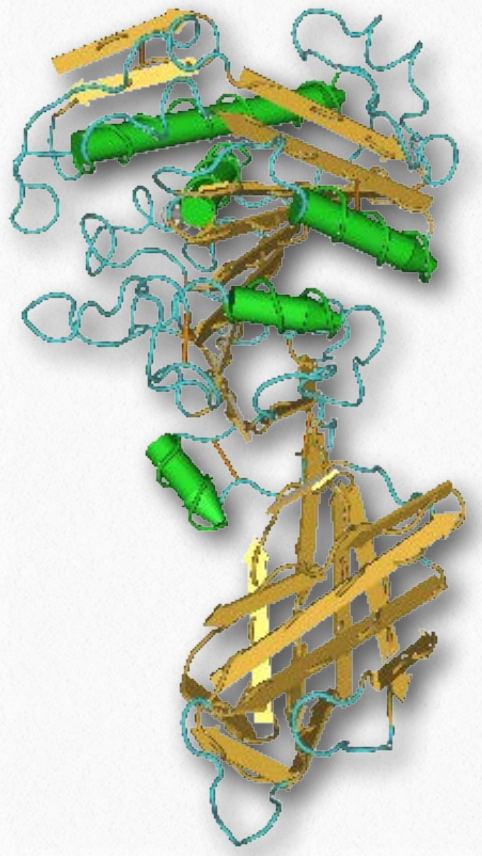

Figure 2.198 - Pancreatic lipase

ids from the fat. A second enzyme, monoacylglycerol lipase, cleaves the last fatty acid. Fats can be synthesized by replacing the phosphate on phosphatidic acid with a fatty acid.

Glycerophospholipids

Glycerophospholipids (phosphoglycerides) are important components of the lipid bilayer of cellular membranes. Phosphoglycerides are structurally related to fats, as both are derived from phosphatidic acid (Figure 2.199). Phosphatidic acid is a simple glycerophospholipid that is usually converted into phosphatidyl compounds. These are made by esterifying various groups, such as ethanolamine, serine, choline, inositol, and others (Figure 2.200) to the phosphate of phosphatidic acid. All of these compounds form lipid bilayers in aqueous solution , due to their amphiphilic nature.

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Phosphatidylethanolamines

Since all glycerolipids can have a variety of fatty acids at positions 1 and 2 on the glycerol, they all are families of compounds. The phosphatidylethanolamines are found in all living cells and are one of the most common phosphatides, making up about 25% of them. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially

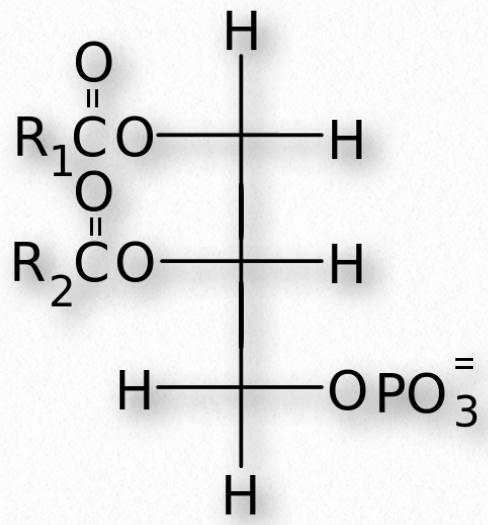
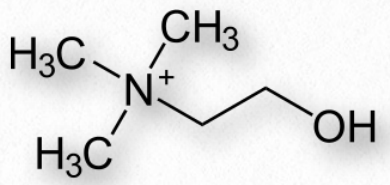
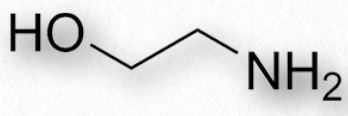


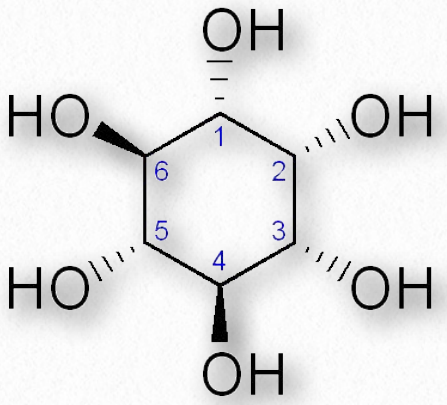
Figure 2.199 - Structure of phosphatidic acid. R_1 and R_2 are alkyl groups of fatty acids.



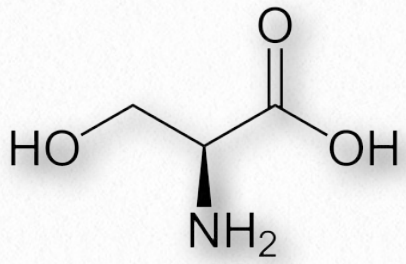
Choline



Ethanolamine



Inositol



Serine

Figure 2.200 - Four common components of phosphatides

Wikipedia

located on the inner leaflet (closest to the cytoplasm) of the plasma membrane. Metabolically, phosphatidylethanloamines are precursors of phosphatidylcholines.

Phosphatidylserines

Phosphatidylserines are another group of phosphatidyl compounds that are preferentially distributed across the lipid bilayer of the plasma membrane. Like the phosphatidylethanolamines, phosphatidylserines are preferentially located on the inner leaflet of the plasma membrane. When apoptosis (cell suicide) occurs, the preferential distribution is lost and the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell.

Phosphatidylcholines

Phosphatidylcholines (Figure 2.201) are another group of important membrane components. They tend to be found more commonly on the outer leaflet of the plasma membrane. Nutritionally, the compounds are readily obtained from eggs and soybeans. Phosphatidylcholines are moved across membranes by Phosphatidylcholine transfer protein (PCTP). This protein, which is sensitive to the levels of phosphatidylcholines, acts to stimulate the activity of a thioesterase (breaks thioester bonds, such as acyl-CoAs) and activates PAX3 transcription factors.

Cardiolipins

Cardiolipins are an unusual set of glycerophospholipids in containing two diacylglycerol backbones joined in the middle

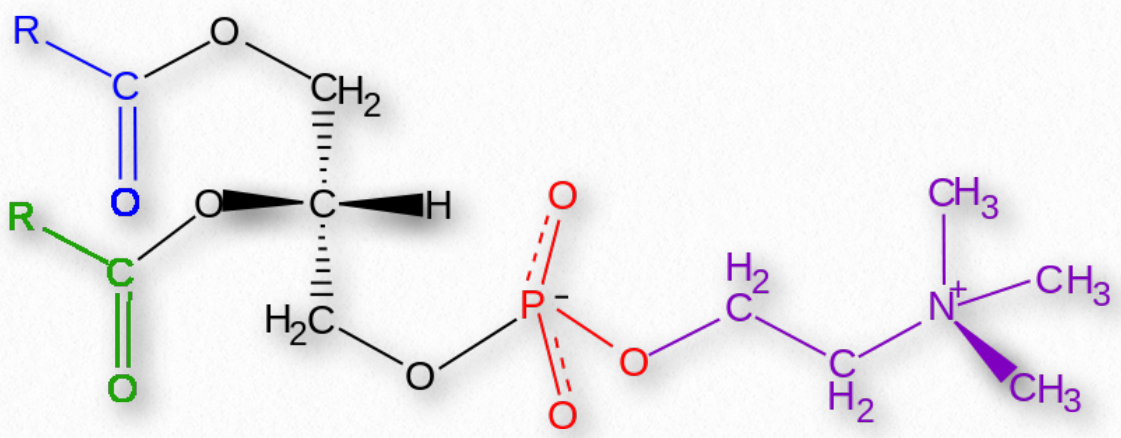


Figure 2.201 - Phosphatidylcholine

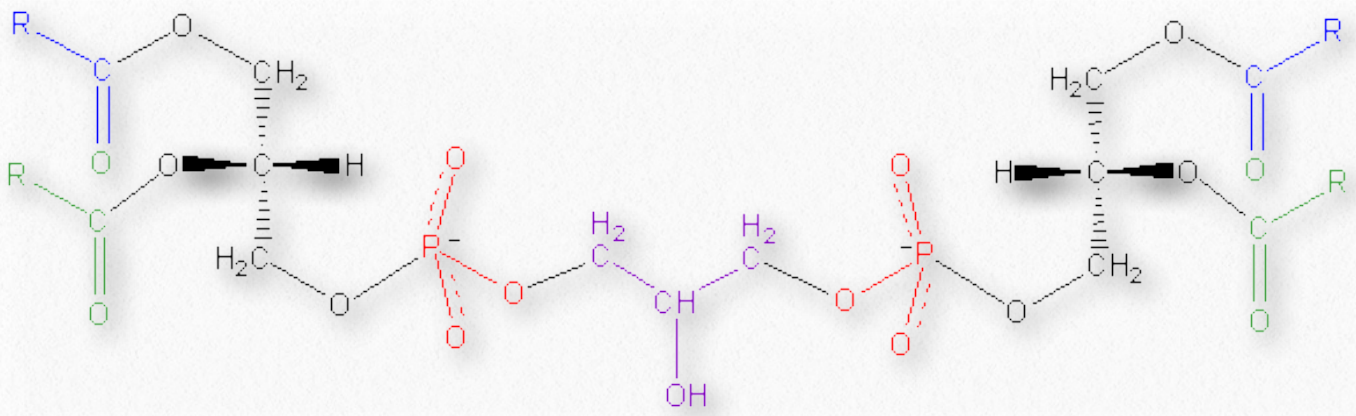


Figure 2.202 - Cardiolipin

by a diphosphoglycerol (Figure 2.202). It is an important membrane lipid, constituting about 20% of the inner mitochondrial membrane and is found in organisms from bacteria to humans. In both plants and animals, it is found almost totally in the inner mitochondrial membrane.

The molecules appear to be required for both Complex IV and Complex III of the electron transport chain to maintain its structure. The ATP synthase enzyme (Complex V) of the oxidative phosphorylation system also binds four molecules of cardiolipin. It has been proposed that cardiolipin functions as a proton trap in the process of proton pumping by Complex IV.

Cardiolipin also plays a role in apoptosis. As shown in Figure 2.203, oxidation of cardiolipin by a cardiolipin-specific oxygenase causes cardiolipin to move from the inner mitochondrial membrane to the outer one, helping to form a permeable pore and facilitating

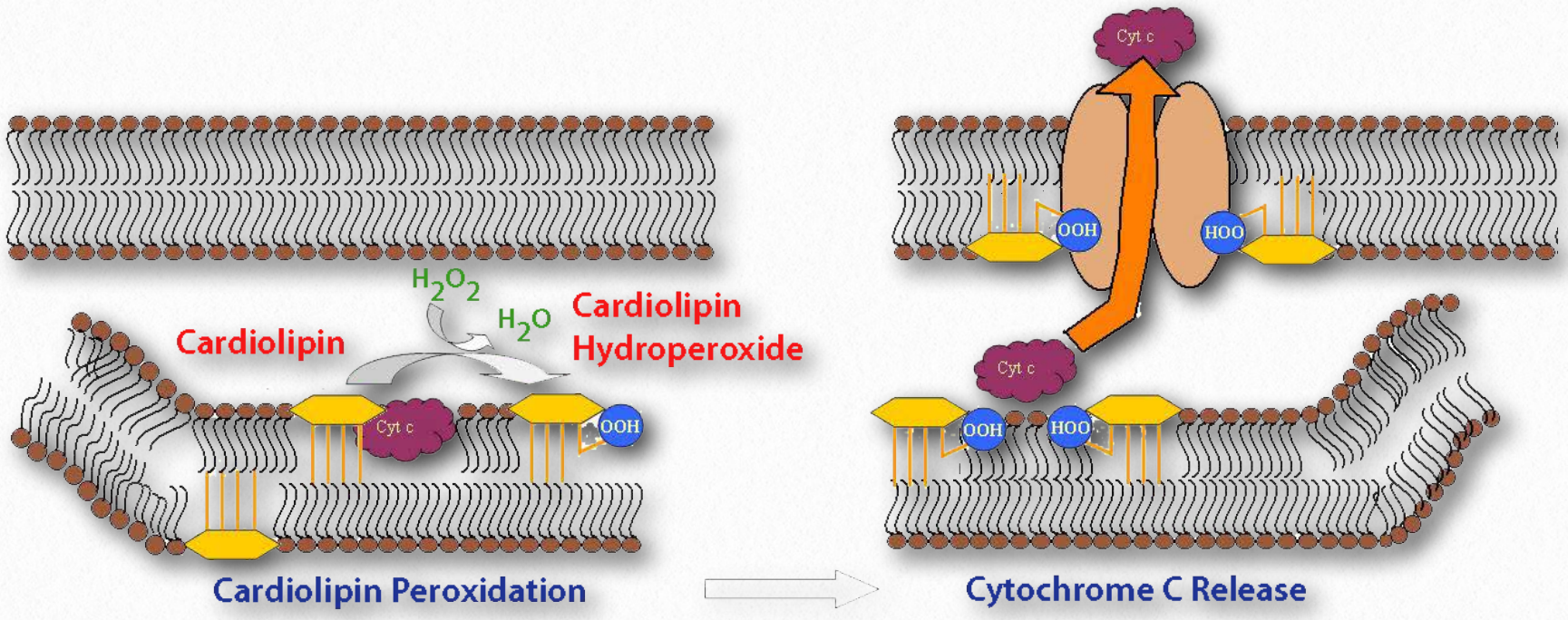


Figure 2.203 - Cardiolipin oxidation and the release of cytochrome C in apoptosis

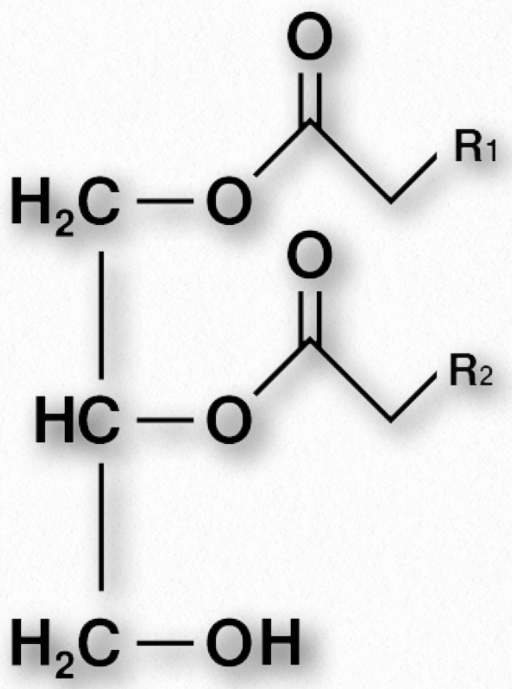


Figure 2.204 - Diacylglycerol

the transport of cytochrome c out of the intermembrane space and into the cytoplasm - a step in the process of apoptosis.

Diacylglycerol

Diacylglycerol (also called diglyceride and DAG - Figure 2.204) is an important intermediate in metabolic pathways. It is produced, for example, in the first step of the hydrolysis of fat and is also produced when membrane lipids, such as PIP_2 (phosphatidylinositol-4,5-bisphosphate) are hydrolyzed by phospholipase C in a signaling cascade.

DAG is itself a signaling compound, binding to protein kinase C to activate it to phosphorylate substrates. Synthesis of DAG begins with glycerol-3-phosphate, which gains two fatty acids from two acyl-CoAs to form phosphatidic acid. Dephosphorylation of phosphatidic acid produces DAG. DAG can also be rephosphorylated by DAG kinase to re-make phosphatidic acid or another fatty acid can be added to make fat.

Inositol

Though technically not a lipid itself, inositol is found in many lipids. Inositol is a derivative of cyclohexane containing six hydroxyl groups - one on each carbon (Figure 2.205. It has nine different stereoisomers of which one, *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol (called myo-inositol) is the most common. It has a sweet taste (half that of sucrose).

Numerous phosphorylated forms of the compound exist, from a single phosphate to six (one on each carbon). Phytic acid, for example, in plants, has six phosphates (Figure 2.206) that it uses to store phosphate. Inositol is produced from glucose and was once considered vitamin B_8, but is made by the body in adequate amounts, so it is not now considered a vitamin. Phosphorylated forms of inositol are found in phosphoinositides, such as PIP_2 and PIP_3, both of which are important in signaling processes. Some of these include insulin sig-

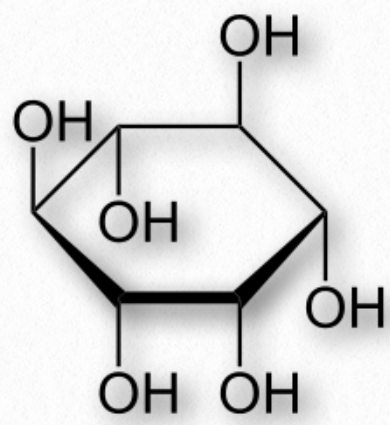


Figure 2.205 - Inositol

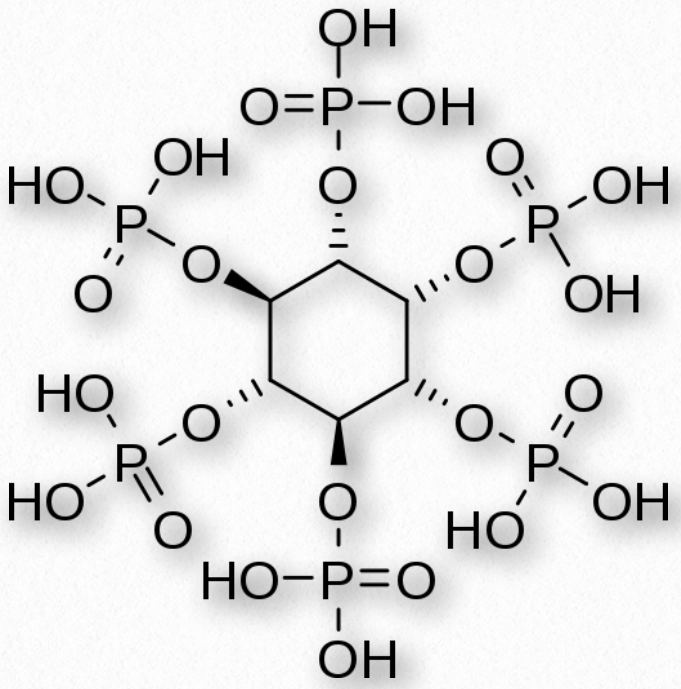


Figure 2.206 - **Phytic acid**

naling, fat catabolism, calcium regulation, and assembly of the cytoskeleton.

Phosphoinositides

Compounds based on phosphatidylinositol (PI) are often called phosphoinositides. These compounds have important

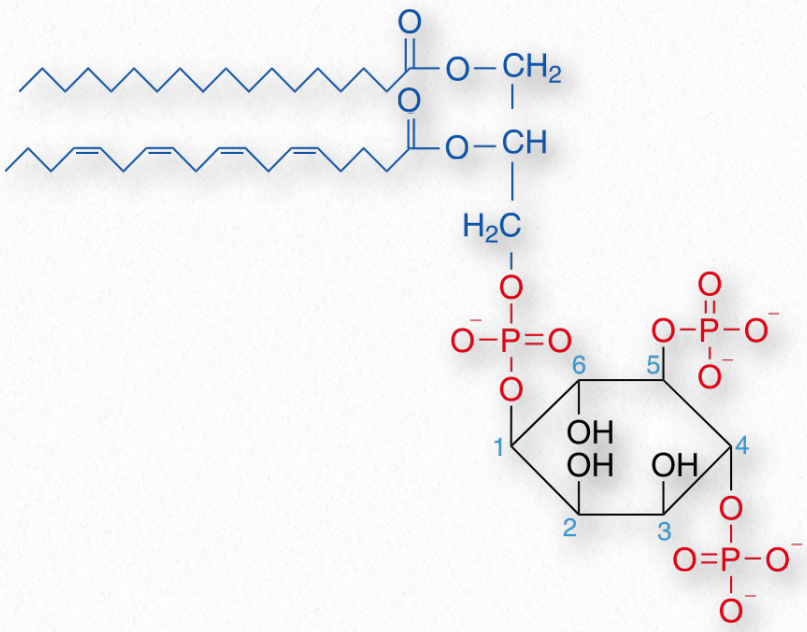


Figure 2.207 - **Structure of PIP_2**

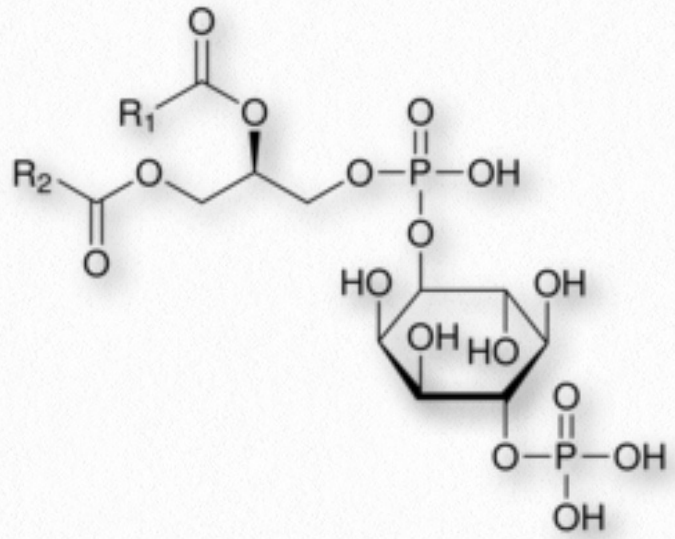


Figure 2.208 - **Phosphatidylinositol-4-phosphate**

roles in signaling and membrane trafficking. Hydroxyls on carbons 3,4, and 5 of the inositol ring are targets for phosphorylation by a variety of kinases. Seven different combinations are used. Steric hindrance inhibits phosphorylation of carbons 2 or 6. Naming of these phosphorylated compounds follows generally as PI(#P)P, PI(#P, #P)P, or PI(#P, #P, #P)P where #P refers to the number of the carbon where a phosphate is located. For example, PI(3)P refers to a phosphatidyl compound with a phosphate added to carbons 3 of the inositol ring, whereas PI(3,4,5)P is a phosphatidyl compound with a phosphate added to carbons 3,4,and 5.

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Phosphatidylinositol-4,5-bisphosphate

Phosphatidylinositol-4,5-bisphosphate (PIP2 - Figure 2.207) is a phospholipid of plasma membranes that functions in the

phospholipase C signaling cascade. In this signaling pathway, hydrolysis catalyzed by phospholipase C releases inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol. Synthesis of PIP_2 begins with phosphatidylinositol, which is phosphorylated at position 4 followed by phosphorylation at position 5 by specific kinases.

PIP_2 can be phosphorylated to form the signaling molecule known as phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). Along with PIP_3, PIP_2 serves as a docking phospholipid for the recruitment of proteins that play roles in signaling cascades. Binding of PIP_2 is also required by inwardly directed potassium channels.

Phosphatidylinositol (3,4,5)-trisphosphate

Phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) is an important molecule for the activation of signaling proteins, such as AKT, which activates anabolic signaling pathways related to growth and survival. PIP_3 can be dephosphorylated by phosphatase PTEN to yield PIP2 and can be synthesized from PIP_2 by kinase action of Class I PI 3-kinases. Kinase activity to synthesize PIP_3 results in movement of PIP_3-binding proteins to the plasma membrane. They include Akt/PKB, PDK1, Btk1, and ARNO and each is activated by binding to PIP_3.

Plasmalogens

A special class of the glycerophospholipids are the plasmalogens (Figure 2.209). They differ in containing a vinyl ether linkage at position 1 of glycerol, in contrast to other glycerophopsholipids, which have an ester linkage at this position. Position 2 of each is an ester. The precursor for the ether linkage is typically a 16 or 18 carbon saturated alcohol or an 18 carbon unsaturated alcohol.

At the phosphate tail, the most commonly attached groups are ethanolamine or choline. Plasmalogens are found abundantly in

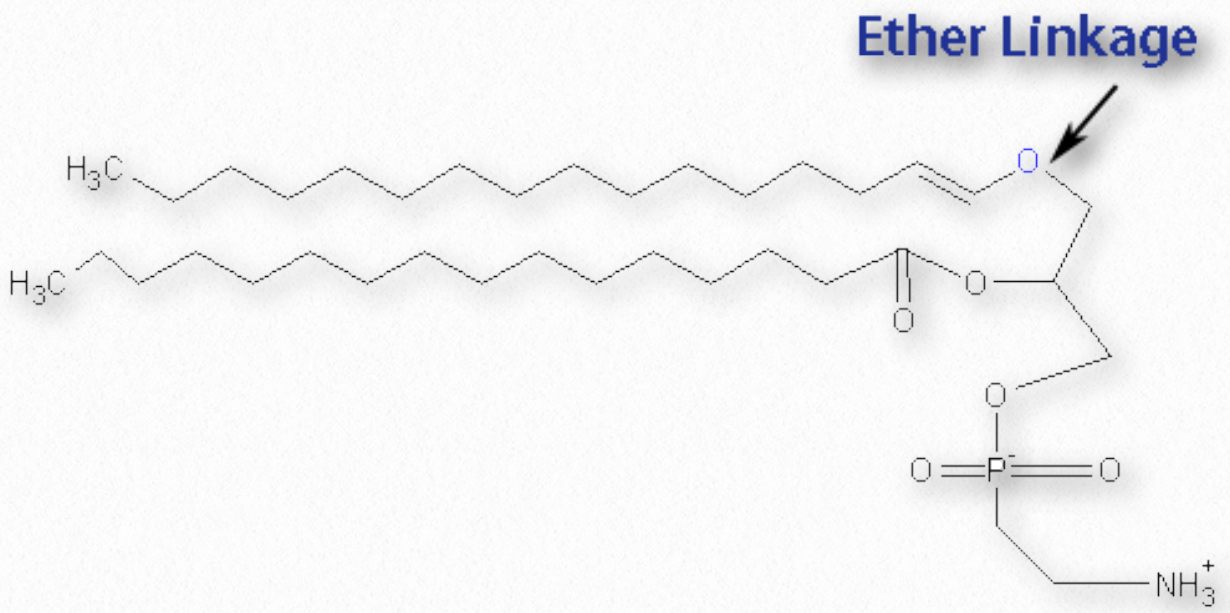

Figure 2.209 - Plasmalogen - A vinyl ether lipid

Wikipedia

humans in heart (30-40% of choline phospholipids). 30% of the glycerophospholipids in brain are plasmalogens and 70% of the ethanolamine lipids of the myelin sheath of nerve cells are plasmalogens.

Though their function is not understood, it is believed that plasmalogens may provide some protection against reactive oxygen species and have roles in signaling.

Lecithin

Lecithin is a generic term for a combination of lipid substances that includes phosphoric acid, glycerol, glycolipids, triglycerides, and phospholipids. Lecithin is a wetting agent helpful with emulsification and encapsulation and is even used as an anti-sludge additive in motor lubricants. Lecithin is used in candy bars to keep cocoa and cocoa butter from separating. Though considered safe as a food ingredient, lecithin can be converted by gut bacteria to trimethylamine-N-oxide which may contribute to cholesterol deposition and atherosclerosis.

Sphingolipids

Fatty acids are also components of a broad class of molecules called sphingolipids. Sphingolipids are structurally similar to glycerophospholipids, though they are synthesized completely independently of them starting with palmitic acid and the amino acid serine. Sphingolipids are named for the amino alcohol known as sphingosine (Figure 2.210), though they are not directly synthesized from it. Figure 2.211 shows the generalized structure of sphingolipids.

If the R-group is a hydrogen, the molecule is called a ceramide. When the R-group is phosphoethanolamine the resulting molecule is sphingomyelin, an important compo-

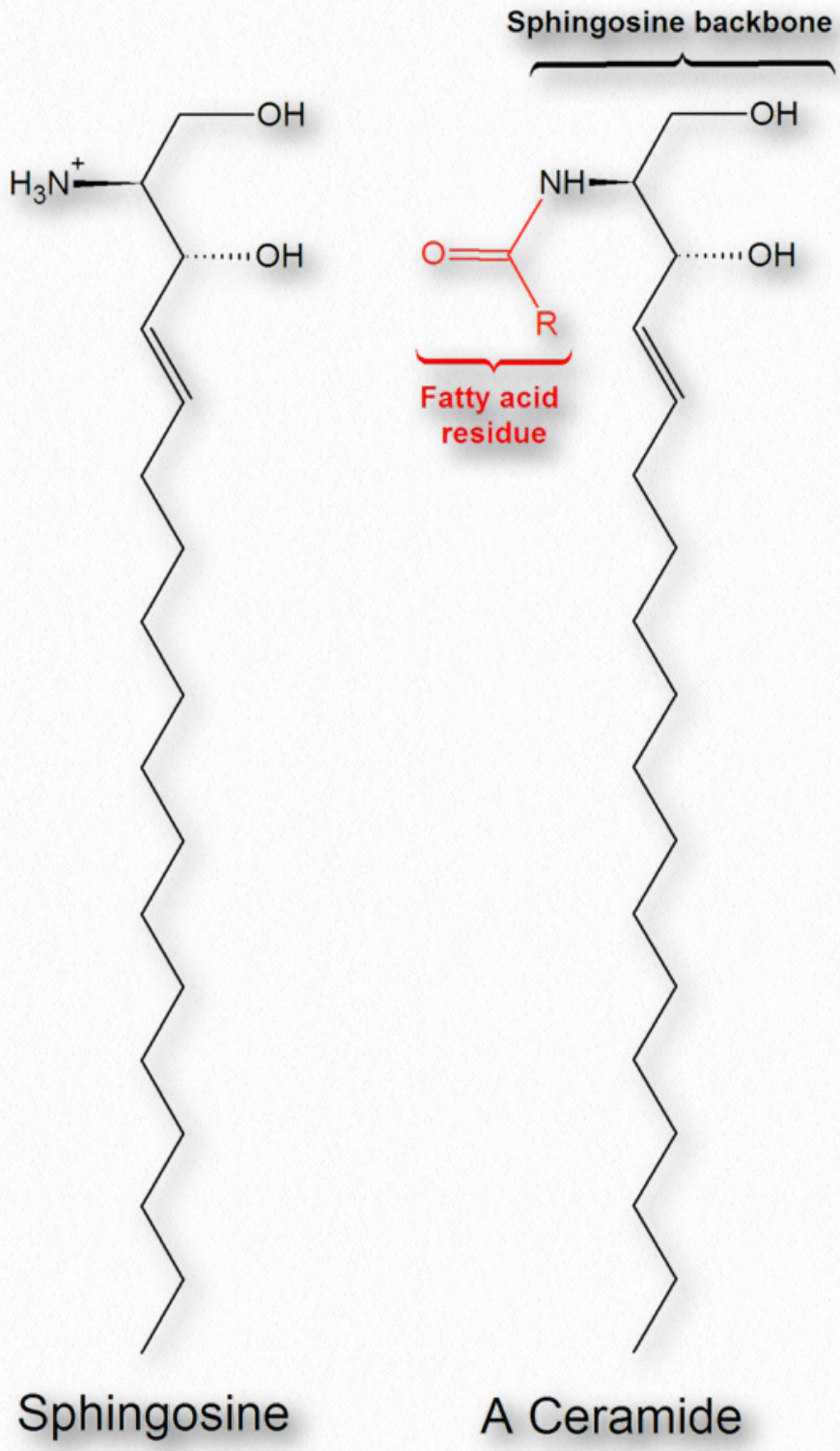

Figure 2.210 - Sphingosine and a ceramide made from it

Wikipedia

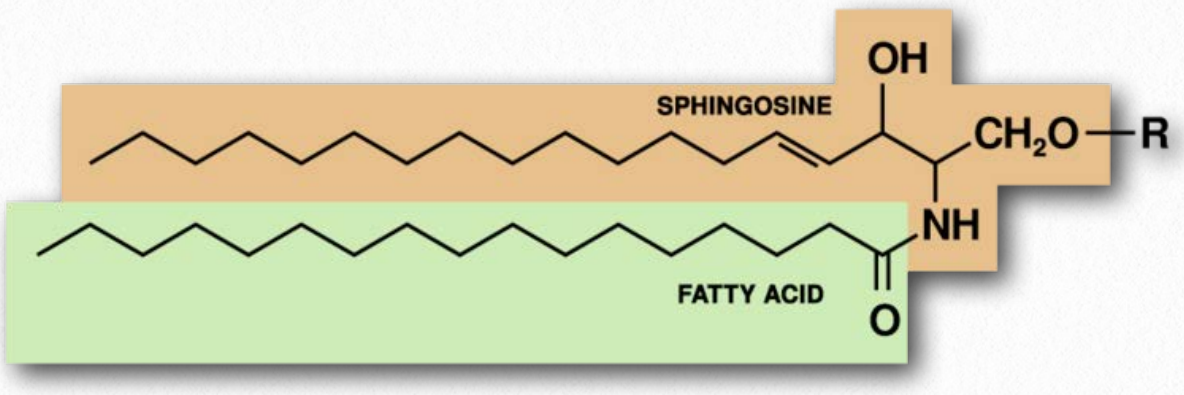

Figure 2.211 Schematic structure of a sphingolipid

nent of the myelin sheath and lipid membranes. If a single, simple sugar is instead added, a cerebroside is created (Figure 2.212). Addition of a complex oligosaccharide creates a ganglioside.

Complex sphingolipids may play roles in cellular recognition and signaling. Sphingolipids are found most abundantly in plasma membrane and are almost completely absent from mitochondrial and endoplasmic reticulum membranes. In animals, dietary sphingolip-

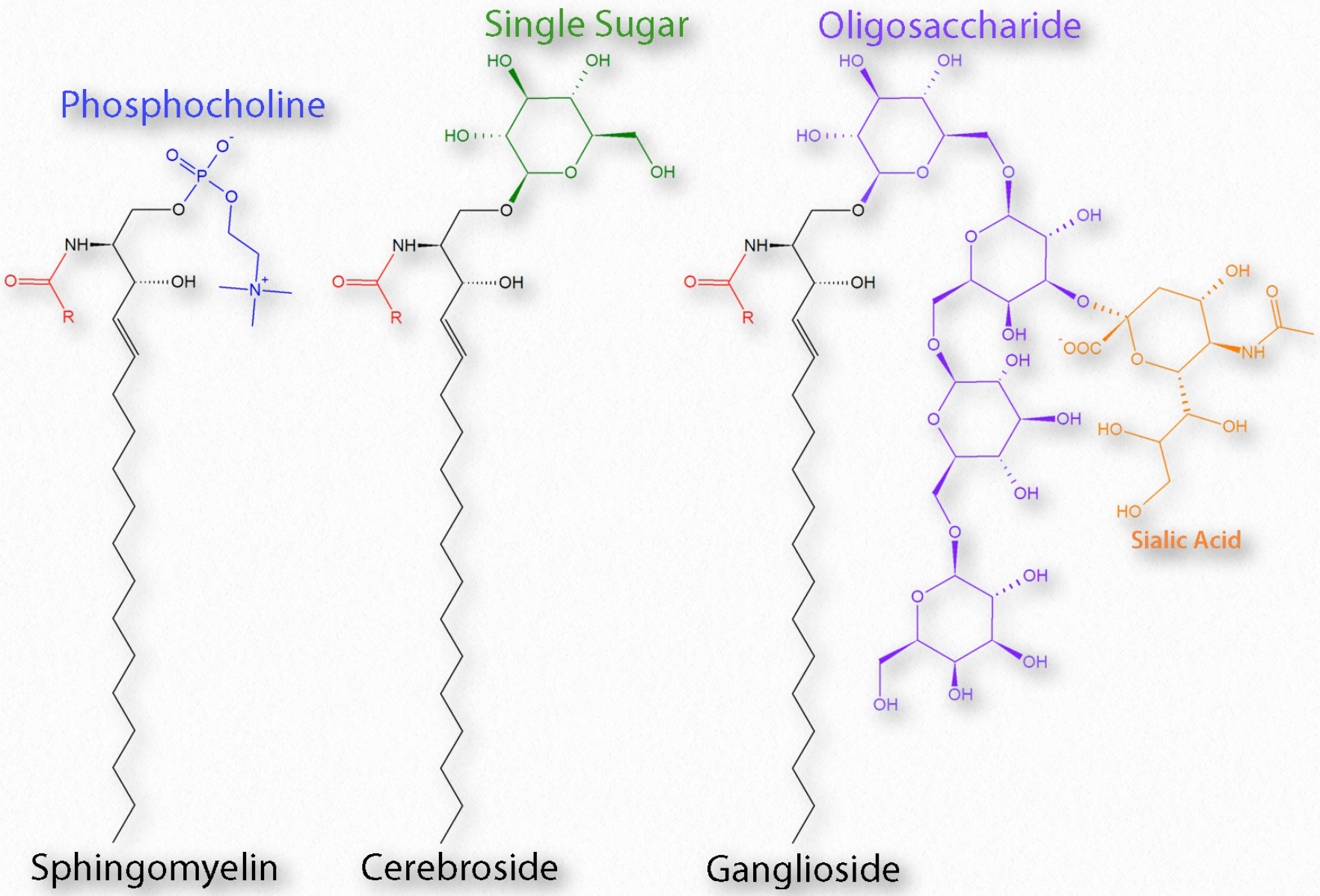

Figure 2.212 - Categories of Sphingolipid

Wikipedia

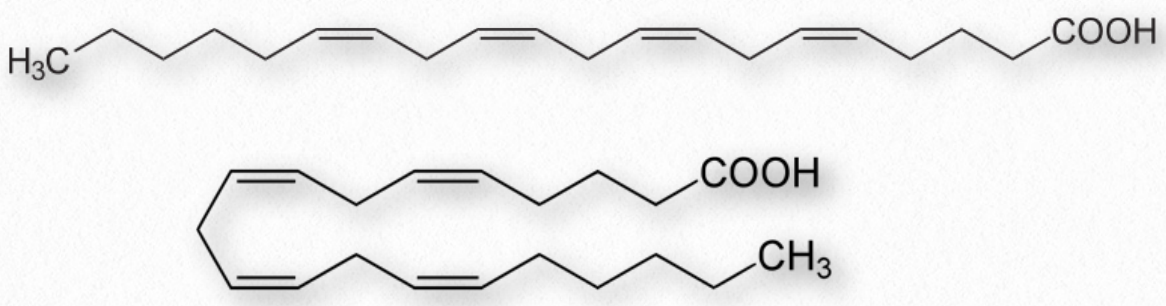

Figure 2.213 - Arachidonic acid drawn as straight (top) and bent (bottom)

ids have been linked to reduced colon cancer, reductions in LDLs, and increases in HDLs. Like the glycerophospholipids, sphingolipids are amphiphilic. Most sphingolipids except sphingomyelin do not contain phosphate.

Eicosanoids

Fatty acids made from omega-6 and omega-3 fatty acids include three important fatty acids containing 20 carbons. They include arachidonic acid (an ω-6 fatty acid with four double bonds (Δ-5,8,11,14) - Figure 2.213), eicosapentaenoic acid (an ω-3 fatty acid with five double bonds, and dihomo-γ-linolenic acid (an ω-6 fatty acid with three double bonds). The class of compounds known as eicosanoids is made by oxidation of these compounds. Subclasses include include prostaglandins, prostacyclins, thromboxanes, lipoxins, leukotrienes, and endocannabinoids (Figures 2.214-2.219). Eicosanoids play important roles affecting inflammation, immunity, mood, and behavior.

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Prostaglandins

A collection of molecules acting like hormones, prostaglandins are derived from arachidonic acid and have many differing (even conflicting) physiological effects. These include constriction or dilation of vascular smooth muscle cells, induction of labor, regulation of inflammation, and action on the thermoregulatory center of the hypothalamus to induce fever, among others.

Prostaglandins are grouped with the thromboxanes (below) and prostacyclins (below), as prostanoids. The prostanoids, which all contain 20 carbons are a subclass of the eicosanoids. Prostaglandins are found

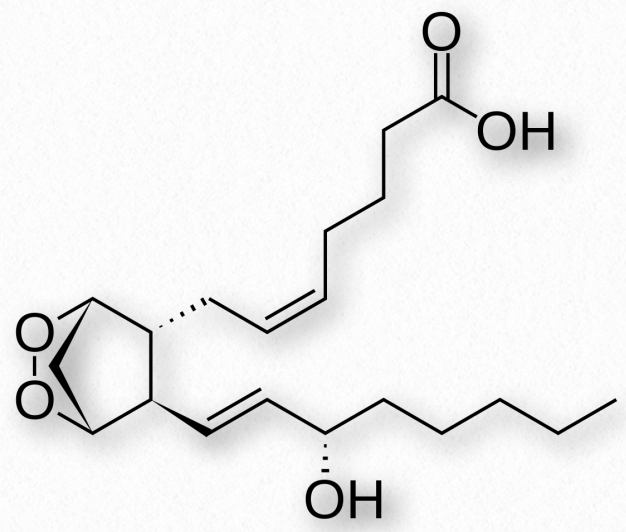

Figure 2.214 - Prostaglandin PGH_2

in most tissues of higher organisms. They are autocrine or paracrine compounds produced from essential fatty acids. The primary precursor of the prostaglandins is the fatty acid known as arachidonic acid and the prostaglandin made from it is known as PGH2 (Figure 2.214), which, in turn is a precursor of other prostaglandins, as well as the prostacyclins and thromboxanes.

Interesting prostaglandins

PGD_2 - inhibits hair follicle growth, vasodilator, causes bronchial constriction, higher in lungs of asthmatics than others.

PGE_2 (Figure 2.215) - exerts effects in labor (soften cervix, uterine contraction), stimulates bone resorption by osteoclasts, induces fever, suppresses T-cell receptor signaling, vasodilator, inhibits release of noradrenalin from sympathetic nerve terminals. It is a potent activator of the Wnt signaling pathway.

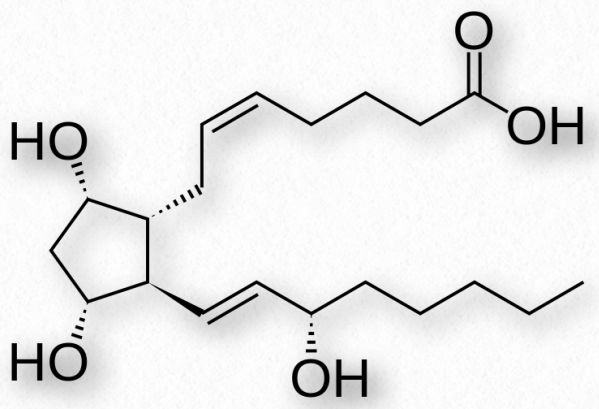

Figure 2.216 - **Prostaglandin $F_{2\alpha}$**

A prostaglandin can have opposite effects, depending on which receptor it binds to. Binding of PGE_2 to the EP_1 receptor causes bronchoconstriction and smooth muscle contraction, whereas binding of the same molecule to the EP_2 receptor causes bronchodilation and smooth muscle relaxation.

PGF2α (Figure 2.216)- uterine contractions, induces labor, bronchoconstriction.

PGI2 - vasodilation, bronchodilation, inhibition of platelet aggregation.

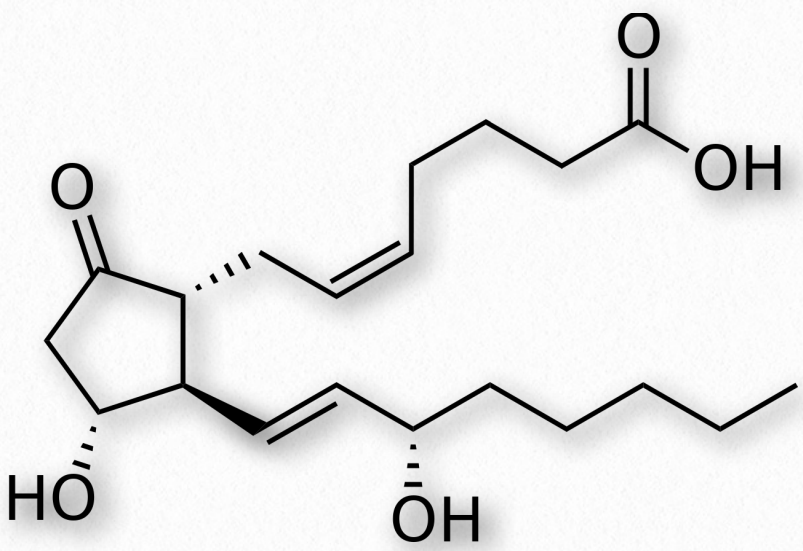

Figure 2.215 **Prostaglandin E_2**

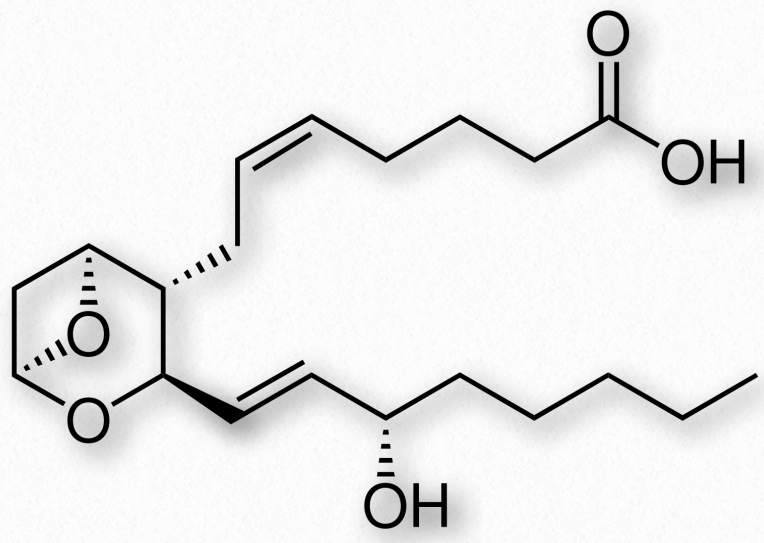

Figure 2.217 **Thromboxane A_2**

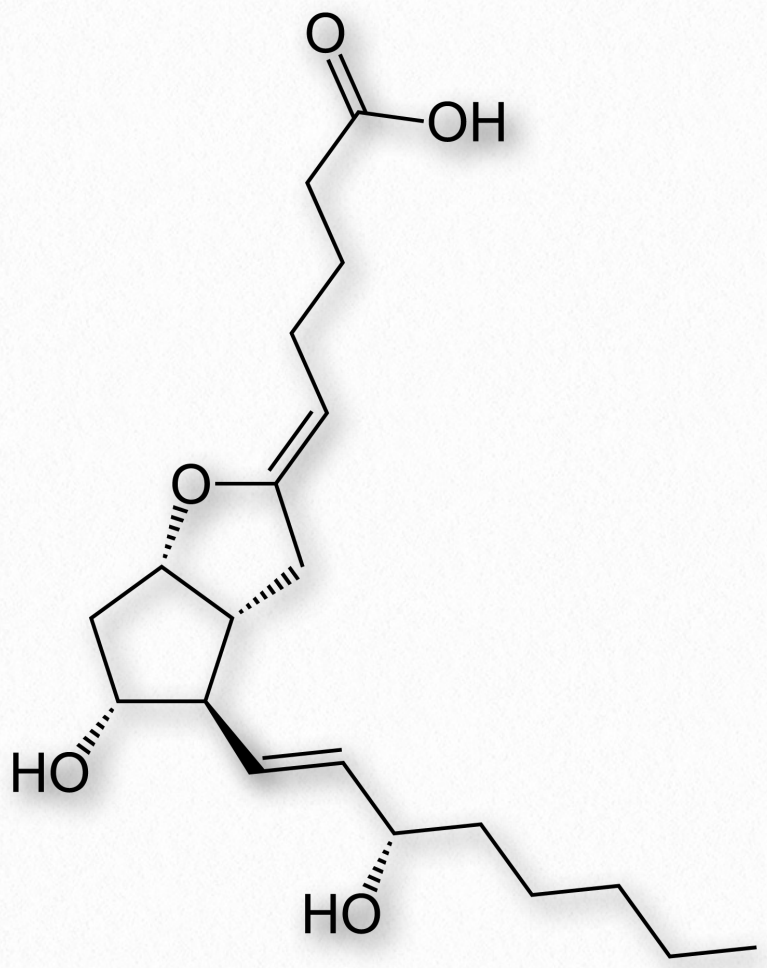

Figure 2.218 - **Prostacyclin**

Thromboxanes

Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH_2, which is the precursor of the thromboxanes. The most common thromboxanes are A_2 (Figure 2.217) and B_2.

Prostacyclin

Prostacyclin (also known as prostaglandin I_2 or PGI_2 - Figure 2.218) counters the effects of thromboxanes, inhibiting platelet activation and acting as vasodilators. It is produced from PGH_2 by action of the enzyme prostacyclin synthase.

Leukotrienes

Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.

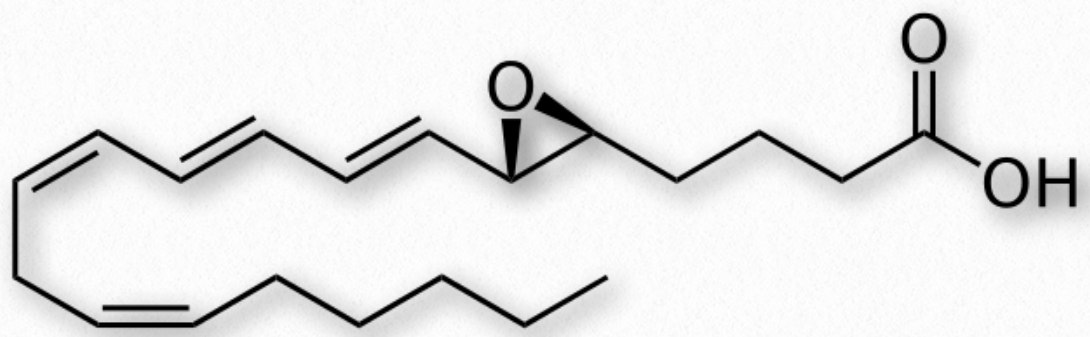

Figure 2.219 - **Leukotriene A_4 (LTA_4)**

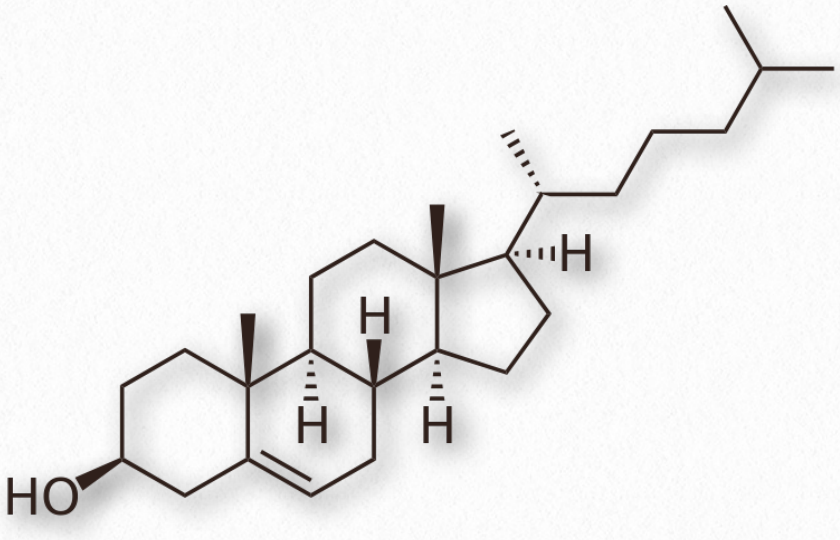

Figure 2.220 - **Structure of cholesterol**

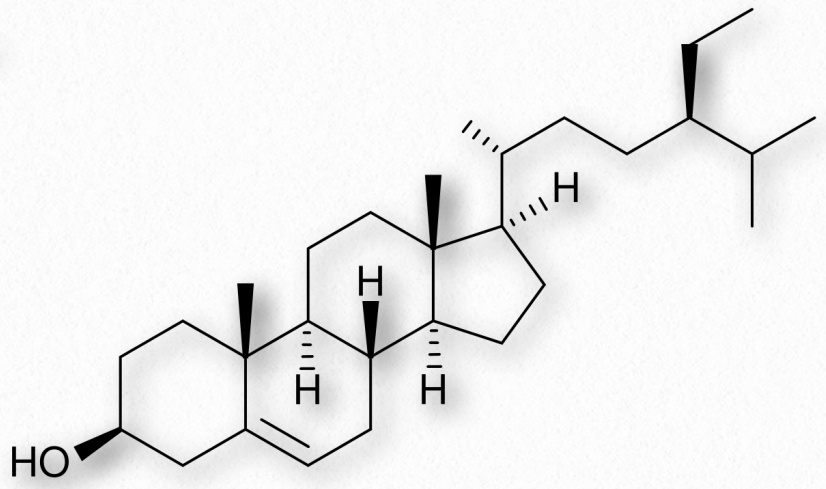

Figure 2.221 - **Sitosterol - A phytosterol**

Cholesterol

Arguably, no single biomolecule has generated as much discussion and interest as has cholesterol (Figure 2.220). Certainly, from the perspective of the Nobel Prize committee, no small molecule even comes close, with 13 people having been awarded prizes for work on it. Evidence for cholesterol's importance comes from the study of brain tissue where it comprises 10-15% of the dry mass.

Membrane flexibility

In animal cells, cholesterol provides for membrane flexibility that allows for cellular movement that is in contrast to plant and bacterial cells with fixed structures. Cholesterol is made in many cells of the body, with the liver making the greatest amount. The anabolic pathway leading to synthesis of cholesterol is known as the isoprenoid pathway and branches of it lead to other molecules including other fat-soluble vitamins.

Cholesterol is only rarely found in prokaryotes (*Mycoplasma*, which requires it for growth, is an exception) and is found in only trace amounts in plants. Instead, plants synthesize similar compounds called phytosterols (Figure 2.221). On average, the body of a 150 pound adult male makes about 1 gram

Figure 2.222 - **Margarine - A common source of *trans* fat**

Wikipedia

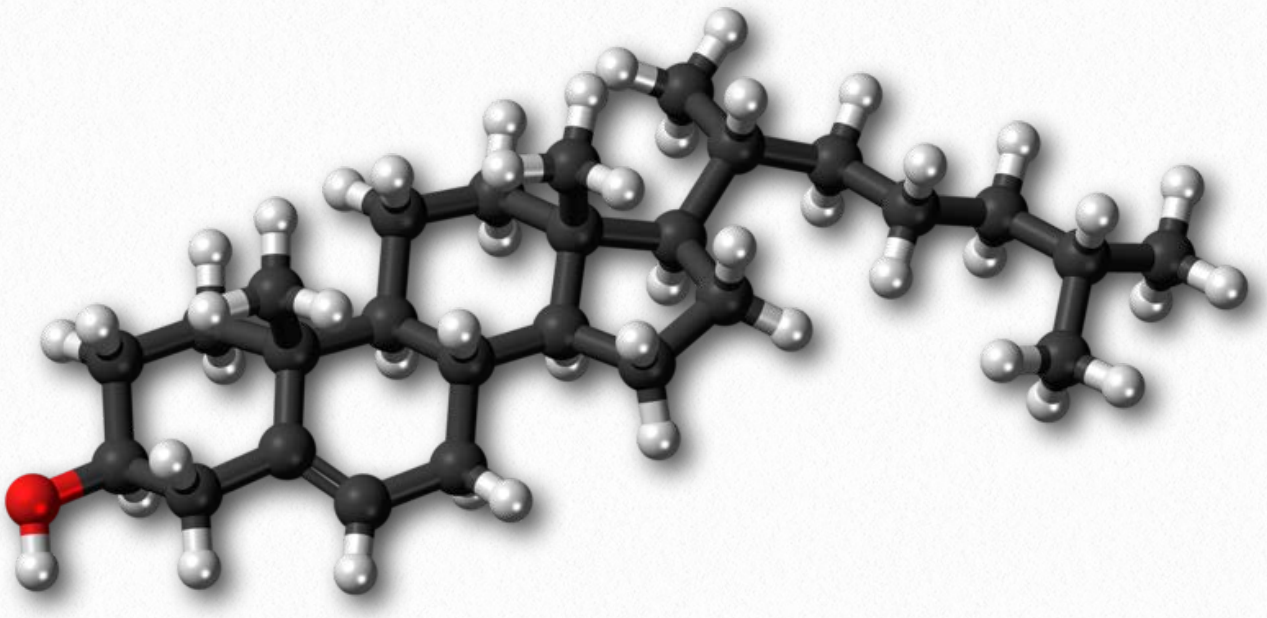

Figure 2.223 - Cholesterol - Ball and stick model

of cholesterol per day, with a total content of about 35 grams.

Packaging

Cholesterol's (and other lipids') hydrophobicity requires special packaging into lipoprotein complexes (called chylomicrons, VLDLs, IDLs, LDLs, and HDLs) for movement in the lymph system and bloodstream. Though cholesterol can be made by cells, they also take it up from the blood supply by absorbing cholesterol-containing LDLs directly in a process called receptor-mediated endocytosis.

Oxidative damage to LDLs can lead to formation of atherosclerotic plaques and this is why cholesterol has gotten such a negative image in the public eye. The liver excretes cholesterol through the bile for elimination into the digestive system, but the compound is recycled there.

YouTube Lectures by Kevin HERE & HERE

Reducing cholesterol levels

Strategies for reducing cholesterol in the body focus primarily on three areas - reducing consumption, reducing endogenous synthesis, and reducing the recycling. Dietary considerations, such as saturated fat versus unsaturated fat consumption are currently debated. Dietary *trans* fats, though, correlate with incidence of coronary heart disease. Consumption of vegetables may provide some assistance with reducing levels of cholesterol recycled in the digestive system, because plant phytosterols compete with cholesterol

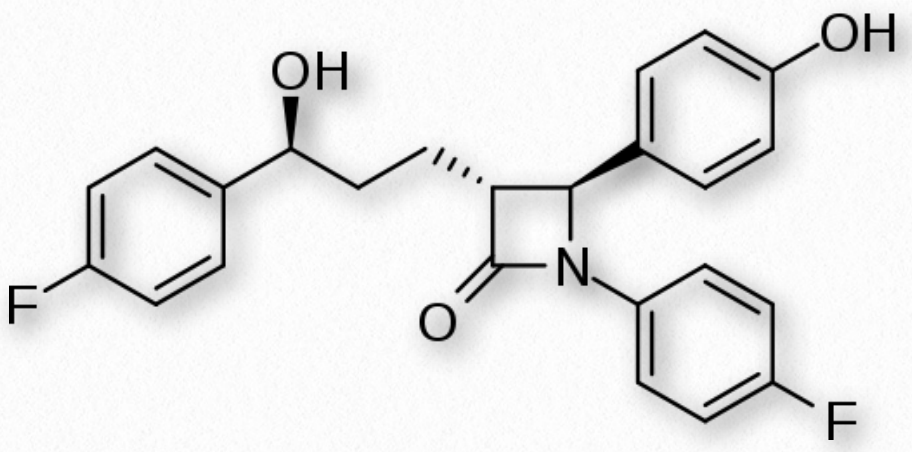

Figure 2.224 - Ezetimibe - An inhibitor of cholesterol absorption

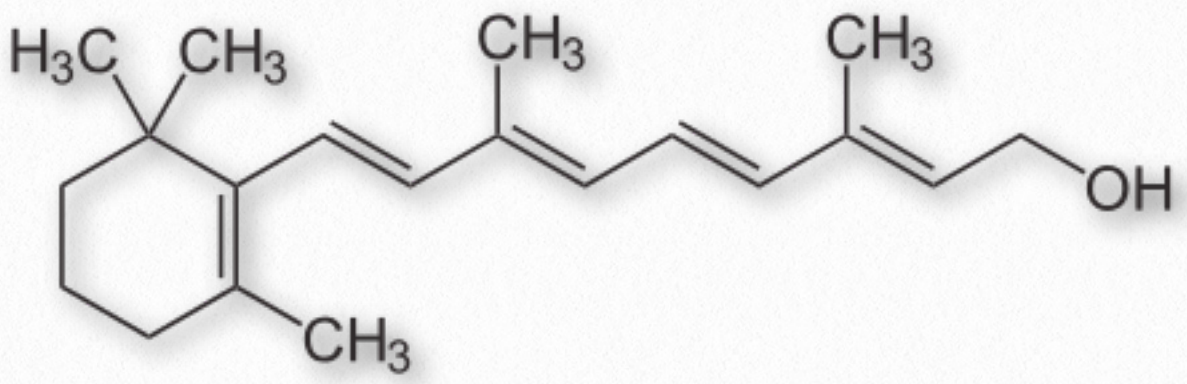

Figure 2.225 - All-*trans* retinol

for reabsorption and when this happens, a greater percentage of cholesterol exits the body in the feces. Drugs related to penicillin are also used to inhibit cholesterol recycling. One of these is ezetimibe, shown in Figure 2.224.

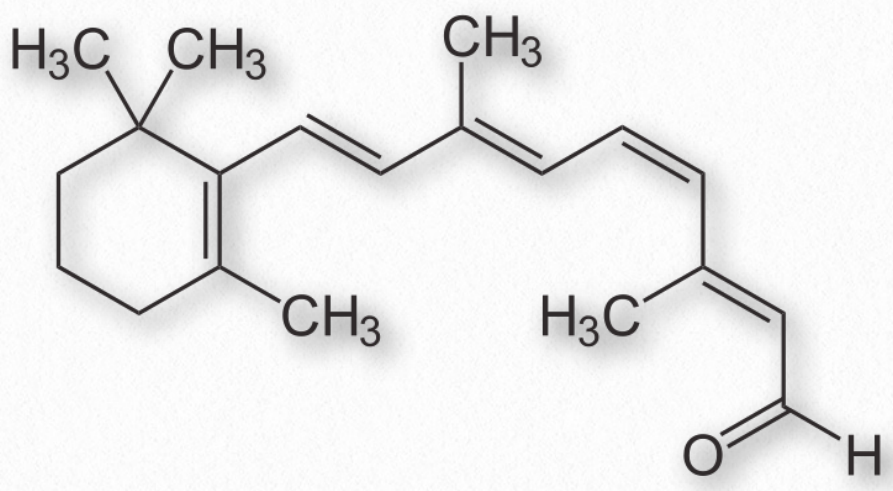

Figure 2.226 - 11-cis retinal

Genetic defects in the cholesterol movement system are a cause of the rare disease known as familial hypercholesterolemia in which the blood of afflicted individuals contains dangerously high levels of LDLs. Left untreated, the disease is often fatal in the first 10-20 years of life. While LDLs have received (and deserve) a bad rap, another group of lipoprotein complexes known as the HDLs (high density lipoprotein complexes) are known as "good cholesterol" because their levels correlate with removal of debris (including cholesterol) from arteries and reduce inflammation.

Membrane function

In membranes, cholesterol is important as an insulator for the transmission of signals in nerve tissue and it helps to manage fluidity of membranes over a wide range of temperatures. Stacked in the lipid bilayer, cholesterol decreases a membrane's fluidity and its permeability to neutral compounds, as well as protons and sodium ions. Cholesterol may

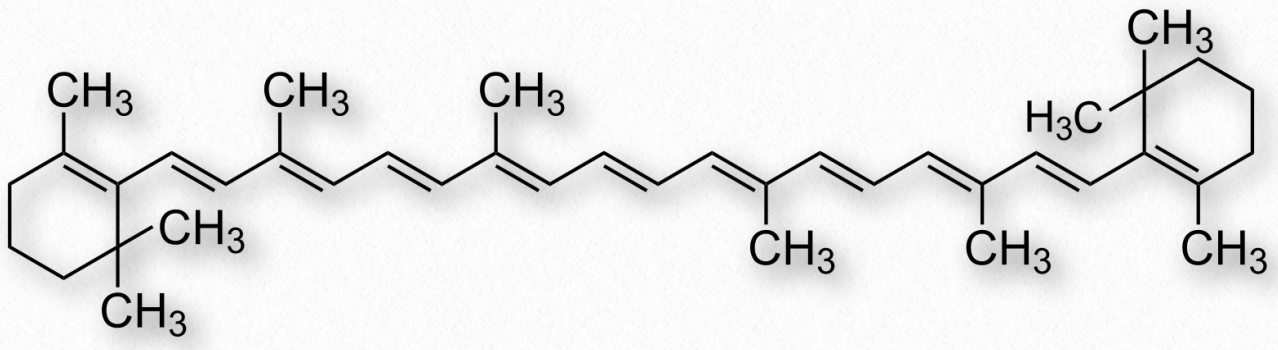

Figure 2.227 - β-Carotene

play a role in signaling by helping with construction of lipid rafts within the cell membrane.

Vitamin A

Vitamin A comes in three primary chemical forms, retinol (storage in liver - Figure 2.225), retinal (role in vision - Figure 2.226), and retinoic acid (roles in growth and development). All vitamin A forms are diterpenoids and differ only in the chemical form of the terminal group. Retinol is mostly used as the storage form of the vitamin.

Retinol is commonly esterified to a fatty acid and kept in the liver. In high levels, the compound is toxic. Retinol is obtained in the body by hydrolysis of the ester or by reduction of retinal. Importantly, neither retinal nor retinol can be made from retinoic acid. Retinoic acid is important for healthy skin and teeth, as well as bone growth. It acts in differentiation of stem cells through a specific cellular retinoic acid receptor.

Sources

Good sources of vitamin A are liver and eggs, as well as many plants, including carrots, which have a precursor, β-carotene (Figure 2.227) from which retinol may be made by action of a dioxygenase.

Light sensitivity

The conjugated double bond system in the side chain of vitamin A is sensitive to light and can flip between *cis* and *trans* forms on exposure to it. It is this response to light that makes it possible for retinal to have a role in vision in the rods and cones of the eyes. Here, the aldehyde form (retinal) is bound to the

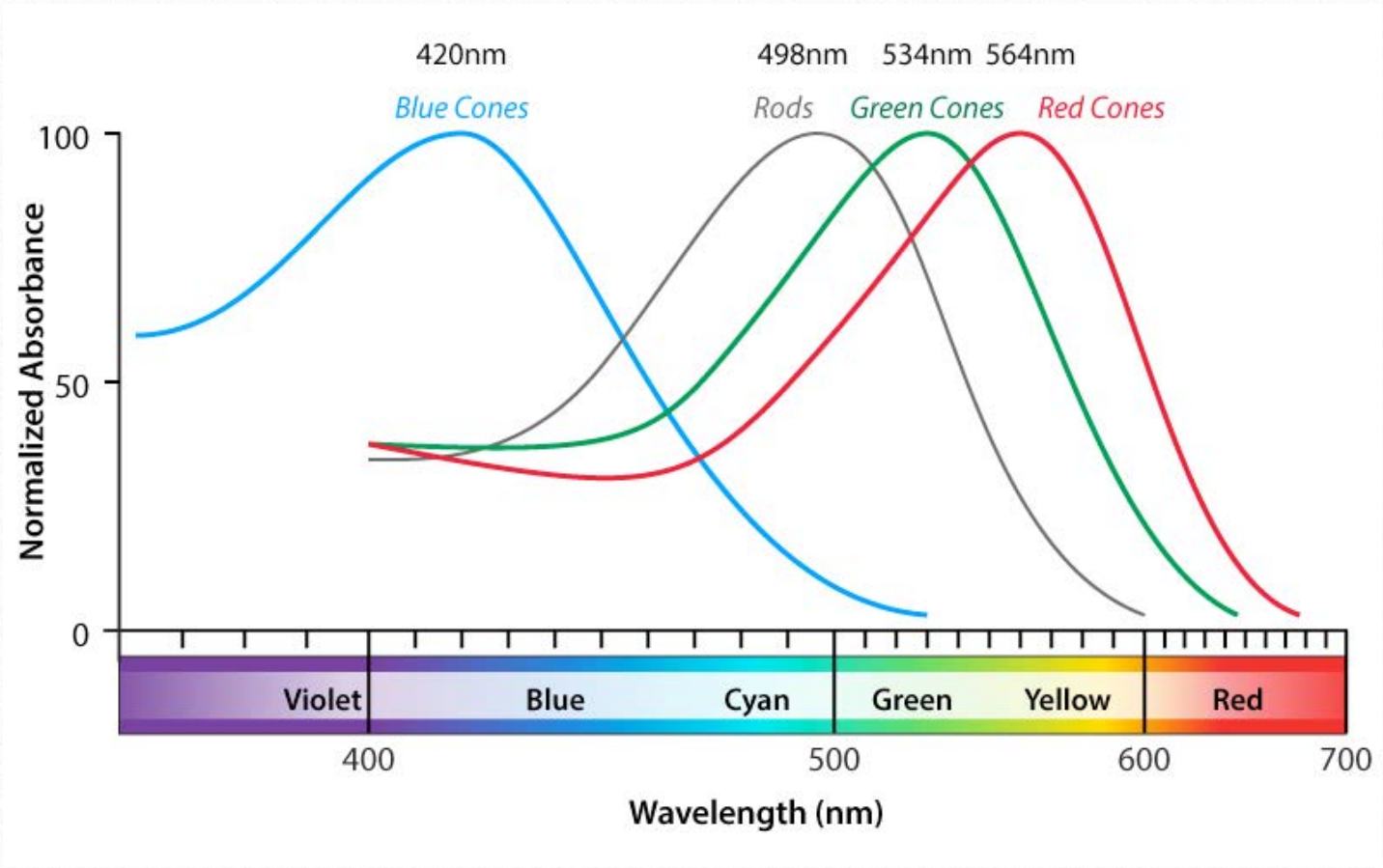

Figure 2.228 - Color sensitivity for cones and rods

Image by Aleia Kim

protein rhodopsin in the membranes of rod and cone cells.

When exposed to light of a particular wavelength, the "tail" of the retinal molecule will flip back and forth from *cis* to *trans* at the double bond at position 11 of the molecule. When this happens, a nerve signal is generated that signals the brain of exposure to light. Slightly different forms of rhodopsin have different maximum absorption maxima allowing the brain to perceive red, green and blue specifically and to assemble those into the images we see (Figure 2.228). Cones are the cells responsible for color vision, whereas rods are mostly involved in light detection in low light circumstances.

Deficiency and surplus

Deficiency of vitamin A is common in developing countries and was inspiration for the design and synthesis of the genetically-modified golden rice, which is used as a source of vitamin A to help prevent blindness in children. Overdose of vitamin A, called hypervitaminosis A is dangerous and can be fatal. Excess vitamin A is also suspected to be linked to osteoporosis. In smokers, excess vitamin A is linked to an increased rate of lung cancer, but non-smokers have a reduced rate.

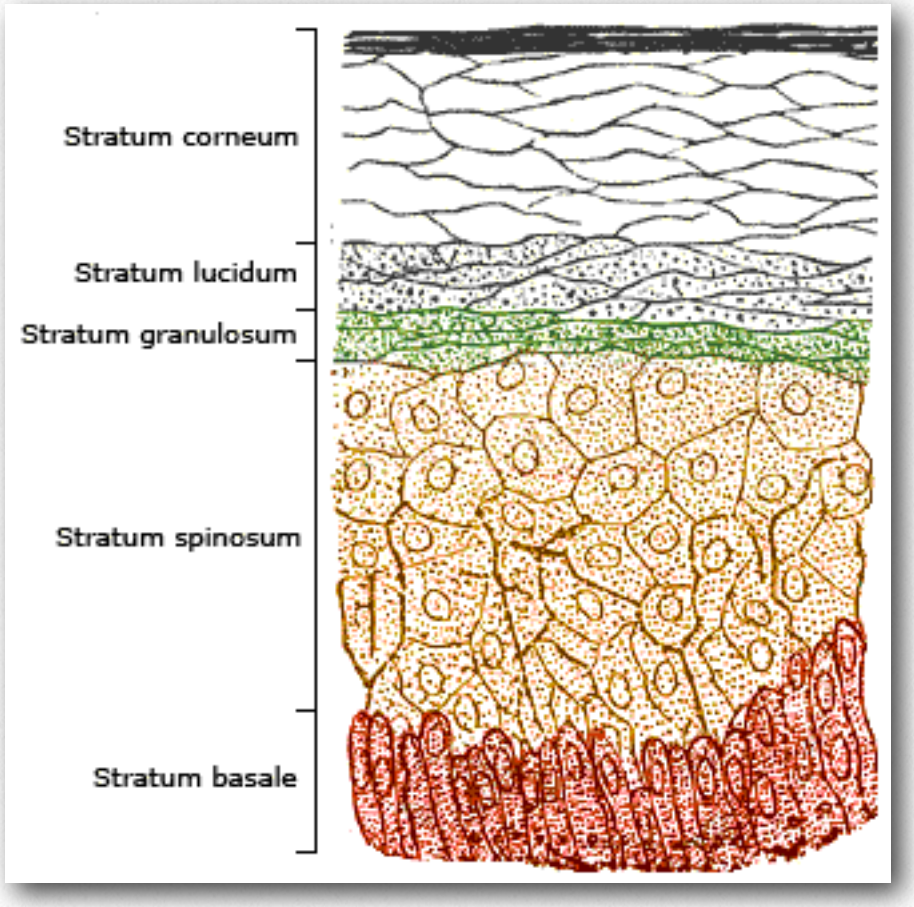

Figure 2.230 - Layers of the skin. Outside is at top.

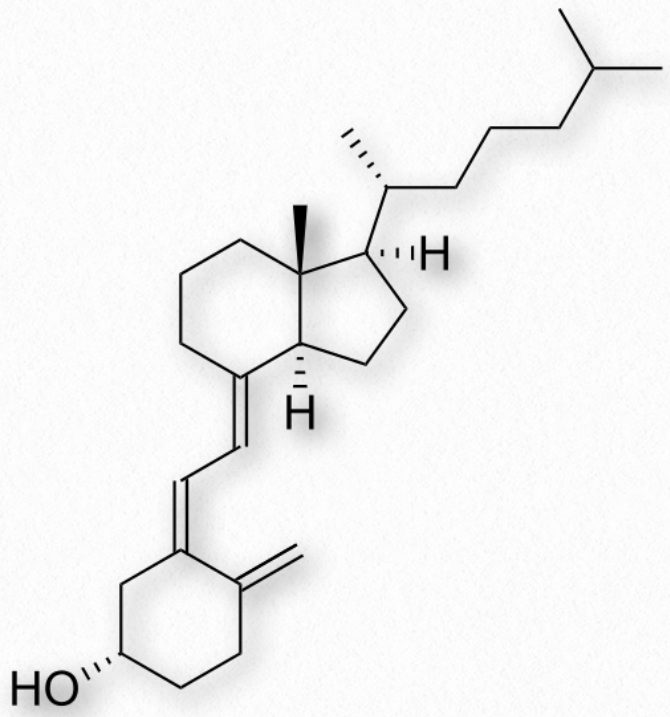

Figure 2.229 - Cholecalciferol - Vitamin D_3

Vitamin D

The active form of vitamin D plays important roles in the intestinal absorption of calcium and phosphate and thus in healthy bones. Technically, vitamin D isn't even a vitamin, as it is a compound made by the

body. Rather, it behaves more like a hormone.

Derived from ultimately from cholesterol, vitamin D can be made in a reaction catalyzed by ultraviolet light. In the reaction, the intermediate 7-dehydrocholesterol is converted to cholecalciferol (vitamin D_3) by the uv light (Figure 2.229). The reaction occurs most readily in the bottom two layers of the skin shown in Figure 2.230.

Forms of vitamin D

Five different compounds are referred to as vitamin D. They are

Vitamin D_1 - A mixture of ergocalciferol and lumisterol
Vitamin D_2 - Ergocalciferol
Vitamin D_3 - Cholecalciferol
Vitamin D_4 - 22-Dihydroergocalciferol
Vitamin D_5 - Sitocalciferol

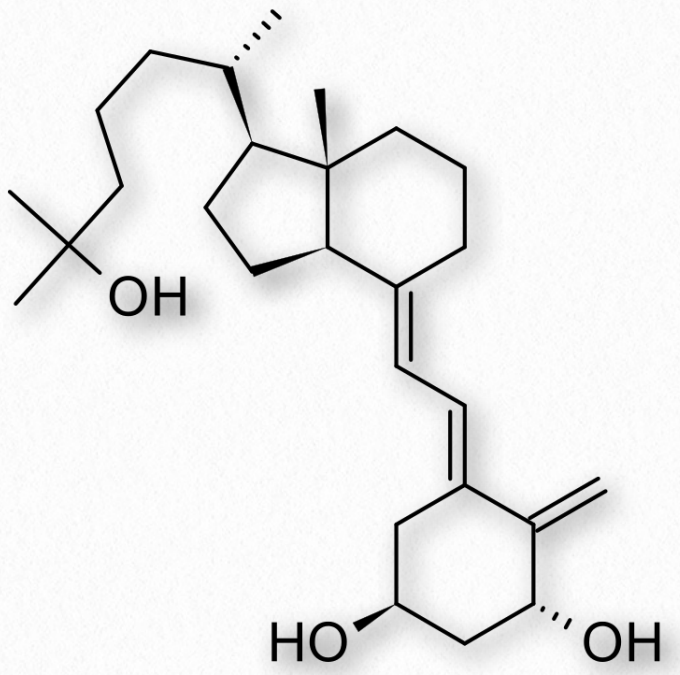

Figure 2.231 - Calcitriol - Active form of vitamin D

Vitamin D_3 is the most common form used in vitamin supplements and it and vitamin D_2 are commonly obtained in the diet, as well. The active form of vitamin D, calcitriol (Figure 2.231), is made in the body in controlled amounts. This proceeds through two steps from cholecalciferol. First, a hydroxylation in the liver produces calcidiol and a second hydroxylation in the kidney produces calcitriol. Monocyte macrophages can also synthesize vitamin D and they use is as a cytokine to stimulate the innate immune system.

Mechanism of action

Calcitriol moves in the body bound to a vitamin D binding protein, which delivers it to target organs. Calcitriol inside of cells acts by binding a vitamin D receptor (VDR), which results in most of the vitamin's physiological effects. After binding calcitriol, the VDR migrates to the nucleus where it acts as a transcription factor to control levels of expression of calcium transport proteins (for example) in the intestine. Most tissues respond to VDR bound to calcitriol and the result is moderation of calcium and phosphate levels in cells.

Deficiency/excess

Deficiency of vitamin D is a cause of the disease known as rickets, which is characterized

by soft, weak bones and most commonly is found in children. It is not common in the developed world, but elsewhere is of increasing concern.

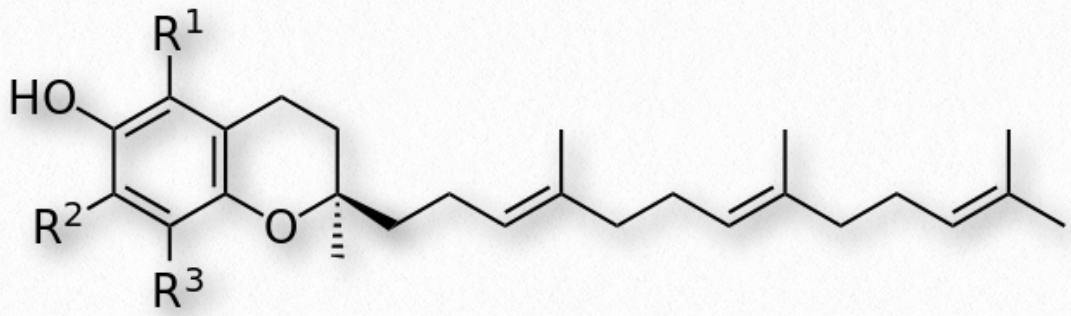

Figure 2.233 - Structure of tocotrienols

Excess of vitamin D is rare, but has toxic effects, including hypercalcemia, which results in painful calcium deposits in major organs. Indications of vitamin D toxicity are increased urination and thirst. Vitamin D toxicity can lead to mental retardation and many other serious health problems.

Vitamin E

Vitamin E comprises a group of two compounds (tocopherols and tocotrienols - Figure 2.232) and stereoisomers of each. It is commonly found in plant oils. The compounds act in cells as fat-soluble antioxidants. α-tocopherol (Figure 2.233), the most active form of the vitamin, works 1) through the glutathione peroxidase protective system and 2) in membranes to interrupt lipid peroxidation chain reactions. In both actions, vitamin E reduces levels of reactive oxygen species in cells.

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Action

Vitamin E scavenges oxygen radicals (possessing unpaired electrons) by reacting with them to produce a tocopheryl radical. This vitamin E radical can be converted back to its original form by a hydrogen donor. Vitamin C is one such donor. Acting in this way, Vitamin E helps reduce oxidation of easily oxidized compounds in the lipid peroxidation reactions (Figure 2.234).

Vitamin E also can affect enzyme activity. The compound can inhibit action of protein kinase C in smooth muscle and simultaneously activate catalysis of protein phosphatase 2A to remove phosphates, stopping smooth muscle growth.

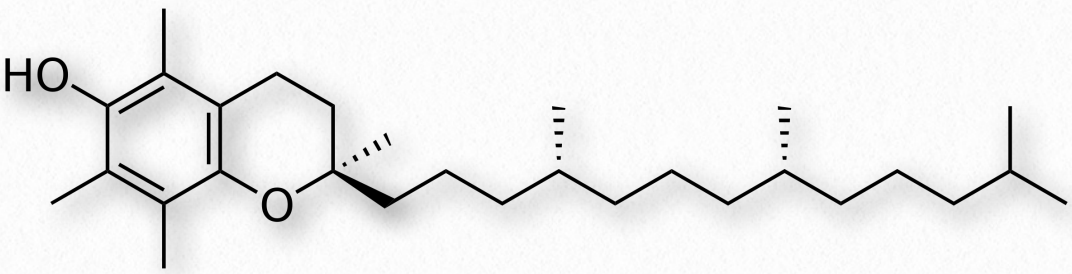

Figure 2.232 α-tocopherol - The most biologically active form of vitamin E

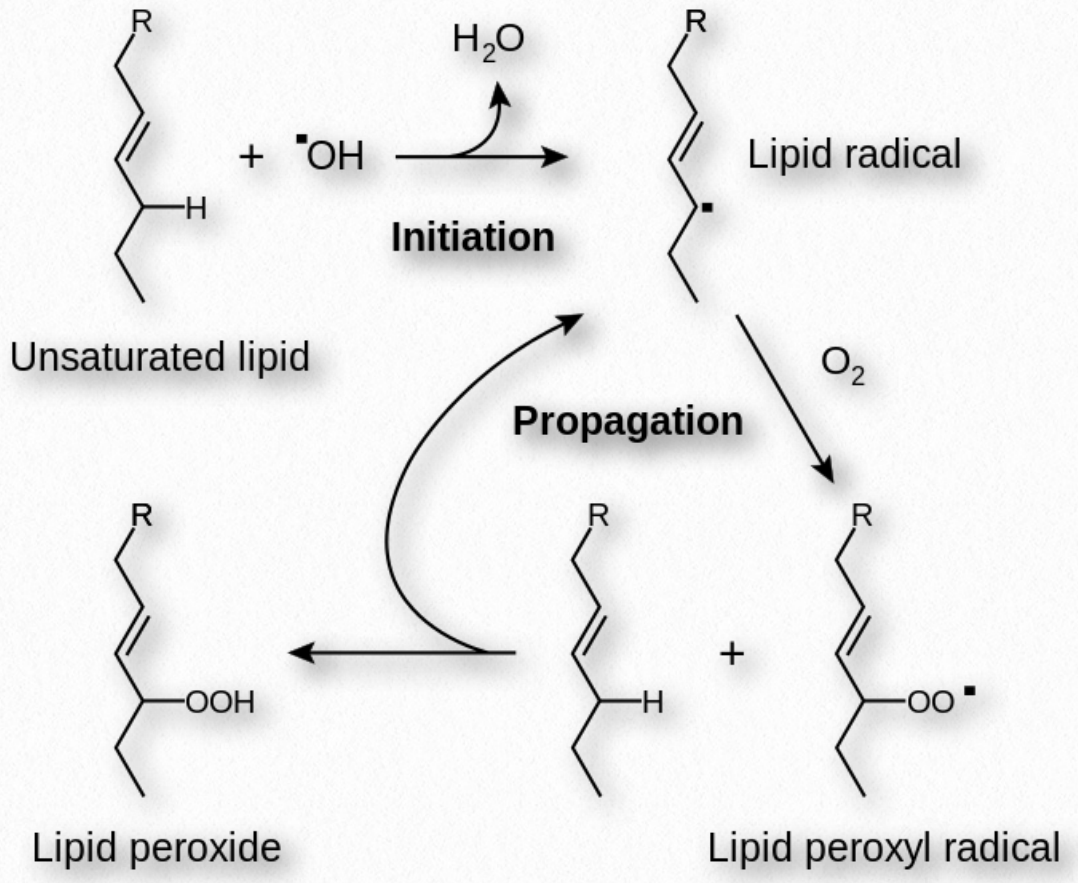

Figure 2.234 - Lipid peroxidation reactions

Deficiency/excess

Deficiency of vitamin E can lead to poor conduction of nerve signals and other issues arising from nerve problems. Low levels of the vitamin may be a factor in low birth weights and premature deliveries. Deficiency, however, is rare, and not usually associated with diet.

Excess Vitamin E reduces vitamin K levels, thus reducing the ability to clot blood. Hypervitaminosis of vitamin E in conjunction with aspirin can be life threatening. At lower levels, vitamin E may serve a preventative role with respect to atherosclerosis by reducing oxidation of LDLs, a step in plaque formation.

Vitamin K

Like the other fat-soluble vitamins, Vitamin K comes in multiple forms (Figure 2.235) and is stored in fat tissue in the body. There are two primary forms of the vitamin - K_1 and K_2 and the latter has multiple sub-forms . Vitamins K_3, K_4, and K_5 are

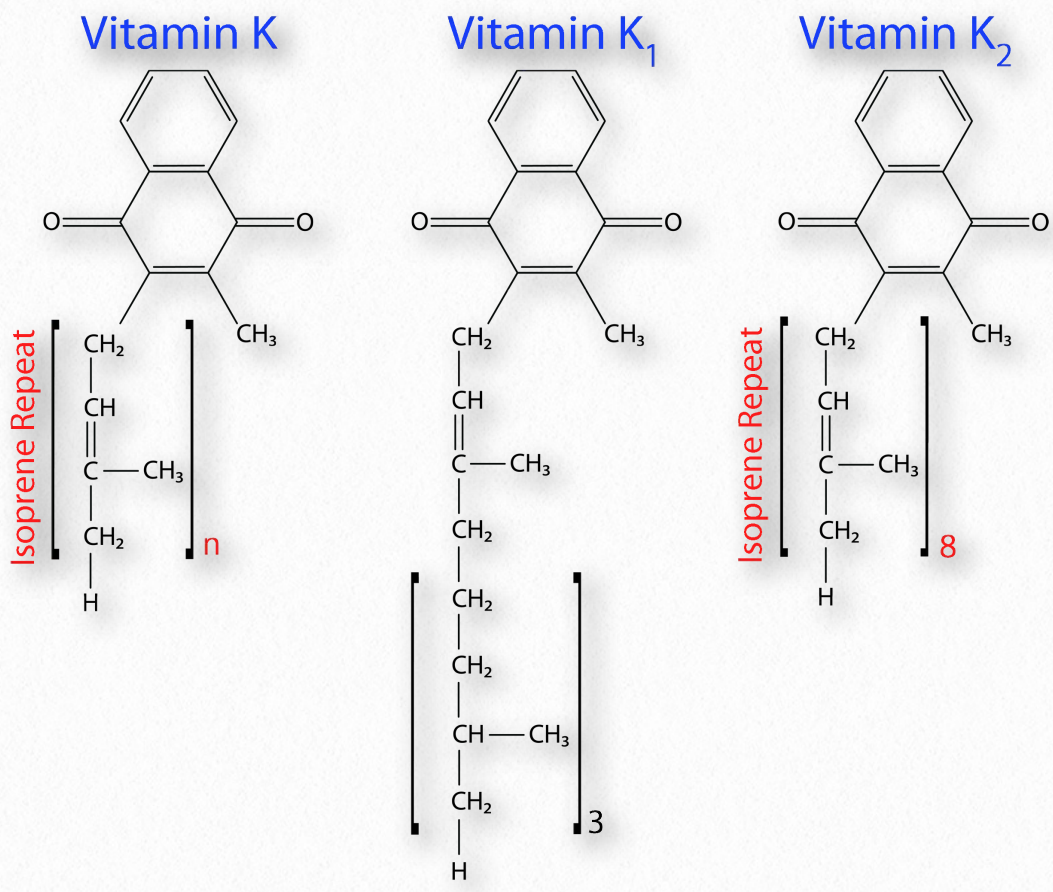

Figure 2.235 - Forms of vitamin K

Image by Pehr Jacobson

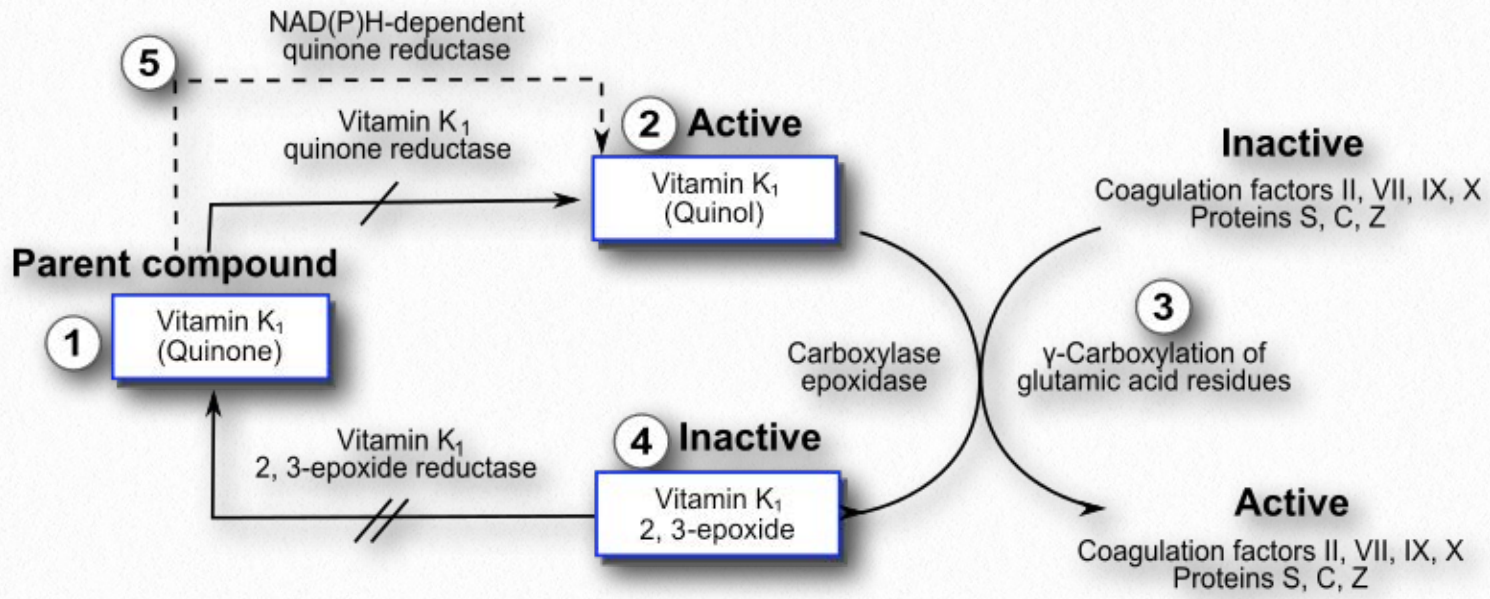

Figure 2.236 - Recycling of vitamin K

Wikipedia

made synthetically, not biologically.

Action

Vitamin K is used as a co-factor for enzymes that add carboxyl groups to glutamate side chains of proteins to increase their affinity for calcium. Sixteen such proteins are known in humans. They include proteins involved in blood clotting (prothrombin (called Factor II), Factors VII, IX, and X), bone metabolism (osteocalcin, also called bone Gla protein (BGP), matrix Gla protein (MGP), and periostin) and others.

Modification of prothrombin is an important step in the process of blood clotting (see HERE). Reduced levels of vitamin K result in less blood clotting, a phenomenon sometimes referred to as blood thinning. Drugs that block recycling of vitamin K (Figure 2.236) by inhibiting the vitamin K epoxide reductase, produce lower levels of the vitamin and are employed in treatments for people prone to excessive clotting. Warfarin (coumadin) is one such compound that acts in this way and is used therapeutically. Individuals respond to the drug differentially, requiring them to periodically be tested for levels of clotting they possess, lest too much or too little occur.

Sources

Vitamin K_1 is a stereoisomer of the plant photosystem I electron receptor known as phylloquinone and is found abundantly in green, leafy vegetables. Phylloquinone is one source of vitamin K, but the compound binds tightly to thylakoid membranes and tends to have low bioavailability. Vitamin K_2 is produced by microbes in the gut and is a primary source of the vitamin. Infants in the first few days before they establish their gut flora and

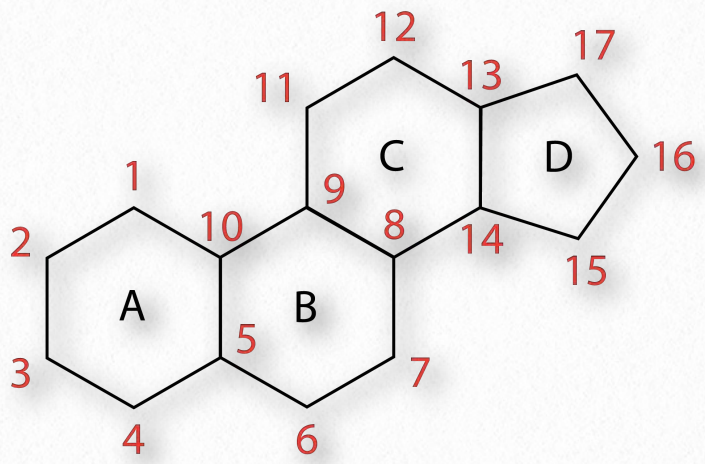

Figure 2.237 - Steroid numbering scheme

Image by Pehr Jacobson

people taking broad spectrum antibiotics may have reduced levels, as a result. Dietary deficiency is rare in the absence of damage to the small bowel. Others at risk of deficiency include people with chronic kidney disease and anyone suffering from a vitamin D deficiency. Deficiencies produce symptoms of easy bruising, heavy menstrual bleeding, anemia, and nosebleeds.

Steroids

Steroids, such as cholesterol are found in membranes and act as signaling hormones in traveling through the body.

Steroid hormones are all made from cholesterol and are grouped into five categories - mineralocorticoids (21 carbons), glucocorticoids (21 carbons), progestagens (21 carbons), androgens (19 carbons), and estrogens (18 carbons).

Mineralocorticoids

Mineralocorticoids are steroid hormones that influence water and electrolyte balances. Aldosterone (Figure 2.238) is the primary mineralocorticoid hormone, though other steroid hormones (including progesterone) have some functions like it. Aldosterone stimulates kidneys to reabsorb sodium, secrete potassium, and passively reabsorb water. These actions have the effect of increasing blood pressure and blood volume. Mineralocorticoids are produced by the zona glomerulosa of the cortex of the adrenal gland.

Glucocorticoids

Glucocorticoids (GCs) bind to glucocorticoid receptors found in almost every vertebrate animal cell and act in a feedback mechanism in the immune system to reduce its activity. GCs are used to treat diseases associated with overactive immune systems. These include allergies, asthma, and autoimmune dis-

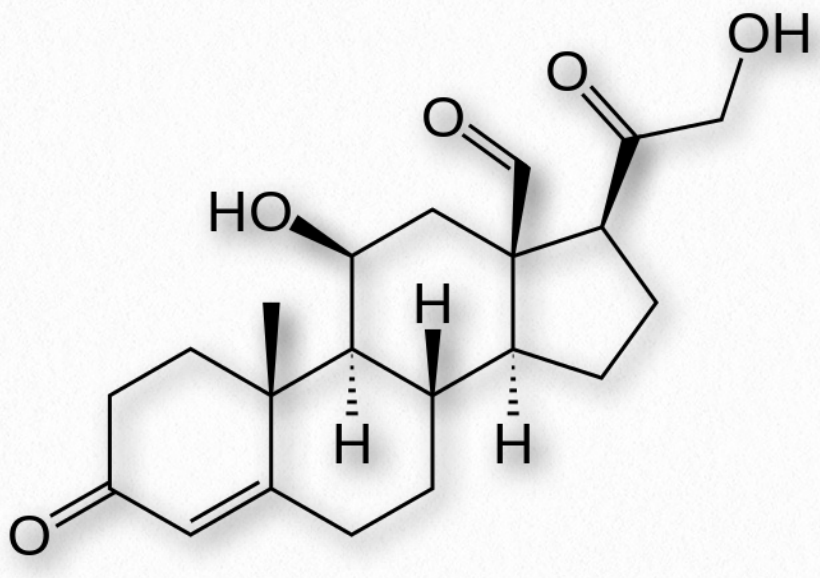

Figure 2.238 - Aldosterone - A mineralocorticoid

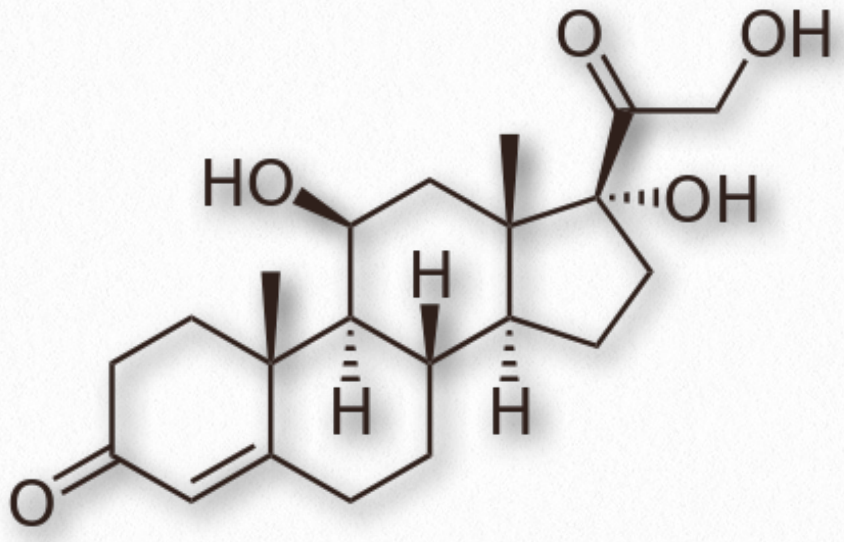

Figure 2.239 - Cortisol - A glucocorticoid

eases. Cortisol (Figure 2.239) is an important glucocorticoid with cardiovascular, metabolic, and immunologic functions. The synthetic glucocorticoid known as dexamethasone has medical applications for treating rheumatoid arthritis, bronchospasms (in asthma), and inflammation due to its increased potency (25-fold) compared to cortisol. Glucocorticoids are produced primarily in the zona fasciculata of the adrenal cortex.

Progestagens

Progestagens (also called gestagens) are steroid hormones that work to activate the progesterone receptor upon binding to it. Synthetic progestagens are referred to as progestins. The most common progestagen is progesterone (also called P4 - Figure 2.240) and it has functions in maintaining pregnancy. Progesterone is produced primarily in the diestrus phase of the estrous cycle by the corpus luteum of mammalian ovaries. In pregnancy, the placenta takes over most progesterone production.

Androgens

Androgens are steroid hormones that act by binding androgen receptors to stimulate development and maintenance of male characteristics in vertebrates. Androgens are precursors of estrogens (see below). The primary androgen is testosterone (Figure 2.241). Other important androgens include dihydrotestosterone (stimulates differentiation of penis, scrotum, and prostate in embryo) and androstenedione (common precursor of male and female hormones).

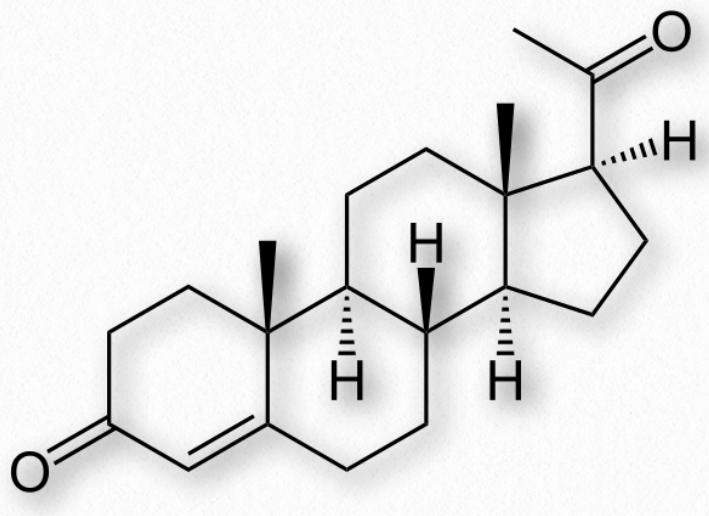

Figure 2.240 Progesterone - A progestagen

Estrogens

The estrogen steroid hormones are a class of compounds with important roles in menstrual and estrous cycles. They are the most important female sex hormones. Estrogens act by

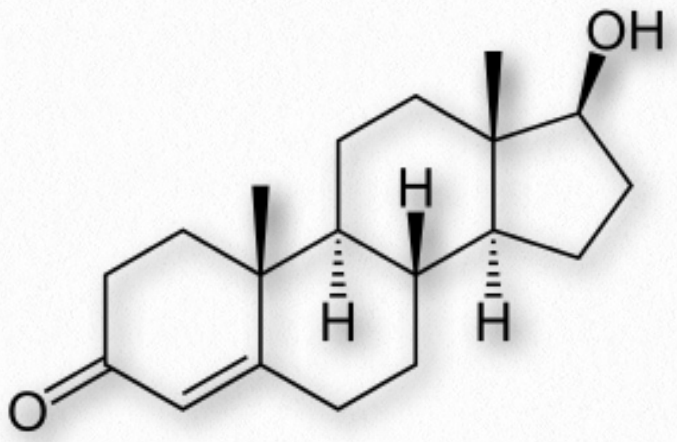

Figure 2.241 - Testosterone - An androgen

activating estrogen receptors inside of cells. These receptors, in turn, affect expression of many genes. The major estrogens in women include estrone (E_1), estradiol (E_2 - Figure 2.242), and estriol (E_3). In the reproductive years, estradiol predominates. During pregnancy, estriol predominates and during menopause, estrone is the major estrogen.

Estrogens are made from the androgen hormones testosterone and androstenedione in a reaction catalyzed by the enzyme known as aromatase. Inhibition of this enzyme with aromatase inhibitors, such as exemestane, is a strategy for stopping estrogen production. This may be part of a chemotherapeutic treatment when estrogen-responsive tumors are present.

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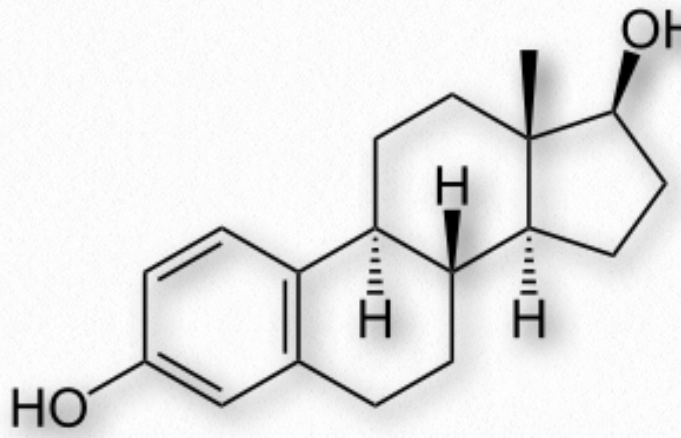

Figure 2.242 - Estradiol - An estrogen

Cannabinoids

Cannabinoids are a group of chemicals that bind to and have effects on brain receptors (cannabinoid receptors), repressing neurotransmitter release. Classes of these compounds include endocannabinoids (made in the body), phytocannabinoids (made in plants, such as marijuana), and synthetic cannabinoids (man-made).

Endocannabinoids are natural molecules derived from arachidonic acid. Cannabinoid receptors are very abundant, comprising the largest number of G-protein-

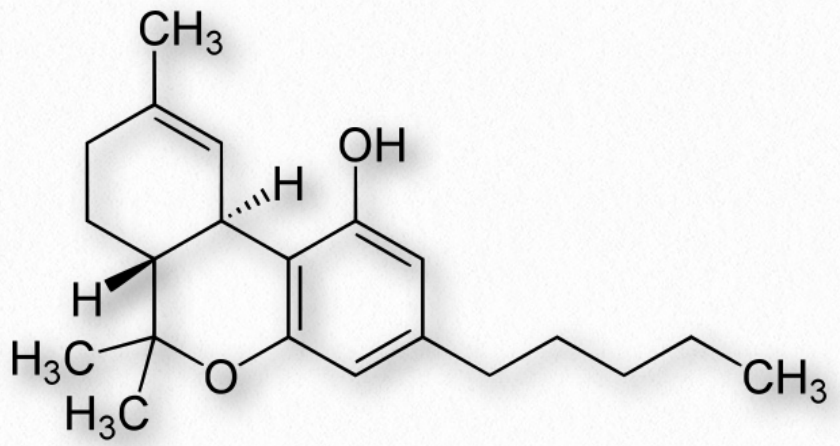

Figure 2.243 - Tetrahydrocannabinol - Active ingredient in marijuana

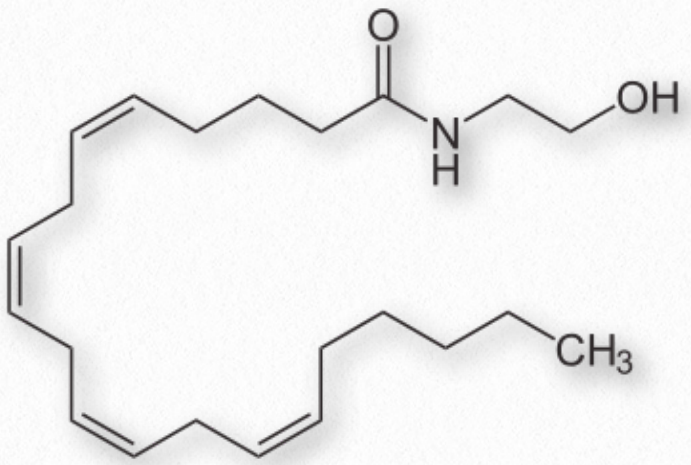

Figure 2.244 - Anandamide - An endocannabinoid

coupled receptors found in brain. The best known phytocannabinoid is Δ-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient (of the 85 cannabinoids) of marijuana (Figure 2.243).

Anandamide

Anandamide (N-arachidonoylethanolamine - Figure 2.244) is an endocannabinoid neurotransmitter derived from arachidonic acid. It exerts its actions primarily through the CB1 and CB2 cannabinoid receptors, the same ones bound by the active ingredient in marijuana, Δ9-tetrahydrocannabinol. Anandamide has roles in stimulating eating/appetite and affecting motivation and pleasure. It has been proposed to play a role in "runners high," an analgesic effect experienced from exertion, especially among runners. Anandamide appears to impair memory function in rats.

Anandamide has been found in chocolate and two compounds that mimic its effects (N-oleoylethanolamine and N-linoleoylethanolamine) are present as well. The enzyme fatty acid amide hydrolase (FAAH) breaks down anandamide into free arachidonic acid and ethanolamine.

Lipoxins

Lipoxins (Figure 2.245) are eicosanoid compounds involved in modulating immune responses and they have anti-inflammatory effects. When lipoxins appear in inflammation it begins the end of the process. Lipoxins act to attract macrophages to apoptotic cells at the site of inflammation and they are engulfed. Lipoxins further act to start the resolution phase of the inflammation process.

At least one lipoxin (aspirin-triggered LX4) has its synthesis stimulated by aspirin. This occurs as a byproduct of aspirin's acetylation of COX-2. When this occurs, the enzyme's catalytic activity is re-directed to synthesis of 15R-hydroxyeicosatetraenoic acid (HETE) instead of prostaglandins.

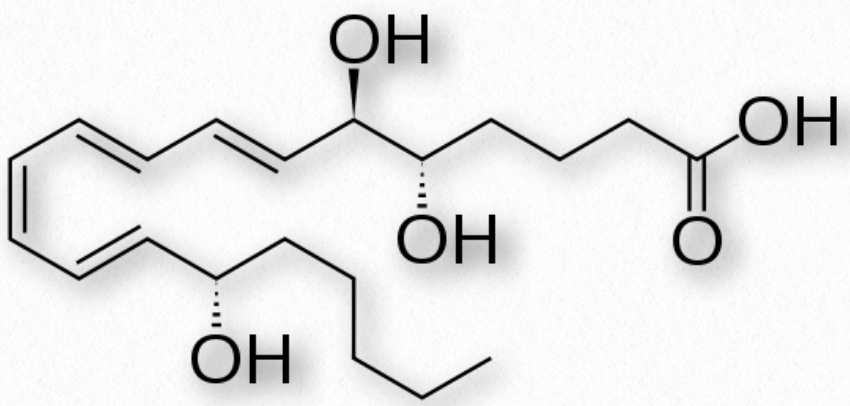

Figure 2.245 - Lipoxin A4

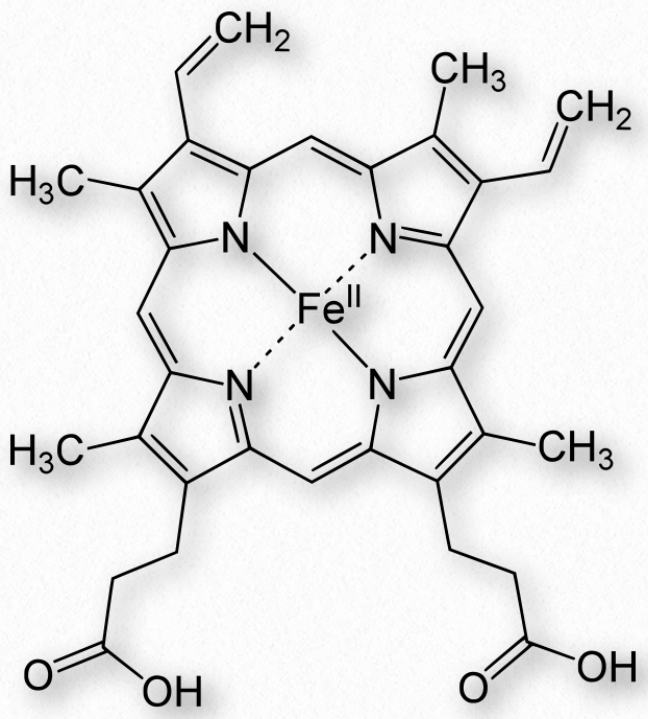

Figure 2.246 - Structure of heme B

15R-HETE is a procursor of 15-epimer lipoxins, including aspirin-triggered LX4.

Heme

Heme groups are a collection of protein/enzyme cofactors containing a large heterocyclic aromatic ring known as a porphyrin ring with a ferrous (Fe^{++}) ion in the middle. An example porphyrin ring with an iron (found in Heme B of hemoglobin), is shown in Figure 2.246. When contained in a protein, these are known collectively as hemoproteins (Figure 2.247).

Heme, of course, is a primary component of hemoglobin, but it is also found in other proteins, such as myoglobin, cytochromes, and the enzymes catalase and succinate dehydrogenase. Hemoproteins function in oxygen transport, catalysis, and electron transport. Heme is synthesized in the liver and bone marrow in a pathway that is conserved across a wide range of biology.

Porphobilinogen

Porphobilinogen (Figure 2.248) is a pyrrole molecule involved in porphyrin metabolism. It is produced from aminolevulinate by action of the enzyme known as ALA dehydratase. Porphobilinogen is acted upon by the enzyme porphobilinogen deaminase. Deficiency of the latter enzyme (and others in porphyrin metabolism) can result in a condition known as porphyria, which results in accumulation of porphobilinogen in the cytoplasm of cells. The disease can manifest itself with acute abdominal pain and numerous psychiatric issues. Both Vincent van Gogh and King

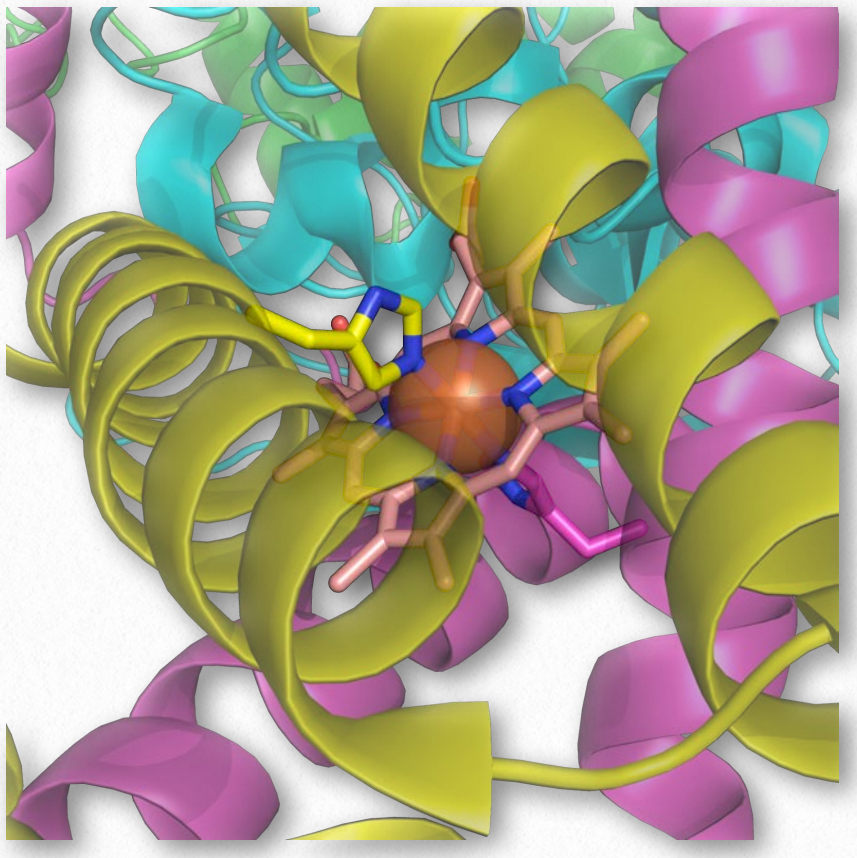

Figure 2.247 - Heme embedded in the succinate dehydrogenase hemoprotein
Wikipedia

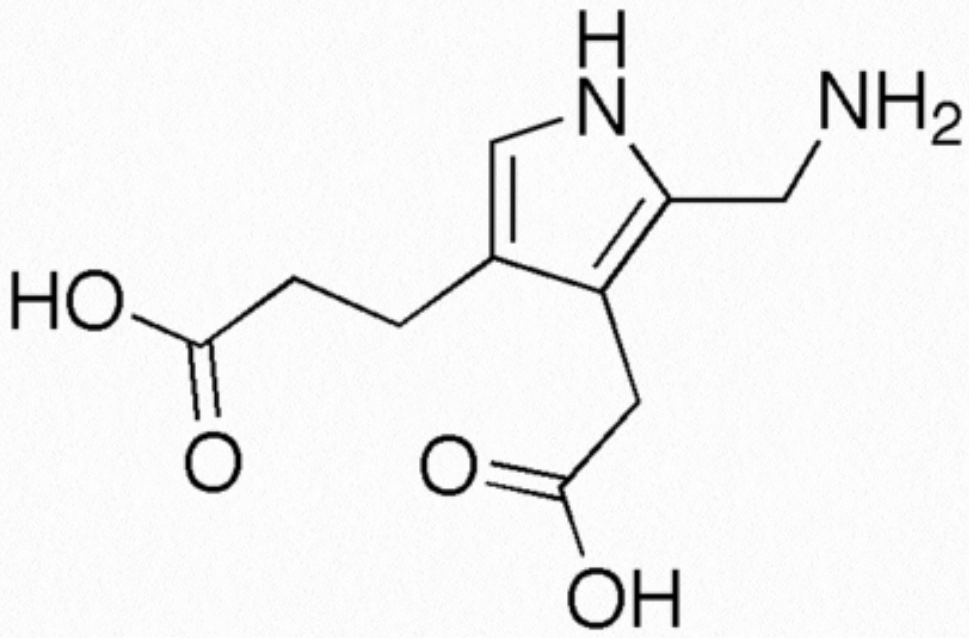

Figure 2.248 - Porphobilinogen

George III are suspected to have suffered from porphyria, perhaps causing the "madness of King George III." Porphyria is also considered by some to be the impetus for the legend of vampires seeking blood from victims, since the color of the skin in non-acute forms of the disease can be miscolored, leading some to perceive that as a deficiency of hemoglobin and hence the "thirst" for blood imagined for vampires.

Dolichols

Dolichol is a name for a group of non-polar molecules made by combining isoprene units together. Phosphorylated forms of dolichols play central roles in the N-glycosylation of proteins. This process, which occurs in the endoplasmic reticulum of eukaryotic cells, begins with a membrane-embedded dolichol pyrophosphate (Figure 2.249) to which an oligosaccharide is attached (also see HERE). This oligosaccharide contains three molecules of glucose, nine molecules of mannose and two molecules of N-acetylglucosamine.

Interestingly, the sugars are attached to the dolichol pyrophosphate with the pyrophosphate pointing outwards (away from) the endoplasmic reticulum, but after attachment, the dolichol complex flips so that the sugar portion is situated on the inside of the endoplasmic reticulum. There, the entire sugar complex is transferred to the amide of an asparagine side chain of a target protein.

The only asparagine side chains to which the attachment can be made are in proteins where the sequences Asn-X-Ser or Asn-X-Thr occur. Sugars can be removed/added after the transfer to the protein. Levels of dolichol in the

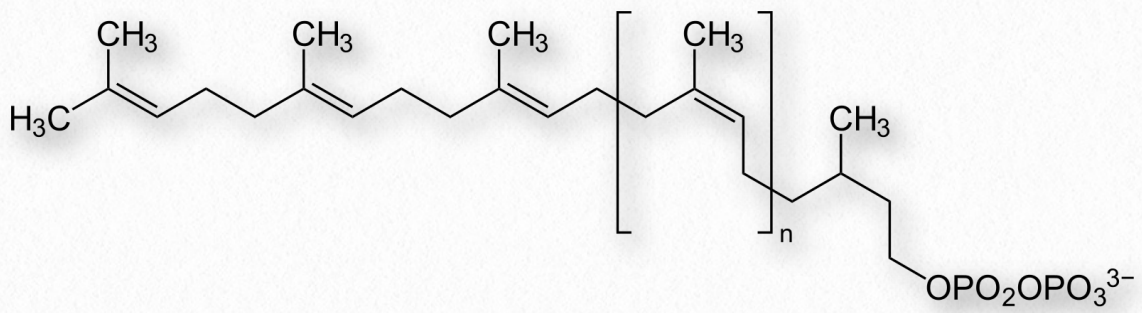

Figure 2.249 - Structure of dolichol pyrophosphate

Figure 2.250 - Pine tree resin - A source of terpenes

Wikipedia

human brain increase with age, but in neurodegenerative diseases, they decrease.

Terpenes

Terpenes are members of a class of nonpolar molecules made from isoprene units. Terpenes are produced primarily by plants and by some insects. Terpenoids are a related group of molecules that contain functional groups lacking in terpenes.

Terpenes have a variety of functions. In plants, they often play a defensive role protecting from insects. The name of terpene comes from turpentine, which has an odor like some of the terpenes. Terpenes are common components of plant resins (think pine) and they are widely used in medicines and as fragrances. Hops, for example, gain some of their distinctive aroma and flavor from terpenes. Not all terpenes, however have significant odor.

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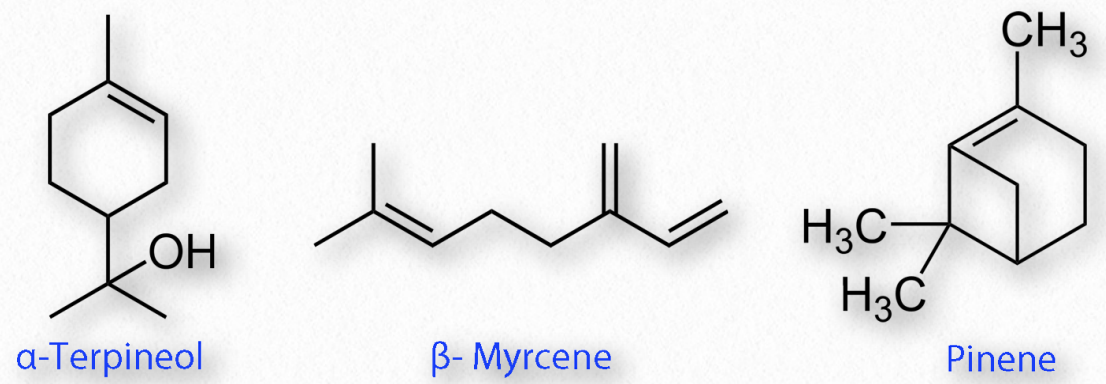
Synthesis

Terpenes, like steroids, are synthesized starting with simple building blocks known as isoprenes. There are two of them - dimethylallyl pyrophosphate and the related isopentenyl pyrophosphate and (Figures 2.252 and 2.253) which combine 1-2 units at a time to make higher order structures. Terpene synthesis overlaps and includes steroid synthesis.



α-Terpineol β- Myrcene Pinene

Figure 2.251 - Three monoterpenes

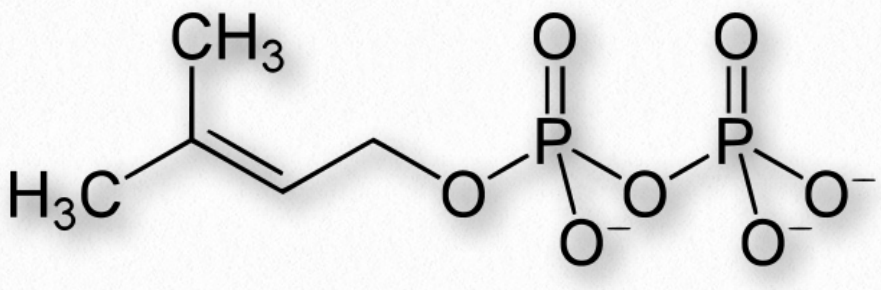


Figure 2.252 - Dimethylallyl pyrophosphate

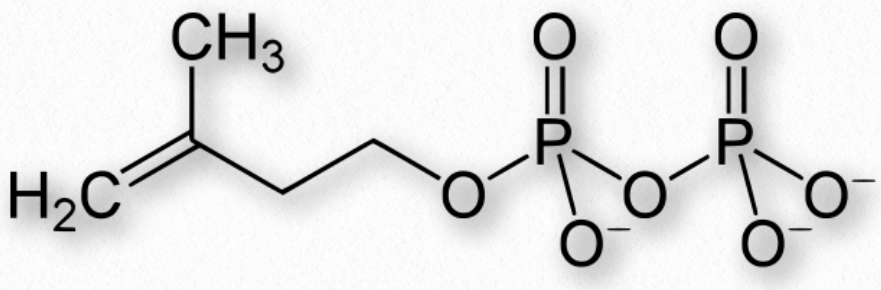


Figure 2.253 - Isopentenyl pyrophosphate

Terpenes and terpenoids are classified according to how many isoprene units they contain. They include hemiterpenes (one unit), monoterpenes (two units), sesquiterpenes (three units), diterpenes (four units), sesterterpenes (five units), triterpenes (six units), sesquarterpenes (seven units), tetraterpenes (eight units), polyterpenes (many units).

Another class of terpene-containing molecules, the norisoterpenoids arise from peroxidase-catalyzed reactions on terpene molecules.

Examples

Common terpenes include monoterpenes of terpineol (lilacs), limonene (citrus), myrcene (hops), linalool (lavender), and pinene (pine). Higher order terpenes include taxadiene (diterpene precursor of taxol), lycopene (tetraterpenes), carotenes (tetraterpenes), and natural rubber (polyterpenes).

Steroid precursors geranyl pyrophosphate (monoterpene derivative), farnesyl pyrophosphate (sesquiterpene derivative), and squalene (triterpene) are all terpenes or derivatives of them. Vitamin A and phytol are derived from diterpenes.

Caffeine

Caffeine is the world's most actively consumed psychoactive drug (Figure 2.255). A methylxanthine alkaloid, caffeine is closely

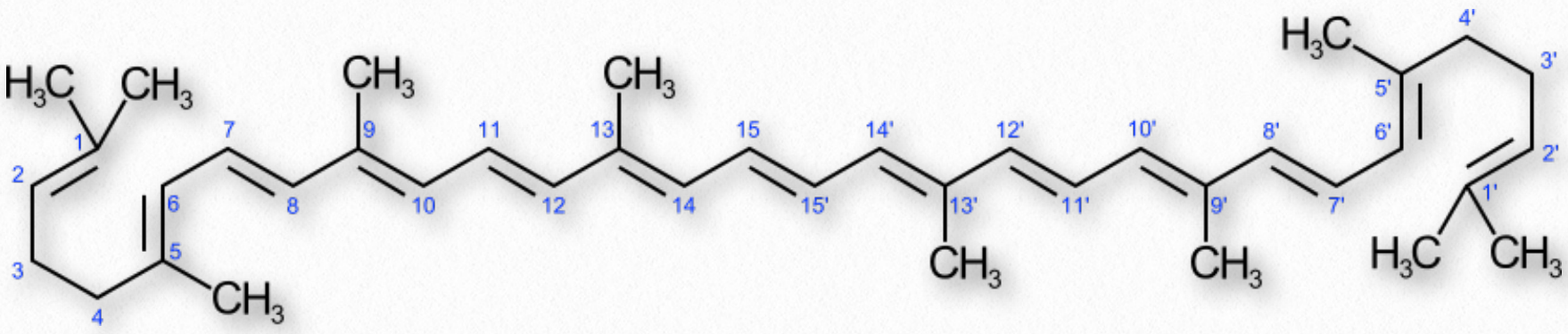


Figure 2.254 - Lycopene - A tetraterpene

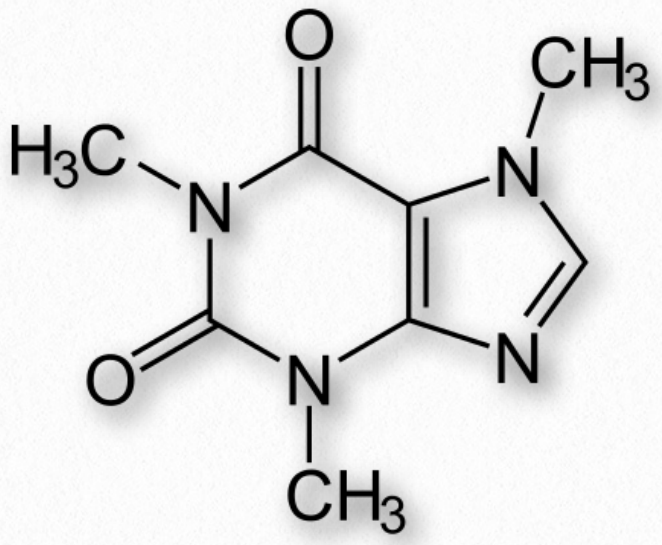


Figure 2.255 - Caffeine

related to adenine and guanine and this is responsible for many effects on the body. Caffeine blocks the binding of adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine. Caffeine readily crosses the blood-brain barrier and stimulates release of neurotransmitters. Caffeine stimulates portions of the autonomic nervous system and inhibits the activity of phosphodiesterase. The latter has the result of raising cAMP levels in cells, which activates protein kinase A and activates glycogen breakdown, inhibits TNF-α and leukotriene synthesis, which results in reduction of inflammation and innate immunity.

Caffeine also has effects on the cholinergic system (acetylcholinesterase inhibitor), is an inositol triphosphate receptor 1 antagonist, and is a voltage independent activator of ryanodin receptors (a group of calcium channels found in skeletal muscle, smooth muscle, and heart muscle cells).

The half-life of caffeine in the body varies considerably. In healthy adults, it has a half-life of about 3-7 hours. Nicotine decreases the half-life and contraceptives and pregnancy can double it. The liver metabolizes caffeine, so the health of the liver is a factor in the half-life. CYP1A2 of the cytochrome P450 oxidase enzyme is primarily responsible. Caffeine is a natural pesticide in plants, paralyzing predator bugs.

Lipoprotein complexes and lipid movement in the body

Lipoprotein complexes are combinations of apolipoproteins and lipids bound to them that solubilize fats and other non-polar molecules, such as cholesterol, so they can travel in the bloodstream between various tissues of the body. The apolipoproteins provide the emulsification necessary for this. Lipoprotein complexes are formed in tiny “balls” with the water soluble apolipoproteins on the outside and non-polar lipids, such as fats, cholesteryl esters, and fat soluble vitamins on the inside.

They are categorized by their densities. These include (from highest density to the lowest) high density lipoproteins (HDLs), Low Density Lipoproteins (LDLs), Intermediate Density Lipoproteins (IDLs), Very Low Density Lipoproteins (VLDLs) and the chylomi-

Name	Lipoprotein Complex(es)	Function
ApoA-I	HDL	Promotes Fat Movement to Liver
ApoA-II	HDL	Inhibit LCAT
ApoA-IV	Chylomicrons / HDL	Activate LCAT
AboB-48	Chylomicrons	Cholesterol Transport
AboB-100	VLDL / LDL	Bind LDL Receptor
ApoC-I	VLDL / LDL	Unknown
ApoC-II	All	Activate Lipoprotein Lipase
ApoC-III	All	Inhibit Lipoprotein Lipase
ApoD	HDL	Unknown
ApoE	VLDL / Chylomicrons / HDL	Clearance of Chylomicrons Remnants and VLDLs

Figure 2.256 - Apolipoproteins

crons. These particles are synthesized in the liver and small intestines.

Apolipoproteins

Each lipoprotein complex contain a characteristic set of apolipoproteins, as shown in Figure 2.256. ApoC-II and ApoC-III are notable for their presence in all the lipoprotein complexes and the roles they play in activating (ApoC-II) or inactivating (ApoC-III) lipoprotein lipase. Lipoprotein lipase is a cellular enzyme that catalyzes the breakdown of fat from the complexes. ApoE (see below) is useful for helping the predict the likelihood of the occurrence of Alzheimer's disease in a patient.

Gene editing

ApoB-48 and ApoB-100 are interesting in being coded by the same gene, but a unique mRNA sequence editing event occurs that converts one into the other. ApoB-100 is made in the liver, but ApoB-48 is made in the small intestine. The small intestine contains an enzyme that deaminates the cyti-

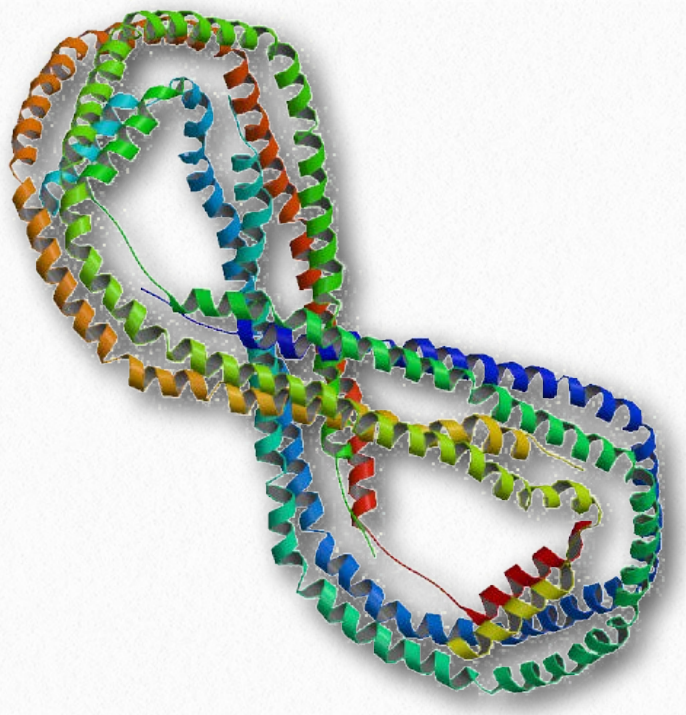


Figure 2.257 - ApoA-I

dine at nucleotide #2153 of the common mRNA. This changes it to a uridine and changes the codon it is in from CAA (codes for glutamine) to UAA (stop codon). The liver does not contain this enzyme and does not make the change in the mRNA. Consequently, a shorter protein is synthesized in the intestine (ApoB-48) than the one that is made in the liver (ApoB-100) using the same gene sequence in the DNA.

Movement

The movement of fats in the body is important because they are not stored in all cells. Only specialized cells called adipocytes store fat. There are three relevant pathways in the body for moving lipids. As described below, they are 1) the exogenous pathway; 2) the endogenous pathway, and 3) the reverse transport pathway.

Exogenous pathway

Dietary fat entering the body from the intestinal system must be transported, as appropriate, to places needing it or storing it. This is the function of the exogenous pathway of lipid movement in the body. All dietary lipids (fats, cholesterol, fat soluble vitamins, and other lipids) are moved by it. In the case of dietary fat, it begins its journey after ingestion first by being solubilized by bile acids in the intestinal tract. After passing through the stomach, pancreatic lipases clip two fatty acids from the fat, leaving a monoacyl glycerol. The fatty acids and monoacyl glycerol are absorbed by intestinal cells (enterocytes) and reassembled back into a fat, and then this is mixed with phospholipids, cholesterol esters, and apolipoprotein B-48 and processed to form chylomicrons (Figures 2.258 & 2.259) in the

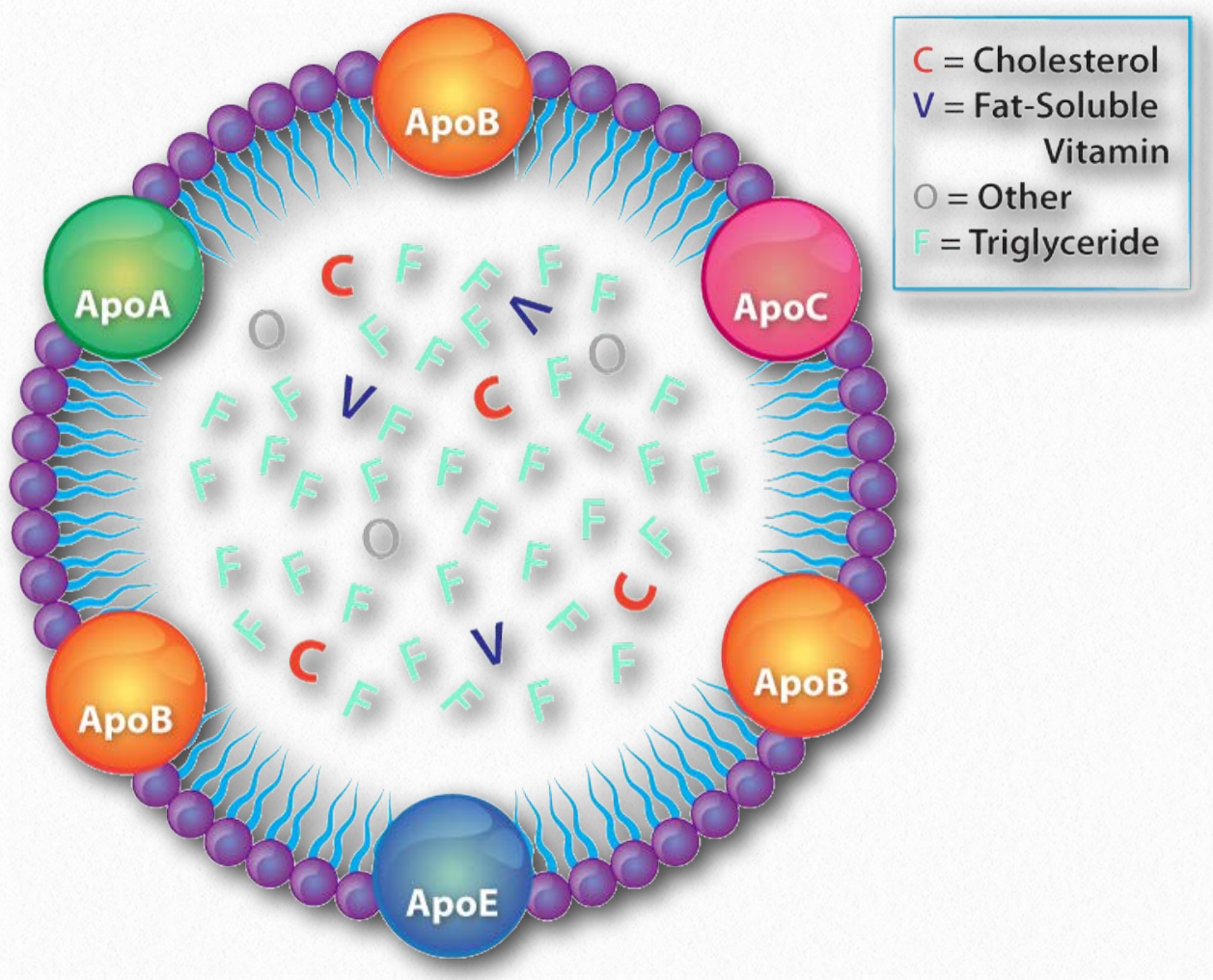


Figure 2.258 - Schematic diagram of a chylomicron

Image by Aleia Kim

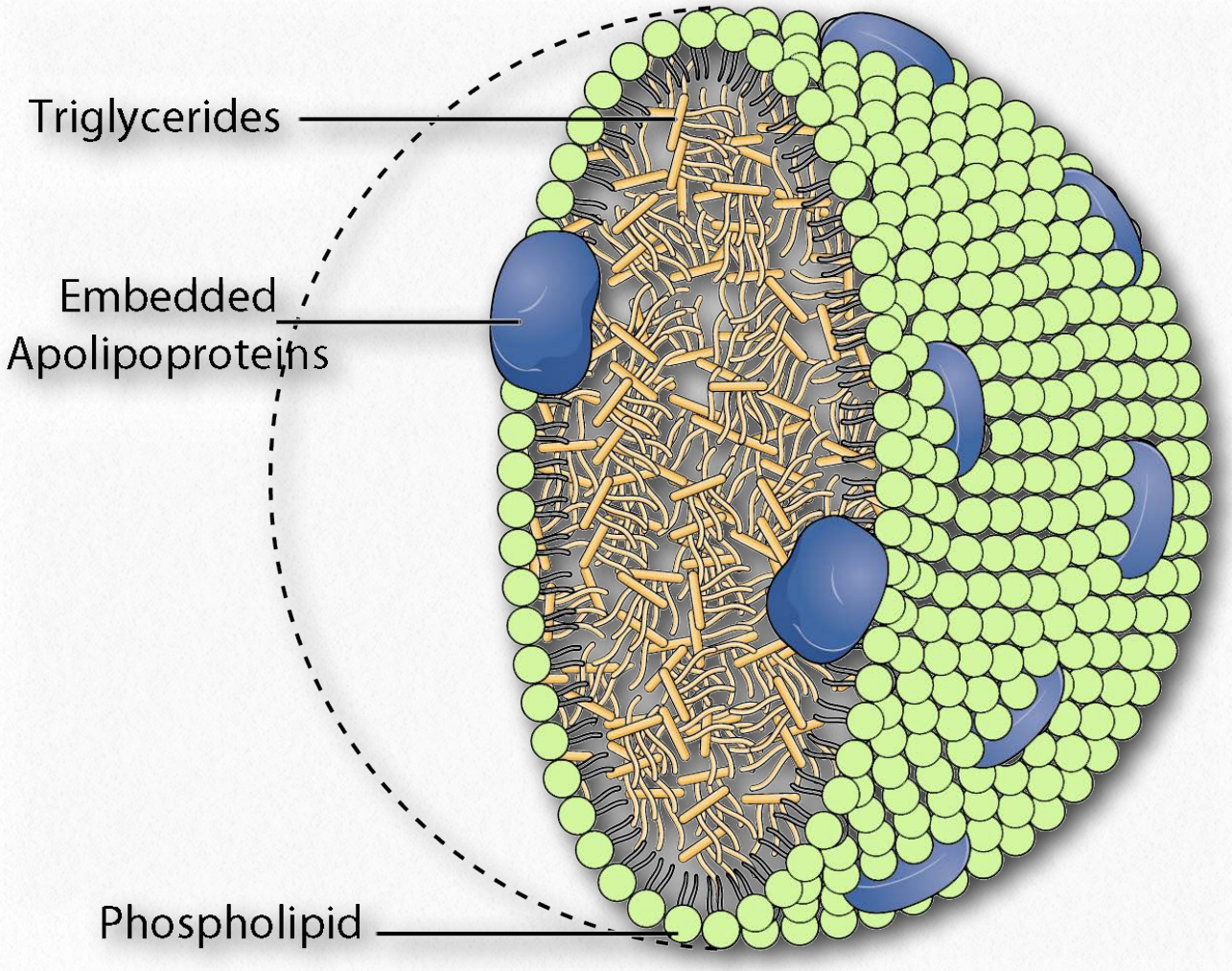


Figure 2.259 - Another perspective of a chylomicron

Wikipedia

Golgi apparatus and smooth endoplasmic reticulum.

Exocytosis

These are exocytosed from the cell into lymph capillaries called lacteals. The chylomicrons pass through the lacteals and enter the bloodstream via the left subclavian vein. Within the bloodstream, lipoprotein lipase breaks down the fats causing the chylomicron to shrink and become what is known as a chylomicron remnant. It retains its cholesterol and other lipid molecules.

The chylomicron remnants travel to the liver where they are absorbed (Figure 2.260).

This is accomplished by receptors in the liver that recognize and bind to the ApoE of the chylomicrons. The bound complexes are then internalized by endocytosis, degraded in the lysosomes, and the cholesterol is disbursed in liver cells.

Endogenous pathway

The liver plays a central role in managing the body's needs for lipids. When lipids are needed by the body or when the capacity of the liver to contain more lipids than is supplied by the diet, the liver packages up fats and cholesteryl esters into Very Low Density Lipoprotein (VLDL) complexes and exports them via the endogenous pathway. VLDL complexes contain ApoB-100, ApoC-I, ApoC-II, ApoC-III, and ApoE apolipoproteins. VLDLs enter the blood and travel to muscles and adipose tissue where lipoprotein lipase is activated by ApoC-II. In the muscle cells, the released fatty acids are taken up and oxidized. By contrast, in the adipoctyes, the fatty acids are taken up and reassembled back into triacylglycerides (fats) and stored in fat droplets. Re-

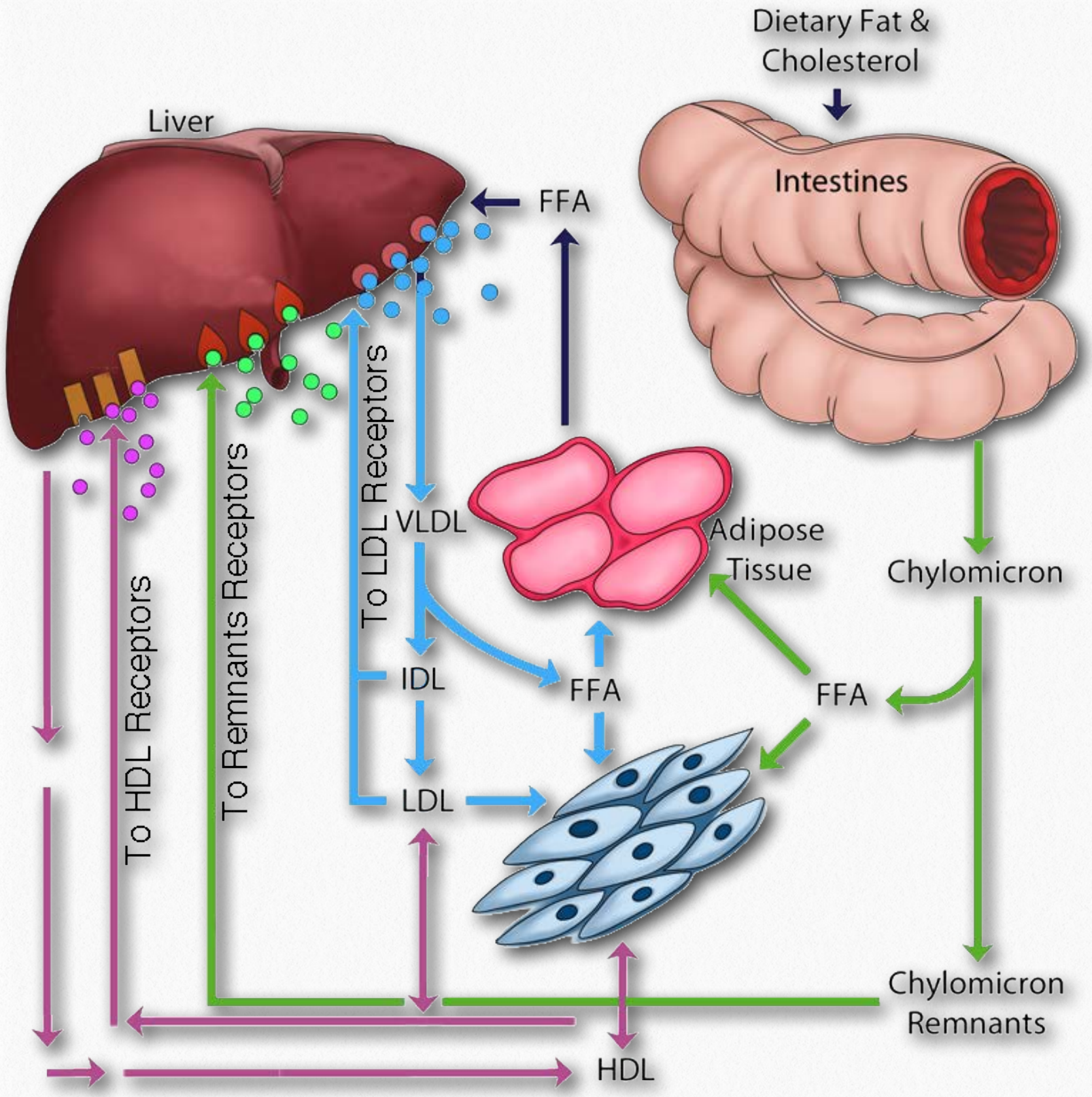


Figure 2.260 - Movement of lipids in the body - Green = exogenous pathway; Blue = endogenous pathway; Purple = reverse transport pathway

Image by Aleia Kim

moval of fat from the VLDLs causes them to shrink, first to Intermediate Density Lipoprotein (IDL) complexes (also called VLDL remnants) and then to Low Density Lipoprotein (LDL) complexes.

YouTube Lectures by Kevin HERE & HERE

Shrinking of VLDLs is accompanied by loss of apolipoproteins so that LDLs are comprised primarily of ApoB-100. This lipoprotein complex is important because cells have receptors for it to bind and internalize it by receptor-mediated endocytosis (Figure 2.261). Up until this point, cholesterol and cholesteryl esters have traveled in chylomicrons, VLDLs, and IDLs as fat has been stripped stripped away. For cholesterol compounds to get into the cell from the lipoprotein complexes, they must be internalized by cells and that is the job of receptor-mediated endocytosis.

Reverse transport pathway

Another important consideration of the movement of lipids in the body is the reverse transport pathway (Figure 2.260). It is also called the reverse cholesterol transport pathway, since cholesterol is the primary molecule involved. This pathway involves the last class of lipoprotein complexes known as the High Density Lipoproteins (HDLs). In contrast to the LDLs, which are commonly referred to as “bad cholesterol” (see below also), the HDLs are known as “good cholesterol.”

HDLs are synthesized in the liver and small intestine. They contain little or no lipid when made (called depleted HDLs), but serve the role of “scavenger” for cholesterol in the blood and from remnants of other (damaged) lipoprotein complexes in the blood. To perform its task, HDLs carry the enzyme known as lecithin-cholesterol acyl transferase (LCAT), which they use to form cholesteryl esters using fatty acids from lecithin (phosphatidylcholine) and then they internalize them.

The cholesterol used for this purpose comes from the bloodstream, from macrophages, and from foam cells (macrophage-LDL complexes - Figure 2.262). Addition of cholesteryl esters causes the HDL to swell and

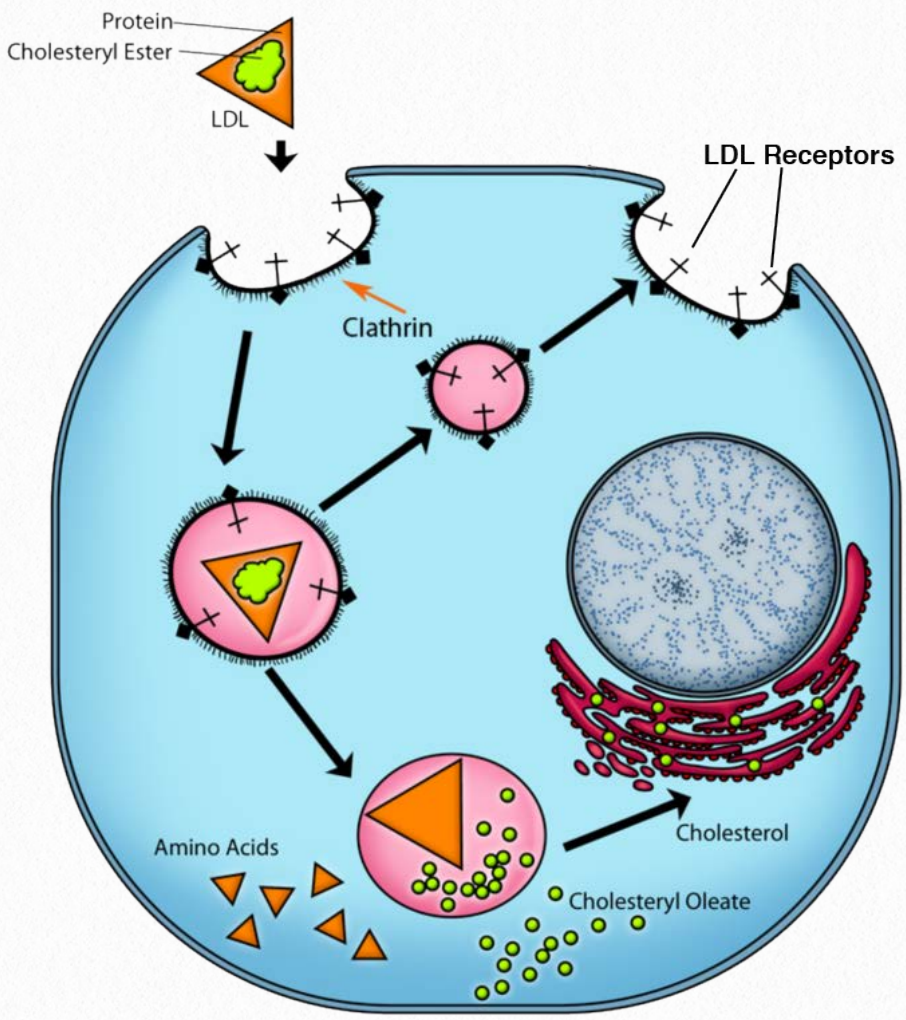


Figure 2.261 - The process of receptor-mediated endocytosis

Image by Aleia Kim

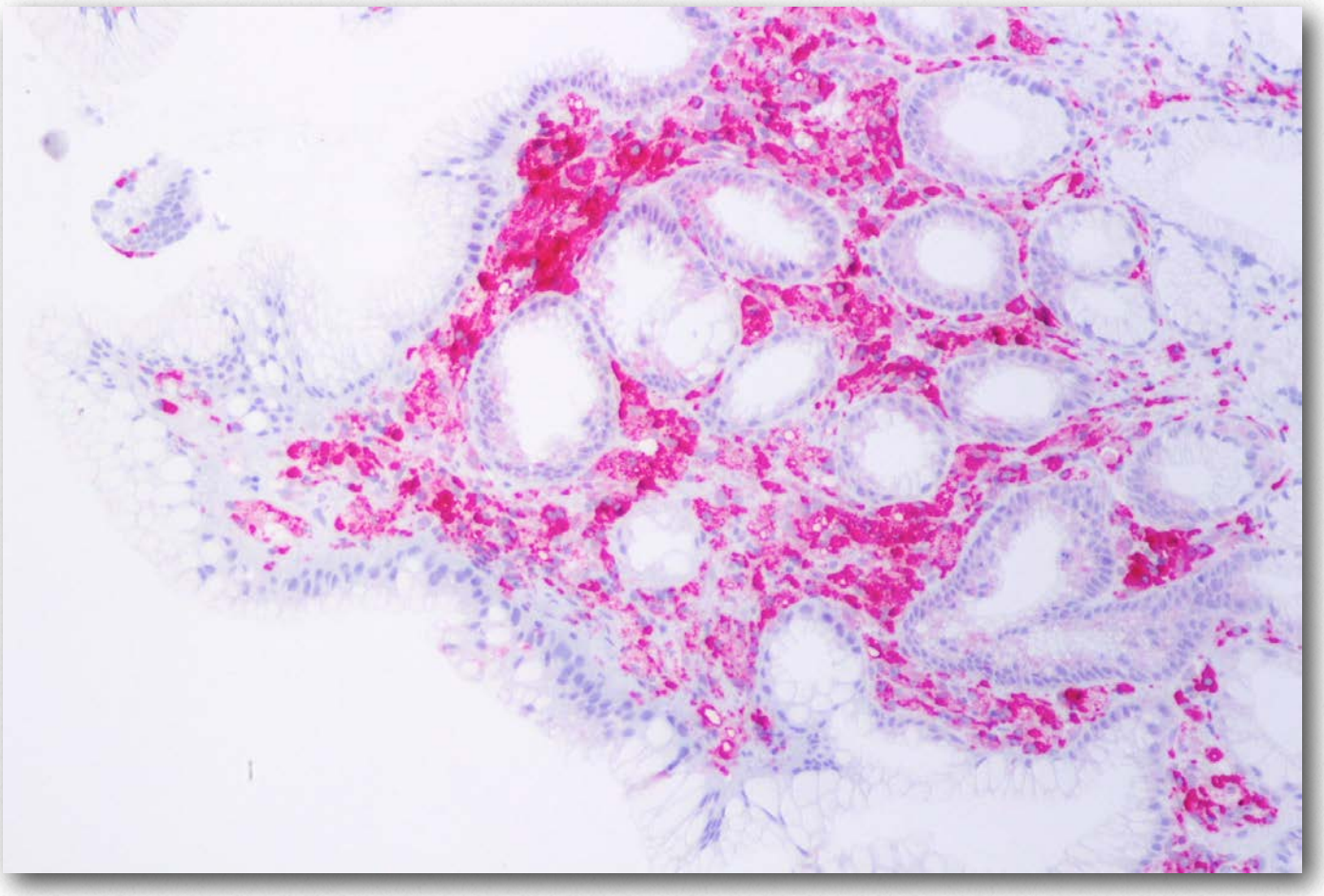


Figure 2.262 - Foam cell aggregate

Wikipedia

when it is mature, it returns its load of cholesterol back to the liver or, alternatively, to LDL molecules for endocytosis. HDLs have the effect of lowering levels of cholesterol and it is for that reason they are described as “good cholesterol.”

Regulation of lipid transfer

It is important that cells get food when they need it so some control of the movement of nutrients is critical. The liver, which plays the central role in modulating blood glucose levels, is also important for performing the same role for lipids. It accomplishes this task the use of specialized LDL receptors on its surface. Liver LDL receptors bind LDLs that were not taken up by other cells in their path through the bloodstream. High levels of LDLs are a signal to the liver to reduce the creation of VLDLs for release.

People with the genetic disease known as familial hypercholesterolemia, which manifests with dangerously high levels of LDLs, lack properly functioning LDL receptors on their liver cells.

In sufferers of this disease, the liver never gets the signal that the LDL levels are high. In fact, to the liver, it appears that all VLDLs and LDLs are being taken up by peripheral tissues, so it creates more VLDLs to attempt to boost levels. Untreated, the disease used to be fatal early, but newer drugs like the statins have significantly increased life spans of patients. Cellular needs for the contents of LDLs are directly linked to the levels of synthesis of LDL receptors on their membranes. As cells are needing more cholesterol, their synthesis of components for receptors goes up and it decreases as need diminishes.

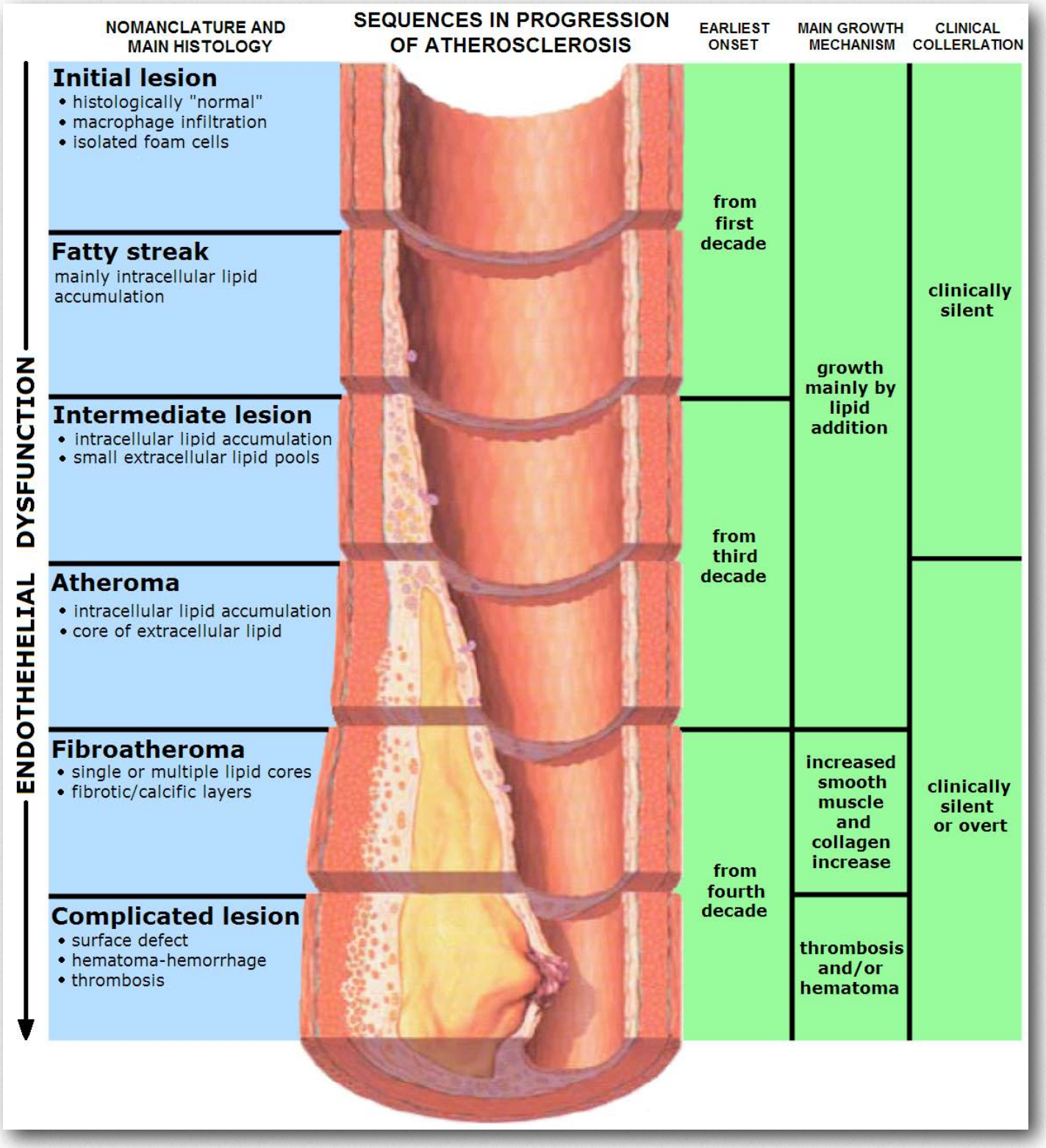


Figure 2.263 - Progression of atherosclerosis

Wikipedia

Good cholesterol / bad cholesterol

It is commonly accepted that “high cholesterol” levels are not healthy. This is due, at least indirectly, to the primary carriers of cholesterol, the LDLs. A primary function of the LDLs is to deliver cholesterol and other lipids directly into cells by receptor mediated endocytosis (Figure 2.237). High levels of LDLs, though, are correlated with formation of atherosclerotic plaques (Figure 2.263 & 2.264) and incidence of atherosclerosis, leading to the description of them as “bad cholesterol.” This is because when LDL levels are very high, plaque formation begins. It is thought that reactive oxygen species (higher in the blood of smokers) causes partial oxidation of fatty acid groups in the LDLs. When levels are high, they tend to accumulate in the extracellular matrix of the epithelial cells on the inside of the arteries. Macrophages of the immune system take up the damaged LDLs (including the cholesterol).

Since macrophages can’t control the amount of cholesterol they take up, cholesterol be-

gins to accumulate in them and they take on appearance that leads to their being described as "foam cells." With too much cholesterol, the foam cells, however, are doomed to die by the process of programmed cell death (apoptosis). Accumulation of these, along with scar tissue from inflammation result in formation of a plaque. Plaques can grow and block the flow of blood or pieces of them can break loose and plug smaller openings in the blood supply, ultimately leading to heart attack or stroke.

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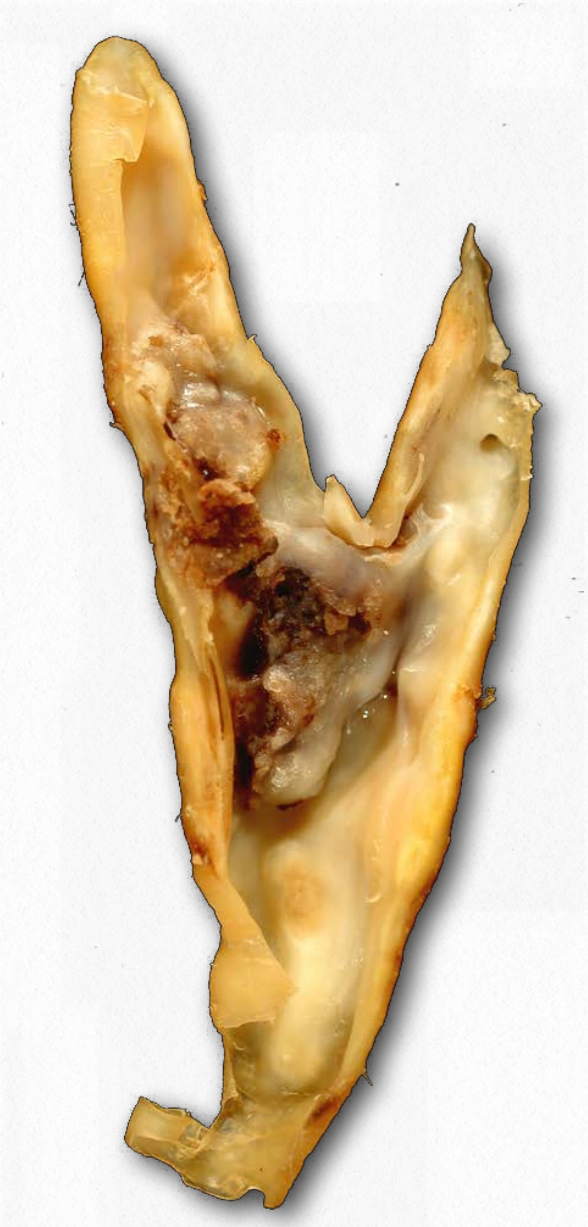

Figure 2.264 - Actual carotid artery plaque

Wikipedia

Good cholesterol

On the other hand, high levels of HDL are inversely correlated with atherosclerosis and arterial disease. Depleted HDLs are able to remove cholesterol from foam cells. This occurs as a result of contact between the ApoA-I protein of the HDL and a transport protein on the foam cell (ABC-G1). Another transport protein in the foam cell, ABCA-1 transports extra cholesterol from inside the cell to the plasma membrane where it is taken up into the HDL and returned to the liver or to LDLs by the reverse transport cholesterol pathway.

Deficiency of the ABCA-1 gene leads to Tangier disease. In this condition, HDLs are almost totally absent because they remain empty as a result of not being able to take up cholesterol from foam cells, so they are destroyed by the body.

ApoE and Alzheimer's disease

ApoE is a component of the chylomicrons and is also found in brain, macrophages, kidneys, and the spleen. In humans, it is found in three different alleles, E2, E3, and E4. The E4 allele (present at about 14% of the population) is associated with increased likelihood of contracting Alzheimer's disease. People heterozygous for the allele are 3 times as likely

to contract the disease and those homozygous for it are 15 times as likely to do so. It is not known why this gene or allele is linked to the disease. The three alleles differ only slightly in amino acid sequence, but the changes do cause notable structural differences. The E4 allele is associated with increased calcium ion levels and apoptosis after injury. Alzheimer's disease is associated with accumulation of aggregates of the β-amyloid peptide. ApoE does enhance the proteolytic breakdown of it and the E4 isoform is not as efficient in these reactions as the other isoforms.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Your Poor Veins

To the tune of "*You're So Vain*"

Metabolic Melodies Website HERE

Well I raced off to my doctor
Cause I was feelin' the twinges of pain
I was worried about my heart 'cause I
Was overweight once a-gain
She took one look at my profile and
Just shook her head and complained

"You gotta wake up and change all that junk you've been eating
Junk you've been eating. 'Cause
Your poor veins
Are plugged 'cause you are wolfin' the butter
And LDLs
Are makin' your heart go a-flutter
Flutter, Flutter"

She had warned me several months before
But I just ignored what was said
She told me, "You look like a heart attack"
"It's surprising that you're not dead"
I walked away in disbelief
And ate more bad food instead

I loaded oodles of cream in my tall Macchiatos
Tall Macchiatos and
LDLs
Went up as I was gulping 'em down my
LDLs
Just turned a smile right into a frown
A frown, a frown

I decided to make a change right there
The diet was merely step one
All the *trans* fats were banished from my food
And I started to jog just for fun
I had one foot in the grave when I
Discovered what I had done

I moved away from the edge of the doorstep of death to
Re-gaining my breath when my
HDLs
Increased since I was eating more smartly
HDLs
They lowered my cholesterol partly
Partly, partly

Well you know I'm feeling much better now
And my heart is surely relieved
A factor certainly is the unsaturates
Contained in my sunflower seeds
Yeah the fatty acids were the keys
Essential things that we need

Those fish oil capsules and o-mega threes cleaned
My ar-ter-ies with
HDLs
They're more than just the latest hot crazes
HDLs
They saved me so I'm singing their praises
Praises, Praises

Recording by Barbara and Neal Gladstone
Lyrics by Kevin Ahern

Prostaglandins!

To the tune of "*Oklahoma*!"

Metabolic Melodies Website HERE

Prossss-taglandins
The ei-co-sa-noids creating pain
Are the ones to blame - when you get inflamed
And ouch(!) - they hurt inside your brain

Prossss-taglandins
Every throb and ache gets magnified
If you hope to win, cyclo-oxygen's
Generation's got to be denied
The Vioxx has all been recalled
So go get yourself Tylenol-ed

And if you aaaaaaaaaaaache
Blame PGH synthaaaaaaaase!
We must complain that
You make the aches prostaglandins
Prostaglandin - D2, F1, G2, E2
Prostaglandin, it's you

Recording by Tim Karplus
Lyrics by Kevin Ahern

God Rest Ye Merry Dieters

To the tune of "*God Rest Ye Merry Gentlemen*"

Metabolic Melodies Website HERE

God rest ye merry dieters
With high cholesterol
Your chylomicrons all contain
Triacylglycerols
And move from lymph to capillaries
Where their progress stalls
Tha-anks lipo protein li-pase,
Protein lipase
O-oh thank you lipo protein li-pase

And after their fat goodies
Have been hydrolyzed away
The chylomicron remnants
Go along their merry way
The liver grabs them from the blood
And puts them all away
Just as we should do with Kenneth Lay, Kenneth Lay
O-oh just as we should do with Kenneth Lay (Enron scandal guy)

And when the liver gets a message
From the body's cells
It makes up little packages
We call VLDLs
They seem like chylomicrons, but turn
In to something else
Please don't become the LDLs, LDLs

O-oh please don't become the LDLs
For LDLs cause chaos
When their insides oxidize
The macrophages bind to them
And foam cells can arise
You'd better watch your diet
Or your blood flow will downsize
And that would not be very wise, very wise
No-oh that would not be very wise

So if you take some lessons from
This little comic bit
Your diet should be healthy
And you should try to stay fit
Eat greens and drink red wine but try
Not to overdo it
And your heart will never ever quit, want to quit
No, no your heart will never ever quit

Recording by Tim Karplus
Lyrics by Kevin Ahern

3

Membranes

"The greatest mistake you can make in your life is to be continually fearing you will make one."

-Elbert Hubbard

The membranes and surrounding tissues of cells and their organelles vary immensely in composition, not only in the lipids comprising their bilayers, but also of the protein gatekeepers and in the supporting structures, such as cell walls, which some cells, like our own, don't even have at all. In this chapter, we explore the structure and function of the cell's protective boundary, the membrane.

Membranes: Basic Concepts

Lipid bilayers

The protective membrane around cells contains many components, including cholesterol, proteins, glycolipids, glycerophospholipids, and sphingolipids. The last two of these will, when mixed vigorously with water, spontaneously form what is called a lipid bilayer (Figure 3.1), which serves as a protective boundary for the cell that is largely impermeable to the movement of most materials across it.

YouTube Lectures by Kevin HERE & HERE

With the notable exceptions of water, carbon dioxide, carbon monoxide, and oxygen, most polar/ionic require transport proteins to help them to efficiently navigate across the bilayer. The orderly movement of these compounds is critical for the cell to be able to 1) get food for energy; 2) export materials; 3) maintain osmotic balance; 4) create gradients for secondary transport; 5) provide electromotive force for nerve signaling; and 6) store energy in electrochemical gradients for ATP production (oxidative phos-

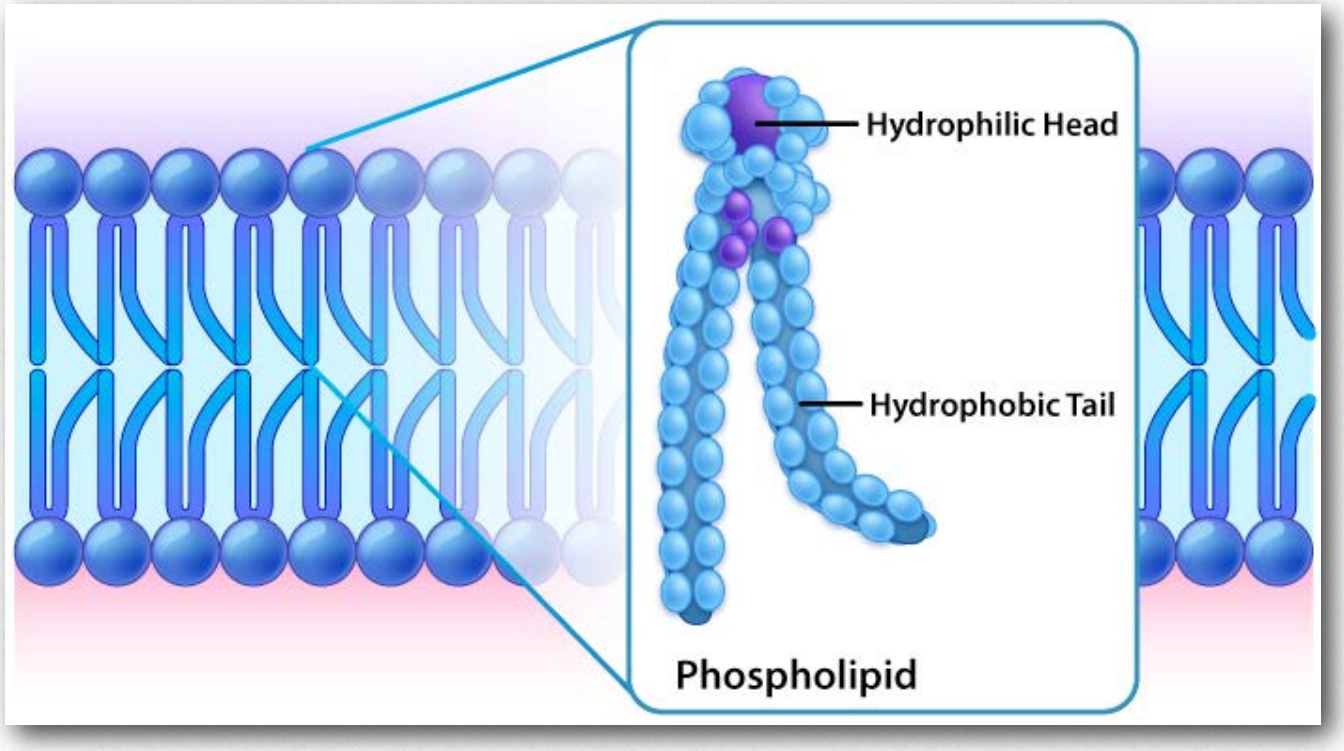

Figure 3.1 - Lipid bilayer closeup

Image by Aleia Kim

phorylation or photosynthesis). In some cases, energy is required to move the substances (active transport).

Facilitated diffusion

In other cases, no external energy is required and they move by diffusion through specific cellular channels. This is referred to as facilitated diffusion. Before we discuss movement of materials across membranes, it is appropriate we discuss the composition of cellular membranes.

Plasma membranes differ from cell walls both in the materials comprising them and in their flexibility. Cell walls will be covered near the end of this chapter (HERE).

Though some cells do not have cell walls (animal cells) and others do (bacteria, fungi, and plants), there is commonality among cells in that they all possess plasma membranes. There is also

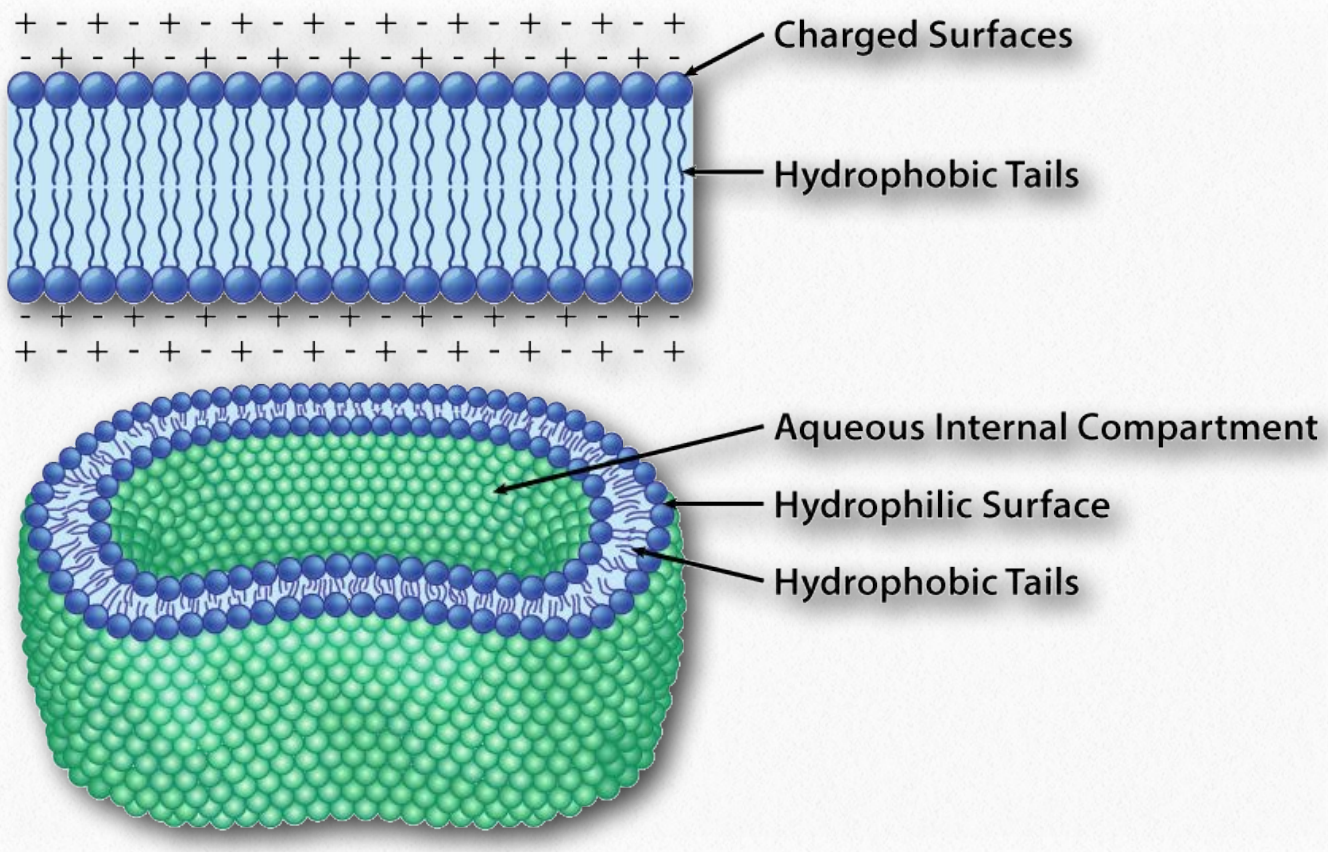

Figure 3.2 - Organization of the lipid bilayer

Image by Aleia Kim

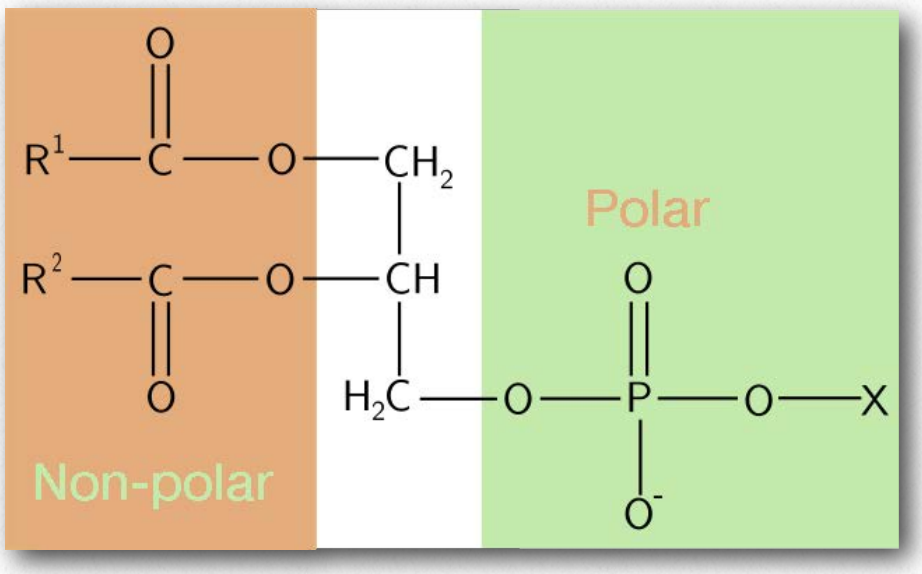

Figure 3.3 - Schematic diagram of a phosphatide

commonality in the components of the membranes, though the relative amount of constituents varies. Figures 3.1 and 3.2 illustrate the structure and environments of plasma membranes. All plasma membranes contain a significant amount of amphiphilic substances linked to fatty acids. These include the glycerophospholipids and the sphingolipids. The fatty acid(s) are labeled as hydrophobic tails in the figures.

Hydrophilic heads

The composition of the hydrophilic heads varies considerably. In glycerophospholipids, a phosphate is always present, of course, and it is often esterified to another substance to make a phosphatide (Figure 3.3). Common compounds linked to the phosphate (at the X position) include serine, ethanolamine, and choline. These vary in the their charges so in this way, the charge on the external or internal surface can be controlled. Cells tend to have more negative charges on the exterior half of the lipid bilayer (called the outer leaflet) and more positive charges on the interior half (inner leaflet).

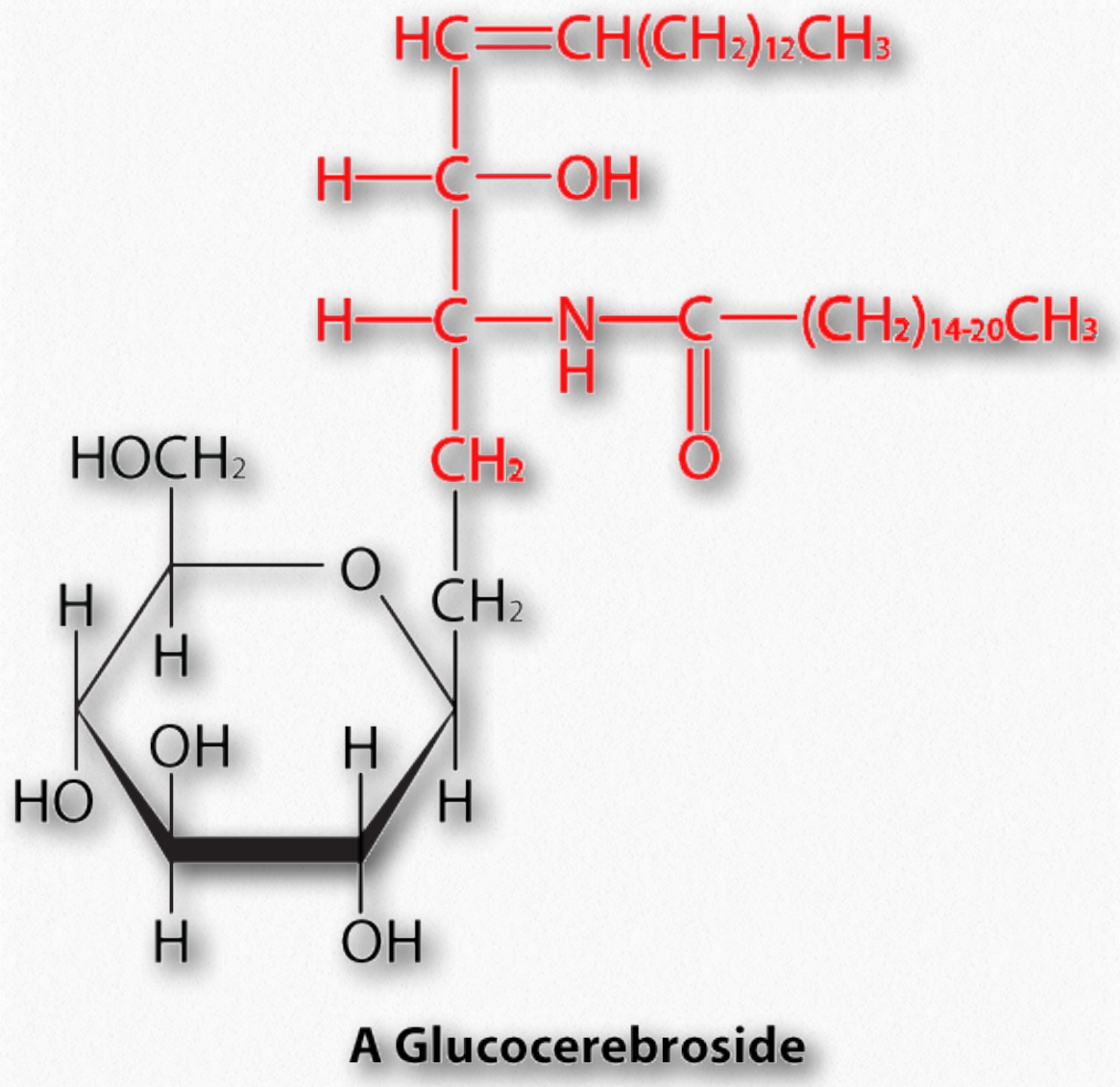

Figure 3.4 - A sphingolipid. Polar head in black. Non-polar tail in red

Image by Aleia Kim

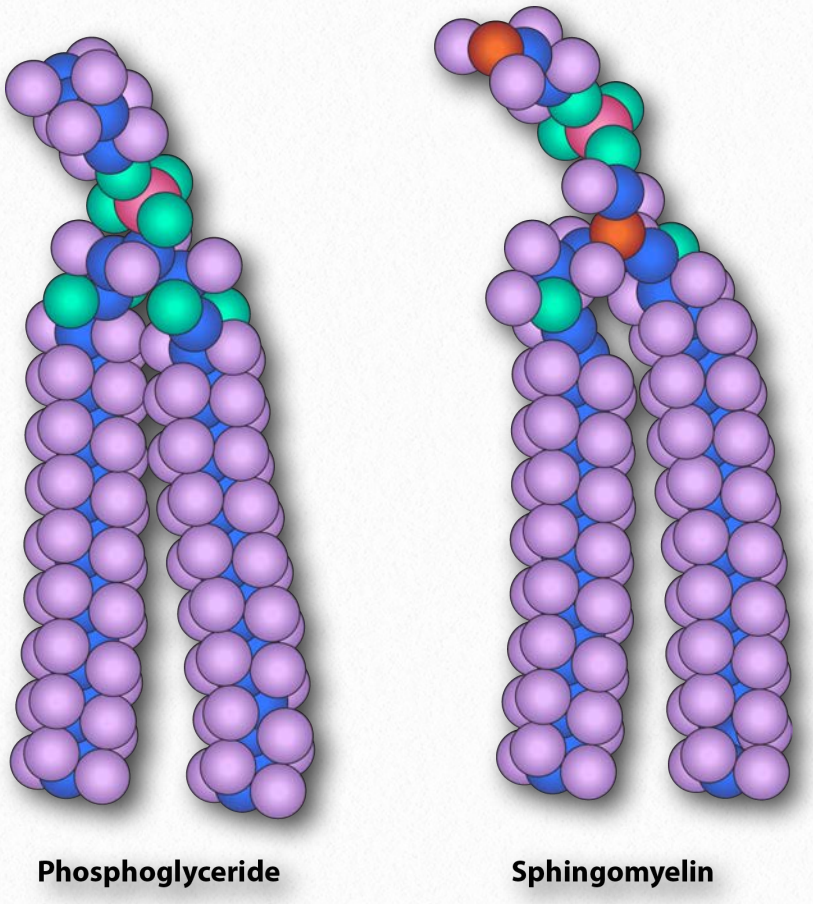

Figure 3.5 - Similarity of form between a phosphoglyceride and sphingomyelin

Image by Aleia Kim

Sphingolipids

In sphingolipids (Figure 3.4), the hydrophilic head can contain a phosphate linked to ethanolamine or choline and this describes the structure of sphingomyelin, an important component of neural membranes. Most sphingolipids lack the phosphate and have instead a hydrophilic head of a single sugar (cerebrosides) or a complex oligosaccharide (gangliosides).

Water exclusion

In each case, the glycerophospholipid or sphingolipid has one end that is polar and one end that is non-polar. As we saw in the organization of amino acids with hydrophobic side chains occurring preferentially on the inside of a folded protein to exclude water, so too do the non-polar portions of these amphiphilic molecules arrange themselves so as to exclude water. Remember that the cytoplasm of a cell is mostly water and the exterior of the cell is usually bathed in an aqueous layer. It therefore makes perfect sense that the polar portions of the membrane molecules arrange themselves as they do - polar parts outside interacting with water and non-polar parts in the middle of the bilayer avoiding/excluding water.

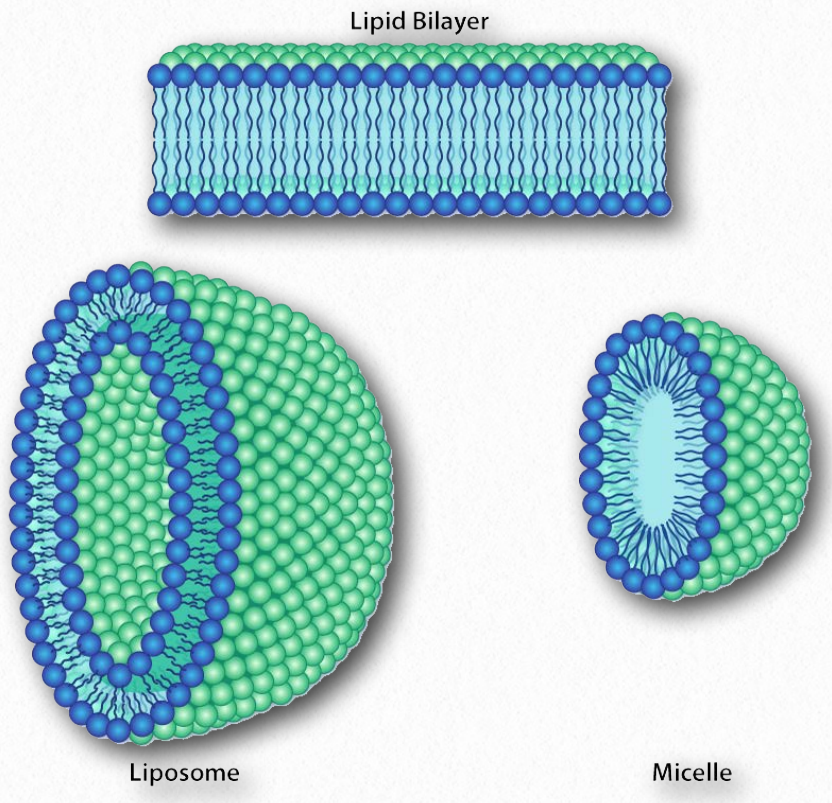

Figure 3.6 - Different lipid bilayer structures

Image by Aleia Kim

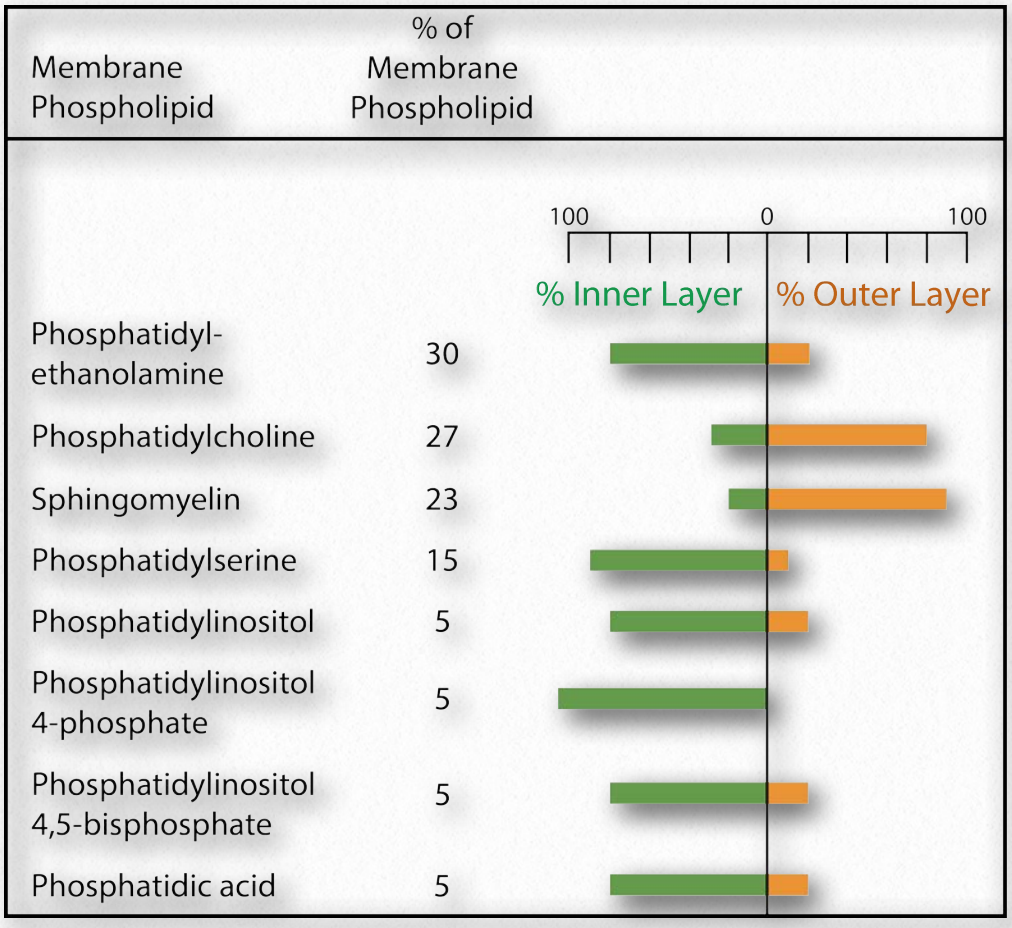

Figure 3.7 - Differential distribution of membrane lipids by inner and outer leaflet

Image by Pehr Jacobson

YouTube Lectures by Kevin HERE & HERE

Composition bias

The plasma membrane has distinct biases of composition relative to its inside and the outside (Figure 3.7). First, glycosylation (of lipids and proteins) has the sugar groups located almost exclusively on the outside of the cell, away from the cytoplasm (Figure 3.8). Among the membrane lipids, sphingolipids are much more commonly glycosylated than glycerophospholipids. In addition,

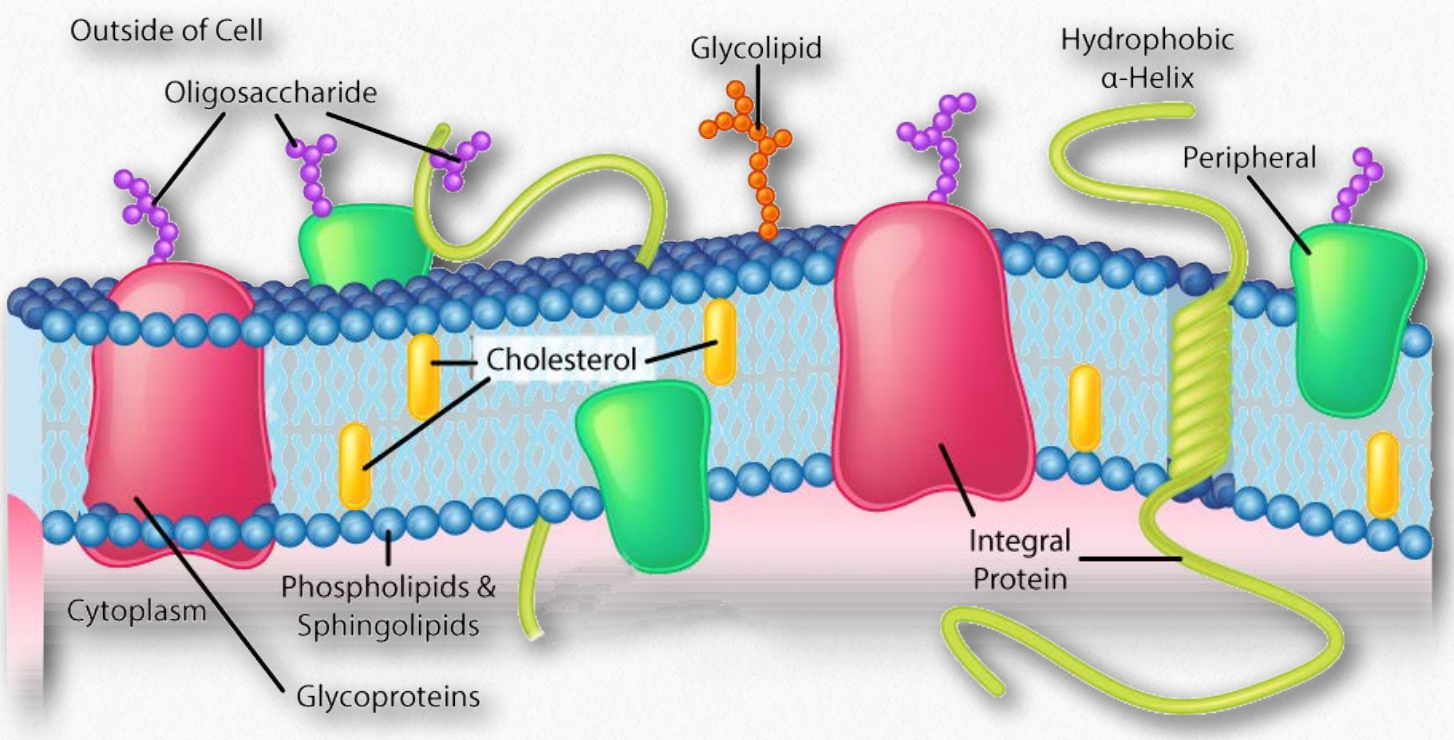

Figure 3.8 - Molecular organization of the lipid bilayer

Image by Aleia Kim

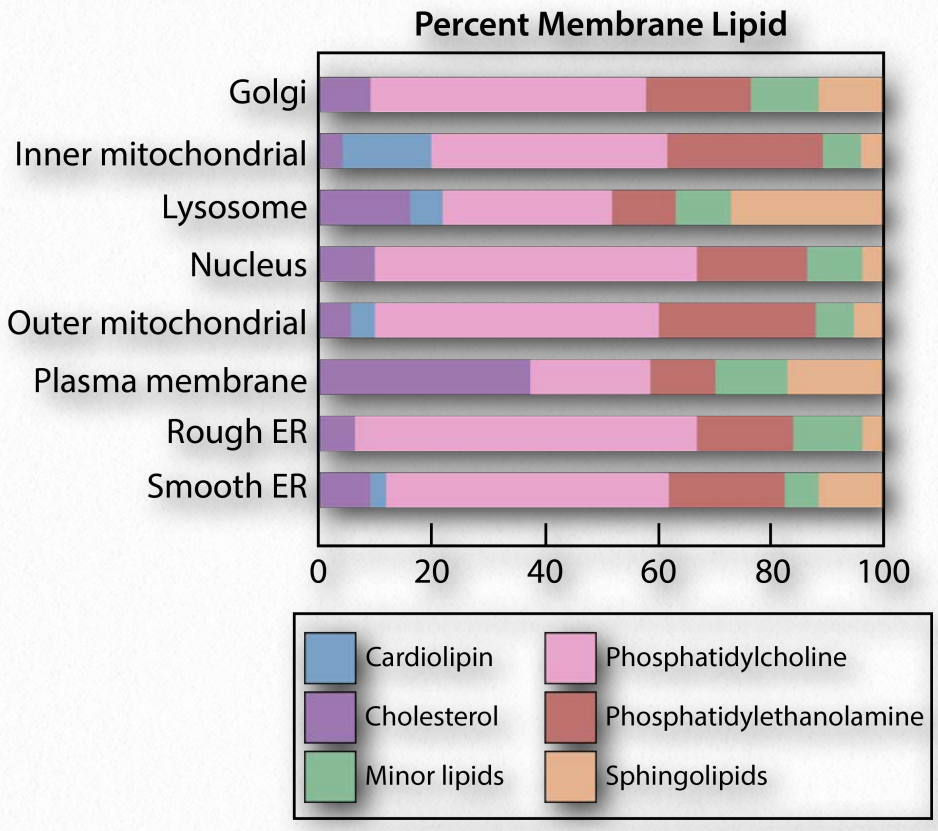

Figure 3.9 - Distribution of lipids in organelle membranes

Image by Pehr Jacobson

some of the glyerophospholipids are found preferentially on one side or the other (Figure 3.7). Phosphatidylserine and phosphatidylethanolamine are found preferentially within the inner leaflet of the plasma membrane, whereas phosphatidylcholine tends to be located on the outer leaflet. In the process of apoptosis, the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell. Sphingolipids are found preferentially in the plasma membrane and are almost completely absent from mitochondrial and endoplasmic reticulum membranes (Figure 3.9).

Organelle membranes

Bias of lipid composition also exists with respect to organelle membranes. The unusual diphosphodiglycerolipid known as cardiolipin, for example, is almost only found in mitochondrial membranes (see HERE) and like phosphatidylserine, its movement is an important step in apoptosis. In signaling, phosphatidylinositols play important roles providing second messengers upon being cleaved (see HERE).

Lateral diffusion

Movement of lipids within each leaflet of the lipid bilayer occurs readily and rapidly due to membrane fluidity. This type of movement is called lateral diffusion and can be measured by the technique called FRAP (Figure 3.10, see HERE also). In this method, a laser strikes and stains a section of the lipid bilayer of a cell, leaving a spot as shown in B. Over time, the stain diffuses out ultimately across the entire lipid bilayer, much like a drop of ink will diffuse throughout when added to a glass of water. A measurement of the rate of diffusion gives an indication of the fluidity of a membrane.

Transverse diffusion

While the movement in lateral diffusion occurs rapidly, movement of molecules from one leaflet over to the other leaflet occurs much more slowly. This type of molecular

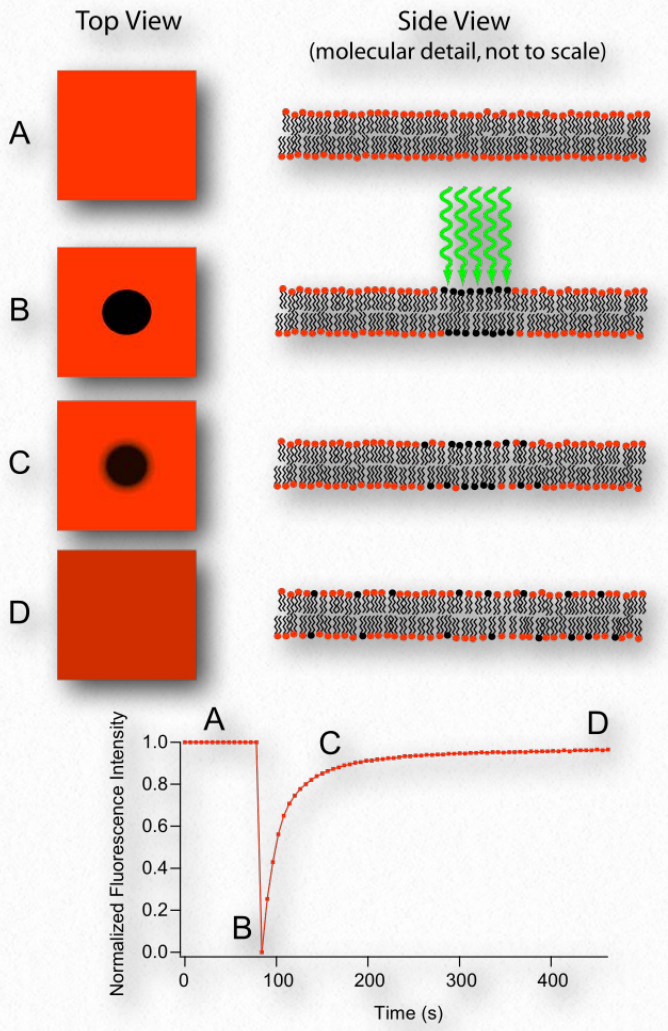

Figure 3.10 - Fluorescence recovery after photobleaching (FRAP)

movement is called transverse diffusion and is almost nonexistent in the absence of enzyme action. Remember that there is a bias of distribution of molecules between leaflets of the membrane, which means that something must be moving them.

There are three enzymes that catalyze movement of compounds in transverse diffusion. Flippases move membrane glycerophospholipids/ sphingolipids from outer leaflet to inner leaflet (cytoplasmic side) of cell. Floppases move membrane lipids in the opposite direction. Scramblases move in either direction.

Other components of lipid bilayer

Besides glycerophospholipids and sphingolipids, there are other materials commonly found in lipid bilayers of cellular membranes. Two important prominent ones are cholesterol (Figure 3.13) and proteins.

Besides serving as a metabolic precursor of steroid hormones and the bile acids, cholesterol's main role in cells is in the membranes. The flatness and hydrophobicity of the sterol rings allow cholesterol to interact with the nonpolar portions of the lipid bilayer while the hydroxyl group on the end can interact with the hydrophilic part.

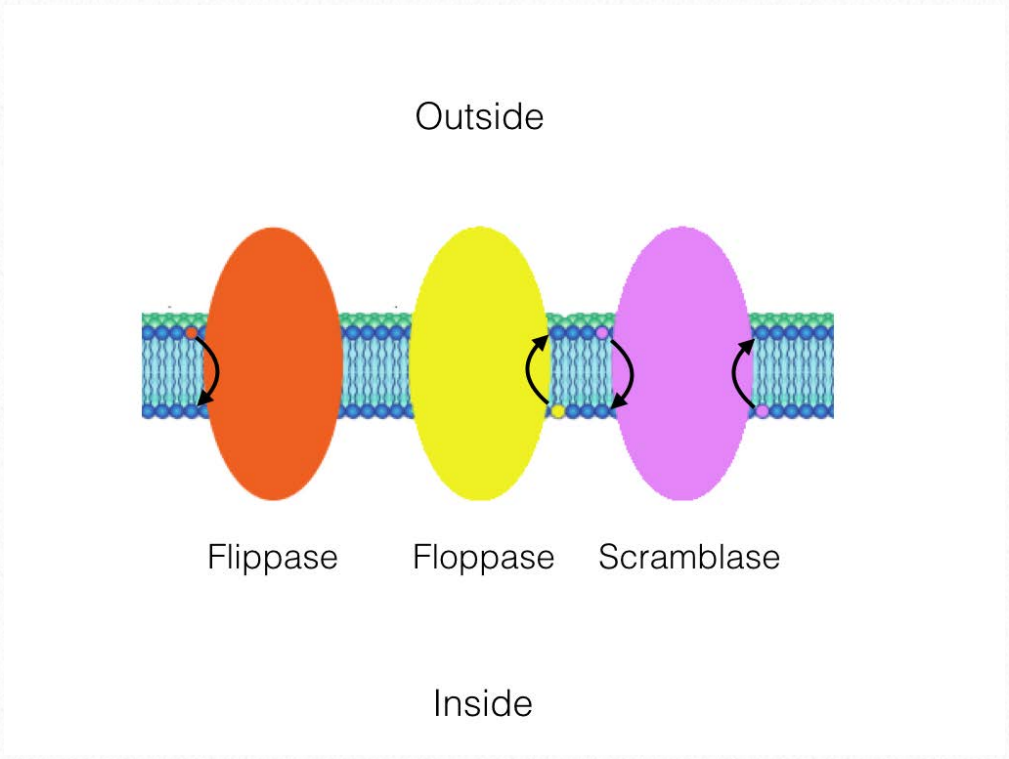

Figure 3.11 - Catalytic action of a flippase, a floppase, and a scramblase

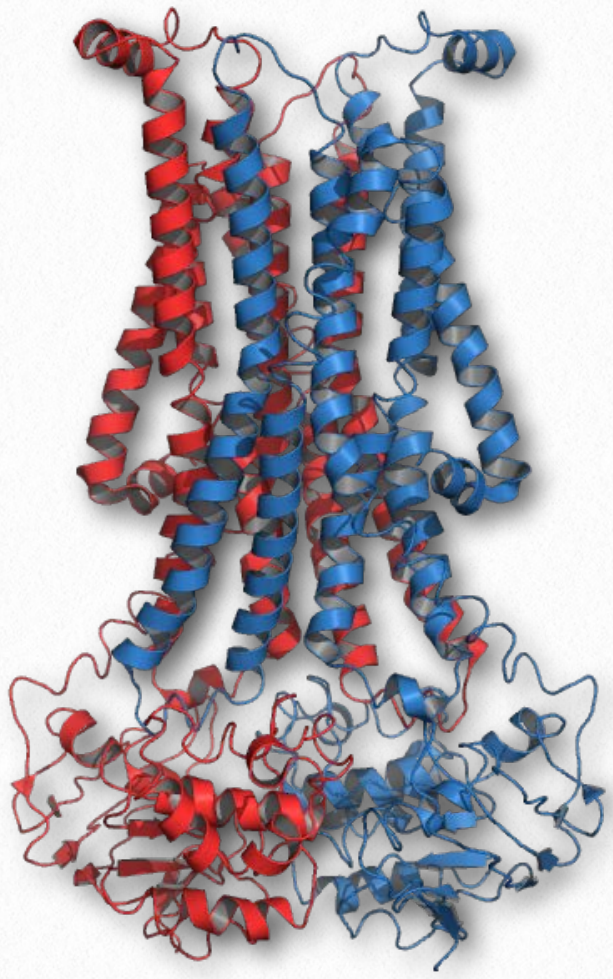

Figure 3.12 - **Structure of a flippase**

Wikipedia

Membrane fluidity

Cholesterol's function in the lipid bilayer is complex (Figure 3.13). It influences membrane fluidity. Figure 3.14 shows the phase transition for a membrane as it is heated, moving from a more "frozen" character to that of a more "fluid" one as the temperature rises. The mid-point of this transition, referred to as the T_m, is influenced by the fatty acid composition of the lipid bilayer compounds. Longer and more saturated fatty acids will favor higher T_m values, whereas unsaturation and short fatty acids will favor lower T_m values. It is for this reason that fish, which live in cool environments,

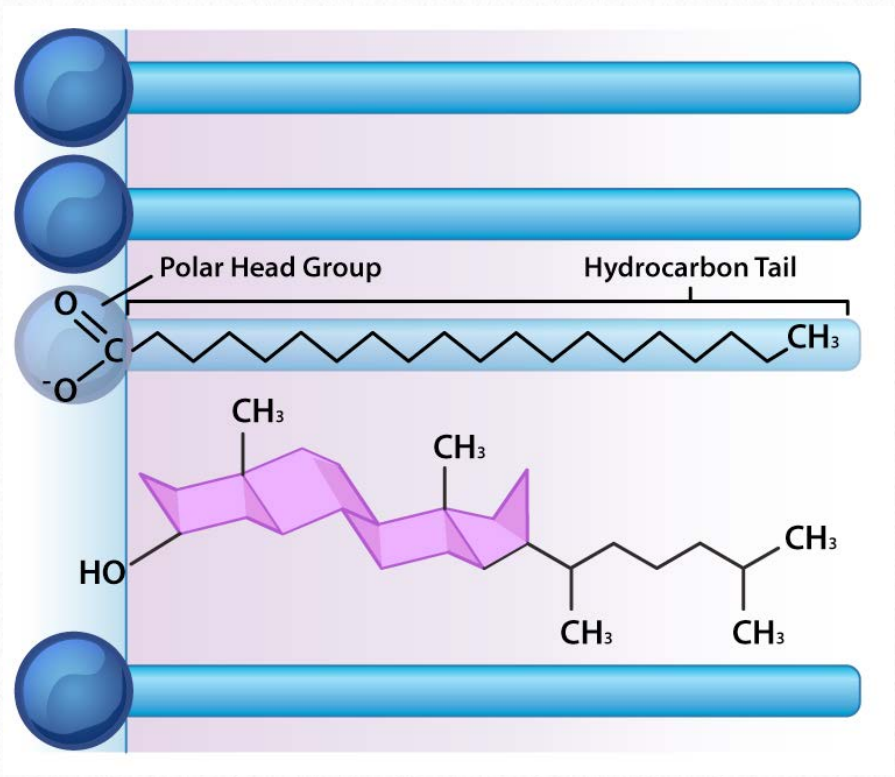

Figure 3.13 - **Cholesterol in the lipid bilayer**

Image by Aleia Kim

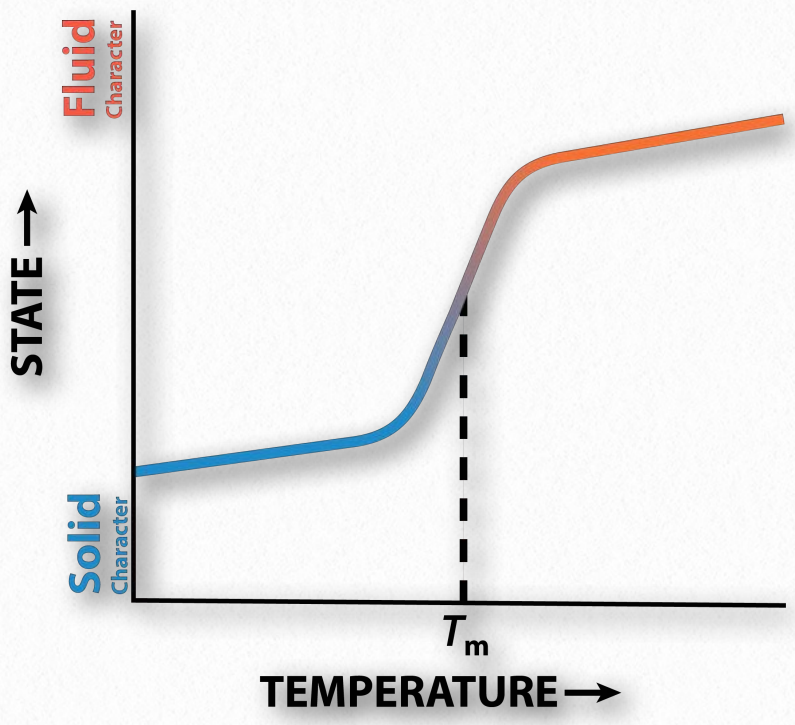

Figure 3.14 - **Membrane transition temperature**

Image by Aleia Kim

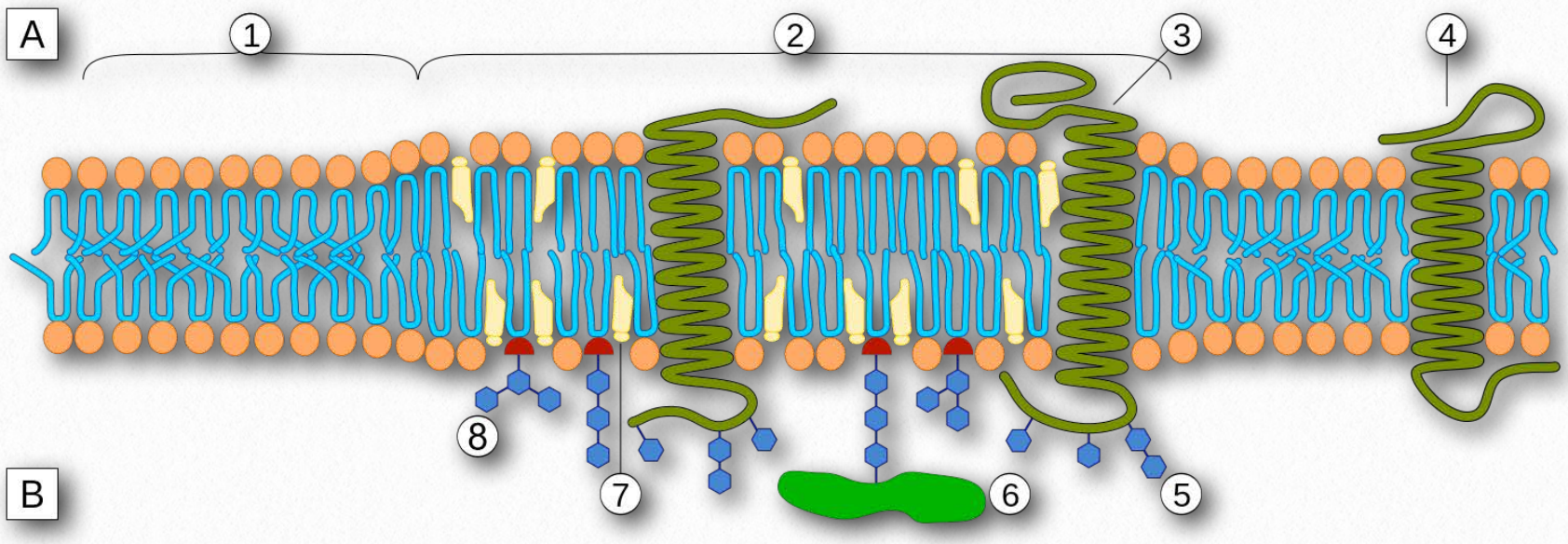

Figure 3.15 - A lipid raft - 1 = Non-raft membrane / 2 = Lipid raft / 3 = Lipid raft associated transmembrane protein / 4 = Non-raft membrane protein / 5 = Glycosylation modifications (on glycoproteins and glycolipids) / 6 = GPI-anchored protein / 7 = Cholesterol / 8 = Glycolipid

have a higher level of unsaturated fatty acids in them - to use to make membrane lipids that will remain fluid at ocean temperatures. Interestingly, cholesterol does not change the T_m value, but instead widens the transition range between frozen and fluid forms of the membrane, allowing it to have a wider range of fluidity.

Lipid rafts

Cholesterol is also abundantly found in membrane structures called lipid rafts. Depicted in Figure 3.15, lipid rafts are organized structures within the membrane typically containing signaling molecules and other integral membrane proteins. Lipid rafts affect membrane fluidity, neurotransmission, and trafficking of receptors and membrane proteins.

YouTube Lectures by Kevin HERE & HERE

Features

Distinguishing features of the rafts is that they are more ordered than the bilayers surrounding them, containing more saturated fatty acids (tighter packing and less disorganization, as a result) and up to 5 times as much cholesterol. They also are relatively rich in sphingolipids, with as much as 50% greater quantities of sphingomyelin than surrounding areas of the bilayer. The higher concentration of cholesterol in the rafts may be due to its greater ability to associate with sphingolipids (Figure 3.16). Some groups, such as prenylated proteins, like RAS, may be excluded from lipid rafts.

Lipid rafts may provide concentrating platforms after individual protein receptors bind to ligands in signaling. After receptor activation takes place at a lipid raft, the signaling

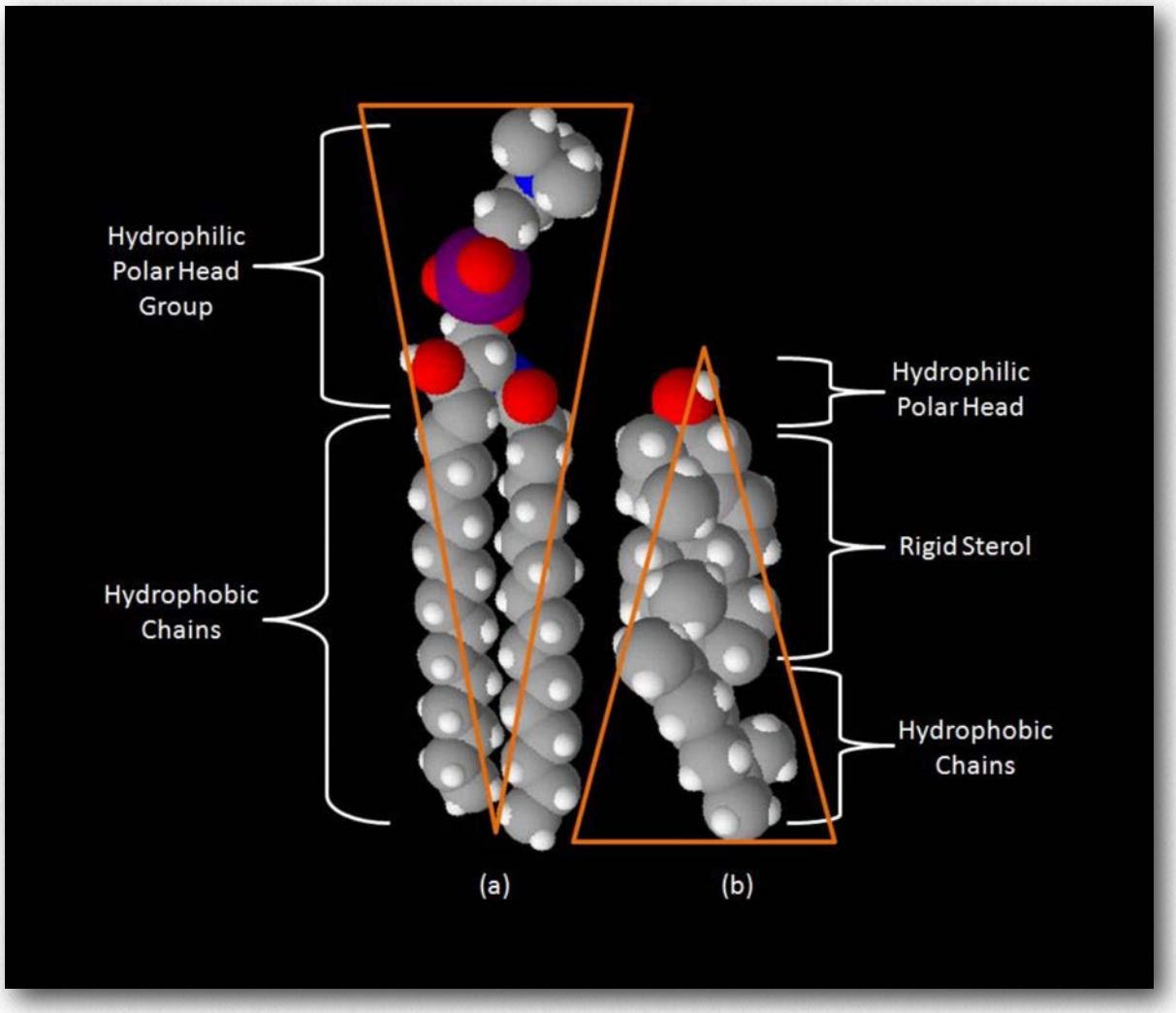

Figure 3.16 - A sphingolipid (left) associating with cholesterol (right)

complex would provide protection from non-raft enzymes that could inactivate the signal. For example, a common feature of signaling systems is phosphorylation, so lipid rafts might provide protection against dephosphorylation by enzymes called phosphatases. Lipid rafts appear to be involved in many signal transduction processes, such as T cell antigen receptor signaling, B cell antigen receptor signaling, EGF receptor signaling, immunoglobulin E signaling, insulin receptor signaling and others. For more on signaling, see HERE.

Barrier

Transport of materials across membranes is essential for a cell to exist. The lipid bilayer is an effective barrier to the entry of most molecules and without a means of allowing food molecules to enter a cell, it would die. The primary molecules that move freely across the lipid bilayer are small, uncharged ones, such as H_2O, CO_2, CO, and O_2, so larger molecules, like glucose, that the cell needs for energy, would be effectively excluded if there were not proteins to facilitate its movement across the membrane.

Figure 3.17 depicts the barrier that the lipid bilayer provides to movement across it and the pressures (ionic attraction, in this case) that can affect movement. Potential energy from charge and concentration differences are harvested by cells for purposes that include synthesis of ATP, and moving materials against a concentration gradient in a process called active transport.

Membrane proteins

Proteins in a lipid bilayer can vary in quantity enormously, depending on the mem-

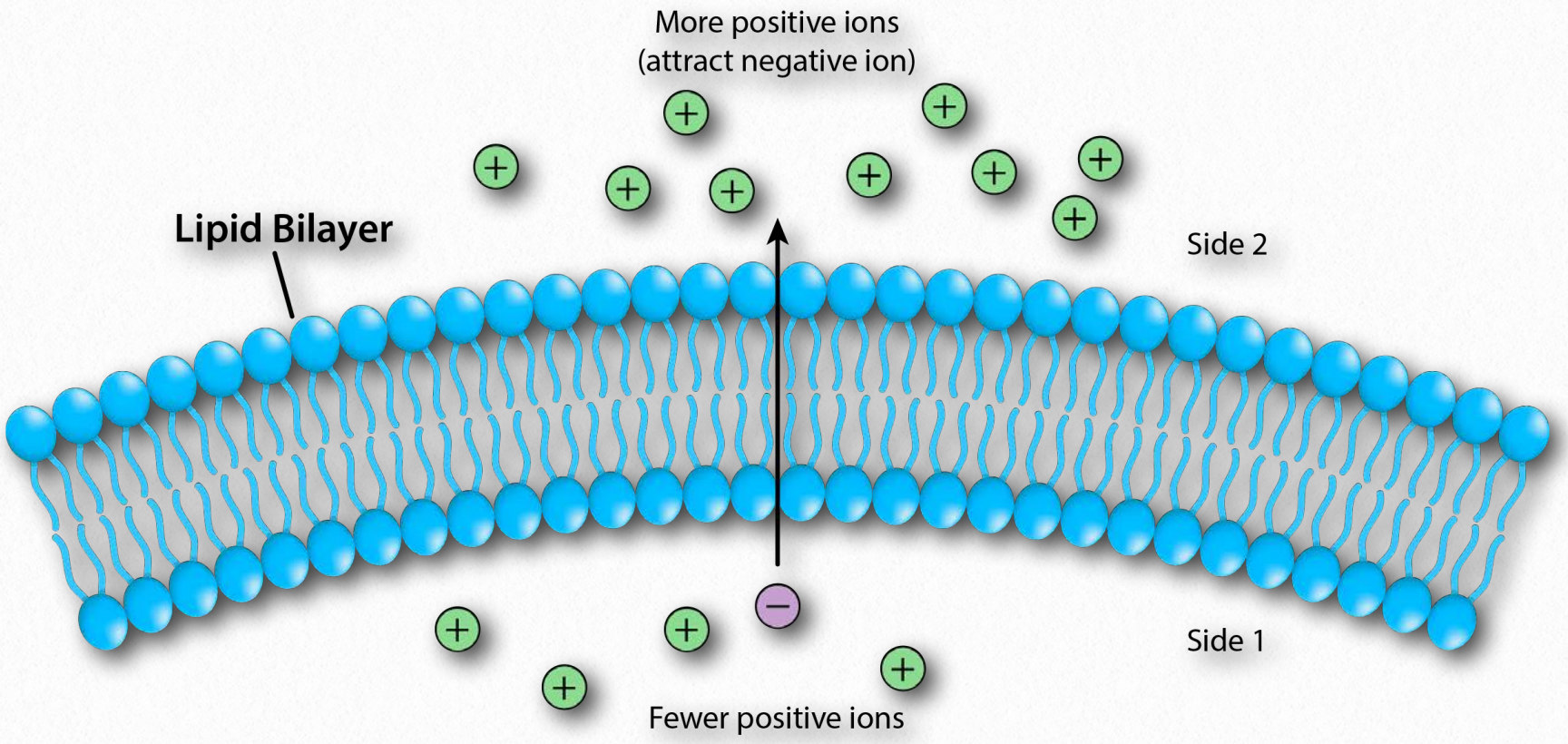

Figure 3.17 - The lipid bilayer as a barrier

Image by Pehr Jacobson

brane. Protein content by weight of various membranes typically ranges between 30 and 75% by weight. Some mitochondrial membranes can have up to 90% protein. Proteins linked to and associated with membranes come in several types.

Transmembrane proteins

Transmembrane proteins are integral membrane proteins that completely span from one side of a biological membrane to the other and are firmly embedded in the membrane (Figure 3.18). Transmembrane proteins can function as docking sites for attachment (to the extracellular matrix, for example), as receptors in the cellular signaling system, or facilitate the specific

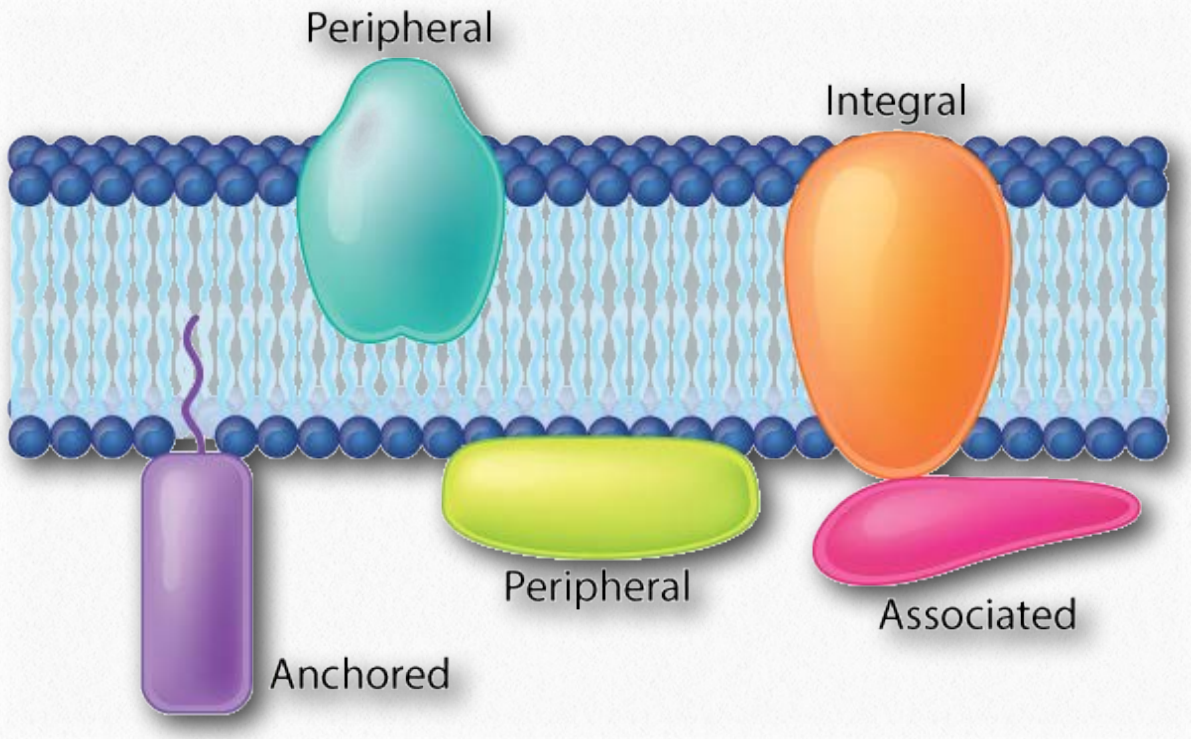

Figure 3.18 - Membrane protein types

Image by Aleia Kim

transport of molecules into or out of the cell.

Example of integrated/transmembrane proteins include those involved in transport (e.g., Na+/K+ ATPase), ion channels (e.g., potassium channel of nerve cells) and signal transduction across the lipid bilayer (e.g., G-Protein Coupled Receptors).

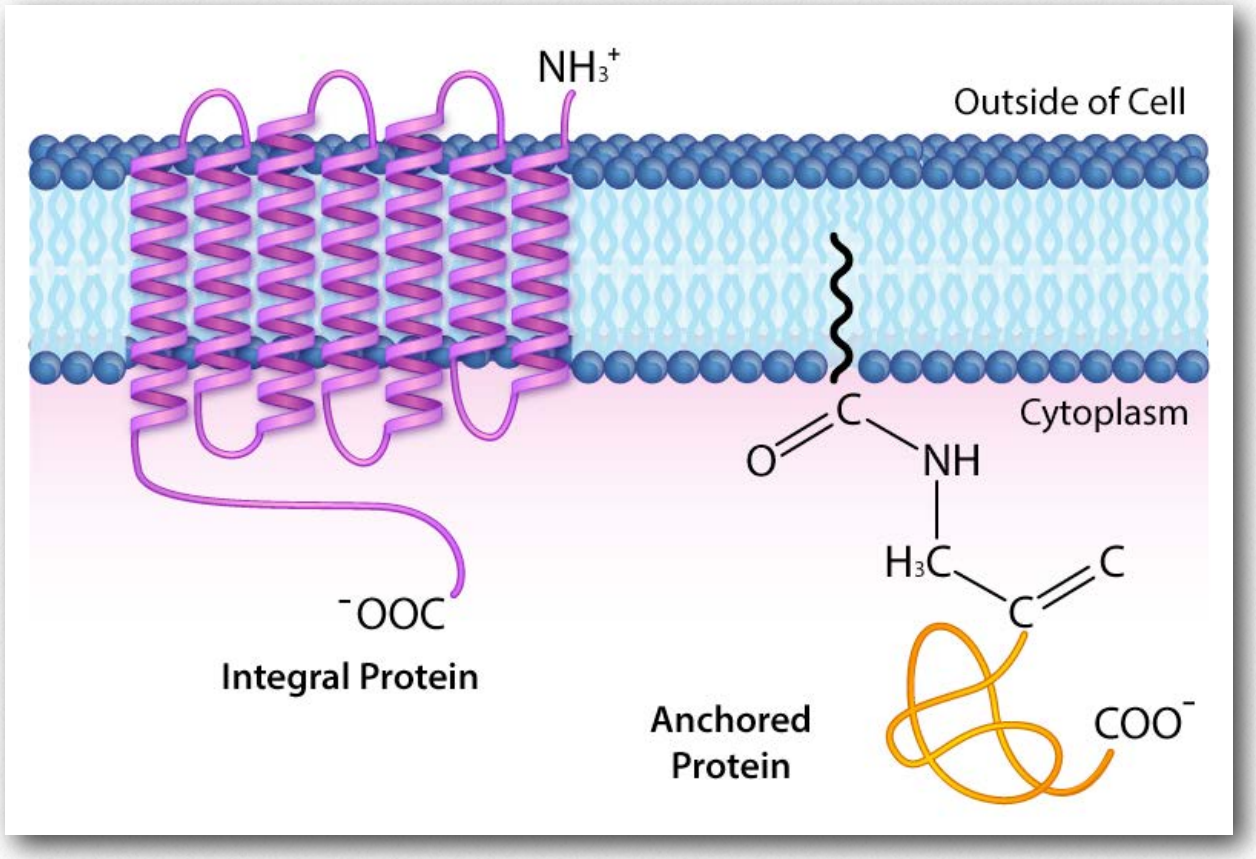

Figure 3.19 - Integral and anchored proteins

Image by Aleia Kim

Peripheral membrane proteins interact with part of the bilayer (usually does not involve hydrophobic interactions), but do not project through it. A good example is phospholipase A_2, which cleaves fatty acids from glycerophospholipids in membranes. Associated membrane proteins typically do not have external hydrophobic regions, so they cannot embed in a portion of the lipid bilayer, but are found near them. Such association may arise as a result of interaction with other proteins or molecules in the lipid bilayer. A good example is ribonuclease.

Anchored membrane proteins

Anchored membrane proteins are not themselves embedded in the lipid bilayer, but instead are attached to a molecule (typically a fatty acid) that is embedded in the membrane (Figure 3.19). The oncogene family of proteins known as ras are good examples. These proteins are anchored to the lipid bilayer by attachment to non-polar farnesyl groups catalyzed by the enzyme farnesyltransferase.

Finer classification

A more detailed classification scheme further categorizes the integral and anchored proteins into six different types (Figure 3.20). Type I and Type II have only one portion of the protein pass through the membrane. They differ in the orientation of the amine and carboxyl end with respect to inside/outside. Type I transmembrane proteins have the amino terminus on the outside and carboxy terminus on the inside, whereas Type II pro-

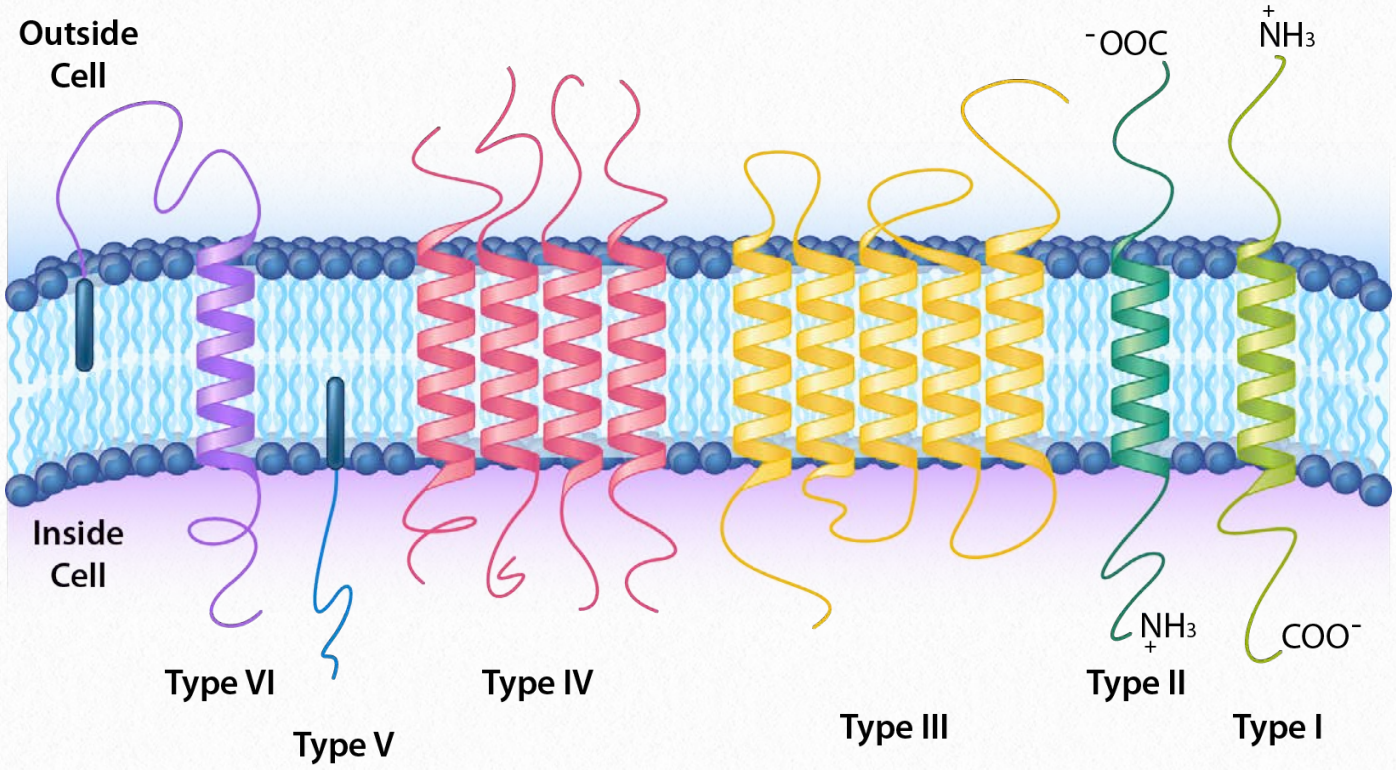

Figure 3.20 Types of integral and anchored membrane proteins

Image by Aleia Kim

teins have this reversed. Type III proteins are a single polypeptide chain that has multiple regions of it cross back and forth across the membrane, often to form a channel. Type IV is a multi-polypeptide protein which has multiple crossings of the membrane. Type V transmembrane proteins do not have a part of them that crosses the membrane, but they are anchored to the membrane by a lipid (such as a fatty acid) embedded in the lipid bilayer. Type VI transmembrane proteins both have a portion of them that crosses the membrane and they are attached to a lipid embedded in the lipid bilayer.

Blood types

Cells have hundreds-thousands of membrane proteins and the protein composition of a membrane varies with its function and location. Glycoproteins embedded in membranes play important roles in cellular identification. Blood types, for example, differ from each other in the structure of the carbohydrate chains projecting out from the surface of the glycoprotein in their membranes (Figure 3.21).

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Osmotic pressure

Membranes provide barriers/boundaries for most molecules, but the permeability of water across a lipid bilayer creates a variable that must be considered. The variable here is osmotic pressure. Osmotic pressure (loosely) refers to the tendency of a solution to take in water by the process of osmosis. In Figure 3.22, one can see a visual representation of the concept of the pressure.

A U-shaped tube has at its bottom a semi-permeable membrane. Water can pass through the membrane, but sugar molecules ($C_6H_{12}O_6$) cannot. On the left side, sugar is added creating a concentration difference be-

	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies in Plasma	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in Red Blood Cell	A antigen	B antigen	A and B antigens	None

Figure 3.21 - Blood types arise from cell surface glycoproteins

tween the right and left chambers. Water diffuses across the membrane from right to left in an attempt to equalize the concentrations, causing the level of the right side to decrease and the left side to increase. The pressure resulting from the differences in height is felt at the membrane.

Equalizing concentrations

The liquid on the right does not completely move to the left, though, as might be expected if the only force involved is equalizing the concentration of sugar across the membrane (no sugar on right = no water). Instead, an equilibrium of sorts of water levels is reached even though the concentrations don't equal out. The pressure existing at the membrane then from the differences in level corresponds to the osmotic pressure of the mixture. The osmotic pressure of a solution is the pressure difference needed to halt the flow of solvent across a semipermeable membrane. Osmotic pressure can also be thought of as the pressure required to counter osmosis. The osmotic pres-

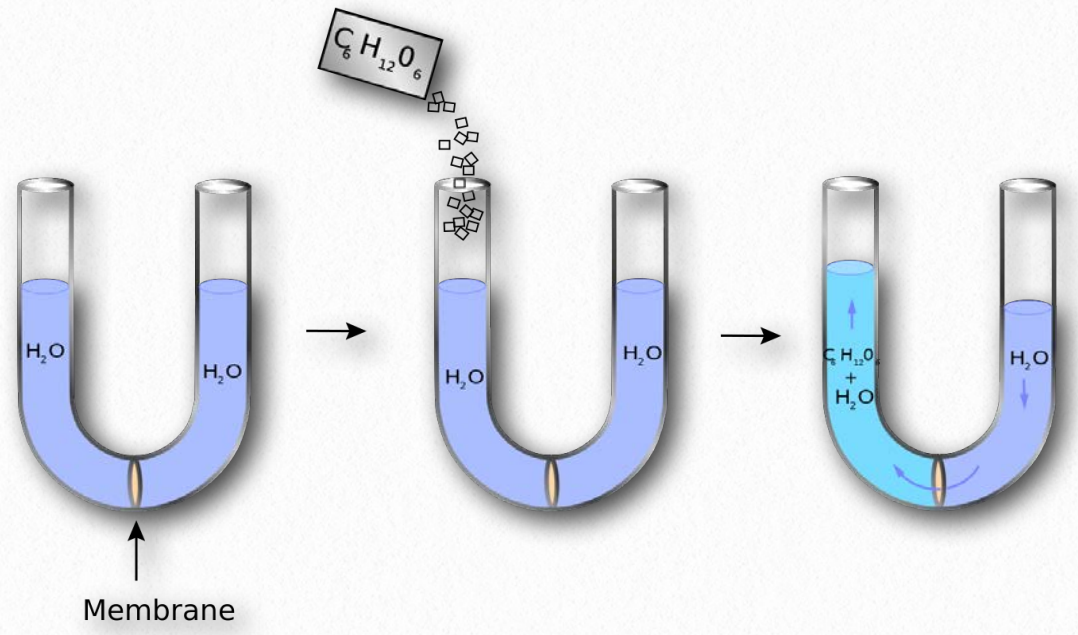

Figure 3.22 - Osmotic pressure. Water diffuses leftwards to try to equalize the solute concentration. The pressure realized at the membrane in the right figure is the osmotic pressure

sure of a dilute solution mathematically behaves like the ideal gas law

$$P_{osmotic} = nRT/V$$

where n is the number of moles, R is the gas constant, T is the temperature in Kelvin, and V is the volume.

It is more convenient in solutions to work with molarity, so

$$P_{osmotic} = MR^*T$$

where M is the molarity of the dissolved molecules, R* is the gas constant expressed in (L atm)/(K mol), and T is the temperature.

The Greek letter Π is used to refer to the $P_{osmotic}$ term, so

$$\Pi = MR^*T$$

Remember when calculating the molarity to include the molarity of each particle. For example, when one dissolves sucrose in solution, it does not split into smaller particles, so $Molarity_{Particles} = Molarity_{Sucrose}$.

However, for salts, like KOH, which forms two ions in solution (K^+ and OH^-),

$Molarity_{Particles} = 2^* Molarity_{KOH}$.

Significant consideration

Osmotic pressure is a significant consideration for cells. Consider the fact that water can move freely across cellular membranes, but most of the contents of the cell, such as proteins, DNA, ions, sugars, etc., cannot. Second, the concentration of these compounds inside the cell is different than the concentration of them outside of the cell. Third, since water can move through the lipid bilayer, it will tend to move in the direction that will tend to equalize solute

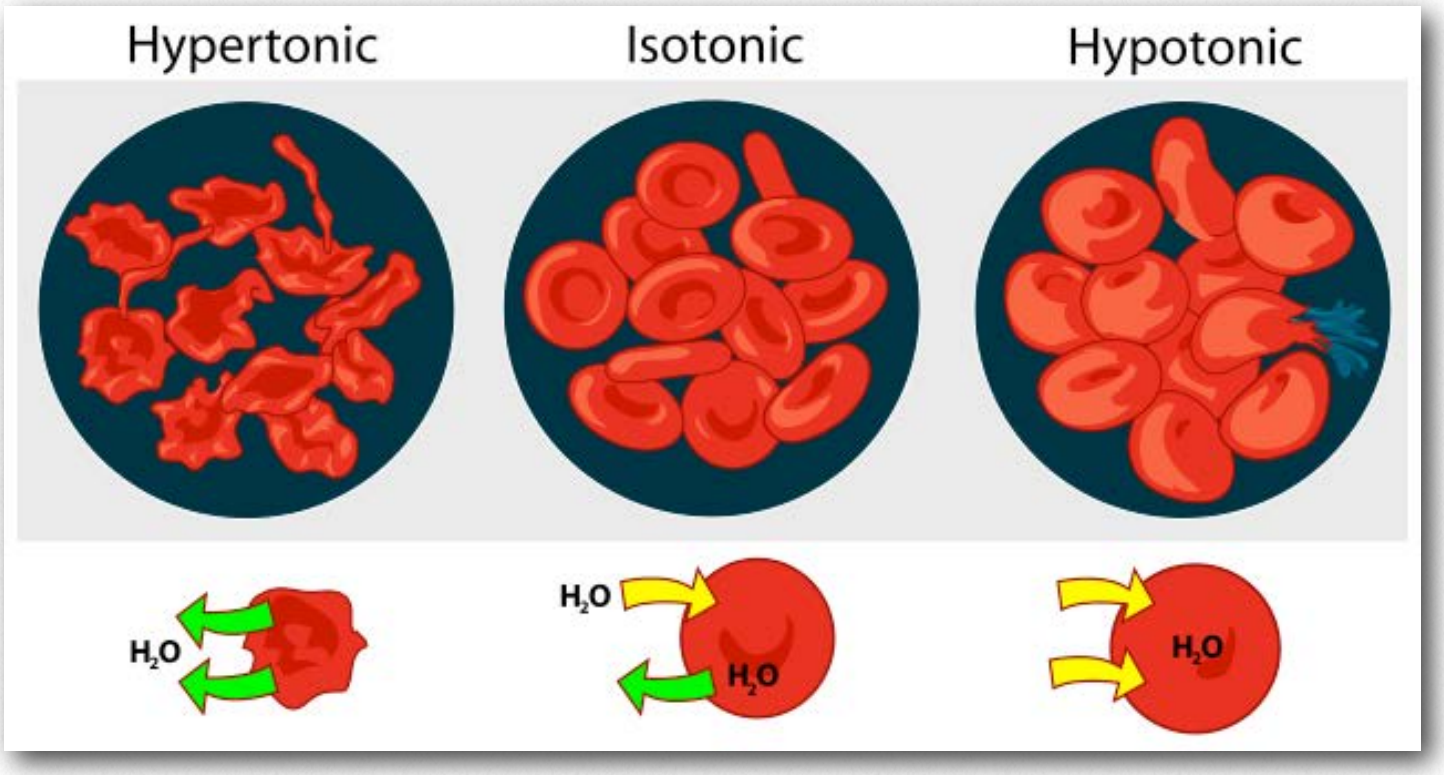

Figure 3.23 - The effect of three different osmotic conditions on red blood cells

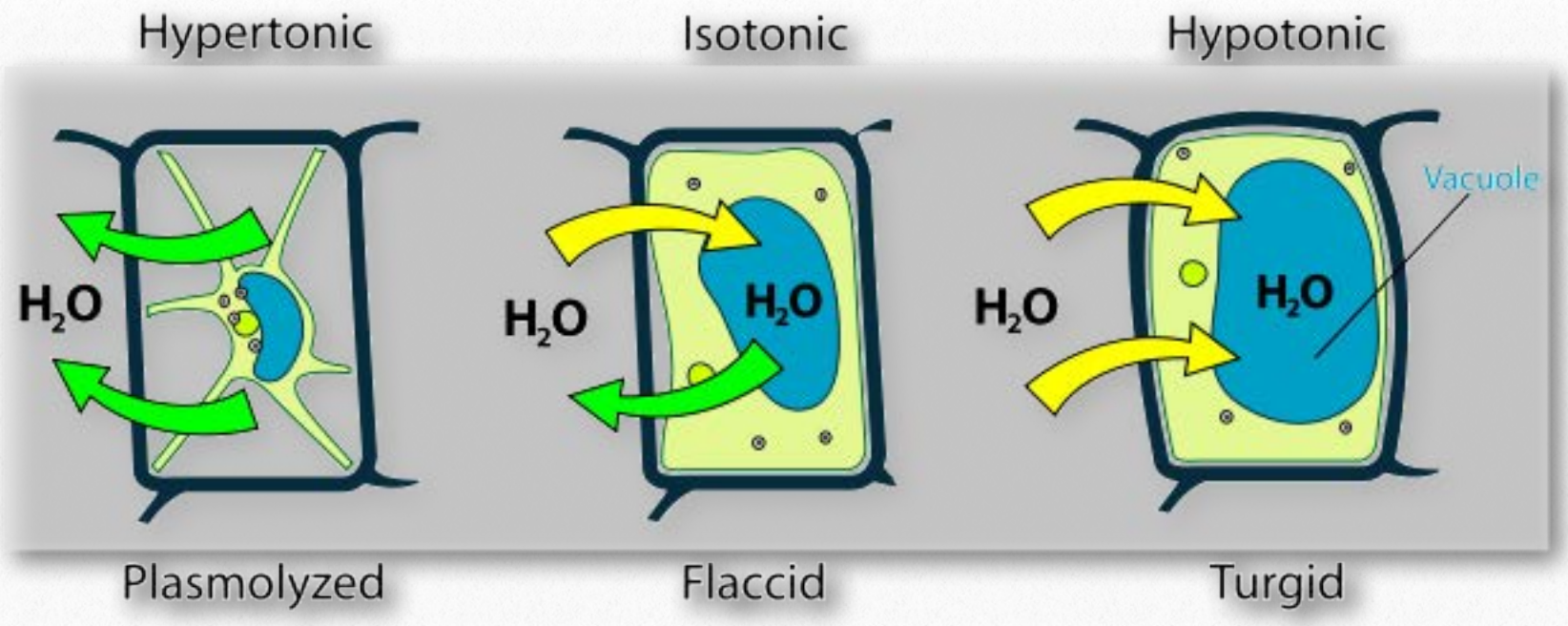

Figure 3.24 - The plant cell wall protects the plasma membrane from rupture in hypotonic conditions

concentrations on either side of the membrane.

Hypotonic, hypertonic, isotonic

YouTube Lectures by Kevin HERE & HERE

We consider three situations (Figure 3.23). First, if the concentration of solutes is greater inside the cell than outside, water will tend to move into the cell, causing the cell to swell. This circumstance is called hypotonic. Conversely, if the solute concentration is greater outside the cell than inside of it, water will exit the cell and the cell with shrink. This is a hypertonic situation. Last, if the concentrations of solutes into and outside of the cell is equal, this is called an isotonic solution. Here, no movement of water occurs across the cell membrane and the cell retains its size.

If the osmotic pressure is greater than the forces holding together a cellular membrane, the cell will rupture. Because of this, some cells have built in defenses to prevent problems. Plant cells, for example have a fairly rigid cell wall that resists expansion in hypotonic solutions (Figure 3.24). Bacteria also have a cell wall that provides protection.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

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Fatty Acids in Our Cells

To the tune of "*Halls of Montezuma*"

Metabolic Melodies Website HERE

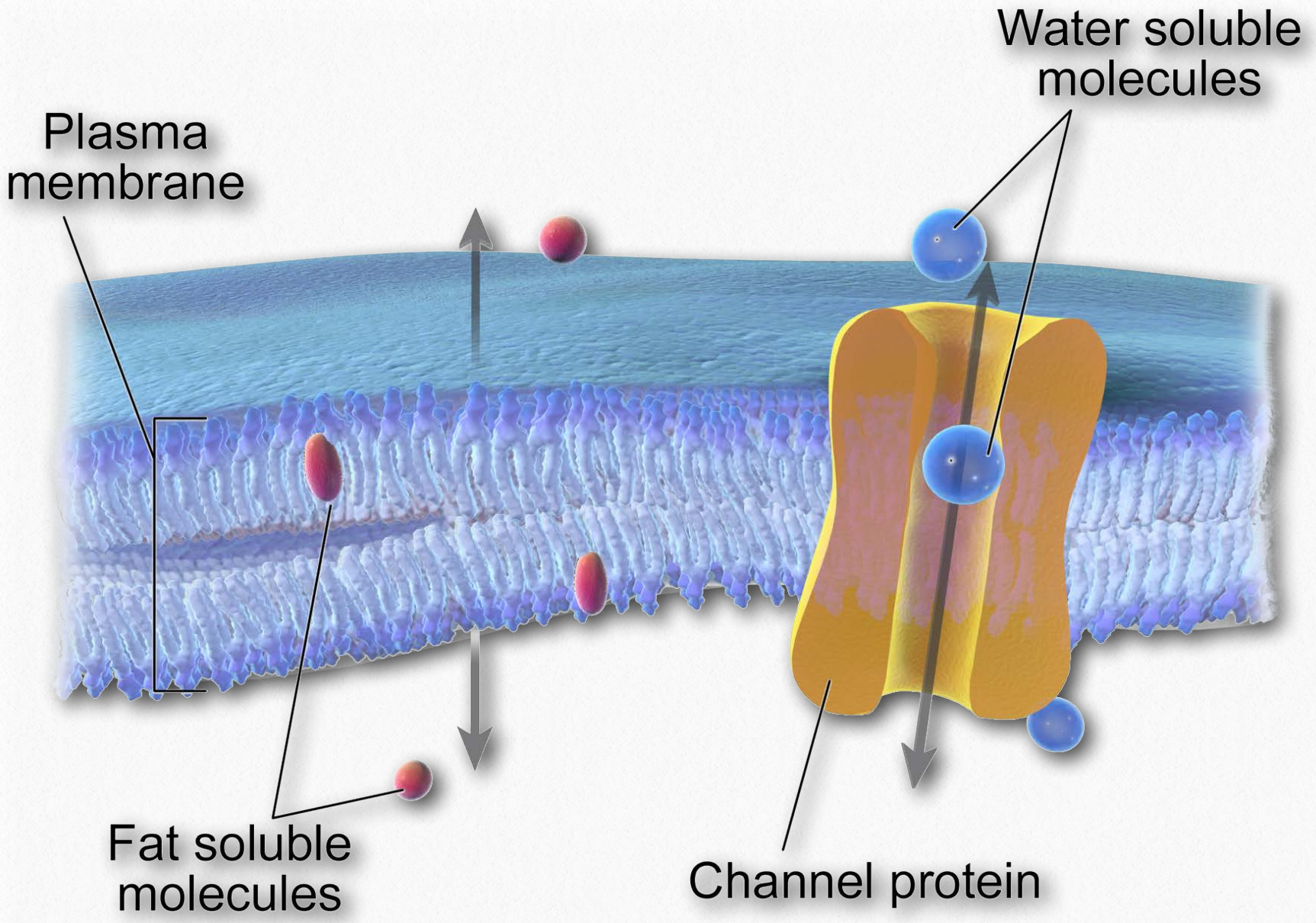
From the fatty acids in our cells
To the lipids in our brains
We are made of biochemicals
Built in metabolic chains
Using glycolytic ATP
And electron energy
We can synthesize most everything
With the help of Delta G

A cell will tend to pump out sodium
But potassium it imports
It accomplishes this magic with
ATPase antiports
Our bilayer lipid membranes
Protect the cells' insides
Partly made of sphingolipids
We know as gangliosides

When it comes to regulation
The little cell has got it made
It phosphorylates a lot of things
With its own kinase cascade
Stimulated at a hormone site
Metabolic yang and yin
That's turned on by epinephrine

Recording by Tim Karplus
Lyrics by Kevin Ahern

Membranes: Transport



Wikipedia

Movement of materials across membranes

As noted earlier, it is essential for cells to be able to uptake nutrients. This function along with movement of ions and other substances is provided by proteins/protein complexes that are highly specific for the compounds they move.

Selective movement of ions by membrane proteins and the ions' extremely low permeability across the lipid bilayer are important for helping to maintain the osmotic balance of the cell and also for providing for the most important mechanism for it to make ATP - the process of oxidative phosphorylation.

YouTube Lectures by Kevin
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Terminology

A protein involved in moving only one molecule across a membrane is called a uniport (Figure 3.25). Proteins that move two molecules in the same direction across the membrane are called symports (also called syn-

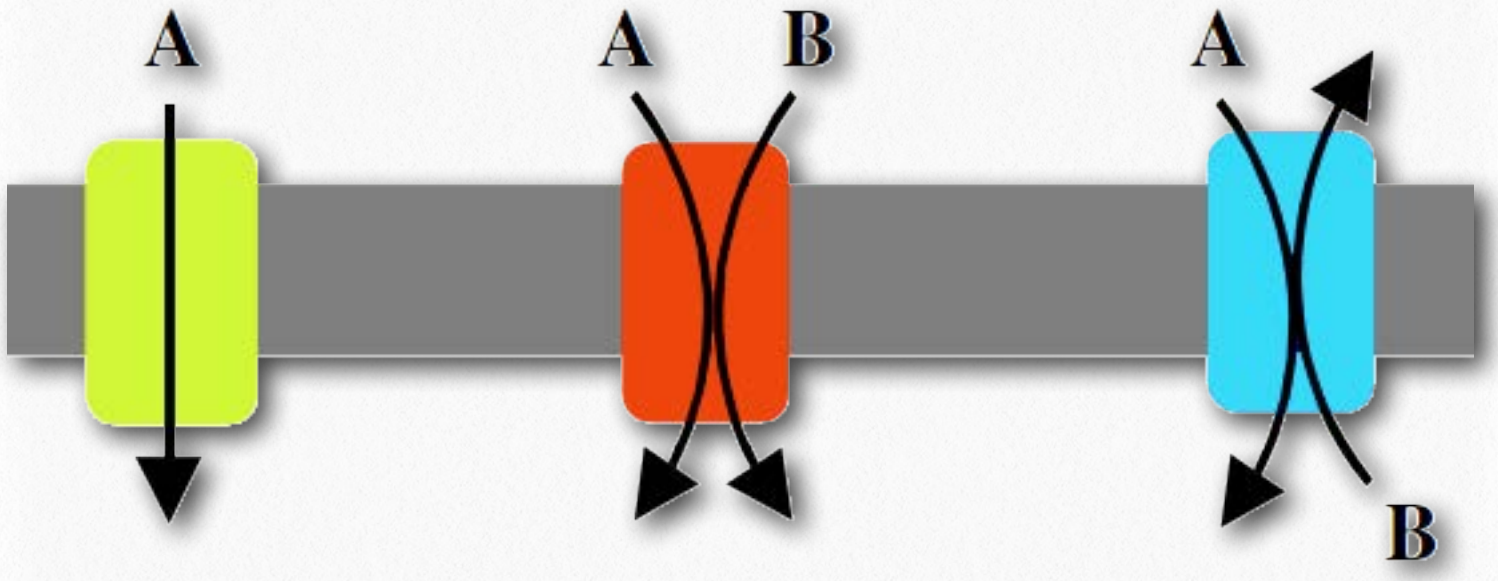

Figure 3.25 - A uniport, a symport, and an antiport

porters, synports, or symporters). If two molecules are moved in opposite directions across the bilayer, the protein is called an antiport. Proteins involved in moving ions are called ionophores.

If the action of a protein in moving ions across a membrane results in a net change in charge, the protein is described as electrogenic and if there is no change in charge the protein is described as electroneutral (Figure 3.26). When the driving force for movement through the membrane protein is simply diffusion, the process is called facilitated diffusion or passive transport and when the process requires other energy input, the process is called active transport.

Channels and transporters

With respect to movement of materials through membrane proteins, there is a difference between channels (sometimes called

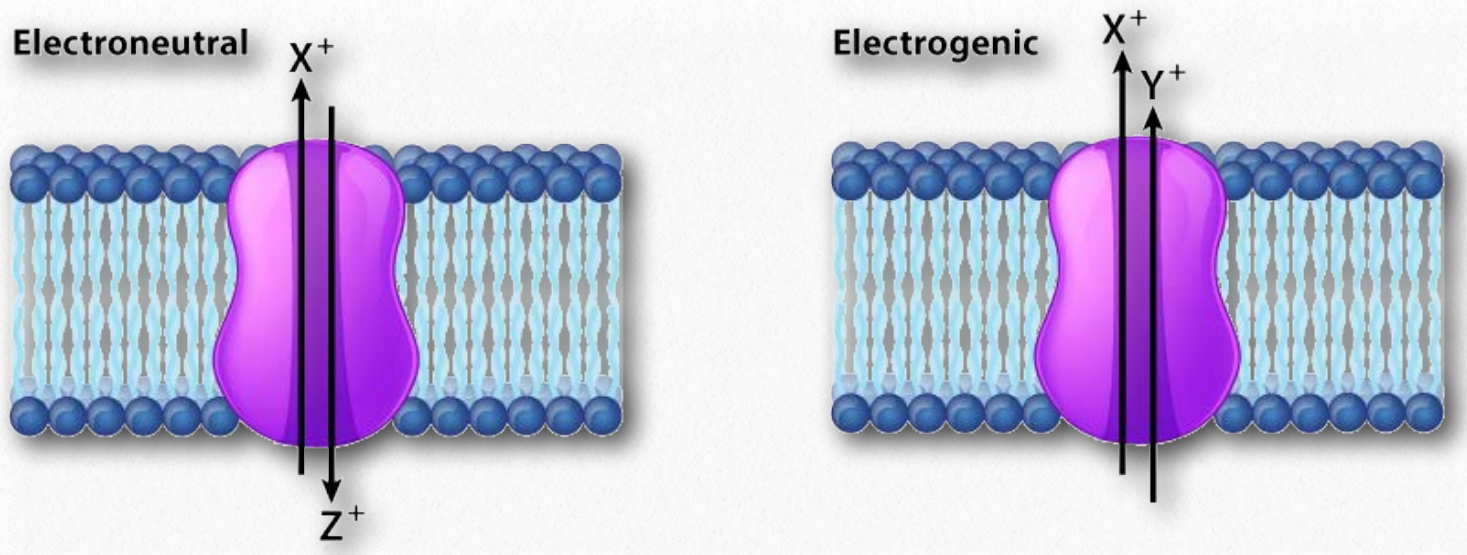

Figure 3.26 - Electroneutral and electrogenic transporters

Image by Aleia Kim

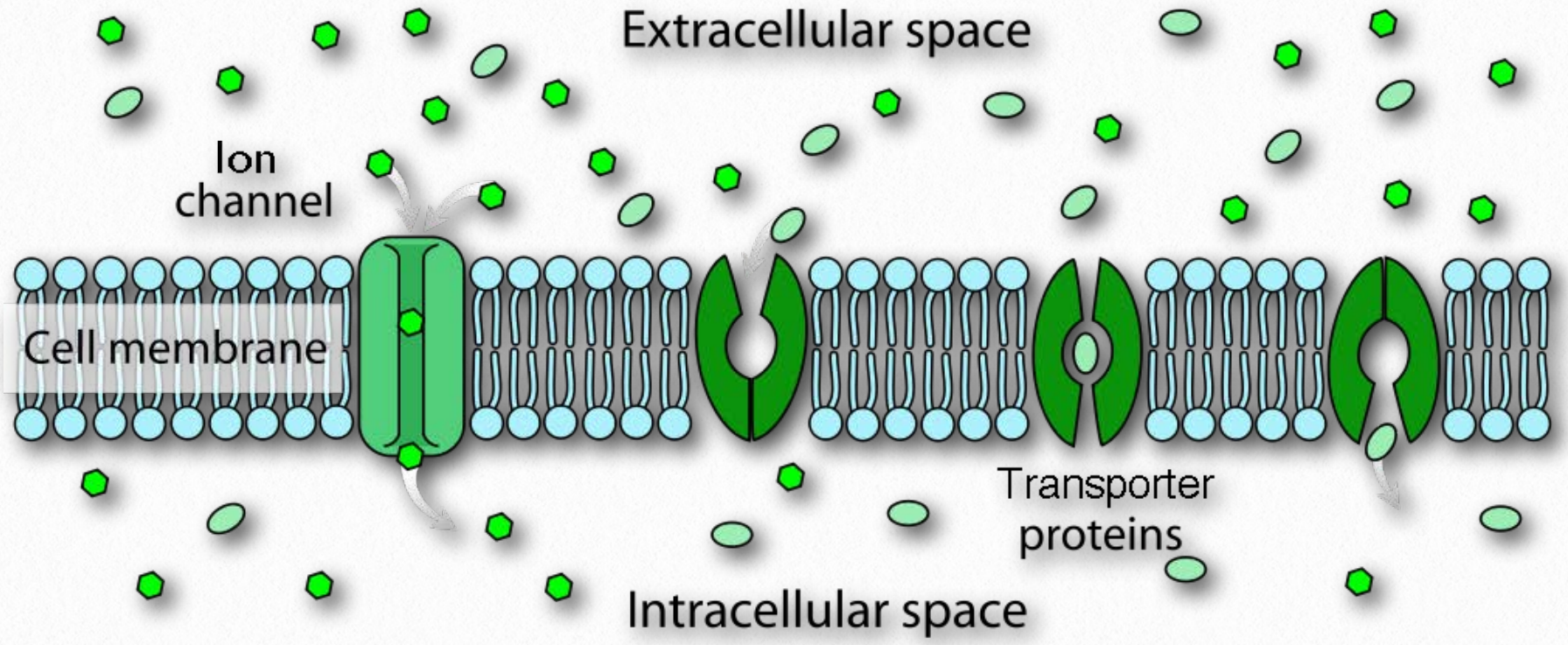

Figure 3.27 - Ion channel and transporter proteins

pores) and transporters. Channels largely provide openings with some specificity and molecules pass through them at close to the rate of diffusion. They usually involve movement of water or ions. Examples would be the sodium or potassium channels of nerve cells. Transporters have high specificity and transfer rates that are orders of magnitude slower. Transport proteins include the sodium-potassium pump, the sodium-calcium exchanger, and lactose permease, amongst many others).

Facilitated diffusion

As noted, the driving force for facilitated diffusion is concentration, meaning that in facilitated diffusion, materials will only move from a higher concentration to a lower concentration and that at the end of the process, the concentration of materials on each side of a bilayer will be equal (Figure 3.28). This may work well in many cases.

For example, the blood concentration of glucose is sufficiently high that red blood cells can use facilitated diffusion as a means of

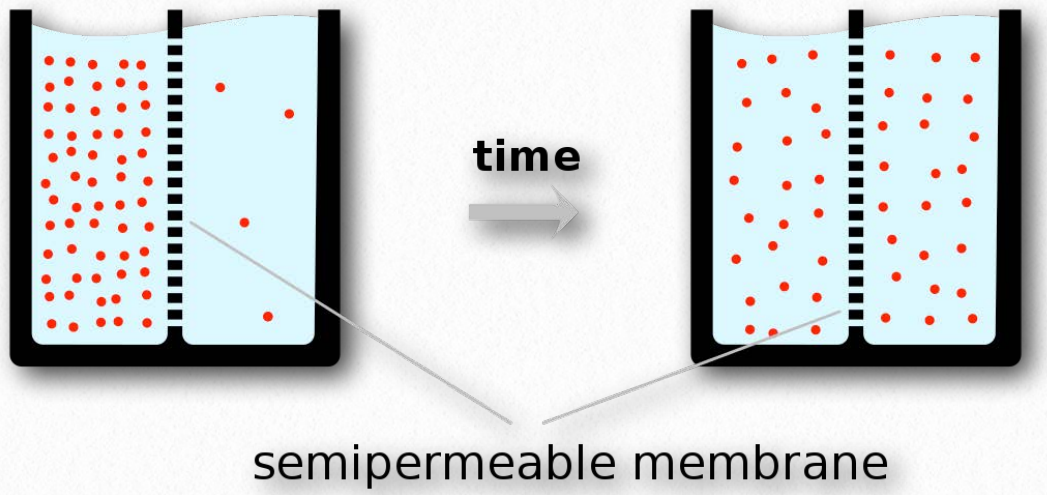

Figure 3.28 - In diffusion, solutes move from high concentration to lower concentration and eventually equalize

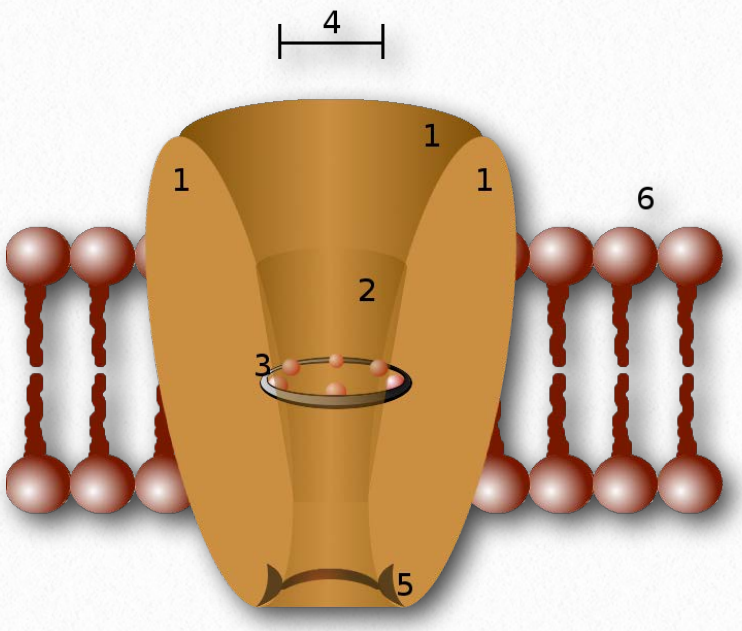

Figure 3.29 - Schematic structure of an ion channel protein - 1 = General structure / 2 = Entrance / 3 = Selectivity filter / 4 = Effective diameter / 5 = Controllable opening

acquiring glucose. Other cells, further removed from the blood supply where the glucose concentration is lower, must use active transport mechanisms because there is not a sufficient concentration of glucose to provide cells with the glucose they need.

Ion channels

Ion channels are pore-forming membrane proteins in the membranes of all cells that regulate movement of selected ions across a membrane (Figures 3.29 & 3.30). They help to establish the resting membrane potential and to affect action potentials and other electrical signals. They are very important in the process of nerve transmission. Ion channels control the flow of ions across secretory and epithelial cells, and consequently help to regulate cell volume by affecting osmotic pressure.

Ion channels are essential features of almost all cells, functioning as selective "tunnels" that restrict movement through them to ions with specific characteristics (typically size). The size of the opening is very narrow (usually one or two atoms wide) and is able to select even against ions that are too small.

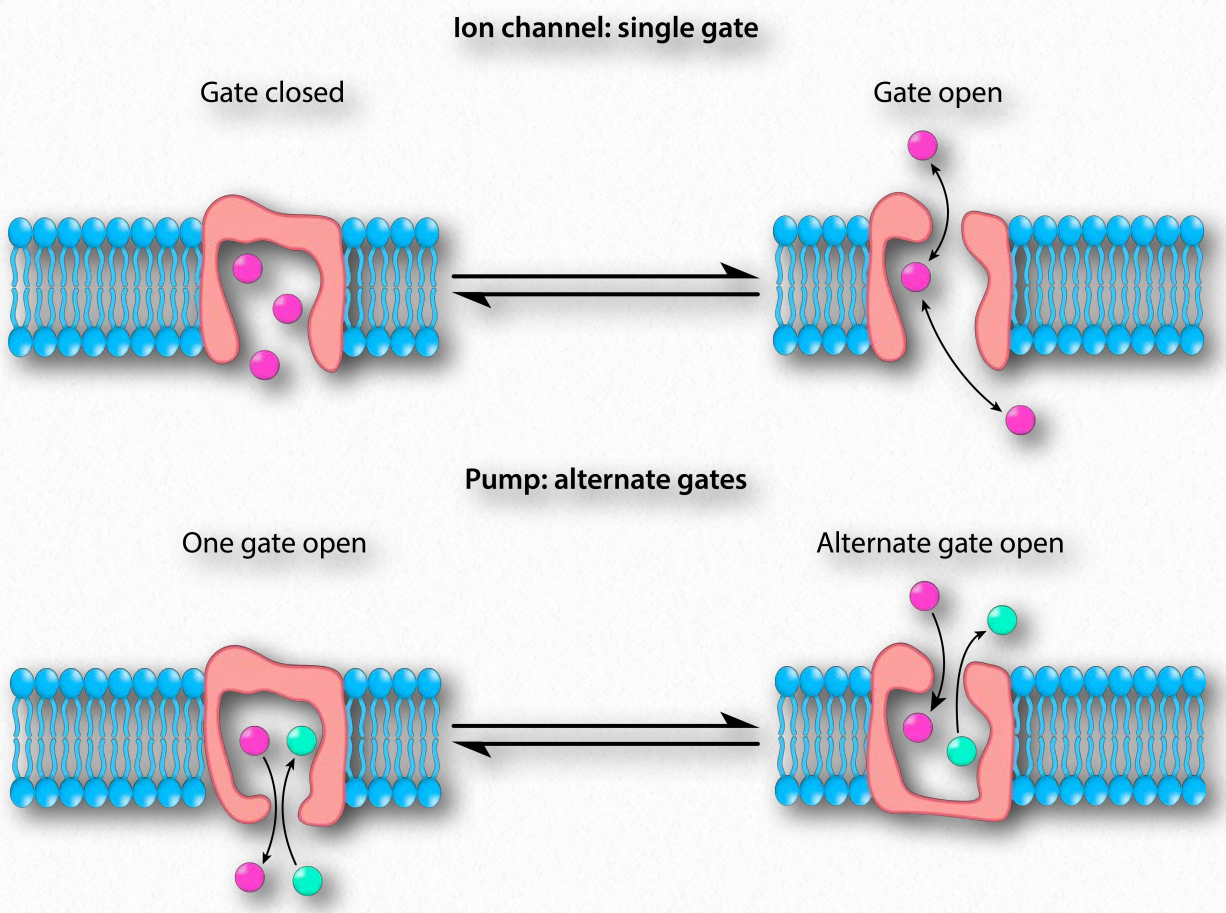

Figure 3.30 - Two types of ion channel - single and double gates

Image by Pehr Jacobson

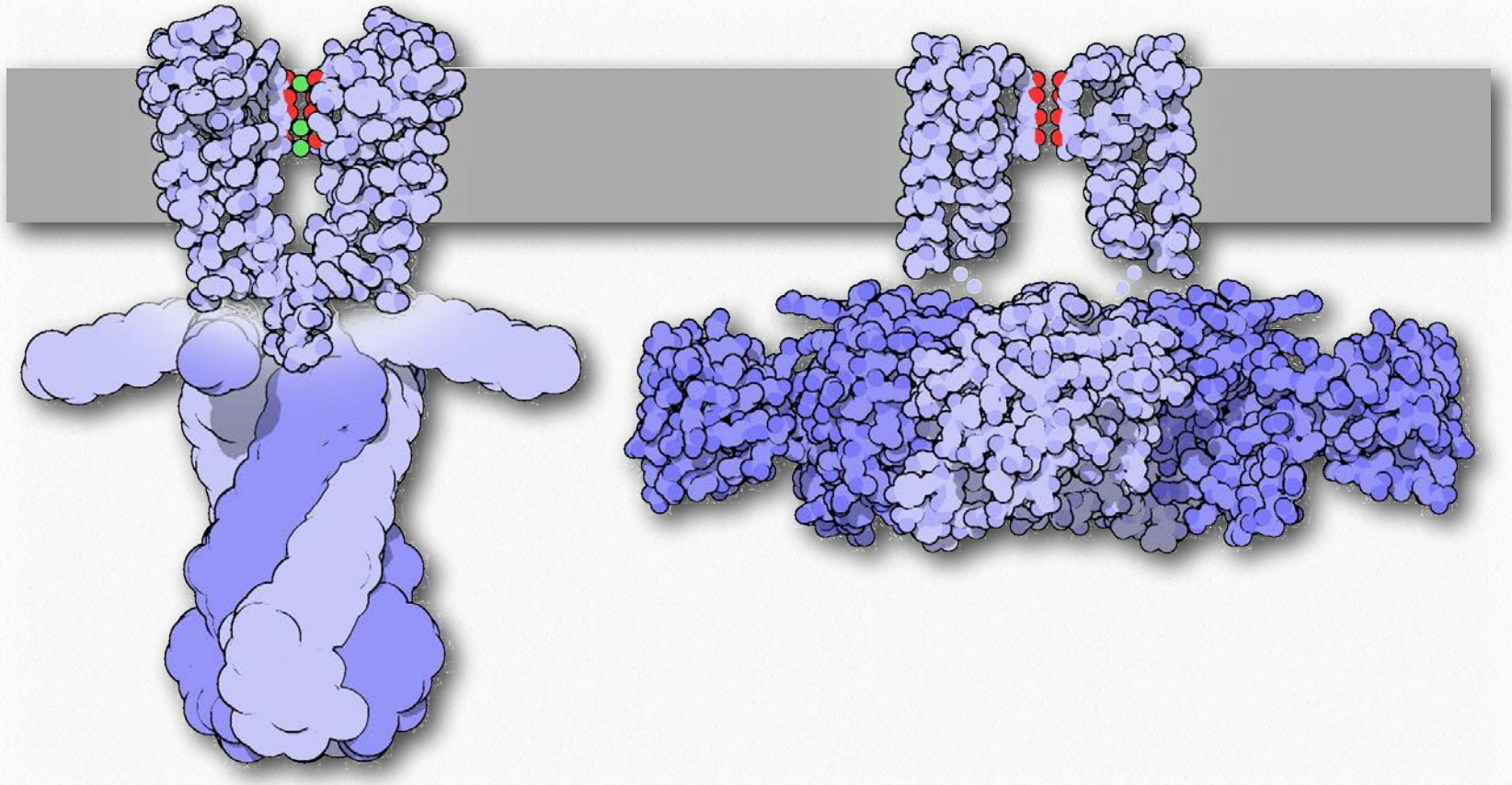

Figure 3.31 - **A potassium channel closed (left) and open (right)**

Wikipedia

Control mechanisms

Ion channels are controlled by mechanisms that include voltage, ligands, light, temperature, and mechanical deformation (stretch activated). Ligand-gated ion channels (LGICs) are transmembrane proteins which open to selectively allow ions such as Na^+, K^+, Ca^{++}, or Cl^- to pass through the membrane in response to the binding of a ligand messenger.

Sound waves cause mechanical deformation of hair cells in the ear. This results in the opening of ion channels and initiation of a nerve signal to the brain.

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Sodium ion channels in the tongue for sugar receptors open in response to binding of sucrose, allowing sodium concentration in the nerve cell to increase and initiate a nerve signal to the brain. In this case, the default for the gate is to be closed and it opens in response to binding of a ligand (sucrose).

In light sensing cells of the eye, calcium gates are open by default, but stimulation by light causes them to close, triggering a series of events that result in a signal being sent the brain about the perception of light. Thus, in this case, the stimulus (light) causes an open channel to close.

Moving the other direction, nerve signals originating in the brain travel to muscle tissue and through a complicated set of exchanges, result in the opening of calcium gates of muscle cells, increasing the concentration of calcium and stimulating muscular contraction (see HERE).

Voltage gated channels are essential for transmission of nerve signals, a process discussed in more depth HERE.

Ion movement through channels

The ability of ion channels to select against ions too large is intuitive - the size of the opening in the ion channel simply isn't big enough for a larger ion to fit through the opening. Potassium, for example, passes through sodium channels rarely because the opening is too small.

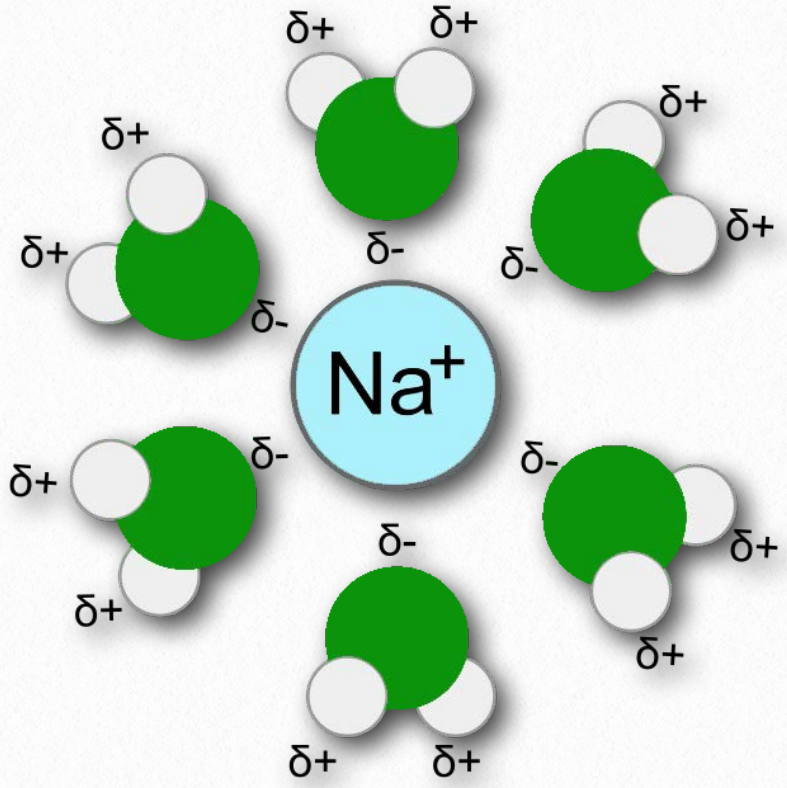

Figure 3.32 - Sodium surrounded by water molecules in a hydration shell

Potassium channels that are selective for potassium ions must be big enough to allow potassium to enter, but if size were the only selection means, then sodium ions would also readily pass through potassium channels, since sodium ions (0.95 Å) are smaller than potassium ions (1.33 Å). In order for potassium channels to select against sodium ions and favor potassium ions, other considerations come into play.

Hydration shell

To understand this unique selectivity, it is important to understand how ions move through channels. Before an ion can pass through a channel, it must first be dissociated from (stripped of) the water molecules in its hydration shell - water molecules surrounding ions in aqueous solutions (Figure 3.32). This process requires an input of energy. The initial energy required to strip the water molecules from the hydration shell has been compared to the activation energy of an enzymatic reaction.

Comparable to enzymes

Just as enzymes lower the activation energy of enzymatic reactions and thus allow them to more readily occur, so too do channel proteins

lower the energy requirements for a molecule to traverse a lipid bilayer. In the absence of the channel protein, the dehydration energy is mostly prohibitive for most polar molecules to occur, so very few make it across the lipid bilayer without the channel protein. This is why ion channel/transport proteins are so important to the cell.

After the water has been stripped, the ion can pass through the channel and when it arrives at the other side of the channel, the diffusing ion becomes rehydrated, thus regaining the energy that was required initially to strip away the water molecules from the ion.

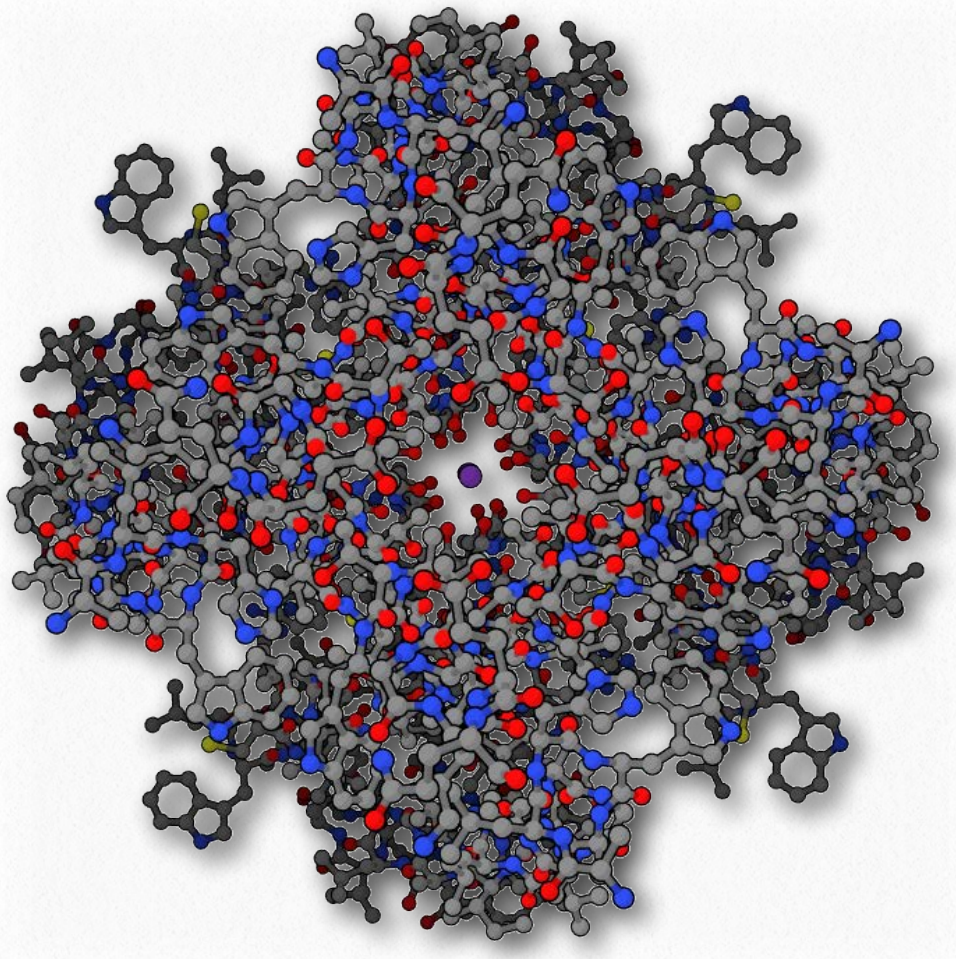

Figure 3.33 - A potassium ion (center) transiting the potassium channel

Selectivity of the potassium channel

The potassium channel (Figure 3.33) uses the dimensions of the potassium ion precisely to shepherd it through the channel. The sodium ion, which has different dimensions has a more difficult time making it through the channel despite its smaller size. The reason this is rooted in the energy required for dehydration.

For potassium ions, after the water has been stripped off, precisely positioned carbonyl groups along the channel help to stabilize the ion as it moves. The sodium ion, on the other hand is too small and does not make efficient connections with carbonyl groups and thus has a more difficult path. Because of this, the energy difference between dehydration and rehydration of a sodium ion in a potassium channel is energetically unfavorable (requires net input of energy) but the same process for a potassium ion is energetically favorable (results in a net gain of energy).

Energy factor

Thus the selection in favor of potassium and against sodium ions in a potassium channel is based on energy, not physical size, whereas in

Movie 3.1 - Gramicidin A

Wikipedia

Gramicidin

Gramicidins (Movie 3.1) are antibiotic polypeptides synthesized by the soil bacterium known as *Bacillus brevis.* These small pentadecapeptides (15 amino acids) are synthesized by the bacterium to kill other bacteria.

When released by the *Bacillus brevis*, the gramicidins insert themselves in the membranes of Gram positive bacteria and allow the movement of sodium ions into the target cells, ultimately killing them. Gramicidins can also cause hemolysis in humans so they cannot be used internally, but instead are used topically.

the selection of sodium ions over potassium ions in a sodium channel, size is the primary consideration.

Ion balance

The movement of ions across a lipid bilayer is tightly regulated, and with good reason. Maintaining a proper balance of ions inside and outside of cells is important for maintaining osmotic balance. It is also important inside and outside of organelles like the mitochondria and chloroplasts for energy generation. If the ionic balance of a cell is sufficiently disturbed by an uncontrolled ionophore, a cell may die.

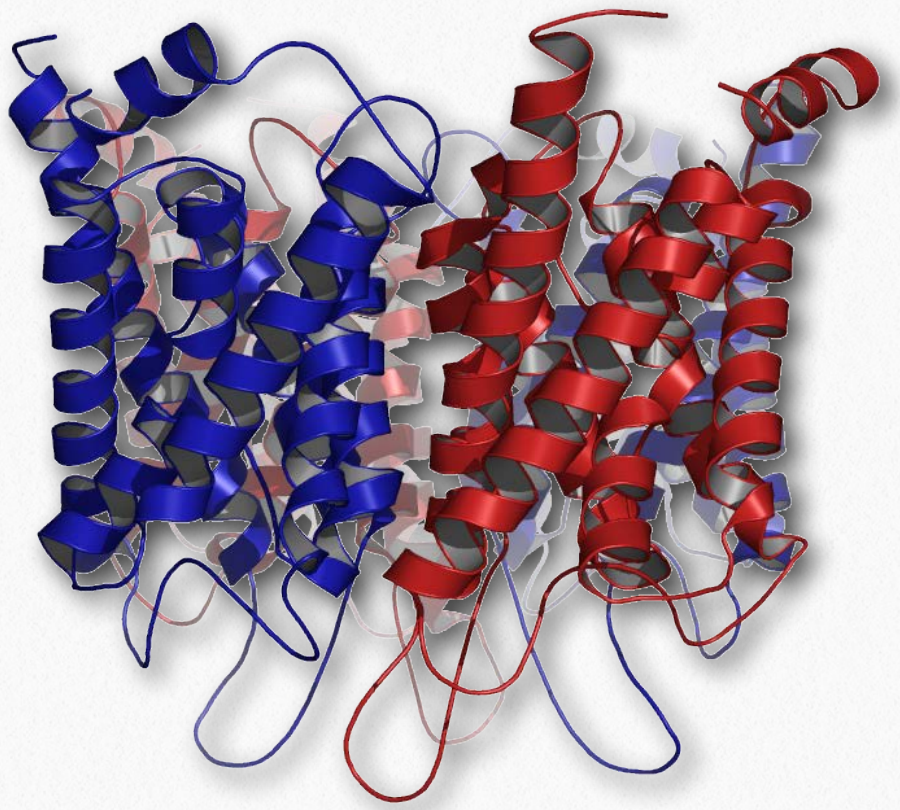

Figure 3.34 - View of aquaporin from the side

Wikipedia

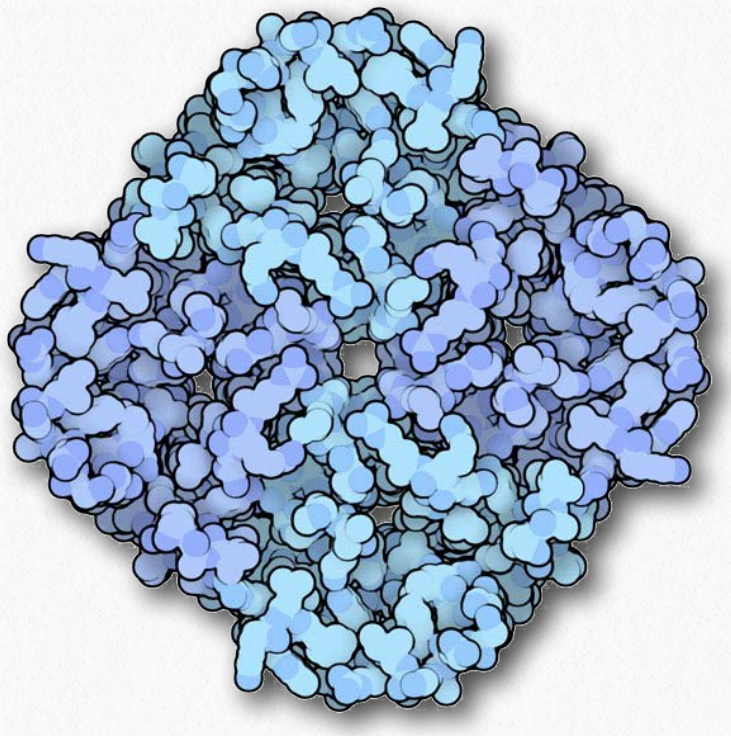

Figure 3.35 - View of aquaporin from the top

Wikipedia

Aquaporins

Aquaporins are pore-containing integral membrane proteins that selectively permit passage of water molecules in and out of the cell, while preventing ions and other solutes from moving (Figures 3.34 & 3.35). Some aquaporins called aquaglyceroporins, also transport other small uncharged entities, such as glycerol, ammonia, urea, and CO_2, across the membrane,. The water pores are completely impermeable to charged molecules, such as protons, which is important for the preserving the membrane's electrochemical potential difference.

Porins

Porins are proteins containing a β-barrel structure that crosses the cell membrane/ wall and acts as a pore/channel through which specific molecules diffuse. Porins are found in the outer membrane of Gram-negative bacteria and some Gram-positive bacteria, mitochondria, and chloroplasts.

Porins typically transport only one group of molecules or, in some cases, one specific molecule. Antibiotics, such as β-lactam and fluoroquinolone pass through porins to reach the cytosol of Gram negative bacteria. Bacteria may develop resistance to these antibiotics when a mutation occurs to the porin involved that results in exclusion of the antibiotics that would otherwise pass through.

Transporter proteins

Not all facilitated transport occurs through ion channel proteins. Transporter proteins, as noted earlier (HERE and Figure 3.27) facilitate movement of materials across a lipid bilayer, but are slower than ion channels. Figure 3.36 illustrates a transporter protein in action. As can be seen, transporter proteins rely on a specific receptor site for proper recognition of the molecule to be moved.

Binding of the proper molecule causes a conformational change in the shape of the protein (an eversion) which results in a flipping of the open side of the protein to the other side of the lipid bilayer. In this way, the molecule is moved. Like ion channels, transporter proteins facilitate movement of materials in ei-

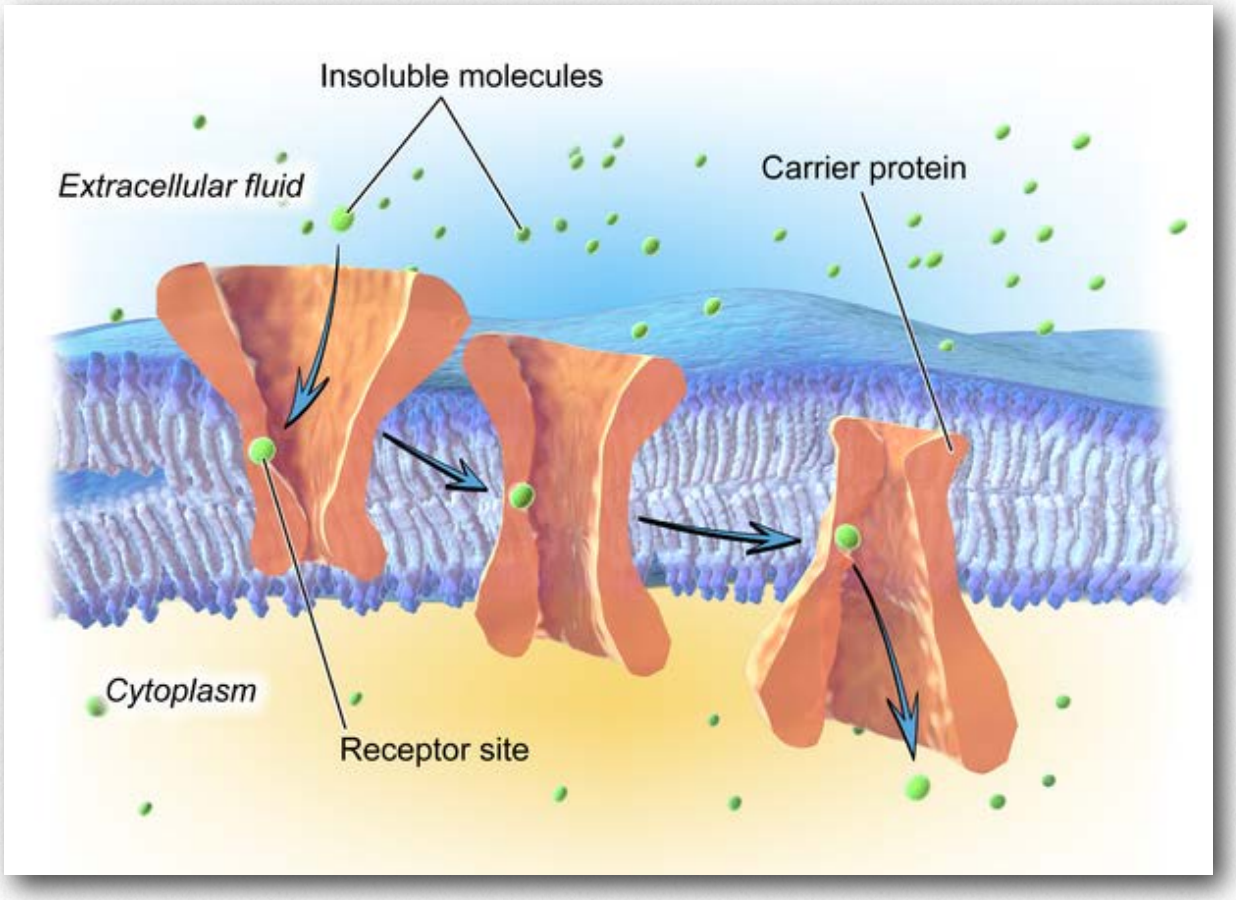

Figure 3.36 - Facilitated diffusion with a transporter protein
Wikipedia

ther direction, driven only by the concentration difference between one side and the other.

Active transport

All of the transport mechanisms described so far are driven solely by a concentration gradient - moving from higher concentrations in the direction of lower concentrations. These movements can occur in either direction and, as noted, result in equal concentrations on either side of the bilayer, if allowed to go to completion. Many times, however, cells must move materials against a concentration gradient and when this occurs, another source of energy is required. This process is known as active transport.

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A good definition of active transport is that in active transport, at least one molecule is being moved against a concentration gradient. A common, but not exclusive, energy source is ATP (see Na^+/K^+ ATPase), but other energy sources are also employed. For example, the sodium-glucose transporter uses a sodium gradient as a force for actively transporting glucose into a cell. Thus, it is important to know that not all active transport uses ATP energy.

Na^+/K^+ ATPase

An important integral membrane transport protein is the Na^+/K^+ ATPase antiport (Figures 3.37 and 3.38), which moves three sodium ions out of the cell and two potassium ions into the cell with each cycle of action. In each case, the movement of ions is against the concentration gradient. Since three positive charges are moved out for each two positive charges moved in, the system is electrogenic.

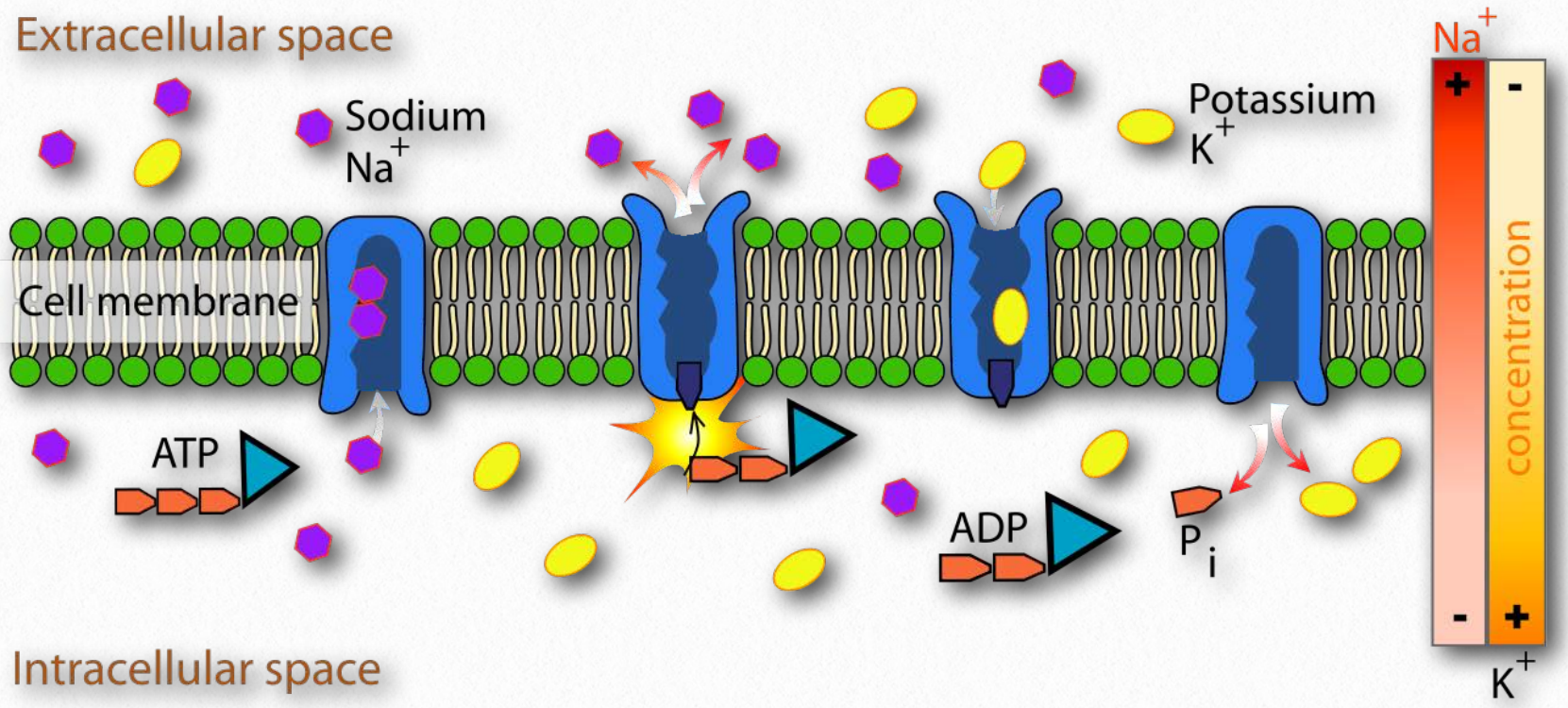

Figure 3.37 - An overview of active transport by the Na^+K^+ ATPase

The protein uses the energy of ATP to create ion gradients that are important both in maintaining cellular osmotic pressure and (in nerve cells) for creating the sodium and potassium gradients necessary for signal transmission. Failure of the system to function results in swelling of the cell due to movement of water into the cell through osmotic pressure. The transporter expends about one fifth of the ATP energy of animal cells. The cycle of action occurs as follows:

1. Pump binds ATP followed by binding of 3 Na^+ ions from cytoplasm of cell

2. ATP hydrolysis results in phosphorylation of aspartate residue of pump. ADP is released

3. Phosphorylated pump undergoes conformational change to expose Na^+ ions to exterior of cell. Na^+ ions are released.

4. Pump binds 2 extracellular K^+ ions.

5. Pump dephosphorylates causing it to expose K^+ ions to cytoplasm as pump returns to original shape.

6. Pump binds 3 Na^+ ions, binds ATP and releases 2 K^+ ions to restart process

The Na^+/K^+ ATPase is classified as a P-type ATPase. This category of pump is notable for having a phosphorylated aspartate intermediate and is present across the biological kingdoms - bacteria, archaeans, and eukaryotes.

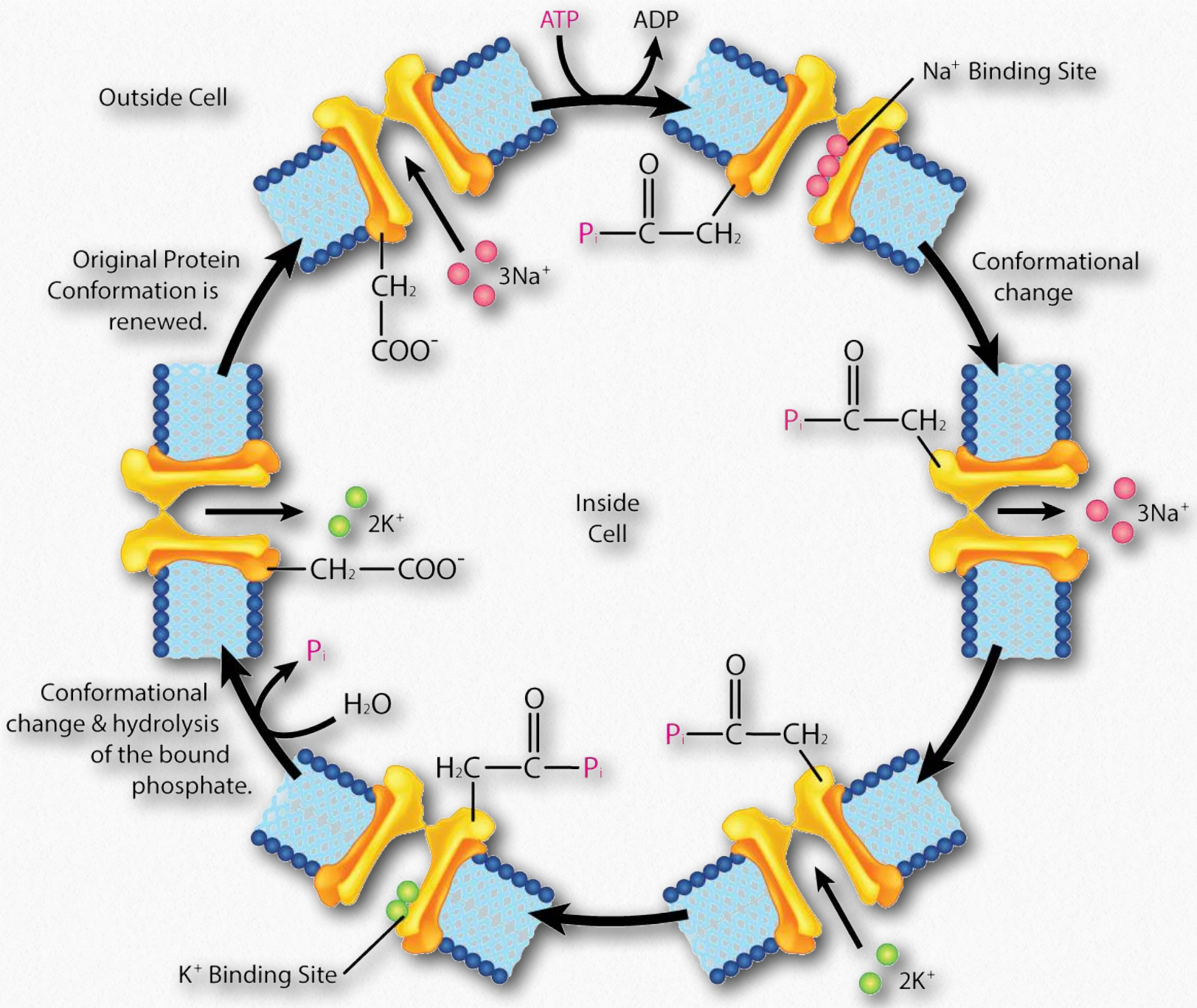

Figure 3.38 - Sequential steps in the active transport of ions by the Na^+K^+ ATPase

Wikipedia

ATPase types

ATPases have roles in either the synthesis or hydrolysis of ATP and come in several different forms.

• F-ATPases (F_1F_O-ATPases) are present in mitochondria, chloroplasts and bacterial plasma membranes and are the prime ATP synthesizers for these systems. Each uses a proton gradient as its energy source for ATP production. Complex V of the mitochondrion is an F-type ATPase.

• V-ATPases (V_1V_O-ATPases) are mostly found in vacuoles of eukaryotes. They utilize energy from ATP hydrolysis to transport solutes and protons into vacuoles and lysosomes, thus lowering their pH values.

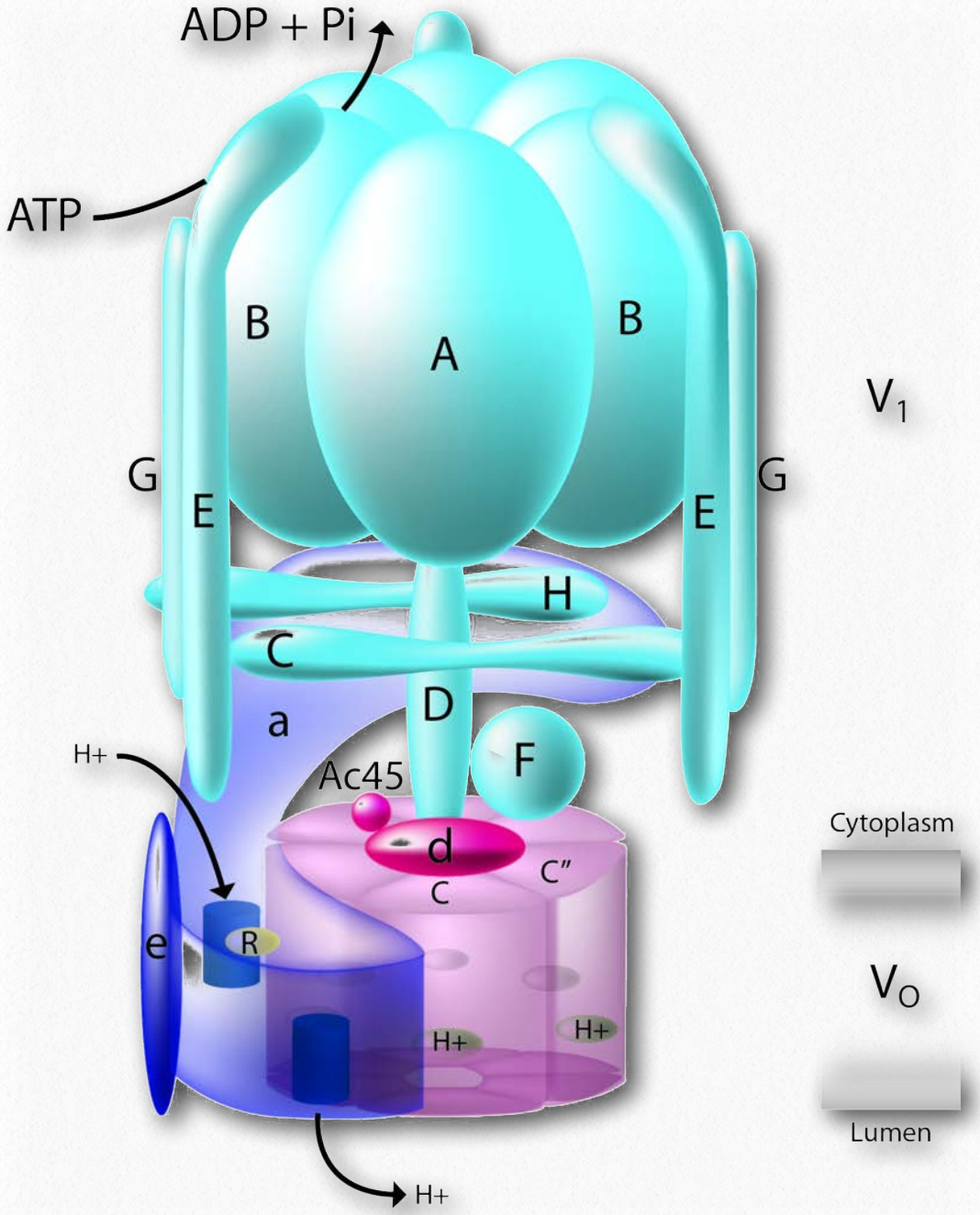

Figure 3.39 - Schematic structure of V-ATPases
Wikipedia

The V-type and F-type ATPases are very similar in structure. The V-type (Figure 3.39) uses ATP to pump protons into vacuoles and lysosomes, whereas F-types use proton gradients of the mitochondria and chloroplasts to make ATP.

• A-ATPases (A_1A_O-ATPases) are found in archaeans and are similar to F-ATPases in function.

• P-ATPases (E_1E_2-ATPases) are in bacteria, fungi and in eukaryotic plasma membranes and organelles. They transport a diversity of ions across membranes. Each has a common mechanism of action which include autophosphorylation of a conserved aspartic acid side chain within it. Examples of P-type ATPases include the Na+/K+ ATPase and the calcium pump.

• E-ATPases are enzymes found on the cell surface. They hydrolyze a range of extracellular nucleoside triphosphates, including ATP.

Nerve transmission

Now that you have seen how the Na^+/K^+ ATPase functions, it is appropriate to discuss how nerve cells use ion gradients created with it to generate and transmit nerve signals. Neurons are cells of the nervous system that use chemical and electrical signals to rapidly transmit information across the body (Figure 3.40). The sensory nerve system links receptors for vision, hearing, touch, taste, and smell to the brain for perception. Motor neurons run from the spinal cord to muscle cells. These neurons have a cell body and a very long, thin extension called an axon, that stretches from the cell body in the spinal cord all the way to the muscles they control. Nerve impulses travel down the axon to

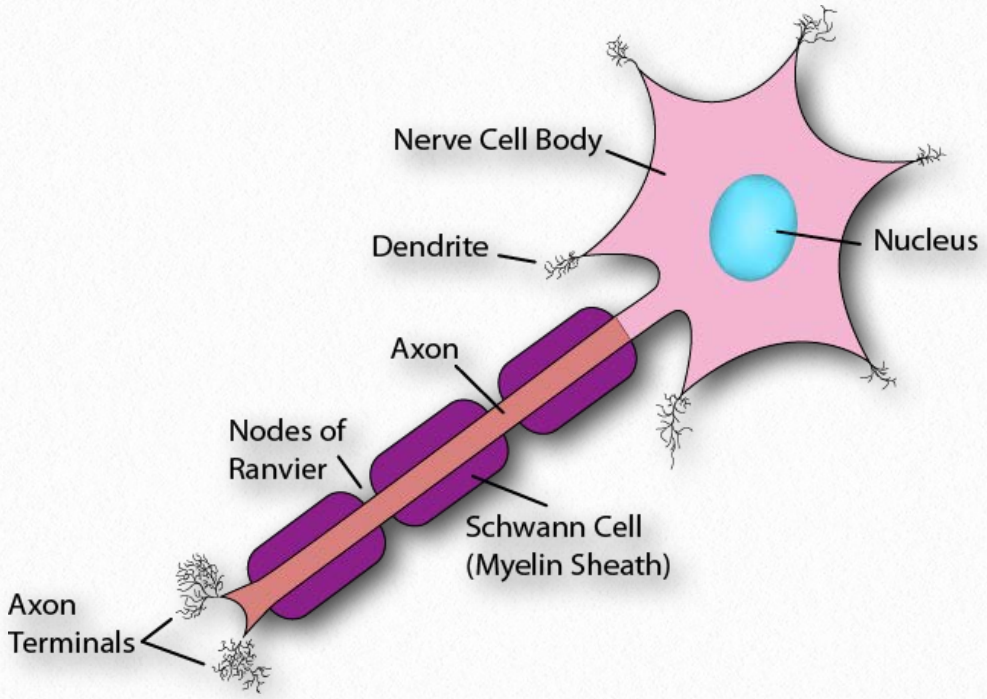

Figure 3.40 - Anatomy of a nerve cell

Image by Pehr Jacobson

the neuron releases neurotransmitters that exit the nerve cell and travel across the junction to a recipient cell where a response is generated. That response may be creating another nerve signal, if the adjacent cell is a nerve cell or it may be a muscular contraction if the recipient is a muscle cell (Figure 3.41).

stimulate muscle contraction.

Signals travel through neurons, ultimately arriving at junctions with other nerve cells or target cells such as muscle cells. Note that neurons do not make physical contact with each other or with muscle cells. The tiny space between two neurons or between a neuron and a muscle cell is called the synaptic cleft. At the synaptic cleft,

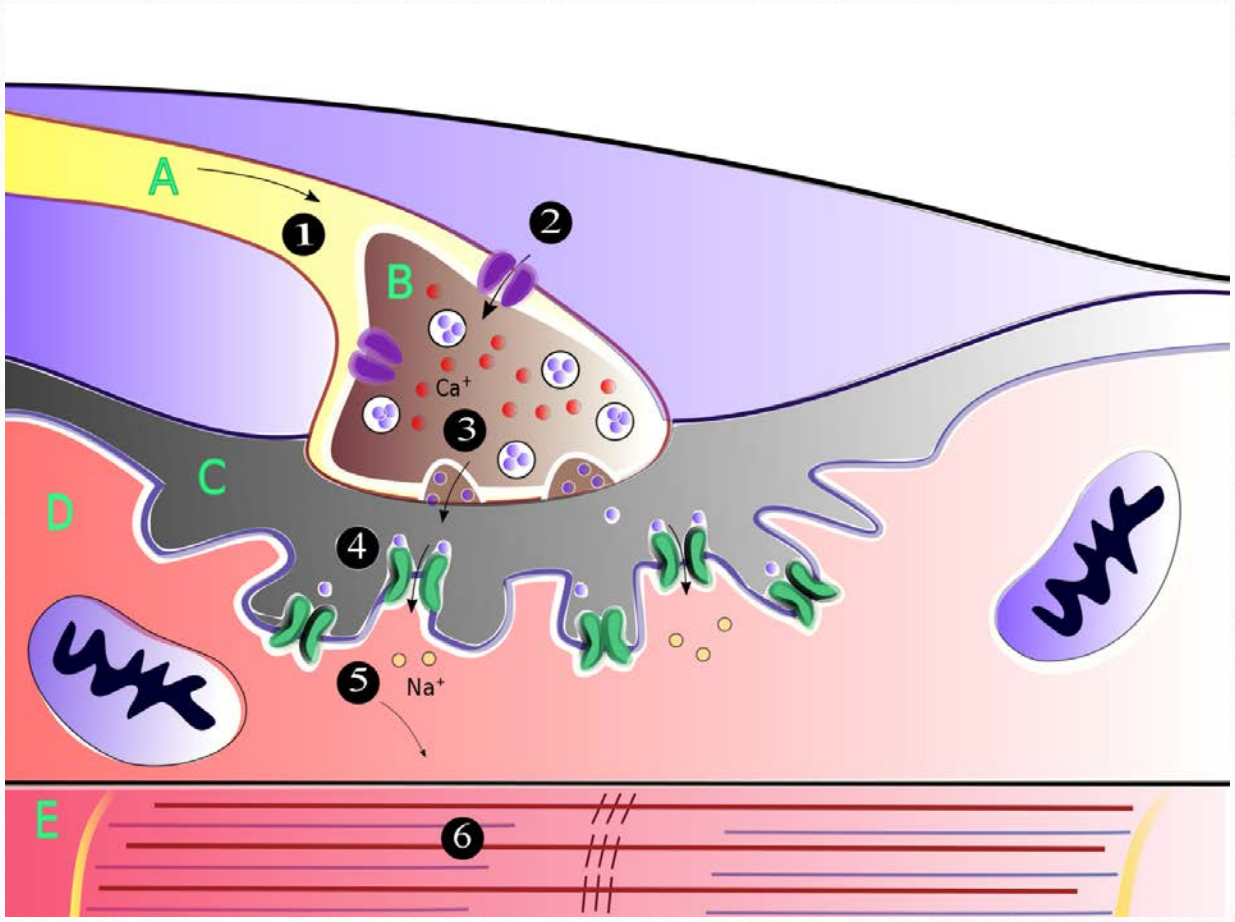

Figure 3.41 - (1) The action potential reaches the axon terminal; (2) voltage-dependent calcium gates open - calcium enters the axon terminal; (3) neurotransmitter vesicles fuse with the presynaptic membrane and release acetylcholine (ACh); (4) ACh binds to postsynaptic receptors on the sarcolemma; (5) ion channels open in response and allow sodium ions to flow into the muscle cell; (6) The flow of sodium ions into the muscle cell generates an action potential which travels to the myofibril and results in muscle contraction.

Wikipedia

In considering information movement via nerve cells, then, we will discuss two steps - 1) creation and propagation of a signal in a nerve cell and 2) action of neurotransmitters exiting a nerve cell and transiting a synaptic junction.

Signal source

Creation of a nerve signal begins with a stimulus to the nerve cell. In the case of muscle contraction, the motor cortex of the brain sends signals to the appropriate motor neurons, stimulating them to generate a nerve impulse. How is such an impulse generated?

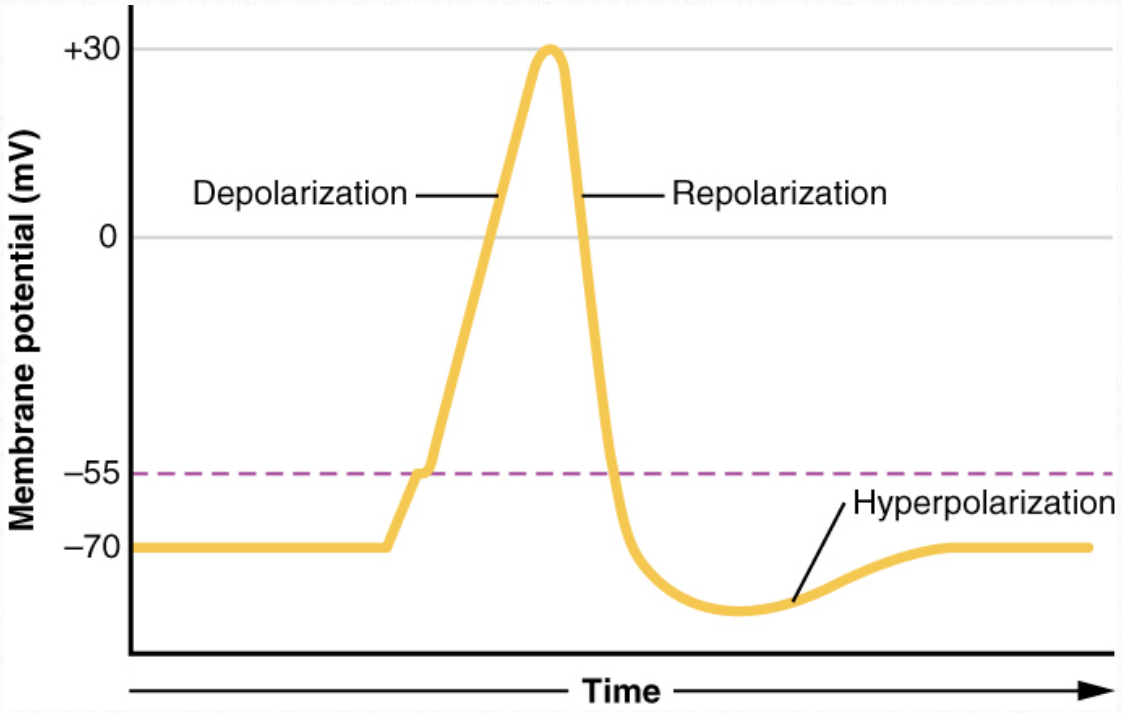

Figure 3.42 - Depolarization and repolarization of a nerve cell

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Resting potential

In the unstimulated state, all cells, including nerve cells, have a small voltage difference (called the resting potential) across the plasma membrane, arising from unequal pumping of ions across the membrane. The Na^+/K^+ ATPase, for example, pumps sodium ions out of the cell and potassium ions into cells. Since three sodium ions get pumped out for every two potassium ions pumped in, a charge and chemical gradient is created. It is the charge gradient that gives rise to the resting potential.

Altering the gradients of ions across membranes provide the driving force for nerve signals. This happens as a result of opening and closing of gated ion channels. Opening of gates to allow ions to pass through the membrane swiftly changes the ionic balance across the membrane resulting in a new voltage difference called the action potential. It is the action potential that is the impetus of nerve transmission.

Initiation of signal

The signal generated by a motor neuron begins with opening of sodium channels in the membrane of the nerve cell body causing a rapid influx of sodium ions into the nerve cell. This step, called depolarization (Figure 3.42), triggers an electrochemical

signal - the action potential. Remember that the Na^+/K^+ ATPase has created a large sodium gradient, so sodium ions rush into the cell when sodium channels open. After the initial depolarization, potassium channel gates, responding to the depolarization, open, allowing potassium ions to rapidly diffuse out of the cell (remember K^+ ions are more abundant inside of the cell). This phase is called the repolarization phase and during it, the sodium gates close.

The rapid exit of potassium ions causes the voltage difference to "overshoot" the resting potential and potassium gates close. This followed by the so-called refractory period, when the Na^+/K^+ ATPase begins its work to re-establish the original conditions by pumping sodium ions out and potassium ions into the nerve cell. Eventually, the system recovers and the resting potential is re-established. The initiating end of the nerve cell is then ready for another signal.

Propagation of action potential

What we have described here is only the initiation of the nerve signal in one part of the nerve cell. For the signal to be received, the action potential must travel the entirety of the length of the nerve cell (the axon) and cause a chemical signal to be released into the synaptic cleft to get to its target. Propagating the nerve signal (action potential) in the original nerve cell is the function of all of the rest of the gated ion channels (Figure 3.43) positioned on the sides of the nerve cell. The sodium and potassium gates involved in propagation of the signal all act in response to voltage changes created by the electrochemical gradient moving down

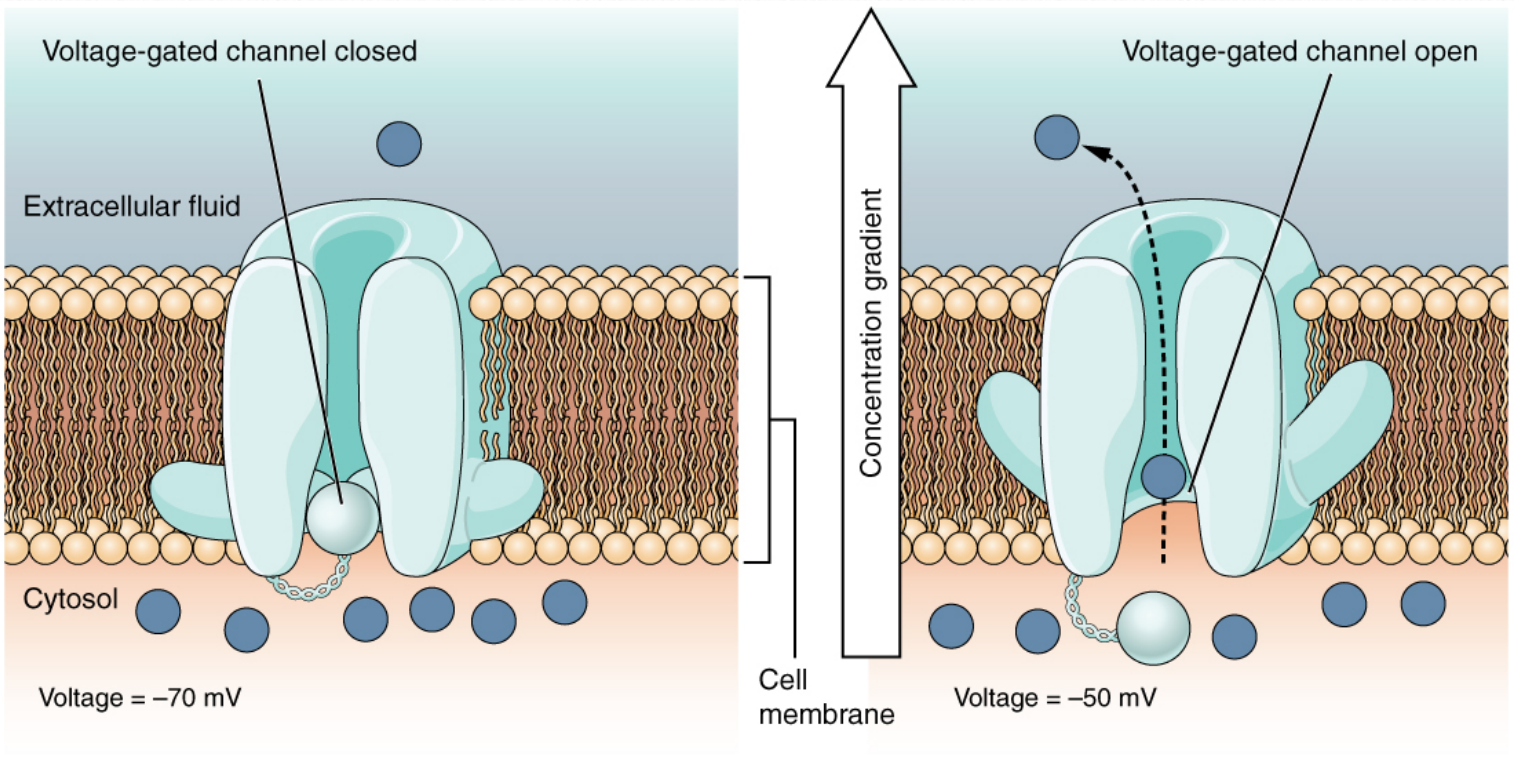

Figure 3.43 - Voltage gated ion channels

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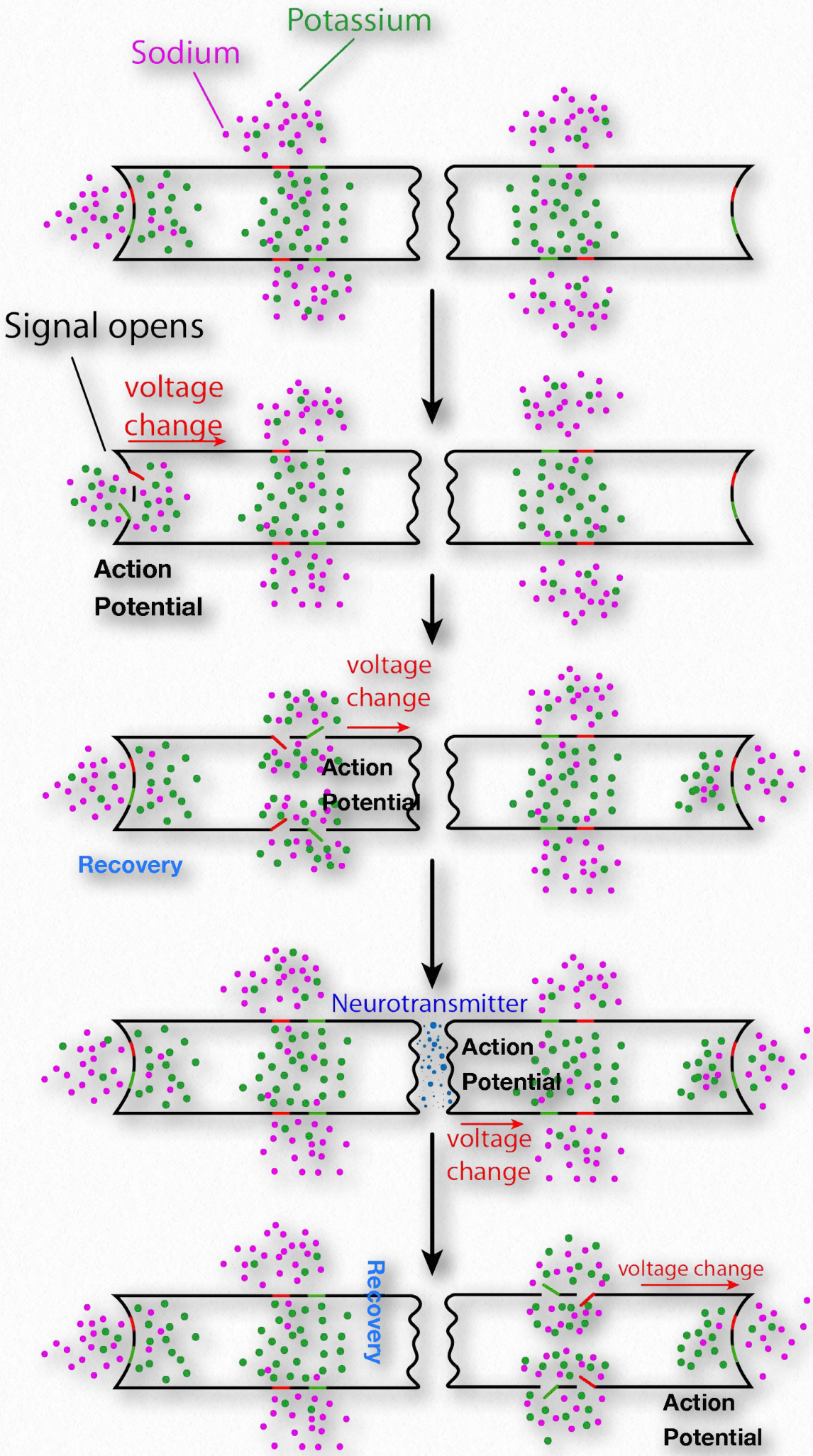


Figure 3.44 - Action potential moving across a synaptic junction of two nerve cells

Image by Pehr Jacobson

the nerve cell (Figure 3.44). Remember that opening of the initial gates at initiation of the signal created an influx of sodium ions and an efflux of potassium ions.

Moving signal

This chemical and electrical change that creates the ac-

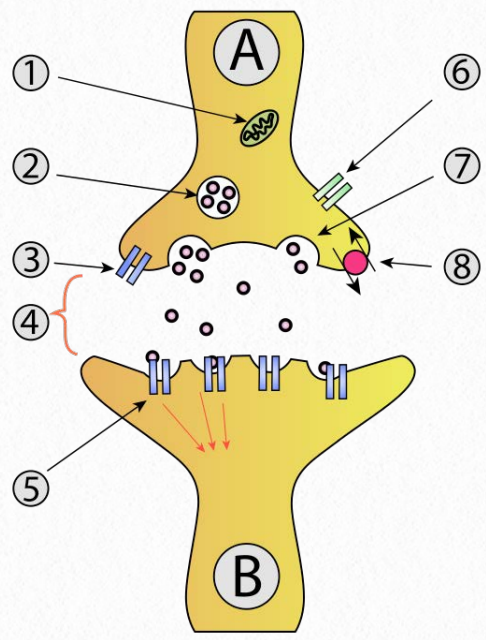


Figure 3.45 - A) Pre-synaptic neuron; B) post-synaptic neuron; 1) Mitochondria; 2) synaptic vesicle with neurotransmitters; 3) autoreceptor; 4) synapse with neurotransmitter released (serotonin); 5) postsynaptic receptors activated by neurotransmitter; 6) calcium channel; 7) exocytosis of a vesicle; 8) recaptured neurotransmitter.

Wikipedia

tion potential leaves the end of the nerve cell where it started and travels down the axon towards the other end of the nerve cell. Along the way, it encounters more sodium and potassium gated channels. In each case, these respond simply to the voltage change of the action potential and open and close, exactly in the same way the gates opened to start the signal. Thus, a rapid wave of increasing sodium ions and decreasing potassium ions moves along the nerve cell, propagated (and amplified) by gates opening and closing as the ions and charges move down the nerve cell. Eventually, the ionic tidal wave reaches the end of the nerve cell (axon terminal) facing the synaptic cleft.

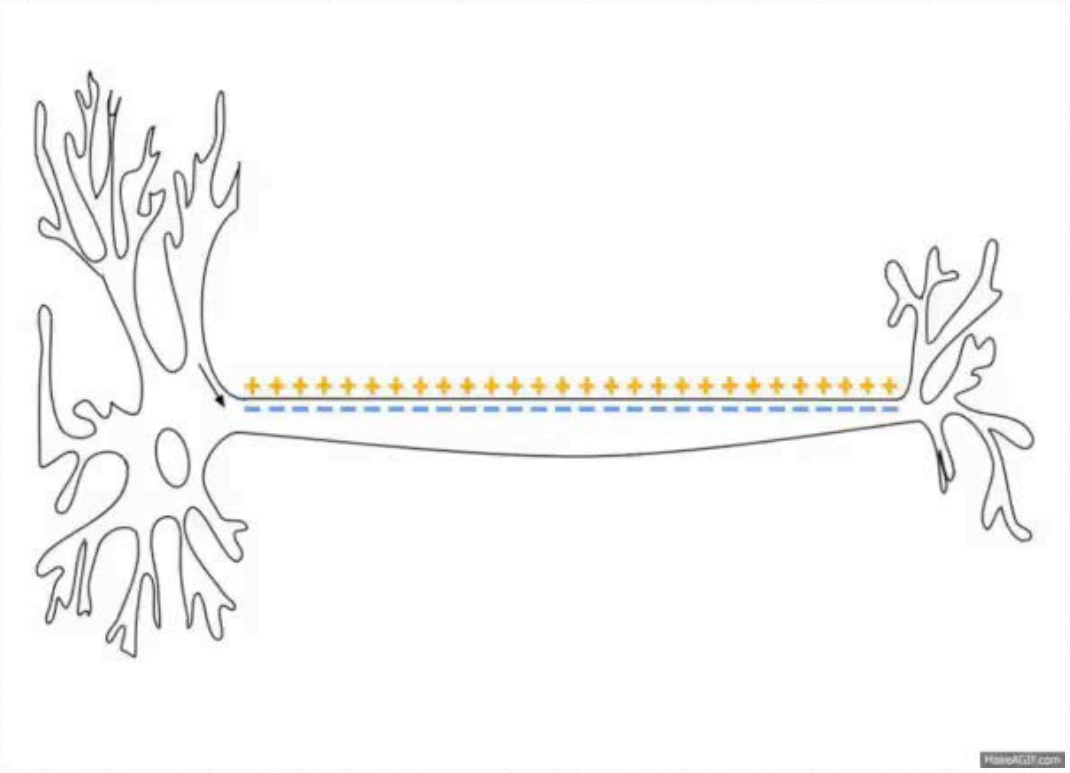
Crossing the synaptic cleft

For the signal to be received by the intended target (postsynaptic cell) from the originating neuron (presynaptic neuron), it must cross the synaptic cleft and stimulate the neighboring cell (Figure 3.45). Communicating information across a synaptic cleft is the job of neurotransmitters. These are small molecules synthesized in nerve cells that are packaged in membrane vesicles called synaptic vesicles in the nerve cell. Neurotransmitters come in all shapes and chemical forms, from small chemicals like acetylcholine to peptides like neuropeptide Y. The most abundant neurotransmitter is glutamate, which acts at over 90% of the synapses in the human brain.

Into the cleft

As the action potential in the presynaptic neuron approaches the axon terminus, synaptic vesicles begin to fuse with the membrane and their neurotransmitter contents spill into the synaptic cleft. Once in the cleft, the neurotransmitters diffuse, some of them reaching receptors on the postsynaptic cell. Binding of the neurotransmitter to the receptors on the membrane of the postsynaptic cell stimulates a response.

For motor neurons, the postsynaptic cell will be a muscle cell, and the response will be



Movie 3.2 - Movement of an action potential down a nerve cell

Wikipedia

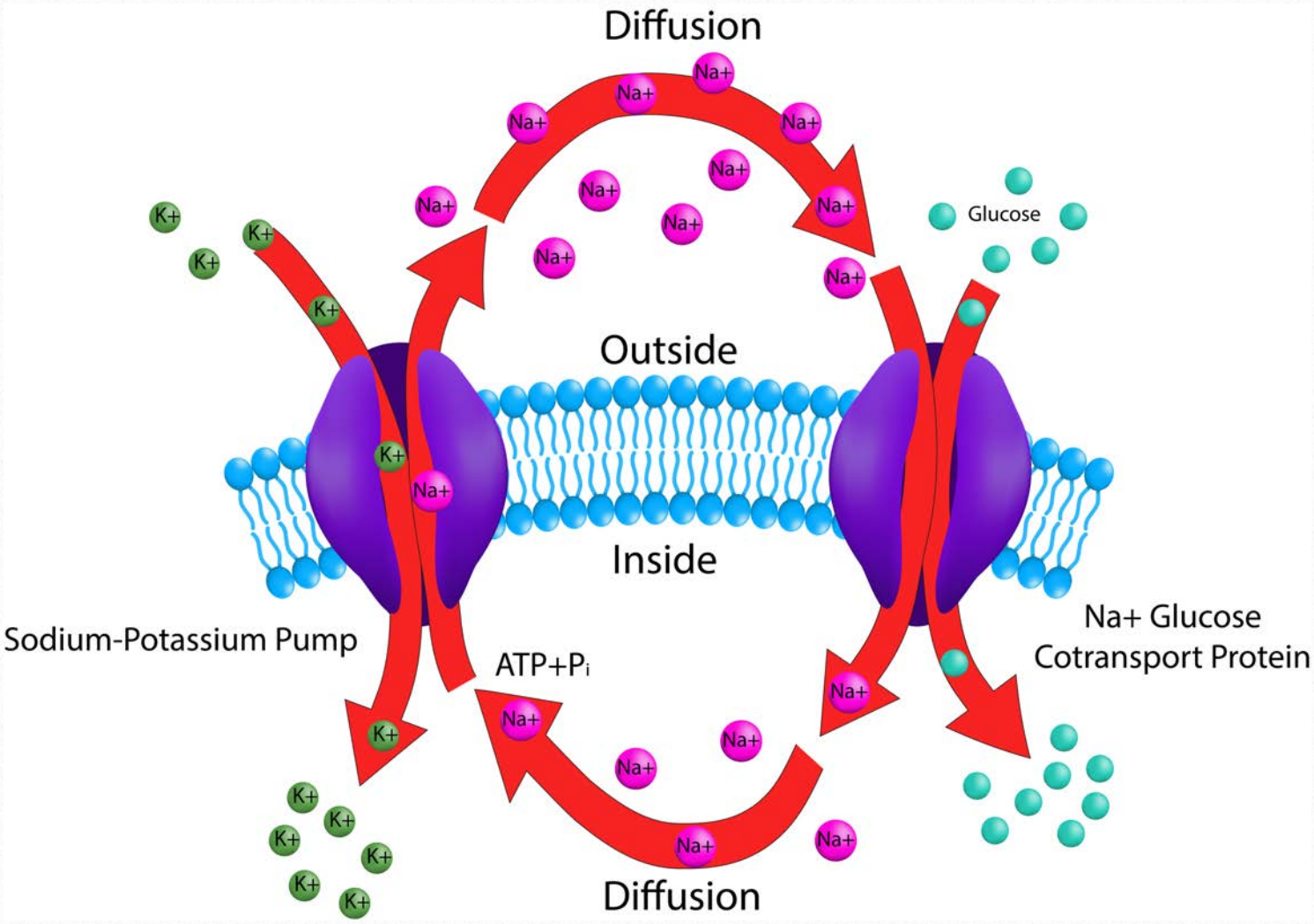


Figure 3.46 - The sodium/glucose pump (right) and the Na^+/K^+ ATPase (left). The sodium gradient generated by the Na^+/K^+ ATPase is used by the sodium/glucose pump to import glucose into the cell.

Wikipedia

muscle contraction/relaxation. At this point, the originating nerve cell has done its job and communicated its information to its immediate target. If the postsynaptic cell is a nerve cell, the process repeats in that cell until it gets to its destination.

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Na^+/glucose transporter

Absorbing nutrients from the digestive system is necessary for animal life. The sodium/glucose transport protein is an electrogenic symporter that moves glucose into intestinal cells. It is found in the intestinal mucosa and the proximal tubule of the nephron of the kidney. The sodium/glucose transport system functions in the latter to promote reabsorption of glucose. The pump works in conjunction with the Na^+/K^+ transport system. The gradient of sodium ions built up by the Na^+/K^+ pump is used as an energy source to drive movement of glucose into cells (see Figure 3.38). Use of an ion gradient established by a separate pump is known as secondary active transport. For intestinal mucosa, the pump transports glucose out of the gut and into gut cells. Later, the glucose is exported out the other side of the gut cells to the interstitial space for use in the body.

Calcium pumps

Calcium ions are necessary for muscular contraction and play important roles as signaling molecules within cells. In addition, when calcium concentrations rise too high, DNA in chromosomes can precipitate. Calcium concentration in cells is therefore managed carefully. It is kept very low in the cytoplasm as a result of action of pumps, both in the plasma membrane, which pump calcium outwards from the cytoplasm and in organelles, such as the endoplasmic reticulum (sarcoplasmic reticulum of muscle cells), which pump calcium out of the cytoplasm and into these organelles.

Opening of calcium channels, then, increases calcium concentration quickly in the cytoplasm resulting in a quick response, whether the intention is signaling or contraction of a muscle. After the response is generated, the calcium is pumped back out of the cytoplasm by the respective calcium pumps.

Some calcium pumps use ATP as an energy source to move calcium and others use ion gradients, such as sodium for the same purpose.

Na^+/Ca^{++} transporter

One calcium pump of interest uses the sodium gradient as an energy source. It is the sodium/calcium pump. This electrogenic antiport system uses sodium's movement into the cell as a driving force to move calcium out of the cell, although its direction can reverse in some circumstances. The pump is a high capacity system to move a lot of calcium quickly, moving up to 5000 calcium ions per second and is found in many tissues with many functions.

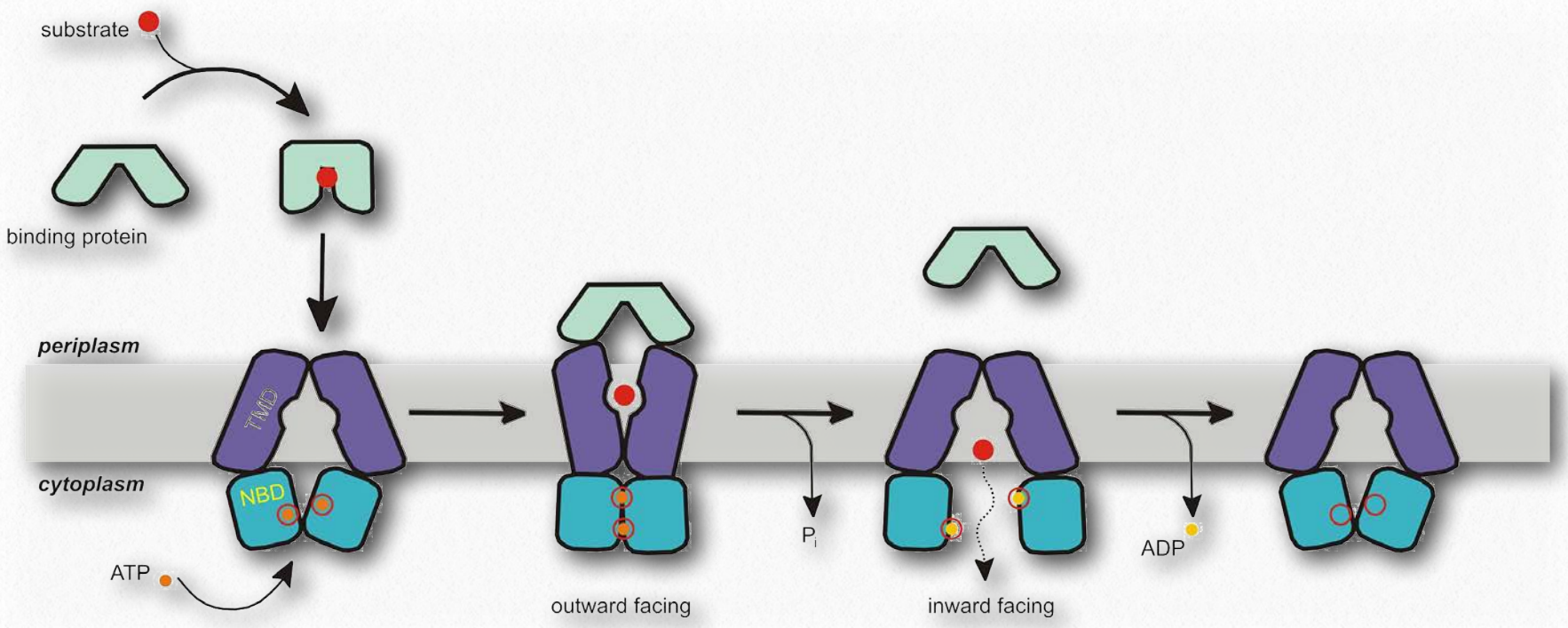

Figure 3.47 - Mechanism of an ABC importer

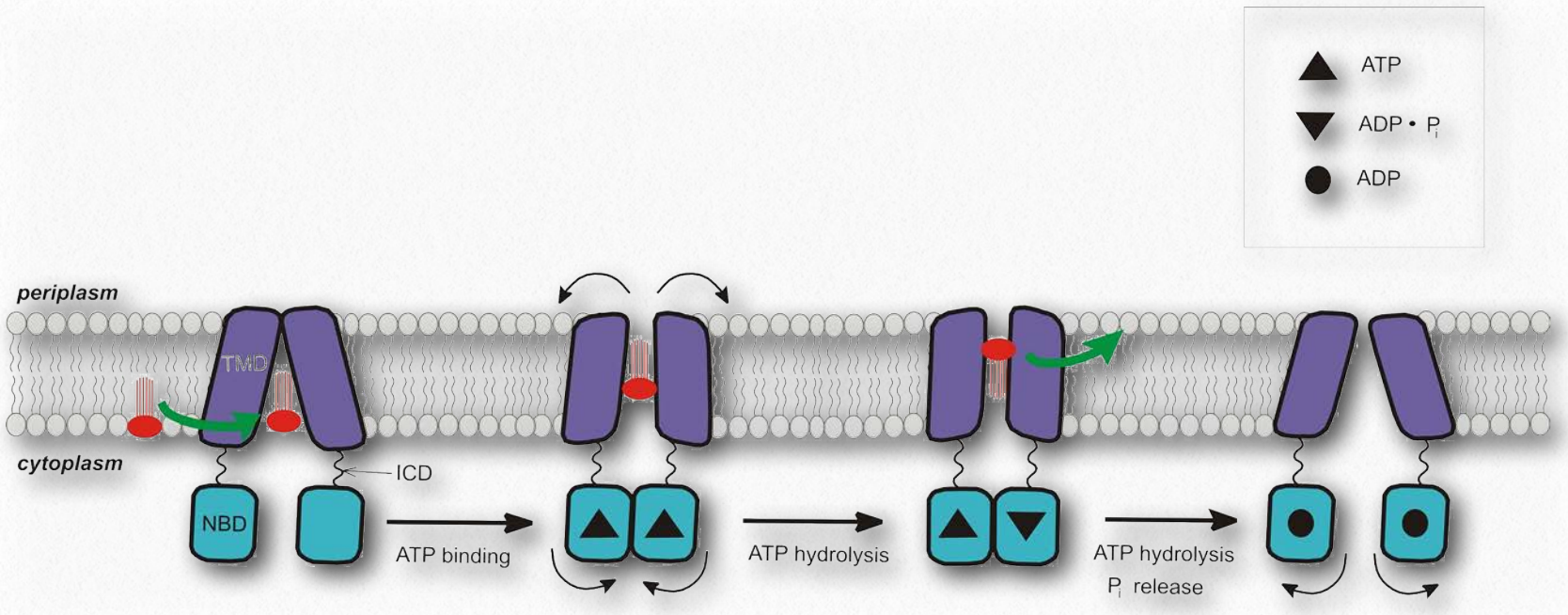

Figure 3.48 - Another view of an ABC exporter. NBD = Nucleotide Binding Domain

Digitalis

One important function of the Na^+/Ca^{++} pump occurs in heart cells. Ca^{++} is important for contraction of heart muscle. Calcium efflux from the cells is the normal operation of the pump, however, during the upstroke of the cycle, there is a large movement of sodium ions into the heart cell. When this occurs, the pump reverses and pumps Na^+ out and Ca^{++} in briefly. Since calcium helps stimulate contraction of cardiac muscle, this can help make the heart beat stronger and is the focus of the use of digitalis to treat congestive heart failure.

Digitalis blocks the sodium-potassium ATPase and interferes with the sodium ion gradient. As noted above, when the Na^+ gradient is oriented in the wrong direction, calcium is pumped in. Digitalis is therefore used to treat congestive heart failure because it increases the concentration of calcium in the heart cells, favoring more forceful beats.

ABC transporters

ABC transporters are another class of transmembrane proteins that use ATP energy to transport things against concentration gradients (Figures 3.47 & 3.48). This protein superfamily includes hundreds of proteins (48 in humans alone) and spans all extant phyla from prokaryotes to humans. These proteins function not only in membrane transport, but also in processes that include DNA repair and the process of translation.

Transport

Substances that ABC transporters move across membranes include metabolic prod-

ucts, lipids, sterols, and drugs. ABC transporters function in multi-drug resistance of many cells, and provide resistance to antibiotics in bacteria as well as resistance to chemotherapy in higher cells by exporting drugs used to treat both of these types of cells.

ABC transporters are divided into three main groups - 1) importers (prokaryotes only); 2) exporters (prokaryotes and eukaryotes), and 3) non-transporters with roles in DNA repair and translation. All ABC transport proteins have four protein domains - two that are cytoplasmic and two that are membrane bound. They are alternately open to the cytoplasmic or extracellular (or periplasmic) regions and this is controlled by hydrolysis of ATP.

Disease

ABC transporters have roles in cystic fibrosis and other inherited human diseases. They are very involved in development of resistance to multiple drugs by a diverse group of cells. ABC transporters provide multi-drug resistance by expelling drug(s) from cells. $ABCB_1$ protein, for example, pumps tumor suppression drugs out of the cell. Another ABC transporter known as

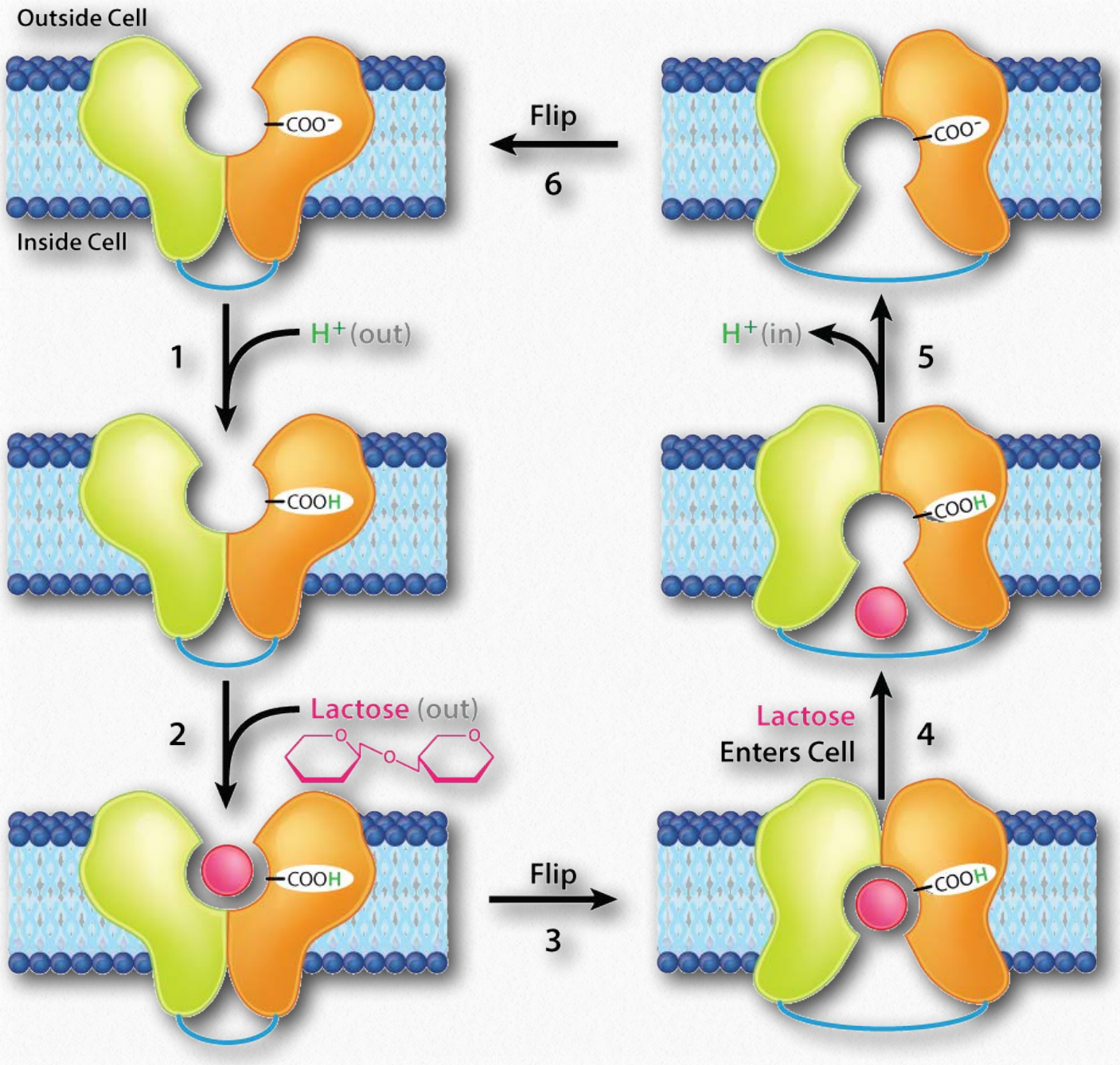

Figure 3.49 - Mechanism of action of lactose permease - Note that the proton acts by altering the charge of a carboxyl group

Image by Aleia Kim

Pgp transports organic cationic or neutral compounds.

Cystic fibrosis

Cystic fibrosis (CF) is a an autosomal recessive genetic disorder arising from mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This ABC transporter system, which moves chloride and thiocyanate ions across epithelial tissue membranes exerts its effect mostly in the lungs but the pancreas, liver, kidneys, and intestine are all also affected by it.

Function

CFTR has roles in the production of sweat, mucus, and digestive fluids. Manifestations of the disease include breathing difficulty and overproduction of mucus in the lungs. When CFTR is functional, these fluids are normally thin, but when the gene is non-functional, they become much thicker and are points of infection.

CFTR contains two ATP-hydrolyzing domains and two cell membrane-crossing domains with 6 α-helices each. It can be activated by phosphorylation by a cAMP-dependent protein kinase. The carboxyl end of CFTR is linked to the cytoskeleton by a PDZ domain.

Lactose permease

Another integral membrane protein performing active transport is lactose permease. It facilitates the movement of the sugar lactose across the lipid bilayer of the cell membrane (Figures 3.49-3.51). The transport mechanism is classified as a secondary active transport since it exploits the inwardly directed H^+ electrochemical gradient as an energy source. When lactose is transported into cells, it is broken down into its substituent monosaccharide sugars - glucose and galactose - for energy creation.

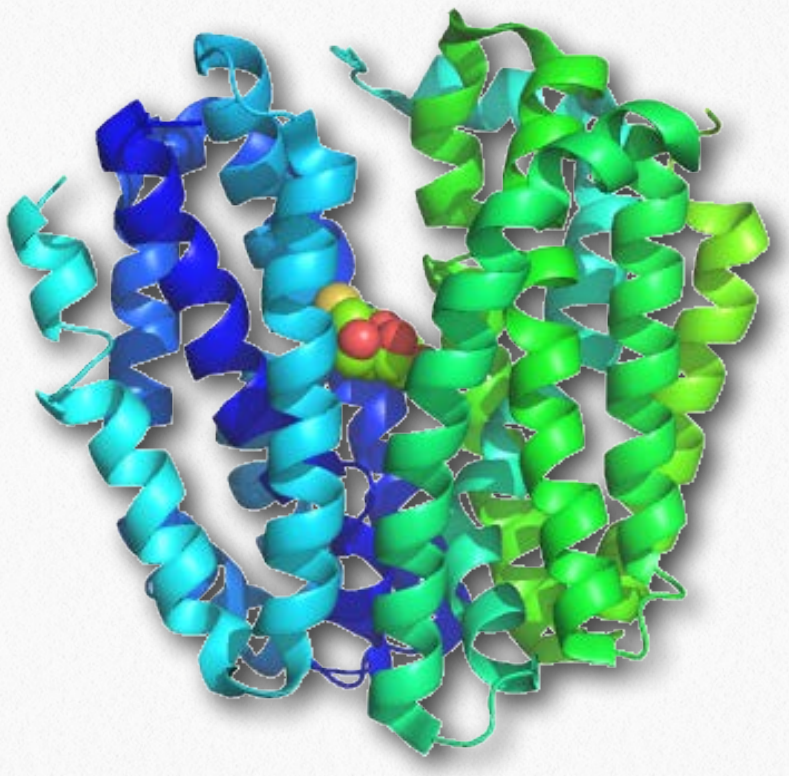

Figure 3.50 - Structure of lactose permease

Wikipedia

The enzyme catalyzing this reaction is known as lactase and deficiency of it in humans leads to lactose intolerance (see HERE).

GLUTs

GLUTs (GLUcose Transport proteins) are uniport, type III integral membrane

proteins that participate in the transport of glucose across membranes into cells. GLUTs are found in all phyla and are abundant in humans, with 12 GLUT genes. GLUT1, in erythrocytes is well-studied. Through GLUT 1, glucose enters and passes through it via facilitated diffusion at a rate that is 50,000 higher than in its absence. GLUTs of various types are found in different cells of the body. The one in red blood cells is known as GLUT 1 and has 12 membrane-spanning hydrophobic helices.

Though the structure of GLUT 1 is not known, it is speculated that the 12 helices form a chamber able to form hydrophilic bonds with glucose to facilitate its passage.

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GLUT 1 levels in erythrocytes go up as glucose levels decrease and decrease when glucose levels go down. GLUT 1 can also transport ascorbate (vitamin C) in addition to glucose in mammals (such as humans) that do not produce their own vitamin C.

Glut 4

GLUT 4 is regulated by insulin and is found primarily in adipose and striated muscle tissue. Insulin alters intracellular trafficking pathways in response to increases in blood

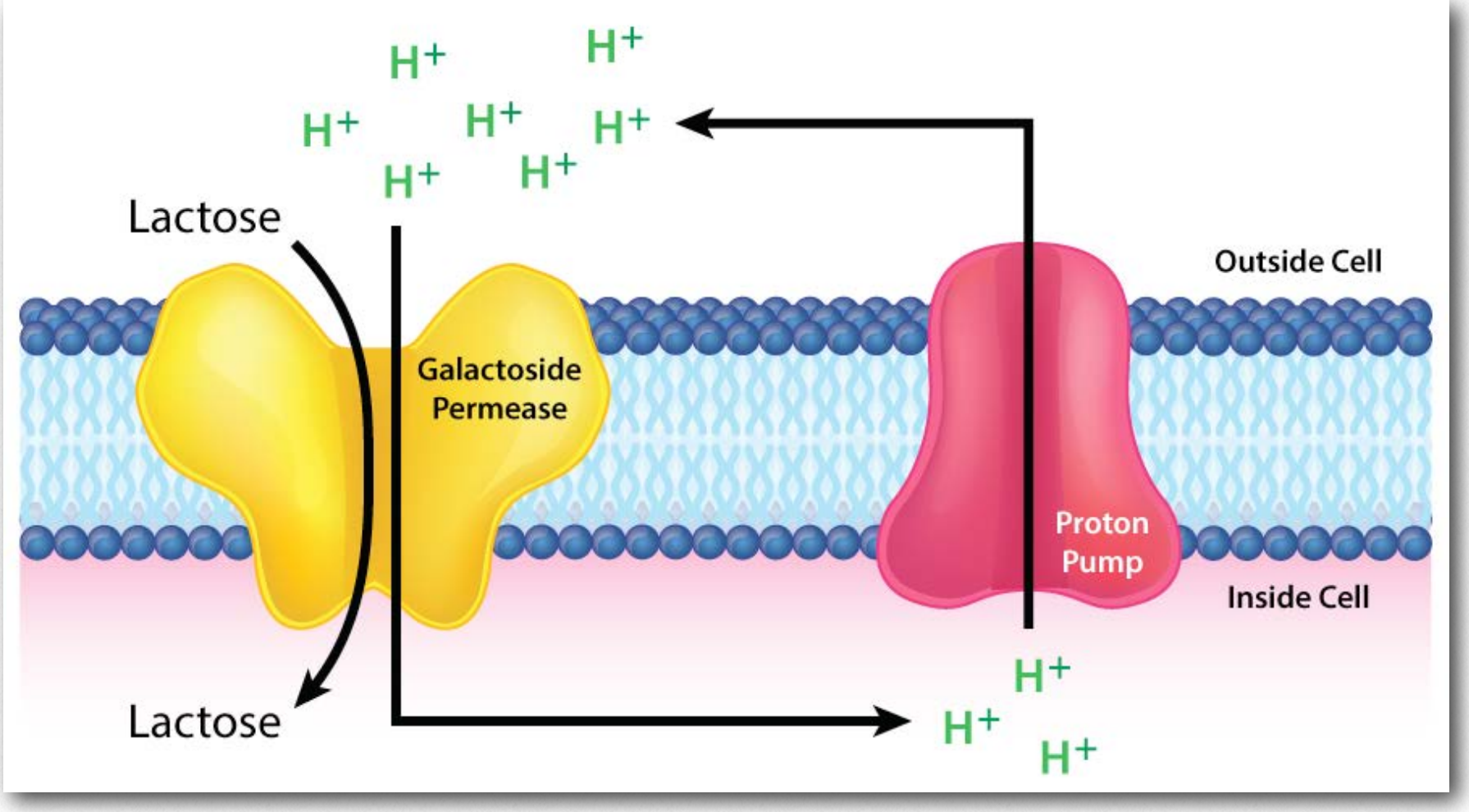

Figure 3.51 - Lactose (galactoside) permease is a secondary transporter, using a proton gradient as an energy source to pump lactose into the cell

Image by Aleia Kim

Glucose Transporters

Name	Tissue	K_M (μM)	Comments
GLUT1	All mammalian tissues	1	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15-20	Participates in insulin regulation in the pancreas; removes excess glucose from the blood in the liver
GLUT3	All mammalian tissues	1	Basal glucose uptake
GLUT4	Muscle and fat cells	5	Concentration in plasma membrane of muscles rises with endurance training
GLUT5	Small intestine	---	Fructose transport

Figure 3.52 - GLUTs found in cells

Image by Aleia Kim

sugar to favor movement of various GLUT proteins (including GLUT 4) from intracellular vesicles to the cell membrane, thus stimulating uptake of the glucose. GLUT 4 is also found in the hippocampus where, if trafficking is disrupted, the result can be depressive behavior and cognitive dysfunction.

For all of the GLUT proteins, a key to keeping the glucose in the cell is phosphorylation of it by the glycolysis enzyme, hexokinase, in the cytoplasm. Phosphorylated molecules cannot enter GLUTs and don't have an easy means of exiting the cell.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Distance Ed

To the tune of "*Mister Ed*"

Metabolic Melodies Website HERE

A course is a source, of course, of course
Of all of the knowledge that we endorse
A major force for better/worse is the campus Distance Ed

It's true to outsource a college course
There are a few standards to be enforced
The long and short's we reinforce the campus Distance Ed

Bridge

A classroom class meets every week the same time every day
But Distance Ed is most unique - its flexible schedule's okay

E-course is a source, of course, of course
Of online assistance for lab reports
You're not enrolled in an online course?

Then sign up for this!

"You'll love Distance Ed"

Recording by David Simmons
Lyrics by Kevin Ahern

This Song's For BB 3-5-0

To the tune of "*This Land is My Land*"

Metabolic Melodies Website HERE

It's one o'clock and
Ahern's talkin'
Henderson and
Hasselbalch and
pKa's and
Buffers I should know
This song's for BB three five oh

I hope that maybe
He'll think the way we
Wrote our answers
Wasn't crazy
I really need the
Partial credit - so
This song's for BB three five oh

It's really groovy
That it improves me
Watching lectures
In Quicktime movies
I really need to
Go and download those
Podcasts for BB three five oh

I'm feeling manic
I'm in a panic
I'd better study
My old organic
It has reactions
That I need to know
This song's for BB three five oh

I know he said it
That's why I dread it
'cause I skipped Friday's
Extra credit
'twil pro'bly haunt me
That lowly ze-ro
Grade in BB three five oh

It could be steric
Or esoteric
That carbons get so
Anomeric
I'm too hysteric
Better let it go
This song's for BB three five oh

Recording by Tim Karplus
Lyrics by Kevin Ahern

Membranes: Other Considerations

There are many functions and factors relating to cell membranes that don't fit into broad categories. Those items will be the focus of this section.

Endocytosis

Besides transporter proteins and ion channels, another common way for materials to get into cells is by the process of endocytosis. Endocytosis is an alternate form of active transport for getting materials into cells. Some of these processes, such as phagocytosis, are able to import much larger particles than would be possible via a transporter protein. Like transporter proteins, endocytosis uses energy for the purpose (though it is not as visible as with protein transporters), but unlike protein transporters, the process is not nearly as specific for individual molecules.

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As a result, the process usually involves the importation of many different molecules each time it occurs. The list of compounds entering cells in this way includes LDLs and their

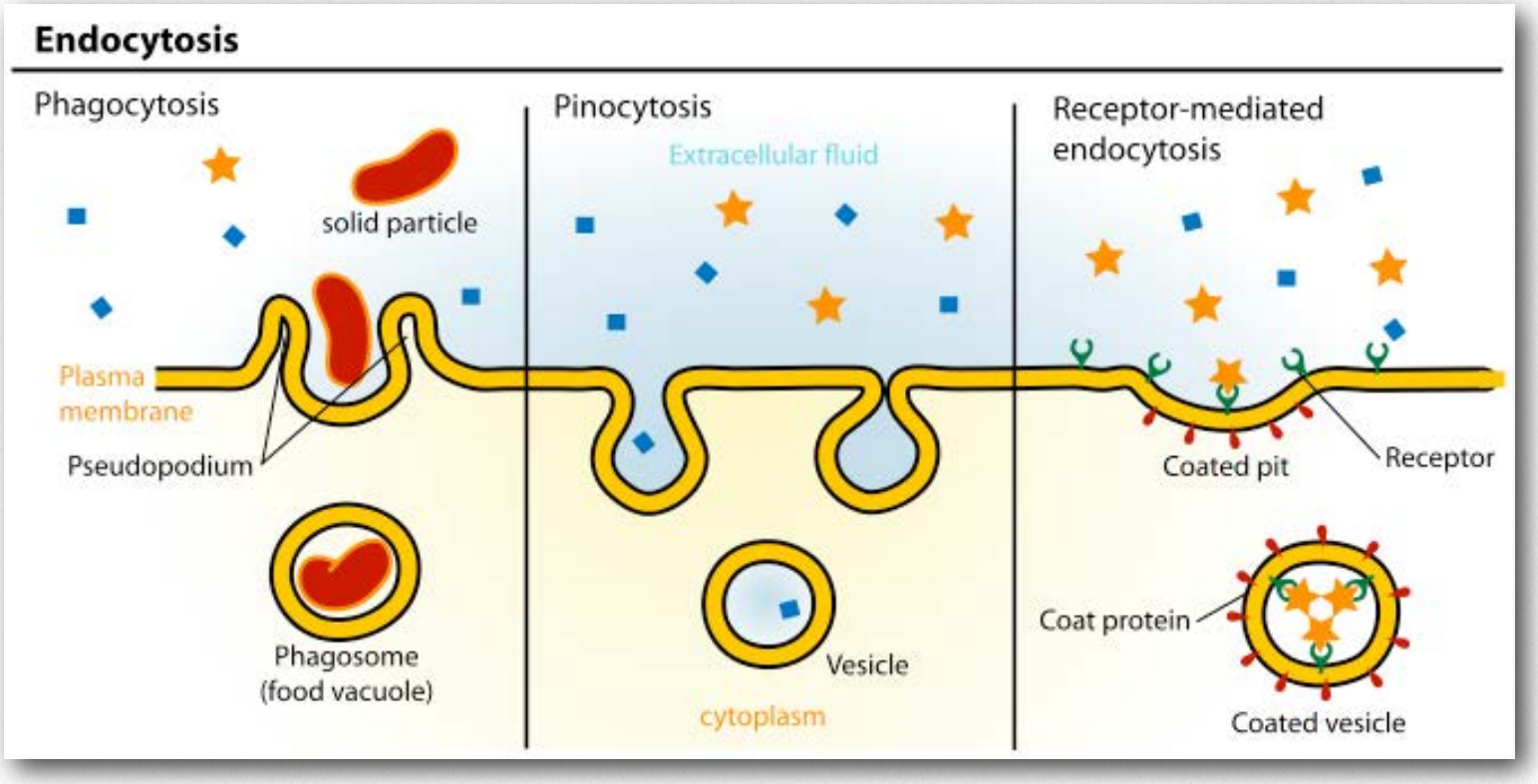

Figure 3.53 - Three types of endocytosis

lipid contents, but it also include things like iron (packaged in transferrin), vitamins, hormones, proteins, and even some viruses sneak in by this means. There are three types of endocytosis we will consider (Figure 3.53).

Receptor mediated endocytosis

The process of receptor mediated endocytosis is a relatively specific means of bringing molecules into cells because it requires the incoming material to be somehow associated with a specific cell surface receptor. In the example of Figure 3.53, the receptor is the cellular LDL receptor. Clathrin-coated invaginations, as

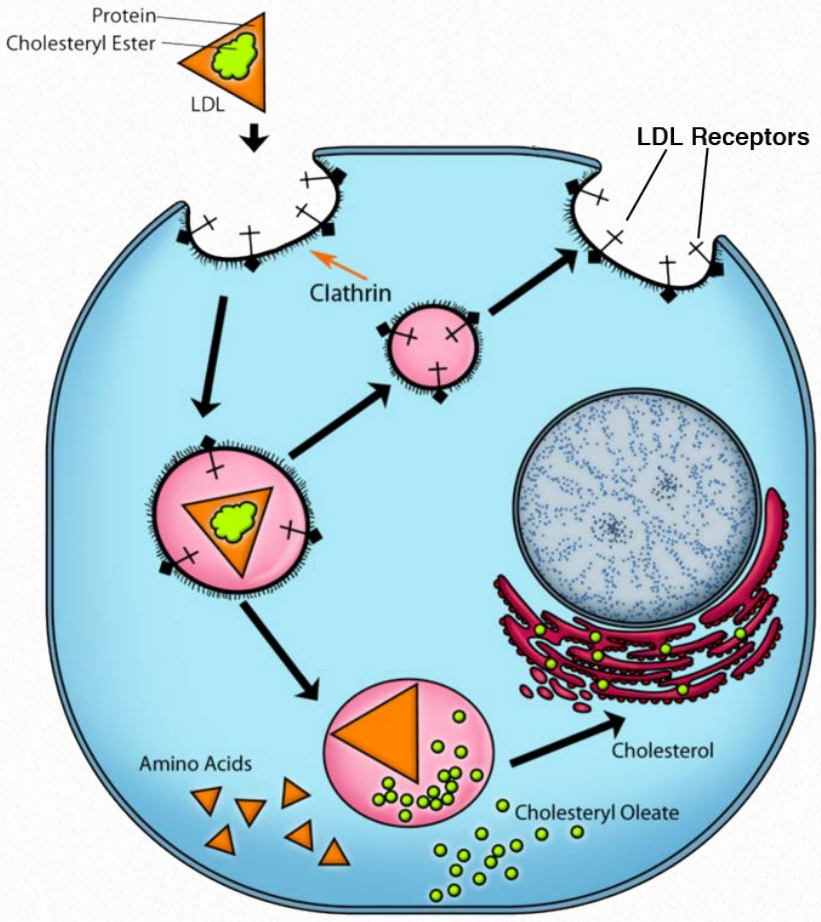

Figure 3.54 - Overview of clathrin-based receptor mediated endocytosis

Image by Aleia Kim

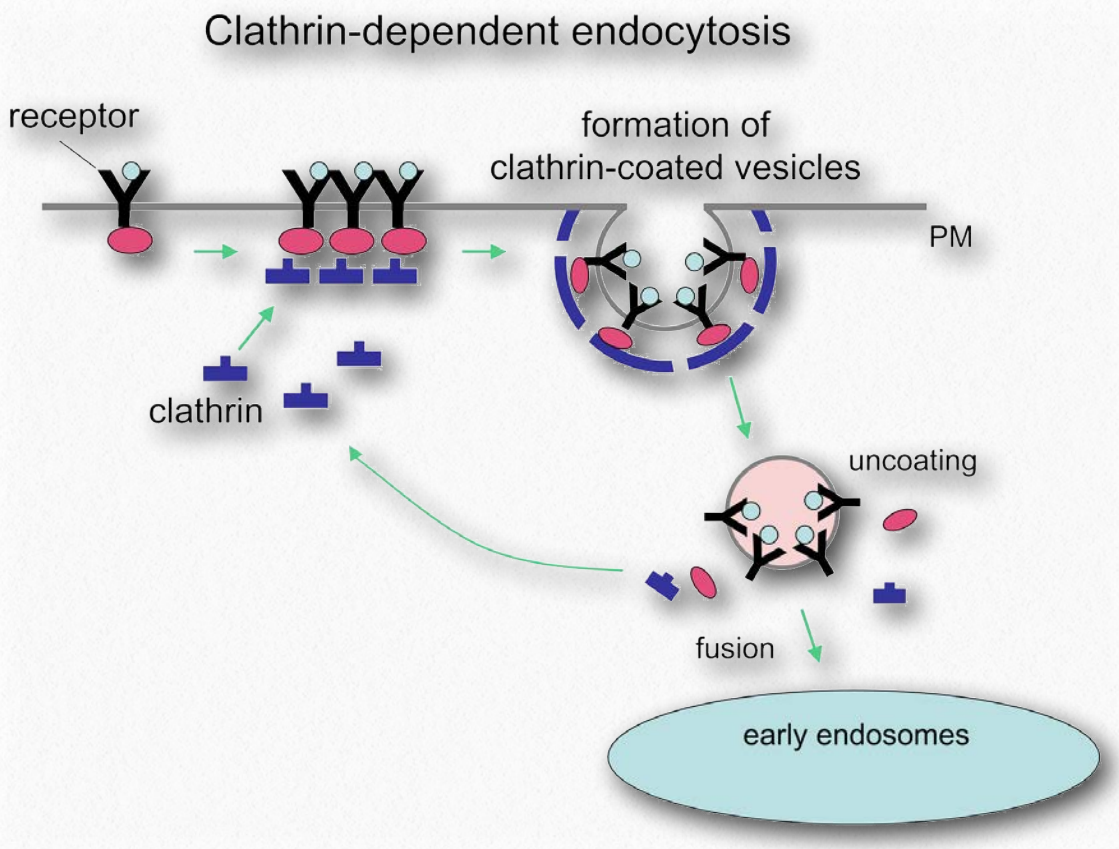

Figure 3.55 - Clathrin-mediated endocytosis of receptors

Wikipedia

shown in the figure are known as “coated pits.” The mechanism proceeds with an inward budding of the plasma membrane receptor (coated vesicles). Binding of the ligand (ApoB-100 of the LDL, for example, in Figure 3.54) to the LDL receptor leads to formation of a membrane invagination. The absorbed LDL particle fuses to form an early endosome (Figure 3.55) and contents are subsequently sorted and processed for use by the cell.

The components from the coated vesicle are recycled to the plasma membrane for additional actions. Receptor mediated endocytosis can also play a role in internalization of cellular receptors that function in the process of signaling. Here, a receptor bound to a ligand is brought into the cell and may ultimately generate a response in the nucleus.

While receptor mediated endocytosis of receptors can have the effect of communicating a signal inwards to the cell, it can also reduce the total amount of signaling occurring, since the number of receptors on the cell surface is decreased by the process.

Non-clathrin endocytosis

There are three types of endocytosis occurring in cells that do not involve clathrin. They are 1) caveolae-based endocytosis, 2) macropinocytosis, and 3) phagocytosis. Caveolae-based endocytosis is based on a receptor molecule known as caveolin. Caveolins are a class of integral membrane proteins that compartmentalize and concentrate signaling molecules in the process of endocytosis. They are named for the cave-like caveolae structures of the plasma membrane where they are found.

Caveolins

Caveolins have affinity for cholesterol and associate with it in the membrane of cells, causing the formation of membrane invaginations of about 50 nm. The caveolin proteins can oligomerize and this is important for

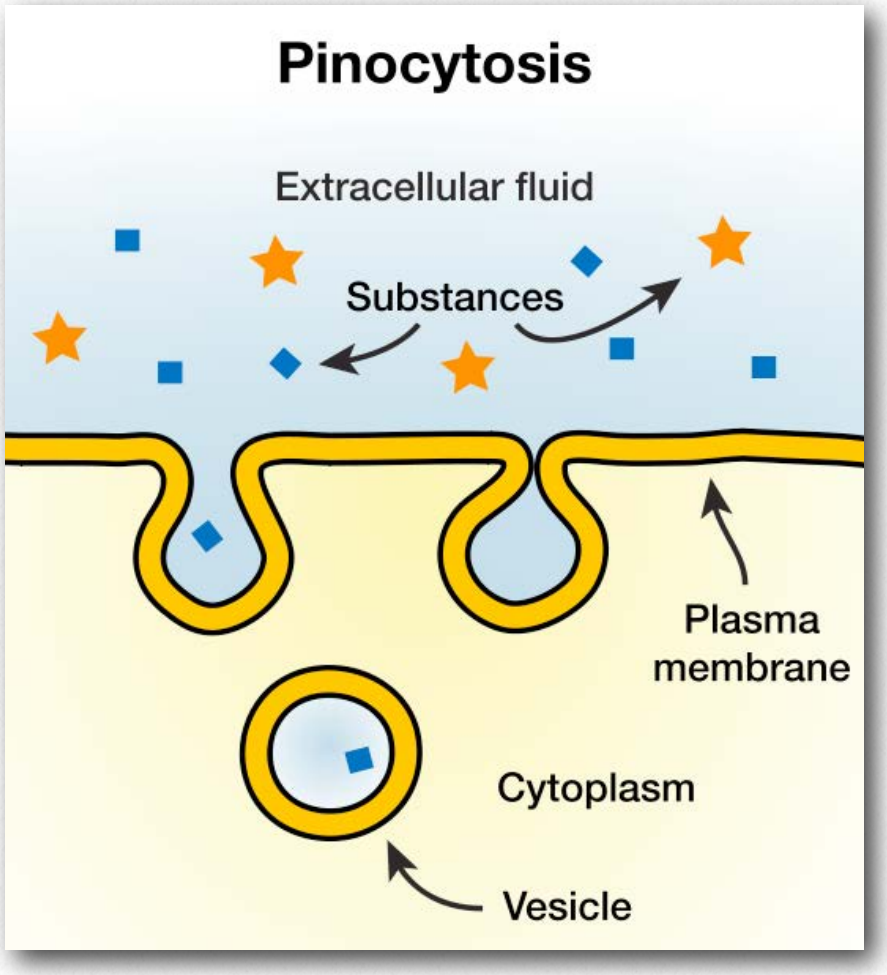

Figure 3.56 - **Macropinocytosis**

the coating and formation of the cave-like structures.

There are three caveolin genes found in vertebrate cells, CAV1, CAV2, and CAV3. Down-regulation of caveolin-1 results in less efficient cellular migration *in vitro*. Caveolins are implicated in both formation and suppression of tumors. High expression of them inhibits cancer-related growth factor signaling pathways, but some caveolin-expressing cancer cells are more aggressive and metastatic, possible due to an enhanced capacity for anchorage-independent growth.

Macropinocytosis

A phenomenon known as "cell drinking," macropinocytosis literally involves a cell "taking a gulp" of the extracellular fluid. It does this, as shown in Figure 3.56, by a simple invagination of ruffled surface features of the plasma membrane. A pocket results, which pinches off internally to create a vesicle containing extracellular fluid and dissolved molecules. Within the cytosol, this internalized vesicle will fuse with endosomes and lysosomes. The process is non-specific for materials internalized.

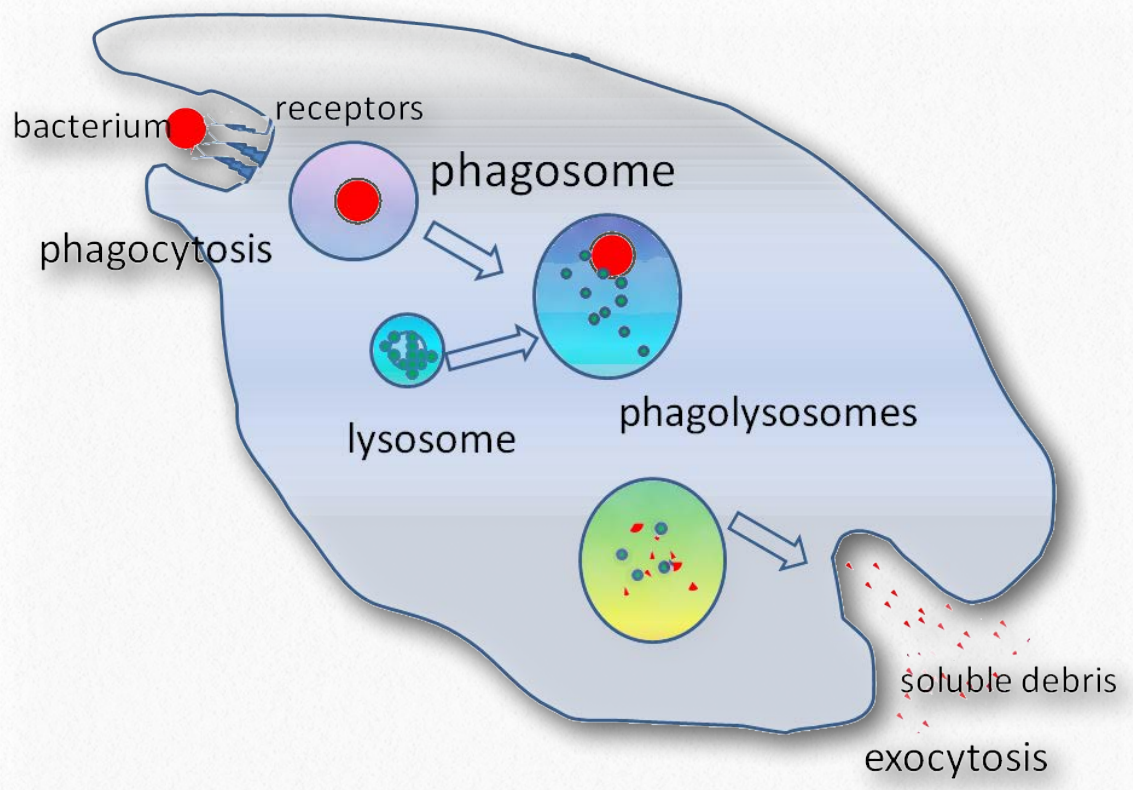

Figure 3.57 - **Generalized scheme for phagocytosis of a bacterium**

Wikipedia

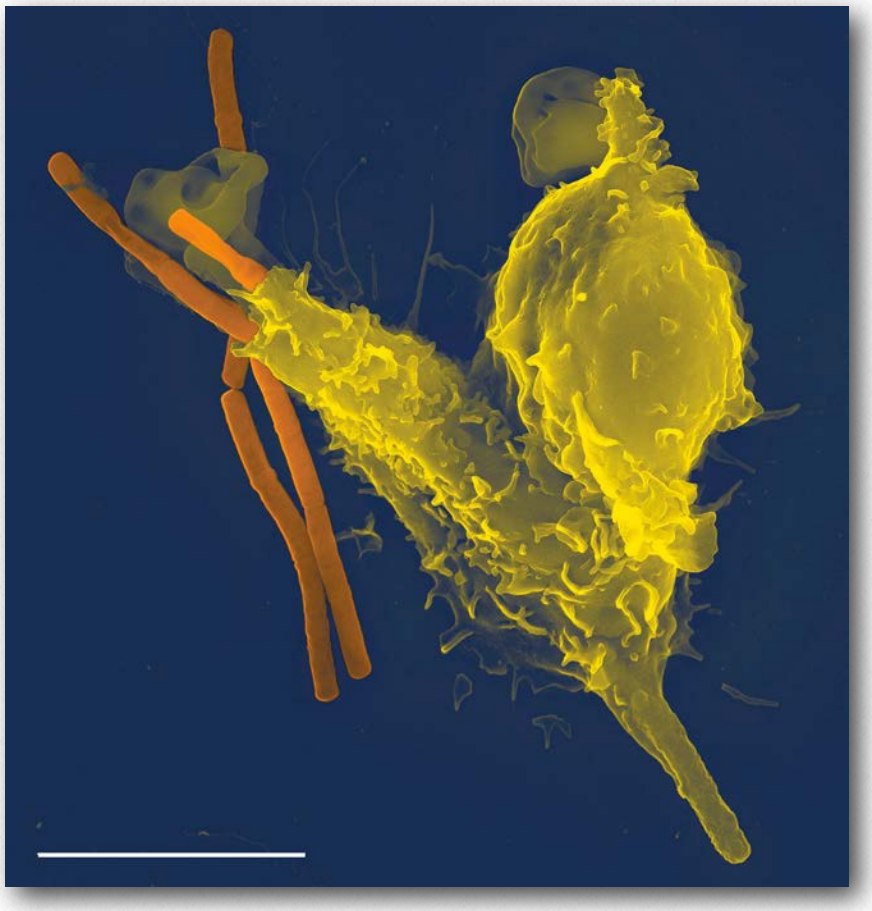

Figure 3.58 - Phagocytosis by a neutrophil (yellow) of an *Anthrax bacillus* (orange)

Wikipedia

Phagocytosis

Phagocytosis is a process whereby relatively large particles (0.75 µm in diameter) are internalized. Cells of the immune system, such as neutrophils, macrophages, and others, use phagocytosis to internalize cell debris, apoptotic cells, and microorganisms.

The process operates through specific receptors on the surface of the cell and phagocytosing cell engulfs its target by growing around it. The internalized structure is known as a phagosome, which quickly merges with a lysosome to create a phagolysosome (Figure 3.58), which subjects the engulfed particle to toxic conditions to kill it, if it is a cell, and/or to digest it into smaller pieces. In some cases, as shown in the figure, soluble debris may be released by the phagocytosing cell.

Endosomes

Internalized material from endocytosis that doesn't involve phagocytosis passes through an internalized structure called an endosome. Endosomes are membrane bounded structures inside of eukaryotic cells that play a role in endocytosis (Figure 3.59). They have a sorting function for material internalized into the cell, providing for retrieval of

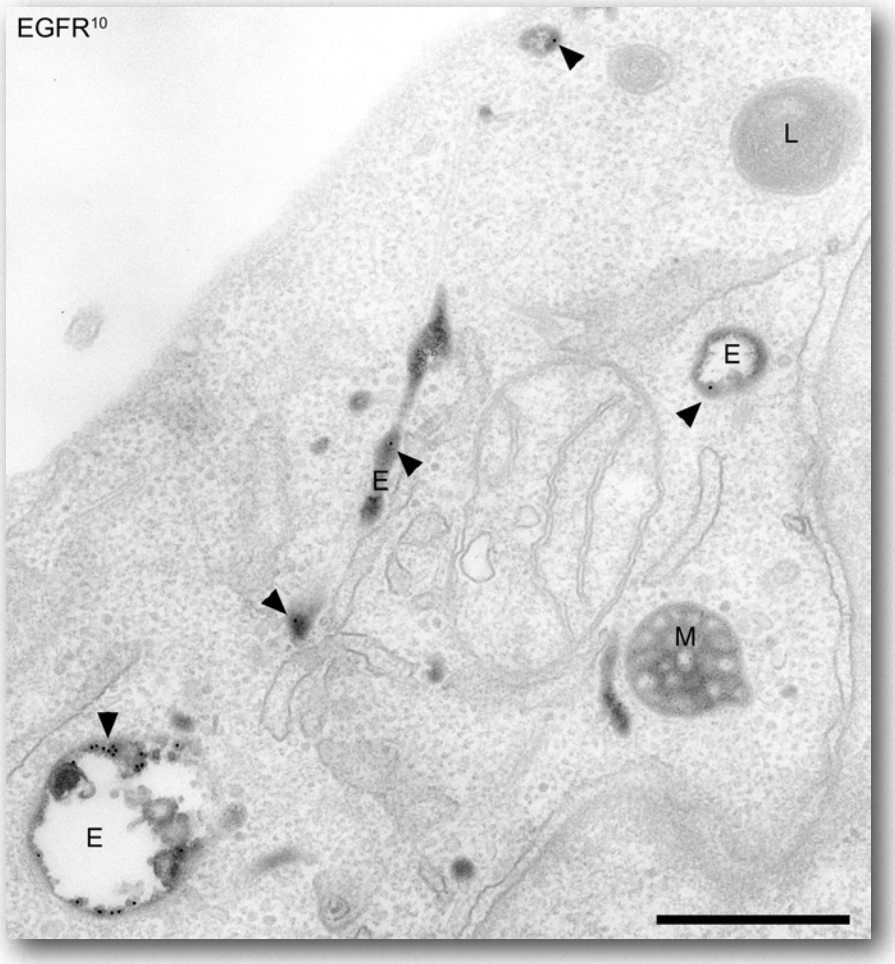

Figure 3.59 - Internalization of the epidermal growth factor receptor (EGFR) into endosomes. Early (E) and late (M) endosomes and lysosomes (L) are labeled.

Wikipedia

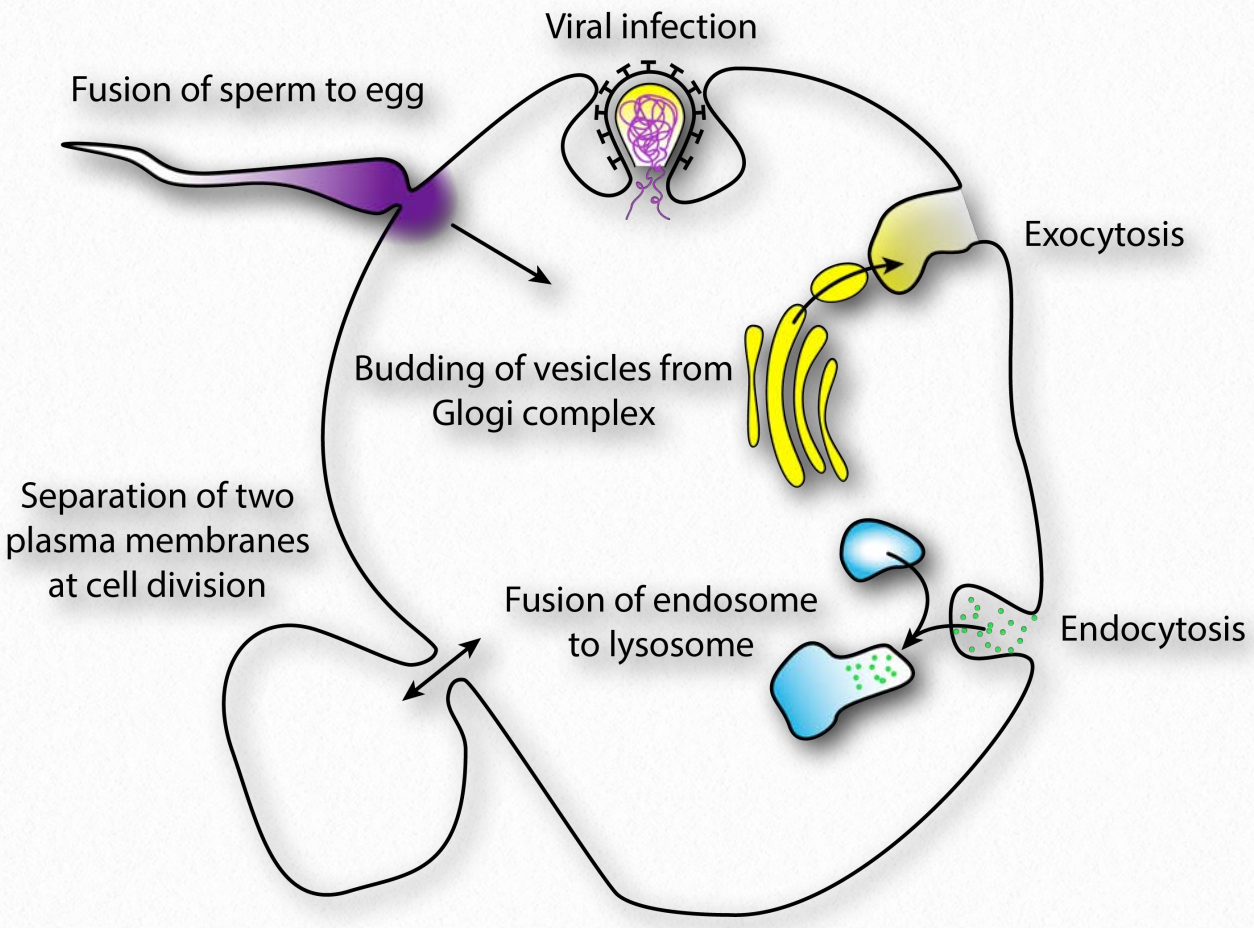

Figure 3.60 - Cell membrane fusions
Image by Pehr Jacobson

materials not destined for destruction in the lysosomes. LDLs, for example, are targeted after endocytosis to the endosomes for processing before part of them is delivered to the lysosome. The endosomes can also receive molecules from the *trans*-Golgi network. These can be delivered to the lysosomes, as well, or redirected back to the Golgi. Endosomes come in three forms - 1) early, 2) late, and 3) recycling.

Exocytosis

The process of exocytosis is used by cells to export molecules out of cells that would not otherwise pass easily through the plasma membrane. In the process, secretory vesicles fuse with the plasma membrane and release their contents extracellularly. Materials, such as proteins and lipids embedded in the membranes of the vesicles become a part of the plasma membrane when fusion between it and the vesicles occurs.

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Membrane fusion

Fusion is a membrane process where two distinct lipid bilayers merge their hydrophobic cores, producing one interconnected structure. Membrane fusion involving vesicles is the mechanism by which the processes of endocytosis and exocytosis occur.

When the fusion proceeds through both leaflets of both bilayers, an aqueous bridge results and the contents of the two structures mix.

Common processes involving membrane fusion (Figure 3.60) include fertilization of an egg by a sperm, separation of membranes in cell division, transport of waste products, and neurotransmitter release (Figure 3.61). Artificial membranes such as liposomes can also fuse with cellular mem-

branes. Fusion is also important for transporting lipids from the point of synthesis inside the cell to the membrane where they are used. Entry of pathogens can also be governed by fusion, as many bilayer-coated viruses use fusion proteins in entering host cells.

SNARE proteins

Mediation of fusion of vesicles in exocytosis is carried out by proteins known as SNAREs (Soluble NSF Attachment Protein REceptor). This large superfamily of proteins spans a wide biological range, from yeast to mammals. Common vesicle fusions occur when synaptic vesicles dock with neurons (Figure 3.61) and release neurotransmitters. These are well-studied. The SNAREs involved in this process can be proteolytically cleaved by bacterial neurotoxins that give rise to the conditions of botulism and tetanus.

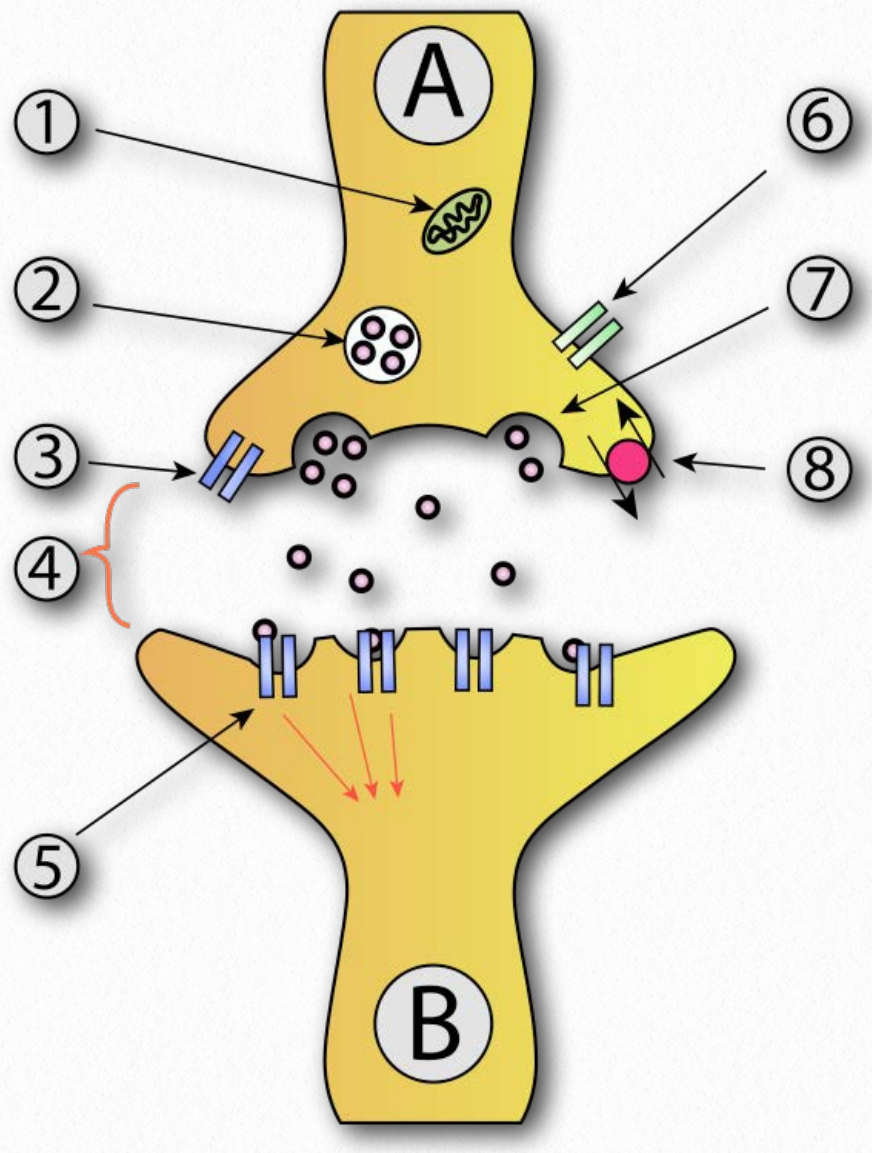

Figure 3.61 - Release of neurotransmitters (small circles) from presynaptic neuron A to postsynaptic neuron B. 1 = Mitochondrion / 2 = Synaptic vesicle with neurotransmitter / 3 = Autoreceptor / 4 = Synaptic cleft / 5 = Neurotransmitter receptor / 6 = Calcium channel / 7 = Fused vesicle releasing neurotransmitter / 8 = Neurotransmitter re-uptake pump

Wikipedia

SNAREs are found in two locations. v-SNAREs are found in the membranes of transport vesicles during the budding process, whereas t-SNARES can be found in the membranes of targeted compartments.

The act of vesicle fusion coincides with increases of intracellular calcium. Fusion of synaptic vesicles in neurotransmission results in activation of voltage-dependent calcium channels in the targeted cell. Influx of calcium helps to stimulate vesicle fusion. In the endocrine system, binding of hormones to G protein coupled receptors activate the IP_3/DAG system to increase levels of calcium.

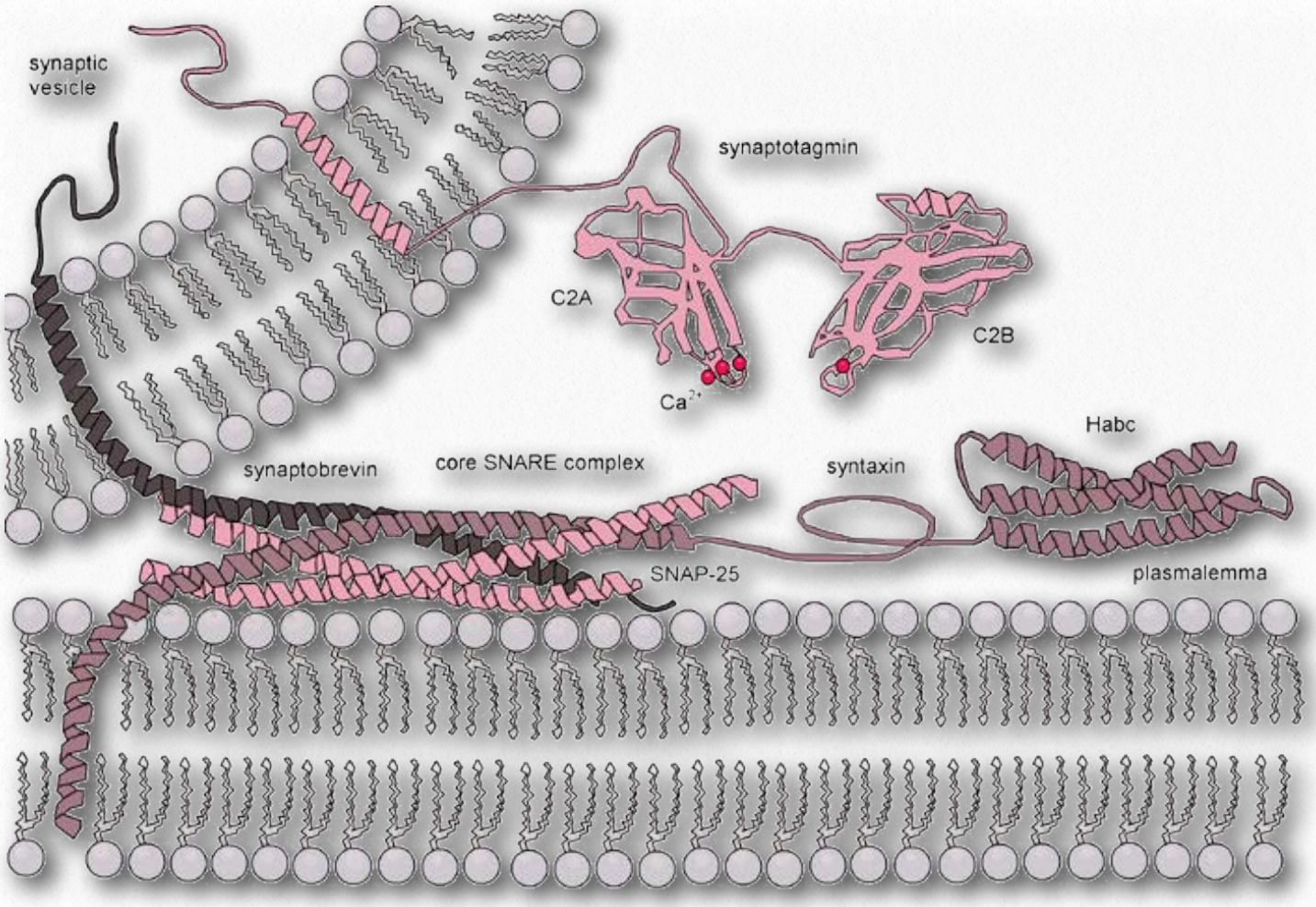

Figure 3.62 - Proteins involved in vesicle fusion in neurotransmission. A SNARE complex between α-helices of synaptobrevin, syntaxin and SNAP-25 intertwine and "zip" membranes together. Synaptotagmin is a calcium sensor regulating the process of zipping

Wikipedia

In the process of membrane fusion (Figure 3.62), the v-SNAREs of a secretory vesicle (upper left) interact with the t-SNAREs of a target membrane (bottom). The v- and t-SNAREs "zipper" themselves together to bring the membrane vesicle and the target membrane closer together.

Zippering also causes flattening and lateral tension of the curved membrane surfaces, favoring hemifusion of the outer layers of each membrane. Continued tension results in subsequent fusion of the inner membranes as well, yielding opening of the contents of the vesicle chamber to its target (usually outside the cell).

Shuttles

Another way to transport items across a membrane for which there is no specific transport system available is the use of shuttles. Shuttles are important when there is no transport mechanism for moving material across a membrane for which no transport system exists.

A great example is NADH. NADH is an important electron carrier that is produced in the cytoplasm and mitochondria of the cell. NADH produced in the mitochondrion goes directly to the electron transport system and delivers electrons to Complex I. NADH produced in the cytoplasm (such as from glycolysis) does not have this option, since the inner membrane of the mitochondrion is impermeable to the molecule

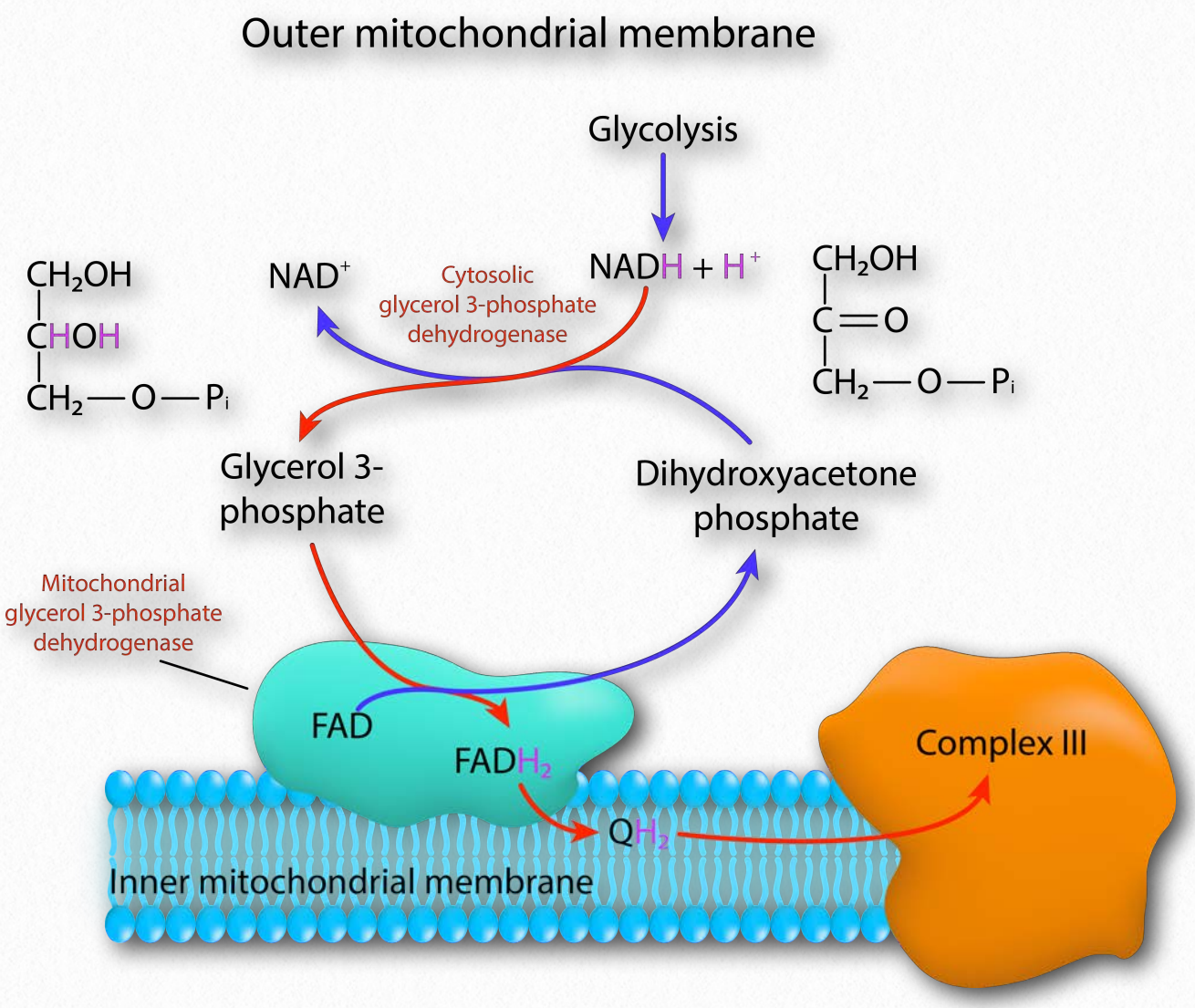

Figure 3.63 - Glycerol phosphate shuttle system in the intermembrane space of a mitochondrion

Image by Pehr Jacobson

Glycerol phosphate shuttle

The first of these methods is the least efficient, but it is rapid. It found commonly in muscles which have needs for rapid energy and brain tissue. This shuttle is referred to as the glycerol phosphate shuttle and is shown in Figure 3.63. It operates in the intermembrane space between the inner and outer mitochondrial membranes. The outer mitochondrial membrane is very porous, allowing many materials to pass freely through it. In the intermembrane space, the cytoplasmic enzyme, glyceraldehyde-3-phosphate dehydrogenase (cGPD) catalyzes transfer of electrons from NADH to dihdydroxyacetone phosphate (#2 in the figure), yielding NAD^+ and glyceraldehyde-3-phosphate (#1 in the figure). The glyceraldehyde-3-phosphate then binds to a glyceraldehyde-3-phosphate dehydrogenase (mGPD) embedded in the outer portion of the inner mitochondrial membrane. mGPD catalyzes the transfer of electrons from glyceraldehyde-3-phosphate to FAD, producing dihycroxyacetone phosphate

and no transporter exists to move it across. The important part of the NADH is its electron cargo, so cells have evolved two ways to move the electrons into the mitochondrial matrix apart from NADH.

Both methods involve shuttles. In each case, an acceptor molecule receives electrons from NADH and the reduced form of the acceptor molecule is transported. It gets transported into the matrix where it is oxidized (electrons are lost) and then donated to the electron transport system.

and $FADH_2$. $FADH_2$ then transfers its electrons to the electron transport system through CoQ (Q above), forming $CoQH_2$ (QH_2 above). As will be discussed in the section on electron transport, this is not an efficient shuttle system because it does not result in production of as much ATP as occurs when electrons are transferred to NAD^+ instead of FAD.

Malate-aspartate shuttle

A more efficient system of transferring electrons is the malate-aspartate shuttle and it is shown in Figure 3.64. As is apparent in the figure, this shuttle involves more steps than the glycerol phosphate shuttle, but the advantage of the malate-aspartate shuttle is that it is more efficient. NADH outside of

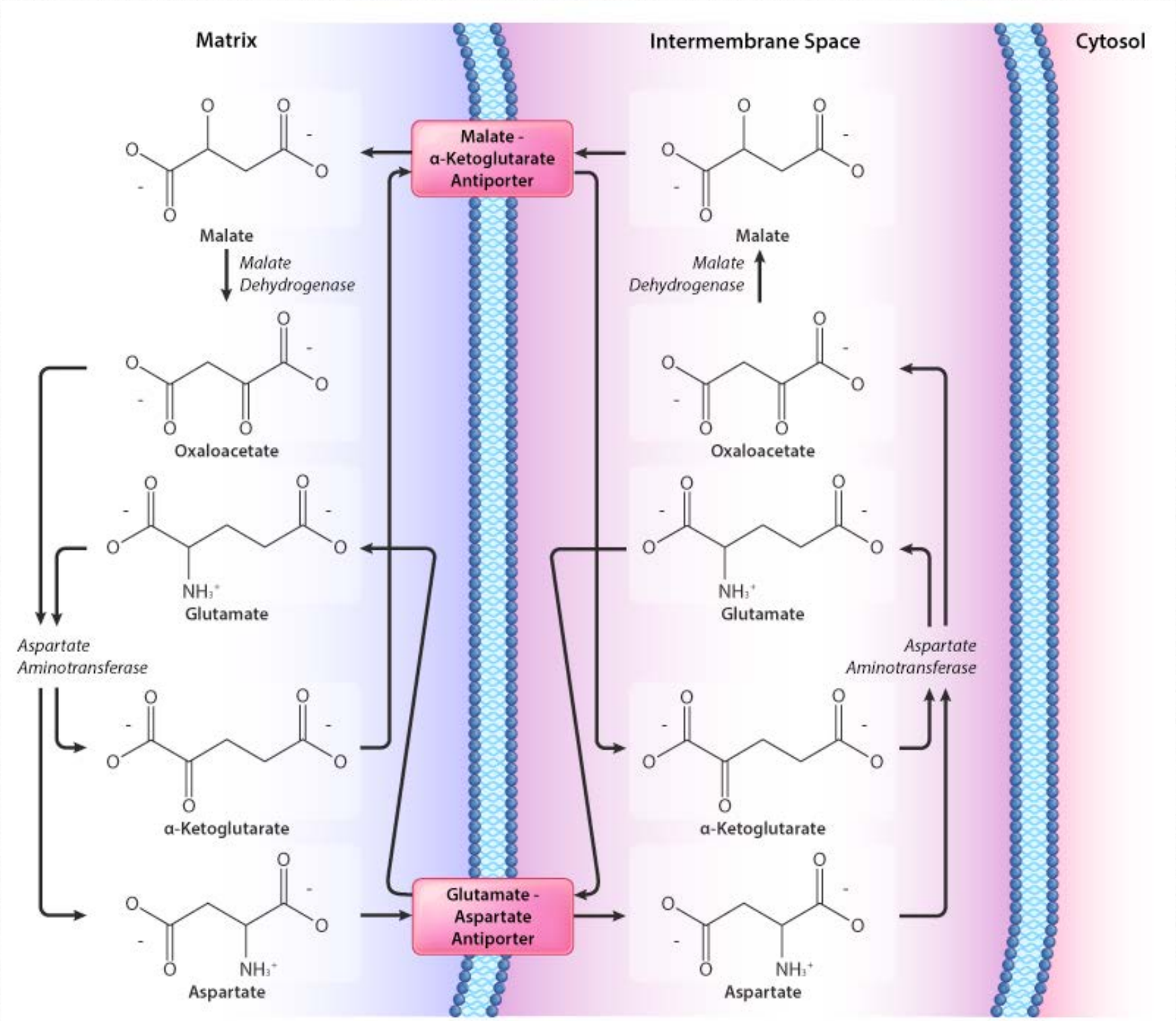

Figure 3.64 - The malate aspartate shuttle

Image by Aleia Kim

the mitochondrion transfers its electrons to the shuttle and then NADH is re-made on the inside of the shuttle. No energy is expended in the process.

When NADH accumulates in the cytoplasm, it moves to the intermembrane space where the enzyme malate dehydrogenase catalyzes the transfer of electrons to oxaloacetate to yield NAD^+ and malate. A transport system for malate moves malate into the mitochondrial matrix in exchange for α-ketoglutarate.

Inside the mitochondrion, malate is reoxidized to oxaloacetate and electrons are given to NAD^+ to recreate NADH. NADH then donates electrons to Complex I of the electron transport system. That's really all there is to the shuttle. The remaining steps are simply to balance the equation of the process. Oxaloacetate accepts an amine group from glutamic acid to yield aspartic acid and α-ketoglutarate. Aspartate then moves out of the mitochondrion through an antiport transport protein that swaps it for glutamate. A series of reactions in the intermembrane space balance the equation.

It is easy to get lost in the mess of balancing equations. The most important thing to understand here is that oxaloacetate accepts electrons on the outside to become malate which is the carrier of electrons across the membrane. Once inside the matrix, malate is converted back to oxaloacetate and its electrons are given to NAD^+, forming NADH. Everything else is simple equation balancing.

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Acetyl-CoA shuttle

Another kind of shuttle also involves the mitochondrion and in this case, the item being moved is a molecule, not a pair of electrons. The molecule of interest here is acetyl-CoA, for which no transport system operates, but which is needed in the cytoplasm for fatty acid synthesis when the cell has abundant energy.

Acetyl-CoA is mostly in the mitochondrion and so long as the citric acid cycle is operating efficiently, its concentration is relatively stable. However, when the citric acid cycle slows, acetyl-CoA and the citrate made from it in the cycle begin to accumulate.

A membrane transport system for citrate exists, so it gets moved out to the cytoplasm. In the cytoplasm, an enzyme known as citrate lyase cleaves citrate to acetyl-CoA and oxaloacetate. Oxaloacetate can be reduced to malate and moved back into the mitochondrion.

As for acetyl-CoA, the more of that cells have in the cytoplasm, the more likely they will begin making fatty acids and fat, since acetyl-CoA is the starting material for fatty acid syn-

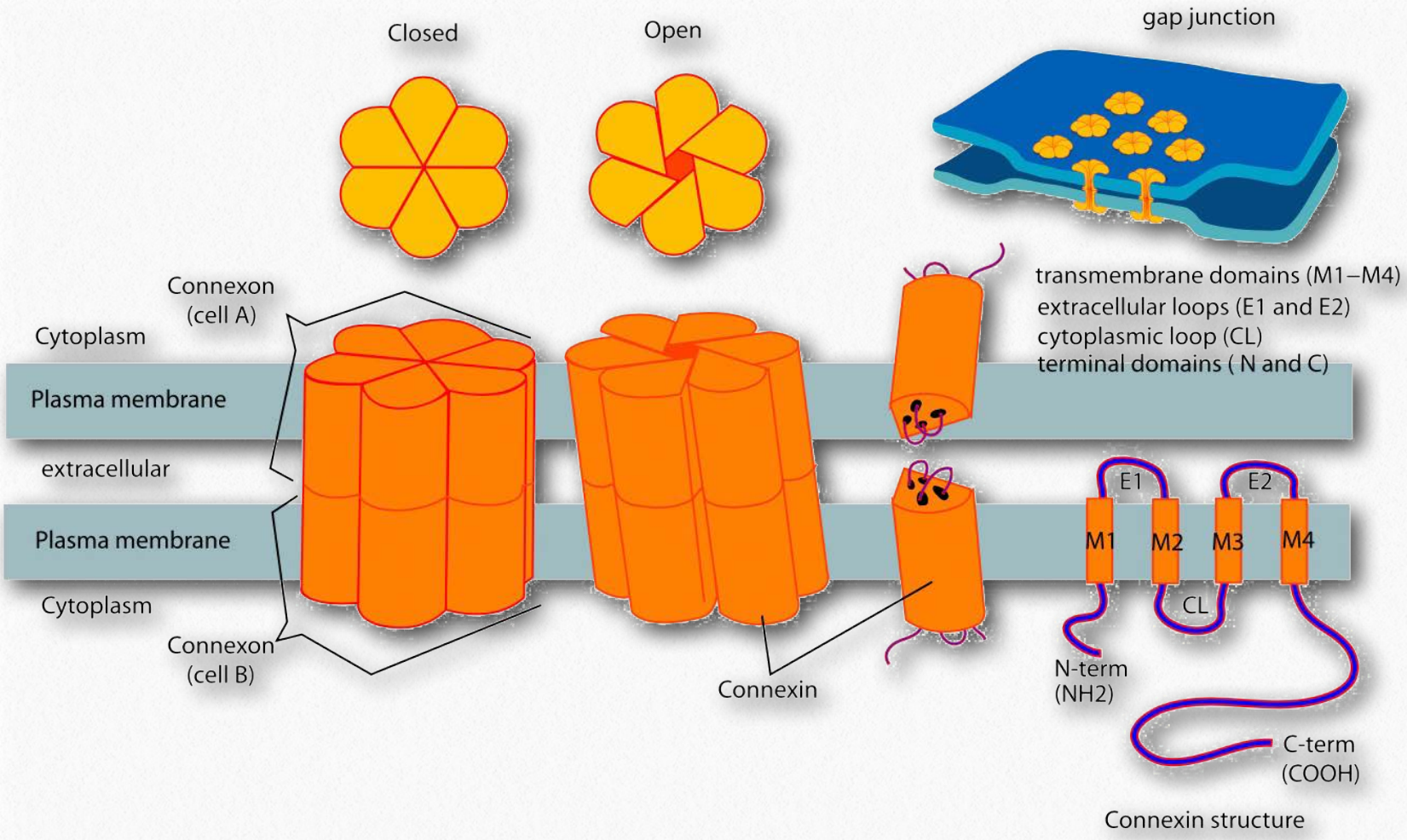

Figure 3.65 - Structure of connexons joining two cells. Bundles of six copies of connexin proteins in the plasma membrane of each cell comprise the connexon structures

thesis, which occurs in the cytoplasm. When does this process occur? As noted above, it occurs when the citric acid cycle stops and this occurs when levels of NADH and $FADH_2$ increase. These, of course, increase when one is not burning off as many calories as one is consuming as a byproduct of respiratory control. Lack of exercise leads to higher levels of reduced electron carriers.

Cell junctions

Cells in multicellular organisms are in close contact with each other and links between them are called junctions. In vertebrate organisms, there are three main types of cell junctions and one of them (gap junctions) is important for movement of materials between cells. The three types are

1. Gap junctions

2. Adherens junctions, (Anchoring Junctions, desmosomes and hemidesmosomes)

3. Tight junctions

Cell junctions in multicellular plants are structured differently from those in vertebrates and are called plasmodesmata. They too

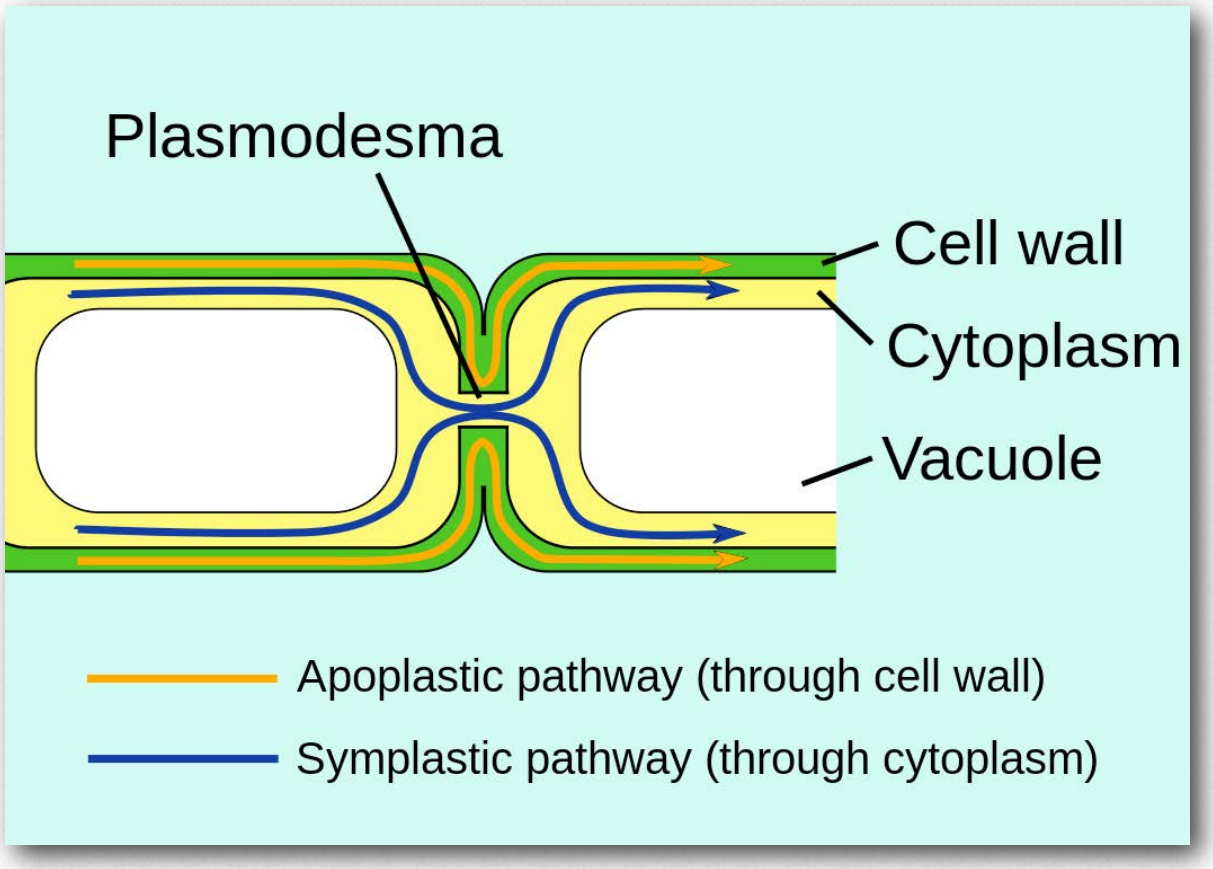

Figure 3.66 - Two means of intercellular communication in plant cells - apoplastic pathway (through cell wall) and symplastic pathway (through the plasodesma)

function in exchange of materials between individual cells.

Gap junctions

Gap junctions are specialized structures made up of two sets of structures called connexons (one from each cell - see Figure 3.65) directly link the cytoplasms of the connected cells. Gap junctions are regulated to control the flow of molecules, ions, and electrical impulses between cells. In plants, similar structures known as plasmodesmata traverse the cell wall (Figure 3.66) and perform similar functions.

Adherens junctions

Adherens junctions (Figure 3.67) are protein complexes on the cytoplasmic side of the cell membranes of epithelial and endothelial tissues that link cells to each other or to the extracellular matrix. They correspond to the fascia adherens found in non-epithelial/non-endothelial cells.

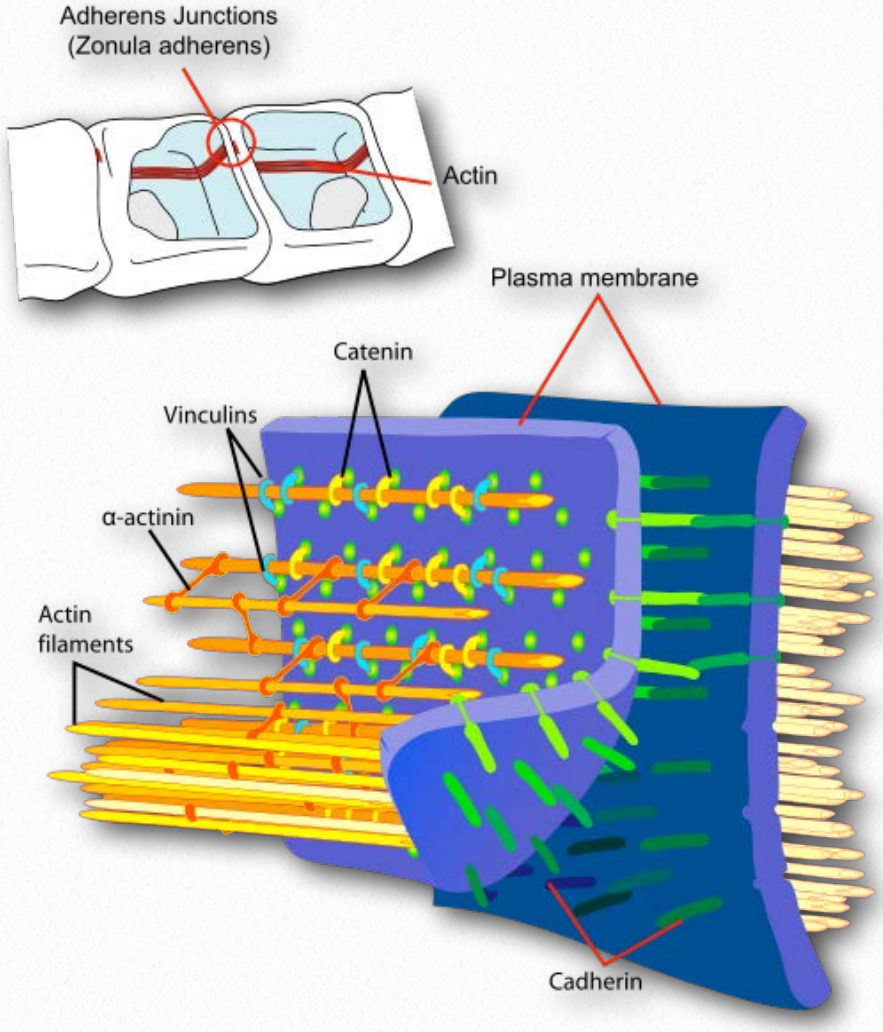

Figure 3.67 - Adherens junction

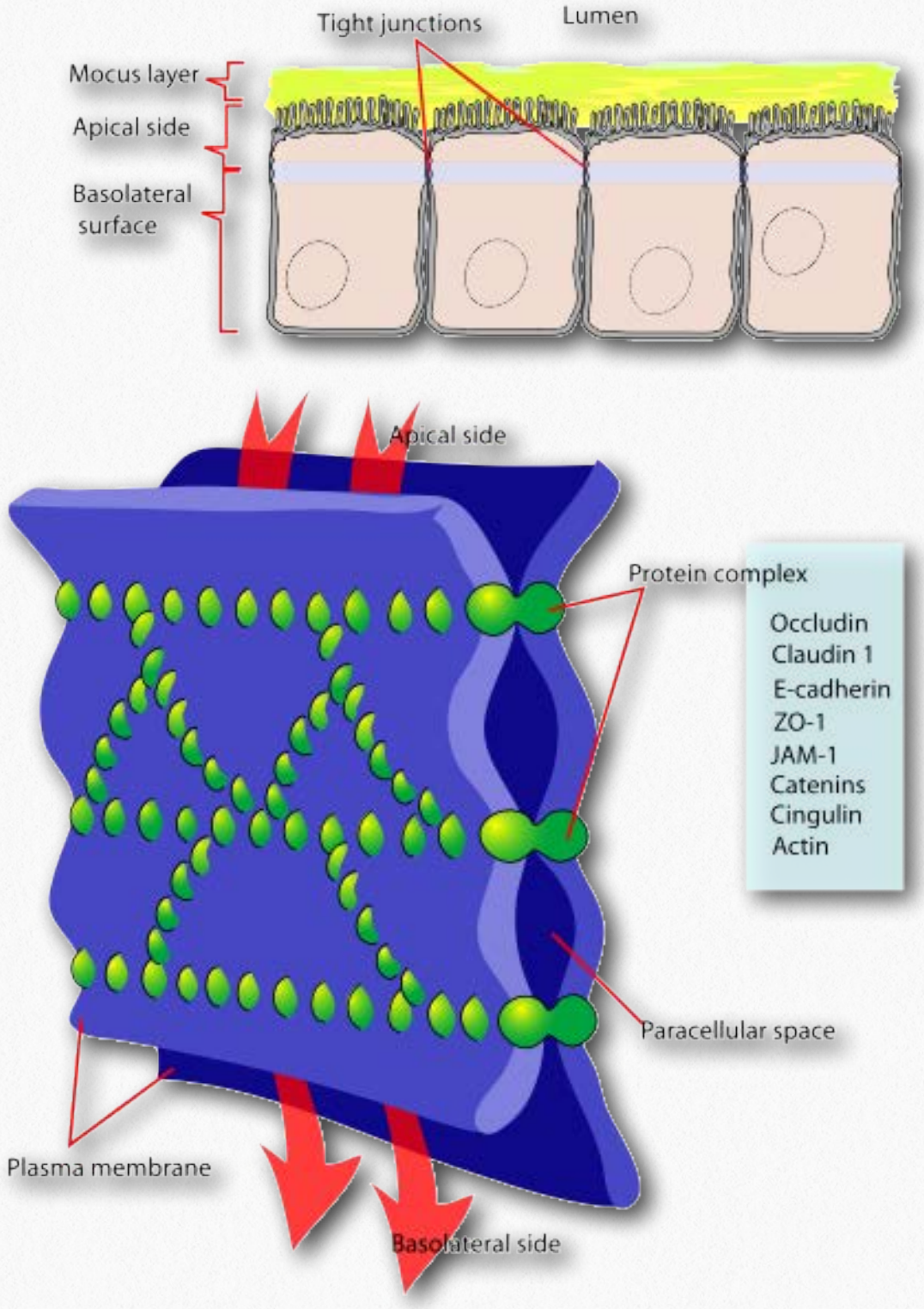

Figure 3.68 - Tight junctions

Adherens junctions contain the following proteins - 1) α-catenin (binds cadherin through β-catenin); 2) β-catenin (attachment for α-catenin to cadherin; 3) γ-catenin (binds to cadherin); 4) cadherins (group of transmembrane proteins that dimerize with cadherins on adjacent cells; 5) p120 (also called Δ-catenin - binds to cadherin); 6) plakoglobin (catenin family protein homologous to and acting like β-catenin); 7) actin; 8) actinin; and 9) vinculin. Adherens junctions may help to maintain the actin contractile ring which forms in the process of cytokinesis.

Tight junctions

Tight junctions (Figure 3.68) are a network of protein strands that seal cells together and restrict the flow of ions in the spaces between them. The effect of their structure is to restrict the movement of materials through tissues by requiring them to pass through cells instead of around them. Tight junctions join together the cytoskeletons of cells and through their structure maintain their apical and basolateral polarity.

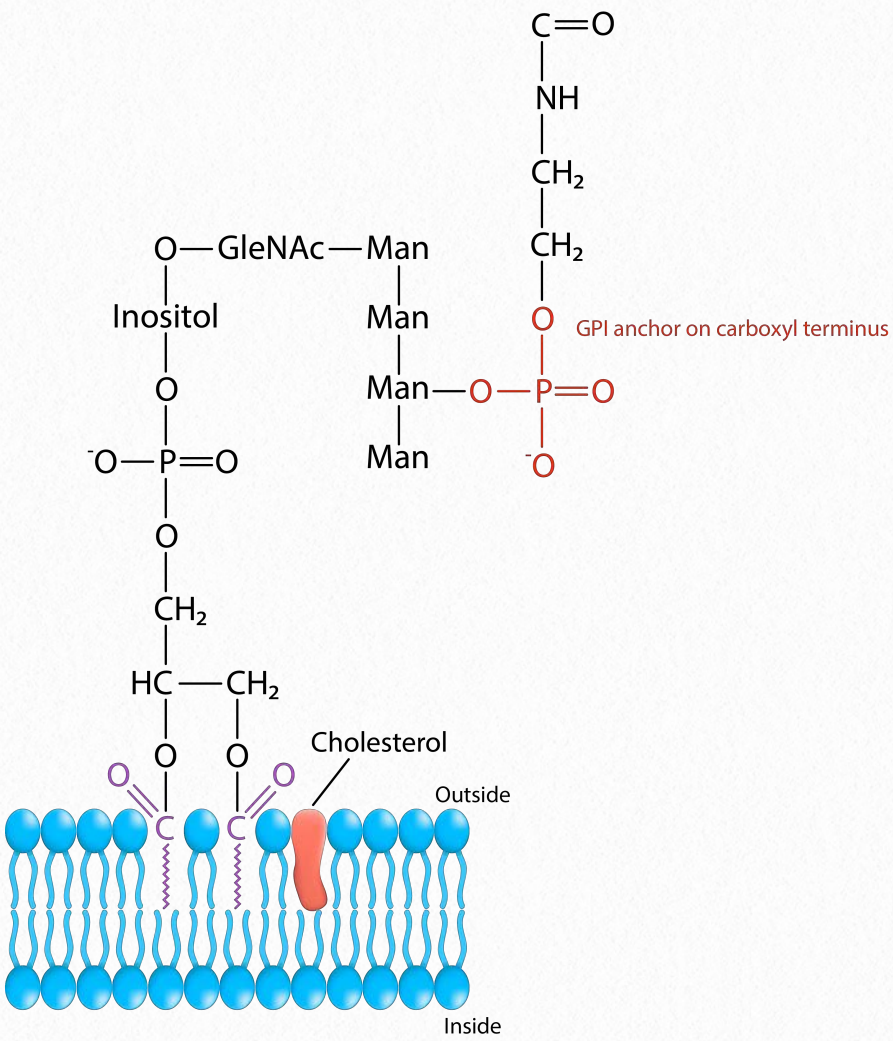

Figure 3.69 - A glypiated protein linked to a membrane-embedded inositol-based molecule. The protein portion is above the red phosphate ion

Image by Pehr Jacobson

GPI anchors

Membrane proteins attached to glycosylphosphatidylinositol (also known as a GPI anchor) are referred to as being glypiated. The proteins, which play important roles in many biochemical processes, are attached to the GPI anchor at their carboxyl terminus. Phospholipases, such as phospholipase C can cut the bond between the protein and the GPI, freeing the protein from the outer cell membrane. Proteins destined to be glypiated have two signal sequences. They are 1) An N-terminal signal sequence and 2) A C-terminal signal sequence that is recognized by a GPI transamidase (GPIT). The N-terminal signal sequences is responsible for directing co-translational transport into the endoplasmic reticulum. The C-terminal sequence is recognized by GPI transamidase, which links the carboxy terminus of a protein to the GPI anchor.

Liposomes

The spontaneous ability of phosphoglycerolipid and sphingolipid compounds to form lipid bilayers is exploited in the formation of artificial membranous structures called liposomes (Figure 3.69). Liposomes are useful for delivering their contents into cells via

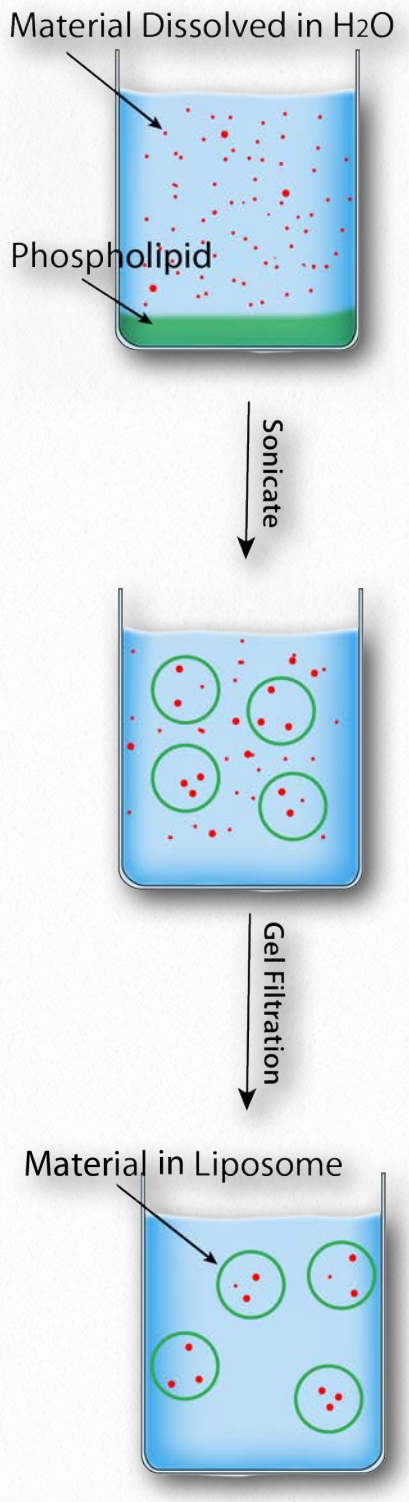

Figure 3.70 - Formation of liposomes from phospholipids in water

Image by Pehr Jacobson

membrane fusion. In the figure, items targeted for delivery to cells would be encased in the middle circular region of the liposome and when the liposome fuses with the cell membrane, it will deliver the contents directly into the cytoplasm.

Hydropathy index

The interior portion of the lipid bilayer is very hydrophobic, which makes it very restrictive to movement of ions and polar substances across it. This property also places limitations on the types of amino acids that will interact with it as well. Because of this, transmembrane protein domains found in integral membrane proteins are biased in the amino acids that interact with either the lipid bilayer or the aqueous material on either side of it.

Hydrophobic amino acids are found within the bilayer, whereas hydrophilic amino acids are found predominantly on the surfaces. An additional clue to identifying membrane crossing regions of a protein is that tryptophan or tyrosine is commonly positioned at nonpolar/polar interface(s) of the lipid bilayer for integral proteins. Such an organization of amino acids can be recognized by computer analysis of amino acid sequences using what is called a hydropathy index/score (Figure 3.71). Though the names and the scorings vary, the idea is to assign a number (usually positive) to amino acid side chains with higher hydrophobicity and negative to those that are ionic. With these scores, a computer program can easily find the average scores of short amino acid segments (say 3 amino acids long) and then plot those values on a graph of hydrophobicity index versus position in polypeptide chain. Doing that for a transmembrane protein such as glycophorin results in the plot shown in Figure 3.72. It is apparent in the analysis that this is a transmembrane protein that has seven domains crossing the lipid bilayer, as labeled.

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Amino Acid	Hydropathy index
Alanine	1.8
Arginine	–4.5
Asparagine	–3.5
Aspartic acid	–3.5
Cysteine	2.5
Glutamic acid	–3.5
Glutamine	–3.5
Glycine	–0.4
Histidine	–3.2
Isoleucine	4.5
Leucine	3.8
Lysine	–3.9
Methionine	1.9
Phenylalanine	2.8
Proline	–1.6
Serine	–0.8
Threonine	–0.7
Tryptophan	–0.9
Tyrosine	–1.3
Valine	4.2

Figure 3.71 - Hydropathy index for amino acids. More positive values indicate higher hydrophobicity.

Wikipedia

Cell walls

Cells walls are found in many cells, including plants, fungi, and bacteria, but are not found

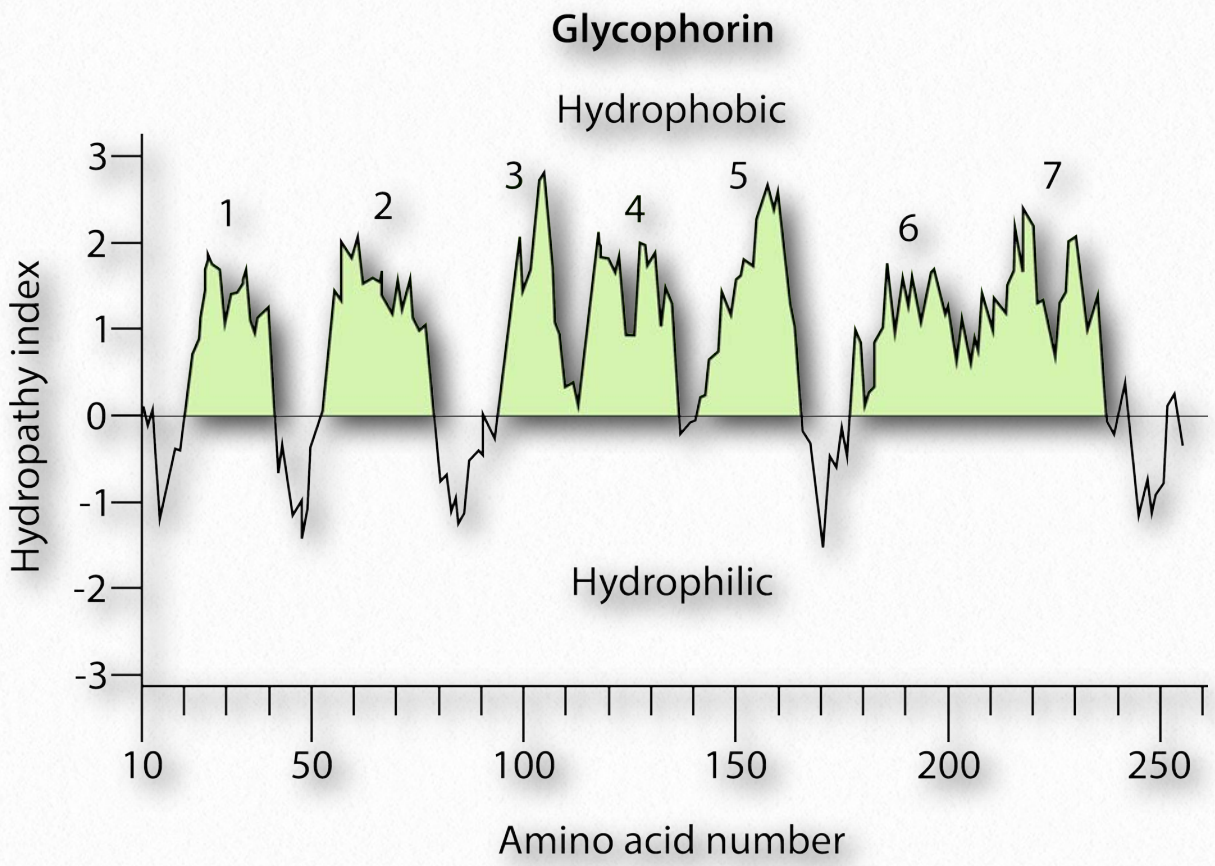

Figure 3.72 - Hydropathy index plot for glycophorin. Each lipid bilayer-crossing domain noted with a number

Image by Pehr Jacobson

in animal cells. They are designed to provide strength and integrity and at least some protection against bursting from osmotic pressure (Figures 3.73-3.75).

Gram positive bacteria (Figure 3.75) have the simplest cell wall design. Moving from outside the cell towards the cytoplasm there is an outer peptidoglycan layer for the cell wall followed by a periplasmic space, a plasma membrane, and then the cytoplasm. Gram negative bacteria add a second protective layer external to all of this, so for them,

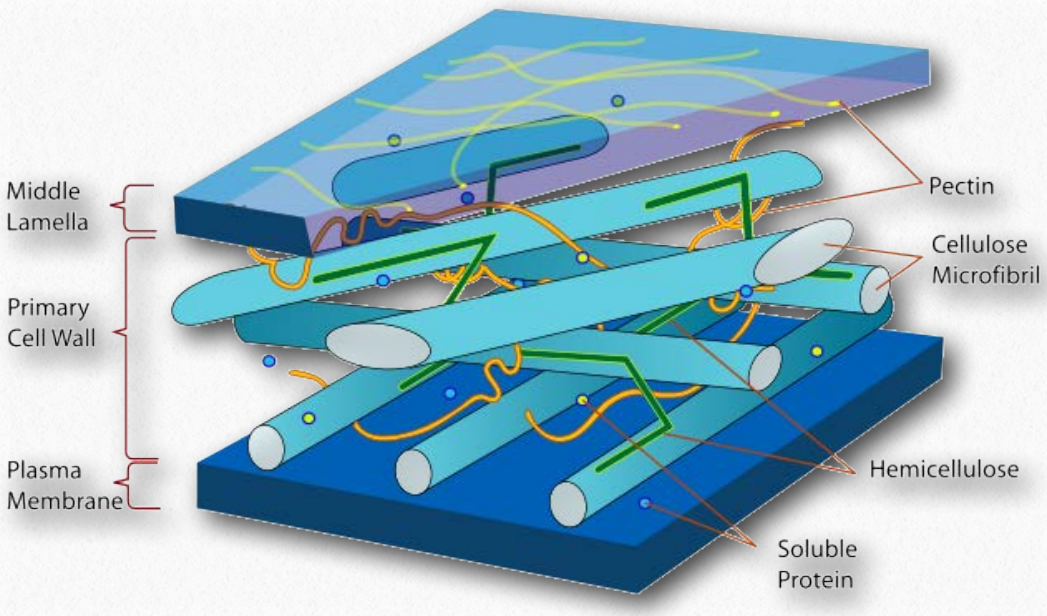

Figure 3.73 - Plant cell wall. Direction of the cytoplasm is down

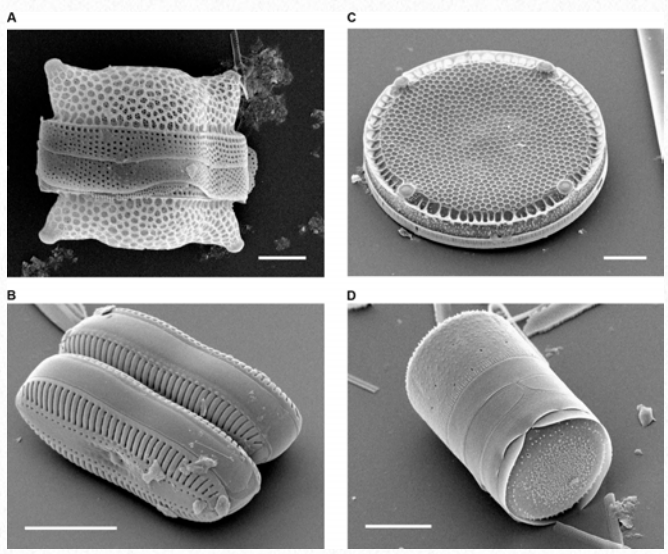

Figure 3.74 - Cell walls of diatoms

Wikipedia

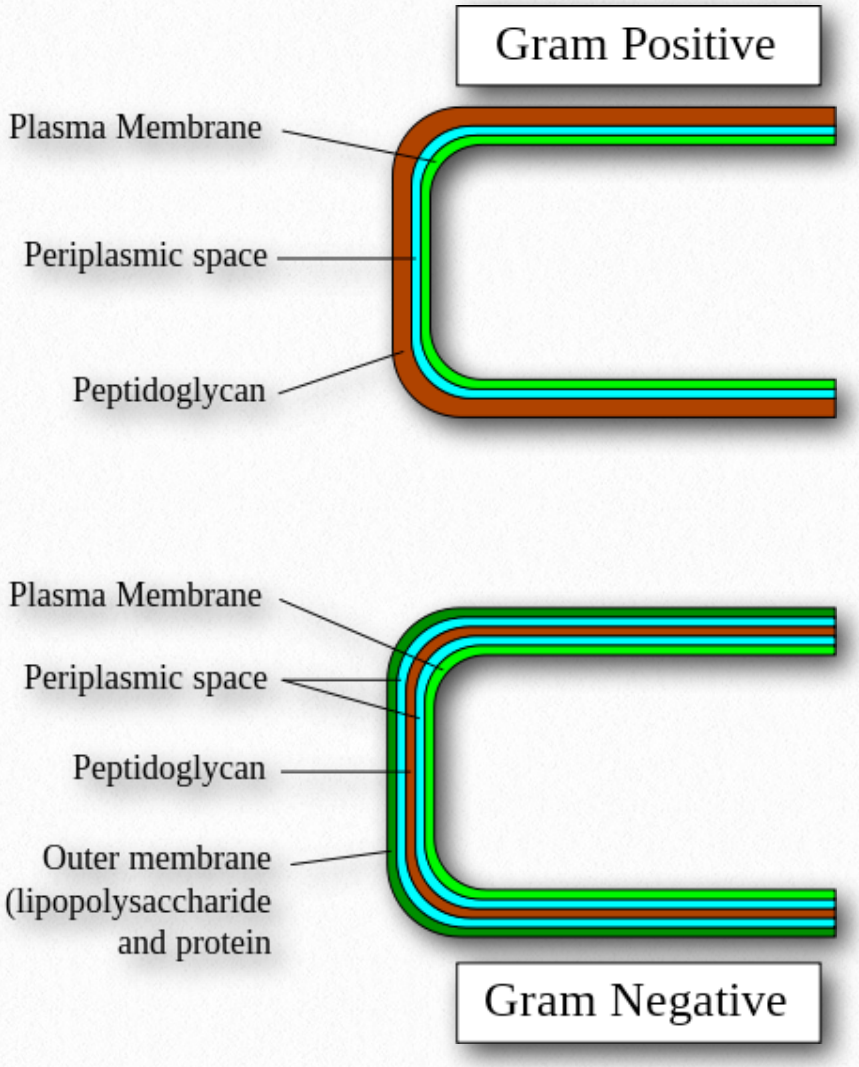

Figure 3.75 - Gram positive versus Gram negative bacteria cell coverings
Wikipedia

starting at the outside and moving inwards, one encounters an outer lipopolysaccharide layer, a periplasmic space, the peptidoglycan cell wall, a second periplasmic space, a plasma membrane and then the cytoplasm.

Herbaceous plants have a rigid outer cell wall (primarily composed of cellulose, hemicellulose, and pectin) and an inner plasma membrane. Woody plants add a second level of wall with lignin between the cellulosic wall and the plasma membrane of herbaceous plants.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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BB Wonderland

To the tune of "*Winter Wonderland*"

Metabolic Melodies Website HERE

Milam Hall - It's 12:30
And Ahern's gettin' wordy

He walks to and fro'
While not talkin' slow
Givin' it to B-B-4-5-0

I was happy when the term got started
Lecture notes and videos galore
MP3s got added to my iPod
But recitations sometimes were a bore

And exams bit me roughly
When the curve turned out ugly

I don't think it's so
My scores are too low
Slidin' by in B-B-4-5-0

Final-LY there's an examination
On December 9th at 6:00 pm
I'll have my card packed with information
So I don't have to memorize it then

And I'll feel like a smarty
With my jam-packed note-cardy
Just one more to go
And then ho-ho-ho
I'll be done with B-B-4-5-0

Recording by David Simmons
Lyrics by Kevin Ahern

Thank God There's a Video

To the tune of "*Thank God I'm a Country Boy*"

Metabolic Melodies Website HERE

There's a bundle of things a student oughta know
And Ahern's talk isn't really very slow
Learnin' ain't easy / the lectures kinda blow
Thank God there's a video

Well we've gone through the cycles and their enzymes too
Studying the regulation everything is new
I gotta admit that I haven't got a clue
What am I gonna do?

So I got me a note card and bought me a Stryer
Got the enzymes down and the names he requires
I hope that I can muster up a little more desire
Thank God there's a video

Just got up to speed about the N-A-D
Protons moving through Complex Vee
Electrons dance in the cytochrome C
Gotta hear the MP3

Fatty acid oxidation makes acetyl-CoA
Inside the inner matrix of the mitochondri-ay
It's very complicated, I guess I gotta say
Thank God there's a video

So I got me a note card and bought me a Stryer
Got the enzymes down and the names he requires
I hope that I can muster up a little more desire
Thank God there's a video

Replication's kind of easy in a simple kind of way
Copyin' the bases in the plasmid DNAs
Gs goes with Cs and Ts go with As
Thanks to polymerase

And the DNA's a template for the RNA
Helices unwinding at T-A-T-A
Termination happens, then the enzyme goes away
Don't forget the poly-A

So I got me a note card and bought me a Stryer
Got the enzymes down and the names he requires
I think that I can muster up a little more desire

Thank
there's a

God
video

Recording by David Simmons
Lyrics by Kevin Ahern

4

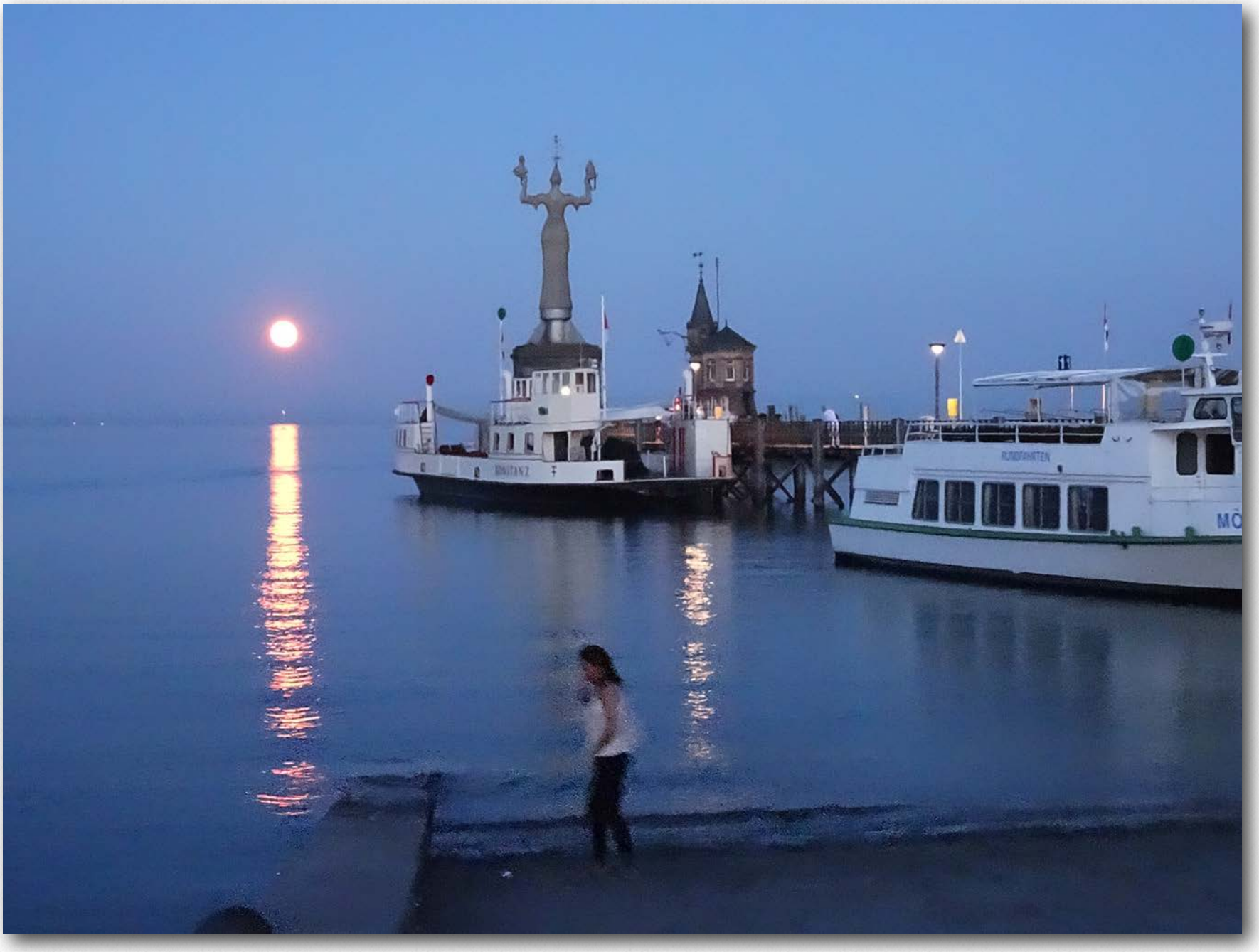
Catalysis

"A clever man commits no minor blunders."

Goethe

Where a good chemical catalyst might accelerate a reaction by a few orders of magnitude, the speed of the best enzyme catalyst boggles the mind, boosting reaction rates by 10^{24} - over 1 trillion trillion times faster than an uncatalyzed one. In this chapter we explore the ways in which the process of enzymatic catalysis occurs.

Catalysis: Basic Principles



If there is a magical component to life, an argument can surely be made for it being catalysis. Thanks to catalysis, reactions that can take hundreds of years to complete in the uncatalyzed "real world," occur in seconds in the presence of a catalyst. Chemical catalysts, such as platinum, can speed reactions, but enzymes (which are simply super-catalysts with a "twist," as we shall see) put chemical catalysts to shame (Figure 4.1). To understand enzymatic catalysis, it is necessary first to understand energy. Chemical reactions follow the universal trend of moving towards lower energy, but they often have a barrier in place that must be overcome. The secret to catalytic action is reducing the magnitude of that barrier.

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Equilibrium

Before discussing enzymes, it is appropriate to pause and discuss an important concept relating to chemical/biochemical reactions. That concept is equilibrium and it is very of-

ten misunderstood. The “equi" part of the word relates to equal, as one might expect, but it does not relate to absolute concentrations. What happens when a biochemical reaction is at equilibrium is that the concentrations of reactants and products do not change over time. This does not mean that the reactions have stopped. Remember that reactions are reversible, so there is a forward reaction and a reverse reaction: if you had 8 molecules of A, and 4 of B at the beginning, and 2 molecules of A were converted to B, while 2 molecules of B were simultaneously converted back to A, the number of molecules of A and B remain unchanged, i.e., the reaction is at equilibrium. However, you will notice that this does not mean that there are equal numbers of A and B molecules.

Concentration matters

So, contrary to the perceptions of many students, the concentrations of products and reactants are not equal at equilibrium, *unless* the **Δ**G°’ for a reaction is zero, because when this is the case,

$\Delta G = \ln\{[Products]/[Reactants]$,

since the ΔG°’ is zero. Because ΔG itself is zero at equilibrium, then [Products] = [Reactants]. This is the only circumstance where [Products] = [Reactants] at equilibrium.

Reiterating, at equilibrium, the concentrations of reactant and product do not change over time. That is, for a reaction

A <=> B

[A] at time zero when equilibrium is reached, $[A]_{T0,}$ will be the same 5 minutes later (assuming A and B are chemically stable). Thus,

$[A]_{T0} = [A]_{T+5}$.

Similarly,

$[B]_{T0} = [B]_{T+5}$

Enzyme	Nonenzymatic Half-Life	Uncatalyzed Rate (k_{un} s^{-1})	Catalyzed Rate (k_{cat} s^{-1})	Rate Enhancement (k_{cat} s^{-1}/k_{un} s^{-1})
OMP decarboxylase	78,000,000 years	28×10^{-16}	39	1.4×10^{17}
Staphylococcal nuclease	130,000 years	1.7×10^{-13}	95	5.6×10^{14}
Carboxypeptidase A	7.3 years	3.0×10^{-9}	578	1.9×10^{11}
Ketosteroid isomerase	7 weeks	1.7×10^{-7}	66,000	3.9×10^{11}
Triose phosphate isomerase	1.9 days	4.3×10^{-6}	4,300	1.0×10^{9}
Chorismate mutase	7.4 hours	2.6×10^{-5}	50	1.9×10^{6}
Carbonic anhydrase	5 seconds	1.3×10^{-1}	1×10^{6}	7.7×10^{6}

Abbreviations:
OMP - Orotine monophosphate
AMP - Adenosine monophosphate

Figure 4.1 - Rate enhancement for several enzymes

Image by Aleia Kim

For that matter, at any amount of time X after equilibrium has been reached,

$$[A]_{T0} = [A]_{T+5} = [A]_{TX}$$

and

$$[B]_{T0} = [B]_{T+5} = [B]_{TX}$$

However, unless $\Delta G^{\circ\prime} = 0$, it is *wrong* to say

$$[A]_{T0} = [B]_{T0}$$

As we study biochemical reactions and reaction rates, it is important to remember that 1) reactions do not generally start at equilibrium; 2) all reactions move in the direction of equilibrium; and 3) reactions in cells behave just like those in test tubes - they do not begin at equilibrium, but they move towards it.

Dynamic reactions

The reactions occurring in cells, though, are very dynamic and complex. In a test tube, they can be studied one at a time. In cells, the product of one reaction is often the substrate for another one. Reactions in cells are interconnected in this way, giving rise to what are called metabolic pathways.

There are, in fact, thousands of different interconnected reactions going on continuously in cells. Attempts to study a single reaction in the chaos of a cell is daunting to say the least. For this reason, biochemists isolate enzymes from cells and study reactions individually.

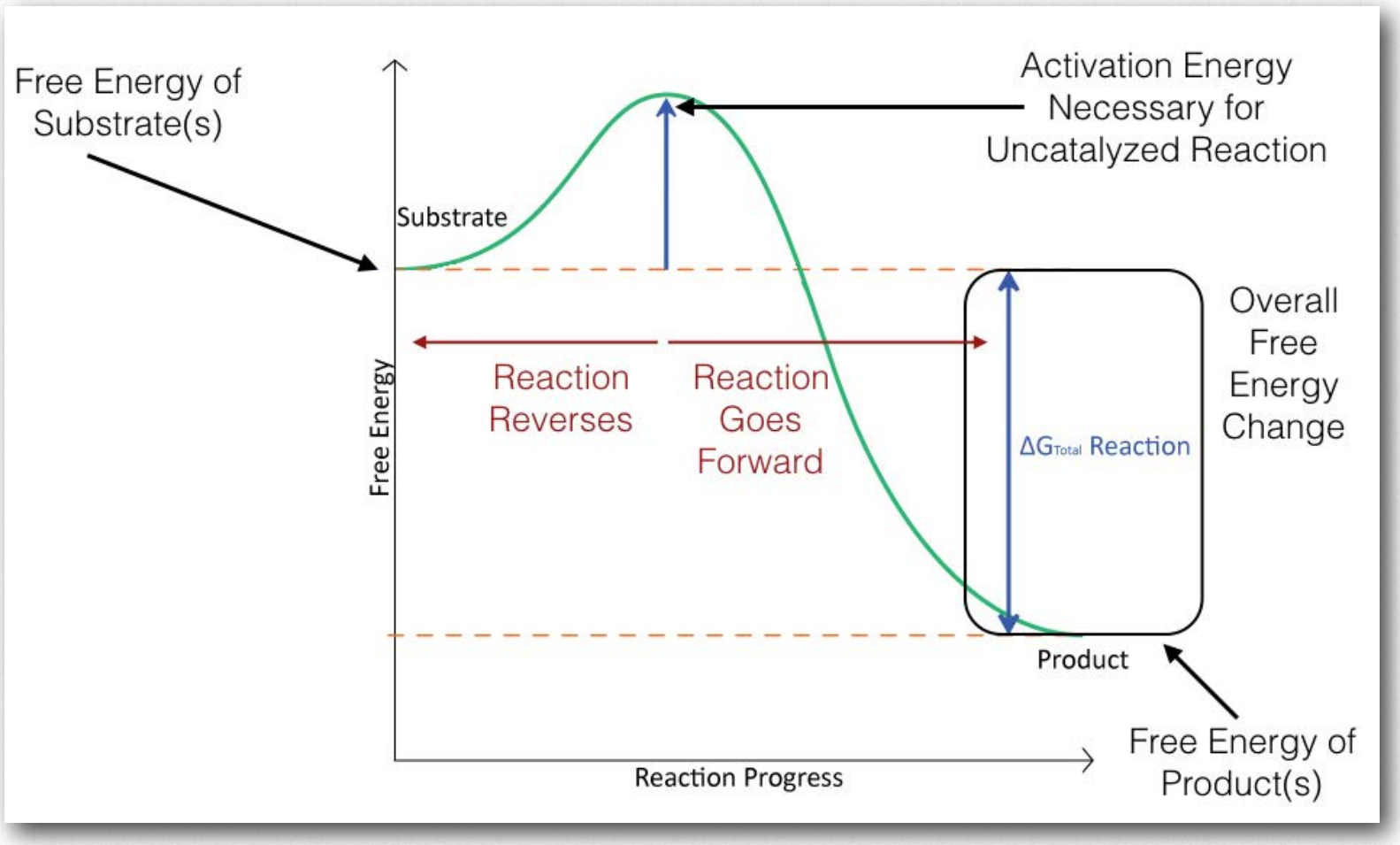

Figure 4.2 - Energy changes during the course of an uncatalyzed reaction

Image by Aleia Kim

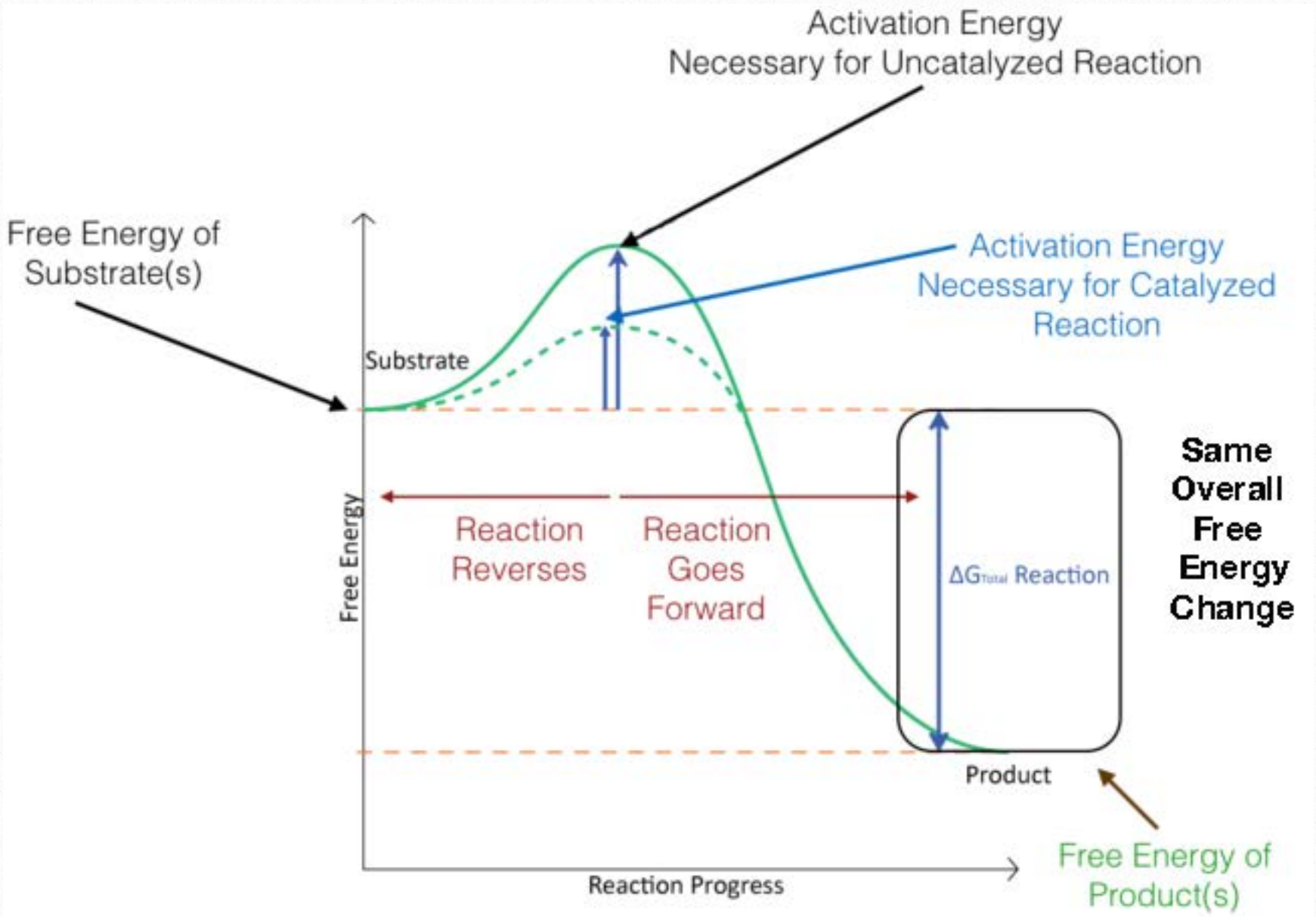

Figure 4.3 - Energy changes during the course of an uncatalyzed reaction (solid green line) and a catalyzed reaction (dotted green line).

Image by Aleia Kim

It is with this in mind that we begin our consideration of the phenomenon of catalysis by describing, first, the way in which enzymes work.

Activation energy

Figure 4.2 schematically depicts the energy changes that occur during the progression of a simple reaction. In order for the reaction to proceed, an activation energy must be overcome in order for the reaction to occur.

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In Figure 4.3, the activation energy for a catalyzed reaction is overlaid. As you can see, the reactants start at the same energy level for both catalyzed and uncatalyzed reactions and that the products end at the same energy for both as well. The catalyzed reaction, however, has a lower energy of activation (dotted line) than the un-

catalyzed reaction. This is the secret to catalysis - overall ΔG for a reaction does NOT change with catalysis, but the activation energy is lowered.

Reversibility

The extent to which reactions will proceed forward is a function of the size of the energy difference between the product and reactant states. The lower the energy of the products compared to the reactants, the larger the percentage of molecules that will be present as *products* at equilibrium. It is worth noting that since an enzyme lowers the activation energy for a reaction that it can speed the reversal of a reaction just as it speeds a reaction in the forward direction. At equilibrium, of course, no change in concentration of reactants and products occurs. Thus, enzymes speed the time required to reach equilibrium, but do not affect the balance of products and reactants at equilibrium.

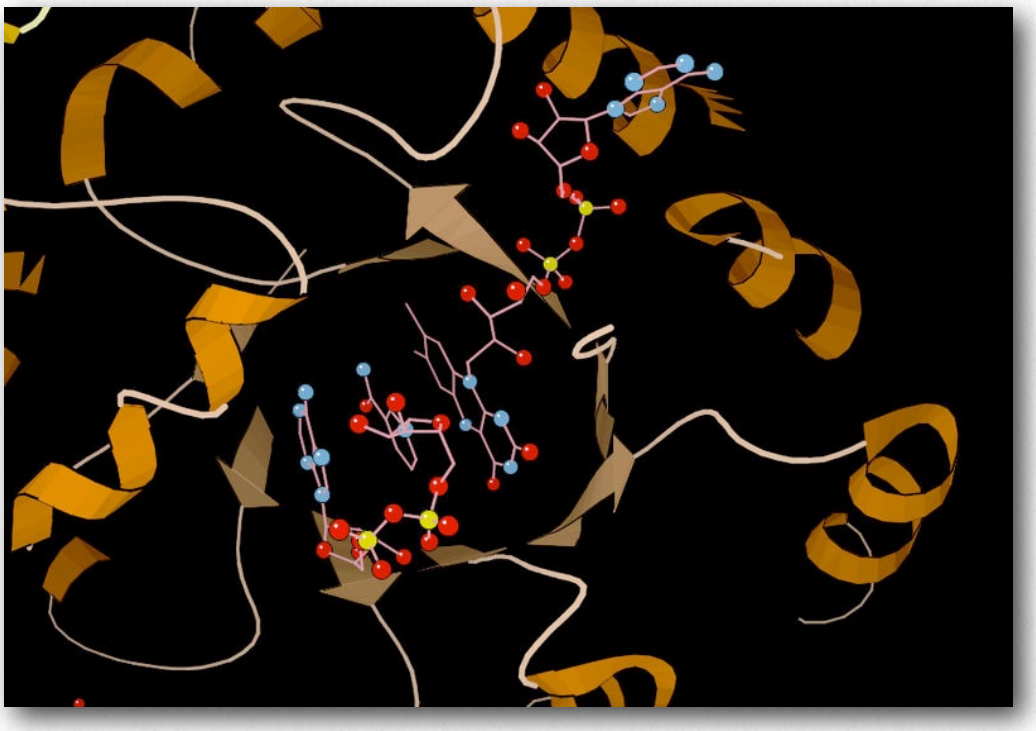

Figure 4.4 - Substrate binding by methylenetetrahydrofolate reductase

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Exceptions

The reversibility of enzymatic reactions is an important consideration for equilibrium, the measurement of enzyme kinetics, for Gibbs free energy, for metabolic pathways, and for physiology.

There are some minor exceptions to the reversibility of reactions, though. They are related to the disappearance of a substrate or product of a reaction. Consider the first reaction below which is catalyzed by the enzyme carbonic anhydrase:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

In the forward direction, carbonic acid is produced from water and carbon dioxide. It can either remain intact in the solution or ionize to produce bicarbonate ion and a proton. In the reverse direction, water and carbon dioxide are produced. Carbon dioxide, of course, is a gas and can leave the solution and escape.

When reaction molecules are removed, as they would be if carbon dioxide escaped, the reaction is pulled in the direction of the molecule being lost and reversal cannot occur unless the missing molecule is replaced. In the second reaction occurring on the right, carbonic acid (H_2CO_3) is "removed" by ionization. This too would limit the reaction going back to carbon dioxide in water. This last type of "removal" is what occurs in metabolic pathways. In this case, the product of one reaction (carbonic acid) is the substrate for the next (formation of bicarbonate and a proton).

In the metabolic pathway of glycolysis, ten reactions are connected in this manner and reversing the process is much more complicated than if just one reaction was being considered.

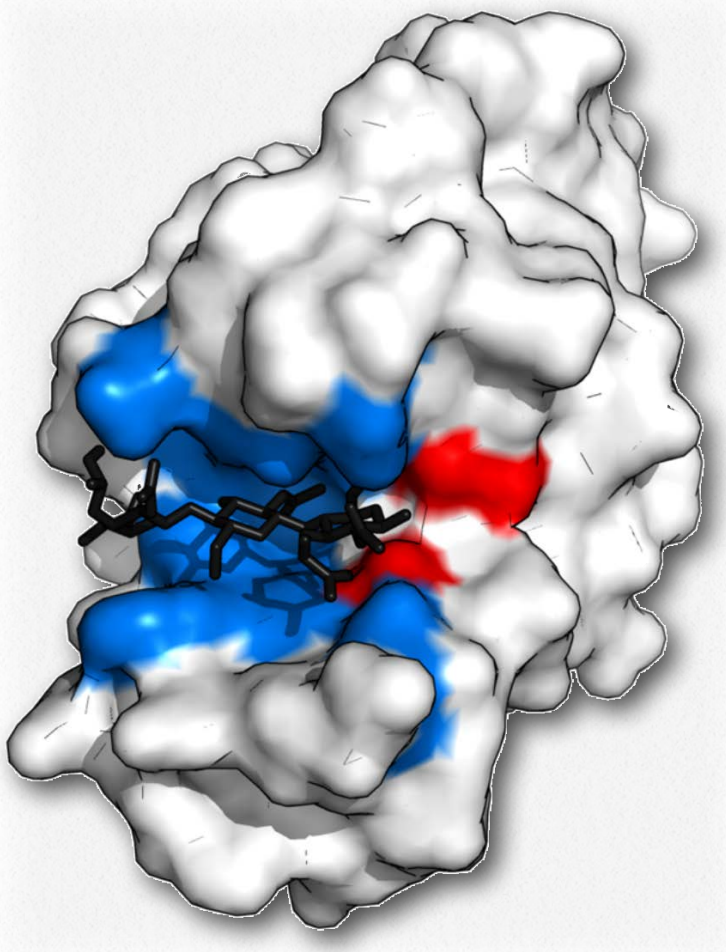

Figure 4.5 - Lysozyme with substrate binding site (blue), active site (red) and bound substrate (black).

Wikipedia

General mechanisms of action

As noted above, enzymatically catalyzed reactions are orders of magnitude faster than uncatalyzed and chemical-catalyzed reactions.

The secret of their success lies in a fundamental difference in their mechanisms of action.

Every chemistry student has been taught that a catalyst speeds a reaction without being consumed by it. In other words, the catalyst ends up after a reaction just the way it started so it can catalyze other reactions, as well. Enzymes share this property, but in the middle, during the catalytic action, an enzyme is transiently changed. In fact, it is the ability of an enzyme to change that leads to its incredible efficiency as a catalyst.

Changes

These changes may be subtle electronic ones, more significant covalent modifications, or structural changes arising from the flexibility inherent in enzymes, but not present in chemical catalysts. Flexibility allows movement and movement facilitates alteration of electronic environments necessary for catalysis. Enzymes are, thus, much more efficient than rigid chemical catalysts as a result of their abilities to facilitate the changes necessary to optimize the catalytic process.

Substrate binding

Another important difference between the mechanism of action of an enzyme and a chemical catalyst is that an enzyme has binding sites that not only 'grab' the substrate (molecule involved in the reaction being catalyzed), but also place it in a position to be electronically induced to react, either within itself or with another substrate.

The enzyme itself may play a role in the electronic induction or the induction may occur as a result of substrates being placed in very close proximity to each other. Chemical catalysts have no such ability to bind substrates and are dependent upon them colliding in the right orientation at or near their surfaces.

Active site

Reactions in an enzyme are catalyzed at a specific location within it known as the 'active site'. Substrates bind at the active site and are oriented to provide access for the relevant portion of the molecule to the electronic environment of the enzyme where catalysis occurs.

Enzyme flexibility

As mentioned earlier, a difference between an enzyme and a chemical catalyst is that an enzyme is flexible. Its slight changes in shape (often arising from the binding of the substrate itself) help to optimally position substrates for reaction after they bind.

Induced fit

These changes in shape are explained, in part, by Koshland's Induced Fit Model of Catalysis (Figure 4.6), which illustrates that not only do enzymes change substrates, but that substrates also transiently change enzyme struc-

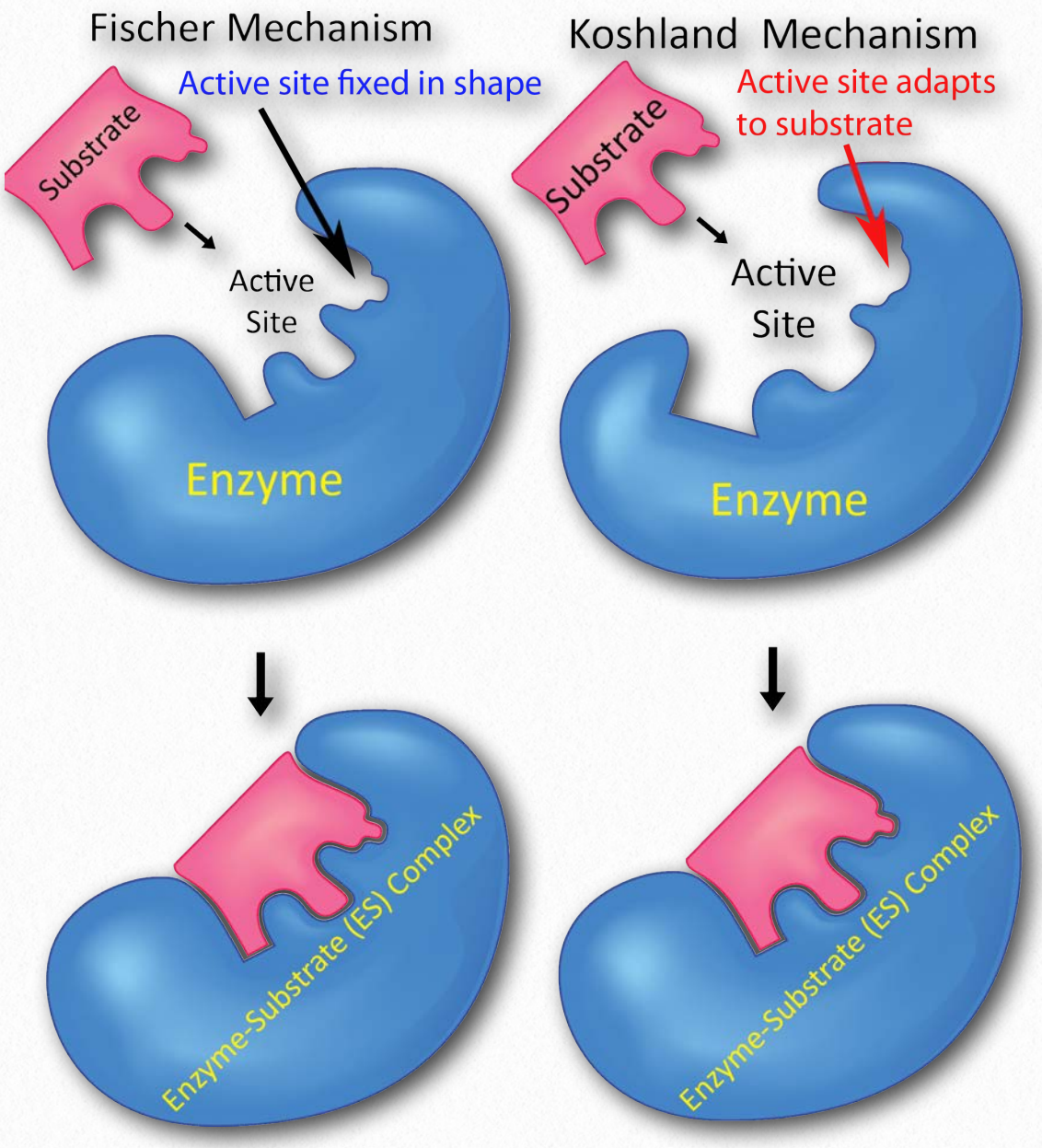

Figure 4.6 - Fischer's lock and key model (left) Vs. Koshland's induced fit model (right)

Image by Aleia Kim

ture. At the end of the catalysis, the enzyme is returned to its original state. Koshland's model is in contrast to the Fischer Lock and Key model, which says simply that an enzyme has a fixed shape that is perfectly matched for binding its substrate(s). Enzyme flexibility also is important for control of enzyme activity. Enzymes alternate between the T (tight) state, which is a lower activity state and the R (relaxed) state, which has greater activity.

Induced Fit

The Koshland Induced Fit model of catalysis postulates that enzymes are flexible and change shape on binding substrate. Changes in shape help to 1) aid binding of additional substrates in reactions involving more than one substrate and/or 2) facilitate formation of an electronic environment in the enzyme that favors catalysis. This model is in contrast to the Fischer Lock and Key Model of catalysis which considers enzymes as having pre-formed substrate binding sites.

Ordered binding

The Koshland model is consistent with multi-substrate binding enzymes that exhibit ordered binding of substrates. For these systems, binding of the first substrate induces structural changes in the enzyme necessary for binding the second substrate.

There is considerable experimental evidence supporting the Koshland model. Hexokinase, for example, is one of many enzymes known to undergo significant structural alteration after binding of substrate. In this case, the two substrates are brought into very close proximity by the induced fit and catalysis is made possible as a result.

Types of Reactions

Single Substrate - Single Product : $A \rightleftarrows B$

Single Substrate - Multiple Products : $A \rightleftarrows B + C$

Multiple Substrates - Single Products : $A + B \rightleftarrows C$

Multiple Substrates - Multiple Products : $A + B \rightleftarrows C + D$

Figure 4.7 - Categories of enzymatic reactions

Reaction types

Enzymatic reactions can be of several types, as shown in Figure 4.7.

Enzymes that catalyze reactions involving more than one substrate, such as

$$A + B \rightleftarrows C + D$$

can act in two different ways. In one mechanism, called sequential reactions, at some point in the reaction, both substrates will be bound to the enzyme. There are, in turn, two

different ways in which this can occur - random and ordered.

Consider lactate dehydrogenase, which catalyzes the reaction below:

NADH + Pyruvate

⇅

Lactate + **NAD**$^+$

This enzyme requires that NADH must bind prior to the binding of pyruvate. As noted earlier, this is consistent with an induced fit model of catalysis. In this case, binding of the NADH changes the enzyme shape/ environment so that pyruvate can bind and without binding of NADH, the substrate cannot access the pyruvate binding site.

This type of multiple substrate reaction is called sequential ordered binding, because the binding of substrates must occur in the right order for the reaction to proceed.

YouTube Lectures by Kevin HERE & HERE

For this enzyme, substrates can bind to it in any order. Creatine kinase displays sequential random binding. It is worth mentioning that random binding is *not* inconsistent with Koshland's induced fit model. Rather, random binding simply means that the enzyme's induced fit doesn't affect substrate binding sites and involves other parts of the enzyme. In summary, sequential binding can occur as ordered binding or as random binding.

Random binding

A second mechanism of binding/catalysis is exhibited by creatine kinase which catalyzes the following reaction:

Creatine + **ATP**

⇅

Creatine phosphate + **ADP**

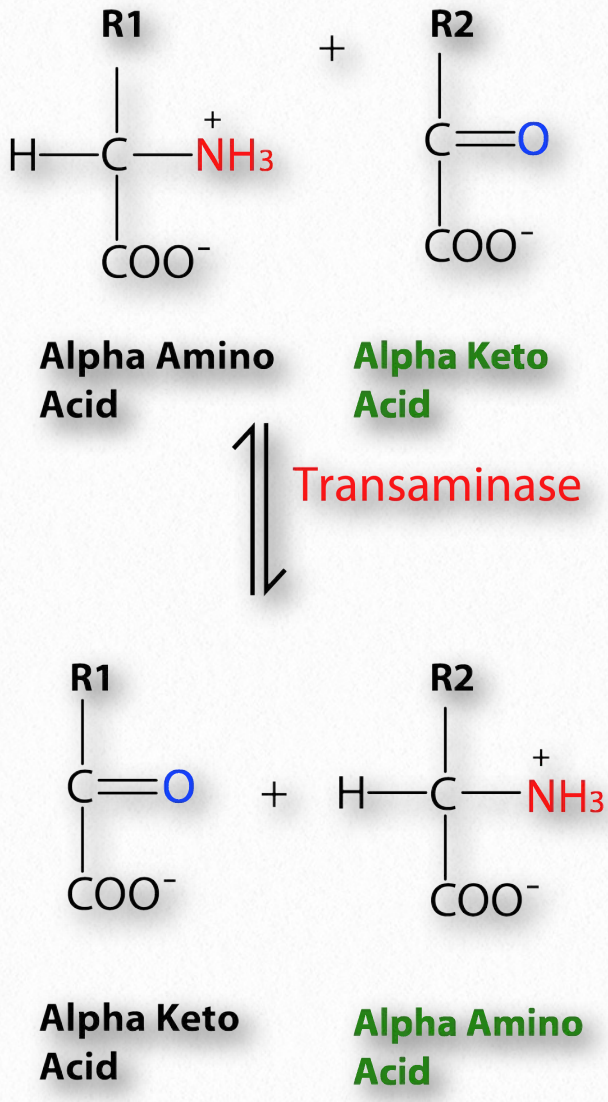

Figure 4.8 - Double displacement reaction mechanism of a transaminase

Double displacement reactions

Not all enzymes that catalyze multi-substrate reactions, though, bind A and B by the sequential mechanisms above. This other category of enzyme includes those that exhibit what are called "ping-pong" (or double displacement) mechanisms. In these enzymes, the enzyme functions as both a catalyst and a carrier of a group between individually bound substrates. Examples of this type of enzyme include the class of enzymes known as transaminases. A general form of the reactions catalyzed by these enzymes is shown in Figure 4.8.

In reversible transaminase reactions, an oxygen and an amine are swapping between the molecules. It can be represented as follows (where N is the amine and O is the oxygen).

$$A{=}O + C{=}N \rightleftarrows B{-}N + D{=}O$$

This reaction occurs not as one transfer reaction swapping the N and the O, but rather as a set of two half-reactions. In this case, the enzyme is a both donor and a carrier of the group being swapped. The first half-reaction goes as follows

$$A{=}O + Enz{-}N \rightleftarrows B{-}N + Enz{=}O$$

Next a second half-reaction goes as

$$C{-}N + Enz{=}O \rightleftarrows D{=}O + Enz{=}N$$

The sum of these half-reactions then is

$$A{=}O + C{=}N \rightleftarrows B{-}N + D{=}O$$

Note that at no time did the enzyme bind both A and C simultaneously. It is also important to recognize that the enzyme existed in two states - Enz=O and Enz-N. The shuffling of the enzyme between these two states is what

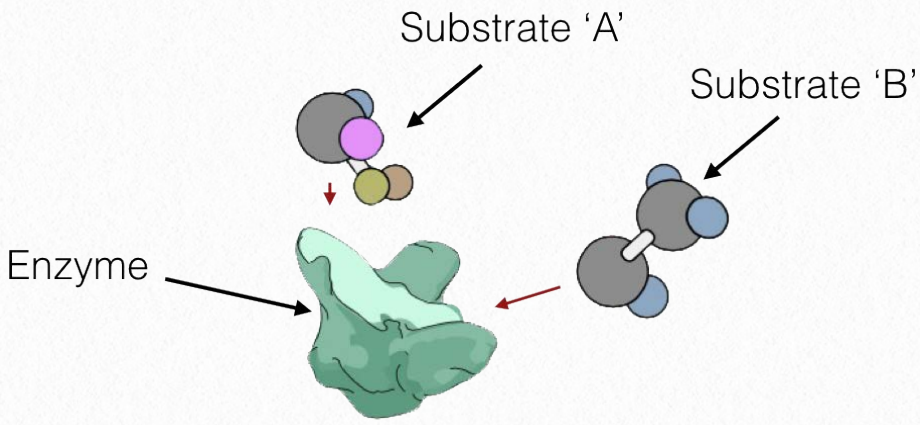

Figure 4.9 - Binding of substrates (A+B) to free enzyme

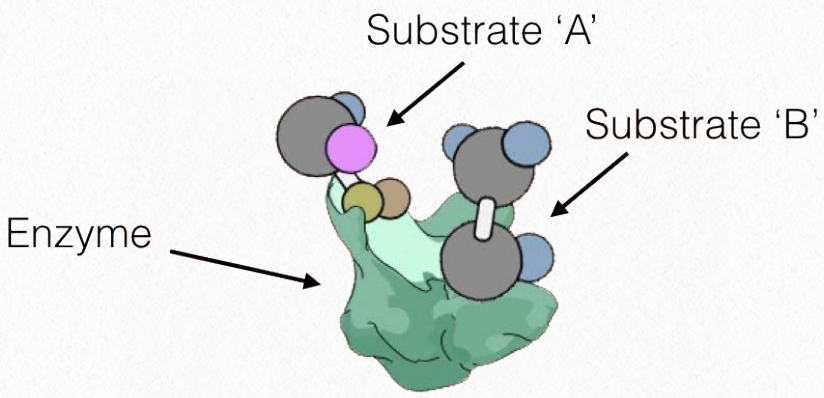

Figure 4.10 ES complex formation

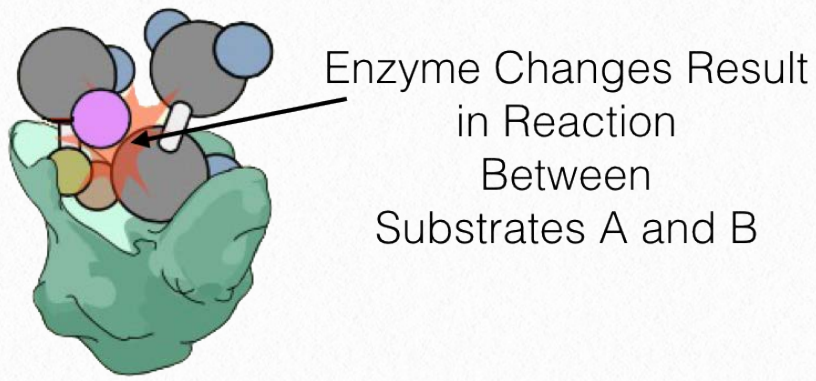

Figure 4.11 - ES* complex - The reaction occurs.

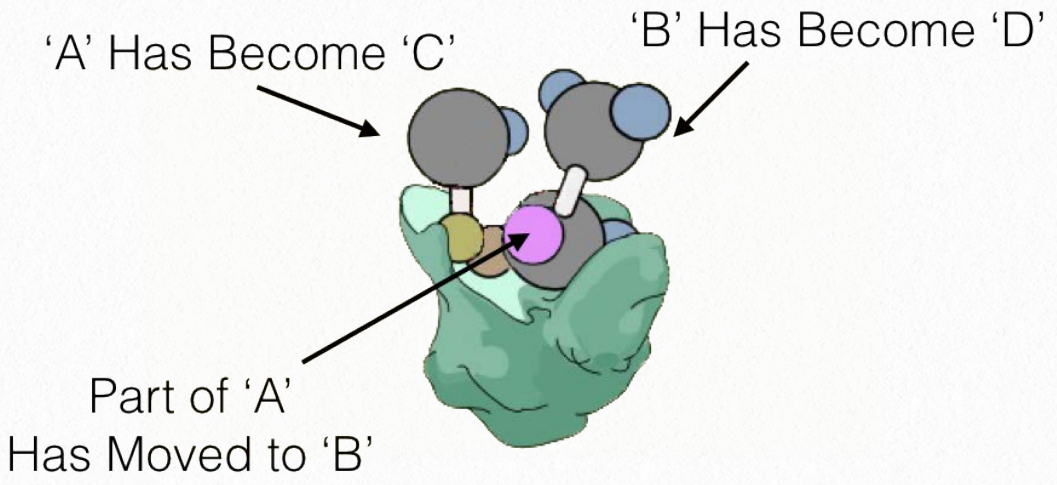

Figure 4.12 - EP complex - the reaction is complete.

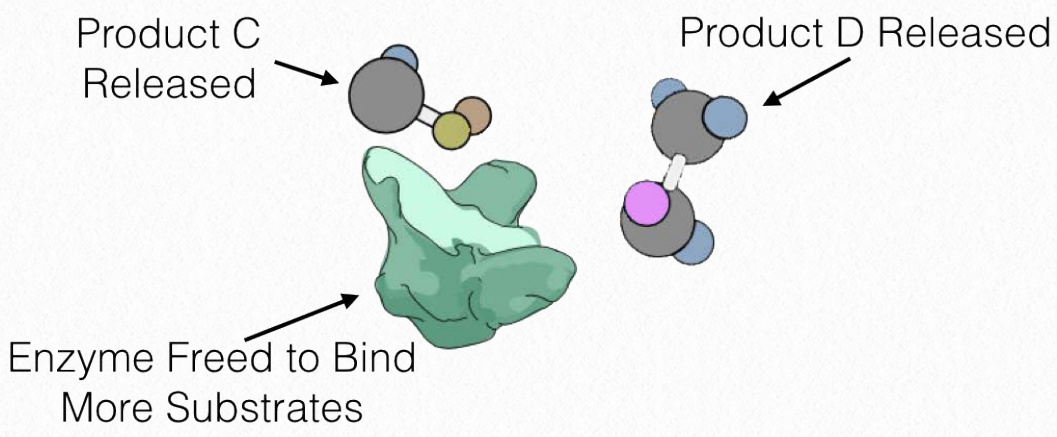

Figure 4.13 - E + P - the products are released

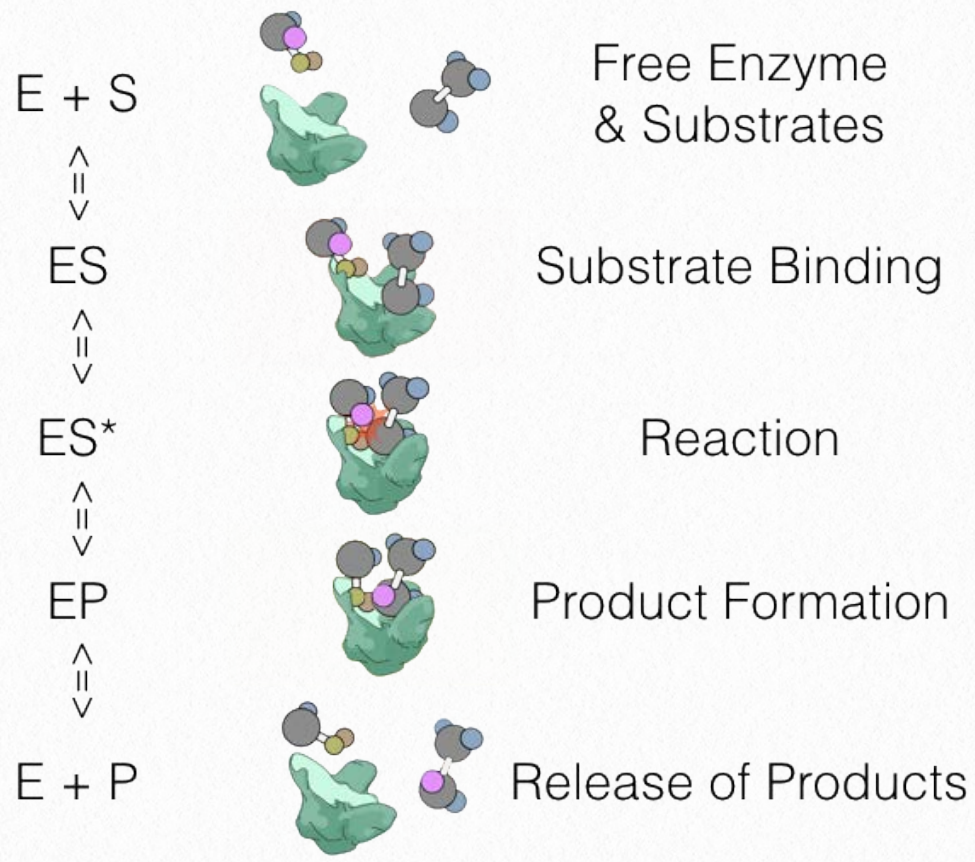

Figure 4.14 - Summary

gives rise to the ping-pong name of this mechanism - it literally goes back and forth like a ping-pong ball in a table tennis match.

Enzyme kinetics

To understand how an enzyme enhances the rate of a reaction, we must understand enzyme kinetics. We present a model here proposed by Leonor Michaelis and Maud Menten. In order to understand the model, it is necessary to understand a few parameters.

First, we describe a reaction in simple terms proceeding as follows

$$E + S \rightleftarrows ES \rightarrow E + P$$

where E is enzyme, S is substrate, and P is product. In this scheme, ES is the Enzyme-Substrate complex, which is simply the enzyme bound to its substrate.

We could define the ES state a bit further with

$$E + S \rightleftarrows ES \rightarrow ES^* \rightarrow EP \rightarrow E + P$$

where ES* is the activated state and EP is the enzyme-product complex before release of the product.

The first consideration we have is

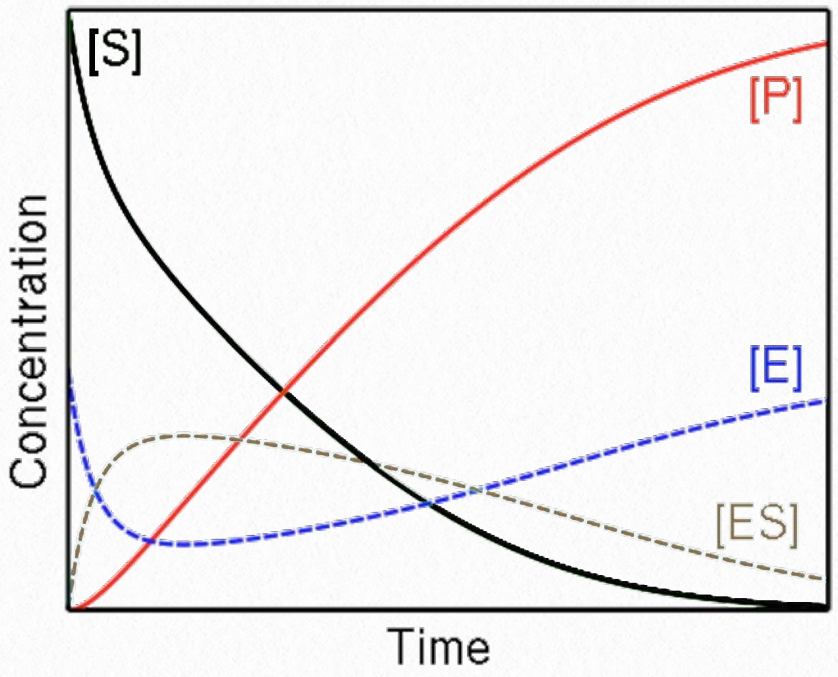

Figure 4.15 - Concentration of product (P), substrate (S), enzyme (E), and enzyme-substrate complex (ES) versus time for an enzymatic reaction

velocity. The velocity of a reaction is the rate of creation of product over time, measured as the concentration of product per time. The time is a critical consideration when measuring velocity. In a closed system (in which an enzyme operates), all reactions will advance towards equilibrium. Enzymatically catalyzed reactions are no different in the end result from non-enzymatic reactions, except that they get to equilibrium faster.

Equilibrium

At equilibrium, the ratio of product to reactant does not change. That is a property of equilibrium. Since the system is closed, the concentration of product over time will not change. The velocity will thus be zero under these conditions and we will have learned nothing about the reaction if we wait too long to study it.

Velocity

Consequently, in Michaelis-Menten kinetics, velocity is measured as initial velocity (V_0). This is accomplished by measuring the rate of formation of product early in the

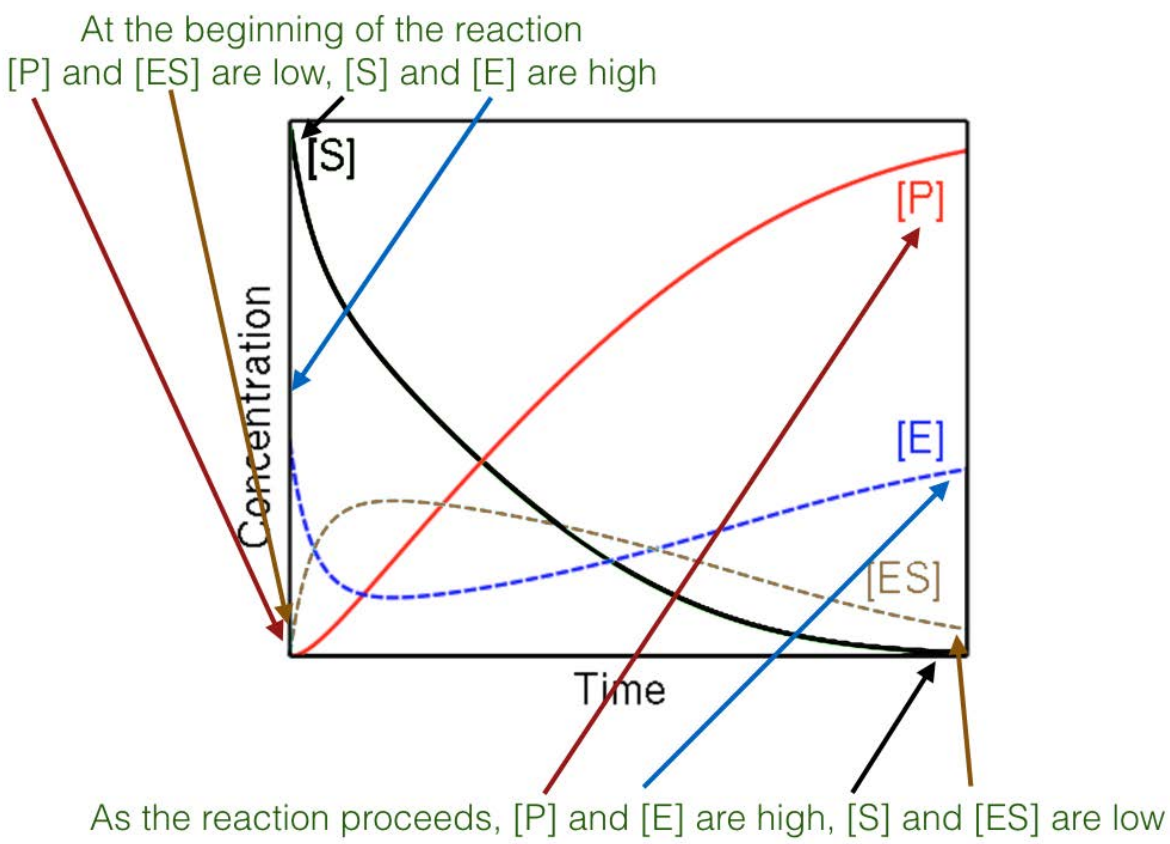

Figure 4.16 - Change in concentration of reaction materials over time

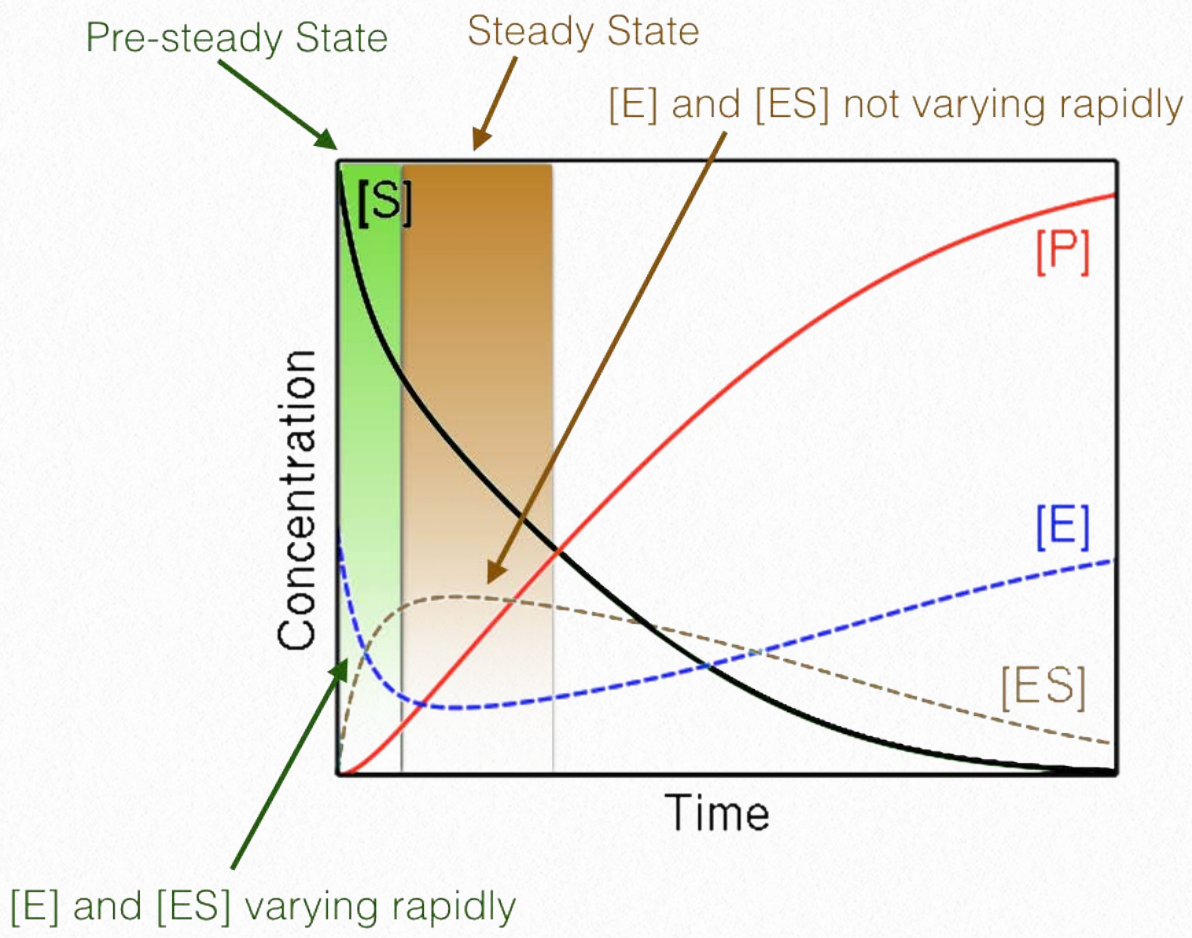

Figure 4.17 - Steady state versus non-steady state conditions

reaction before equilibrium is established and under these conditions, there is very little if any of the reverse reaction occurring.

The other two assumptions are related. First, we use conditions where there is much more substrate than enzyme. This makes sense. If the substrate is not in great excess, then the enzyme's conversion of substrate to product will occur much faster than the enzyme can bind substrate.

Waiting for substrate

Thus, the enzyme would "wait" for substrate to bind if there were not sufficient amounts of it to bind to the enzyme in a timely fashion (when substrate concentration is low). This would not give an accurate measure of velocity, since the enzyme would be inactive a good deal of the time. Because of this, we assume saturation of the enzyme with substrate will give a maximal velocity of the reaction.

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Steady state

Last, the high concentration of substrate combined with measuring initial conditions results in studying reactions that are under so-called steady state conditions (Figure 4.17). When steady state occurs, the concentration of the ES complex over time is not significantly changing during the period of analysis.

Reiterating, the three assumptions for Michaelis-Menten kinetics are

1. Measurement of initial velocity of a reaction

2. Substrate in great excess compared to enzyme

3. Reaction conditions occurring under steady state

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Experimental considerations

Now we turn our attention to how studies of the kinetic properties of an enzyme are conducted. To perform an analysis, one would do the following experiment - 20 different tubes would be set up with enzyme buffer (to keep the enzyme stable), the same amount of enzyme, and then a different amount of substrate in each tube, ranging from tiny amounts in the first tubes to very large amounts in the last tubes. The reaction would be allowed to proceed for a fixed, short amount of time and then the reaction would be stopped and the amount of product contained in each tube would be determined.

The initial velocity (V_0) of the reaction then would be the concentration of product found in each tube divided by the time that the reaction was allowed to run. Data from the experiment would be plotted on a graph using initial velocity (V_0) on the Y-axis and the concentration of substrate on the X-axis, each tube, of course having a unique reaction velocity corresponding to a unique substrate concentration.

For an enzyme following Michaelis-Menten kinetics, a curve like that shown in Figure 4.18 or 4.19 would result. At low concentration of substrate, it is limiting and the enzyme converts it into product as soon as it can bind it. Consequently, at low concentrations of substrate, the rate of increase of [P] is almost linear with [S] (Figure 4.19).

Non-linear increase

As the substrate concentration increases, however, the velocity of the reaction in tubes with higher substrate concentration ceases to in-

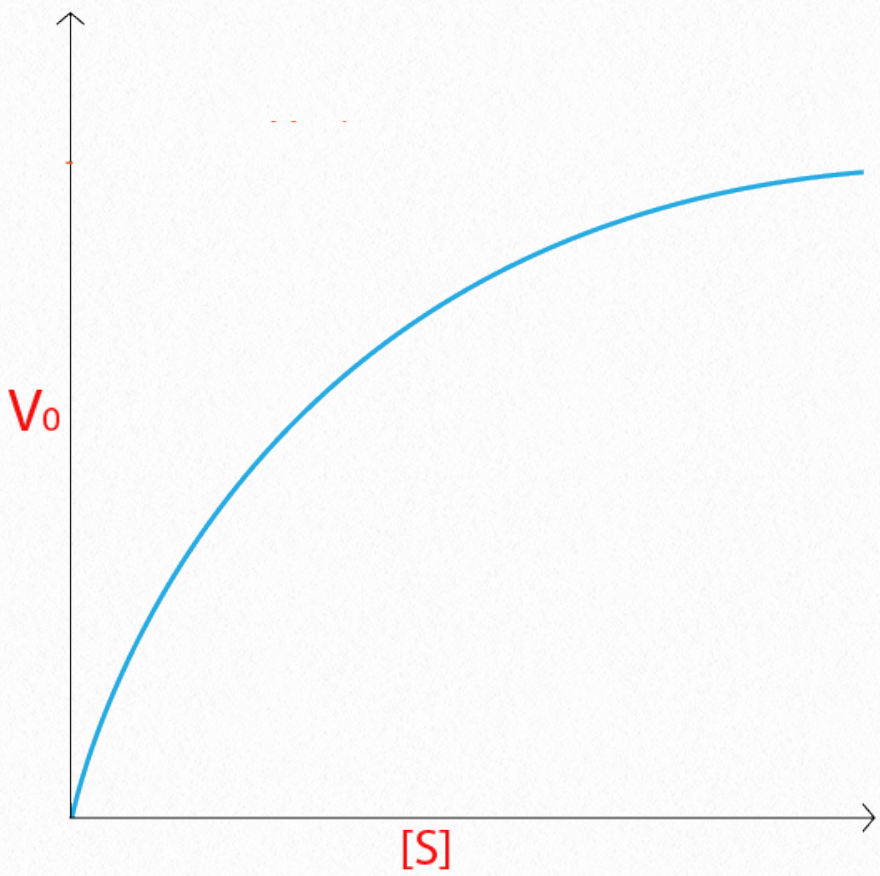

Figure 4.18 - Kinetics of an enzyme obeying Michaelis-Menten kinetics

Image by Aleia Kim

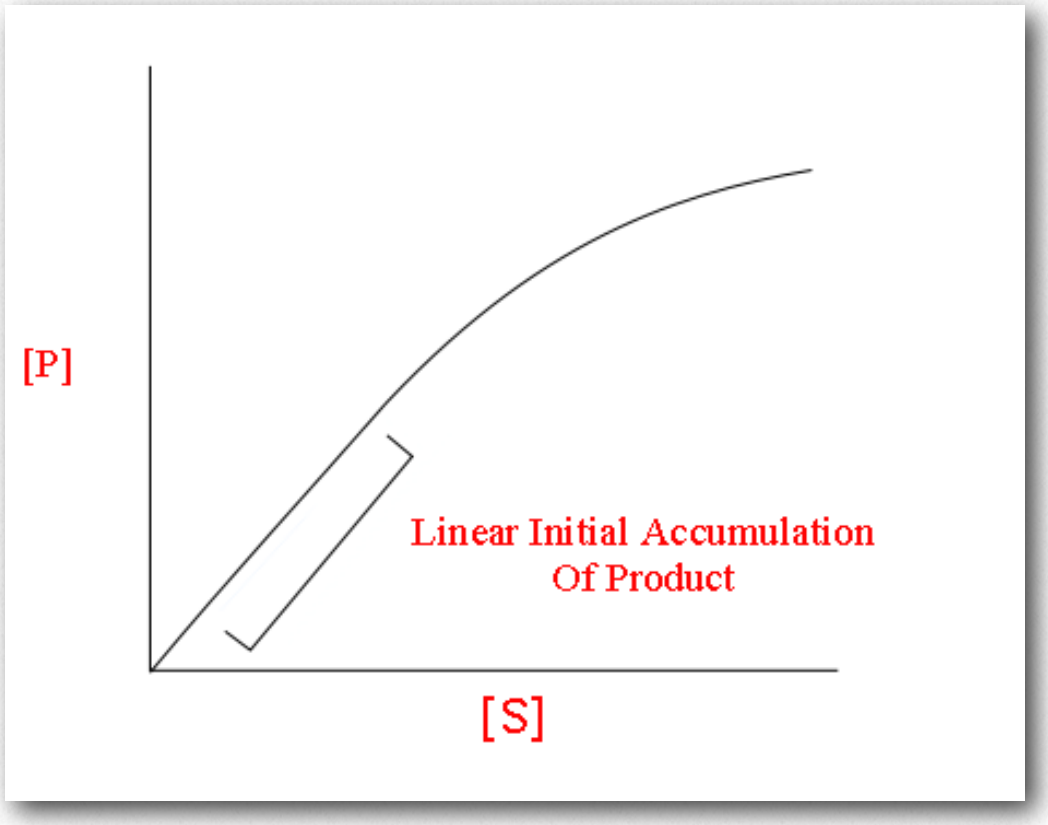

Figure 4.19 - Linear relationship between [P] and [S] at low [S]

crease linearly and instead begins to flatten out, indicating that as the substrate concentration gets higher and higher, the enzyme has a harder time keeping up to convert the substrate to product.

Saturation

Not surprisingly, when the enzyme becomes completely saturated with substrate, it will not have to wait for substrate to diffuse to it and will therefore be operating at maximum velocity.

For an enzyme following Michaelis-Menten kinetics will have its velocity (v) at any given substrate concentration given by the following equation:

$$v = \frac{V_{max}[S]}{K_m + [S]}$$

V_{max}

Two terms in the equation above require explanation. The first is V_{max}. It refers to the maximum velocity of an enzymatic reaction. Maximum velocity for a reaction occurs when an enzyme is saturated with substrate. Saturation is important because it means (per the assumption above) that none of the enzyme molecules are "waiting" for substrate after a product is released. Saturation ensures that another substrate is always instantly available. The unit of V_{max} is concentration of product per time = [P]/time.

On a plot of initial velocity versus substrate concentration (V_0 vs. [S]), V_{max} is the value on the Y axis that the curve asymptotically approaches (dotted line in Figure 4.20). It should be noted that the value of V_{max} depends on the amount of enzyme used in a reaction. If you double the amount of enzyme used, you will double the V_{max}. If one wanted to compare the velocities of two different enzymes, it would be necessary to use the same amounts of enzyme in the reaction each one catalyzes.

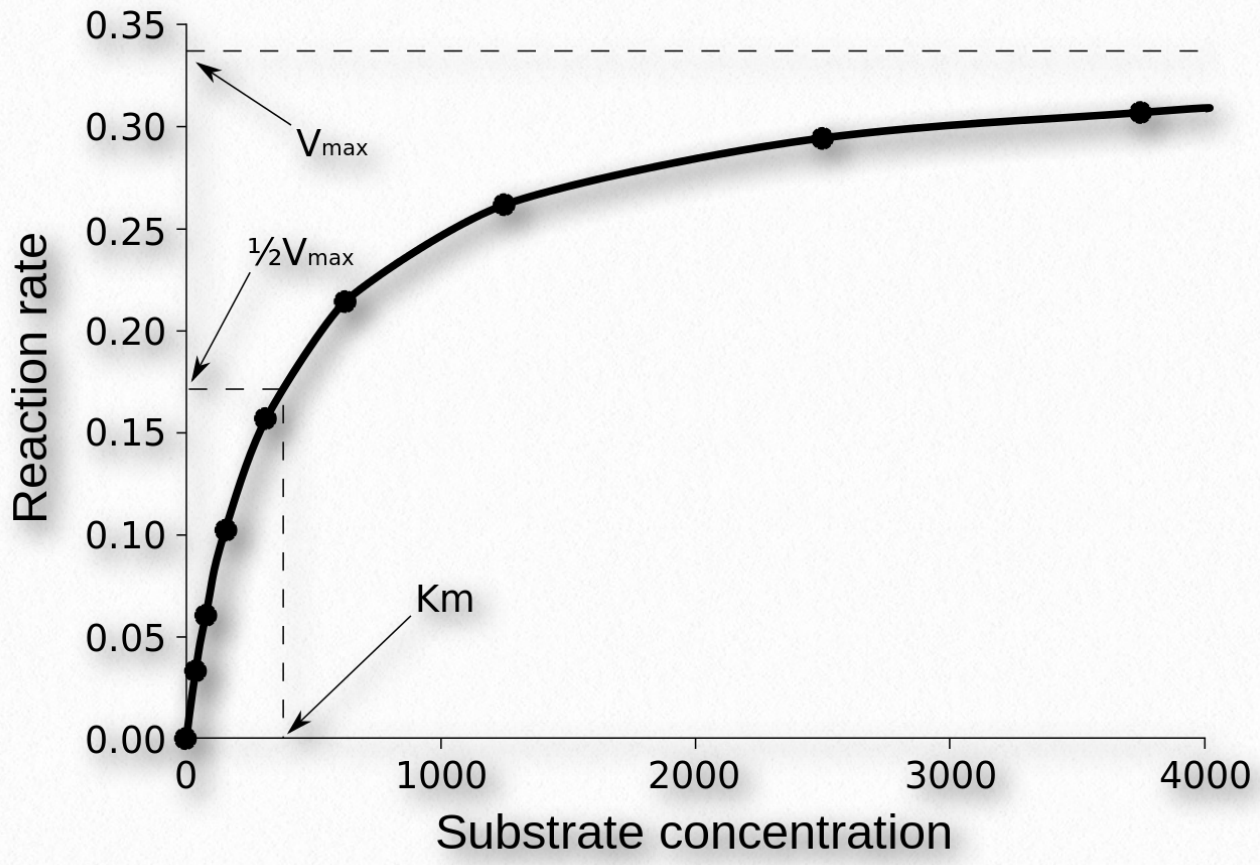

Figure 4.20 - V_{max}, $V_{max}/2$, and K_m

Affinities of enzymes for substrates vary considerably, so knowing K_m helps us to understand how well an enzyme is suited to the substrate being used. Measurement of K_m depends on the measurement of V_{max}.

Common mistake

A common mistake students make in describing V_{max} is saying that $K_m = V_{max}/2$. This is, of course, not true. K_m is a substrate concentration and is the amount of substrate it takes for an enzyme to reach $V_{max}/2$. On the other hand $V_{max}/2$ is a velocity and a velocity certainly cannot equal a concentration.

K_m

The second term is Km (also known as K_s). Referred to as the Michaelis constant, K_m is the substrate concentration that causes the enzyme to work at half of maximum velocity ($V_{max}/2$). What it measures, in simple terms, is the affinity an enzyme has for its substrate. The value of K_m is inversely related to the affinity of the enzyme for its substrate. Enzymes with a high K_m value will have a lower affinity for their substrate (will take more substrate to get to $V_{max}/2$) whereas those with a low K_m will have high affinity and take less substrate to get to $V_{max}/2$. The unit of K_m is concentration.

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K_{cat}

It is desirable to have a measure of velocity that is independent of enzyme concentration. Remember that V_{max} depended on the amount of enzyme used. For this, we use the K_{cat}, also known as the turnover number. K_{cat} is a number that requires one to first determine V_{max} for an enzyme and then divide the V_{max} by the concentration of enzyme used to determine V_{max}. Thus,

$$K_{cat} = V_{max} / [Enzyme]$$

Since V_{max} has units of concentration per time and [Enzyme] has units of concentration, the units on K_{cat} are time^{-1}. While that might seem unintuitive, it means that the value of K_{cat} is the number of molecules of product made by each molecule of enzyme in the time given. So, a K_{cat} value of 1000/sec means each enzyme molecule in the reaction at V_{max} is producing 1000 molecules of product per second. Note that since K_{cat} is a calculated value, it cannot be read from a V vs [S] graph as V_{max} and K_m can.

Amazing K_{cat} values

A K_{cat} value of 1000 molecules of product per enzyme per second might seem like a high value, but there are enzymes known (carbonic anhydrase, for example) that have a K_{cat} value of over 600,000/second (Figure 4.21). This astonishing value illustrates clearly why enzymes seem almost magical in their action.

Enzyme	Turnover Number (per second)
Carbonic anhydrase	600,000
3-Ketoesteroid isomerase	280,000
Acetylcholinesterase	25,000
Penicillinase	2,000
Lactate dehydrogenase	1,000
Chymostrypsin	100
DNA Polymerase I	15
Tryptophan synthetase	2
Lysozyme	0.5

Figure 4.21 - K_{cat} (turnover number) values for several enzymes

Image by Aleia Kim

In contrast to V_{max}, which varies with the amount of enzyme used, K_{cat} is a constant for an enzyme under given conditions.

As seen earlier, enzymes that follow Michaelis-Menten kinetics produce hyperbolic plots of Velocity (V0) versus Substrate Concentration [S] (Figure 4.18). Not all enzymes, though, follow Michaelis-Menten kinetics. Many enzymes have multiple protein subunits and these sometimes interact differently upon binding of a substrate or an external molecule. See ATCase (HERE) for an example.

Perfect enzymes

Now, if we think about what an ideal enzyme might be, it would be one that has a very high velocity and a very high affinity for its substrate. That is, it wouldn't take much substrate to get to V_{max}/2 and the K_{cat} would be very high. Such enzymes would have values of K_{cat} / K_m that are maximum. Interestingly, there are several en-

Enzyme	K_{Cat} / K_M ($s^{-1}M^{-1}$)
Acetylcholinesterase	1.6×10^8
Carbonic anhydrase	8.3×10^7
Catalase	4.0×10^7
Crotonase	2.8×10^8
Fumarase	1.6×10^8
Triose phosphate isomerase	2.4×10^8
β-Lactamase	1.0×10^8
Superoxide dismutase	7.0×10^9

Figure 4.22 - K_{cat}/K_m values for perfect enzymes

Image by Aleia Kim

zymes that have this property and their maximal K_{cat} / K_m values are all approximately the same. Such enzymes are referred to as being "perfect" because they have reached the maximum possible value.

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Diffusion limitation

Why should there be a maximum possible value of K_{cat} / K_m? The answer is that movement of substrate to the enzyme becomes the limiting factor for perfect enzymes. Movement of substrate by diffusion in water has a fixed rate at any temperature and that limitation ultimately determines the maximum speed an enzyme can catalyze at. In a macroscopic world analogy, factories can't make products faster than suppliers can deliver materials. It is safe to say for a perfect enzyme that the only speed limit it has is the rate of substrate diffusion in water.

Given the "magic" of enzymes alluded to earlier, it might seem that all enzymes should have evolved to be "perfect." There are very good reasons why most of them have not.

Speed

Speed is a dangerous thing. The faster a reaction proceeds in catalysis by an enzyme, the harder it is to control. As we all know from learning to drive, speeding causes accidents. Just as drivers need to have speed limits for operating automobiles, so too must cells exert some control on the 'throttle' of their enzymes. In view of this, one might wonder then why any cells have evolved any enzymes to perfection. There is no single answer to the ques-

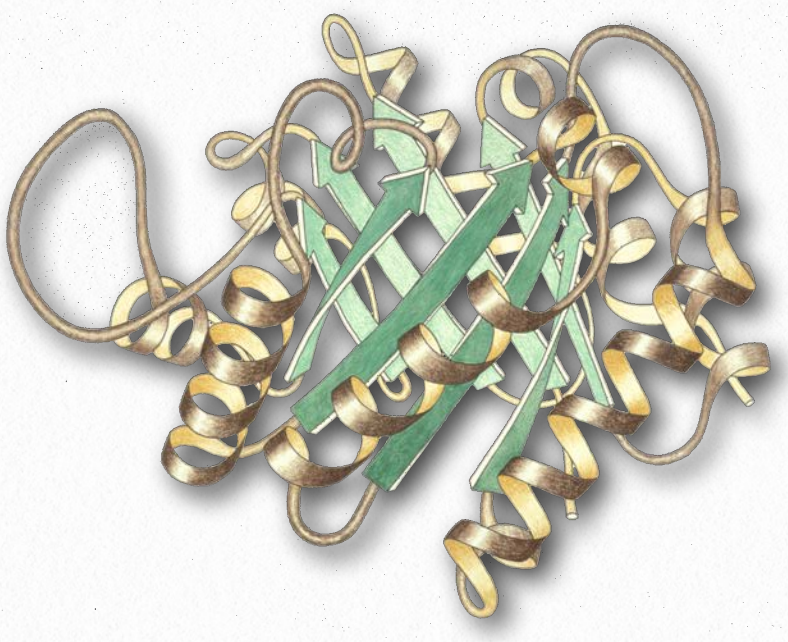

Figure 4.23 - Triose phosphate isomerase - A perfect enzyme

Wikipedia

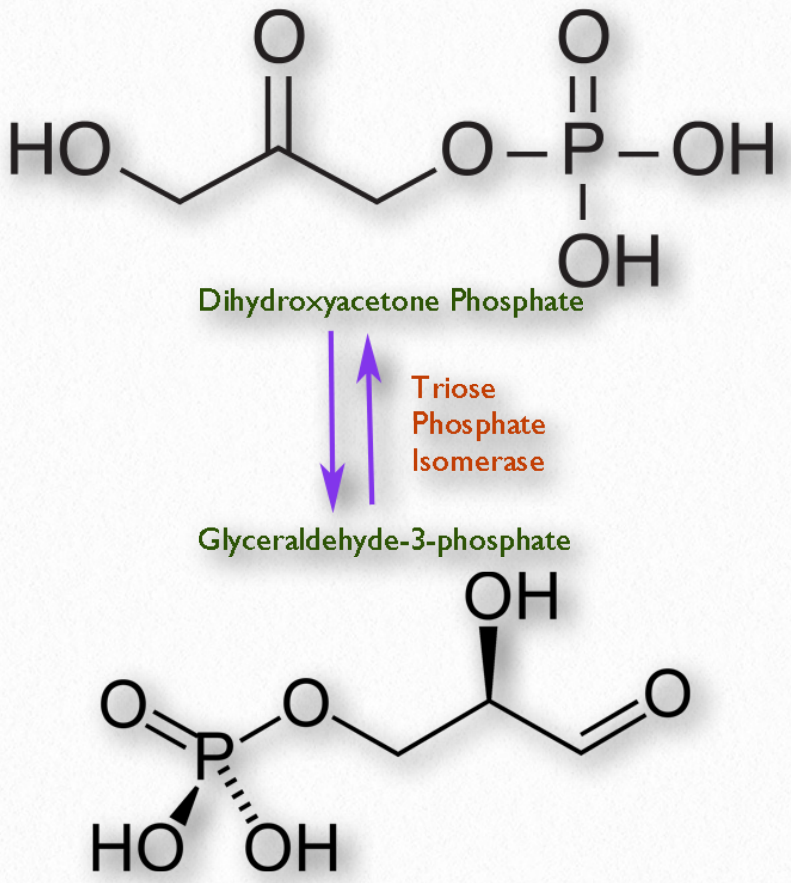

Figure 4.24 - Triose phosphate isomerase-catalyzed reaction

tion, but a common one is illustrated by triose phosphate isomerase, which catalyzes a reaction in glycolysis shown in Figure 4.24.

The enzyme appears to have evolved this ability because at lower velocities, there is breakdown of an unstable enediol intermediate that then readily forms methyl glyoxal, a cytotoxic compound (Figure 4.25). Speeding up the reaction provides less opportunity for the unstable intermediate to accumulate and fewer undesirable byproducts to be made.

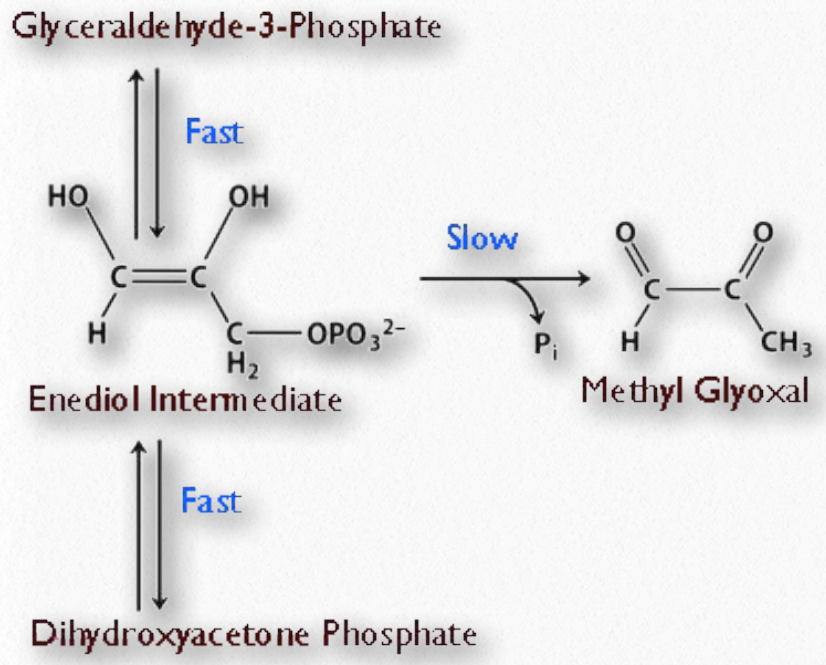

Figure 4.25 - A high speed reaction avoids production of methyl glyoxal

Image by Aleia Kim

Dissociation constant

In studying proteins and ligands, it is important to understand the "tightness" with which a protein (P) "holds onto" a ligand (L). This is measured with the dissociation constant (K_d).

The formation of a ligand-protein complex LP occurs as

$$L + P <=> LP$$

The dissociation of the complex, therefore, is the reverse of this reaction, or

$$LP <=> L + P$$

so the corresponding dissociation constant is defined as

$$K_d = [L][P]/[LP]$$

where [L], [P], and [LP] are the molar concentrations of the protein, ligand and the complex when they are joined together.

Smaller values of K_d indicate tight binding, whereas larger values indicate loose binding. The dissociation constant is the inverse of the association constant.

$K_a = 1/K_d$

Where multiple molecules bond together, such as

$$JxKy <=> xJ + yK$$

(complex JxKy is breaking down into x subunits of J and y subunits of K)

the dissociation constant is then defined as

$$K_d = [J]^x[K]^y/[JxKy]$$

where [J], [K], and [JxKy] are the concentrations of J, K, and the complex JxKy, respectively.

Lineweaver-Burk plots

The study of enzyme kinetics is typically the most math intensive component of biochemistry and one of the most daunting aspects of the subject for many students. Although attempts are made to simplify the mathematical considerations, sometimes they only serve to confuse or frustrate students. Such is the case with modified enzyme plots, such as Lineweaver-Burk (Figure 4.26).

Indeed, when presented by professors as simply another thing to memorize, who can blame students? In reality, both of these plots are aimed at simplifying the determination of parameters, such as K_m and V_{max}. In making either of these modified plots, it is important to recognize that the same data is used as in making a V_0 vs. [S] plot. The data are simply manipulated to make the plotting easier.

Double reciprocal

For a LineWeaver-Burk plot, the manipulation is using the reciprocal of the values of both the velocity and the substrate concentration. The inverted values are then plotted on a graph as $1/V_0$ vs. $1/[S]$. Because of these

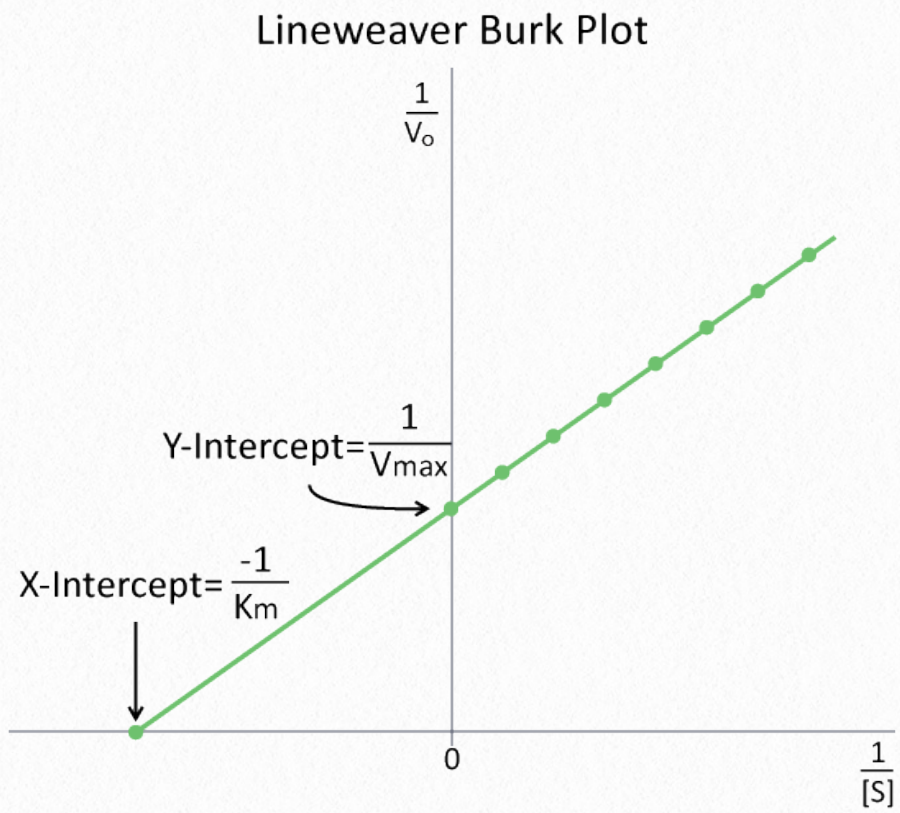

Figure 4.26 - A Lineweaver-Burk plot of $1/V_0$ vs $1/[S]$

Image by Aleia Kim

Cofactor	Enzyme
Coenzyme	
5′-Deoxyadenosyl cobalamin	Methylmalonyl mutase
Biotin	Pyruvate carboxylase
Coenzyme A (CoA)	Acetyl CoA carboxylase
Flavin adenine nucleotide	Monoamine oxidase
Nicotinamide adenine dinucleotide	Lactate dehydrogenase
Pyridoxal phosphate	Glycogen phosphorylase
Tetrahydrofolate	Thymidylate synthase
Thiamine pyrophosphate	Pyruvate dehydrogenase
Metal	
K^+	Propionyl CoA carboxylase
Mg^{2+}	Restriction Endonucleases; Hexokinase
Mn	Superoxide dismutase
Mo	Nitrate reductase
Ni^{2+}	Urease
Se	Glutathione peroxidase
Zn^{2+}	Carbonic anhydrase; Carboxypeptidase

Figure 4.27 - Enzyme cofactors

Image by Aleia Kim

inversions, Lineweaver-Burk plots are commonly referred to as ‘double-reciprocal’ plots. As can be seen in Figure 4.26, the value of K_m on a Lineweaver Burk plot is easily determined as the negative reciprocal of the x-intercept , whereas the V_{max} is the inverse of the y-intercept. Other related manipulation of kinetic data include Eadie-Hofstee diagrams, which plots V_0 vs $V_0/[S]$ and gives V_{max} as the Y-axis intercept with the slope of the line being $-K_m$.

Molecularity of reactions

The term molecularity refers to the number of molecules that must come together in order for a reaction to take place. Reactions of the sort of A -> B (where ‘A’ is the reactant and ‘B’ is the product) are unimolecular, since A is directly changed into B. The rate of the reaction is related only to the concentration of reactant A. For a bimolecular reaction where A + B ⇄ C the reaction depends on the concentration of both A and B and its

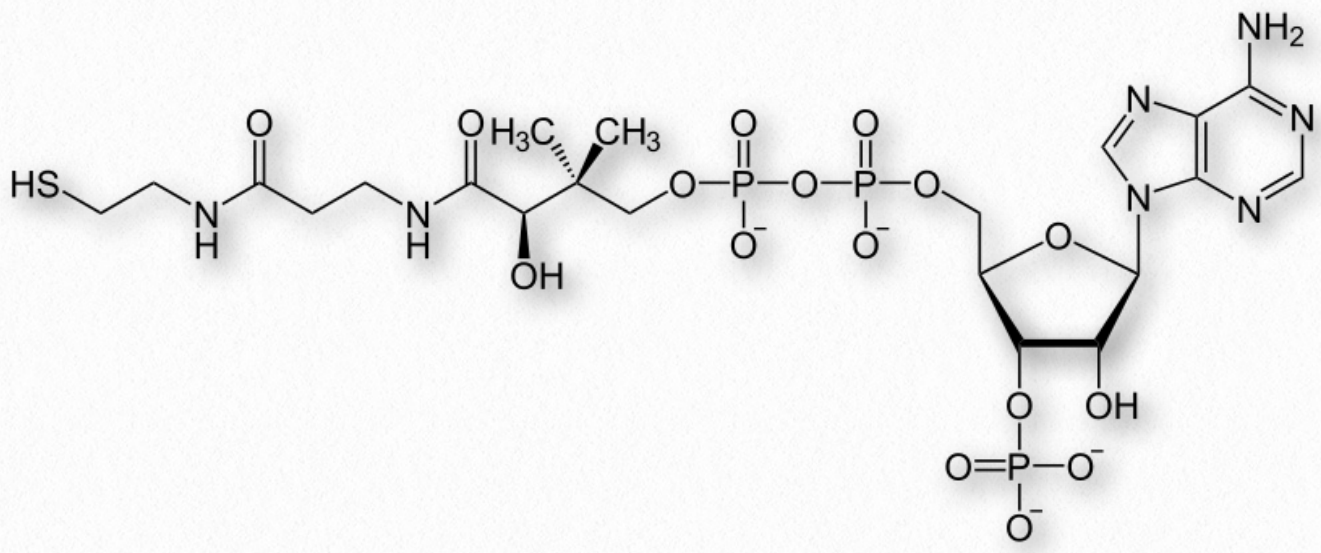

Figure 4.28 - Coenzyme A (CoA)

rate will be related to the product of the concentration of A and of B.

Coenzymes

Organic molecules that assist enzymes and facilitate catalysis are co-factors called coenzymes. The term co-factor is a broad category usually subdivided into inorganic ions and coenzymes. If the coenzyme is very tightly or covalently bound to the enzyme, it is referred to as a prosthetic group. Enzymes without their co-factors are inactive and referred to as apoenzymes. Enzymes containing all of their co-factors are called holoenzymes.

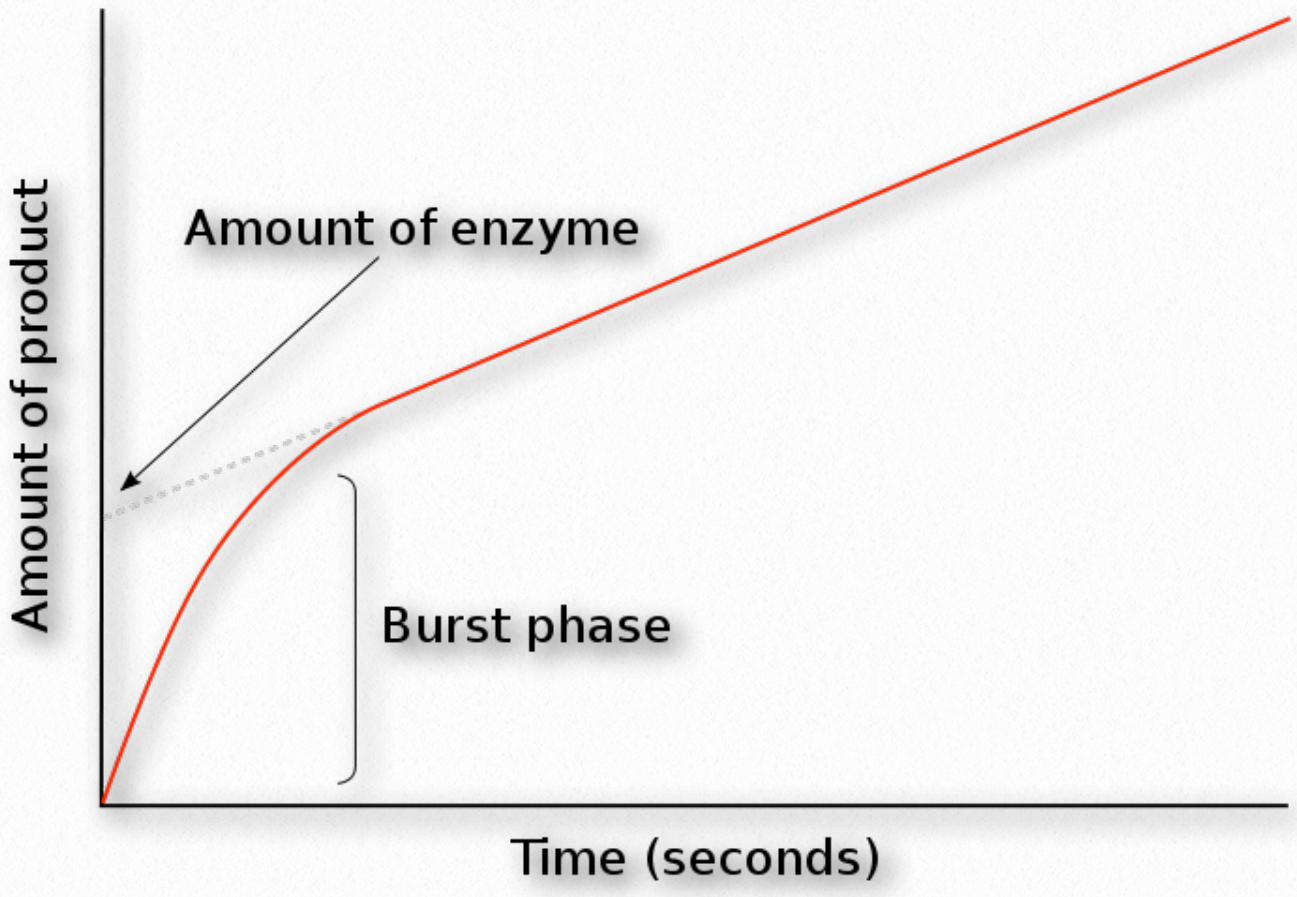

Figure 4.29 - Burst phase of product formation

YouTube Lectures by Kevin HERE & HERE

Pre-steady state kinetic studies

In the study of kinetic rates of enzymatic reactions, time zero is a very critical point. It establishes when the mixing of substrate with enzyme and measurement of formation of product begins. At time zero, there is no product. As shown in Figure 4.29, the appearance of product (on a short time scale) goes through an early burst phase with a steep slope for [product]/time and then changes.

This change occurs during a critical period in an enzymatic reaction and gives information about the rate of reaction cycles. The duration of the burst phase tells how long a single reaction turnover occurs, whereas the slow of the line post-burst phase tells the amount of “functional” enzyme performing the reaction.

After the burst phase, the slope of the line of the amount of product versus time decreases. This is due to the reaction entering conditions of steady state, used to study Michaelis-

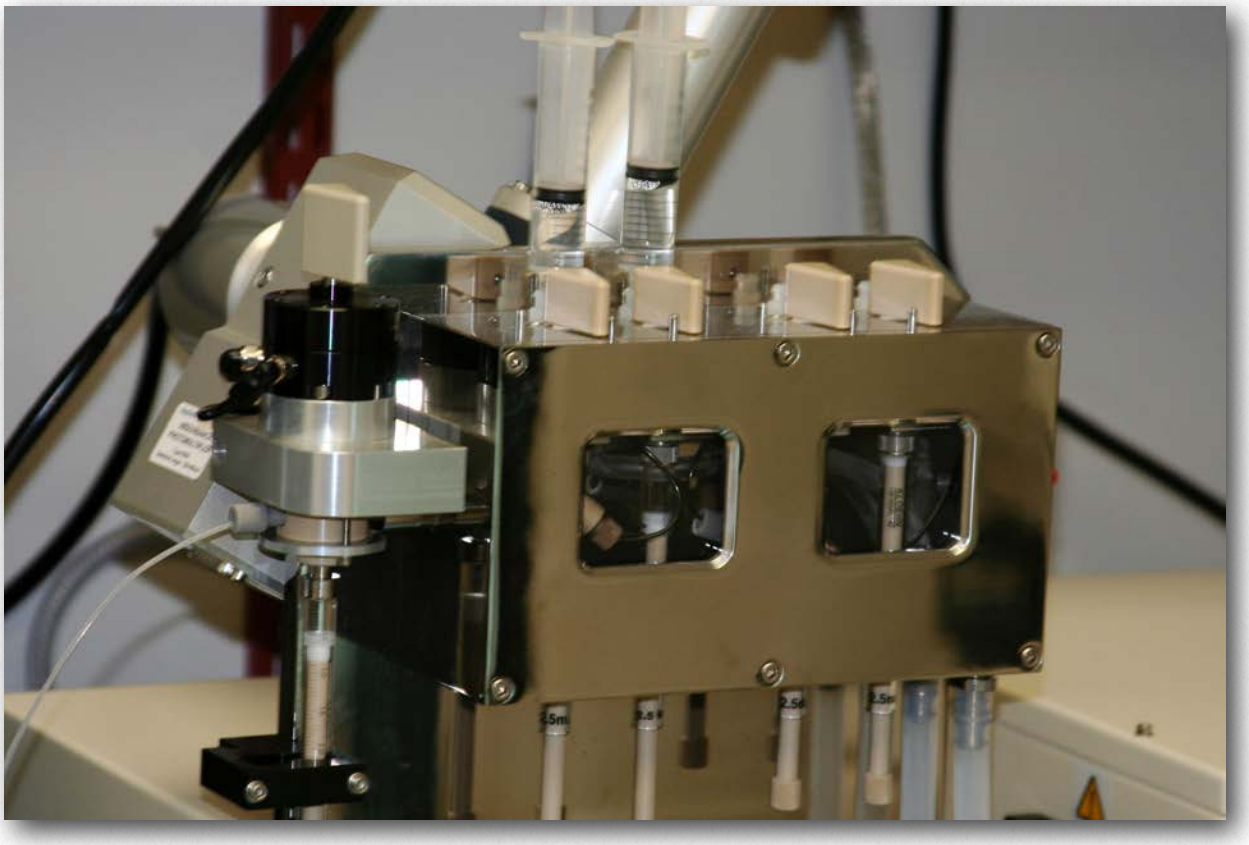

Figure 4.30 - Stopped flow instrument for studying pre-steady state kinetics

Wikipedia

Menten kinetics. In steady state conditions, the amount of the enzyme-substrate complex (ES) is relatively constant over time. In simple terms, this occurs when the rate of formation of the ES complex equals the rate of conversion of the substrate to product by the enzyme with release of the product.

Earlier events

Events occurring prior to the conditions of steady state are referred to as pre-steady state. Depending on the enzyme, in as short as a few milliseconds, steady state conditions can be present meaning that if one hopes to study formation of reaction intermediates in pre-steady state, tools for this analysis must work very rapidly. One instrument commonly used for studying pre-steady state kinetics is called a stopped flow instrument.

It loads an enzyme solution and a substrate into separate syringes whose output is pointed into a mixing chamber. The solutions are rapidly mixed and measurements of product concentration begin. With a stopped flow instrument, dead times (time between mixing and detection) can be achieved of as small as 0.3 msec.

Ribozymes

Proteins do not have a monopoly on acting as biological catalysts. Some RNA molecules are also capable of speeding reactions. The most famous of these molecules was discovered by Tom Cech in the early 1980s Studying excision of an intron in *Tetrahymena*, Cech was puzzled at his inability to find any proteins catalyzing the process. Ultimately, the catalysis was recognized as coming from the intron itself. It was a self-splicing RNA and since then, many other examples of catalytic

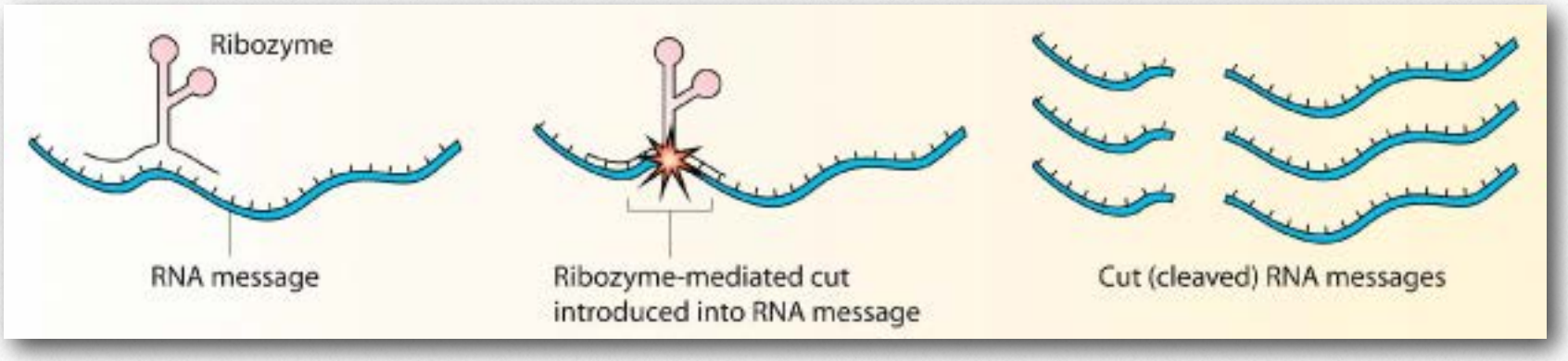

Figure 4.31 - Cleavage of an RNA by a ribozyme

Wikipedia

RNAs have been found. Catalytic RNA molecules are known as ribozymes.

Not unusual

Ribozymes, however, are not rarities of nature. The protein-making ribosomes of cells are essentially giant ribozymes. The 23S rRNA of the prokaryotic ribosome and the 28S rRNA of the eukaryotic ribosome catalyze the formation of peptide bonds.

Ribozymes are also important in our understanding of the evolution of life on Earth. They have been shown to be capable via selection to evolve self-replication. Indeed, ribozymes actually answer a chicken/egg dilemma - which came first, enzymes that do the work of the cell or nucleic acids that carry the information required to produce the enzymes. As both carriers of genetic information and catalysts, ribozymes are likely both the chicken and the egg in the origin of life.

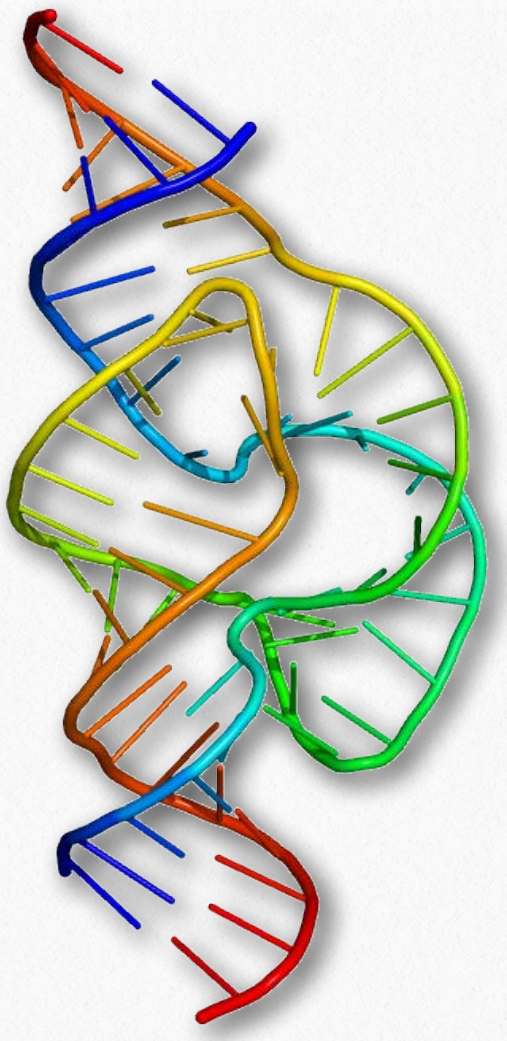

Figure 4.32 - Hammerhead ribozyme

Wikipedia

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Enzymes!

To the tune of "*Downtown*"

Metabolic Melodies Website HERE

Reactions alone
Could starve your cells to the bone
Thank God we all produce
Enzymes

Units arrange
To make the chemicals change
Because you always use
Enzymes!

Sometimes mechanisms run like
They are at the races
Witness the Kcat of the
Carbonic anhydrases

How do they work?
Inside of the active site
It just grabs onto a substrate
and squeezes it tight
In an
ENZYME!
CAT-al-y-sis
In an
ENZYME!
V versus S
In an
ENZYME!
All of this working for you

Energy peaks
Are what an enzyme defeats
In its catalysis
Enzymes!

Transition state
Is what an enzyme does great
And you should all know this

Enzymes!

Catalytic action won't run wild
Don't get hysteric

Cells can throttle pathways
With an enzyme allosteric

You know it's true
So when an effector fits
It will just rearrange
all the sub-u-nits
Inside an
ENZYME!
Flipping from R to T
ENZYME!
Slow catalytically
ENZYME!
No change in Delta G
(*Enzyme, enzyme*)

You should relax
When seeking out the Vmax
Though there are many steps
Enzymes!

Lineweaver Burk
Can save a scientist work
With just two intercepts
Enzymes!

Plotting all the data from
Kinetic exploration
Lets you match a line into a
Best fitting equation

Here's what you do
Both axes are inverted then
You can determine V_{max} and
Establish K_m
for your
ENZYMES!
Sterically holding tight
ENZYMES!
Substrates positioned right
ENZYMES!
Inside the active site
Enzymes (*Enzymes, enzymes, enzymes*)

Recorded by Barbara and Neal Gladstone
Lyrics by Kevin Ahern

Catalysis: Control of Activity

Regulation of enzyme activity

Apart from their ability to greatly speed the rates of chemical reactions in cells, enzymes have another property that makes them valuable. This property is that their activity can be regulated, allowing them to be activated and inactivated, as necessary. This is tremendously important in maintaining homeostasis, permitting cells to respond in controlled ways to changes in both internal and external conditions.

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Inhibition of specific enzymes by drugs can also be medically useful. Understanding the mechanisms that control enzyme activity is, therefore, of considerable importance.

Inhibition

We will first discuss four types of enzyme inhibition – competitive, non-competitive, uncompetitive, and suicide inhibition. Of these, the first three types are reversible. The last one, suicide inhibition, is not.

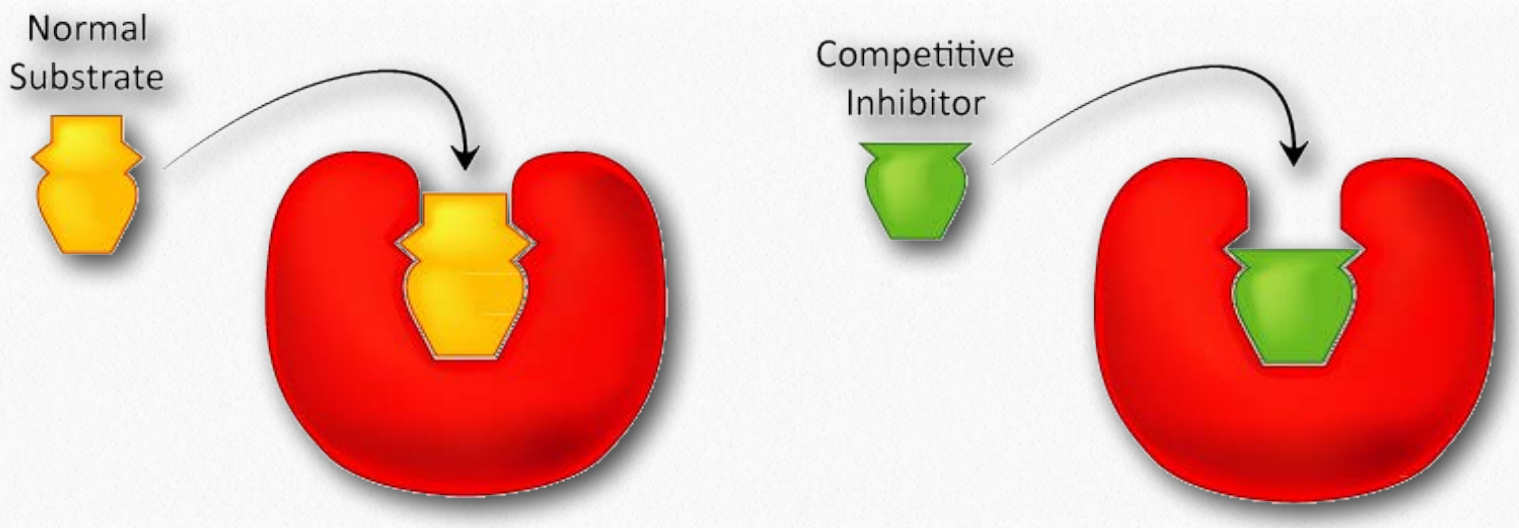

Figure 4.33 - Competitive inhibitors resemble the normal substrate and compete for binding at the active site

Image by Aleia Kim

Competitive inhibition

Probably the easiest type of enzyme inhibition to understand is competitive inhibition and it is the one most commonly exploited pharmaceutically. Molecules that are competitive inhibitors of enzymes resemble one of the normal substrates of an enzyme. An example is methotrexate, which resembles the folate substrate of the enzyme dihydrofolate reductase (DHFR). This enzyme normally catalyzes the reduction of folate, an important reaction in the metabolism of nucleotides.

Inhibitor binding

When the drug methotrexate is present, some of the DHFR enzyme binds to it, instead of to folate, and during the time methotrexate is bound, the enzyme is inactive and unable to bind folate. Thus, the enzyme is inhibited. Notably, the binding site on DHFR for methotrexate is the active site, the same place that folate would normally bind.

As a result, methotrexate 'competes' with folate for binding to the enzyme. The more

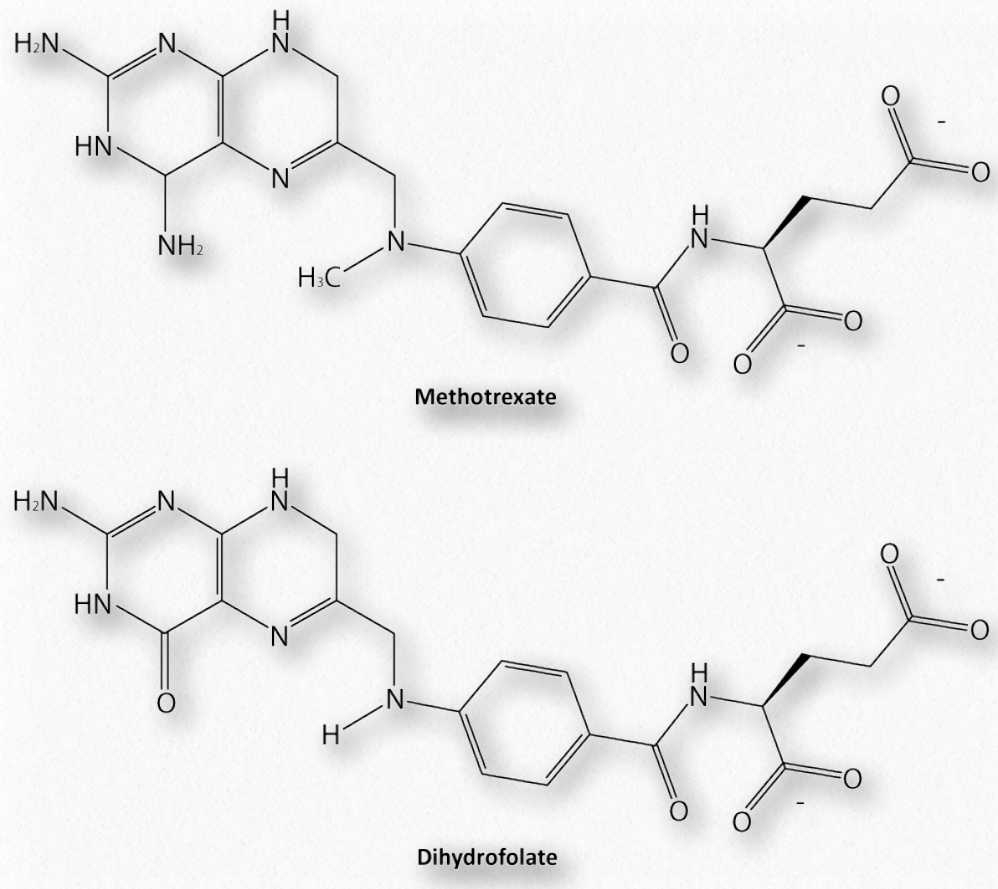

Figure 4.34 - Methotrexate and dihydrofolate

Image by Ben Carson

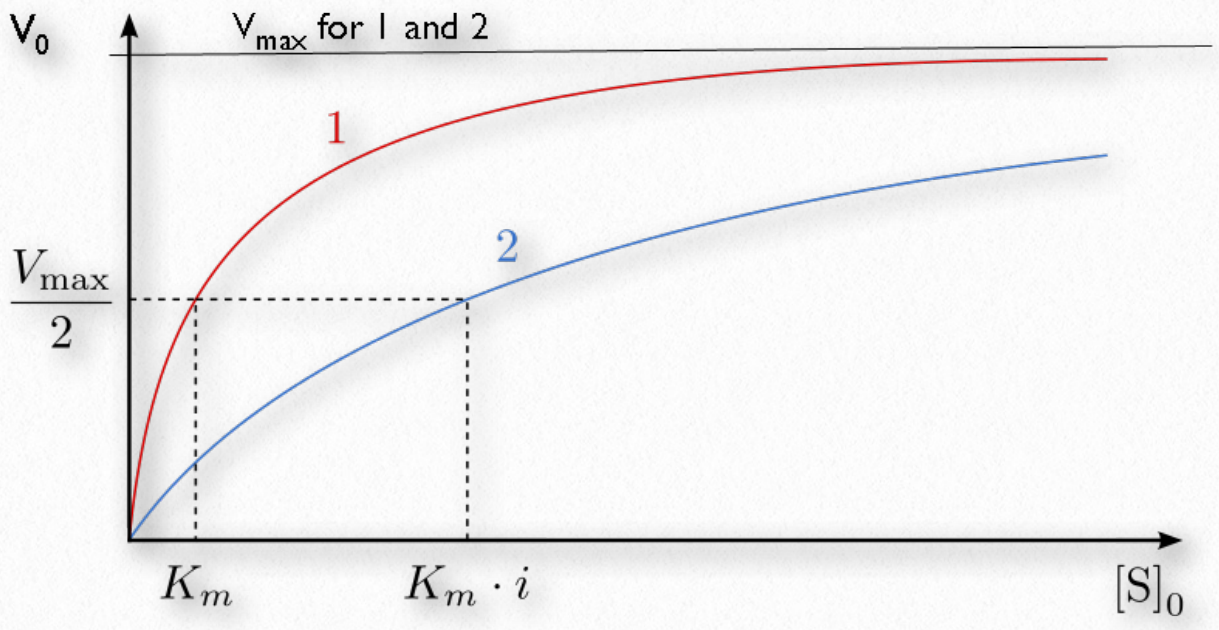

Figure 4.35 V_0 vs [S] Plots for uninhibited reactions (red) and competitively inhibited reactions (blue). Both ultimately have same V_{max}

methotrexate there is, the more effectively it competes with folate for the enzyme's active site. Conversely, the more folate there is, the less of an effect methotrexate has on the enzyme because folate outcompetes it.

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No effect on V_{max}

How do we study competitive inhibition? It is typically done as follows. First, one performs a set of V0 vs. [S] reactions without inhibitor (20 or so tubes, with buffer and constant amounts of enzyme, varying amounts of substrate, equal reaction times). V_0 vs. [S] is plotted (Figure 4.35 red line), as well as $1/V_0$ *vs.* 1/[S] (Figure 4.36 green line). Next, a second set of reactions is performed in the same manner as before, except that a fixed amount of the methotrexate inhibitor is added to each tube. At low concentrations of substrate, the methotrexate competes for the enzyme effectively, but at high concentrations of substrate, the inhibitor will have a much reduced effect, since the substrate outcompetes it, due to its higher concentration (remember that the inhibitor is at fixed concentration).

Graphically, the results of these inhibitor experiments are shown in Figure 4.35 (blue line) and Figure 4.36 (orange line). Notice that at high substrate concentrations, the competitive inhibitor has essentially no effect, causing the V_{max} for the enzyme to remain unchanged. To reiterate, this is due to the fact that at high substrate concentrations, the inhibitor doesn't compete well. However, at lower substrate concentrations, it does.

Increased K_m

In competitively inhibited reactions, the apparent K_m of the enzyme for the substrate increases ($-1/K_m$ gets closer to zero - red line in Figure 4.36) when the inhibitor is present compared to when the inhibitor is absent,

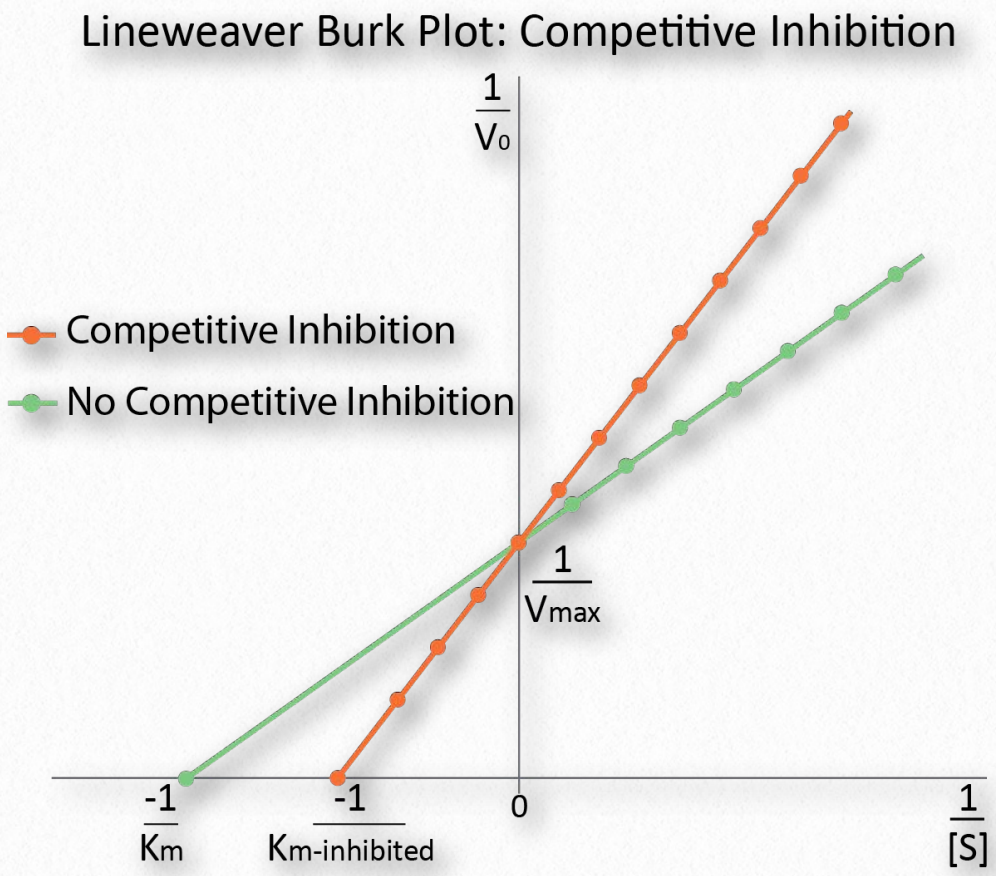

Figure 4.36 - Lineweaver-Burk plots - uninhibited reactions (green). Competitively inhibited reactions (orange). Lines cross on Y-axis at 1/V_{max} Since V_{max} is the same for both reactions

Image by Aleia Kim

thus illustrating the better competition of the inhibitor at lower substrate concentrations.

It may not be obvious why we call the changed K_m the apparent K_m of the enzyme. The reason is that the inhibitor doesn't actually change the enzyme's affinity for the folate substrate. It only appears to do so. This is because of the way that competitive inhibition works. When the competitive inhibitor binds the enzyme, it is effectively 'taken out of action.' Inactive enzymes have NO affinity for substrate and no activity either. We can't measure K_m for an inactive enzyme.

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The enzyme molecules that are not bound by methotrexate can, in fact, bind folate and are active. Methotrexate has no effect on them and their K_m values are unchanged. Why then, does K_m appear higher in the presence of a competitive inhibitor? The reason is that the competitive inhibitor is having a greater effect of reducing the amount of active enzyme at lower concentrations of substrate than it does at higher concentrations of substrate. When the amount of enzyme is reduced, one must have more substrate to supply the reduced amount of enzyme sufficiently to get to Vmax/2.

It is worth noting that in competitive inhibition, the percentage of inactive enzyme changes drastically over the range of [S] values used. To start, at low [S] values, the greatest percentage of the enzyme is inhibited. At high [S], no significant percentage of enzyme is inhibited. This is not always the case, as we shall see in non-competitive inhibition.

Non-competitive inhibition

A second type of inhibition employs inhibitors that do not resemble the substrate and bind not to the active site, but rather to a separate site on the enzyme (Figure 4.37). The effect of binding a non-competitive inhibitor is significantly different from

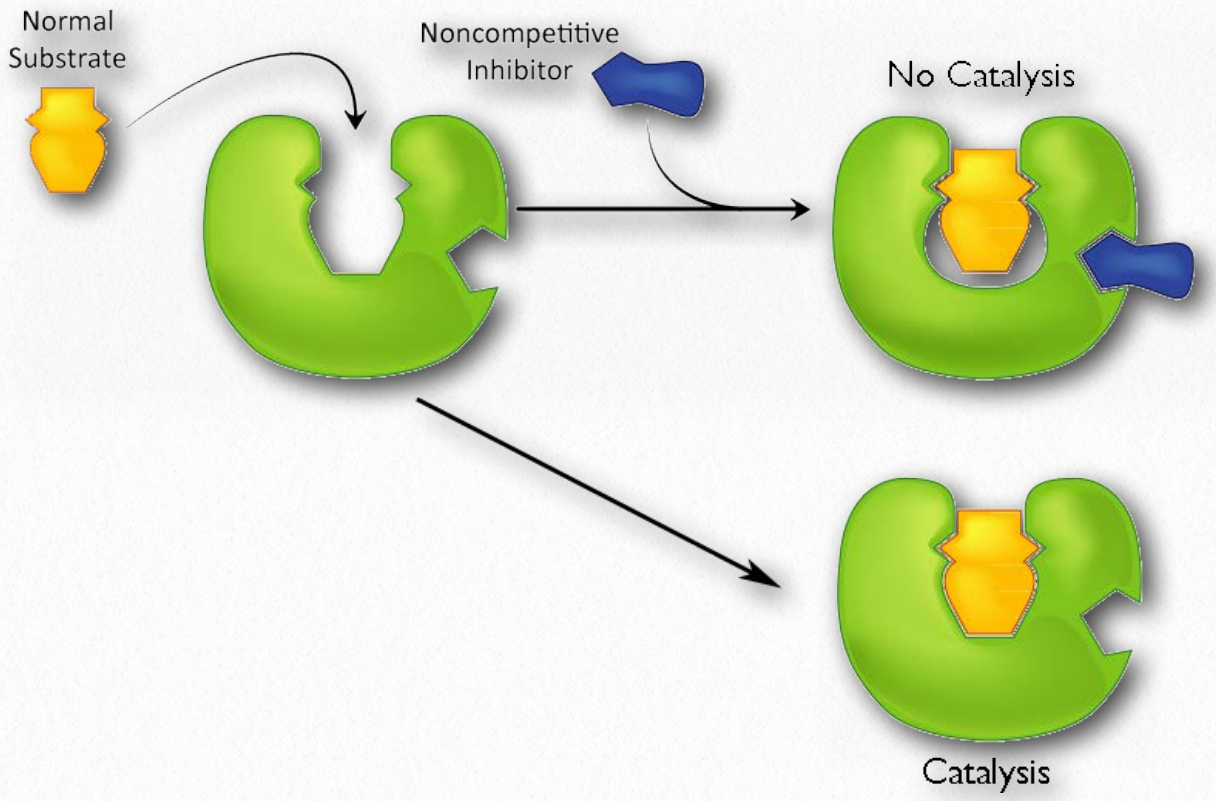

Figure 4.37 - Non-competitive inhibition - inhibitor does not resemble the substrate and binds to a site other than the active site

Image by Aleia Kim

binding a competitive inhibitor because there is no competition. In the case of competitive inhibition, the effect of the inhibitor could be reduced and eventually overwhelmed with increasing amounts of substrate. This was because increasing substrate made increasing percentages of the enzyme active. With non-competitive inhibition, increasing the amount of substrate has no effect on the percentage of enzyme that is active. Indeed, in non-competitive inhibition, the percentage of enzyme inhibited remains the same through all ranges of [S].

This means, then, that non-competitive inhibition effectively reduces the amount of enzyme by the same fixed amount in a typical experiment at every substrate concentration used The effect of this inhibition is shown in Figure 4.38 & 4.39. As you can see, V_{max} is reduced in non-competitive inhibition compared to uninhibited reactions.

This makes sense if we remember that V_{max} is dependent on the amount of enzyme present.

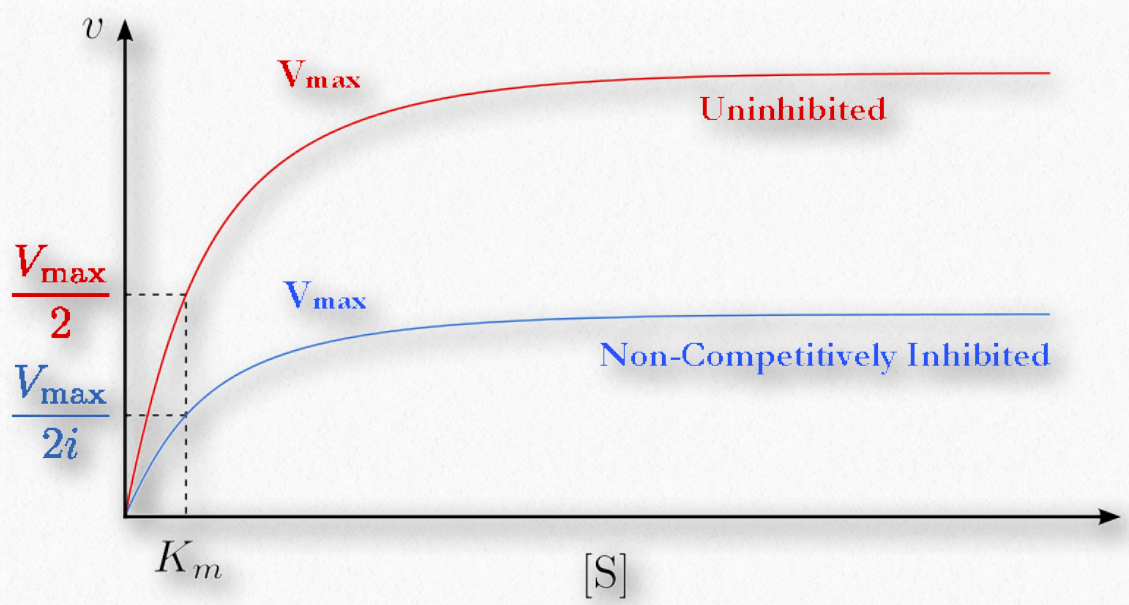

Figure 4.38 - V_0 vs [S] plots of uninhibited reactions (red) and non-competitively inhibited reactions (blue). V_{max} is reduced, but K_m values are unchanged in non-competitively inhibited reactions

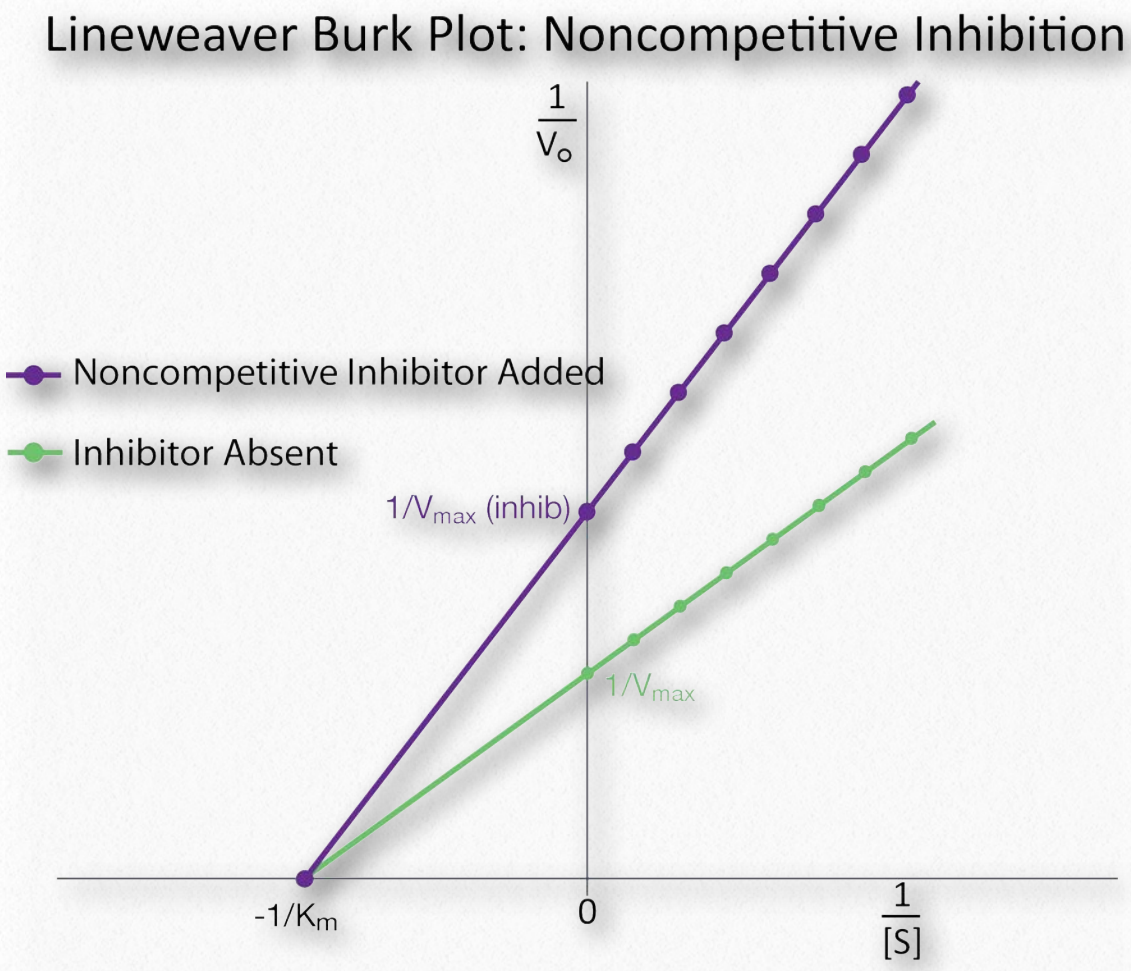

Figure 4.39 - Lineweaver Burk plots of uninhibited reactions (green) and non-competitively inhibited reactions (purple).

Image by Aleia Kim

100% of the enzyme active and the V_{max} appears not to change. Additionally, K_m for non-competitively inhibited reactions does not change from that of uninhibited reactions. This is because, as noted previously, one can only measure the K_m of active enzymes and K_m is a constant for a given enzyme.

Uncompetitive inhibition

A third type of enzymatic inhibition is that of uncompetitive inhibition, which has the odd property of a reduced V_{max} as well as a reduced K_m. The explanation for these seemingly odd results is rooted in the fact that the uncompetitive inhibitor binds only to the enzyme-substrate (ES) complex (Figure 4.40). The inhibitor-bound complex forms mostly under concentrations

Reducing the amount of enzyme present reduces V_{max}. In competitive inhibition, this doesn't occur detectably, because at high substrate concentrations, there is essentially

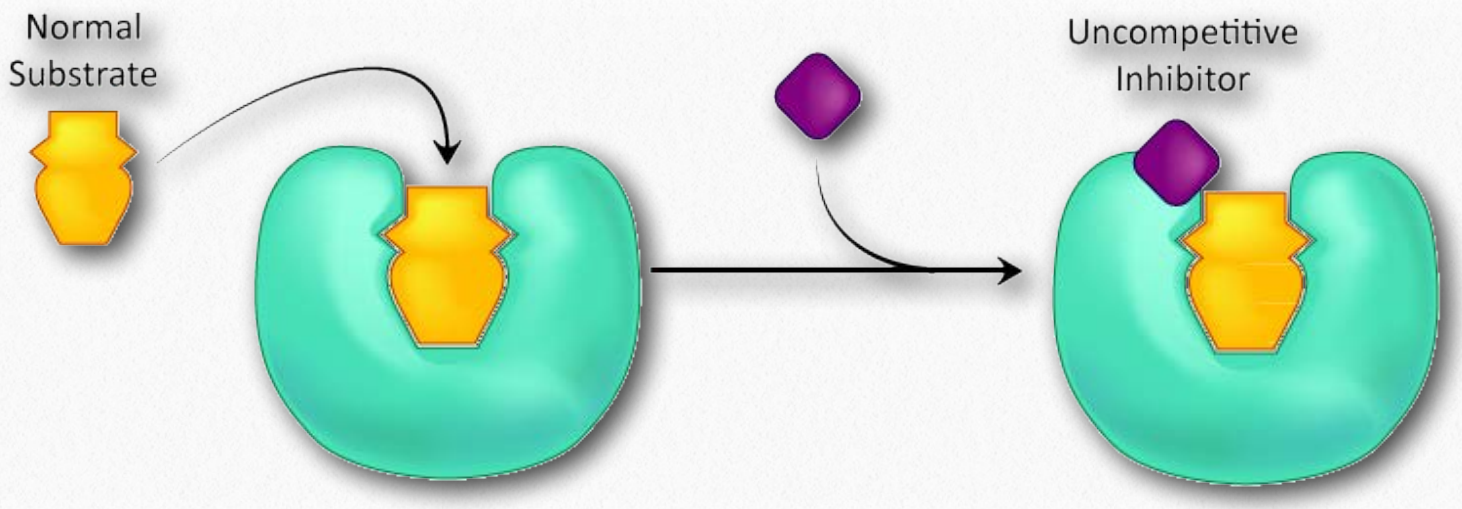

Figure 4.40 - Uncompetitive inhibition

Image by Aleia Kim

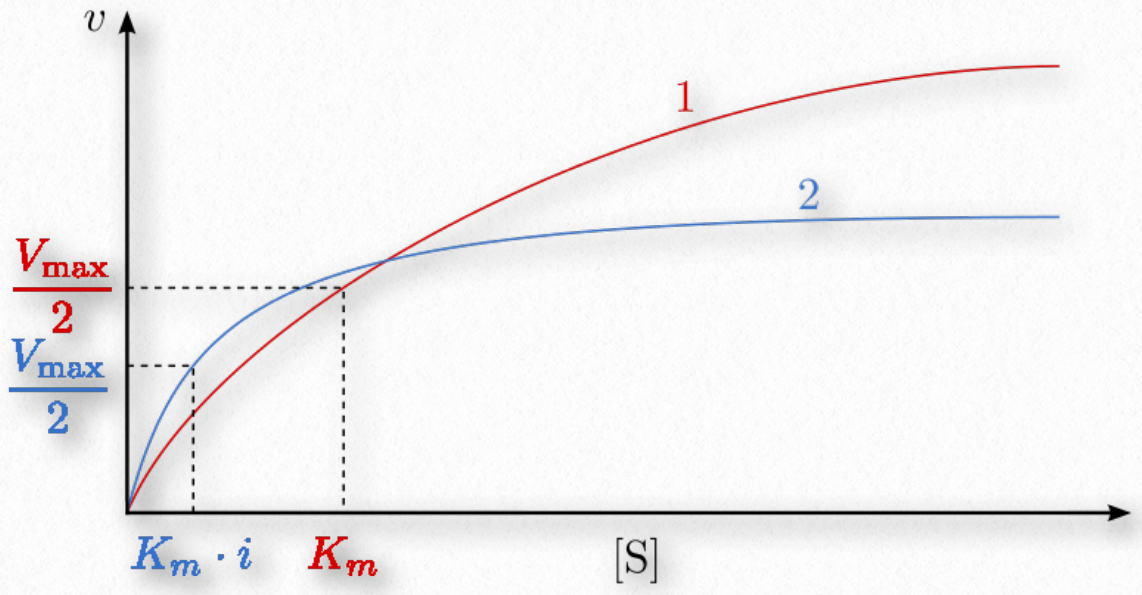

Figure 4.41 - V_0 vs [S] plot for uncompetitive inhibition (blue) and uninhibited reactions (red)

By Le Chatelier's Principle, a shift occurs to form additional ES complex, resulting in less free enzyme and more enzyme in the forms ES and ESI (ES with inhibitor). Decreases in free enzyme correspond to an enzyme with greater affinity for its substrate. Thus, paradoxically, uncompetitive inhibition both decreases V_{max} and increases an enzyme's affinity for its substrate (K_m - Figures 4.41 & 4.42).

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of high substrate and the ES-I complex cannot release product while the inhibitor is bound, thus explaining the reduced V_{max}.

The reduced K_m is a bit harder to conceptualize. The reason is that the inhibitor-bound complex effectively reduces the concentration of the ES complex.

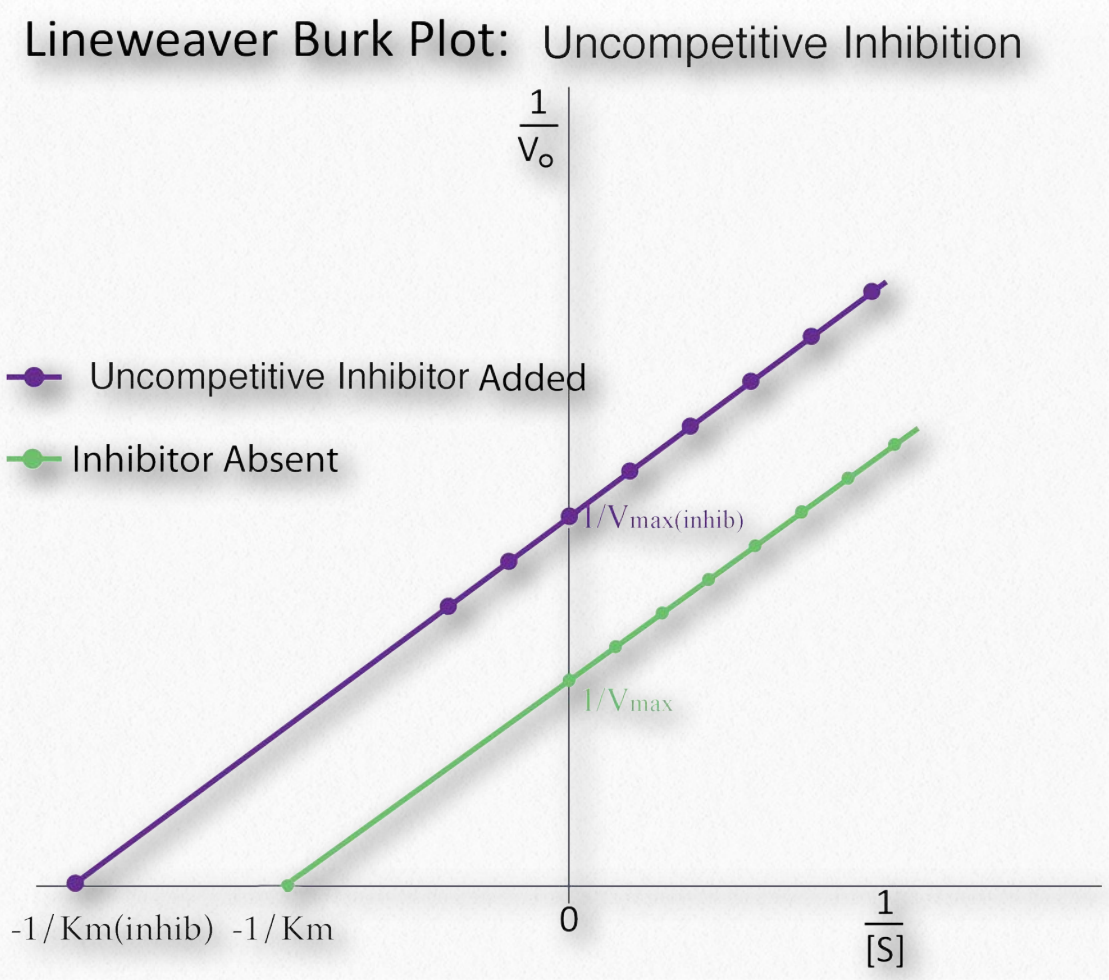

Figure 4.42 - Uncompetitive inhibition (purple) and uninhibited reactions (green)

Image by Aleia Kim

Suicide inhibition

In contrast to the first three types of inhibition, which involve reversible binding of the inhibitor to the enzyme, suicide inhibition is irreversible, because the inhibitor becomes covalently bound to the enzyme during the inhibition. Suicide inhibition rather closely resembles competitive inhibition because the inhibitor generally resembles the substrate and binds to the active site of the enzyme. The primary difference is that the suicide inhibitor is chemically reactive in the active site and makes a bond with it that precludes its removal. Such a mechanism is that employed by penicillin (Figure 4.43), which covalently links to the bacterial enzyme, DD transpeptidase and stops it from functioning. Since the normal function of the enzyme is to make a bond necessary for the peptidoglycan complex of the bacterial cell wall, the cell wall cannot properly form and bacteria cannot reproduce.

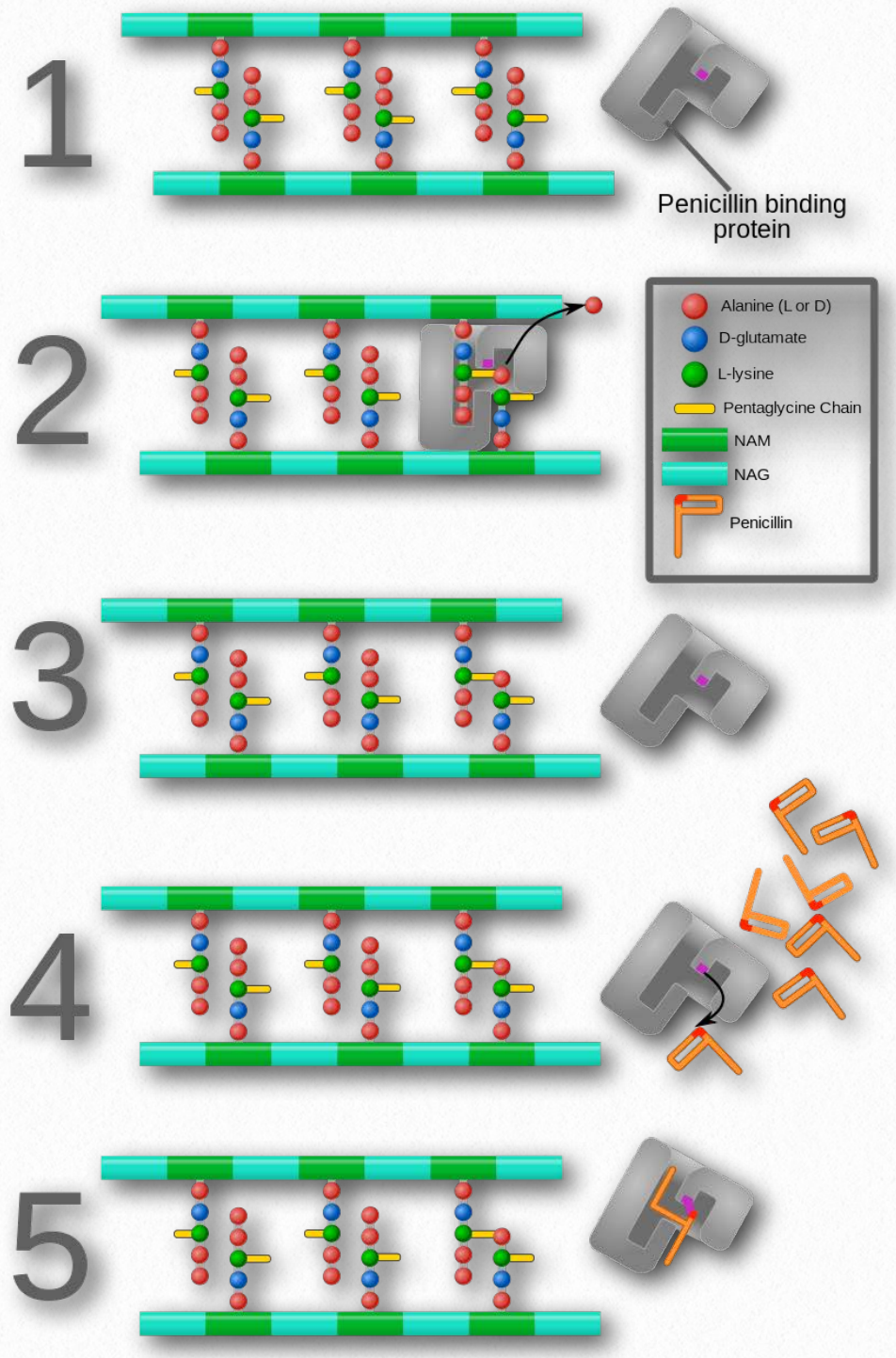

Figure 4.43 - Action of penicillin. DD-transpeptidase builds peptidoglycan layer of bacterial cell wall (1-3). Binding of penicillin by DD-transpeptidase stops peptidoglycan synthesis (4-5)

Wikipedia

For inhibition, here are rules
To give to students in the schools
Non-competers muddy facts
And drop the value of V_{max}
Competers, everyone should know
Will make the K_M values grow
Uncompetition makes them think
Since both K_M and V_{max} shrink
And suicide covalently
Stops enzymes irreversibly

Control of enzymes

It is appropriate to talk at this point about mechanisms cells use to control enzymes. There are four general methods that are employed. They include 1) allosterism; 2) covalent modification; 3) access to substrate;

and 4) control of enzyme synthesis/ breakdown. Some enzymes are controlled by more than one of these methods.

Allosterism

The term allosterism refers to the fact that the activity of certain enzymes can be affected by the binding of small molecules. Molecules causing allosteric effects come in two classifications. Ones that are substrates for the enzymes they affect are called homotropic effectors and those that are not substrates are called heterotropic effectors.

The homotropic effectors usually are activators of the enzymes they bind to and the results of their action can be seen in the conversion of the hyperbolic curve typical of a V_0 vs. [S] plot for an enzyme (Figure 4.18) , being converted to a sigmoidal plot (Figure 4.44). This is due to the conversion of the enzyme from the T-state to the R-state on binding the substrate/homotropic effector.

The V_0 vs. [S] plot of allosteric enzyme reactions resembles the oxygen binding curve of hemoglobin (see Figure 2.83). Even though hemoglobin is not an enzyme and is thus not catalyzing a reaction, the similarity of the plots is not coincidental. In both cases, the binding of an external molecule is being measured – directly, in the hemoglobin plot, and indirectly by the V_0 vs. [S] plot, since substrate binding is a factor in enzyme reaction velocity.

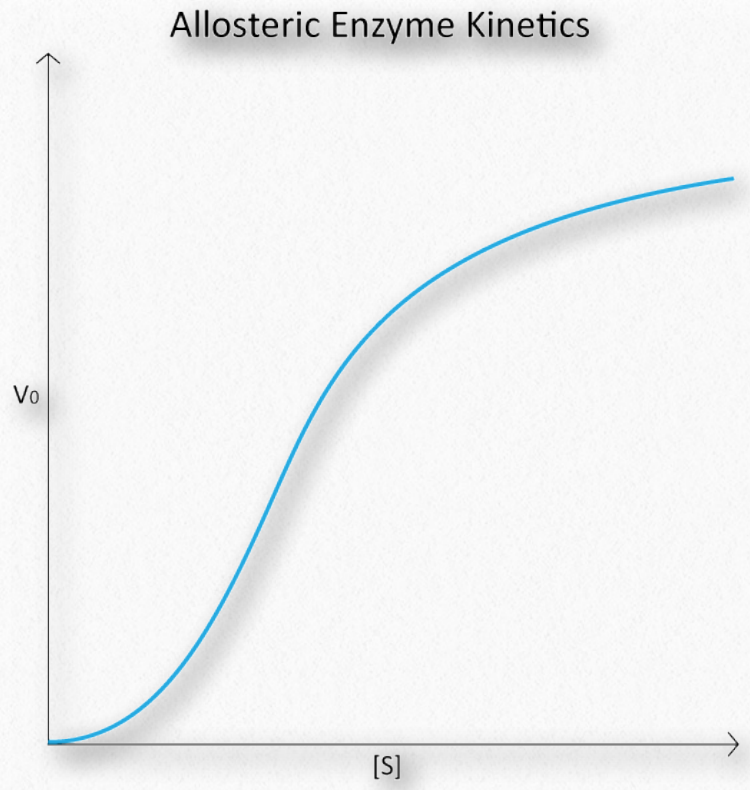

Figure 4.44 - Kinetic profile of an allosteric enzyme whose activity is controlled by a homotropic effector

Image by Aleia Kim

Allosteric inhibition

Allosterically, regulation of these enzymes works by inducing different physical states (shapes, as it were) that affect their ability to bind to substrate. When an enzyme is inhibited by binding an effector, it is converted to the T-state (T=tight), it has a reduced affinity for substrate and it is through this means that the reaction is slowed.

Allosteric activation

On the other hand, when an enzyme is activated by effector binding, it converts to the R-state (R=relaxed) and binds substrate much more readily. When no effector is present, the enzyme may be in a mixture of T- and R-states.

Feedback inhibition

An interesting kind of allosteric control is exhibited by HMG-CoA reductase, which catalyzes an important reaction in the pathway leading to the synthesis of cholesterol. Binding of cholesterol to the enzyme reduces the enzyme's activity significantly. Cholesterol is not a substrate for the enzyme, so it is therefore a heterotropic effector.

Notably, though, cholesterol is the end-product of the pathway that HMG-CoA reductase catalyzes a reaction in. When enzymes are inhibited by an end-product of the pathway in which they participate, they are said to exhibit feedback inhibition.

Feedback inhibition always operates by allosterism and further, provides important and efficient control of an entire pathway. By inhibiting an early enzyme in a pathway, the flow of materials (and ATP hydrolysis required for their processing) for the entire pathway is stopped or reduced, assuming there are not alternate supply methods.

Pathway control

In the cholesterol biosynthesis pathway, stopping this one enzyme has the effect of shutting off (or at least slowing down) the entire pathway. This is significant because after catalysis by HMG-CoA reductase, there are over 20 further reactions necessary to make cholesterol, many of them requiring ATP energy. Shutting down one reactions stops all of them. Another excellent example of allosteric control and feedback inhibition is the enzyme ATCase, discussed below.

ATCase

Another interesting example of allosteric control and feedback inhibition is associated with the enzyme Aspartate Transcarbamoylase (ATCase). This enzyme, which catalyzes a step in the synthesis of pyrimidine nucleotides, has 12 subunits. These include six identical catalytic subunits and six identical regulatory subunits. The catalytic subunits bind to substrate and catalyze a reaction. The regulatory subunits bind to either ATP or CTP. If they bind to ATP, the enzyme

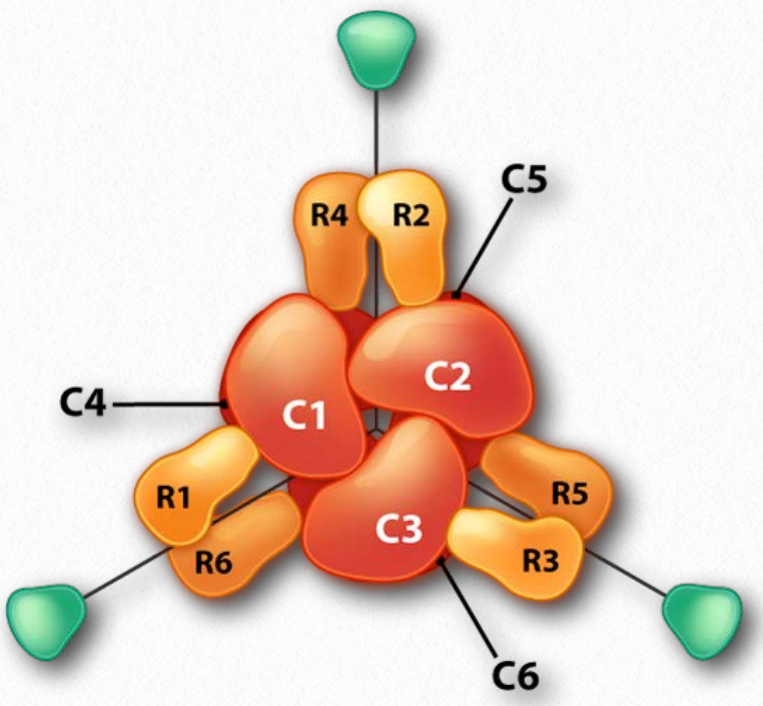

Figure 4.45 - Schematic structure of ATCase. Regulatory Units = R, Catalytic Units = C
Image by Aleia Kim

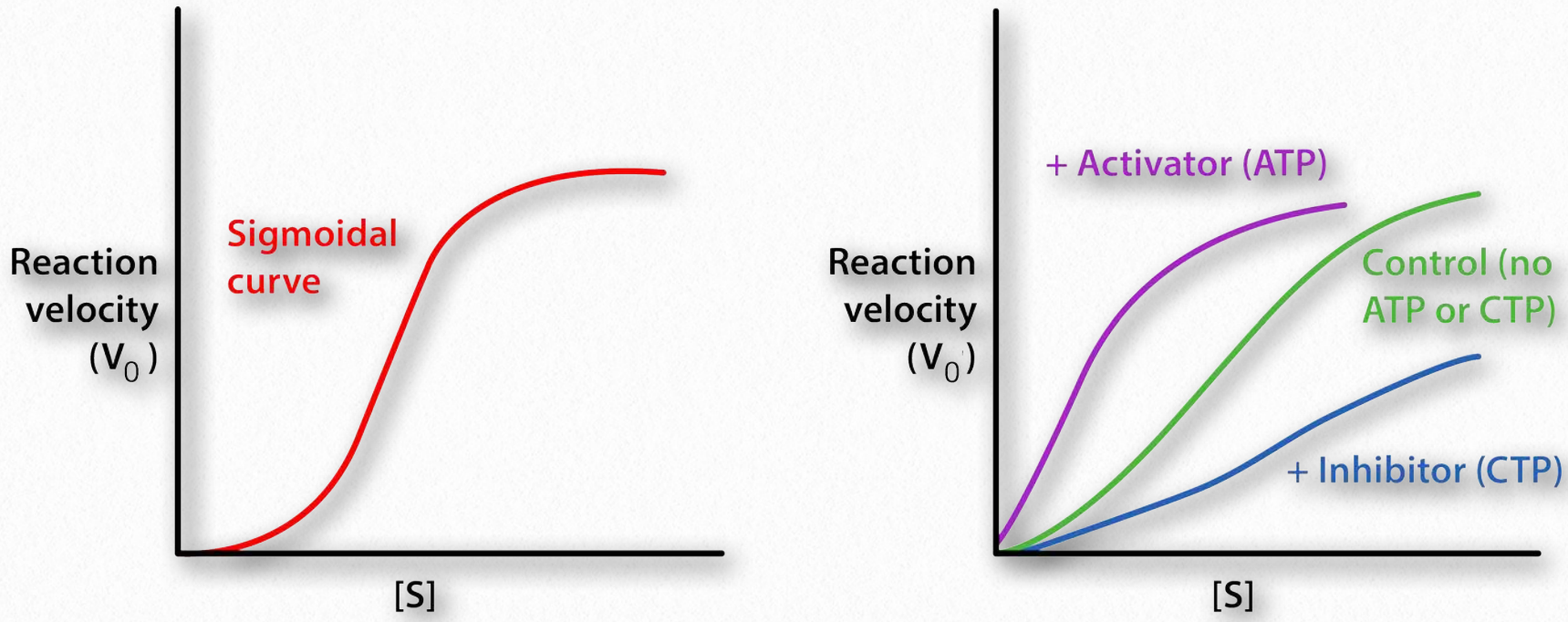

Figure 4.46 - Plots of V_0 vs. [S] for ATCase. Left - Allosteric effect of aspartate. Right - Allosteric effects of ATP (activator) and CTP (inhibitor)

Image by Pehr Jacobson

subunits arrange themselves in the R-state.

R-state

The R-state of ATCase allows the substrate to have easier access to the six active sites and the reaction occurs more rapidly. For the same amount of substrate, an enzyme in the R-state will have a higher velocity than the same enzyme that is not in the R-state.

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By contrast, if the enzyme binds to CTP on one of its regulatory subunits, the subunits will arrange in the T-state and in this form, the substrate will not have easy access to the active sites, resulting in a slower velocity for the same concentration of substrate compared to the R-state. ATCase is interesting in that it can also flip into the R-state when one of the substrates (aspartate) binds to an active site within one of the catalytic subunits.

Aspartate has the effect of activating the catalytic action of the enzyme by favoring the R-state. Thus, aspartate, which is a substrate of the enzyme is a homotropic effector and ATP and CTP, which are not substrates of the enzyme are heterotropic effectors of ATCase.

Allosteric models

There are three models commonly used to explain how allosterism regulates multi-subunit enzyme activity. They are known as the Monod-Wyman-Changeux (MWC) model (also known as the concerted model), the sequential model (also known as KNF), and the morpheein model. All models describe a

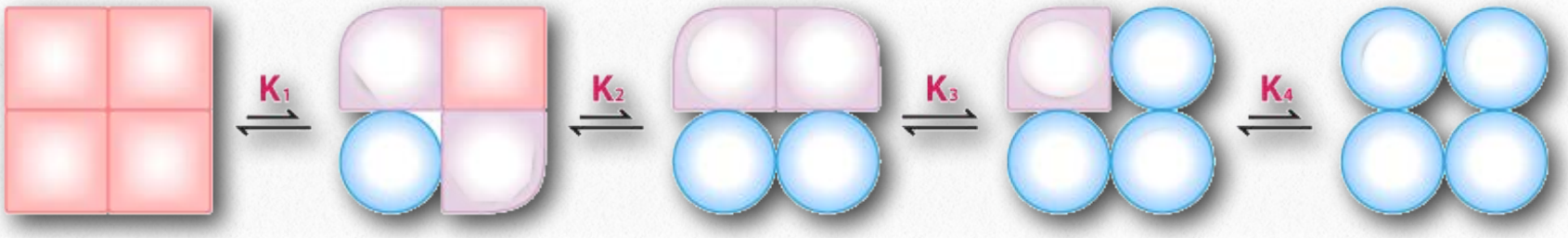

Figure 4.47 - Sequential model of allosteric regulation. Round = R-State. Square = T-state.

Image by Aleia Kim

Tense (T) state that is less catalytically active and a Relaxed (R) state that is more catalytically active. The models differ in how the states change.

Sequential model

In the sequential model, binding of an allosteric effector by one subunit causes it to change from T to R state (or vice versa) and that change makes it easier for adjacent subunits to similarly change state. With this model , there is a cause/effect relationship between binding of an effector by one subunit and change of state by an adjacent subunit.

In hemoglobin, for example, binding of one oxygen by one unit of the complex may induce that unit to flip to the R-state and, through interactions with other subunits, cause them to favor adopting the R configuration before they bind to oxygen. In this way, binding of one subunit favors binding of others and cooperativity can be explained by the change in binding affinity as oxygen concentration changes.

MWC model

The MWC model is less intuitive. In it, the entire complex changes state from T to R (or vice versa) independently of the binding of effectors. Flipping between T-states and R-states is postulated to be in an equilibrium of states in the absence of effector (for example, a 50 to 1 ratio of T/R. This ratio is referred to as L, so L = T/R). Binding of effector by the enzyme complex has the tendency of “locking” the complex in a state. Binding of inhibitors will increase the ratio of T/R whereas binding of activators will increase R and thus decrease the ration of T/R.

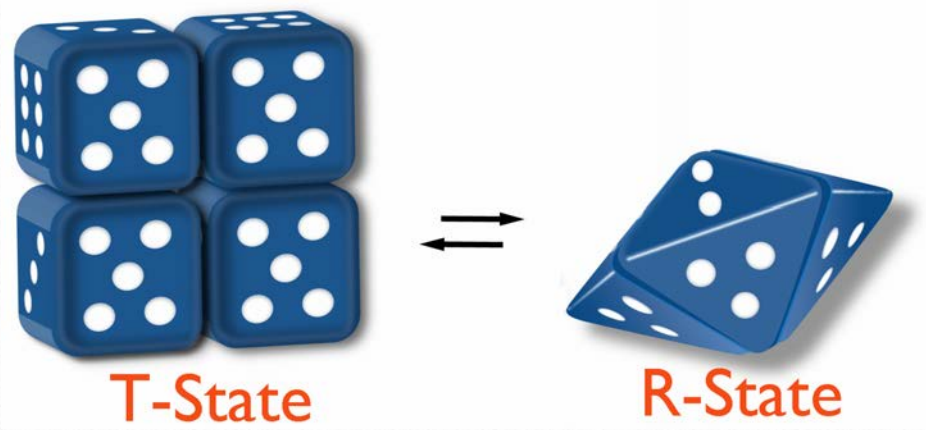

Figure 4.48 - The MWC Model - The multisubunit complex flips as a whole and is in equilibrium

Wikipedia

Morpheein model

The morpheein model is similar to the MWC model, but with an added step of dissociation of the subunits. The MWC model proposes that flipping between R and T states occurs by the complex as a whole and occurs on all units simultaneously.

The morpheein model instead proposes that the multi-subunit enzyme breaks down to individual units which can then flip in structure and re-form the complex. In the morpheein model, only identically shaped units (all R, for example) can come together in the complex, thus explaining the "all-R-" or "all-T-" state found in the MWC model.

A large number of enzymes, including prominent ones like citrate synthase, acetyl-CoA carboxylase, glutamate dehydrogenase, ribonucleotide reductase and lactate dehydrogenase have behavior consistent with the morpheein model.

Covalent control of enzymes

Some enzymes are synthesized in a completely inactive form and their activation requires covalent bonds in them to be cleaved. Such inactive forms of enzymes are called zymogens. Examples include the proteins involved in blood clotting and proteolytic enzymes of the digestive system, such as trypsin, chymotrypsin, pepsin, and others.

Synthesizing some enzymes in an inactive form makes very good sense when an enzyme's activity might be harmful to the tissue where it is being made. For example, the painful condition known as pancreatitis arises when digestive enzymes made in the pancreas are activated too soon and end up attacking the pancreas.

Cascades

For both the blood clotting enzymes and the digestive enzymes, the zymogens are activated in a protease cascade. This occurs when activation of one enzyme activates oth-

Figure 4.49 - Morpheein model of allosterism. States flip as monomers and aggregate only with same monomer.

Wikipedia

ers in a sort of chain reaction. In such a scheme the first enzyme activated proteolytically cleaves the second zymogen, causing it to be activated, which in turn activates a third and this may proceed through several levels of enzymatic action (Figure 4.50).

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The advantage of cascades is that they allow a large amount of zymogens to become activated fairly quickly, since there is an amplification of the signal at each level of catalysis.

Zymogens are also abundant in blood. Blood clotting involves polymerization of a protein known as fibrin. Since random formation of fibrin is extremely hazardous because it can block the flow of blood, potentially causing heart attack/stroke, the body synthesizes fibrin as a zymogen (fibrinogen) and its activation results from a "cascade" of activations of proteases that arise when a signal is received from a wound. Similarly, the enzyme catalyzing removal of fibrin clots (plasmin) is also synthesized as a zymogen (plasminogen), since random clot removal would also be hazardous (see below also).

Phosphorylation/ dephosphorylation

Another common mechanism for control of enzyme activity by covalent modification is phosphorylation. The phosphorylation of enzymes (on the side chains of serine, threonine or tyrosine residues) is carried out by protein kinases. Enzymes activated by phos-

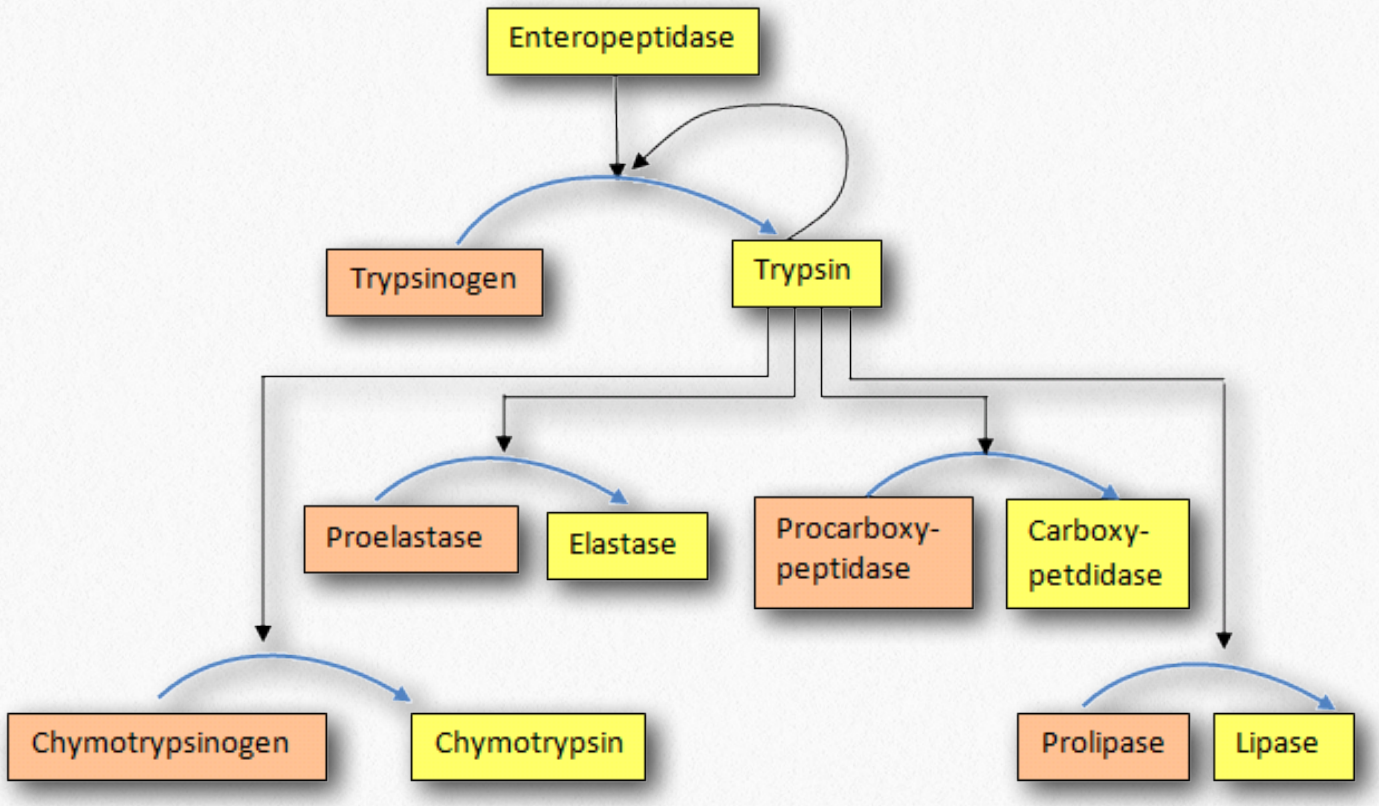

Figure 4.50 - Protease activation scheme

Wikipedia

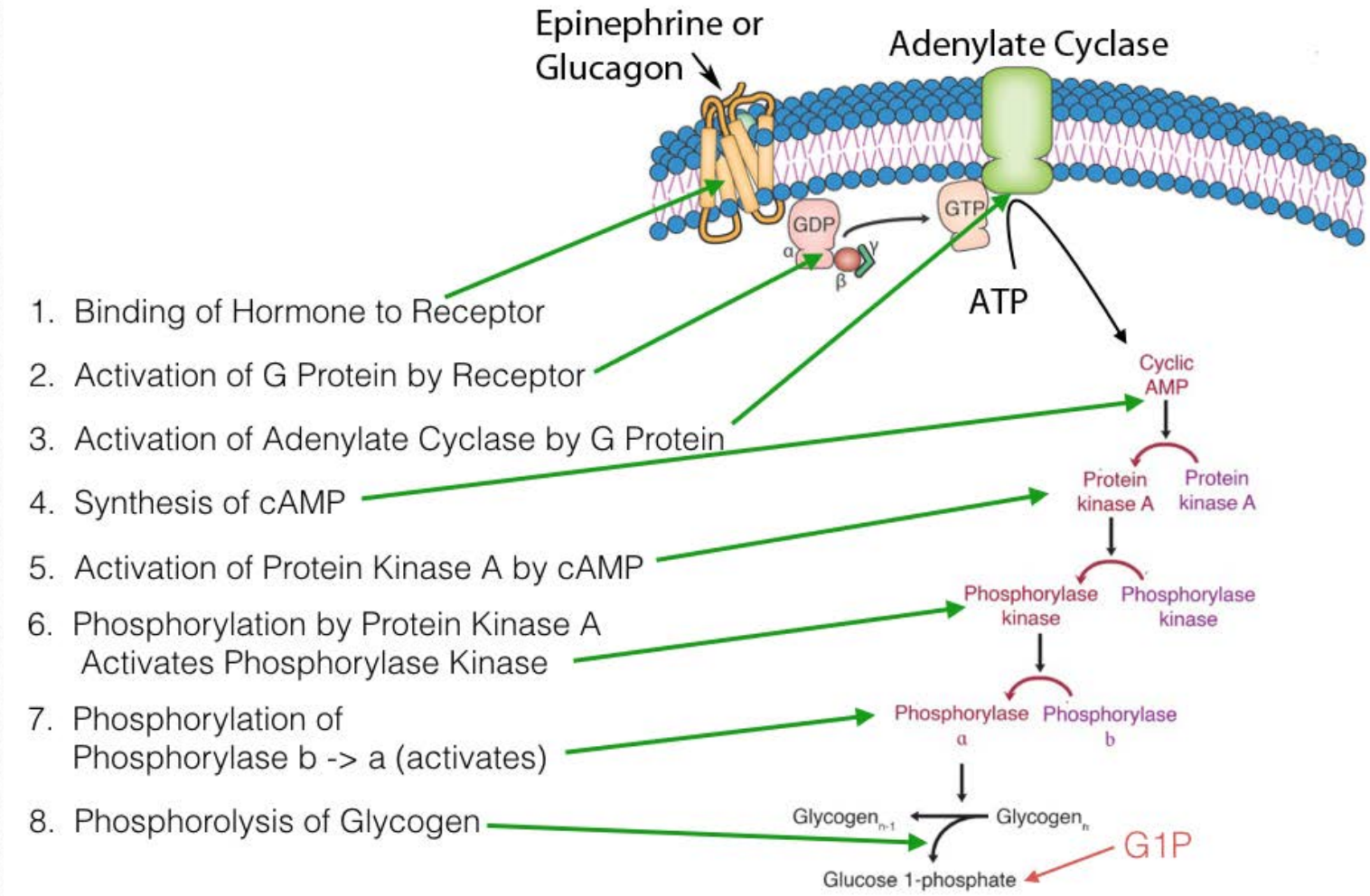

Figure 4.51 - Regulation by covalent modification of glycogen catabolism enzymes

phorylation can be regulated by the addition of phosphate groups by kinases or their removal by phosphatases. Thus, this type of covalent modification is readily reversible, in contrast to proteolytic cleavage.

Reduction/oxidation

An interesting covalent control of enzymes using reduction/oxidation is exhibited in photosynthetic plants. In the light phase of photosynthesis, electrons are excited by light and flow through carriers to $NADP^+$, forming NADPH. Thus, in the light, the NADPH concentration is high. When NADPH concentration is high, the concentration of reduced ferredoxin (a molecule donating electrons to $NADP^+$) is also high.

Reduced ferredoxin can transfer electrons to thioredoxin, reducing it. Reduced thioredoxin can, in turn, transfer electrons to proteins to reduce their disulfide bonds. Four enzymes related to the Calvin cycle can receive electrons from thioredoxin and become activated, as a result.

These include sedoheptulose 1,7-bisphosphatase, ribulose-5-phosphate kinase, fructose 1,6-bisphosphatase, and glyceraldehyde 3-phosphate dehydrogenase. Thus, in the light, electrons flow, causing NADPH to accumulate and ferredoxin to push electrons in the direction of these enzymes above, activating them and favoring the Calvin cycle. In the dark, the concentration of reduced NADPH, reduced ferredoxin, and reduced thioredoxin fall, resulting in loss of electrons by the Calvin cycle enzymes (oxidations that reform disulfide bonds) and the Calvin cycle inactivates.

Other enzyme control mechanisms

Other means of controlling enzymes relate to access to substrate (substrate-level control) and control of enzyme synthesis. Hexokinase is an enzyme that is largely regulated by availability of its substrate, glucose. When glucose concentration is low, the product of the enzyme's catalysis, glucose-6-phosphate, inhibits the enzyme's function.

Regulation of enzymes by controlling their synthesis is covered later in the book in the discussion relating to control of gene expression.

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Catalyze

To the tune of "*Close to You*"

Metabolic Melodies Website HERE

My enzymes
Truly are inclined
To convert
Things they bind
Turn the key
Covalently
Cat-a-lyze

How do cells
Regulate these roles?
Allo-ster
-ic controls
Two forms, you see
States R and T
Mod-u-late

Competing inhibition keeps
The substrates from the active site
They raise Km, but leave Vmax and shirk
While the non-competers bind elsewhere
And lift the plot made on Lineweaver-Burk

Other ways
Enzymes can be blocked
When things bind
Then get locked
Stuck not free
Tied to the key
Su-i-cide

Penicillin's action stops
Peptidoglycan cross-links in
Bacterial cell walls in awesome ways
Beta lactam ring's reactive site
Starts bonding with D-D-transpeptidase

So there are
Several enzyme states
Counteract
-ing substrates
Now you see
Blocking the key
Regulates

Cat-a-lysts
Have to be controlled
Some get slowed
Put on hold
It's sublime
How the enzymes
(slow) Cat-a-lyze

It's sublime
How the enzymes
(slow) Cat-a-lyze

ahhhhhhhhhhhhhhhhhh - cat-a-lyze
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Recorded by Barbara and Neal Gladstone
Lyrics by Kevin Ahern

Catalysis: Mechanism

Introduction

The magic of enzymes, as noted, is in their ability to create electronic environments conducive to initiation of a reaction. There are more mechanisms of reaction than we could ever hope to cover in a book like this, and comprehensive discussion of these is not our aim. Instead, we will cite some examples and go into detail on one of them - the mechanism of action of serine proteases.

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Chymotrypsin

We will begin with mechanism of action of one enzyme - chymotrypsin. Found in our digestive system, chymotrypsin's catalytic activity is cleaving peptide bonds in proteins and it uses the side chain of a serine in its mechanism of catalysis. Many other protein-cutting enzymes employ a very similar mechanism and they are known collectively as serine proteases (Figure 4.52). These enzymes are found in prokary-

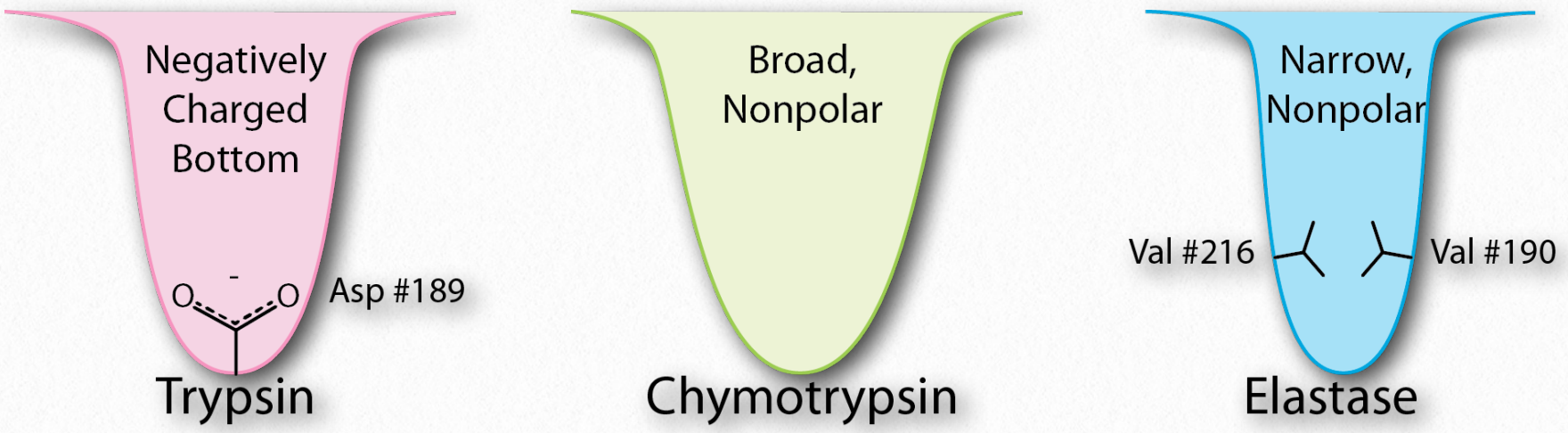

Figure 4.52 - Substrate binding sites (S1 pockets) of three serine proteases

Image by Aleia Kim

otic and eukaryotic cells and all use a common set of three amino acids in the active site called a catalytic triad (Figure 4.53). It consists of aspartic acid, histidine, and serine. The serine is activated in the reaction mechanism to form a nucleophile in these enzymes and gives the class their name. With the exception of the recognition that occurs at the substrate binding site, the mechanism shown here for chymotrypsin would be applicable to any of the serine proteases.

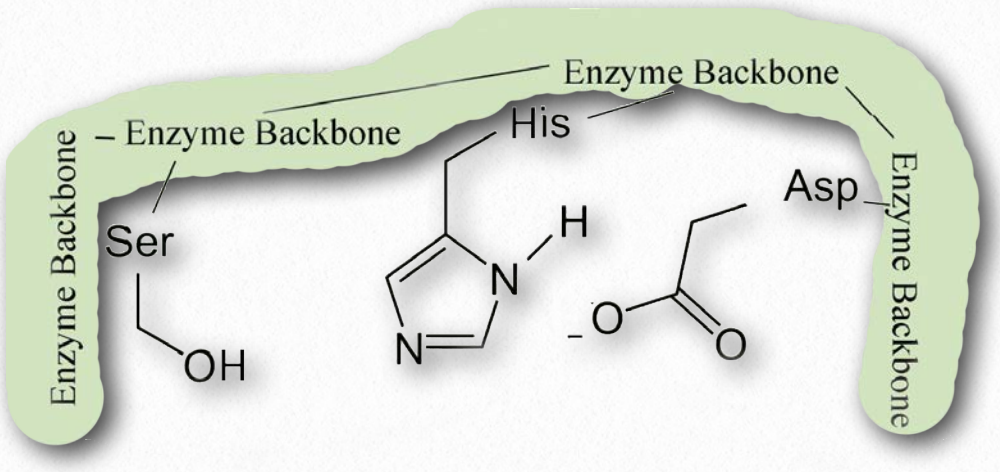

Figure 4.53 - 1. Active site of chymotrypsin showing the catalytic triad of serine - histidine-aspartic acid

Specificity

As a protease, chymotrypsin acts fairly specifically, cutting not all peptide bonds, but only those that are adjacent to relatively nonpolar amino acids in the protein. One of the amino acids it cuts adjacent to is phenylalanine. The enzyme's action occurs in two phases – a fast phase that occurs first and a slower phase that follows. The enzyme has a substrate binding site that includes a region of the enzyme known as the S1 pocket. Let us step through the mechanism by which chymotrypsin cuts adjacent to phenylalanine.

Substrate binding

The process starts with the binding of the substrate in the S1 pocket (Figure 4.54). The S1 pocket in chymotrypsin has a hydrophobic hole in which the substrate is bound. Preferred substrates will include amino acid side

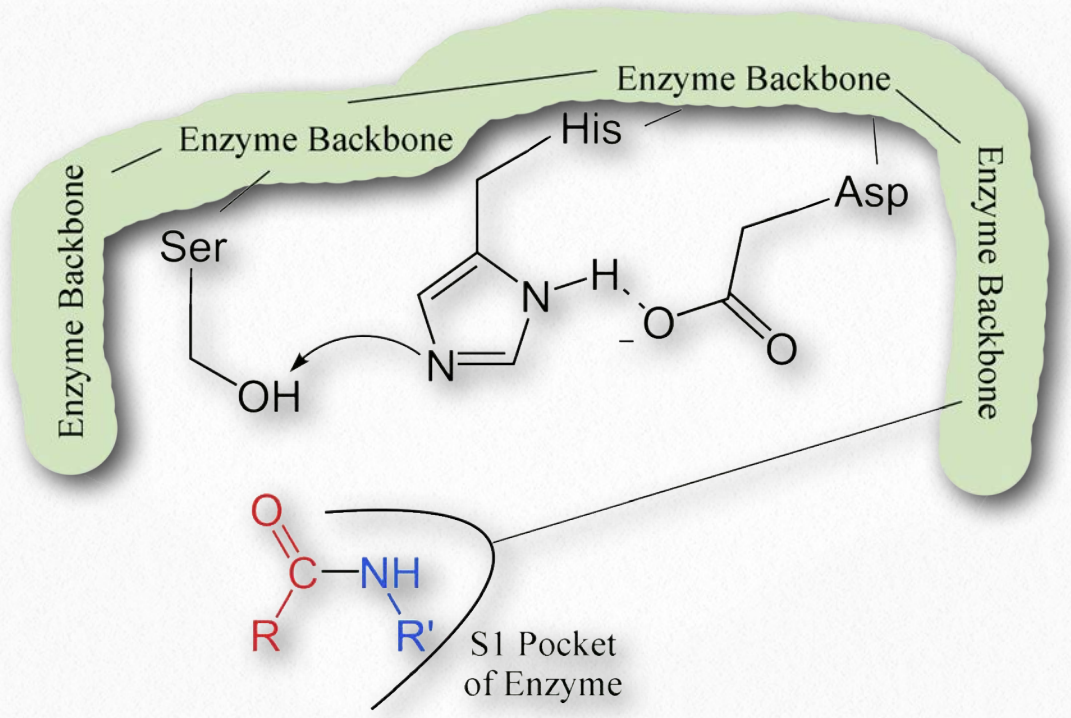

Figure 4.54 - 2. Binding of substrate to S1 pocket in the active site

chains that are bulky and hydrophobic, like phenylalanine. If an ionized side chain, like that of glutamic acid binds in the S1 pocket, it will quickly exit, much like water would avoid an oily interior.

Shape change on binding

When the proper substrate binds in the S1 pocket, its presence induces an ever so slight change in the shape of the enzyme. This subtle shape change on the binding of the proper substrate starts the steps of the catalysis. Since the catalytic process only starts when the proper substrate binds, this is the reason that the enzyme shows specificity for cutting at specific amino acids in the target protein. Only amino acids with the side chains that interact well with the S1 pocket start the catalytic wheels turning.

The slight changes in shape involve changes in the positioning of three amino acids (aspartic acid, histidine, and serine) in the active site known as the catalytic triad.

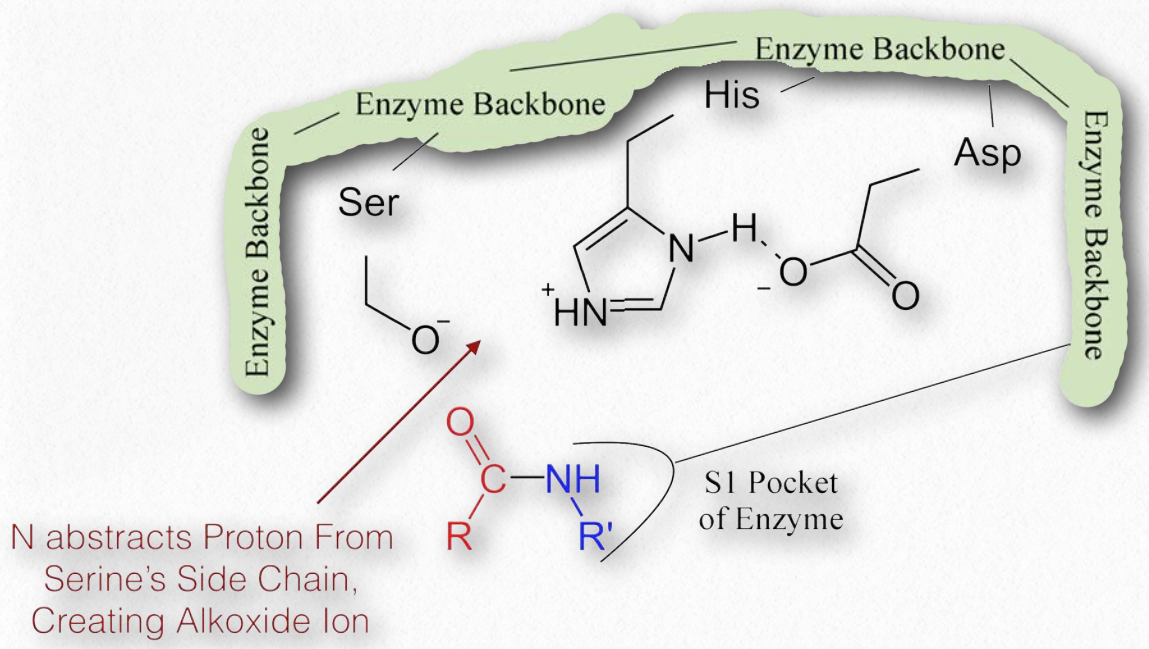

Figure 4.55 - 3. Formation of alkoxide ion

The shift of the negatively charged aspartic acid towards the electron rich histidine ring favors the abstraction of a proton by the histidine from the hydroxyl group on the side chain of serine, resulting in production of a very reactive alkoxide ion in the active site

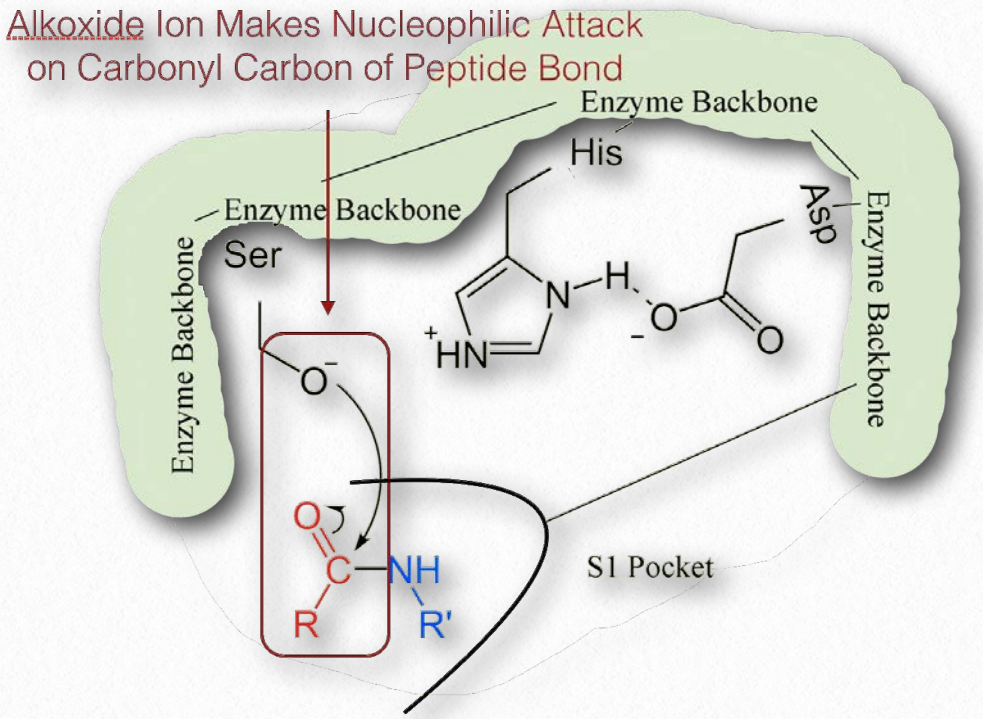

Figure 4.56 - 4. Nucleophilic attack

(Figure 4.55). Since the active site at this point also contains the polypeptide chain positioned with the phenylalanine side chain embedded in the S1 pocket, the alkoxide ion performs a nucleophilic attack on the peptide bond on the carboxyl side of phenylalanine sitting in the S1 pocket (Figure 4.56). This reaction breaks the peptide bond (Figure 4.57) and causes two things to happen.

First, one end of the original polypeptide is freed and exits the active site (Figure 4.58). The second is that the end containing the phenylalanine is covalently linked to the oxygen of the serine side chain. At this point we have completed the first (fast) phase of the catalysis.

Slower second phase

The second phase of the catalysis by chymotrypsin is slower. It requires that the covalent bond between phenylalanine and serine's oxygen be broken so the peptide can be released and the enzyme can return to its original state. The process starts with entry of water into the active site. Water is attacked in a fashion similar to that of the serine side chain in the first phase, creating a reactive hydroxyl group

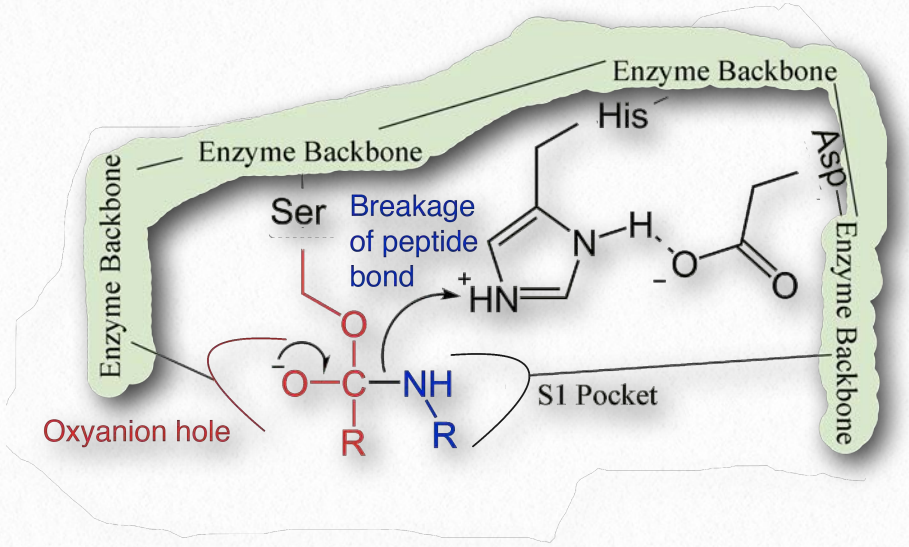

Figure 4.57 - 5. Stabilization by oxyanion hole. Breakage of peptide bond.

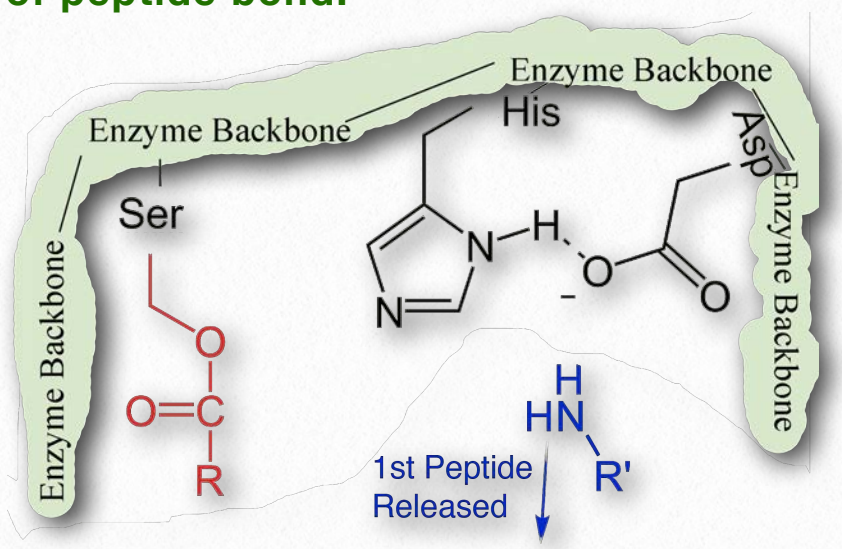

Figure 4.58 - 6. First peptide released. Other half bonded to serine.

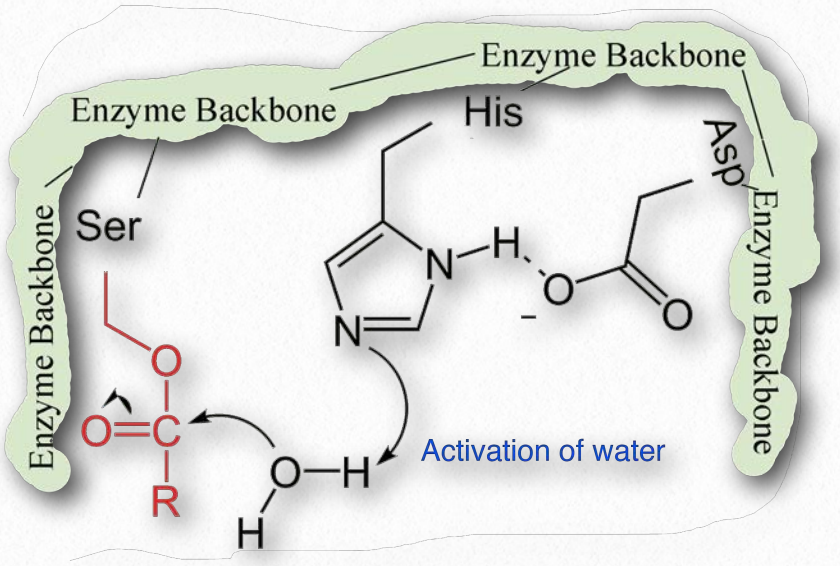

Figure 4.59 - 7. Activation of water by histidine

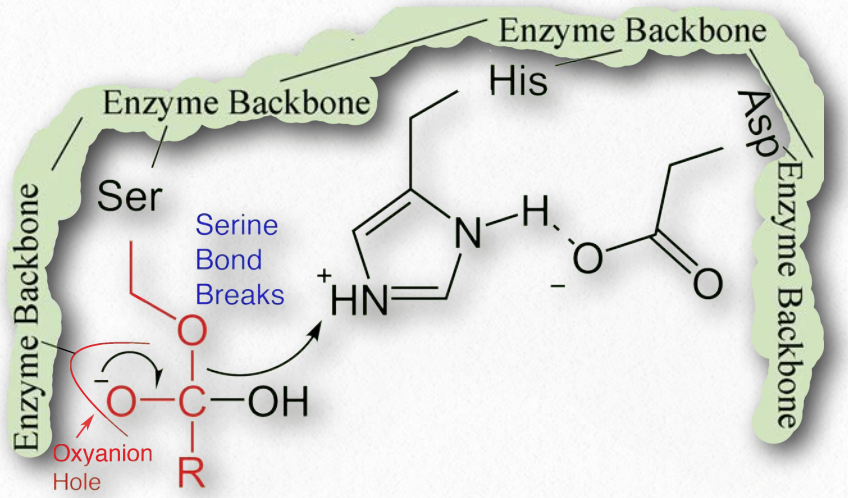

Figure 4.60 - 8. Nucleophile attack by hydroxyl creates tetrahydryl intermediate stabilized by oxyanion hole. Bond to serine breaks.

(Figure 4.59) that performs a nucleophilic attack on the phenylalanine-serine bond (Figure 4.60), releasing it and replacing the proton on serine. The second peptide is released in the process and the reaction is complete with the enzyme back in its original state (Figure 4.61).

Serine proteases

The list of serine proteases is quite long. They are grouped in two broad categories - 1) those that are chymotrypsin-like and 2) those that are subtilisin-like. Though subtilisin-type and chymotrypsin-like enzymes use the same mechanism of action, including the catalytic triad, the enzymes are otherwise not related to each other by sequence and appear to have evolved independently. They are, thus, an example of convergent evolution - a process where evolution of different forms converge on a structure to provide a common function.

The serine protease enzymes cut adjacent to specific amino acids and the specificity is determined by the size/shape/charge of amino acid side chain that fits into the enzyme's S1 binding pocket (Figure 4.52).

Examples of serine proteases include trypsin, chymotrypsin, elastase, subtilisin, signal peptidase I, and nucleoporin. Ser-

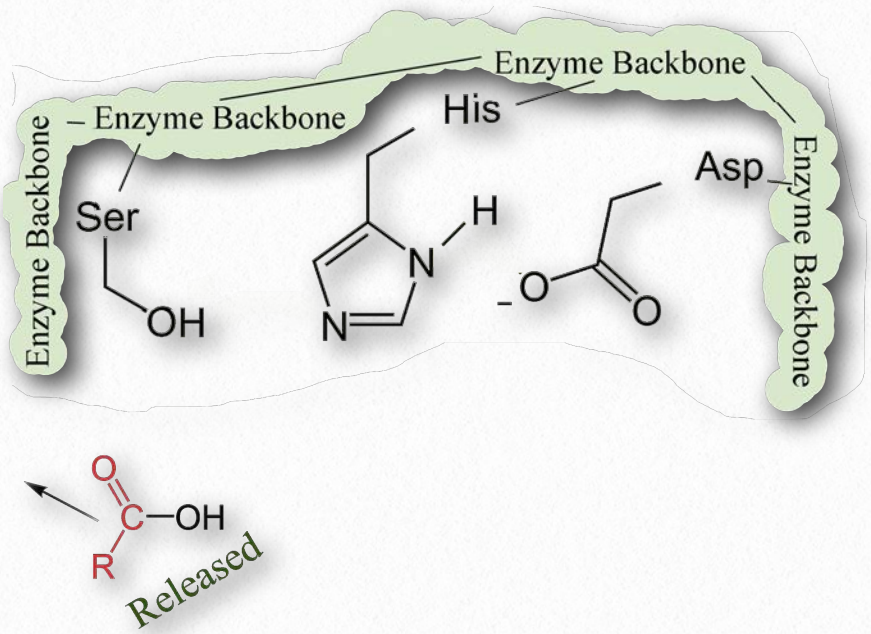

Figure 4.61 - 9. Second half of peptide released. Enzyme active site restored.

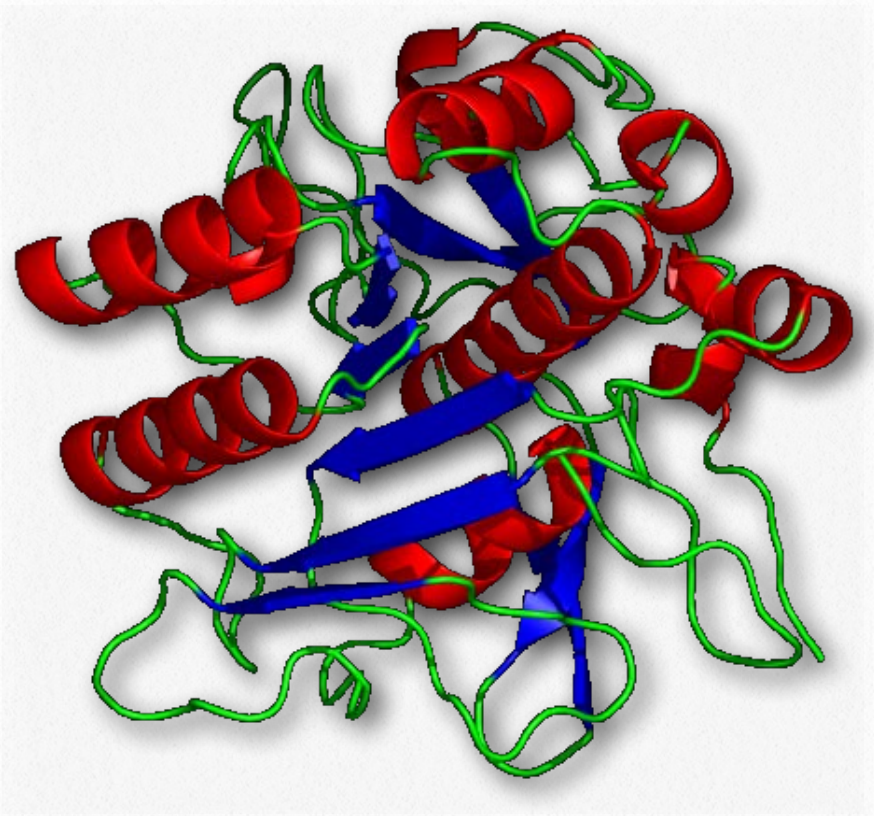

Figure 4.62 - Subtilisin - A serine protease

ine proteases participate in many physiological processes, including blood coagulation, digestion, reproduction, and the immune response.

Cysteine proteases

Cysteine proteases (also known as thiol proteases) catalyze the breakdown of proteins by cleaving peptide bonds using a nucleophilic thiol from a cysteine (Figure 4.63). The cysteine is typically found in a catalytic dyad or triad also involving histidine and (sometimes) aspartic acid (very much like serine proteases). The sulfhydryl group of cysteine proteases is more acidic than the hydroxyl of serine proteases, so the aspartic acid of the triad is not always needed.

The mechanism of action is very similar to that of serine proteases. Binding of proper substrate results in activation of the thiol (removal of the proton by the histidine group). The activated thiol acts as a nucleophile, attacking the peptide bond and causing it break. One peptide is released and the other peptide becomes covalently linked to the sulfur. Hydrolysis by water releases the second peptide and completes the cycle. Examples of cysteine proteases include papain, caspases, hedgehog protein, calpain, and cathepsin K.

YouTube Lectures by Kevin HERE & HERE

Caspases

Caspases (Cysteine-ASPartic ProteASEs) are a family of cysteine proteases that play important roles in the body. At the cellular level they function in apoptosis and necrosis and in the body, they are involved in inflammation and the immune system. Maturation of lymphocytes is one such role. They are best known, however, for their role in apoptosis, which has given rise to descriptions of them as “executioner” proteins or “suicide proteases” that dismantle cells in programmed cell death.

There are 12 known human caspases. The enzymes are synthesized as pro-caspase zymogens with a prodomain and two other

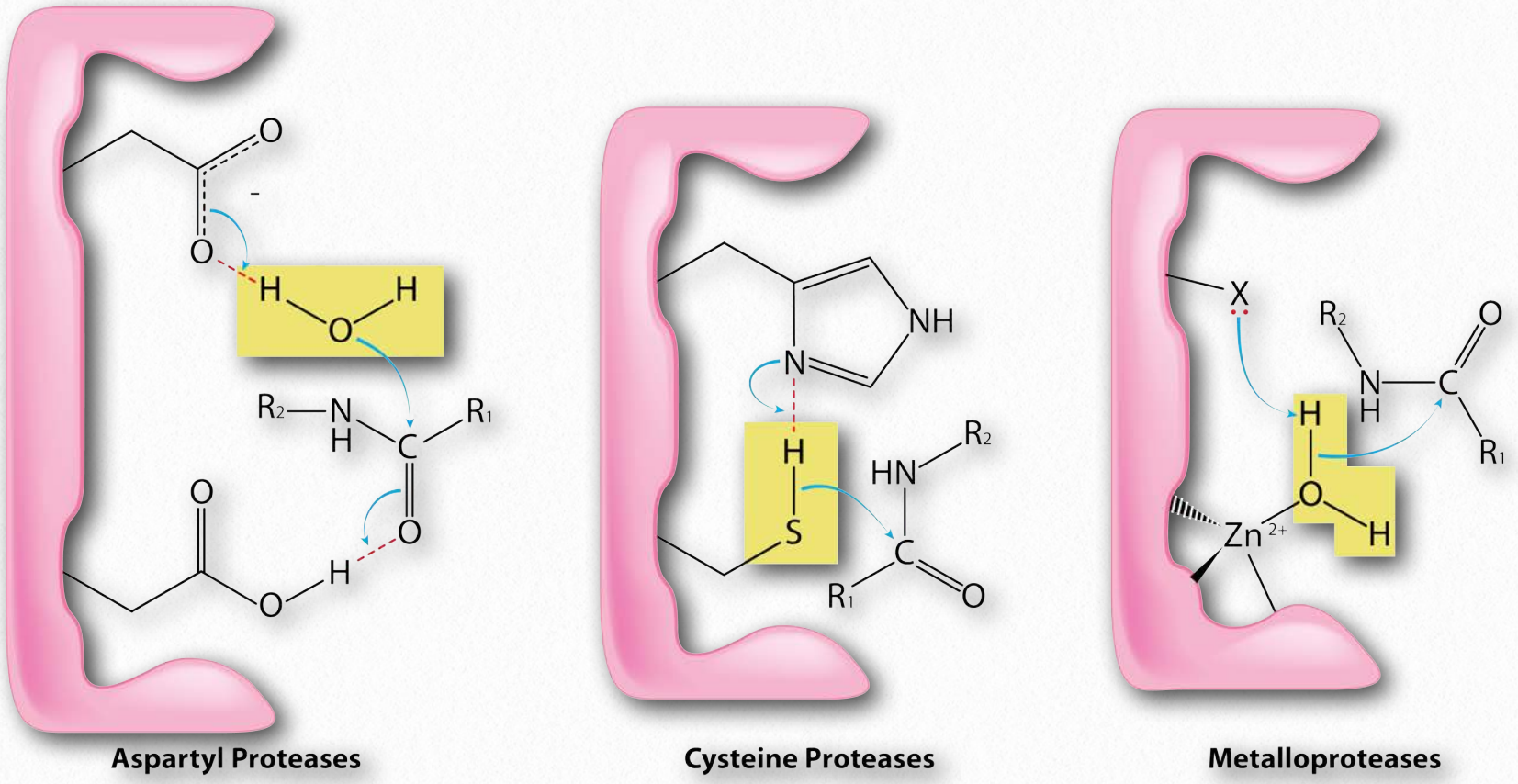

Figure 4.63 - Mechanism of action of proteases. In each case, a nucleophile is created - hydroxyl (aspartyl proteases), thiol (cysteine proteases), and hydroxyl (metalloproteases)

Image by Aleia Kim

subunits. The prodomain contains regions that allow it to interact with other molecules that regulate the enzyme's activity. The caspases come in two forms. The initiator caspases, when activated, activate the effector caspases. The effector caspases cleave other proteins in the cell. Targets for effector caspase cleavage action include the nuclear lamins (fibrous proteins providing structural integrity to the nucleus), ICAD/DFF45 (an inhibitor of DNAse), PARP (flags areas where DNA repair needed), and PAK_2 (apoptotic regulation).

The caspase activation cascade can itself be activated by granzyme B (a serine protease secreted by natural killer cells and cytotoxic T-cells), cellular death receptors, and the apoptosome (large protein structure in apoptotic cells stimulated by release of cytochrome C from the mitochondria). Each of these activators is responsible for activating different groups of caspases.

Metalloproteases

Metalloproteases (Figure 4.63) are enzymes whose catalytic mechanism for breaking peptide bonds involves a metal. Most metalloproteases use zinc as their metal, but a few use cobalt, coordinated to the protein by three amino acid residues with a labile water at the fourth position. A variety of side chains are

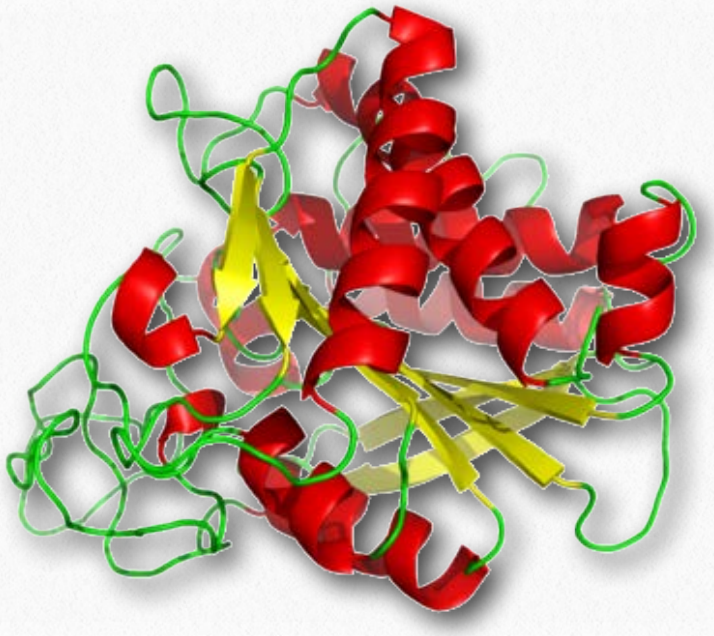

Figure 4.64 - Carboxypeptidase - A metalloprotease

used - histidine, aspartate, glutamate, arginine, and lysine. The water is the target of action of the metal which, upon binding of the proper substrate, abstracts a proton to create a nucleophilic hydroxyl group that attacks the peptide bond, cleaving it (Figure 4.63). Since the nucleophile here is not attached covalently to the enzyme, neither of the cleaved peptides ends up attached to the enzyme during the catalytic process. Examples of metalloproteases include carboxypeptidases, aminopeptidases, insulinases and thermolysin.

Aspartyl proteases

As the name suggests, aspartyl proteases use aspartic acid in their catalytic mechanism (Figures 4.63 & 4.65). Like the metalloproteases, aspartyl proteases activate a water to create a nucleophile for catalysis (Figure 4.65). The activated water attacks the pep-

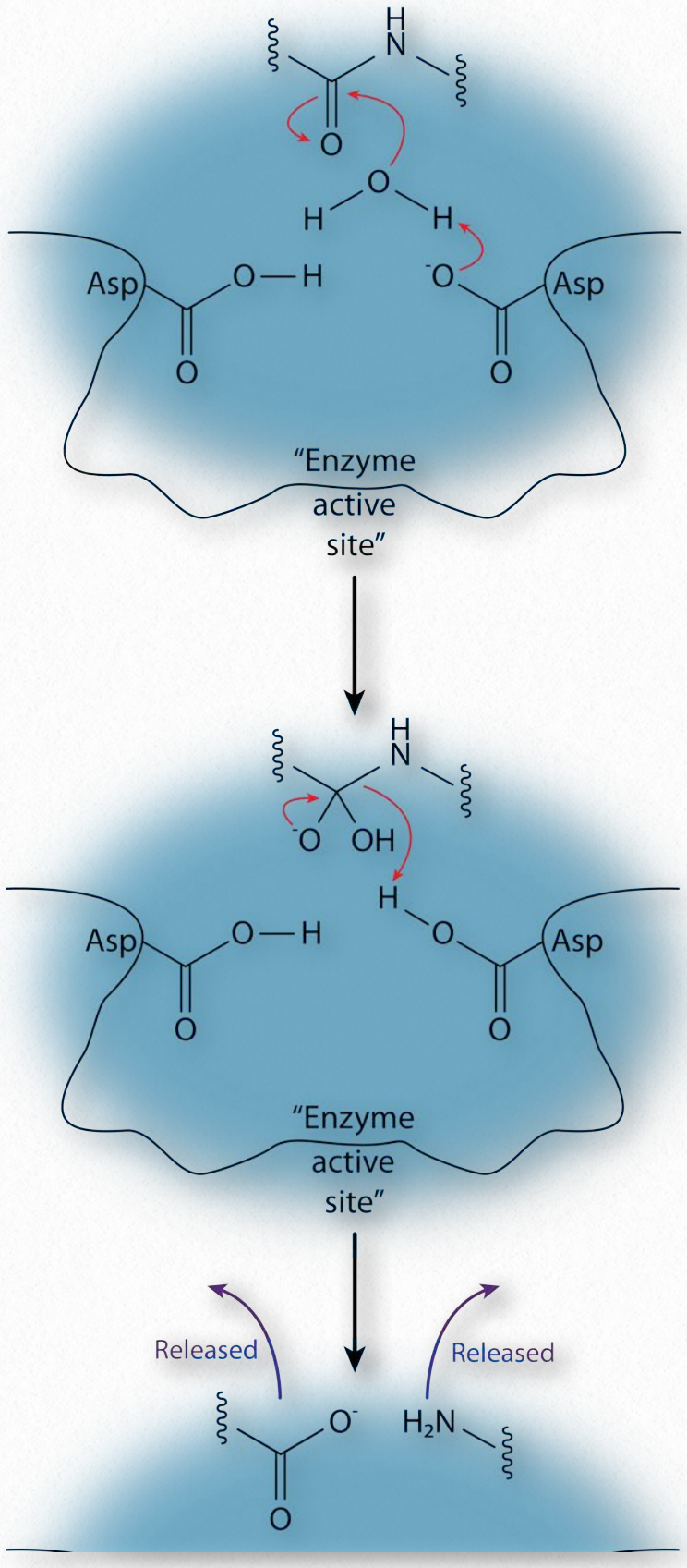

Figure 4.65 - Activation of an aspartyl protease - aspartate side chain abstracts proton (top). Hydroxyl attacks peptide bond (middle). Broken peptide pieces released (bottom)

Image by Pehr Jacobson

tide bond of the bound substrate and releases the two pieces without the need to release a bound intermediate, since water is not covalently attached to the enzyme. Common aspartyl proteases include pepsin, signal peptidase II, and HIV-1 protease.

Threonine proteases

Though threonine has an R-group with a hydroxyl like serine, the mechanism of action of this class of proteases differs somewhat from the serine proteases. There are some similarities. First, the threonine's hydroxyl plays a role in catalysis and that is to act as a nucleophile. The nucleophile is created, however, not by a catalytic triad, but rather as a result of threonine's own α-amine group abstracting a proton.

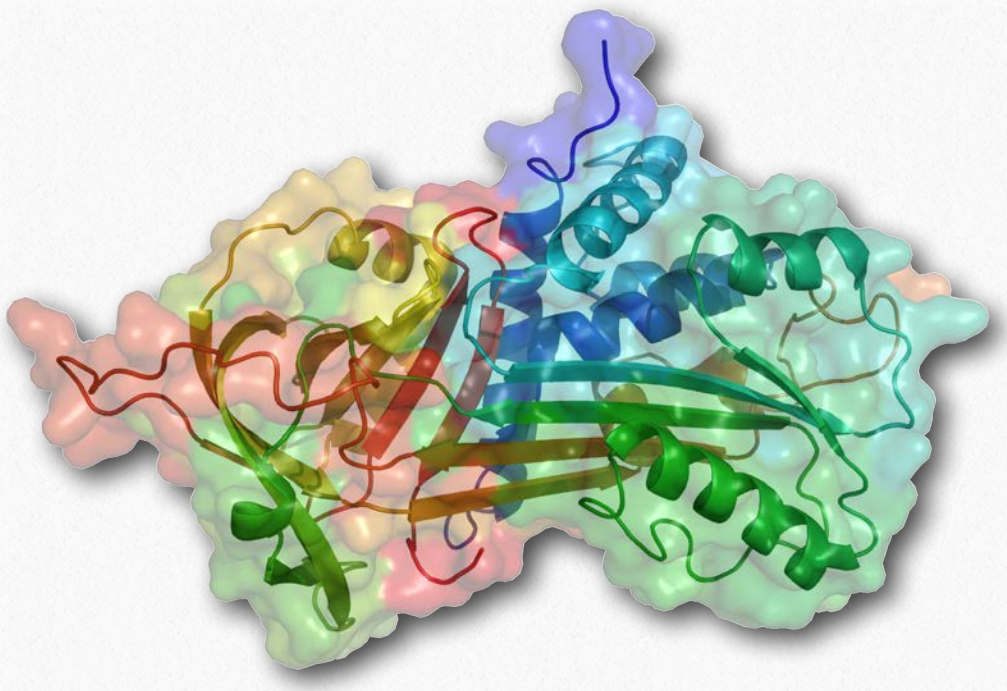

Figure 4.66 - α-1-antitrypsin

Because of this, the nucleophilic threonine in a threonine protease must be at the n-terminus of the enzyme. Nucleophilic attack of the peptide bond in the target protease results in breakage of the bond to release one peptide and the other is covalently attached to serine, like the serine proteases. Also, as with the serine proteases, water must come in to release the covalently linked second peptide to conclude the catalytic mechanism.

Examples

Examples of threonine proteases include the catalytic subunits of the proteasome. Some acyl transferases (such as ornithine acyltransferase) have evolved the same catalytic mechanism by convergent evolution. The latter enzymes use ornithine instead of water to break the enzyme-substrate covalent bond, with the result that the acyl-group becomes attached to ornithine, instead of water.

Protease inhibitors

Molecules which inhibit the catalytic action of proteases are known as protease inhibitors. These come in a variety of forms and have biological and medicinal uses. Many biological inhibitors are proteins themselves. Protease inhibitors can act in several ways, including as a suicide inhibitor, a transition state inhibitor, a denaturant, and as a chelating agent. Some work only on specific classes of enzymes. For example,

most known aspartyl proteases are inhibited by pepstatin. Metalloproteases are sensitive to anything that removes the metal they require for catalysis. Zinc-containing metalloproteases, for example, are very sensitive to EDTA, which chelates the zinc ion.

One category of proteinaceous protease inhibitors is known as the serpins. Serpins inhibit serine proteases that act like chymotrypsin. 36 of them are known in humans.

YouTube Lectures by Kevin HERE & HERE

Serpins are unusual in acting by binding to a target protease irreversibly and undergoing a conformational change to alter the active site of its target. Other protease inhibitors act as competitive inhibitors that block the active site.

Serpins can be broad in their specificity. Some, for example, can block the activity of cysteine proteases. One of the best known biological serpins is α-1-anti-trypsin (A1AT - Figure 4.66) because of its role in lungs, where it functions to inhibit the elastase protease. Deficiency of A1AT leads to emphysema. This can arise as a result of genetic deficiency or by cigarette smoking. Reactive oxygen species produced by cigarette smoking can oxidize a critical methionine residue (#358 of the processed form) in A1AT, rendering it unable to inhibit elastase. Uninhibited, elastase can attack lung tissue and cause emphysema. Most serpins work extracellularly. In blood, for example, serpins like antithrombin can help to regulate the clotting process.

Anti-viral Agents

Protease inhibitors are used as anti-viral agents to prohibit maturation of viral proteins - commonly viral coat proteins.

They are part of drug "cocktails" used to inhibit the spread of HIV in the body and are also used to treat other viral infections, including hepatitis C. They have also been investigated for use in treatment of malaria and may have some application in anti-cancer therapies as well.

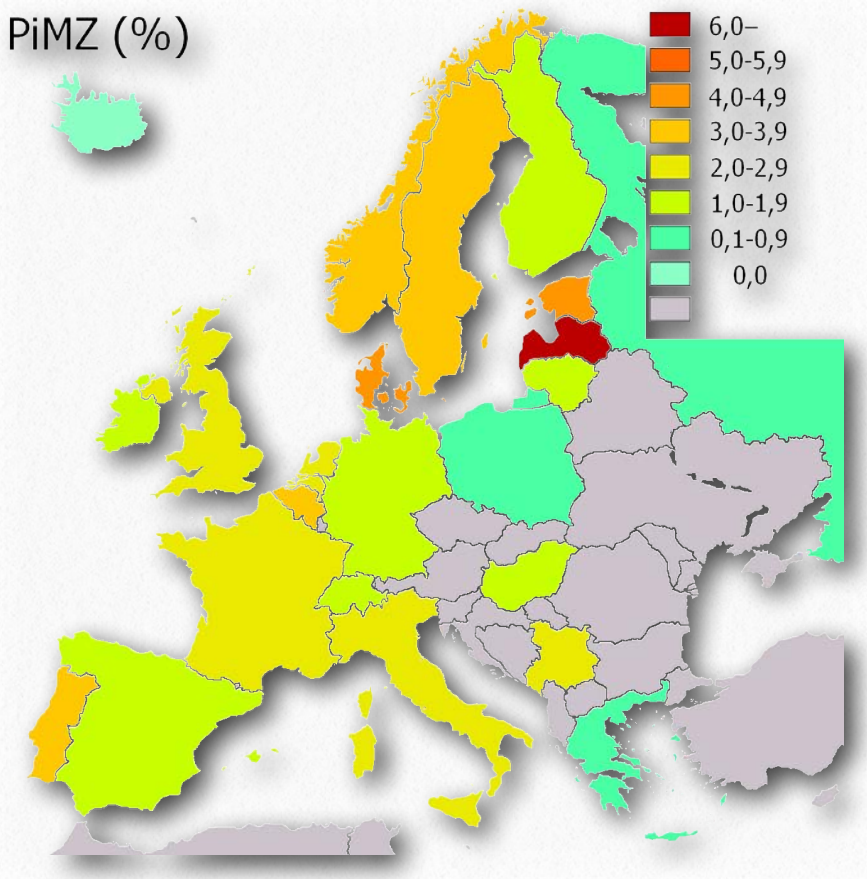

Figure 4.67 - Incidence of α-1-antitrypsin (PiMZ) deficiency in Europe by percent
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I Lost a Lung

To the tune of "*I Left My Heart in San Francisco*"

Metabolic Melodies Website HERE

You've gone and left me breathless, so especially today
An absence from my body makes it hard to say
I'm so horribly upset and reminded evermore
I'll not forget - how you took my breath away

I lost a lung from smoking Camels
Emphysema kills, it seems to me
You see those nicotines and tars
Leave alveolar scars
My raspy throat will often choke, from the smoke

I've no respect for RJ Reynolds
And its cor---por-a-toc-rac-y
Now when I hear the name, RJ Reynolds
I only think malignancy

Recording by David Simmons
Lyrics by Kevin Ahern

The New Serine Protease Song

To the tune of "*Rudolph the Red-Nosed Reindeer*"

Metabolic Melodies Website HERE

All serine proteases
Work almost identically
Using amino acid
Triads catalytically

First they bind peptide substrates
Holding onto them so tight
Changing their structure when they
Get them in the S1 site

Then there are electron shifts
At the active site
Serine gives up its proton
As the RE-ac-tion goes on

Next the alkoxide ion
Being so electron rich
Grabs peptide's carbonyl group
Breaks its bond without a hitch

So one piece is bound to it
The other gets set free
Water has to act next to
Let the final fragment loose

Then it's back where it started
Waiting for a peptide chain
That it can bind itself to

Go and o'er

start all again

Recording by David Simmons
Lyrics by Kevin Ahern

Protein Wonderland

To the tune of "*Winter Wonderland*"

Metabolic Melodies Website HERE

Mechan-i-sm . . determines
How an en . . zyme is workin'
Here are the ways
That each elastase
Breaks a peptide bond so easily

Starting with the binding of the substrate
Catalytic triad is the star
Histidine's electron sink reacts to
Pull a proton from a serine's a-r-r-r-r

Then the al . . . koxide ion
Gets elec . . . trons a-flyin
It makes a big fuss
For one nuc-le-us
And breaks and makes a bond with carbonyl

Then the process switches in its action
Water comes to free the carbonyl
Loss of proton yields hydroxide ion
Attacking on the peptide bound there still -ll -ll

Which the en . . . . zyme releases
Otherwise . . . action ceases
The process is done
Until the S1
Binds a substrate starting up again

Lyrics by Kevin Ahern

No Recording Yet For This Song

Serine Protease Song

To the tune of "*Blackbird*"

Metabolic Melodies Website HERE

Substrate floating in the cell's insides
Enzyme snags it with its binding site
It supplies
Shuffling of electrons in the act to catalyze

Proteases of the serine kind
Break up peptide bonds in rapid time
Fast and slow
Steps in breaking bonds are mechanisms you should know

Asp – his - ser
Bonds beware
Inside the S1 pocket substrate sits

Alkoxides
Break peptides
Nucleophiles give bonds the fits

Peptide one exits easily
But water has to let the other flee
Bound not free
'Cuz the enzyme's linked to it in mechanism three

When it's gone the enzyme's free to catalyze you see
When it's gone the enzyme's free to catalyze you see

Recording by David Simmons
Lyrics by Kevin Ahern

Catalysis: Blood Clotting

Blood clotting

Clotting is a process in which liquid blood is converted into a gelatinous substance that eventually hardens. The aim is to stop the flow of blood from a vessel. The formation of a clot is the result of a series of enzymatic reactions that are triggered upon injury. The process involves 1) a step of activation (wounding) followed by 2) a cellular response (aggregation of blood platelets) and 3) a molecular response (polymerization of the protein called fibrin to create a meshwork that hardens). Factors released in the cellular response help activate the molecular response. The process is highly conserved across species.

YouTube Lectures by Kevin
HERE & HERE

Cellular response

Injury to the epithelial lining of a blood vessel begins the process of coagulation almost instantly. The cellular response has an initial action followed by an amplification step. In the cellular response (Figure 4.68), the platelets bind directly to collagen using Ia/IIa collagen-

binding surface receptors and glycoprotein VI to form a plug. The signal to the platelets to take this action is exposure of the underlying collagen, something that would not happen in the absence of a wound. Upon injury, platelet integrins get activated and bind tightly to the extracellular matrix to anchor them to the site of the wound.

The von Willebrand factor (see below also) assists by forming additional links between the platelets' glycoprotein Ib/IX/V and the fibrils of the collagen.

Amplification

In the amplification part of the cellular response, the activated platelets release a large number of factors, including platelet factor 4 (a cytokine stimulating inflammation and moderating action of the heparin anticoagulant) and thromboxane A2, The latter has the effect of increasing the "stickiness" of platelets, favoring their aggregation. In addition, a a Gq-protein linked receptor cascade is activated, resulting in release of calcium from intracellular stores. This will play a role in the molecular response.

Molecular response

The molecular response results in the creation of a web comprised of polymers of fibrin protein. Like the cellular pathway, the molecular pathway begins with an initiation phase and continues with an amplification phase. Polymerization of fibrin results from convergence of two cascading catalytic pathways. They are the intrinsic pathway (also called the contact activation pathway) and the extrinsic pathway (also referred to as the tissue factor pathway). Of the two pathways, the tissue factor pathway has recently been shown to be the more important.

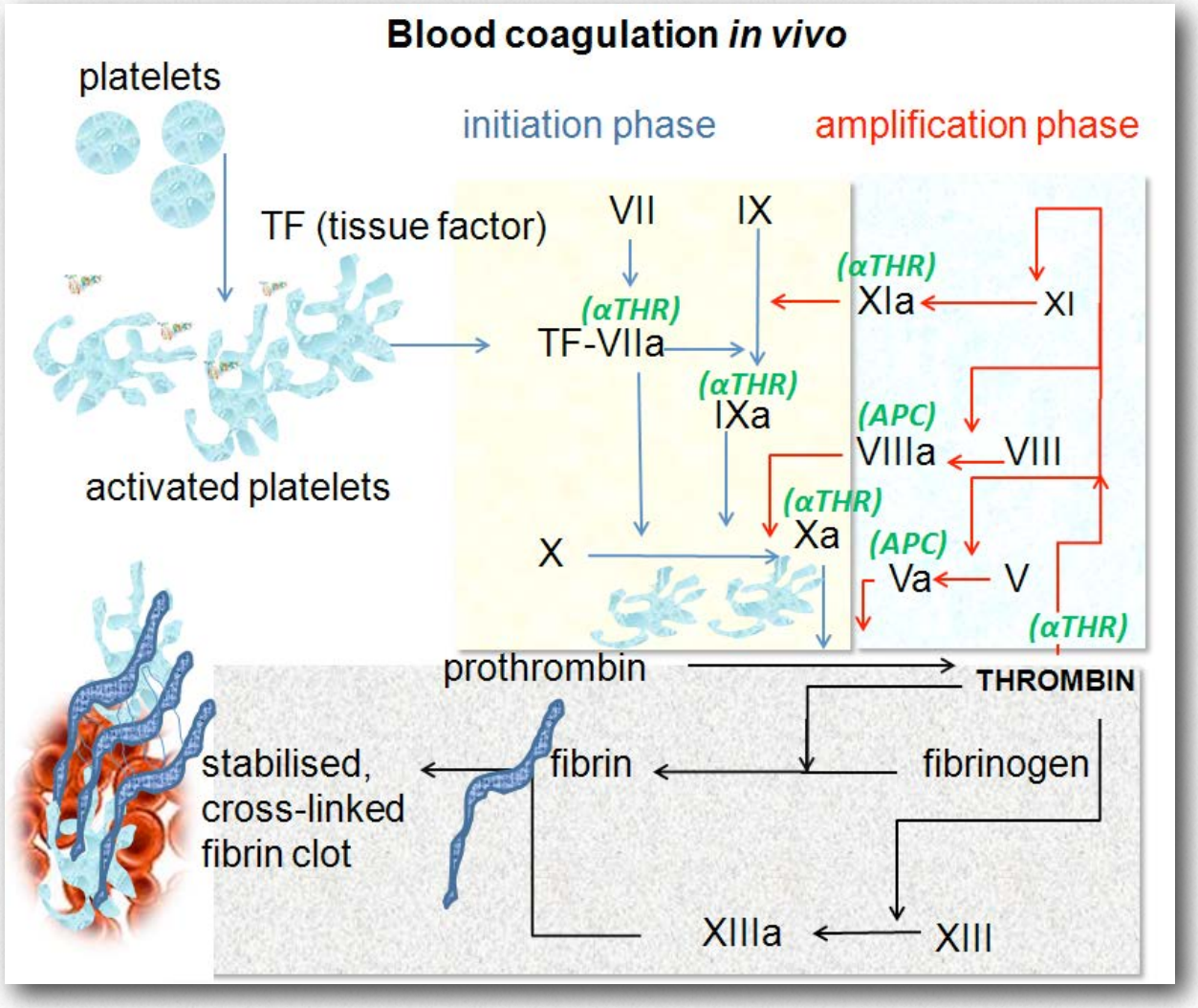

Figure 4.68 - Blood coagulation scheme. The cellular response is shown in white on upper left. Everything else is part of the molecular response

Wikipedia

Serine protease cascade

In both pathways, a series of zymogens of serine proteases are sequentially activated in rapid succession. The advantage of such a cascading system is tremendous amplification of a small signal. At each step of the cascade, activation of a zymogen causes the production of a considerable amount of an active serine protease, which is then able to activate the next zymogen which, in turn, activates an even larger amount of the next zymogen in the system. This results in the ultimate activation of a tremendous amount more fibrin than could be achieved if there were only a single step where an enzyme activated fibrinogen to fibrin.

Nomenclature

A note about nomenclature - the zymogen factors in the molecular response are generally labeled with Roman numerals. A lowercase, subscripted 'a' is used to designate an activated form.

The tissue factor pathway functions to create a thrombin burst, a process in which thrombin is activated very quickly. This is the initiation phase. It is fairly straightforward because it has one focus - activation of throm-

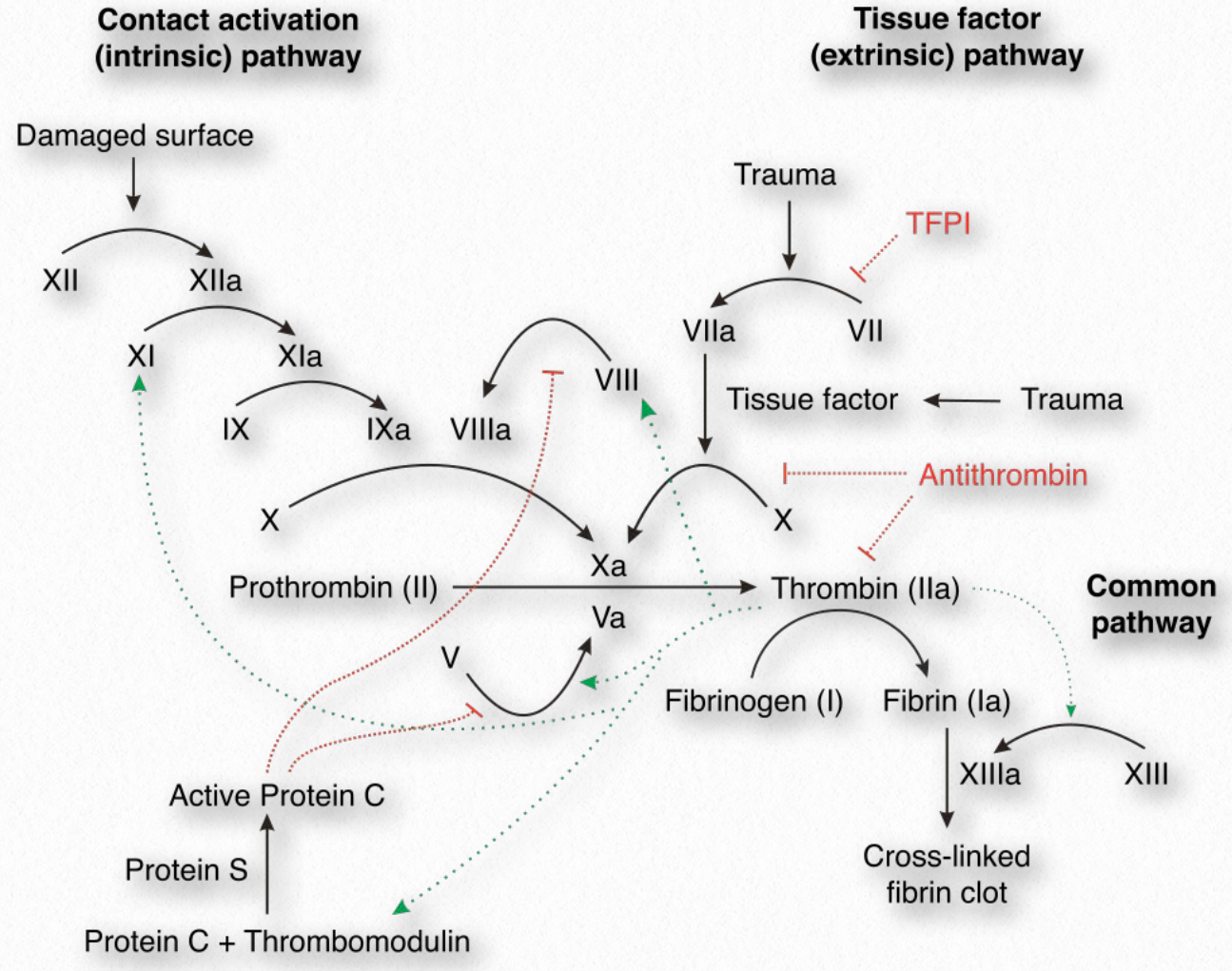

Figure 4.69 - Intrinsic and extrinsic pathways of blood coagulation. The aim is making a fibrin clot (lower right)

Wikipedia

bin. Thrombin, which converts fibrinogen into the fibrin of the clot, is central also to the amplification phase, because it activates some of the factors that activate it, creating an enormous increase in signal and making a lot of thrombin active at once.

Initiation phase

The initiation phase of the molecular response begins when Factor VII (the letter 'F' before the Roman numeral is often used as an abbreviation for 'factor') gets activated to FVIIa after damage to the blood vessel (Figure 4.69 & 4.70). This happens as a result of its interaction with Tissue Factor (TF, also called coagulation Factor III) to make a TF-FVIIa complex. The combined efforts of TF-FVIIa, FIXa, and calcium (from the cellular response) inefficiently convert FX to FXa. FXa, FV, and calcium inefficiently convert prothrombin (zymogen) to thrombin (active). A tiny amount of thrombin has been activated at the end of the initiation phase.

YouTube Lectures by Kevin HERE & HERE

Amplification phase

To make sufficient thrombin to convert enough fibrinogen to fibrin to make a clot, thrombin activates other factors (FV, FXI, FVIII) that help to make more thrombin. This is the amplification phase of the molecular process and is shown in the light blue portion in the upper right part of Figure 4.68. The amplification phase includes factors in both the intrinsic and extrinsic path-

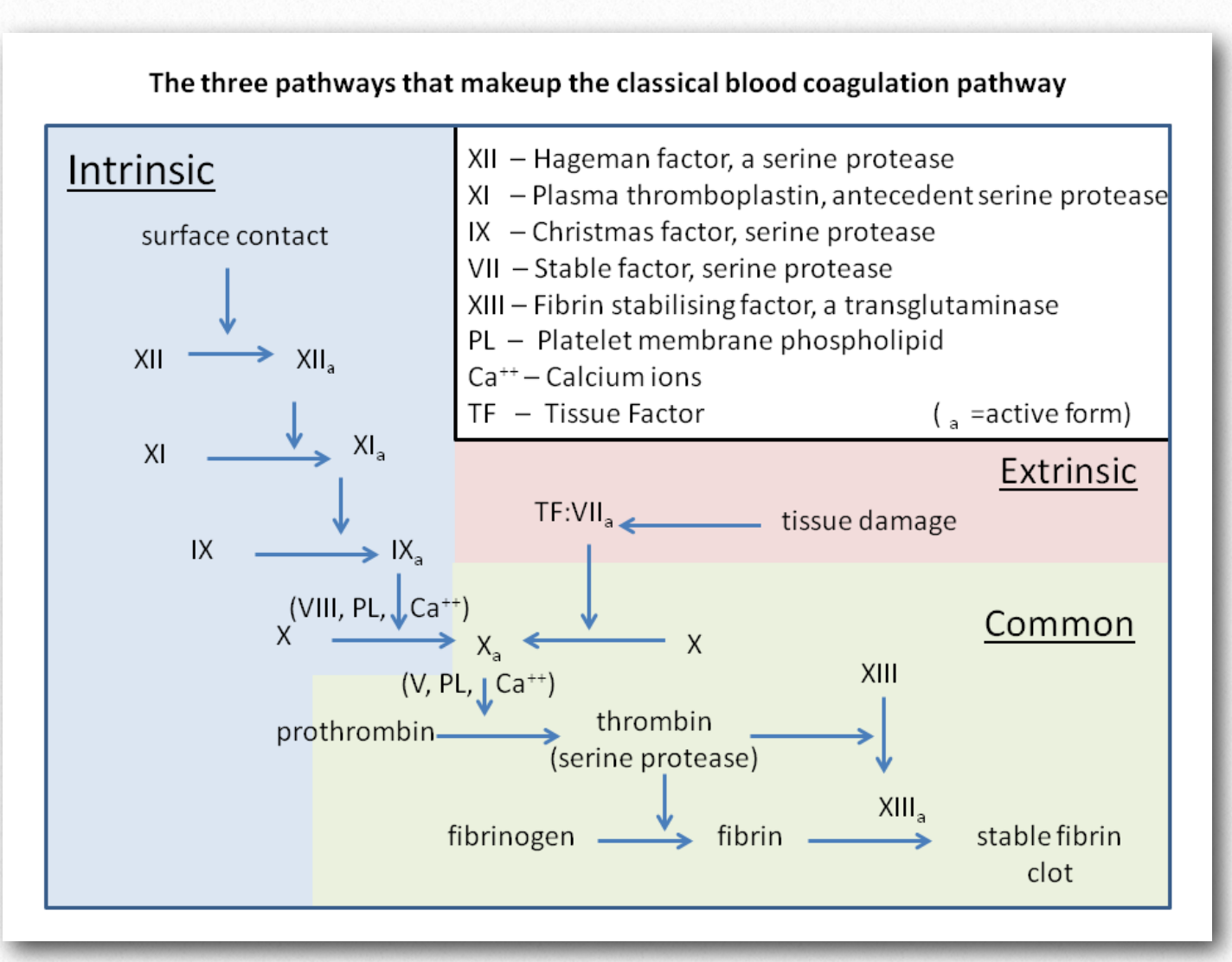

Figure 4.70 - Another view of the molecular response of the blood clotting pathway

Wikipedia

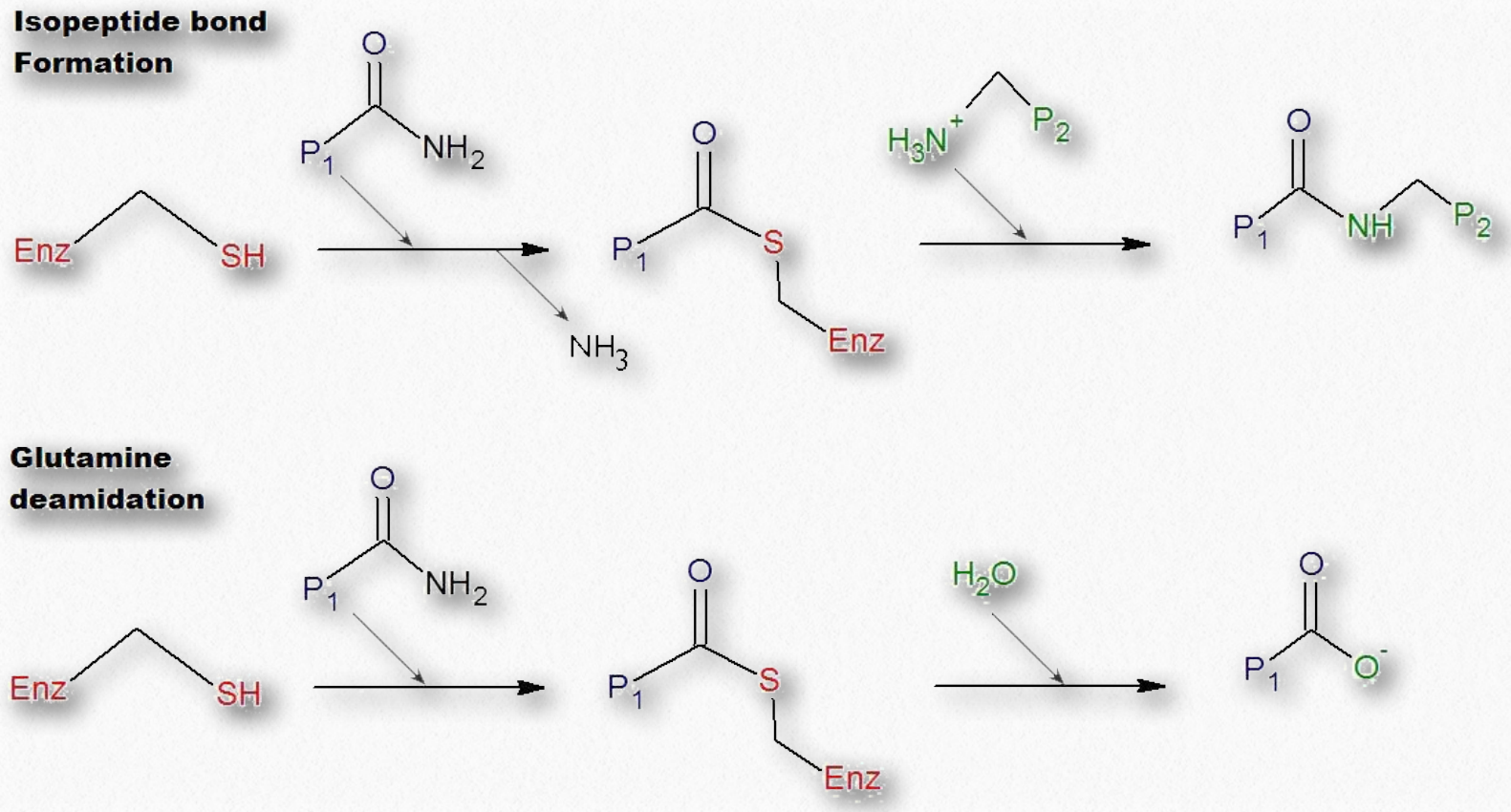

Figure 4.71 - Catalytic action of transglutaminase (top) and breaking of transglutamide bonds by hydrolysis (bottom)

ways. FVIII is normally bound in a complex with the von Willebrand factor and is inactive until it is released by action of thrombin. Activation of FXI to FXIa helps favor production of more FIXa. FIXa plus FVIIIa stimulate production of a considerable amount of FXa. FVa joins FXa and calcium to make a much larger amount of thrombin. Factors FVa and FVIIIa are critical to the amplification process. FVIIIa stimulates FIXa's production of FXa by 3-4 orders of magnitude. FVa helps to stimulate FXa's production of thrombin by about the same magnitude. Thus, thrombin stimulates activation of factors that, in turn, stimulate activation of more thrombin.

Transglutaminase

In addition to helping to amplify product of itself and conversion of fibrinogen to fibrin, thrombin catalyzes the activation of FXIII to FXIIIa. FXIIIa is a transglutami-

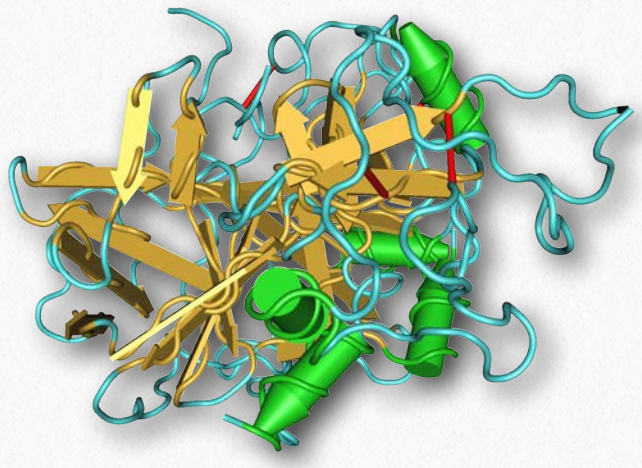

Figure 4.72 - α-thrombin

Wikipedia

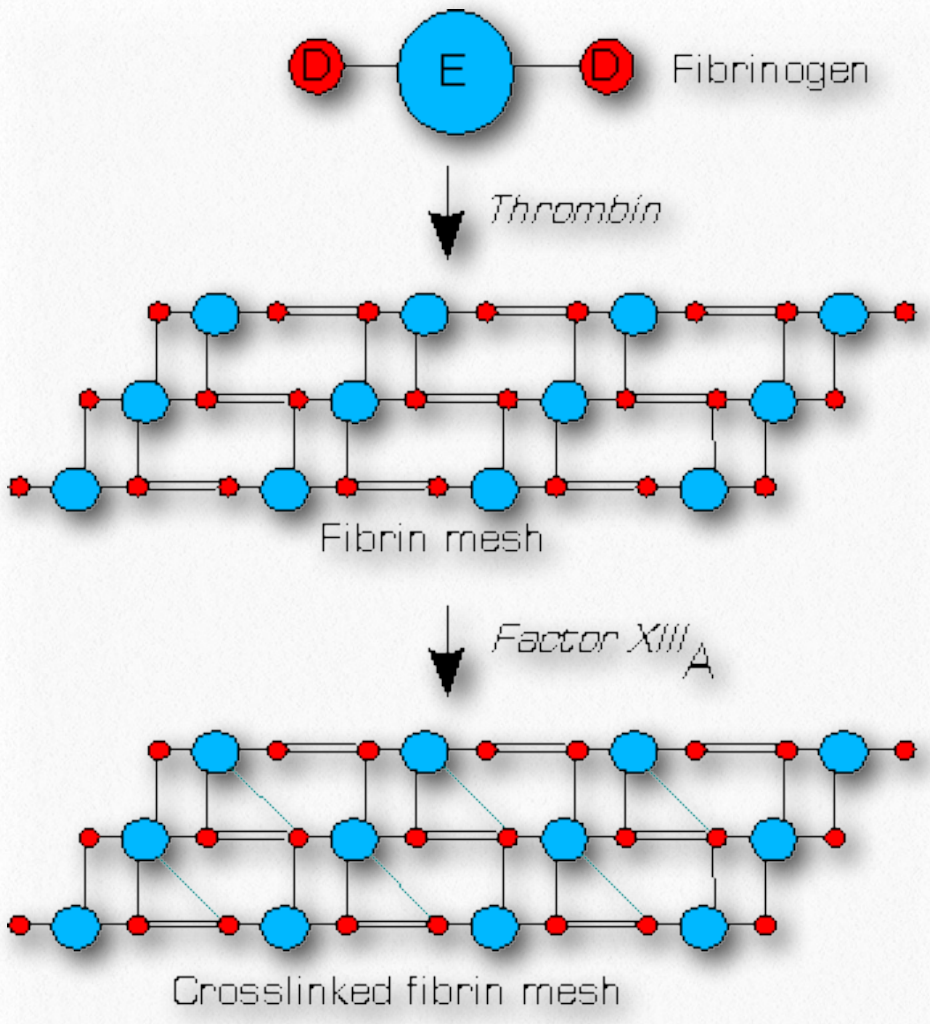

Figure 4.73 - Product of transglutaminase action - cross links

Wikipedia

nase that helps to “harden” the clot (Figure 4.71 & 4.73). It accomplishes this by catalyzing formation of a covalent bond between adjacent glutamine and lysine side chains in the fibrin polymers.

Not all of the factors involved in the clotting process are activated by the pathway, nor are all factors serine proteases. This includes FVIII and FV which are glycoproteins, and FXIII, which is the transglutaminase described above.

The blood clotting process must be tightly regulated. Formation of clots in places where no damage has occurred can lead to internal clots (thrombosis) cutting off the flow of blood to critical regions of the body, such as heart or brain. Conversely, lack of clotting can lead to internal bleeding or, in severe cases, death due to unregulated external bleeding. Such is a danger for people suffering from hemophilia.

Hemophilia

Hemophilia is a hereditary genetic disorder affecting the blood clotting process in afflicted individuals. The disease is X-linked and thus occurs much more commonly in males. Deficiency of FVIII leads to Hemophilia A (about 1 in 5000 to 10,000 male births) and deficiency of FIX produces Hemophilia B (about 1 in 20,000 to 35,000 male births).

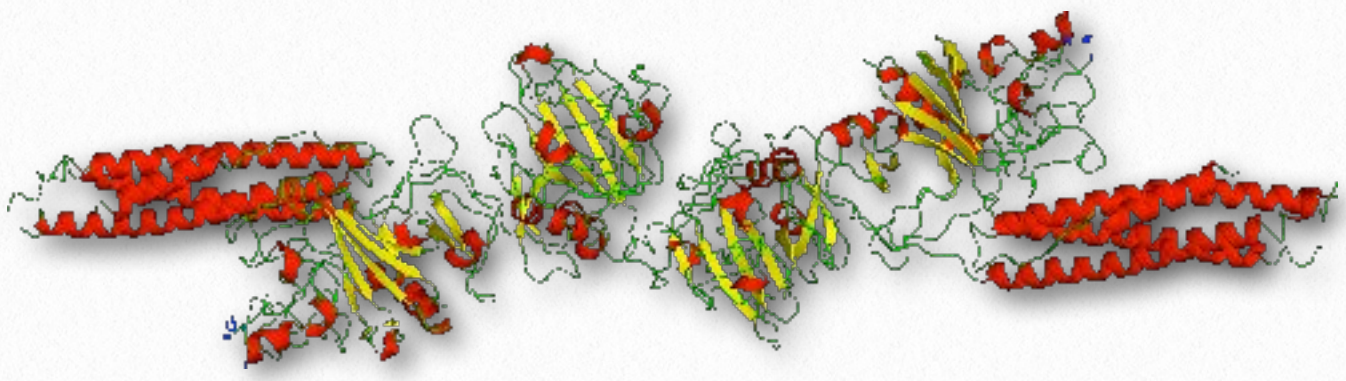

Figure 4.74 - Fibrin dimer - basic unit of a fibrin clot

Wikipedia

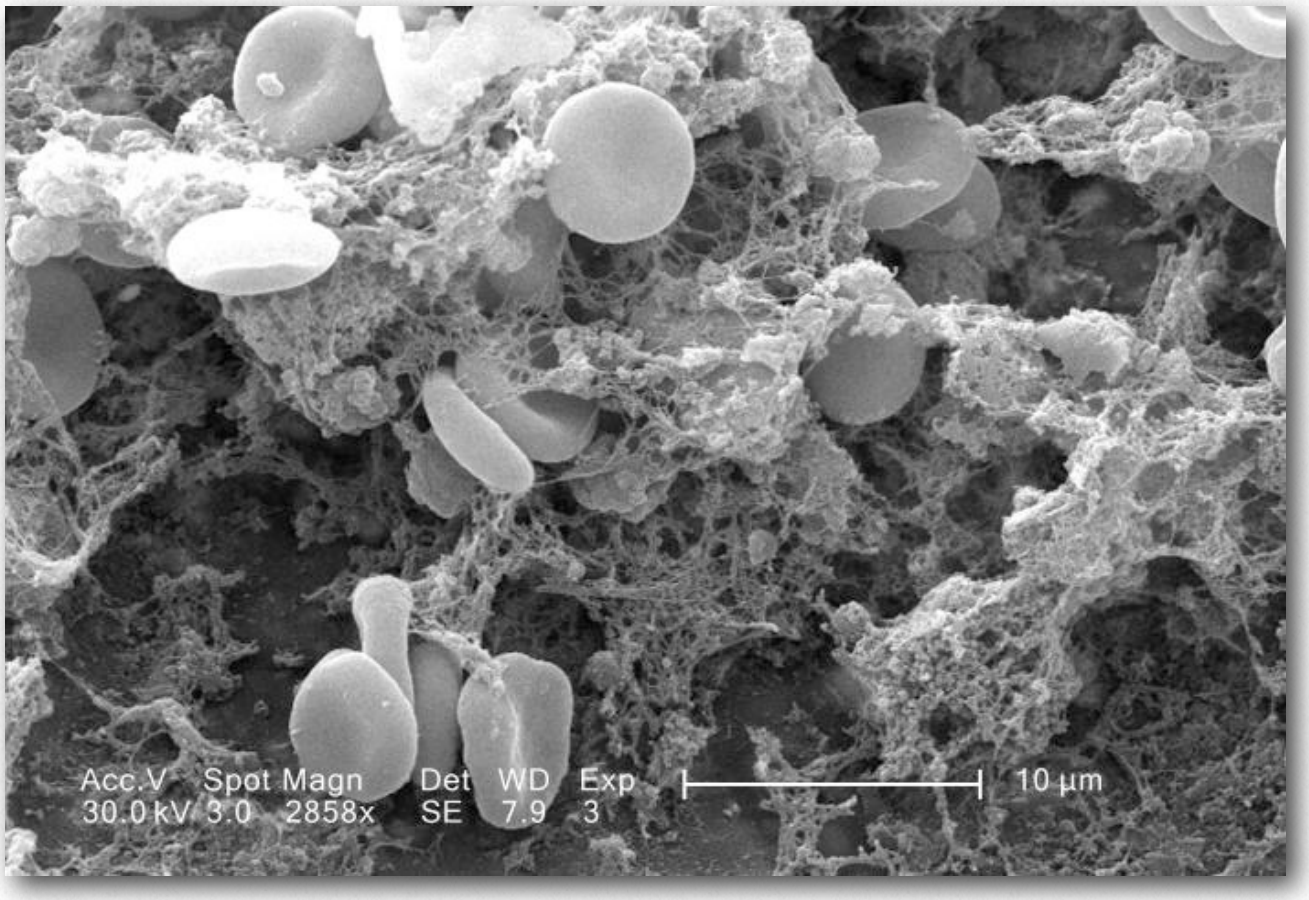

Figure 4.75 - Blood cells enmeshed in a fibrin clot

Hemophilia B spread through the royal families of Europe, beginning with Queen Victoria's son, Leopold. Three of the queen's grandsons and six of her great-grandsons suffered from the disease. Hemophilia is treated by exogenous provision of missing clotting factors and has improved life expectancy dramatically. In 1960, the life expectancy of a hemophiliac was about 11 years. Today, it is over 60.

Figure 4.76 - Queen Victoria, whose descendants suffered from hemophilia B

von Willebrand's disease

A related disease to hemophilia that is also genetically linked is von Willebrand's Disease. The von Willebrand factor plays a role in both the cellular and the molecular responses in blood clotting. First, the factor is a large multimeric glycoprotein present in blood plasma and also is produced in the endothelium lining blood vessels.

The von Willebrand factor helps to anchor platelets near the site of the wound in the cellular response. It binds to several things. First, it binds to platelets' Ib glycoprotein. Second, it binds to heparin and helps moderate its action. Third, it binds to collagen and fourth, the factor binds to FVIII in the molecular response, playing a protective role for it. In the absence of the von Wille-

brand factor, FVIII is destroyed. Fifth, the von Willebrand factor binds to integrin of platelets, helping them to adhere together and form a plug. Defects of the von Willebrand factor lead to various various bleeding disorders.

Blood "thinners"

The clotting of blood is essential for surviving wounds that cause blood loss. However, some people have conditions that predispose them to the formation of clots that can lead to stroke, heart attack, or other problems, like pulmonary embolism. For these people, anti-clotting agents (commonly called blood thinners) are used to reduce the likelihood of undesired clotting.

The first, and more common of these is aspirin. Aspirin is an inhibitor of the production of prostaglandins. Prostaglandins are molecules with 20 carbons derived from arachidonic acid that have numerous physiological effects. Metabolically, the prostaglandins are precursors of a class of molecules called the thromboxanes. Thromboxanes play roles in helping platelets to stick together in the cellular response to clotting. By inhibiting the production of prostaglandins, aspirin reduces the production of thromboxanes and reduces platelet stickiness and the likelihood of clotting.

Vitamin K action

Another approach to preventing blood clotting is one that interferes with an important molecular action of Vitamin K. A pro-clotting factor found in the blood, vitamin K is necessary for an important modification to prothrombin and other blood clotting proteins. Vitamin K serves as an enzyme cofactor that helps to catalyze addition of an extra carboxyl group onto the side chain of glutamic acid residues of several clotting enzymes (see HERE). This modification gives them the ability to bind to calcium (Figure 4.77), which is important for activating the serine protease cascade. During the reaction that adds carboxyl groups to glutamate, the reduced form of vitamin K becomes oxidized. In

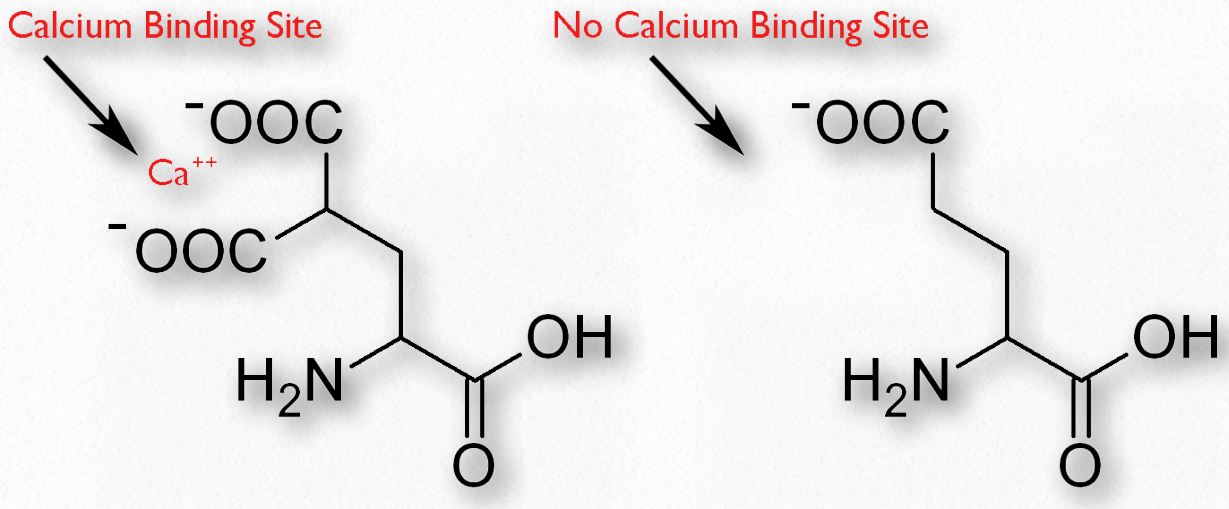

Figure 4.77 - γ-carboxylglutamic acid (left) has a calcium binding Site. Unmodified glutamic acid (right) does not.

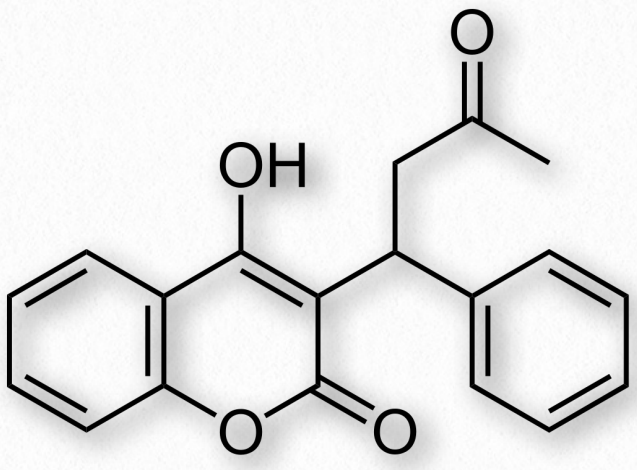

Figure 4.78 - Warfarin

order for vitamin K to stimulate additional carboxylation reactions to occur, the oxidized form of vitamin K must be reduced by the enzyme vitamin K epoxide reductase.

Warfarin blocks reduction

The compound known as warfarin (brand name = coumadin - Figure 4.78) interferes with the action of vitamin K epoxide reductase and thus, blocks recycling of vitamin K. As a consequence, fewer prothrombins (and other blood clotting proteins) get carboxylated, and less clotting occurs.

Vitamin K-mediated carboxylation of glutamate occurs on the γ carbon of the amino acid's side chain, for 16 different proteins, 7 of which are involved in blood clotting, including prothrombin. When the carboxyl group is added as described, the side chain is able to efficiently bind to calcium ions. In the absence of the carboxyl group, the side chain will not bind to calcium. Calcium released near the site of the wound in the cellular response to clotting helps to stimulate activation of proteins in the serine protease cascade of the molecular response.

Vitamin K comes in several forms. It is best described chemically as a group of 2-methyl-1,4-naphthoquinone derivatives. There are five different forms recognized as vitamin Ks (K_1, K_2, K_3, K_4, and K_5). Of these, vitamins K_1 and K_2 come from natural sources and the others are synthetic. Vitamin K_2, which is made from vitamin K_1 by gut microorganisms, has several forms, with differing lengths of of isoprenoid side-chains. The various forms are commonly named as MK-X, where X is a number, and MK stands for menaquinone, which is the name given to this form of vitamin K. Figure 4.79 shows a common form known as MK-4 (menatetrenone).

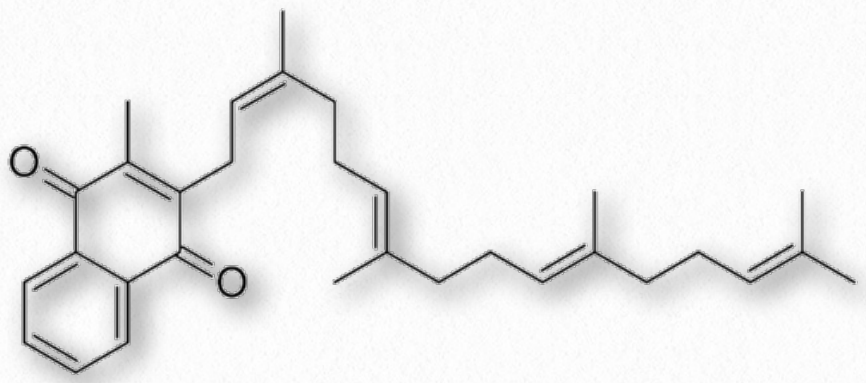

Figure 4.79 - MK-4 (menatetrenone)

Hemorrhaging danger

It is very critical that the proper amount of warfarin be given to patients. Too much can result in hemorrhaging. Patients must have

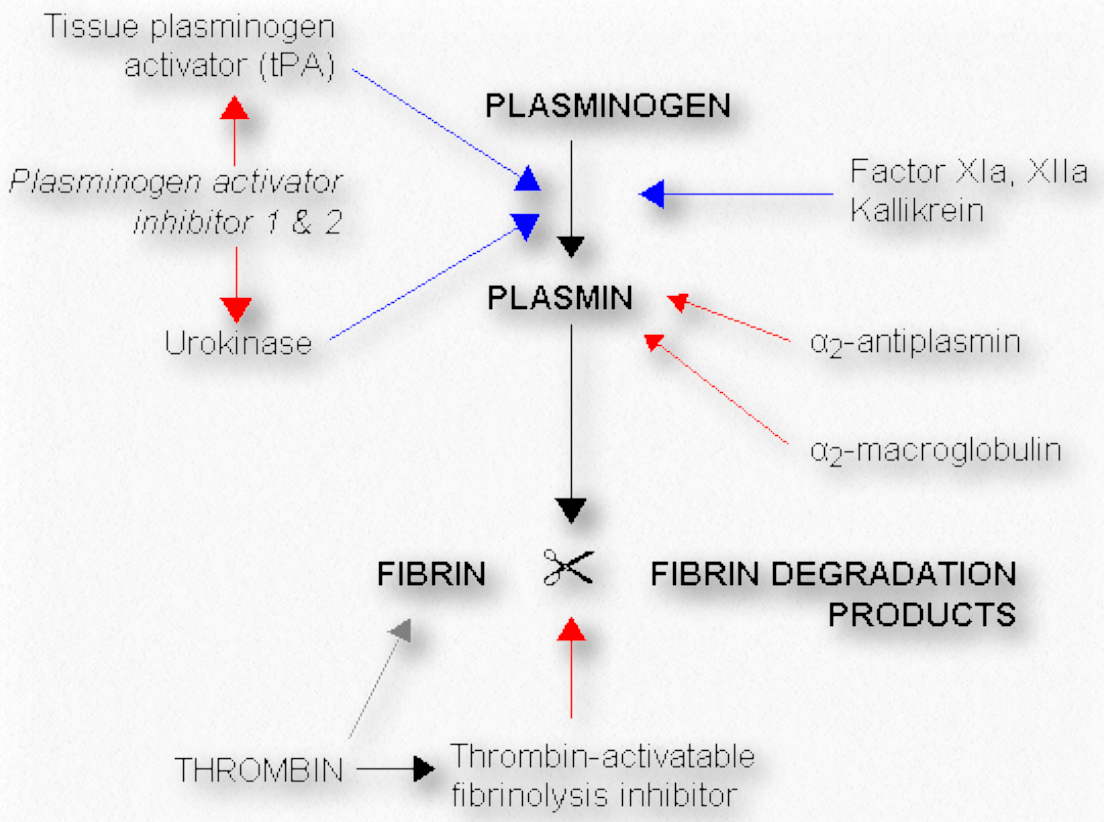

Figure 4.80 - Regulation of fibrin breakdown. Activators in blue. Inhibitors in red.

Wikipedia

their clotting times checked regularly to ensure that they are taking the right dose of anti-coagulant medication. Diet and the metabolism of Vitamin K in the body can affect the amount of warfarin needed. Vitamin K is synthesized in plants and plays a role in photosynthesis. It can be found in the highest quantities in vegetables that are green and leafy. Patients whose diet is high in these vegetables may require a different dose than those who rarely eat greens. Dietary vitamin K is also, as mentioned earlier, metabolized by bacteria in the large intestine, where they convert vitamin K_1 into vitamin K_2.

Plasmin

Clots, once made in the body, do not remain there forever. Instead, a tightly regulated enzyme known as plasmin is activated, when appropriate, to break down the fibrin-entangled clot. Like many of the enzymes in the blood clotting cascade, plasmin is a serine protease. It is capable of cleaving a wide range of proteins. They include polymerized fibrin clots, fibronectin, thrombospondin, laminin, and the von Willebrand factor.

Plasmin plays a role in activating collagenases and in the process of ovulation by weakening the wall of the Graafian follicle in the ovary. Plasmin is made in the liver as the zymogen known as plasminogen. Several different enzymes can activate it.

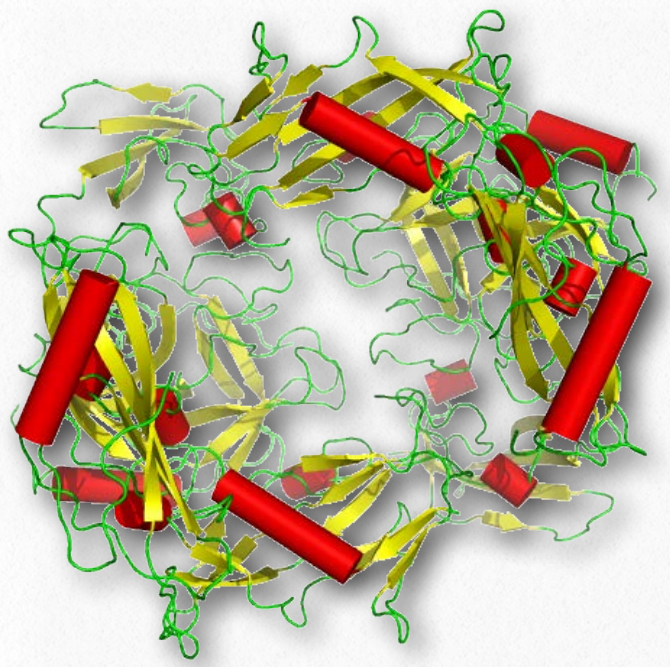

Figure 4.81 - Plasmin

Tissue plasminogen activator (tPA), using fibrin as a co-factor, is one. Others include urokinase plasminogen activator (using urokinase plasminogen activator receptor as a co-factor), kallikrein (plasma serine protease with many forms and blood functions), and FXIa and FXIIa from the clotting cascade.

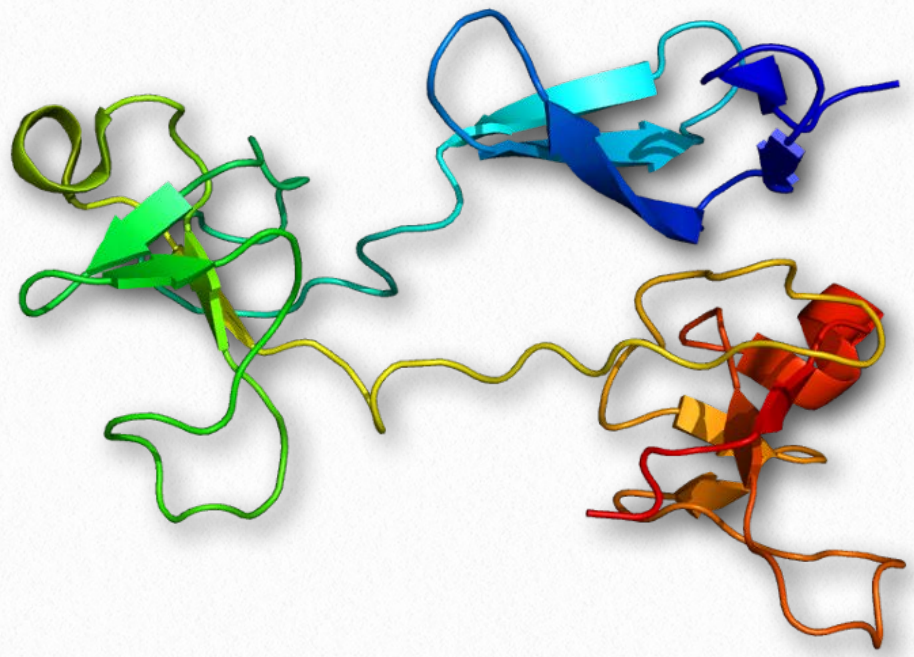

Figure 4.82 - Fibronectin 1

Wikipedia

Plasmin inhibition

Plasmin's activity can also be inhibited. Plasminogen activator inhibitor, for example, can inactivate tPA and urokinase. After plasmin has been activated, it can also be inhibited by α_2-antiplasmin and α_2-macroglobulin (Figure 4.80).

Thrombin also plays a role in plasmin's inactivation, stimulating activity of thrombin activatable fibrinolysis inhibitor. Angiostatin is a sub-domain of plasmin produced by auto-proteolytic cleavage. It blocks the growth of new blood vessels and is being investigated for its anti-cancer properties.

YouTube Lectures by Kevin HERE & HERE

Fibronectin

Fibronectin is a large (440 kDa) glycoprotein found in the extracellular matrix that binds to integral cellular proteins called integrins and to extracellular proteins, including collagen, fibrin, and heparan sulfate. It comes in two forms. The soluble form is found in blood plasma and is made by the liver. It is found in high concentration in the blood stream (300 µg/ml). The insoluble form is found abundantly in the extracellular matrix.

The protein is assembled in the extracellular matrix and plays roles in cellular growth, adhesion, migration, and differentiation. It is very important in wound healing.

Assists in blood clot formation

Fibronectin from the blood plasma is localized to the site of the wound, assisting in formation of the blood clot to stop bleeding. In the initial stages of wound healing, plasma fibronectin interacts with fibrin in clot formation. It also protects tissue sur-

rounding the wound. Later in the repair process, remodeling of the damaged area begins with the action of fibroblasts and endothelial cells at the wound site. Their task is to degrade proteins of the blood clot matrix, replacing them with a new matrix like the undamaged, surrounding tissue.

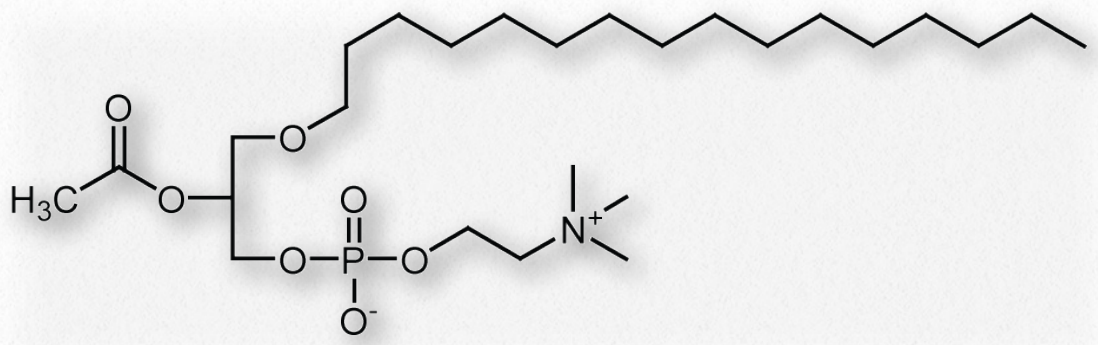

Figure 4.83 - Platelet Activating Factor

Wikipedia

Fibroblasts act on the temporary fibronectin-fibrin matrix, remodeling it to replace the plasma fibronectin with cellular fibronectin. This may cause the phenomenon of wound contraction, one of the steps in wound healing. Secretion of cellular fibronectin by fibroblasts is followed by fibronectin assembly and integration with the extracellular matrix.

Embryogenesis

Fibronectin is essential for embryogenesis. Deleting the gene in mice causes lethality before birth. This is likely due to its role in migration and guiding the attachment of cells as the embryo develops. Fibronectin also has a role in the mouth. It is found in saliva and is thought to inhibit colonization of the mouth by pathogenic bacteria.

Platelet activating factor

Platelet Activating Factor (PAF) is a compound (Figure 4.82) produced primarily in cells involved in host defense. These include platelets, macrophages, neutrophils, and monocytes, among others. It is produced in greater quantities in inflammatory cells upon proper stimulation. The compound acts like a hormone and mediates platelet aggregation/degranulation, inflammation, and anaphylaxis. It can transmit signals between cells to trigger and amplify inflammatory and clotting cascades.

When unregulated, signaling by PAF can cause severe inflammation resulting in sepsis and injury. Inflammation in allergic reactions arises partly as a result of PAF and is an important factor in bronchoconstriction in asthma. In fact, at a concentration of only 10 picomolar, PAF can cause asthmatic inflammation of the airways that is life threatening.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Thank Goodness My Blood is Clotting

To the tune of "*Don't Sleep in the Subway Darling*"

Metabolic Melodies Website HERE

I'm feeling so sad
'Cuz I cut . . . . myself bad
Now I'm all worried 'bout . . . . consequences

It's starting to bleed
There's some clo . . . . sure I need
So the body kicks . . . . in its defenses

It's happened all so many times before
The blood flows out and then it shuts the door

Thank goodness my blood is clotting
Enmeshing the fibrin chains
Thank goodness my blood is clotting
The zymogens
Are activating and all is well
So I'll stop bleeding again

The vitamin K's
Help to . . . . bind to cee-ays
Adding C-O-. . . . O-H to amend things
Um-m-um-um-um-um

It hardens and stays
When a glu. . . . taminase
Creates co. . . . valent bonds . . . . for cementing

In just a moment, things are good to go
The clot's in place and it has stopped the flow

But what about clot dissolving?
Untangling fibrin chains?
This calls for some problem solving
There is a way
Just activate up some t-PA
Get plasmin active in veins

Oh, oh, oh.
And thanks to the dis-enclotting'
As part of repairin' veins
It's part of my body's plotting
The wound is gone
I'm back where I started and
Nothing's wrong
My blood flow is normal again.

Recording by Liz Bacon and David Simmons
Lyrics by Kevin Ahern

5

Energy

"Getting over a painful experience is much like crossing monkey bars. You have to let go at some point in order to move forward."

-C.S Lewis

We know that energy can neither be created or destroyed, so cells must merely convert energy, from one form to another. The two principal organelles that carry out these transformations in eukaryotic cells are mitochondria and chloroplasts, ancient endosymbionts that have now become part of their host cells. In this chapter we examine the energy transformations carried out by these organelles.

Energy: Basics

Introduction

Living organisms are made up of cells, and cells contain a horde of biochemical components. Living cells, though, are not random collections of these molecules. They are extraordinarily organized or "ordered". By contrast, in the nonliving world, there is a universal tendency to increasing disorder. Maintaining and creating order in cells takes the input of energy. Without energy, life is not possible.

YouTube Lectures by Kevin HERE & HERE

Oxidative energy

The primary mechanism used by non-photosynthetic organisms to obtain energy is oxidation and carbon is the most commonly oxidized energy source. The energy released during the oxidative steps is “captured” in ATP and can be used later for energy coupling (see HERE). The more reduced a carbon atom is, the more energy can be realized from its oxidation. Fatty acids are highly reduced, whereas carbohy-

drates are moderately so. Complete oxidation of both leads to carbon dioxide, which has the lowest energy state. Conversely, the more oxidized a carbon atom is, the more energy it takes to reduce it.

In the series shown in Figure 5.1, the most reduced form of carbon is on the left. The energy of oxidation of each form is shown above

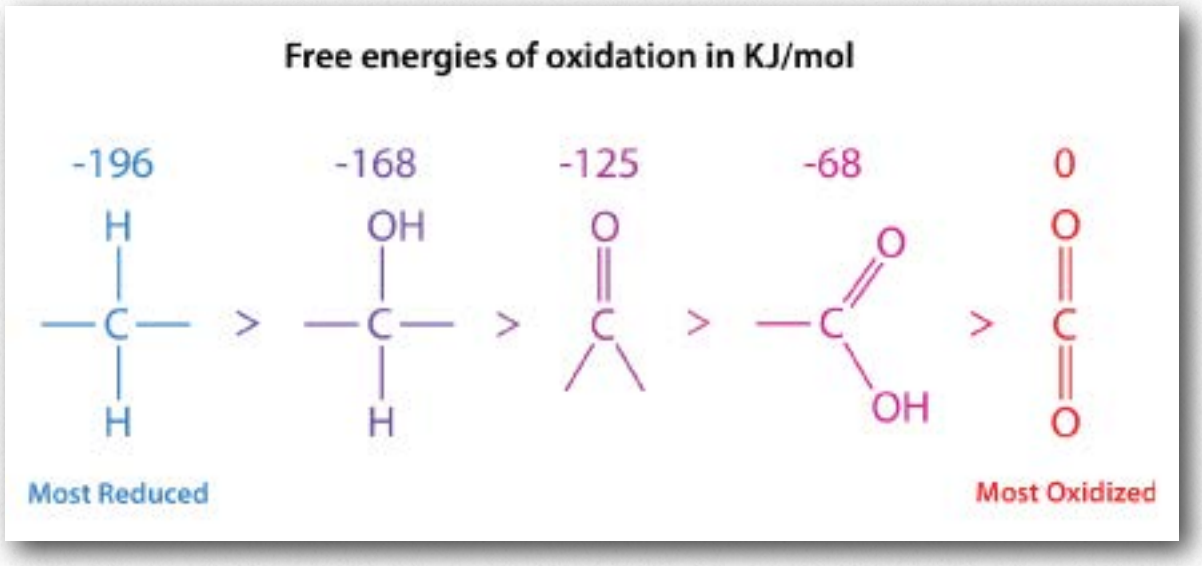

Figure 5.1 - Five oxidation states of carbon
Image by Pehr Jacobson

it. The reduction states of fatty acids and carbohydrates can be seen by their formulas.

Palmitic acid = $C_{16}H_{34}O_2$

Glucose = $C_6H_{12}O_6$

Palmitic acid only contains two oxygens per sixteen carbons, whereas glucose has six oxygen atoms per six carbons. Consequently, when palmitic acid is fully oxidized, it generates more ATP per carbon (128/16) than glucose (38/6). It is because of this that we use fat (contains fatty acids) as our primary energy storage material.

Oxidation vs. reduction in metabolism

Biochemical processes that break things down from larger to smaller are called catabolic processes. Catabolic processes are often oxidative in nature and energy releasing. Some, but not all, of that energy is captured as ATP. If not all of the energy is captured as ATP, what happens to the rest of it? The answer is simple. It is released as heat and it is for this reason we get hot when we exercise.

By contrast, synthesizing large molecules from smaller ones (for example, making proteins from amino acids) is referred to as anabolism. Anabolic processes are often reductive in nature (Figures 5.3 & 5.4) and require energy input. By themselves, they would not occur, as they are reversing oxidation and decreasing entropy (making many small things into a larger one). To overcome this energy barrier, cells must expend energy. For example, if one wishes to reduce CO_2 to carbohydrate, energy must be used to do so. Plants do this during the dark reactions of photosynthesis (Figure 5.3). The energy source for the reduction is ultimately the sun. The electrons for the reduction come from water, and the CO_2 is removed

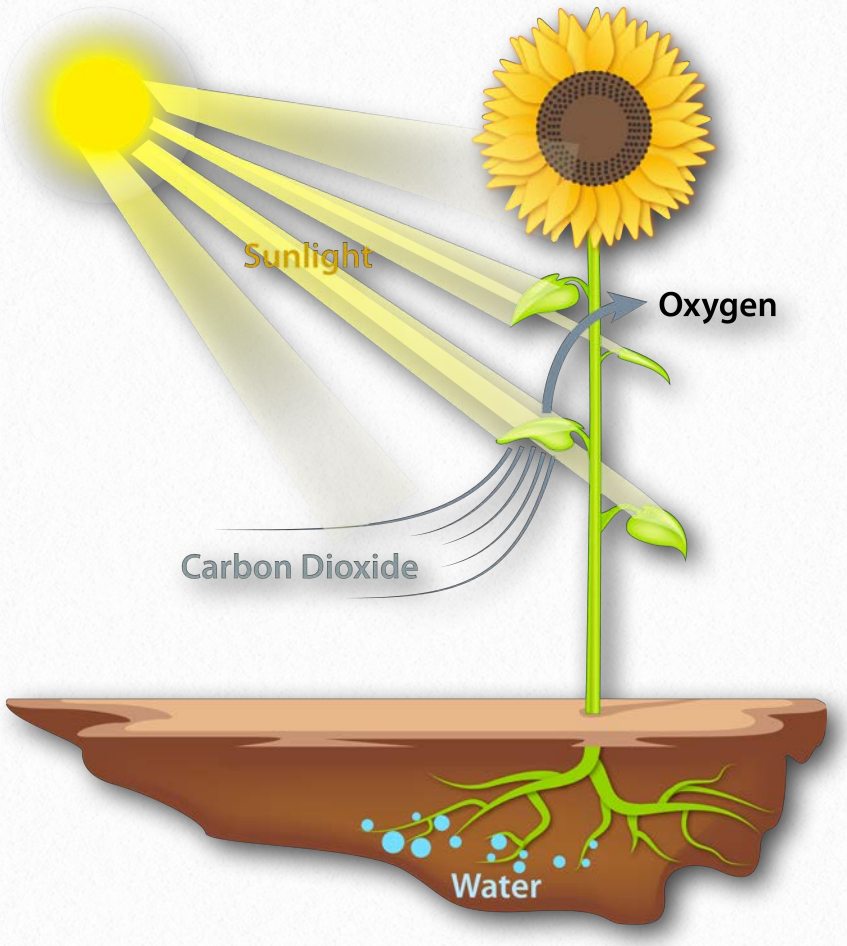

Figure 5.2 - Photosynthesis - The primary source of biological energy

Image by Aleia Kim

from the atmosphere and gets incorporated into a sugar.

Energy coupling

The synthesis of the many molecules needed by cells needs the input of energy to occur. Cells overcome this energy obstacle by using ATP to "drive" the reaction (Figure 5.6). The energy needed to drive reactions is harvested in very controlled conditions in enzymes. This involves a process called 'coupling'. Coupled reactions rely on linking an energetically favorable reaction (i.e., one with a negative $\Delta G°'$) with the reaction requiring an energy input, which has a positive $\Delta G°'$. As long as the overall $\Delta G°'$ of the two reactions together is negative, the reaction can proceed. Hydrolysis of ATP is a very energetically favorable reaction that is commonly linked to many energy requiring reactions in cells. Without the hydrolysis of ATP (or GTP, in some cases), the reaction would not be feasible.

Entropy and energy

Most students who have had some chemistry know about the Second Law of Ther-

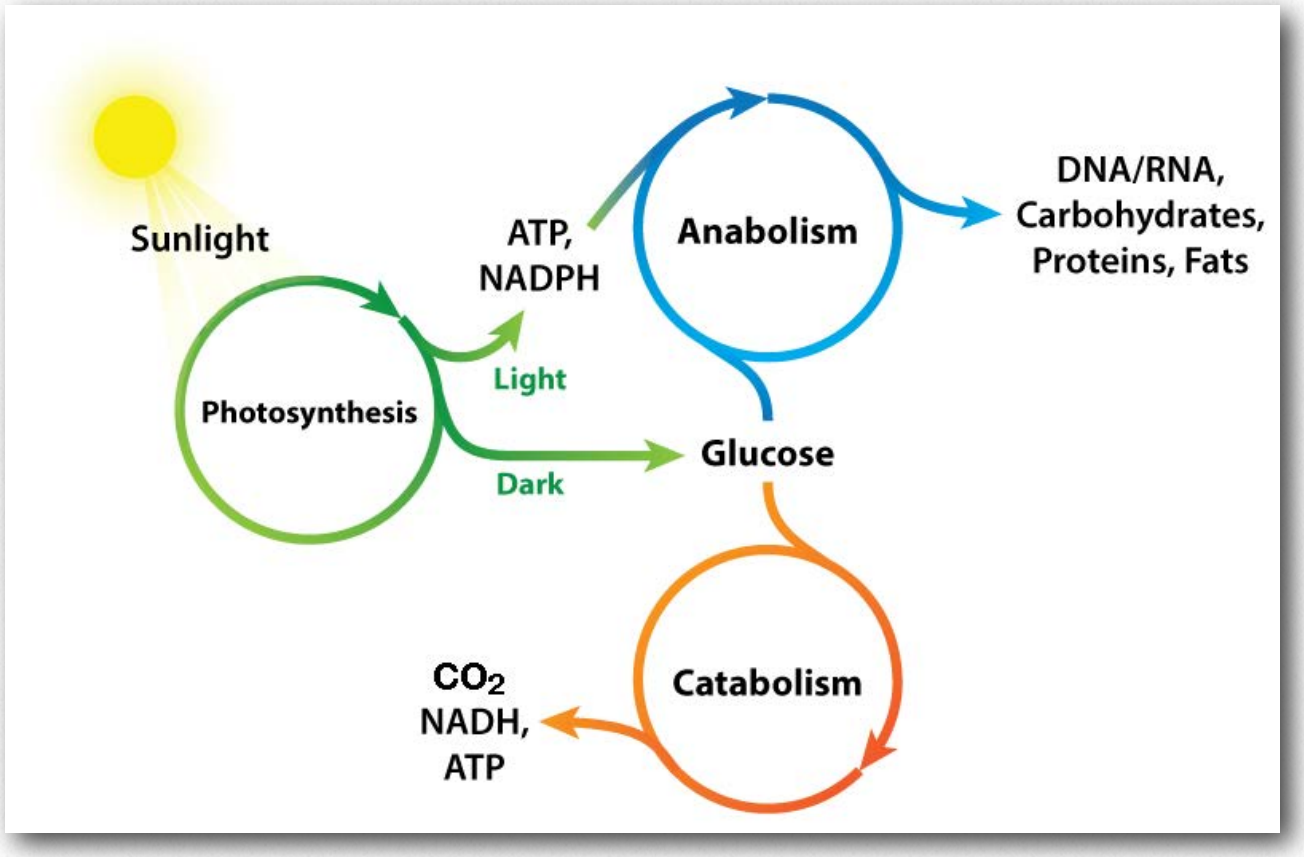

Figure 5.3 - Movement of biological energy

Image by Aleia Kim

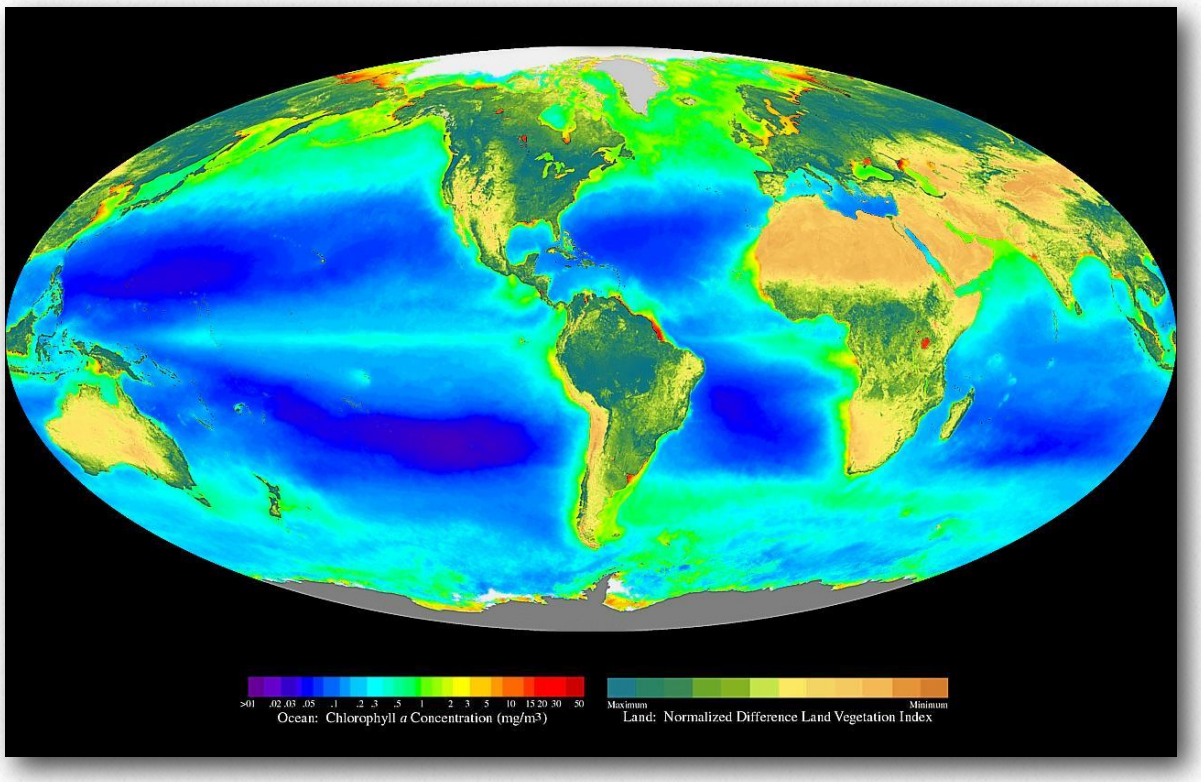

Figure 5.4 - Photosynthesis as measured by chlorophyll concentration

modynamics with respect to increasing disorder of a system. Cells are very organized or ordered structures, leading some to mistakenly conclude that life somehow violates the second law. In fact, that notion is incorrect. The second law doesn't say that entropy always increases, just that, left alone, it tends to do so, in an isolated system. Cells are not isolated systems, though, in that they obtain energy, either from the sun, if they are autotrophic, or food, if they are heterotrophic.

To counter the universal tendency towards disorder on a local scale requires energy. As an example, take a fresh deck of cards which is neatly aligned with Ace-King-Queen . . . . 4,3,2 for each suit. Throw the deck into the air, letting the cards scatter. When you pick them up, they will be

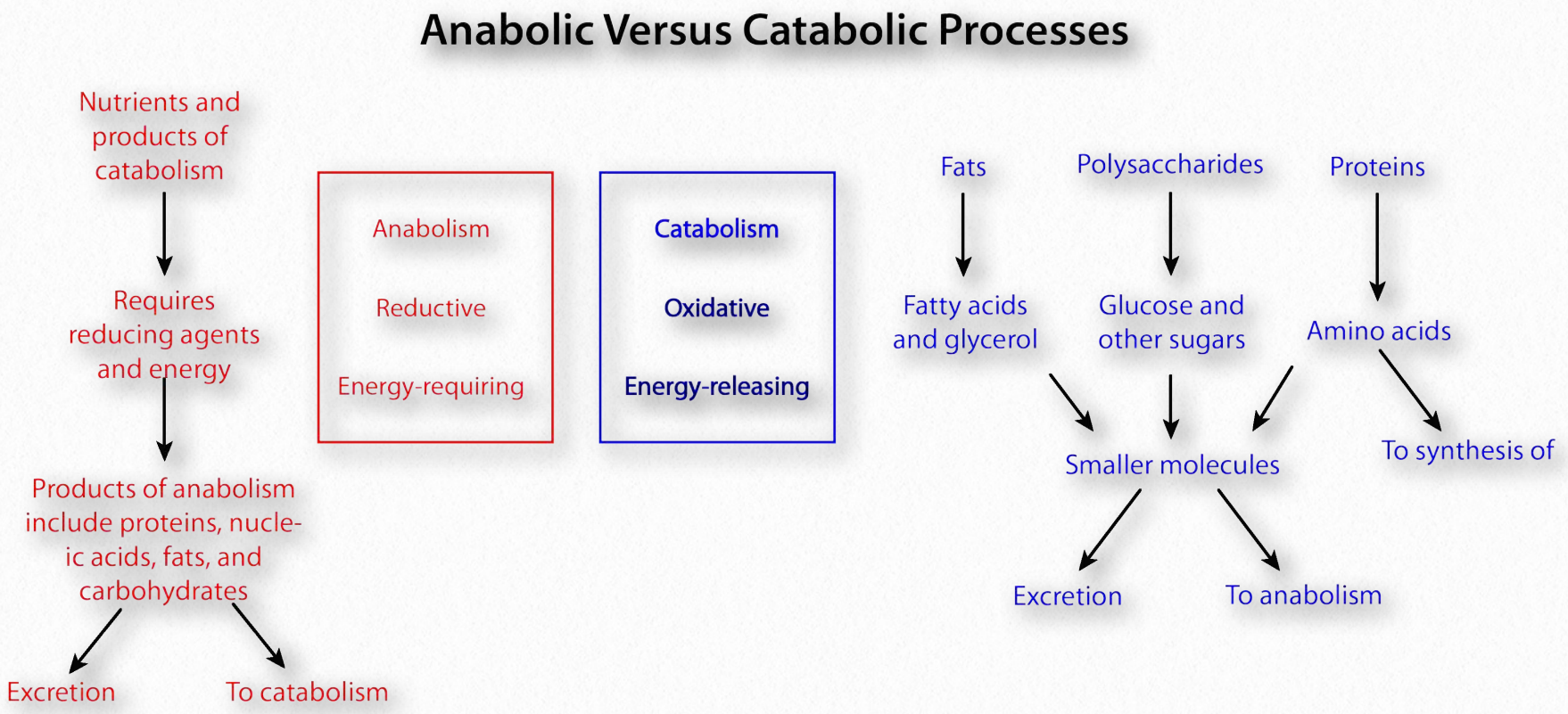

Figure 5.5 - Synthesis and breakdown pathways in metabolism

Image by Pehr Jacobson

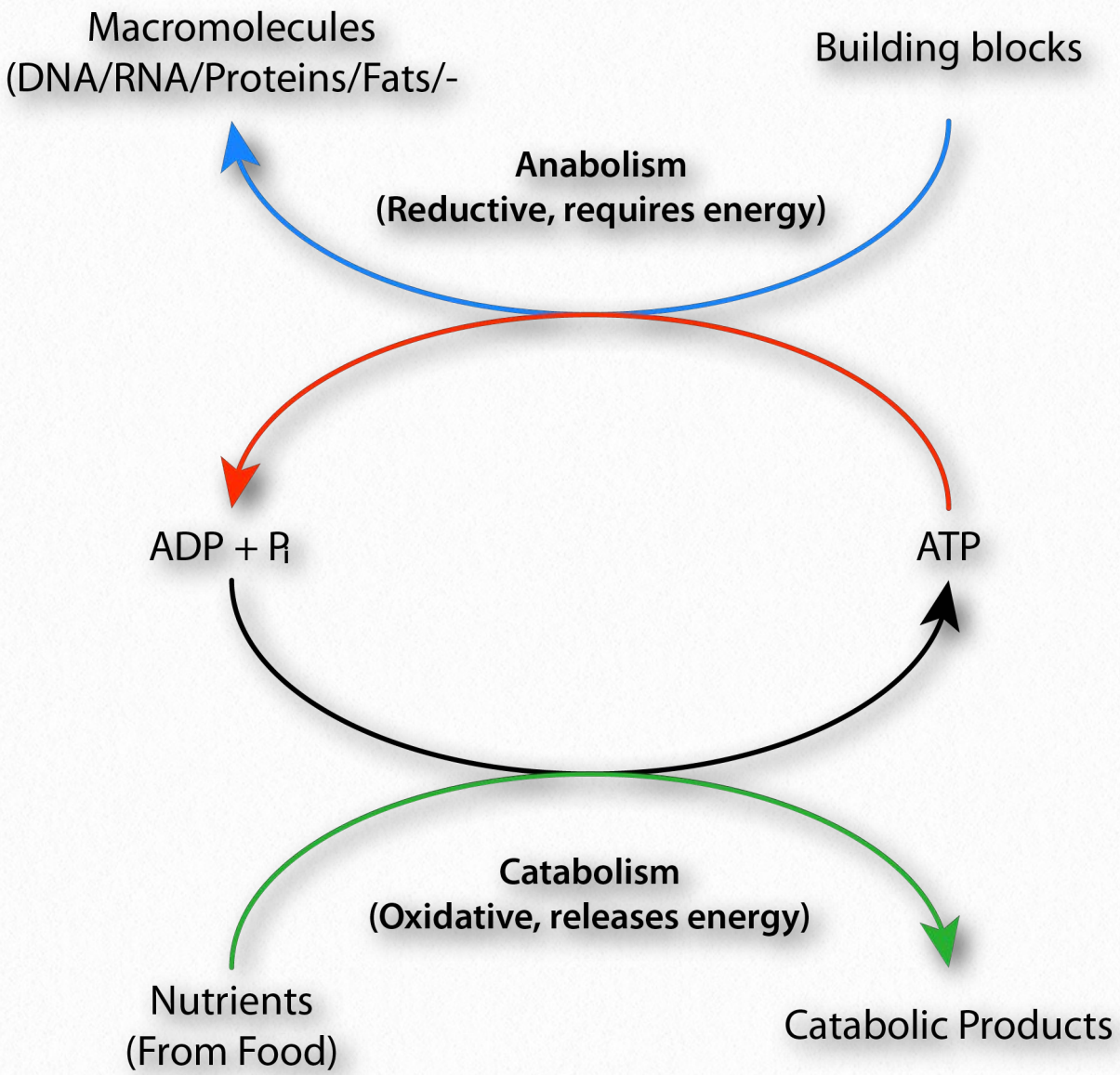

Figure 5.6 - Cycling of biological energy via ADP and ATP
Image by Pehr Jacobson

more disordered than when they started. However, if you spend a few minutes (and expend a bit of energy), you can reorganize the same deck back to its previous, organized state. If entropy always increased everywhere, you could not do this. However, with the input of energy, you overcame the disorder. This illustrates an important concept - the cost of fighting disorder is energy.

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Biological energy

There are, of course, other reasons that organisms need energy. Muscular contraction, synthesis of molecules, neurotransmission, signaling, thermoregulation, and subcellular movements are examples. Where does this energy come from? The currencies of energy are generally high-energy phosphate-containing molecules. ATP is the best known and most abundant, but GTP is also an important energy source (energy source for protein synthesis). CTP is involved in synthesis of glycerophospholipids and UTP is used for synthesis of glycogen and other sugar compounds. In each of these cases, the energy is in the form of potential chemical energy stored in the multi-phosphate bonds. Hydrolyzing those bonds releases the energy in them.

Of the triphosphates, ATP is the primary energy source, acting to facilitate the synthesis of the others by action of the enzyme NDPK. ATP is made by three distinct types of phosphorylation – oxidative phosphorylation (in mitochondria), photophosphorylation (in chloroplasts of

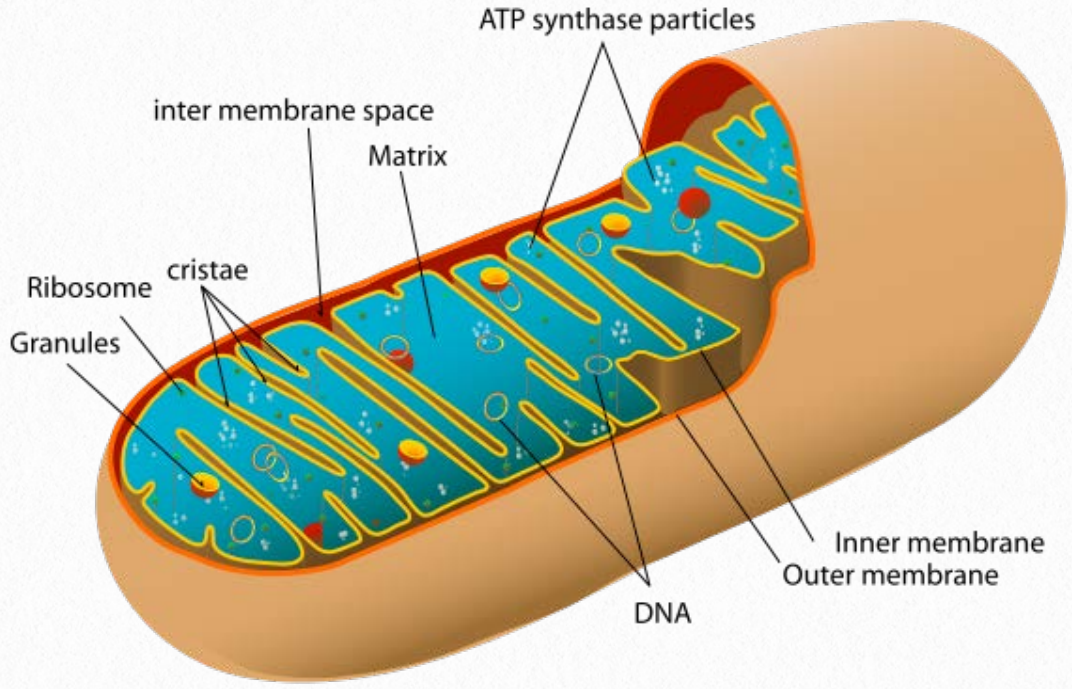


Figure 5.7 A mitochondrion

plants), and substrate level phosphorylation (in enzymatically catalyzed reactions).

Gibbs free energy in biology

ATP is generally considered the "storage battery" of cells (See also 'Molecular Battery Backups for Muscles HERE). In order to understand how energy is captured, we must first understand Gibbs free energy and in doing so, we begin to see the role of energy in determining the directions chemical reactions take.

Gibbs free energy may be thought of as the energy available to do work in a thermodynamic system at constant temperature and pressure.

Mathematically, the Gibbs free energy is given as:

$$G = H - TS$$

where H is the enthalpy, T is the temperature in Kelvin, and S is the entropy.

At standard temperature and pressure, every system seeks to achieve a minimum of free energy. Thus, increasing entropy, S, will reduce Gibbs free energy. Similarly, if excess heat is available (reducing the enthalpy, H), the free energy can also be reduced.

Cells must work within the laws of thermodynamics, as noted, so all of their biochemical reactions, too, are ruled by these laws. Now we shall consider energy in the cell. The change in Gibbs free energy (ΔG) for a reaction is crucial, for it, and it alone, determines whether or not a reaction goes forward.

$\Delta G = \Delta H - T\Delta S$,

There are three cases

One reason we need ATP
Is the high cost of living, you see
'Cause the chaotic entity
Known as the entropy
Requires cells to burn energy

$\Delta G < 0$ - the reaction proceeds as written

$\Delta G = 0$ - the reaction is at equilibrium

$\Delta G > 0$ - the reaction runs in reverse

For a reaction

$$aA \rightleftarrows bB$$

(where 'a' and 'b' are integers and A and B are molecules) at pH 7, ΔG can be determined by the following equation,

$$\Delta G = \Delta G^{\circ\prime} + RT\ln([B]^b/[A]^a)$$

For multiple substrate reactions, such as $aA + cC \rightleftarrows bB + dD$

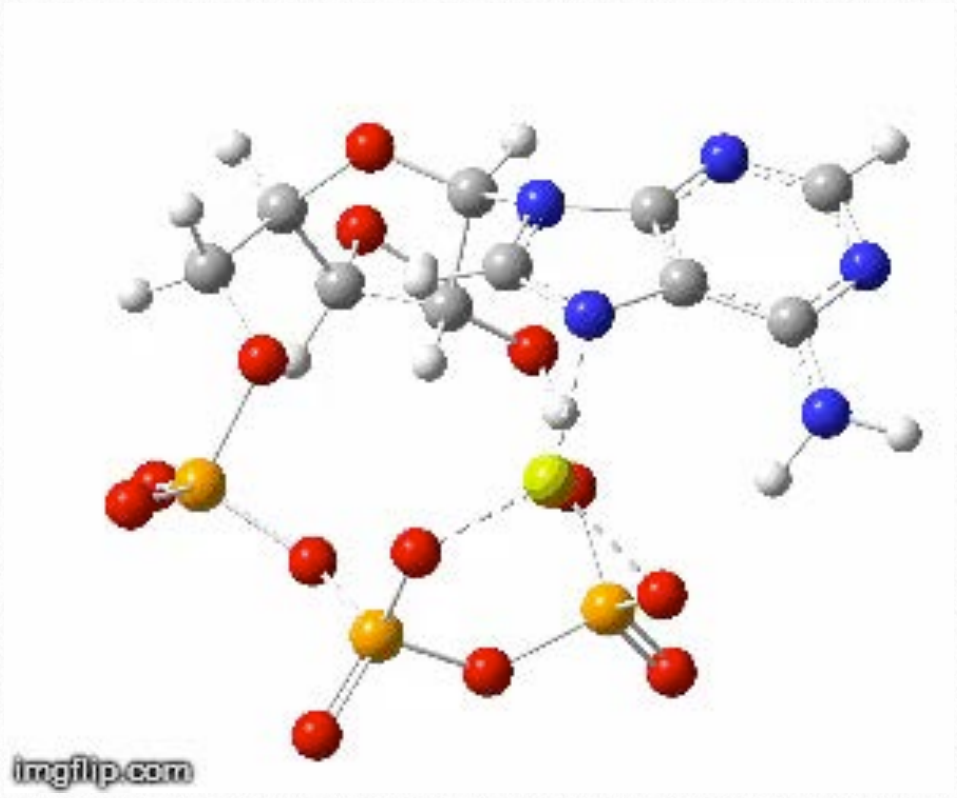
$$\Delta G = \Delta G^{\circ\prime} + RT\ln\{([B]^b[D]^d)/([A]^a[C]^c)\}$$

The $\Delta G^{\circ\prime}$ term is called the change in Standard Gibbs Free energy, which is the change in energy that occurs when all of the products and reactants are at standard conditions and the pH is 7.0. It is a constant for a given reaction.

In simple terms, we can collect all of the terms of the numerator together and call them {Products} and all of the terms of the denominator together and call them {Reactants},

$$\Delta G = \Delta G^{\circ\prime} + RT\ln(\{Products\}/\{Reactants\})$$

For most biological systems, the temperature, T, is a constant for a given reaction. Since $\Delta G^{\circ\prime}$ is also a constant for a given reaction, the ΔG is changed almost exclusively as the ratio of {Products}/{Reactants} changes.



Movie 5.1 - ATP - The fuel of the cell

Wikipedia

Importance of $\Delta G^{\circ\prime}$

If one starts out at standard conditions, where everything except protons is at 1M, the RTln({Products}/{Reactants}) term is zero, so the $\Delta G^{\circ\prime}$ term equals the ΔG, and the $\Delta G^{\circ\prime}$ determines the direction the reaction will take (*only* under those conditions). This is why people say that a negative $\Delta G^{\circ\prime}$ indicates an energetically favorable reaction, whereas a positive $\Delta G^{\circ\prime}$ corresponds to an unfavorable one.

Increasing the ratio of {Products}/{Reactants} causes the value of the natural log (ln) term to become more positive (less negative), thus making the value of ΔG more positive. Conversely, as the ratio of {Products}/{Reactants} decreases, the value of the natural log term becomes less positive (more negative), thus making the value of ΔG more negative.

System response to stress

Intuitively, this makes sense and is consistent with Le Chatelier's Principle – a system responds to stress by acting to alleviate the stress. If we examine the ΔG for a reaction in a closed system, we see that it will always move to a value of zero (equilibrium), no matter whether it starts with a positive or negative value.

Another type of free energy available to cells is that generated by electrical potential. For example, mitochondria and chloroplasts partly use Coulombic energy (based on charge) from a proton gradient across their membranes to provide the necessary energy for the synthesis of ATP. Similar energies drive the transmission of nerve signals (sodium and potassium gradients) and the movement of some molecules in secondary active transport processes across membranes (e.g., H^+ differential driving the movement of lactose). From the Gibbs free energy change equation,

When reactions have product largesse
They will act to address the excess
Henry Le Chatelier
Showed conversion's the way
To suppress the excess by redress

$$\Delta G = \Delta H - T\Delta S$$

it should be noted that an increase in entropy will help contribute to a decrease in ΔG. This happens, for example when a large molecule is being broken into smaller pieces or when the rearrangement of a molecule increases the disorder of molecules around it. The latter situation arises in the hydrophobic effect, which helps drive the folding of proteins.

Chemical and electrical potential

It is said that absence makes the heart grow fonder. We won't tackle that philosophical issue here, but we will say that separation provides potential energy that cells can and do harvest. The lipid bilayer of cell and (in eukaryotic cells) organelle membranes provide the necessary barrier for separation.

Impermeable to most ions and polar compounds, biological membranes are essential for processes that generate cellular energy. Consider Figure 5.8. A lipid bilayer separates two solutions with different concentrations of a solute. There is a greater concentration of negative ions in the bottom and a

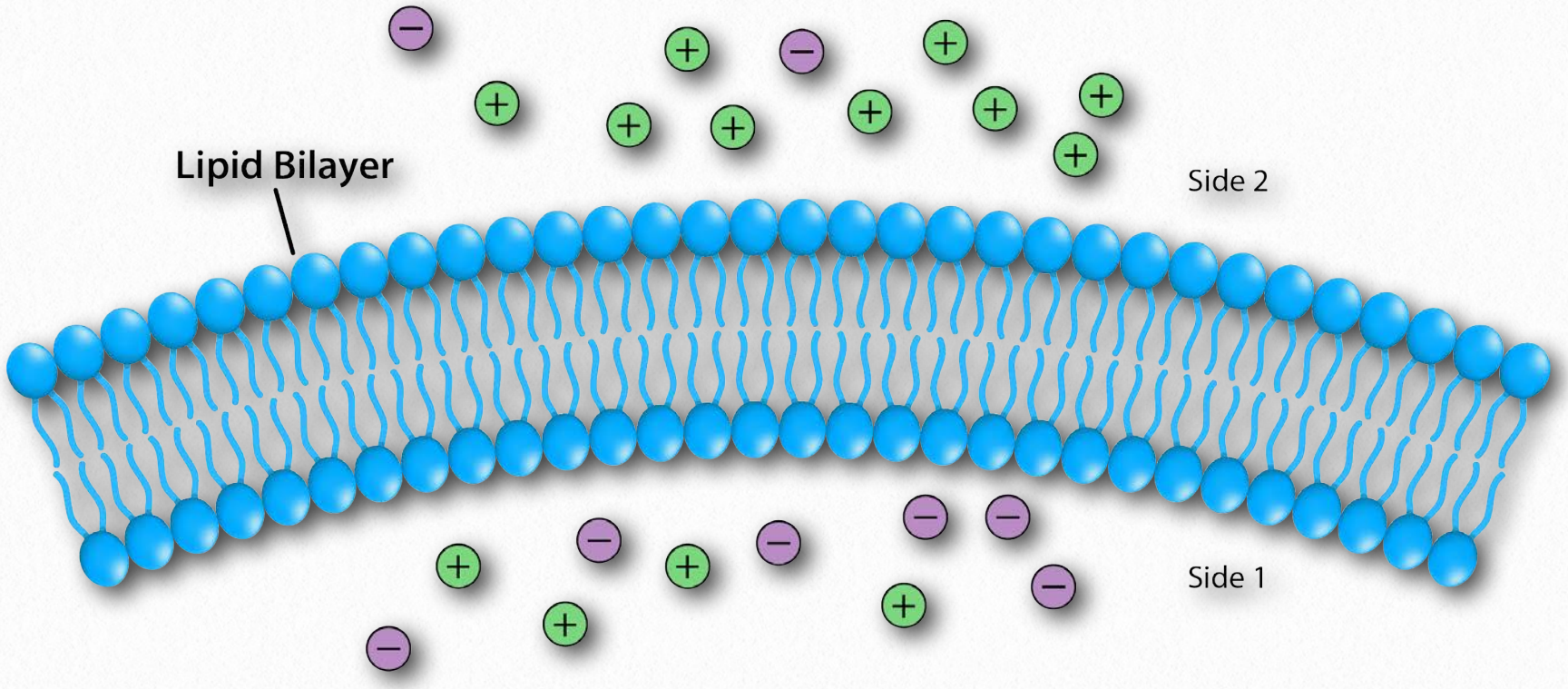


Figure 5.8 - Differences in ion concentration across a membrane give rise to chemical and electrical gradients

Image by Pehr Jacobson

greater concentration of positive ions on the top.

Whenever there is a difference in concentration of molecules across a membrane, there is said to be a concentration gradient across it. A difference in concentration of ions across a membrane also creates a charge (or electrical) gradient. Because there is a difference in both the chemical concentration of the ions and in the charge on the two sides of the membrane, this is described as an electrochemical gradient (Figures 5.8 -5.10).

Potential energy

Such gradients function like batteries and contain potential energy. When the potential energy is harvested by cells, they can create ATP, transmit nerve signals, pump molecules across membranes, and more. It is important, therefore, to understand how to calculate the potential energy of electrochemical gradients.

First, we consider chemical (solute) gradients. In Figure 5.9, two concentrations of glucose are separated by a lipid bilayer. Let's assume C_2 be the concentration of glucose inside the cell (bottom) and C_1 be the glucose concentration outside (top). The Gibbs free energy associated with moving glucose in the direction of C_2 (into the cell) is given by

$$\Delta G = RT\ln[C_2/C_1]$$

To move it in the direction of C_1 (to the outside of the cell) the expression would be

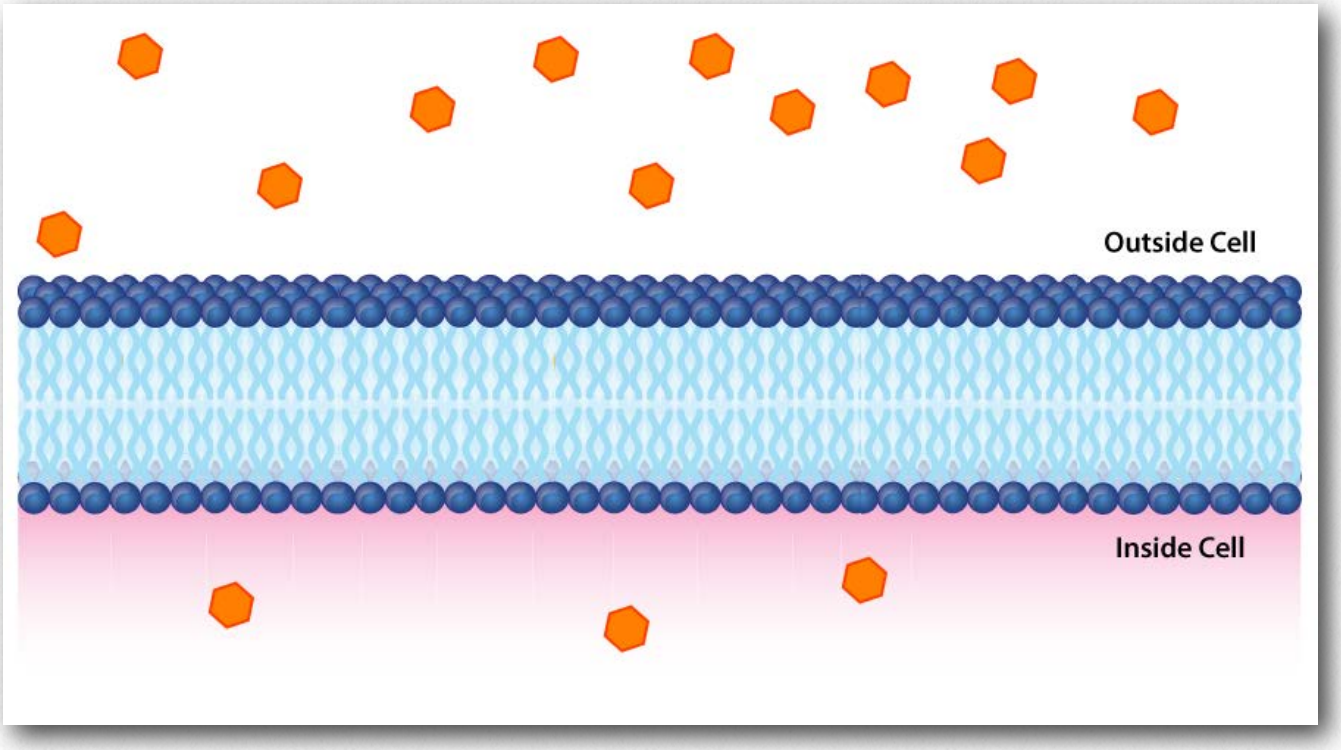


Figure 5.9 - A chemical gradient

Image by Aleia Kim

In the example above, we considered glucose, which is an uncharged molecule. When ions are involved, their charges must also be taken into consideration. Figure 5.10 depicts a similar situation across a lipid bilayer. In this case, a difference of concentration and charge exists. There are more positive charges inside the cell than outside.

$$\Delta G = RT\ln[C_1/C_2]$$

Since C_2 is smaller than C_1 (i.e., there are fewer glucose molecules inside the cell) then the ΔG is negative and diffusion would be favored into the cell, if the glucose could traverse the bilayer.

YouTube Lectures by Kevin HERE & HERE

Conversely, if C_2 was greater than C_1 (more glucose was in the cell than outside) the ΔG would be positive, so movement in the direction of C_2 would not be favored and instead the glucose would tend to move towards C_1, that is, out of the cell.

If $C_2 = C_1$, with the same concentration of glucose inside and outside, then the ΔG would be zero and there would be no net movement, as the system would be at equilibrium.

Using C_2 to indicate the concentration of materials inside the cell and C_1 for the concentration outside the cell (as before), then the free energy for movement of an ion from top to bottom is given by the following equation

$$\Delta G = RT\ln[C_2/C_1] + ZF\Delta\psi$$

Note here that this equation must take into consideration both the concentration differences and the charge differences. Z refers to the charge of the transported species, F is the Faraday constant (96,485 Coulombs/mol), and $\Delta\psi$ is the electrical potential difference (voltage difference) across the membrane.

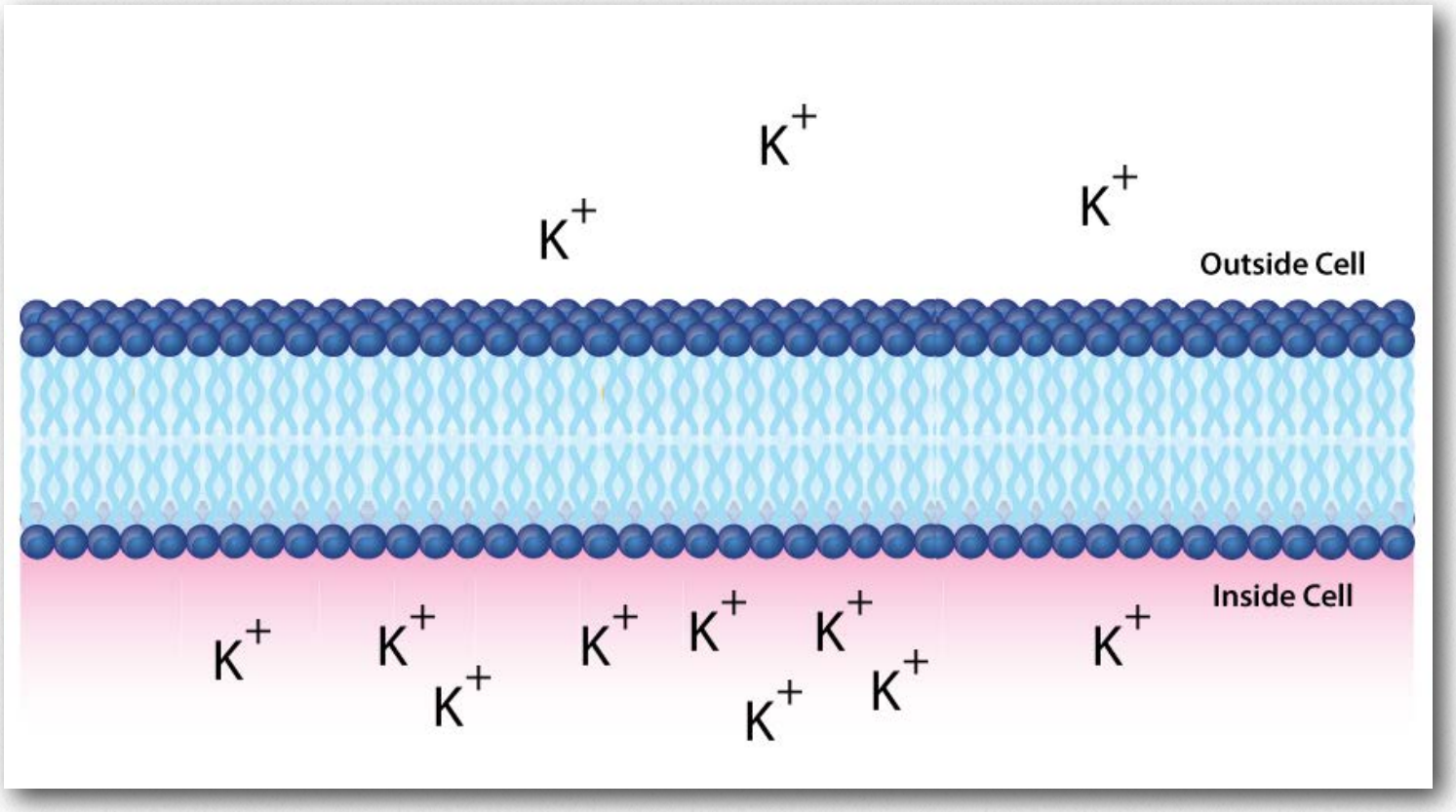


Figure 5.10 - An electrochemical gradient of potassium ions

Image by Aleia Kim

If we were to calculate the ΔG for movement of the potassium ion from top to bottom, it would be positive, since $[C_2/C_1]$ is greater than 1 (making for a positive ln term), and the $ZF\Delta\psi$ is positive because positively charged ions (Z) are moving against a positive charge gradient given by $\Delta\psi$ (greater concentration at the target (bottom) than the starting point (top)). If we were to calculate the concentration of ions moving from bottom to top, then the ln term would be negative (C2<C1) and the $ZF\Delta\psi$ would be negative as well (Z=positive, but $\Delta\psi$ negative).

Reduction potential

In discussing chemical potential, we must also consider reduction potential. Reduction potential measures the tendency of a chemical to be reduced by electrons. It is also designated by several other names/variables. These include redox potential, oxidation/reduction potential, ORP, pE, ε, E, and E_h.

Reduction potential is measured in volts, or millivolts. A substance with a higher reduction potential will have a greater tendency to accept electrons and be reduced. If two substances are mixed in an aqueous solution, the one with the greater (more positive) reduction potential will tend to take electrons away, thus being reduced, from the one with the lower reduction potential, which becomes oxidized.

Relative measures

Absolute reduction potentials are difficult to measure, so reduction potentials are typically defined relative to a reference electrode. In

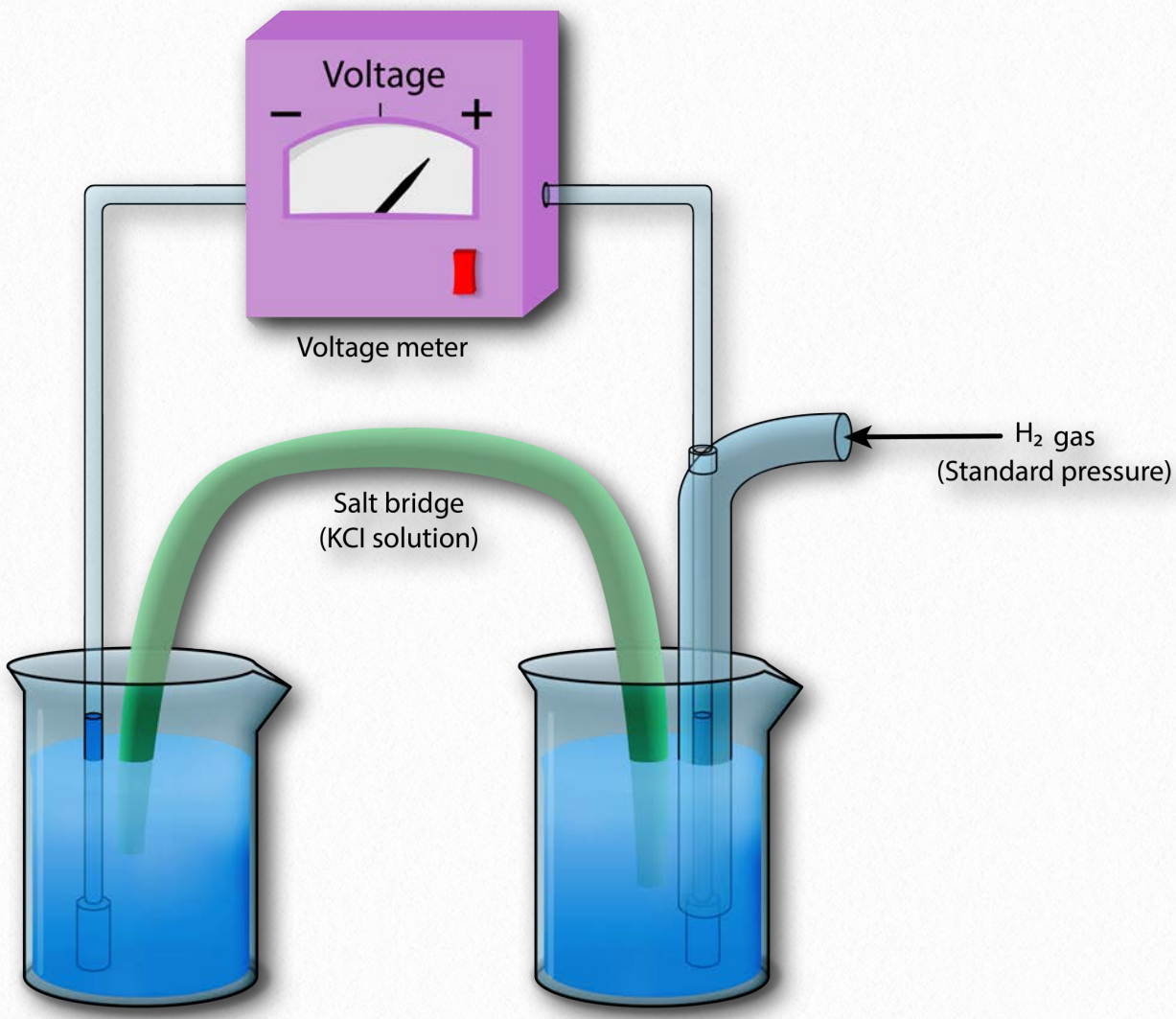


Figure 5.11 - Reference electrode for measuring reduction potentials.

Image by Pehr Jacobson

aqueous solutions, reduction potentials are measured as the potential difference between an inert sensing electrode (typically platinum) in contact with the test solution and a stable reference electrode (measured as a Standard Hydrogen Electrode - SHE) as shown in Figure 5.11. The standard of reference for measurement is the half-reaction

$$H^+ + e^- \rightarrow (1/2)H_2$$

The electrode where this reaction occurs (referred to as a half-cell) is given the value of E° (Standard Reduction Potential) of 0.00 volts. The hydrogen electrode is connected via an external circuit to another half cell containing a mixture of the reduced and oxidized species of another molecule (for example, Fe^{++} and Fe^{+++}) at 1M each and standard conditions of temperature (25°C) and pressure (1 atmosphere).

Direction and voltage measured

The direction and magnitude of electron movement is then measured. If the test mixture takes electrons from the hydrogen electrode, the sign of the voltage is positive and if the direction is reversed, the voltage is negative.

Thus, compounds which have greater affinity for electrons than hydrogen will register a positive voltage and negative voltages correspond to compounds with lesser affinity for electrons than hydrogen.

Movement of electrons

Under standard conditions, electrons will move from compounds generating lower voltages to ones generating higher (more positive) voltages. Just as the standard Gibbs free energy change is the Gibbs free energy change under standard conditions, so, too, is the standard reduction potential E° the reduction potential E under standard conditions.

The actual reduction potential of a half cell will vary with the concentration of each chemical species in the cell. The relationship between the reduction potential E and the standard reduction potential E° is given by the following equation (also called the Nernst equation)

$$E = E^\circ + (RT/nF)*\ln\left(\frac{[\text{reduced molecule}]}{[\text{oxidized molecule}]}\right)$$

where F is the Faraday constant (96,480 J/(Volts*moles), R is the gas constant (8.315 J/(moles*K), n is the number of moles of electrons being transferred, and T is the absolute temperature in Kelvin.

At 25°C, this equation becomes

$$E = E^\circ + (0.026V/n)*\ln\left(\frac{[\text{reduced molecule}]}{[\text{oxidized molecule}]}\right)$$

As for Gibbs free energy, it is useful to measure values at conditions found in cells. This means doing measurements at pH = 7, which differs from having all species at 1M.

Adjustment

Because of this adjustment, a slightly different standard reduction potential is defined and we designate it by E°', just as we defined a special standard Gibbs free energy change at pH 7 as ΔG°'.

There is a relationship between the change in Gibbs free energy ΔG and the change in reduction potential (ΔE). It is

$$\Delta G = -nF\Delta E$$

Similarly, the relation between the change in standard Gibbs free energy and the change in standard reduction potential is

$$\Delta G^{\circ\prime} = -nF\Delta E^{\circ\prime}$$

Energy storage in triphosphates

Formation of triphosphates, like ATP, is essential to meeting the cell's energy needs for synthesis, motion, and signaling. In a given day, an average human body makes and breaks down more than its weight in triphosphates. This is especially remarkable considering that there is only about 250 g of the molecule present in the body at any given time. Energy in ATP is released by hydrolysis of a phosphate from the molecule.

The three phosphates, starting with the one closest to the sugar are referred to as α, β, and γ (Figure 5.12). It is the γ phosphate that is cleaved in hydrolysis and the product is ADP. In a few reactions, the bond between the α and β is cleaved. When this happens, a pyrophosphate (β linked to γ) is released and AMP is produced. This latter reaction to produce AMP releases more energy (ΔG°' = -45.6

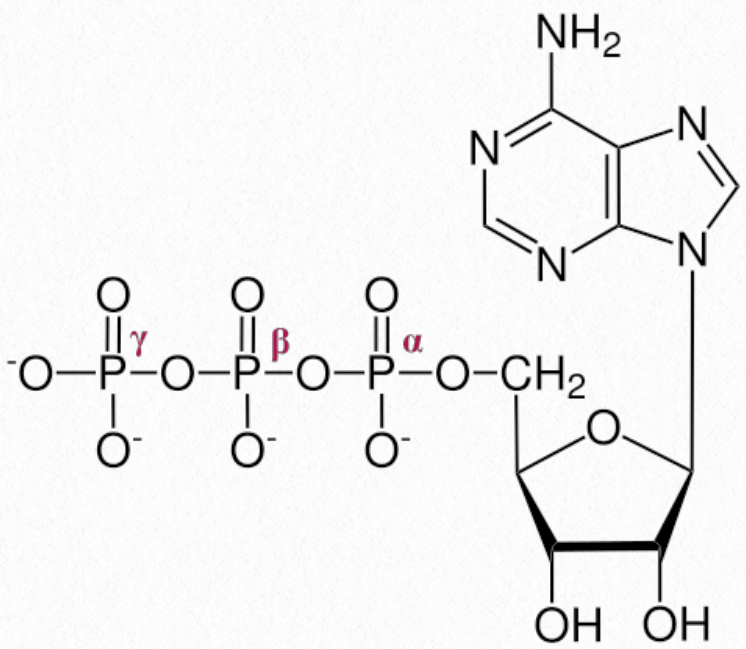


Figure 5.12 ATP showing α, β and γ phosphates

kJ/mol) than the first reaction which produces ADP (ΔG°' = -30.5 kJ/mol).

Since triphosphates are the "currency" that meet immediate needs of the cell, it is important to understand how triphosphates are made. There are three phosphorylation mechanisms – 1) substrate level; 2) oxidative; and 3) photophosphorylation. We consider them here individually.

Substrate level phosphorylation

The easiest type of phosphorylation to understand is that which occurs at the substrate level. This type of phosphorylation involves the direct synthesis of ATP from ADP and a high energy intermediate, typically a phosphate-containing molecule. Substrate level phosphorylation is a relatively minor contributor to the total synthesis of triphosphates by cells. An example substrate phosphorylation comes from glycolysis.

Phosphoenolpyruvate (PEP) + ADP ⇅ Pyruvate + ATP

This reaction has a very negative ΔG°' (-31.4 kJ/mol), indicating that the PEP contains more energy than ATP, thus tending to energetically favor ATP's synthesis. Other triphosphates can be made by substrate level phosphorylation, as well. For example, GTP can be synthesized by the following citric acid cycle reaction.

Succinyl-CoA + GDP + P_i ⇅ Succinate + GTP + CoA-SH

Triphosphates can be interchanged readily in substrate level phosphorylations catalyzed by the enzyme Nucleoside Diphosphate Kinase (NDPK). A generalized form of the reactions catalyzed by this enzyme is as follows:

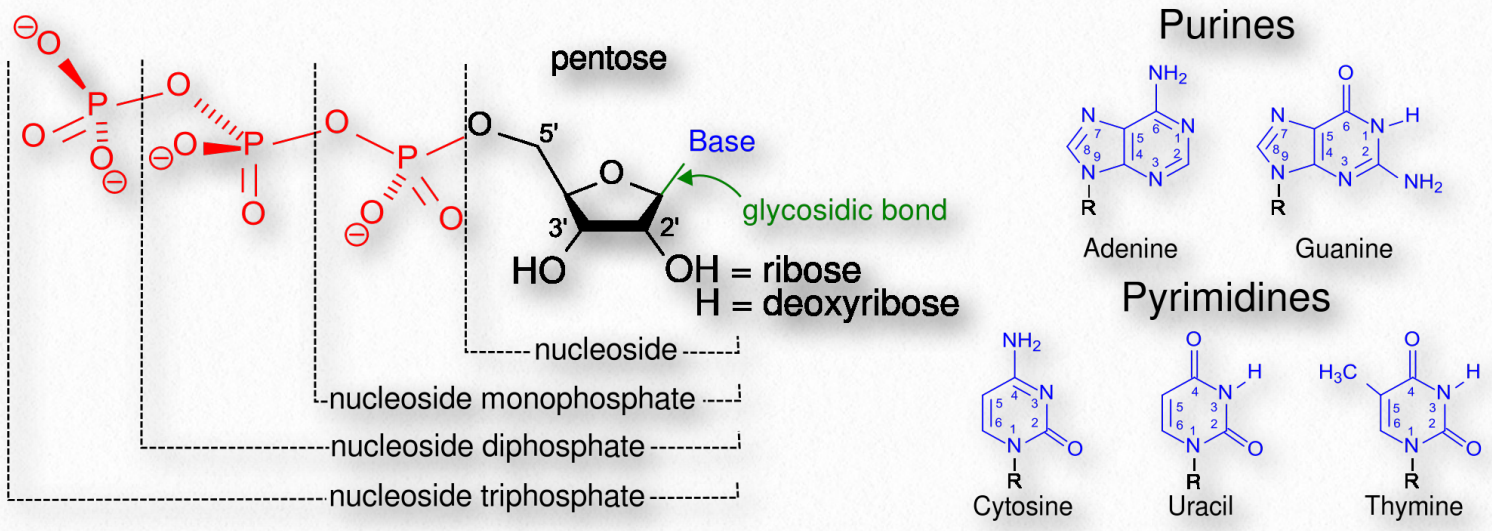


Figure 5.13 - Nucleotides, nucleosides, and bases

$$XTP + YDP \rightleftarrows XDP + YTP$$

where X = adenosine, cytidine, uridine, thymidine, or guanosine and Y can be any of these as well. Further, XTP and YDP can be any of the deoxynucleotides as well.

Last, an unusual way of synthesizing ATP by substrate level phosphorylation is via the reaction catalyzed by adenylate kinase

$$2\ ADP \rightleftarrows ATP + AMP$$

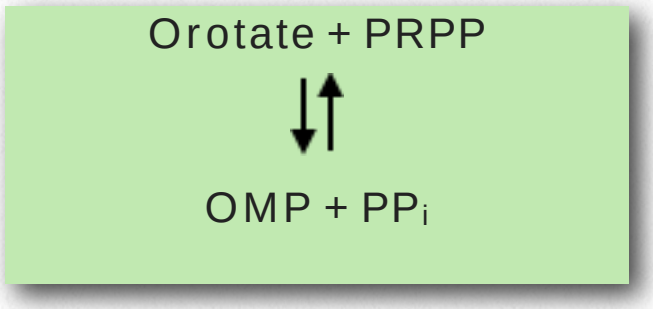
ATP source

This reaction is an important means of generating ATP when the cell doesn't have other sources of energy. Accumulation of AMP resulting from this reaction activates enzymes, such as phosphofructokinase, of glycolysis, which will catalyze reactions to give the cell additional, needed energy.

It is important to note that enzymes cannot make reactions happen that are energetically unfavorable. Enzymes speed reactions, but do not change their direction. Cells are thus bound by the rules of Gibbs free energy. So, how do energetically unfavorable reactions happen in a cell?

Reaction coupling

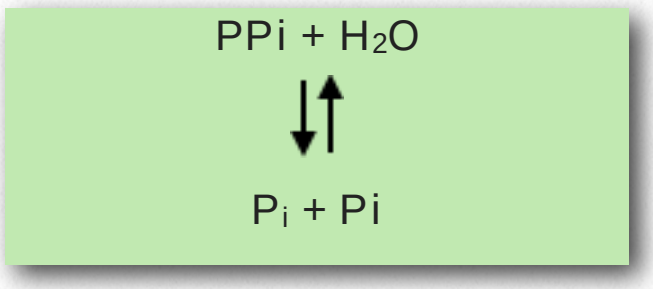
Reactions that are energetically unfavorable, can be made favorable by coupling them with the hydrolysis of ATP, a very energetically favorable reaction. There are numerous parallels in the "real world." Movement of automobiles is energetically unfavorable, but coupling movement of the automobile to oxidation of gasoline makes an unfavorable process favorable. Another approach to making an unfavorable reaction favorable is to manipulate the concentration of reactants and products. Consider the reaction below, which occurs in pyrimidine nucleotide metabolism (top of next page):



The ΔG°' for this reaction is -0.8 kJ/mol, meaning that if one starts with equal concentrations of reactants and products, at equilibrium, there will be a small excess of products. In the cell, however, this reaction moves strongly to the right (ΔG = very negative). Given that the ΔG°' is very close to zero, a very negative ΔG can only occur if the concentrations of reactants and products are altered, since

$$\Delta G = \Delta G^{\circ\prime} + RT\ln \frac{[OMP][PP_i]}{[Orotate][PRPP]}$$

Manipulation is exactly what happens here. The key item whose concentration is adjusted in this reaction is the pyrophosphate (PP_i). This is possible because cells contain an enzyme called pyrophosphorylase that catalyzes the following reaction



Hydrolysis of pyrophosphate is very energetically favored, causing the PPi produced in the reaction to be quickly hydrolyzed. As a result, the concentration of PP_i in the cell is kept very low. A low concentration of a product (PP_i) causes the natural log (ln) term of the orotate equation to become more negative, driving the ΔG term for the overall reaction to become much more negative.

Pushing and pulling

Reactions that yield pyrophosphate as a product are produced in the synthesis of DNA and RNA, as well as many other molecules. As shown in the previous example, this pyrophosphate is rapidly hydrolyzed, causing the overall reaction to move in the direction of pyrophosphate production. When reactants are removed/reduced in a metabolic reaction to decrease the concentration of a product, we say that the reaction is "pulled", to represent the increase in the forward reaction as a result of product depletion.

Pushing happens when reactants in a reaction are added/increased. This too has the effect of reducing the ΔG of a reaction and making it more favorable because the ratio of [Products]/[Reactants] is decreased with increasing [Reactants]. Pushing and pulling of reactions are additional tools for cells to overcome energy barriers, just like coupling energetically favorable processes to energetically unfavorable ones.

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Oh Delta G

To the tune of "*Danny Boy*"

Metabolic Melodies Website HERE

Oh Delta G - the change in Gibbs free energy
Can tell us if a process will advance
'Cause if the value's less than naught it translates that
Reverse reactions haven't got a chance

But when the sign is plus it is the opposite
And then the backwards happens all the time
A factor is the standard Gibbs free energy
So don't forget about the Delta G naught prime

Recording by Tim Karplus
Lyrics by Kevin Ahern

The Cell's Lament

To the tune of "*Yesterday*"
Metabolic Melodies Website HERE

Woe is me
My substrates are losing entropy
Causing gains in Gibbs free energy
Oh I can't lose no en - tro- py

Re-a-lly
I could use a source of enthalpy
To combat the rise in Delta G
Oh I believe in enthalpy

I crave en-er-gy
Don't you see?
It's getting worse
My re-actions all
Soon will stall
And then rever-r-r-se

ATP
It's the metabolic currency
Guess I'll spend a bit judiciously
To help reduce the Delta G
Help reduce the Delta G

Recording by Tim Karplus
Lyrics by Kevin Ahern

Energy: Electron Transport & Oxidative Phosphorylation

In eukaryotic cells, the vast majority of ATP synthesis occurs in the mitochondria in a process called oxidative phosphorylation. Even plants, which generate ATP by photophosphorylation in chloroplasts, contain mitochondria for the synthesis of ATP through oxidative phosphorylation.

Oxidative phosphorylation is linked to a process known as electron transport (Figure 5.14). The electron transport system, located in the inner mitochondrial membrane, transfers electrons donated by the reduced electron carriers NADH and $FADH_2$ (obtained from glycolysis, the citric acid cycle or fatty acid oxidation) through a series of electrons acceptors, to oxygen. As we shall see, movement of electrons through complexes of the electron transport system essentially "charges" a battery that is used to make ATP in oxidative phosphorylation. In this way, the oxidation of sugars and fatty acids is coupled to the synthesis

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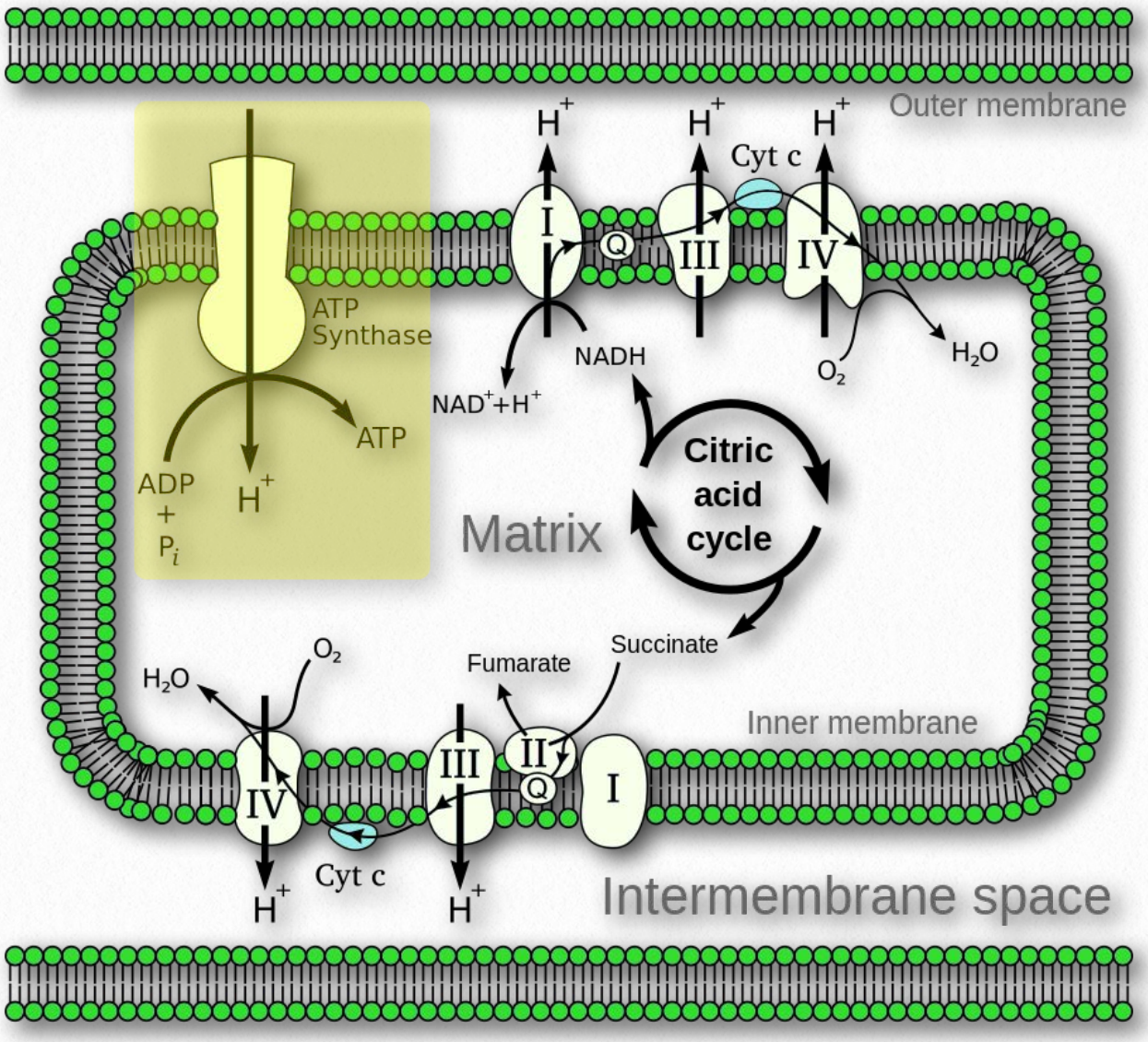

Figure 5.14 - Overview of electron transport (bottom left and top right) and oxidative phosphorylation (top left - yellow box) in the mitochondrion

of ATP, effectively extracting energy from food.

Chemiosmotic model

Dr. Peter Mitchell introduced a radical proposal in 1961 to explain the mechanism by which mitochondria make ATP. It is known as the chemiosmotic hypothesis and has been shown over the years to be correct. Mitchell proposed that synthesis of ATP in mitochondria depends on an electrochemical gradient, across the mitochondrial inner membrane, that arises ultimately from the energy of reduced electron carriers, $NADH$ and $FADH_2$.

Electron transport

Further, the proposal states that the gradient is created when $NADH$ and $FADH_2$ transfer their electrons to an electron transport system (ETS) located in the inner mitochondrial membrane. Movement of electrons through a series of of electron carriers is coupled to the pumping of protons out of the mitochondrial matrix across the inner mitochondrial membrane into the space between the inner and outer membranes. The result is creation of a gradient of protons whose potential energy can be used to make ATP. Electrons combine with oxygen and protons at the end of the ETS to make water.

ATP synthase

In oxidative phosphorylation, ATP synthesis is accomplished as a result of protons re-entering the mitochondrial matrix *via* the transmembrane ATP synthase complex, which combines ADP with inorganic phos-

phate to make ATP. Central to the proper functioning of mitochondria through this process is the presence of an intact mitochondrial inner membrane impermeable to protons.

Tight coupling

When this is the case, tight coupling is said to exist between electron transport and the synthesis of ATP (called oxidative phosphorylation). Chemicals which permeabilize the inner mitochondrial membrane to protons cause *uncoupling*, that is, they allow the protons to leak back into the mitochondrial matrix, rather than through the ATP synthase, so that the movement of electrons through the ETS is no longer linked to the synthesis of ATP.

Power plants

Mitochondria are called the power plants of the cell because most of a cell's ATP is produced there in the process of oxidative phosphorylation. The mechanism by which ATP is made in oxidative phosphorylation is one of the most interesting in all of biology.

Considerations

The process has three primary considerations. The first is electrical – electrons from reduced electron carriers, such as NADH and $FADH_2$, enter the electron transport system *via* Complex I and II, respectively. As seen in Figure 5.16 and Figure 5.17, electrons move from one complex to the next, not unlike the way they move through an electrical circuit. Such movement occurs a a result of a set of reduction-oxidation (redox) reactions with electrons moving from a more nega-

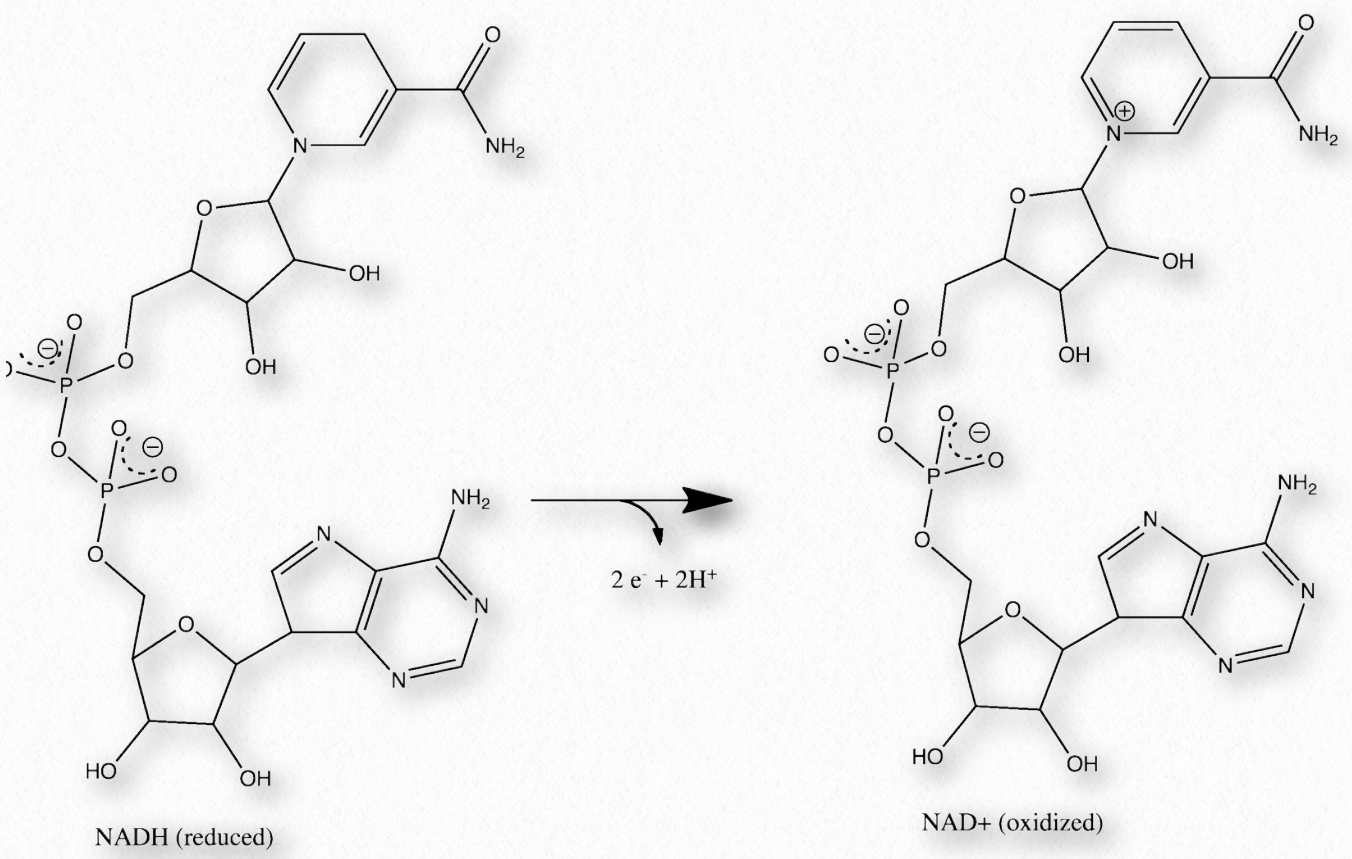

Figure 5.15 - Loss of electrons by NADH to form NAD^+. Relevant reactions occur in the top ring of the molecule.

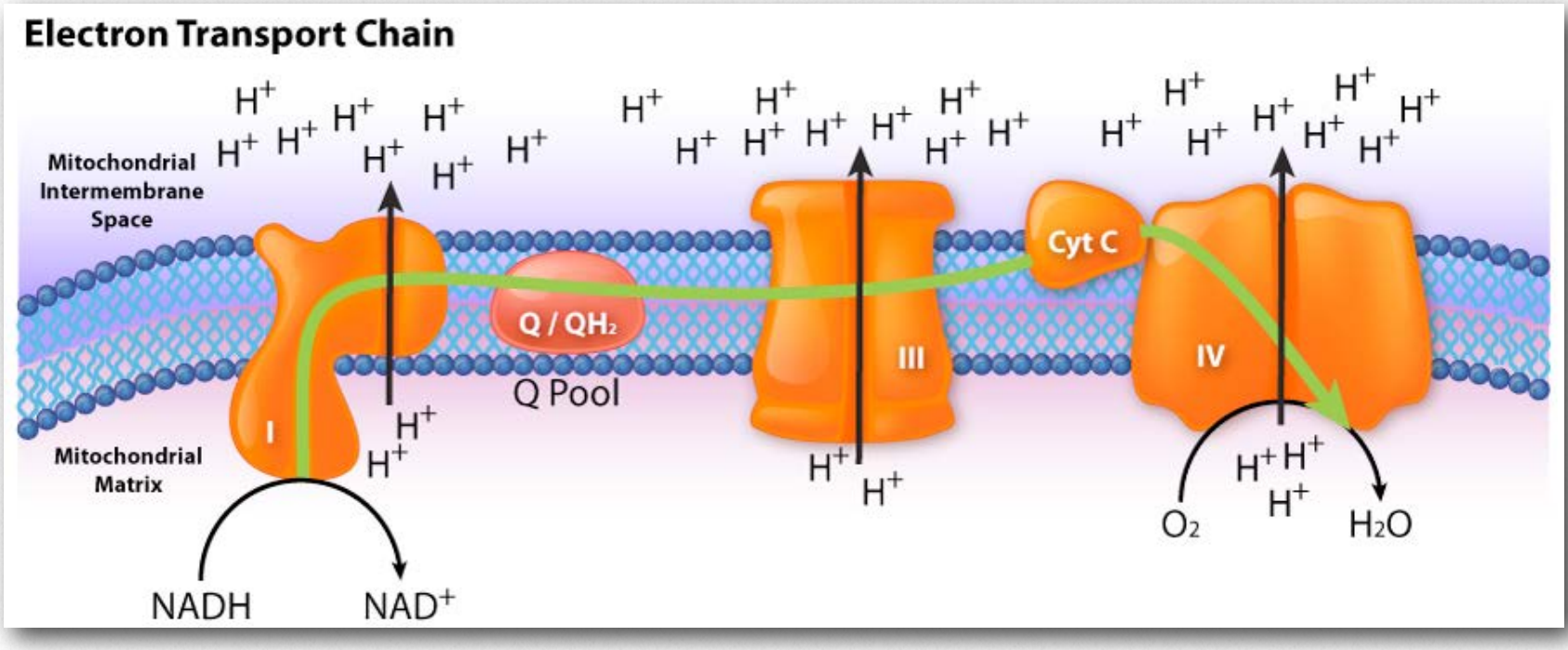

Figure 5.16 - Flow of electrons from NADH into the electron transport system. Entry is through complex I

Image by Aleia Kim

tive reduction potential to a more positive one.

One can think of this occurring as a process where carriers "take" electrons away from complexes with lower reduction potential, much the way a bully takes lunch money from a smaller child. In this scheme, the biggest "bully" is oxygen in Complex IV. Electrons gained by a

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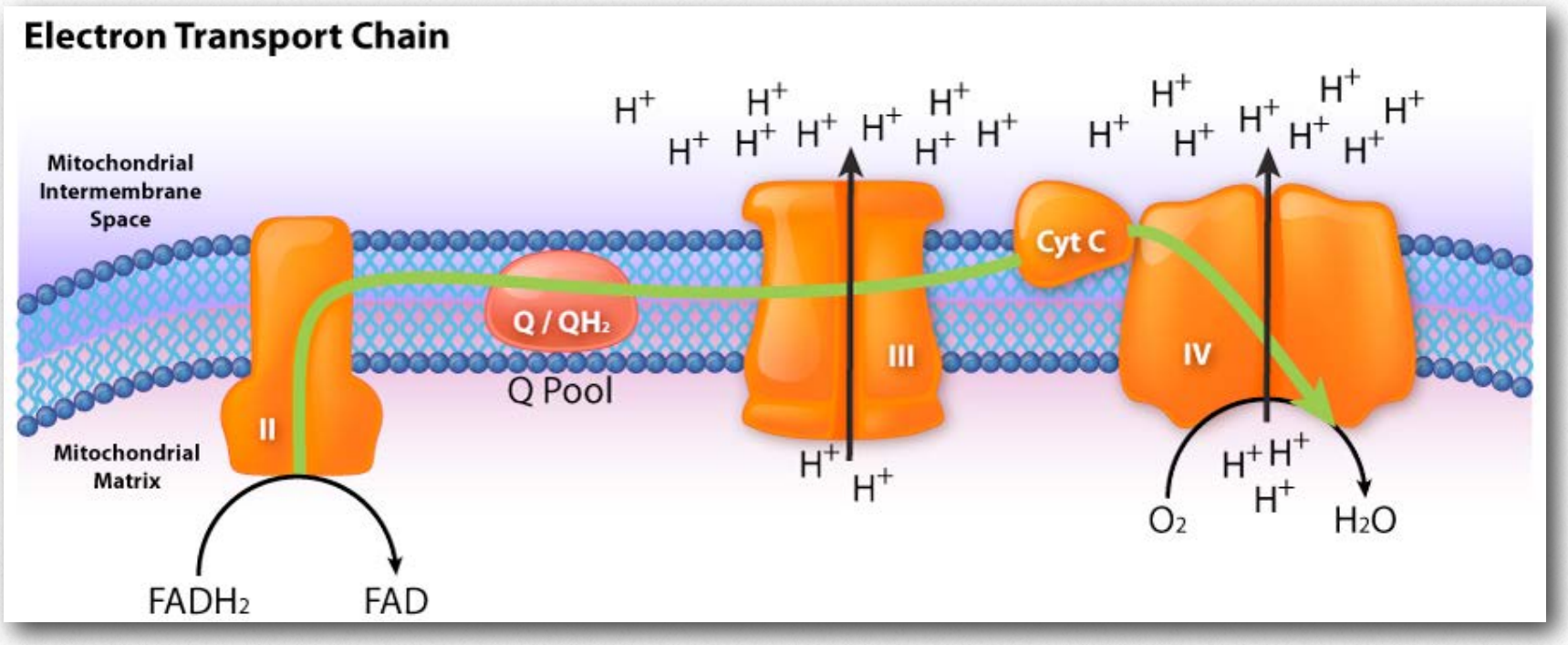

Figure 5.17 - Flow of electrons from $FADH_2$ into the electron transport chain. Entry is through complex II.

Image by Aleia Kim

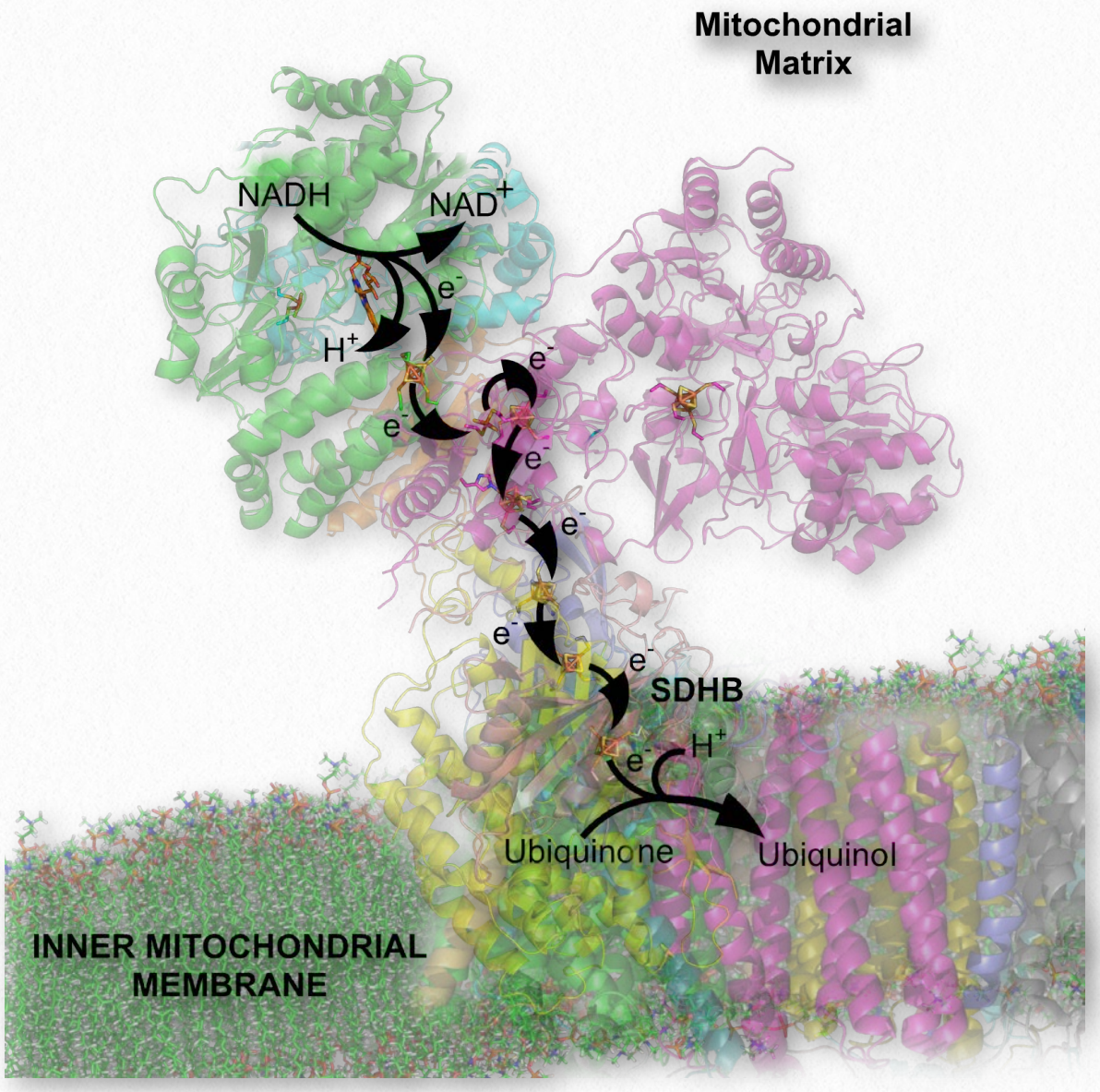

Figure 5.18 - Complex I embedded in the inner mitochondrial membrane. The mitochondrial matrix at at the top

Wikipedia

carrier cause it to be reduced, whereas the carrier giving up the electrons is oxidized.

Entry of electrons to system

Movement of electrons through the chain begins either by 1) transfer from NADH to Complex I (Figure 5.16) or 2) movement of electrons through a covalently bound $FADH_2$ (Figure 5.17) in the membrane-bound succinate dehydrogenase (Complex II). (An alternate entry point for electrons from $FADH_2$ is the Electron Transferring Flavoprotein *via* the electron-transferring-flavoprotein dehydrogenase, not shown).

Traffic cop

Both Complex I and II pass electrons to the inner membrane's coenzyme Q (CoQ - Figures 5.18 & 5.19). In each case, coenzyme Q accepts electrons in pairs and passes them off to Complex III ($CoQH_2$-cytochrome c reductase) singly. Coenzyme Q thus acts as a traffic cop, regulating the flow of electrons through the ETS.

Docking station

Complex III is a docking station or interchange for the incoming electron carrier (coenzyme Q) and the outgoing carrier (cytochrome c). Movement of electrons from Coenzyme Q to Complex III and then to cytochrome C occurs as a result of what is referred to as the Q-cycle (see below).

Complex III acts to ferry electrons from CoQ to cytochrome c. Cytochrome c takes one electron from Complex III and passes it to Complex IV (cytochrome oxidase). Complex IV is the final protein recipient of the electrons. It passes them to molecular oxygen (O_2) to make two molecules of water. Making two water

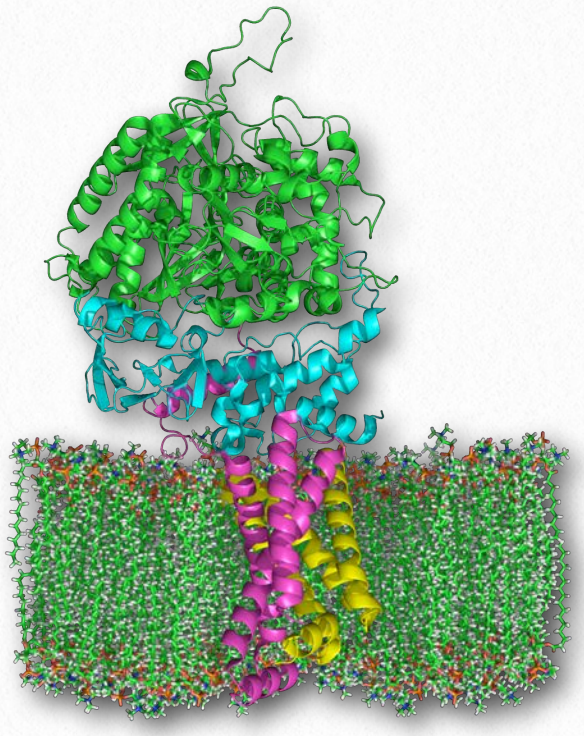

Figure 5.19 - Complex II embedded in inner mitochondrial membrane. Matrix is up.

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molecules requires four electrons, so Complex IV must accept, handle, and pass to molecular oxygen four separate electrons, causing the oxidation state of oxygen to be sequentially changed with addition of each electron.

Proton pumping

As electrons pass through complexes I, III, and IV, there is a release of a small amount of energy at each step, which is used to pump protons from the mitochondrial matrix (inside of mitochondrion) and deposit them in the intermembrane space (between the inner and outer membranes of the mitochondrion). The effect of this redistribution is to increase the electrical and chemical potential across the membrane.

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Potential energy

As discussed earlier, electrochemical gradients have potential energy. Students may think of the process as "charging the battery." Just like a charged battery, the potential arising from the proton differential across the membrane can be used to do things. In the mitochondrion, what the proton gradient does is facilitate the production of ATP from ADP and P_i. This process is known as oxidative phosphorylation, because the phosphorylation of ADP to ATP is dependent on the oxidative reactions occurring in the mitochondria.

Having understood the overall picture of the synthesis of ATP linked to the movement of electrons through the ETS, we will take a closer look at the individual components of the ETS.

Complex I

Complex I (also called NADH:ubiquinone oxidoreductase or NADH dehydrogenase (ubiquinone)) is the electron acceptor from NADH in the electron transport chain and the largest complex found in it.

Complex I contains 44 individual polypeptide chains, numerous iron-sulfur centers, a molecule of flavin mononucleotide (FMN) and has an L shape with

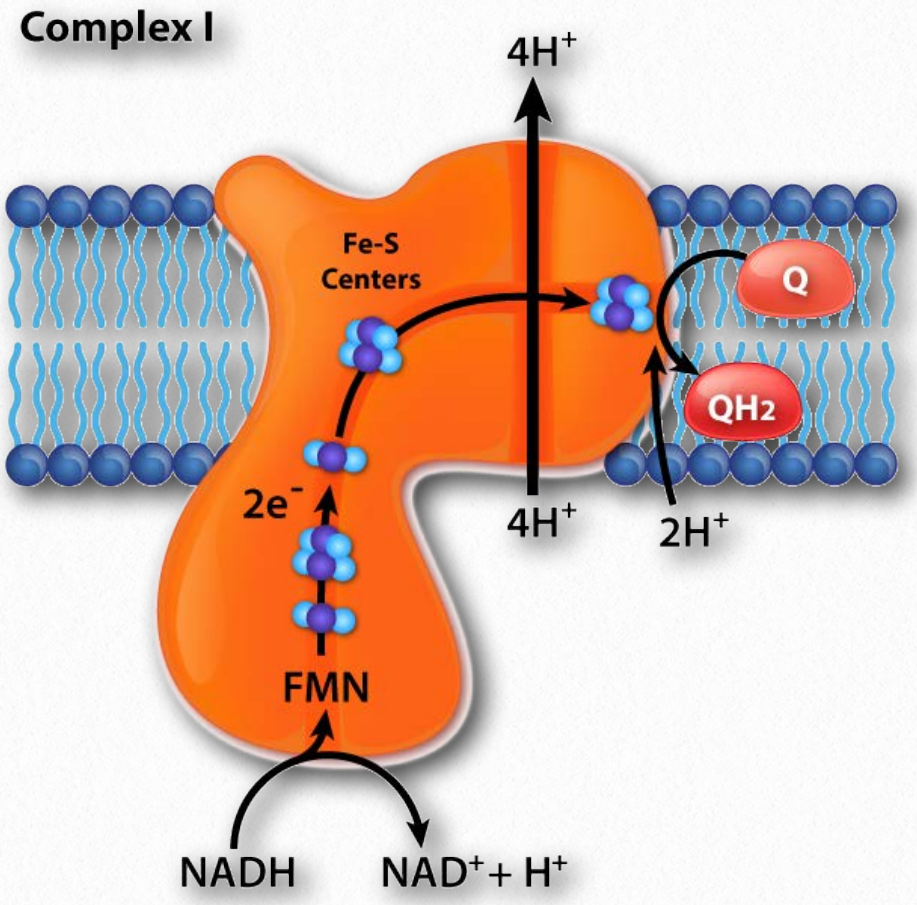


Figure 5.20 - Movement of electrons through complex I from NADH to coenzyme Q. The mitochondrial matrix is at the bottom

Image by Aleia Kim

about 60 transmembrane domains. In the process of electron transport through it, four protons are pumped across the inner membrane into the intermembrane space and electrons move from NADH to coenzyme Q, converting it from ubiquinone (no electrons) to ubiquinol (gain of two electrons). An intermediate form, ubisemiquinone (gain of one electron), is found in the Q-cycle.

Electrons travel through the complex *via* seven primary iron sulfur centers. The best known inhibitor of the complex, rotenone, works by binding to the CoQ binding site. Other inhibitors include ADP-ribose (binds to the NADH site) and piericidin A (rotenone analog). The process of electron transfer through complex I is reversible and when this occurs, superoxide (a reactive oxygen species) may be readily generated.

Complex II

Complex II (also called succinate dehydrogenase or succinate-coenzyme Q reductase) is a membrane bound enzyme of the citric acid cycle that plays a role in the electron transport process, transferring electrons from its covalently bound $FADH_2$ to coenzyme Q. The process occurs, as shown in Figure 5.20 and Figure 5.21, with transfer of electrons from succinate to FAD to

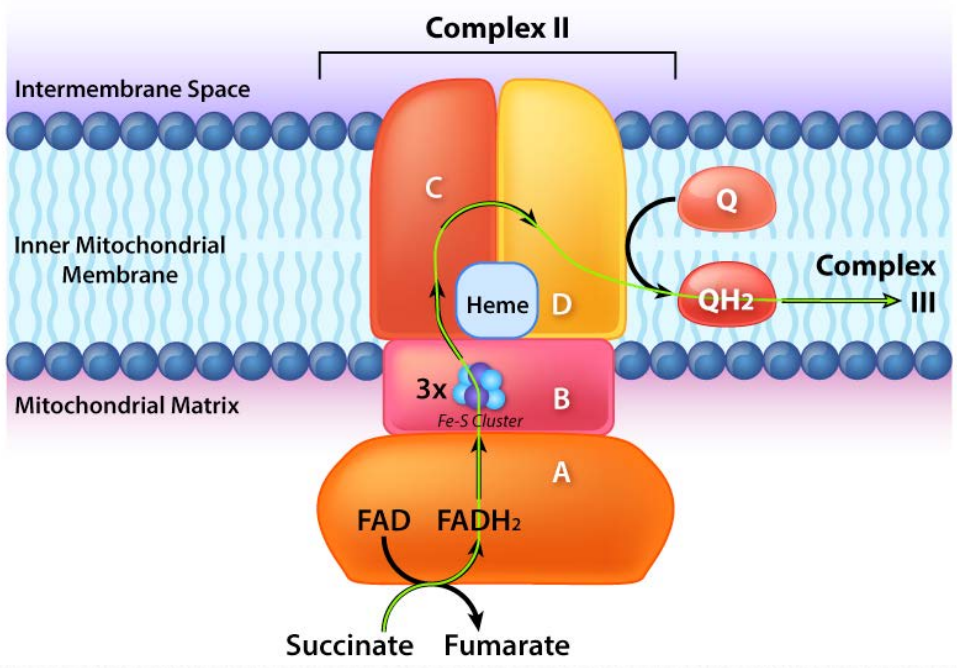


Figure 5.21 - Movement of electrons from succinate through complex II (A->B->C->D->Q). Mitochondrial matrix on bottom.

Image by Aleia Kim

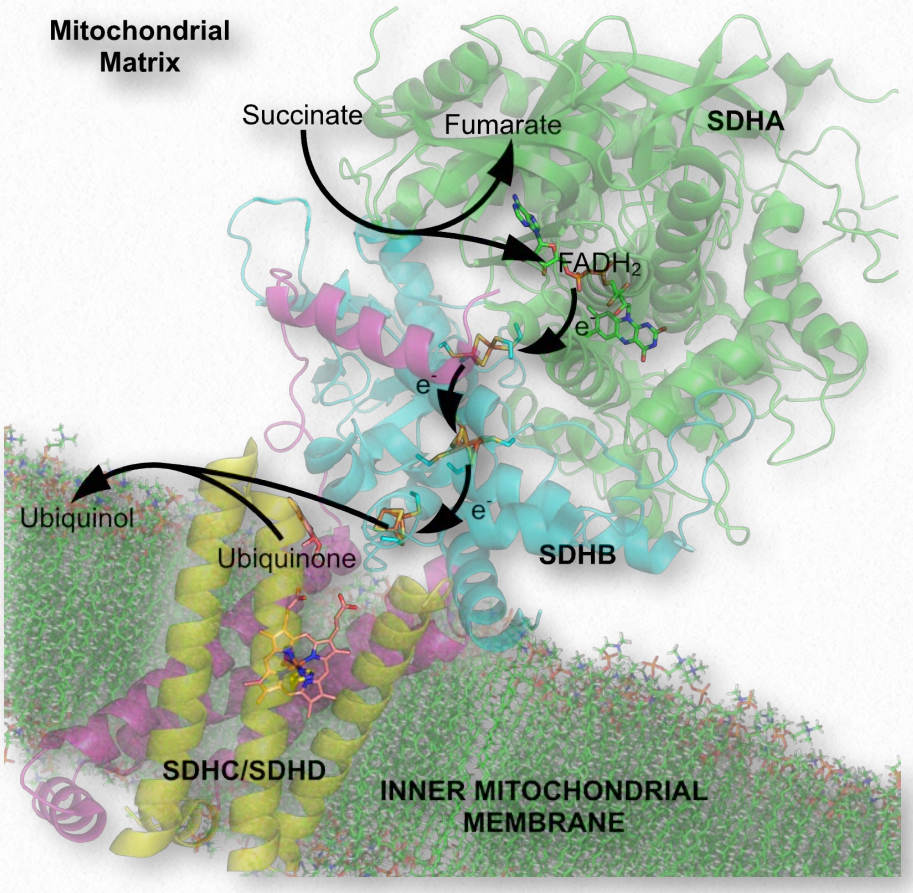


Figure 5.22 - Complex II in inner mitochondrial membrane showing electron flow. Matrix is up.

Wikipedia

form $FADH_2$ and fumarate. $FADH_2$, in turn, donates electrons to a relay system of iron-sulfur groups and they ultimately reduce ubiquinone (CoQ) along with two protons from the matrix to ubiquinol. The role of the heme group in the process is not clear. Inhibitors of the process include carboxin, malonate, malate, and oxaloacetate. The role of citric acid cycle intermediates as inhibitors is thought to be due to inhibition of the reversal of the transfer process which can produce superoxide.

Coenzyme Q

Coenzyme Q (Figure 5.23) is a 1,4 benzoquinone whose name is often given as Coenzyme Q_{10}, CoQ, or Q_{10}. The 10 in the name refers to the number of isoprenyl units it contains that anchor it to the mitochondrial inner membrane. CoQ is a vitamin-like lipid substance found in most eukaryotic cells as a component of the electron transport system. The requirement for CoQ increases with increasing energy needs of cells, so the highest concentrations of CoQ in the body are found in tissues that are the most metabolically active - heart, liver, and kidney.

Three forms

CoQ is useful because of its ability to carry and donate electrons and particularly because it can exist in forms with two extra electrons (fully reduced - ubiquinol), one extra electron (semi-reduced - ubisemiquinone),

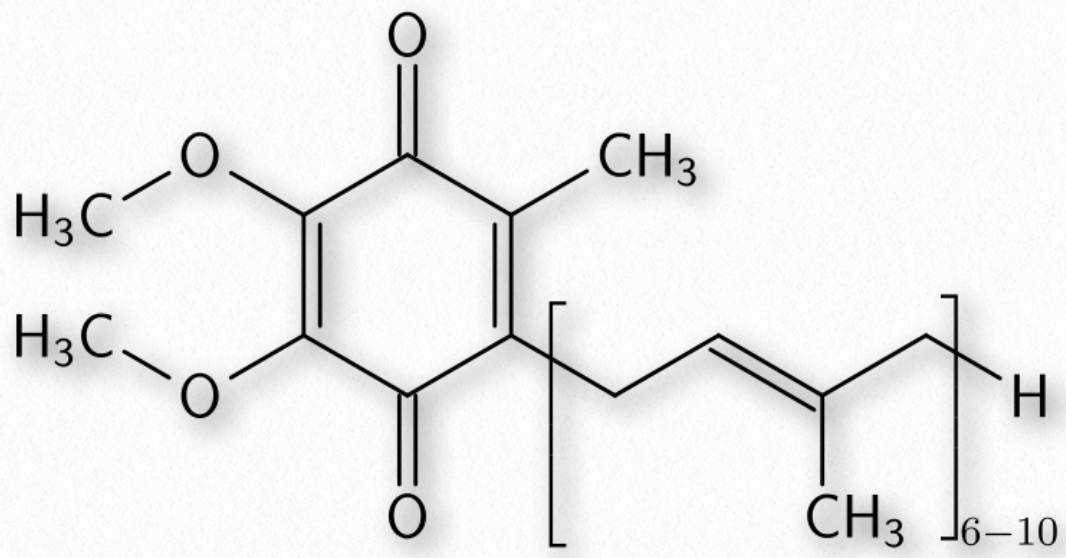


Figure 5.23 - Coenzyme Q

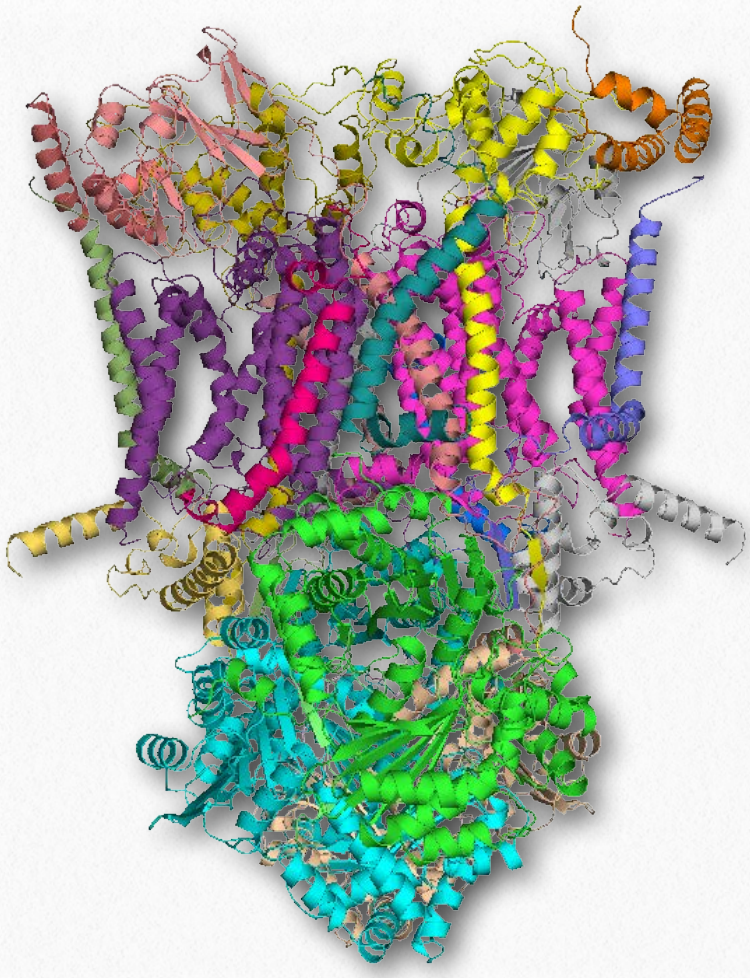


Figure 5.24 - Complex III

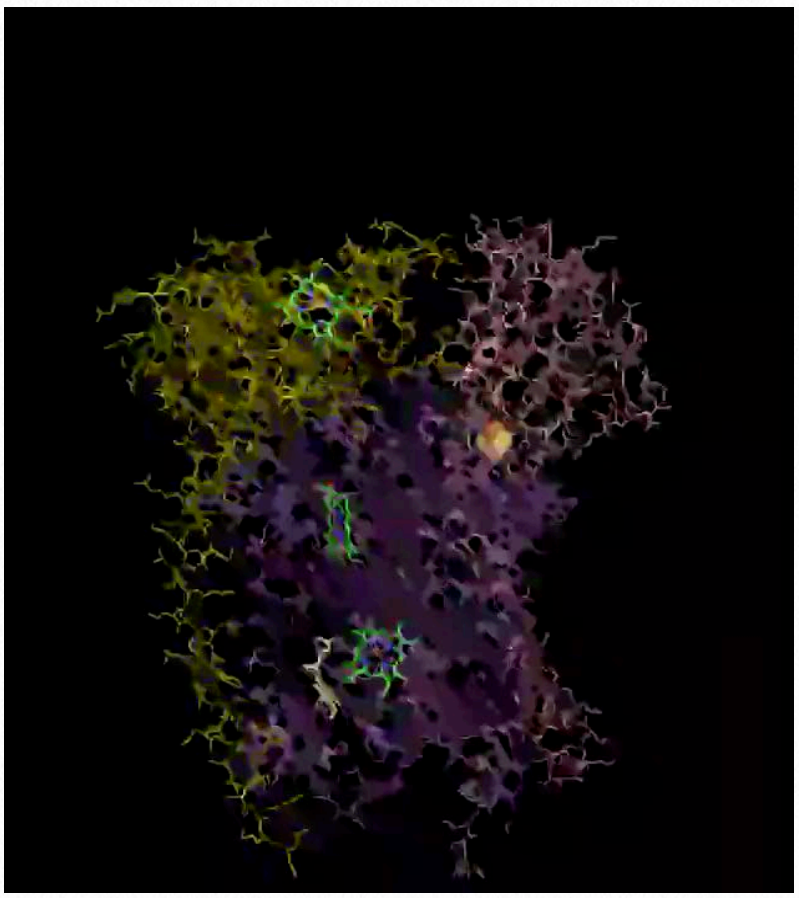
Wikipedia

or no extra electrons (fully oxidized - ubiquinone). This ability allows CoQ to provide transition between the first part of the electron transport system that moves electrons in pairs and the last part of the system that moves electrons one at a time.

Complex III

Complex III (also known as coenzyme Q : cytochrome c — oxidoreductase or the cytochrome bc_1 complex - Figure 5.24) is the third electron accepting complex of the electron transport system. It is a transmembrane protein with multiple subunits present in the mitochondria of all aerobic eukaryotic organisms and and the cell membrane of almost all bacteria. The complex contains 11 subunits, a 2-iron ferredoxin, cytochromes b and c_1 and belongs to the family of oxidoreductase enzymes.

It accepts electrons from coenzyme Q in electron transport and passes them off to cytochrome c. In this cycle, known as the Q cycle, electrons arrive from CoQ in pairs, but get passed to cytochrome c individually. In the overall process, two protons are consumed from the matrix and four protons are pumped into the intermembrane space. Movement of electrons through the complex can be inhibited by antimycin A, myxothiazol, and stigmatellin. Complex III is also implicated in creation of superoxide (a reactive oxygen species) when electrons from it leak



Movie 5.2 - The Q-cycle

Wikipedia

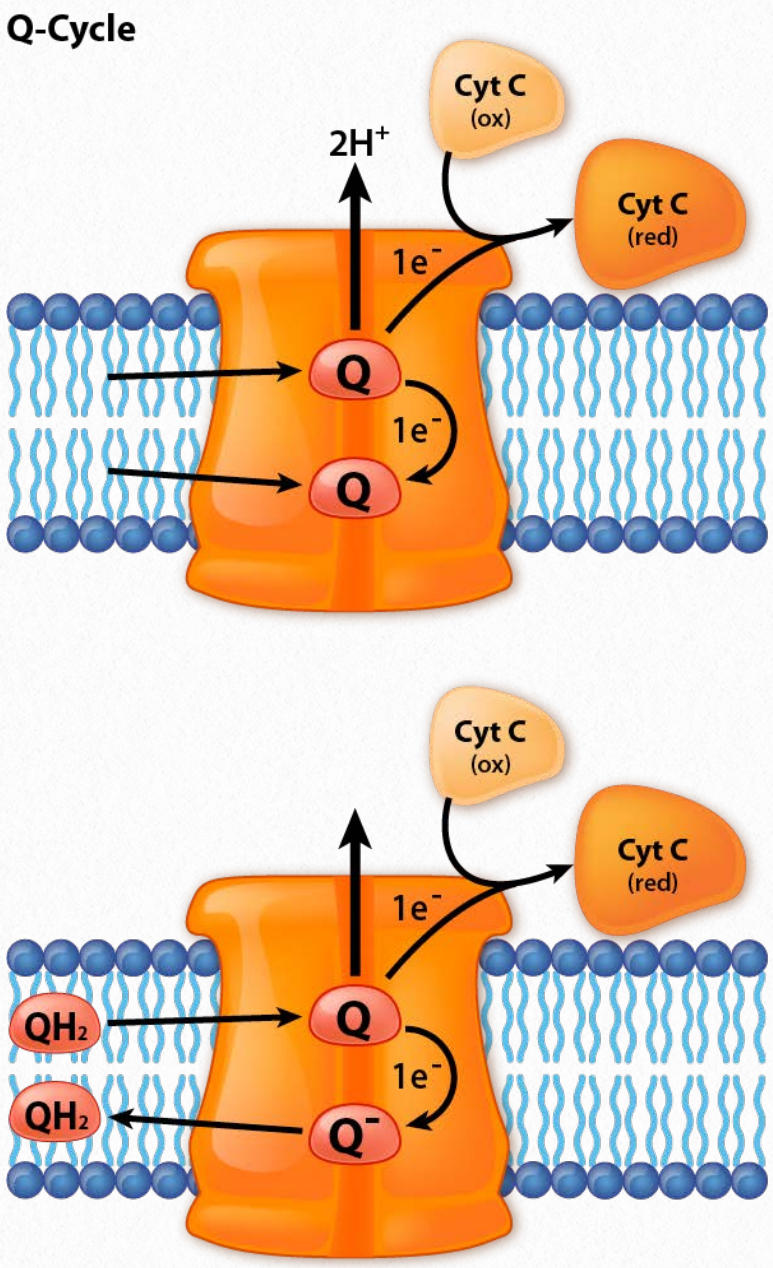


Figure 5.25 - The Q-cycle. Matrix is down.

Image by Aleia Kim

out of the chain of transfer. The phenomenon is more pronounced when antimycin A is present.

Q-cycle

In the Q-cycle, electrons are passed from ubiquinol (QH_2) to cytochrome c using Complex III as an intermediary docking station for the transfer. Two pair of electrons enter from QH_2 and one pair is returned to another CoQ to remake QH_2. The other pair is donated singly to two different cytochrome c molecules.

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Step one

The Q-cycle happens in a two step process. First, a ubiquinol ($CoQH_2$) and a ubiquinone (CoQ) dock at Complex III. Ubiquinol transfers two electrons to Complex III. One electron goes to a docked cytochrome c, reducing it and it exits (replaced by an oxidized cytochrome c). The other goes to the docked uniquinone to create the semi-reduced semiubiquinone ($CoQ.^-$) and leaving behind a ubiquinone, which exits. This is the end of step 1.

Step two

The gap left behind by the ubiquinone (Q) that departed is replaced by another ubiquinol (QH_2). It too donates two electrons to Complex III, which splits them. One goes to the newly docked oxidized cytochrome c, which is reduced and exits. The other goes to the ubisemiquinone. Two protons from the matrix combine with it to make another ubiquinol. It and the ubiquinone created by the electron donation exit Complex III and the process starts again. In the overall process, two protons are consumed from the matrix and four protons are pumped into the intermembrane space.

Cytochrome c

Cytochrome c (Figure 5.26) is a small (12,000 Daltons), highly conserved protein,

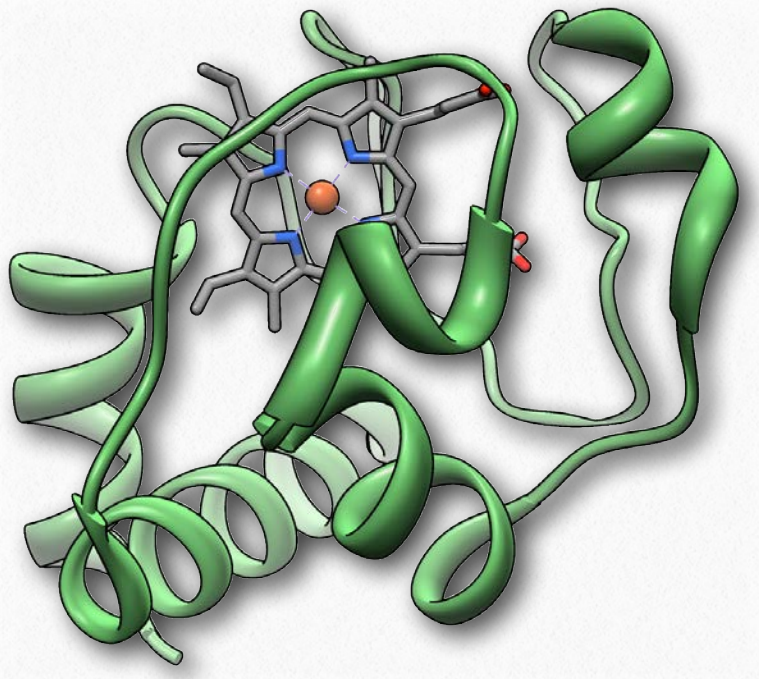

Figure 5.25 - Cytochrome c with bound heme Group

Wikipedia

from unicellular species to animals, that is loosely associated with the inner mitochondrial membrane where it functions in electron transport. It contains a heme group which is used to carry a single electron from Complex III to Complex IV. Cytochrome c also plays an important role in apoptosis in higher organisms. Damage to the mitochondrion that results in release of cytochrome c can stimulate assembly of the apoptosome and activation of the caspase cascade that leads to programmed cell death.

Complex IV

Complex IV, also known as cytochrome c oxidase is a 14 subunit integral membrane protein at the end of the electron transport chain (Figure 5.27). It is responsible for accepting one electron each from four cytochrome c proteins and adding them to molecular oxygen (O_2) along with four protons from the mitochondrial matrix to make two molecules of water. Four protons from the matrix are also pumped into the intermembrane space in the process. The complex has two molecules of heme, two cytochromes (a and a_3), and two copper centers (called CuA ad CuB). Cytochrome c docks near the CuA and donates an electron to it. The reduced CuA passes the electron to cytochrome a, which turns it over to the a_3-CuB center where the oxygen is reduced. The four electrons are thought to pass through the complex rapidly resulting in com-

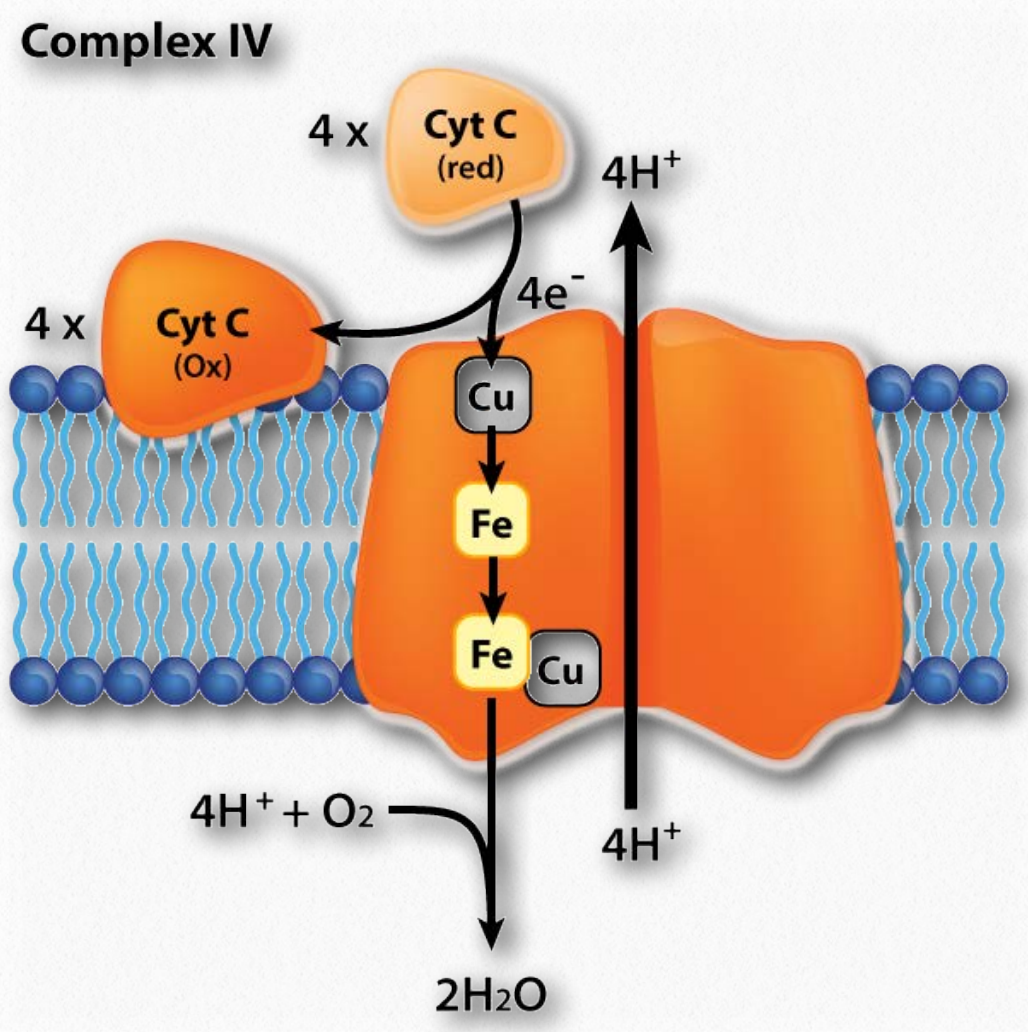

Figure 5.26 - Movement of electrons and protons through complex IV. Matrix is down

Image by Aleia Kim

plete reduction of the oxygen-oxygen molecule without formation of a peroxide intermediate or superoxide, in contrast to previous predictions.

Respirasome

There has been speculation for many years that a supercomplex of electron carriers in the inner membrane of the mitochondrion may exist in cells with individual carriers making physical contact with each other. This would make for more efficient transfer reactions, minimize the production of reactive oxygen species and be similar to metabolons of metabolic pathway enzymes, for which there is some evidence. Now, evidence appears to be accumulating that complexes I, III, and IV form a supercomplex, which has been dubbed the respirasome[1].

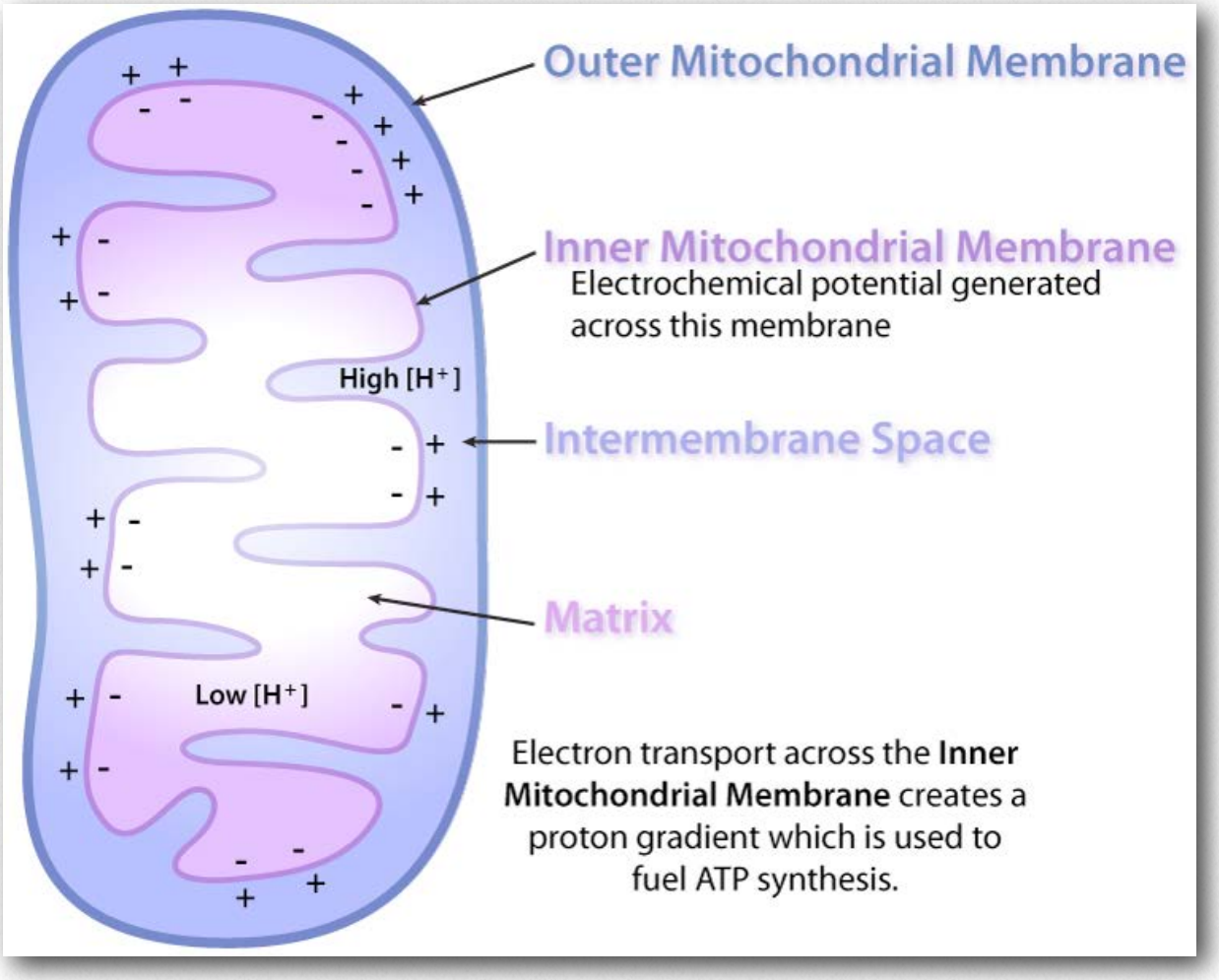

Figure 5.27 - Mitochondrial anatomy. Electron transport complexes and ATP synthase are embedded in the inner mitochondrial membrane

Image by Aleia Kim

Oxidative phosphorylation

The process of oxidative phosphorylation uses the energy of the proton gradient established by the electron transport system as a means of phosphorylating ADP to make ATP. The establishment of the proton gradient is dependent upon electron transport. If electron transport stops or if the inner mitochondrial membrane's impermeability to protons is compromised, oxidative phosphorylation will not occur because without the proton gradient to drive the ATP synthase, there will be no synthesis of ATP.

ATP synthase

The protein complex harvesting energy from the proton gradient and using it to make ATP from ADP is an enzyme that has several

names - Complex V, PTAS (Proton Translocating ATP Synthase), and ATP synthase (Figure 5.29). Central to its function is the movement of protons through it (from the intermembrane space back into the matrix). Protons will only provide energy to make ATP if their concentration is greater in the intermembrane space than in the matrix and if ADP is available.

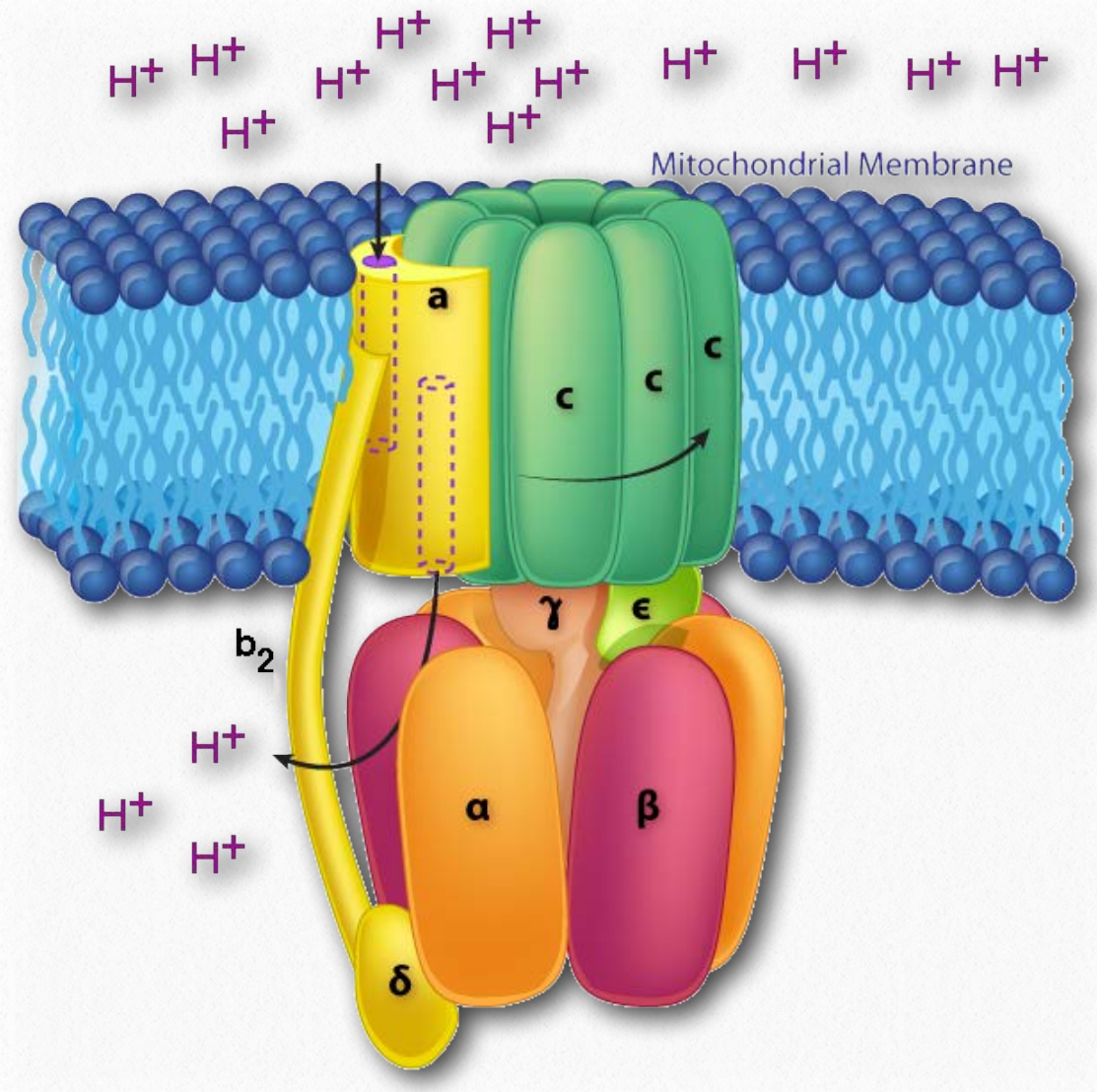

Figure 5.28 - ATP synthase. Protons pass from intermembrane space (top) through the complex and exit in the matrix (bottom).

Image by Aleia Kim

It is possible, in some cases, for the concentration of protons to be greater inside the matrix than outside of it. When this happens, the ATP synthase can run backwards, with protons moving from inside to out, accompanied by conversion of ATP to ADP + P_i. This is usually not a desirable circumstance and there are some controls to reduce its occurrence.

Normally, ATP concentration will be higher inside of the mitochondrion and ADP concentration be higher outside the mitochondrion. However, when the rate of ATP synthesis exceeds the rate of ATP usage, then ATP concentrations rise outside the mitochondrion and ADP concentrations fall everywhere.

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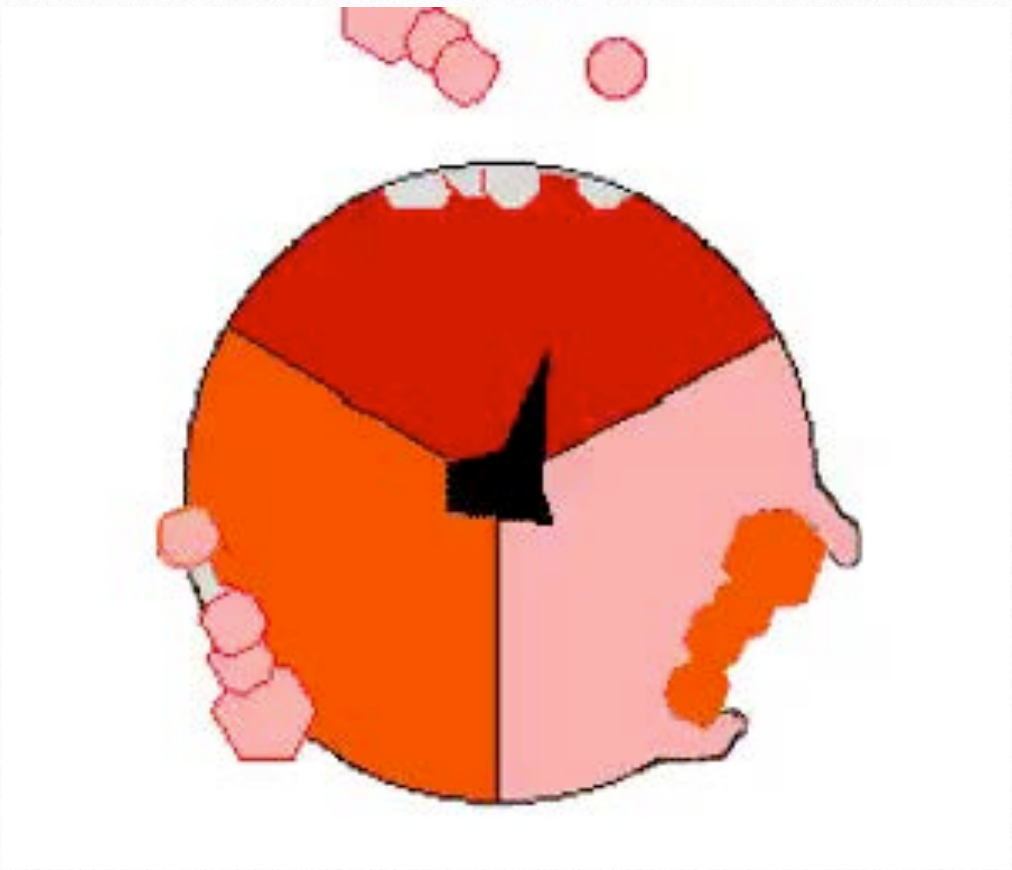
This may happen, for example, during periods of rest. It has the overall effect of reducing transport and thus lowering the concentration of ADP inside the matrix. Reducing ADP concentration in the matrix reduces oxidative phosphorylation and has effects on respiratory control (see HERE).

Another important consideration is that when ATP is made in oxidative phosphorylation, it is released into the mitochondrial matrix, but must be trans-

ported into the cytosol to meet the energy needs of the rest of the cell. This is accomplished by action of the adenine nucleotide translocase, an antiport that moves ATP out of the matrix in exchange for ADP moving into the matrix. This transport system is driven by the concentrations of ADP and ATP and ensures that levels of ADP are maintained within the mitochondrion, permitting continued ATP synthesis.

One last requirement for synthesis of ATP from ADP is that phosphate must also be imported into the matrix. This is accomplished by action of the phosphate translocase, which is a symport that moves phosphate into the mitochondrial matrix along with a proton.



Movie 5.3 - ATP Synthase - ADP + Pi (pink) and ATP (red). The view is end-on from the cytoplasmic side viewing the β subunits

There is evidence that the two translocases and ATP synthase may exist in a complex, which has been dubbed the ATP synthasome.

In summary, the electron transport system charges the battery for oxidative phosphorylation by pumping protons out of the mitochondrion. The intact inner membrane of the mitochondrion keeps the protons out, except for those that re-enter through ATP Synthase. The ATP Synthase allows protons to re-enter the mitochondrial matrix and harvests their energy to make ATP.

ATP synthase mechanism

The ATP Synthase itself is an amazing nanomachine that makes ATP using a gradient of protons flowing through it from the intermembrane space back into the matrix. It is not easy to depict in a single image what the synthase does. Figure 5.31 and Figure 5.32 illustrate the multi-subunit nature of this membrane protein, which acts like a turbine at a hydroelectric dam. The movement of protons through the ATP Synthase c-ring causes it and the γ-ε

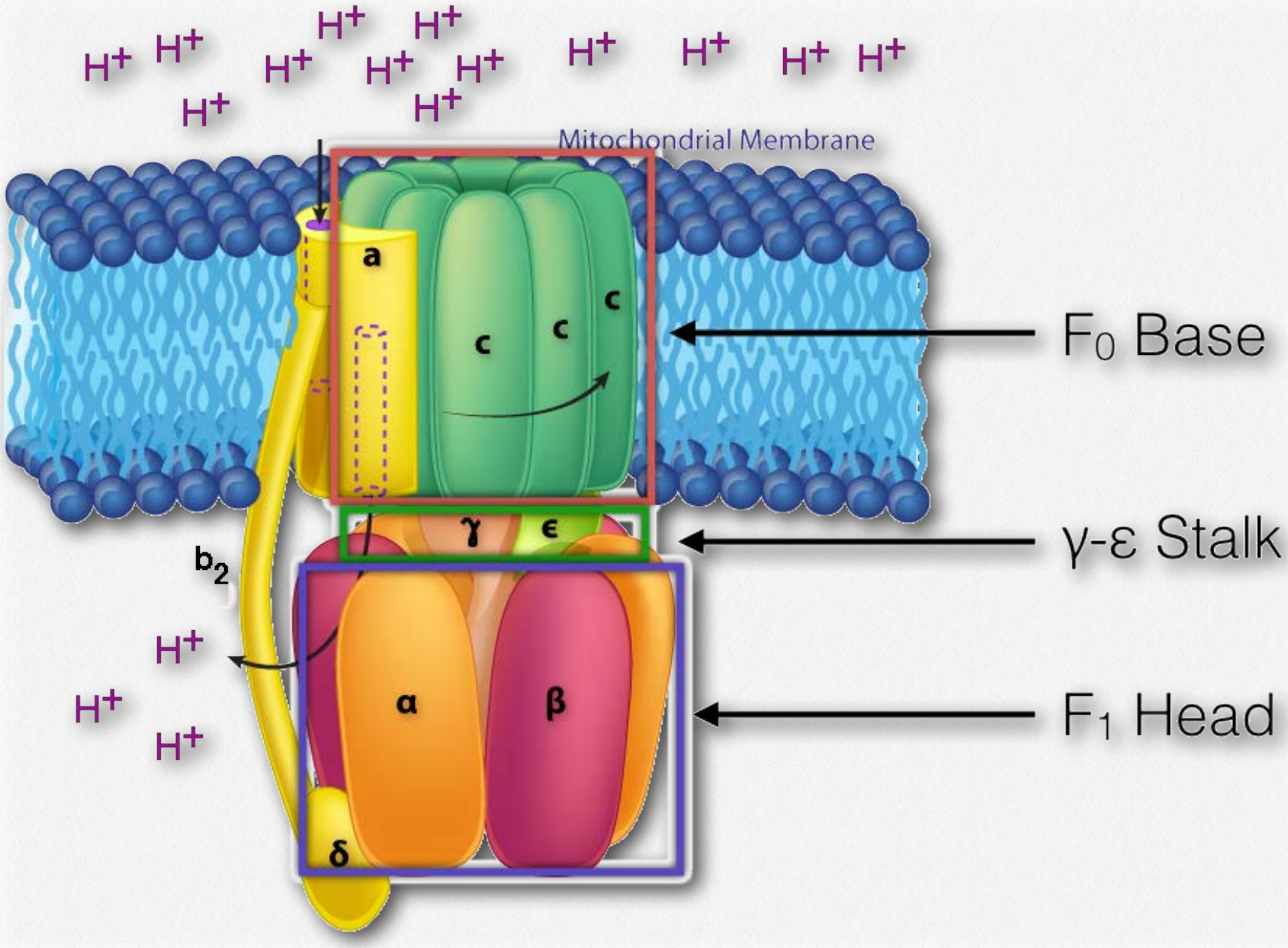


Figure 5.29 - Important structural features of the ATP synthase

Image by Aleia Kim

stalk attached to it to turn. It is this action that is necessary for making ATP.

In ATP Synthase, the spinning components, or rotor, are the membrane portion (c ring) of the F_0 base and the γ-ε stalk, which is connected to it. The γ-ε stalk projects into the F_1 head of the mushroom structure. The F_1 head contains the catalytic ability to make ATP. The F_1 head is hexameric in structure with paired α and β proteins arranged in a trimer of dimers. ATP synthesis occurs within the β subunits.

Rotation of γ unit

Turning of the γ shaft (caused by proton flow) inside the α-β trimer of the F_1 head causes each set of β proteins to change structure slightly into three different forms called Loose, Tight, and Open (L,T,O - Figure 5.31). Each of these forms has a function.

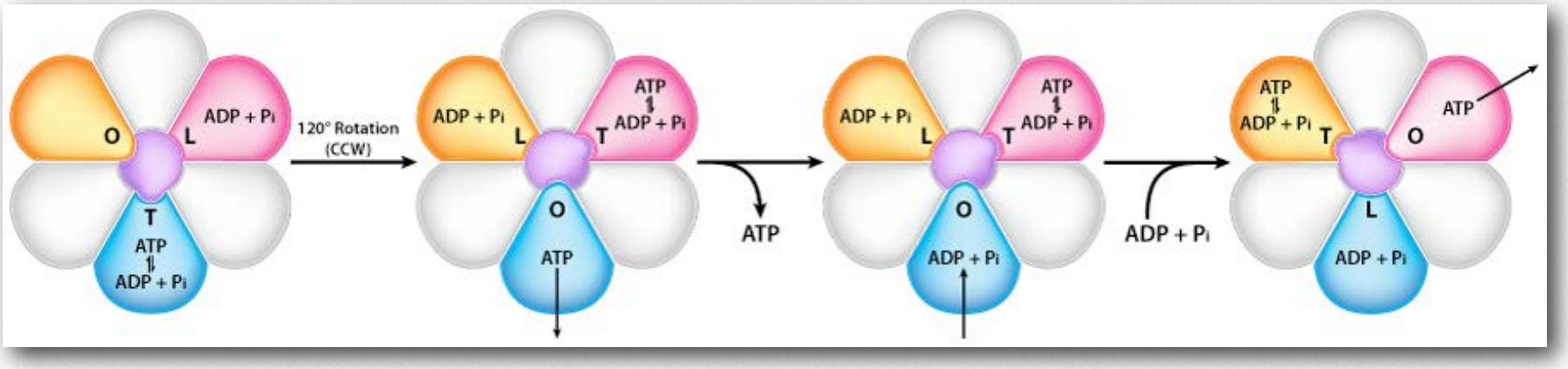


Figure 5.30 - Loose (L), Tight (T), and Open (O) structures of the F_1 head of ATP synthase. Change of structure occurs by rotation of γ-protein (purple) in center as a result of proton movement. Individual α and β units do not rotate

Image by Aleia Kim

The Loose form binds ADP + P_i. The Tight form "squeezes" them together to form the ATP. The Open form releases the ATP into the mitochondrial matrix. Thus, as a result of the proton flow through the ATP synthase, from the intermembrane space into the matrix, ATP is made from ADP and P_i.

Respiratory control

When a mitochondrion has an intact inner membrane and protons can only return to the matrix by passing through the ATP synthase, the processes of electron transport and oxidative phosphorylation are said to be tightly coupled.

Interdependence

In simple terms, tight coupling means that the processes of electron transport and oxidative phosphorylation are interdependent. Without electron transport going on in the cell, oxidative phosphorylation will soon stop. The reverse is also true, because if oxidative phosphorylation stops, the proton gradient will not be dissipated as it is being built by the electron transport system and will grow larger and larger. The greater the gradient, the greater the energy needed to pump protons out of the mitochondrion. Eventually, if nothing relieves the gradient, it becomes too large and the energy of electron transport is insufficient to perform the pumping. When pumping stops, so too does electron transport.

ADP dependence

Another relevant point is that ATP synthase is totally dependent upon a supply of ADP. In the absence of ADP, the ATP synthase stops functioning and when it stops, so too does movement of protons back into the mitochondrion. With this information, it is possible to understand the link between energy usage and metabolism. The root of this, as noted, is respiratory control.

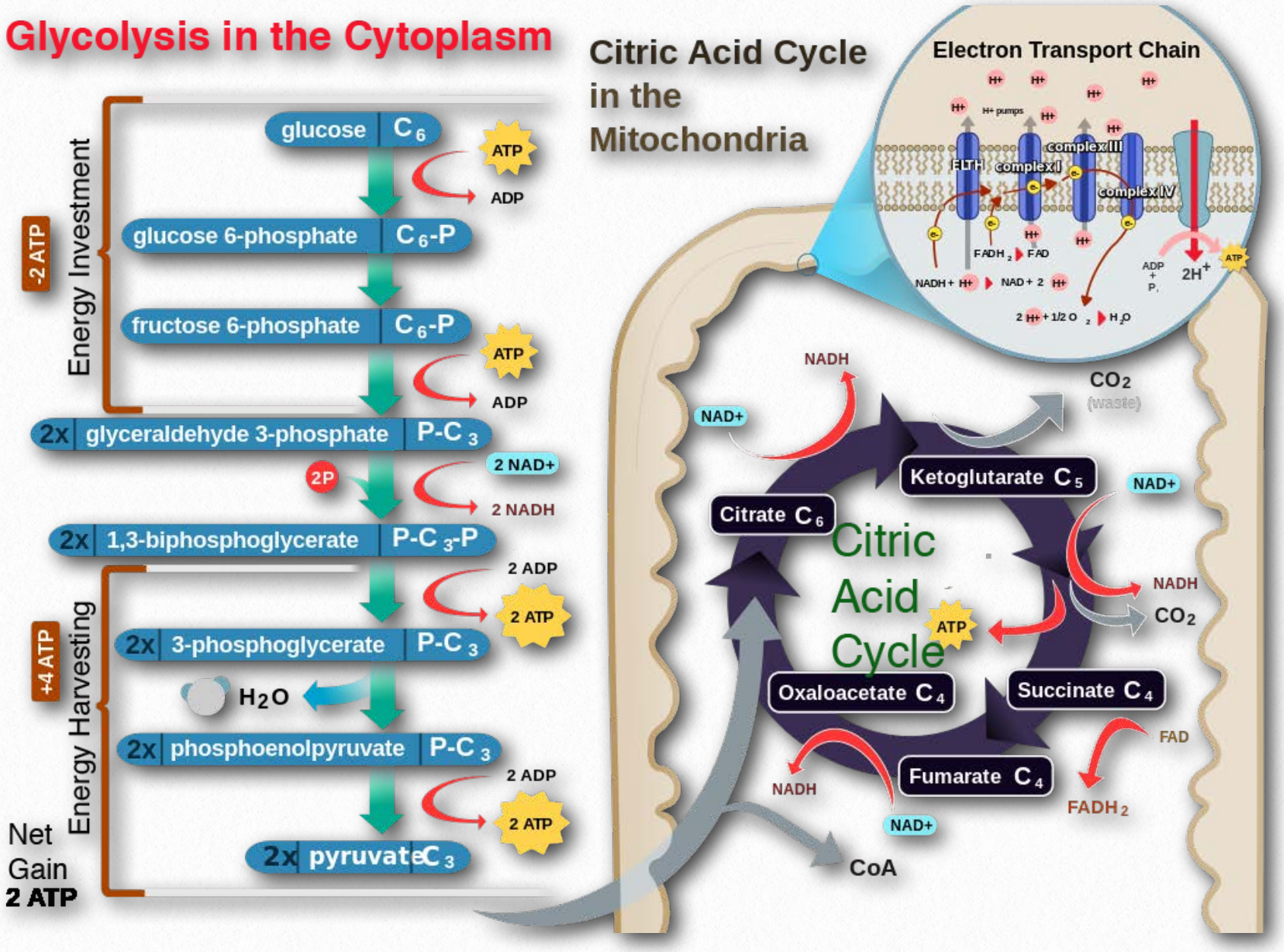


Figure 5.31 - Respiration overview in eukaryotic cells

Wikipedia

At rest

To illustrate these links, let us first consider a person, initially at rest, who then suddenly jumps up and runs away. At first, the person's ATP levels are high and ADP levels are low (no exercise to burn ATP), so little oxidative phosphorylation is occurring and thus the proton gradient is high. Electron transport is moving slowly, if at all, so it is not using oxygen and the person's breathing is slow, as a result.

YouTube Lectures by Kevin HERE & HERE

Exercise

When running starts, muscular contraction, which uses energy, causes ATP to be converted to ADP. Increasing ADP in muscle cells favors oxidative phosphorylation to attempt to make up for the ATP being burned. ATP synthase begins working and protons begin to come back into the mitochondrial matrix. The proton gradient decreases, so electron transport re-starts.

Electron transport needs an electron acceptor, so oxygen use increases and when oxygen use increases, the person starts breathing more heavily to supply it. When the person stops running, ATP concentrations get rebuilt by ATP synthase. Eventually, when ATP levels are completely restored, ADP levels fall and ATP synthase stops or slows considerably. With little or no proton movement, electron transport stops because the proton gradient is too large. When electron transport stops, oxygen use decreases and the rate of breathing slows down.

Interactive Learning Module HERE

Electron transport critical

The really interesting links to metabolism occur relative to whether or not electron transport is occurring. From the examples, we can see that electron transport will be relatively slowed when not exercising and more rapid when exercise (or other ATP usage) is occurring. Remember that electron transport is the way in which reduced electron carriers, NADH and $FADH_2$, donate their electrons to the ETS , becoming oxidized to NAD^+ and FAD, respectively.

Oxidized carriers, such as NAD^+ and FAD are needed by catabolic pathways, like glycolysis, the citric acid cycle, and fatty acid oxidation. Anabolic pathways, such as fatty acid/fat synthesis and gluconeogenesis rely on reduced electron carriers, such as $FADH_2$, NADH, and the related carrier, NADPH.

Links to exercise

High levels of NADH and $FADH_2$ prevent catabolic pathways from operating, since NAD^+ and FAD levels will be low and these are needed to accept the electrons released during catabolism by the oxidative processes.

Thanks to respiratory control, when one is exercising, NAD^+ and FAD levels increase (because electron transport is running), so catabolic pathways that need NAD^+ and FAD can function. The electrons lost in the oxidation reactions of catabolism are captured by

Rest

- ATP High / ADP Low
- Oxidative Phosphorylation Low
- Electron Transport Low
- Oxygen Use Low
- NADH High / NAD^+ Low
- Citric Acid Cycle Slow

Exercise

- ATP Low / ADP High
- Oxidative Phosphorylation High
- Electron Transport High
- Oxygen Use High
- NADH Low / NAD^+ High
- Citric Acid Cycle Fast

NAD^+ and FAD to yield NADH and $FADH_2$, which then supply electrons to the electron transport system and oxidative phosphorylation to make more needed ATP.

Thus, during exercise, cells move to a mode of quickly cycling between reduced electron carriers (NADH/$FADH_2$) and oxidized electron carriers (NAD^+/FAD). This allows rapidly metabolizing tissues to transfer electrons to NAD^+/FAD and it allows the reduced electron carriers to rapidly become oxidized, allowing the cell to produce ATP.

Rest

When exercise stops, NADH and $FADH_2$ levels rise (because electron transport is slowing) causing catabolic pathways to slow/stop. If one does not have the proper amount of exercise, reduced carriers remain high in concentration for long periods of time. This means we have an excess of energy and then anabolic pathways, particularly fatty acid synthesis, are favored, so we get fatter.

Altering respiratory control

One might suspect that altering respiratory control could have some very dire consequences and that would be correct. Alterations can take the form of either inhibiting electron transport/oxidative phosphorylation or uncoupling the two . These alterations can be achieved using compounds with specific effects on particular components of the system.

All of the chemicals described here are laboratory tools and should never be used by people. The first group for discussion are the inhibitors. In tightly coupled mitochondria, inhibiting either electron transport or oxidative phosphorylation has the effect of inhibiting the other one as well.

Electron transport inhibitors

Common inhibitors of electron transport include rotenone and amytal, which stop movement of electrons past Complex I, malonate, malate, and oxaloacetate, which

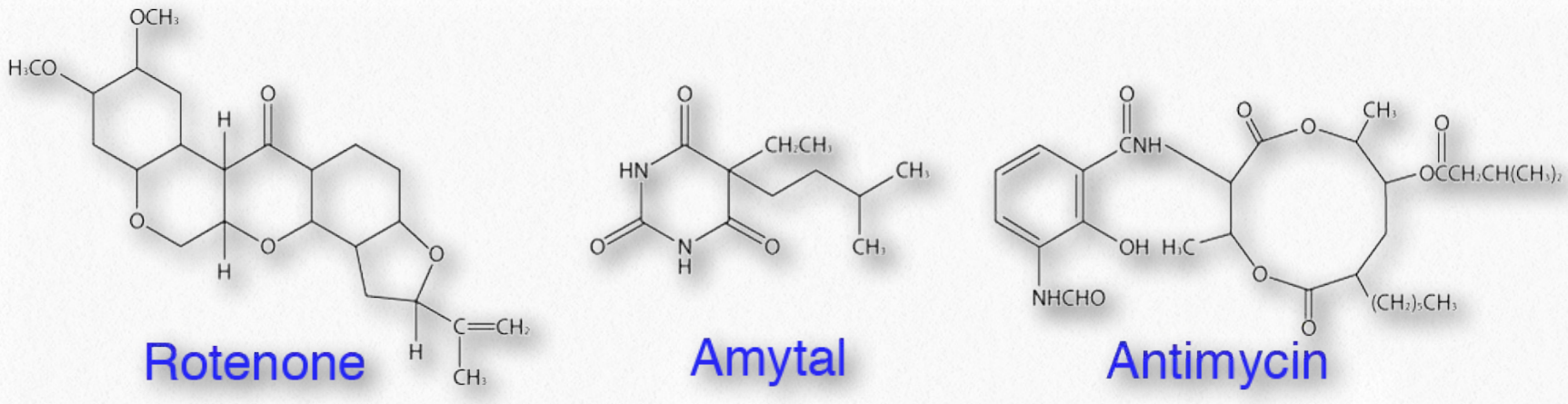


Figure 5.32 - Three inhibitors of electron transport

Image by Aleia Kim

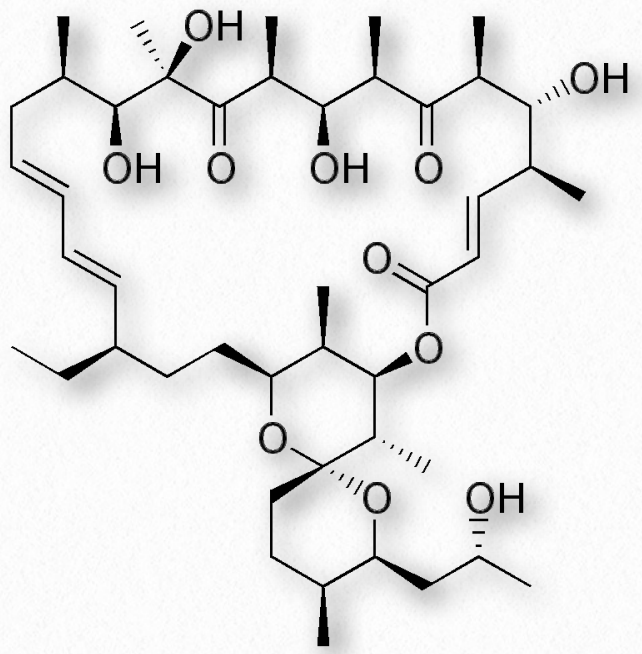


Figure 5.33 - Oligomycin A - An inhibitor of ATP synthase

hibit movement of electrons through Complex II, antimycin A which stops movement of electrons past Complex III, and cyanide, carbon monoxide, azide, and hydrogen sulfide, which inhibit electron movement through Complex IV (Figure 5.33). All of these compounds can stop electron transport directly (no movement of electrons) and oxidative phosphorylation indirectly (proton gradient will dissipate). While some of these compounds are not commonly known, almost everyone is aware of the hazards of carbon monoxide and cyanide, both of which can be lethal.

ATP synthase inhibitor

It is also possible to use an inhibitor of ATP synthase to stop oxidative phosphorylation directly (no ATP production) and electron transport indirectly (proton gradient not relieved so it becomes increasingly difficult to pump protons out of matrix). Oligomycin A (Figure 5.34) is an inhibitor of ATP synthase.

Rotenone

Rotenone, which is a plant product, is used as a natural insecticide that is permitted for organic farming. When mitochondria are treated with this, electron transport will stop at Complex I and so, too, will the pumping of protons out of the matrix. When this occurs, the proton gradient rapidly dissipates, stopping oxidative phosphorylation as a consequence. There are other entry points for electrons than Complex I, so this type of inhibition is not as serious as using inhibitors of Complex IV, since no alternative route for electrons is available. It is for this reason that cyanide, for example, is so poisonous.

2,4-DNP

Respiratory control can be completely destroyed by using a reagent that permeabilizes the inner mitochondrial membrane to protons. There are several such reagents, but the best known one is 2,4

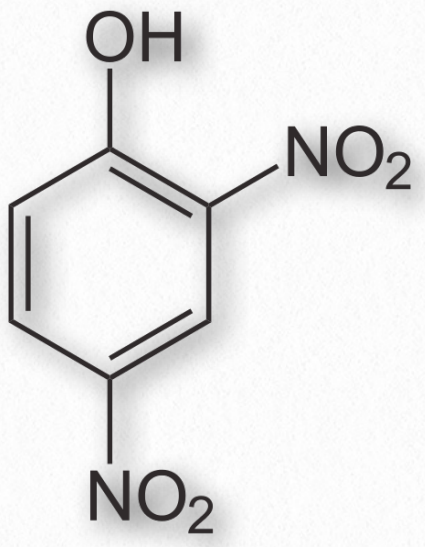


Figure 5.34 - 2,4 DNP - an uncoupler of respiratory control

dinitrophenol (2,4 DNP - Figure 5.35). Treatment of mitochondria with 2,4 DNP makes the mitochondrial inner membrane "leaky" to protons. This has the effect of providing an alternate route for protons to reenter the matrix besides going through ATP synthase, and uncouples oxidative phosphorylation from electron transport.

Imagine a dam holding back water with a turbine generating electricity through which water must flow. When all water flows through the turbine, the maximum amount of electricity can be generated. If one pokes a hole in the dam, though, water will flow through the hole and less electricity will be created. The generation of electricity will thus be uncoupled from the flow of water. If the hole is big enough, the water will all drain out through the hole and no electricity will be made.

YouTube Lectures by Kevin HERE & HERE

Bypassing ATP synthase

Imagine, now, that the proton gradient is the equivalent of the water, the inner membrane is the equivalent of the dam and the ATP synthase is the turbine. When protons have an alternate route, little or no ATP will be made because protons will pass through the membrane's holes instead of spinning the turbine of ATP synthase.

It is important to recognize, though, that uncoupling by 2,4 DNP works differently from the electron transport inhibitors or the ATP synthase inhibitor. In those situations, stopping oxidative phosphorylation resulted in indirectly stopping electron transport, since the two processes were coupled and the inhibitors did not uncouple them. Similarly, stopping electron transport indirectly stopped oxidative phosphorylation for the same reason.

Such is not the case with 2,4 DNP. Stopping oxidative phosphorylation by destroying the proton gradient allows electron transport to continue unabated (it actually stimulates it), since the proton gradient cannot build no matter how much electron transport runs. Consequently, electron trans-

In Cells With Tight Coupling	In Cells That Are Uncoupled
1. O_2 use depends on metabolism	1. O_2 use high
2. NAD^+ levels vary with exercise	2. NAD^+ Levels high
3. Proton gradient high with no exercise	3. Little or no proton gradient
4. Catabolism depends on energy needs	4. Catabolism high
5. ETS runs when OxPhos runs and vice versa	5. OxPhos does not run, but ETS runs rapidly

port runs like crazy but oxidative phosphorylation stops. When that happens, NAD^+ and FAD levels rise, and catabolic pathways run unabated with abundant supplies of these electron acceptors. The reason such a scenario is dangerous is because the body is using all of its nutrient resources, but no ATP is being made. Lack of ATP leads to cellular (and organismal) death. In addition, the large amounts of heat generated can raise the temperature of the body to unsafe levels.

Thermogenin

One of the byproducts of uncoupling electron transport is the production of heat. The faster metabolic pathways run, the more heat is generated as a byproduct. Since 2,4 DNP causes metabolism to speed up, a considerable amount of heat can be produced. Controlled uncoupling is actually used by the body in special tissues called brown fat. In this case, brown fat cells use the heat created to help thermoregulate the temperature of newborn children.

Permeabilization of the inner membrane is accomplished in brown fat by the synthesis of a protein called thermogenin (also known as uncoupling protein). Thermogenin binds to the inner membrane and allows protons to pass through it, thus bypassing the ATP synthase. As noted for 2,4 DNP, this results in activation of catabolic pathways and the more catabolism occurs, the more heat is generated.

Dangerous drug

In uncoupling, whether through the action of an endogenous uncoupling protein or DNP, the energy that would have normally been captured in ATP is lost as heat. In the case of uncoupling by thermogenin, this serves the important purpose of keeping newborn infants warm. But in adults, uncoupling merely wastes the energy that would have been harvested as ATP. In other words, it mimics starvation, even though there is plenty of food, because the energy is dissipated as heat.

This fact, and the associated increase in metabolic rate, led to DNP being used as a weight loss drug in the 1930s. Touted as an effortless way to lose weight without having to eat less or exercise more, it was hailed as a magic weight loss pill. It quickly became apparent, however, that this was very dangerous. Many people died from using this drug before laws were passed to ban the use of DNP as a weight loss aid.

Alternative oxidase

Another approach to generating heat that doesn't involve breaking respiratory control is taken by some fungi, plants, and protozoa. They use an alternative electron transport.

In these organisms, there is an enzyme called alternative oxidase (Figure 5.36). Alternative oxidase is able to accept electrons from CoQ and pass them directly to oxygen.

The process occurs in coupled mitochondria. Its mechanism of action is to reduce the yield of ATP, since fewer protons are being pumped per reduced electron carrier. Thus NAD^+ concentrations increase, oxygen consumption increases, and the efficiency of ATP production decreases.

Organisms using this method must activate catabolic pathways by the increase in NAD^+ concentration. This, in turn produces quantities of NADH and $FADH_2$ necessary to make sufficient amounts of ATP. The byproduct of this increased catabolism is more heat. Not surprisingly, the alternative oxidase pathway can be activated by cold temperatures.

Energy efficiency

Cells are not 100% efficient in energy use. Nothing we know is. Consequently, cells do not get as much energy out of catabolic processes as they put into anabolic processes. A good example is the synthesis and breakdown of glucose, something liver cells are frequently doing. The complete conversion of glucose to pyruvate in glycolysis (catabolism) yields two pyruvates plus 2 NADH plus 2 ATPs. Conversely, the complete conversion of two pyruvates into glucose by gluconeogenesis (anabolism) requires 4 ATPs, 2 NADH, and 2 GTPs. Since the energy of GTP is essentially equal to that of ATP, gluconeogenesis requires a net of 4 ATPs more than glycolysis yields. This difference must be made up in order for the organism to meet its energy needs. It is for this reason that we eat. In addition, the inefficiency of our capture of energy in reactions results in the production of heat and helps to keep us warm, as noted.

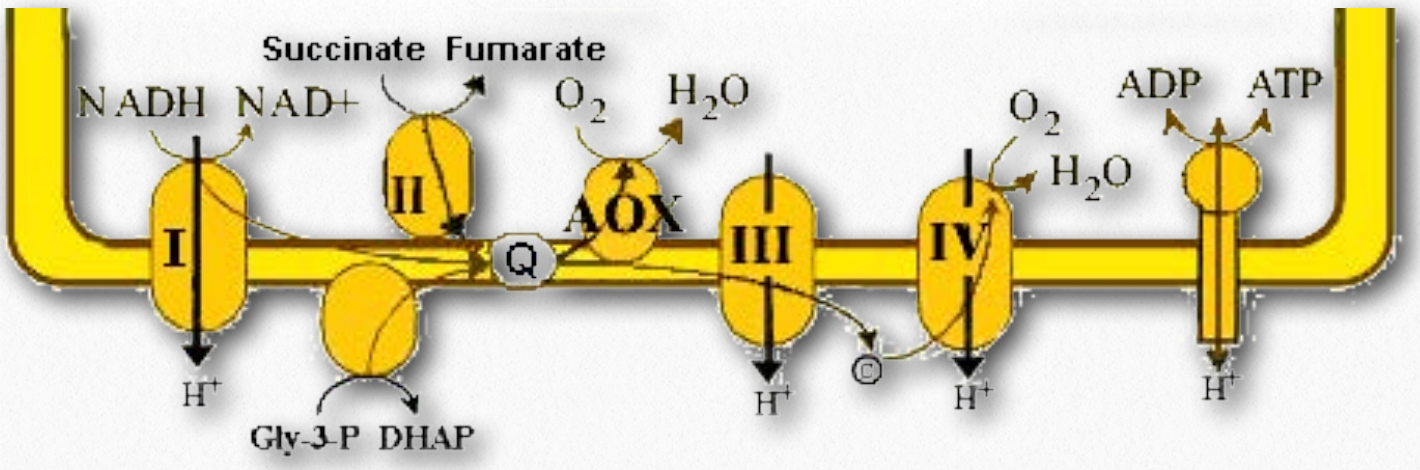


Figure 5.35 - Alternative oxidase (AOX) of fungi, plants, and protozoa bypasses part of electron transport by taking electrons from CoQ and passing them to oxygen.

You can read more about glycolysis (HERE) and gluconeogenesis (HERE).

Metabolic controls of energy

It is also noteworthy that cells do not usually have both catabolic and anabolic processes for the same molecules occurring simultaneously inside of them (for example, breakdown of glucose and synthesis of glucose) because the cell would see no net production of anything but heat and a loss of ATPs with each turn of the cycle. Such cycles are called futile cycles and cells have controls in place to limit the extent to which they occur. Since futile cycles can, in fact, yield heat, they are used as sources of heat in some types of tissue. Brown adipose tissue of mammals uses this strategy, as described earlier. See also HERE for more on heat generation with a futile cycle.

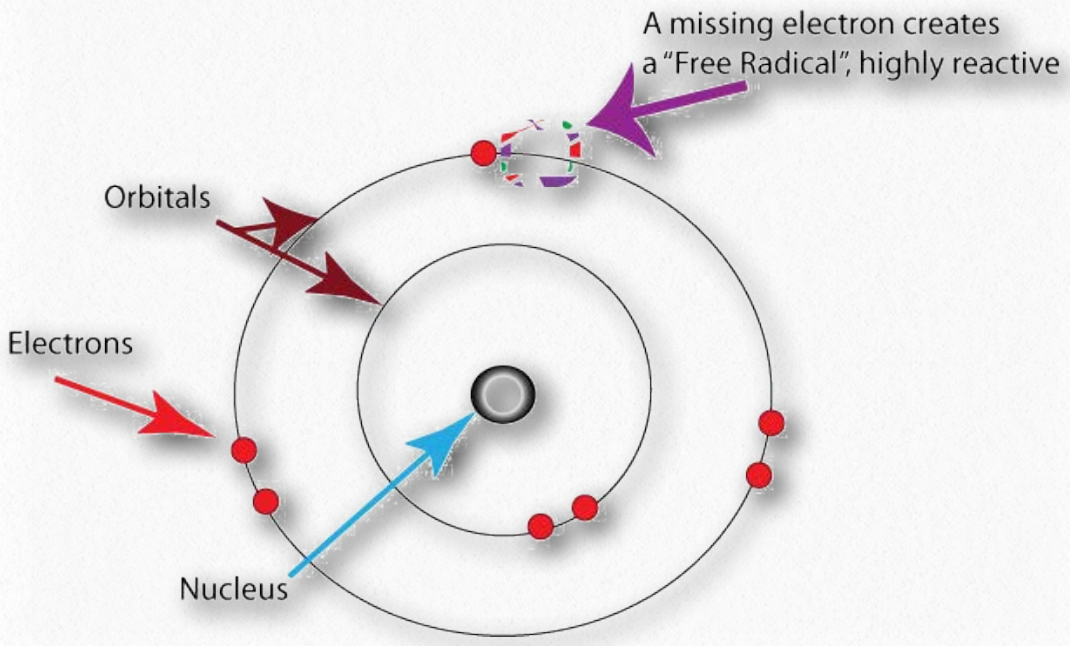


Figure 5.36 - Structure of an oxygen free radical
Wikipedia

Reactive oxygen species

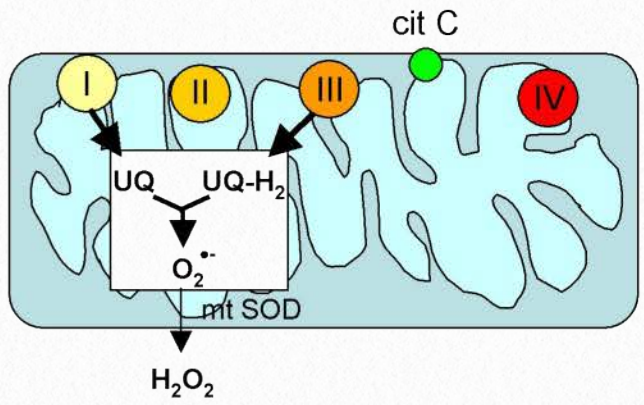
Reactive oxygen species (ROS - Figure 5.37) are oxygen containing molecules, such as peroxides, hydroxyl radical, superoxide, peroxynitrite, and others that are very chemically reactive. Though some ROS, such as peroxide and nitric oxide have important biological functions in signaling, increases in reactive oxygen species in times of stress can cause significant damage in the cell. Exogenous sources of ROS, such as pollution, tobacco, smoke, radiation or drugs can also cause significant problems.

Endogenous production of ROS is directed towards intracellular signaling (H_2O_2 and nitric oxide, for example) and defense. Many cells, for example, have NADPH oxidase (Figure 5.38) embedded in the exterior portion of the plasma membranes, in peroxisomes, and endoplasmic reticulum. It produces superoxides in the reaction below to kill bacteria.

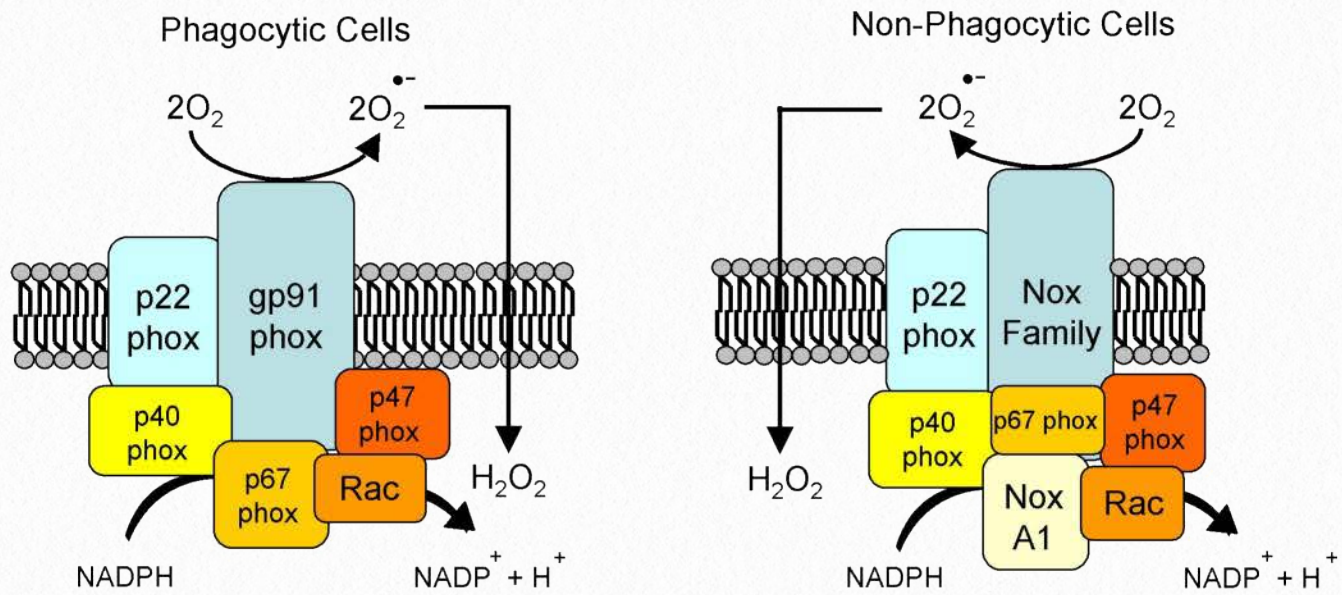
$$\mathbf{NADPH} + 2O_2 \rightleftharpoons \mathbf{NADP^+} + 2\mathbf{O_2^-} + H^+$$

a) Mitochondria

Stimuli inducing increased mitochondrial generation of ROS:	
- serum deprivation	- hypoxia
- integrin signalling	- ceramide
- apoptosis	- p53
- TNFα	- oncogenic Ras



b) NADPH oxidase



Stimuli for activation of NADPH oxidase and 5-lipooxygenase	
- integrin signalling	- immunological stimuli
- growth factors	- hypoxia
- cytokines/hormones	- oncogenic Ras

c) 5-lipoxygenase

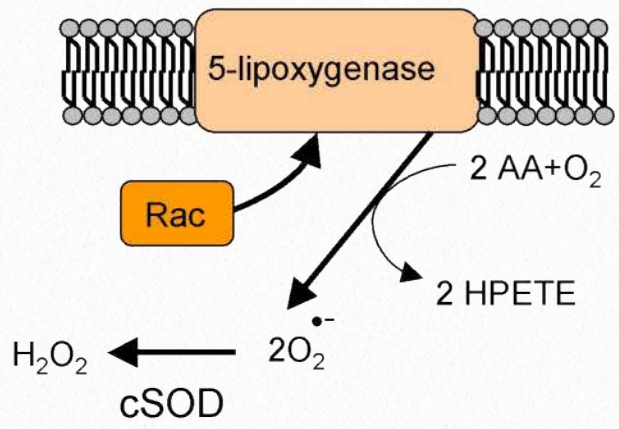


Figure 5.37 - Three sources of reactive oxygen species (ROS) in cells

Wikipedia

In the immune system, cells called phagocytes engulf foreign cells and then use ROS to kill them. ROS can serve as signals for action. In zebrafish, damaged tissues have increased levels of H_2O_2 and this is thought to be a signal for white blood cells to converge on the site. In fish lacking the genes to produce hydrogen peroxide, white blood cells do not converge at the damage site. Sources of hydrogen peroxide include peroxisomes, which generate it as a byproduct of oxidation of long chain fatty acids.

YouTube Lectures by Kevin HERE & HERE

Figure 5.38 A hydroxyl radical
Wikipedia

Aging

Reactive oxygen species are at the heart of the free radical theory of aging, which states that organisms age due to the accumulation of damage from free radicals in their cells. In yeast and *Drosophila*, there is evidence that reducing oxidative damage can increase lifespan. In mice, increasing oxidative damage decreases life span, though in *Caenorhabditis*, blocking production of superoxide dismutase actually increases lifespan, so the role of ROS in aging is not completely clear.

It is clear, though, that accumulation of mitochondrial damage is problematic for individual cells. Bcl-2 proteins on the surface of mitochondria monitor damage and if they detect it, will activate proteins called Bax to stimulate the release of cytochrome c from the mitochondrial membrane, stimulating apoptosis (programmed cell death). Eventually the dead cell will be phagocytosed.

A common endogenous source of superoxide is the electron transport chain. Superoxide can be produced when movement of electrons into and out of the chain don't match well. Under these circumstances, semi-reduced CoQ can donate an electron to O_2 to form superoxide (O_2^-). Superoxide can react with many molecules, including DNA where it can cause damage leading to mutation. If it reacts with the aconitase enzyme, ferrous iron (Fe^{++}) can be released which, in turn, can react in the Fenton reaction to produce another reactive oxygen species, the hydroxyl radical (Figure 5.39).

Countering the effects of ROS are enzymes, such as catalase, superoxide dismutase, and anti-oxidants, such as glutathione and vitamins C and E.

Glutathione protects against oxidative damage by being a substrate for the enzyme glutathione peroxidase. Glutathione peroxidase catalyzes the conversion of hydrogen peroxide to water (next page).

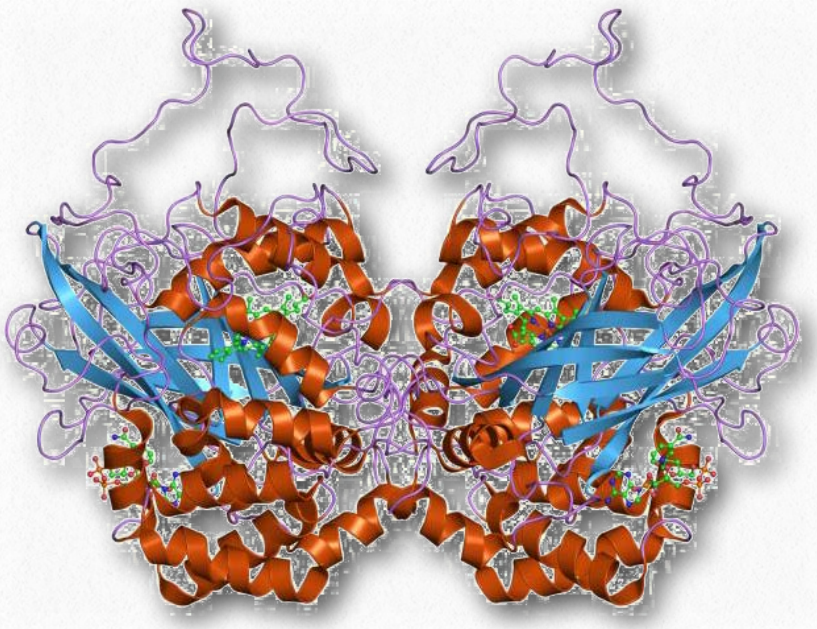


Figure 5.39 - Catalase

Reduced **Glutathione** (GSH) + H_2O_2

Oxidized **Glutathione** (GSSG) + H_2O

Catalase

Catalase (Figure 5.40) is an important enzyme for cells of all types that live in an oxygen environment. A first line of defense against reactive oxygen species, catalase catalyzes the breakdown of hydrogen peroxide into water and oxygen.

$$2\ H_2O_2 <=> 2\ H_2O + O_2$$

The enzyme, which employs four heme groups in its catalysis, works extremely rapidly, converting up to 40,000,000 molecules of hydrogen peroxide to water and oxygen per enzyme per second. It is abundantly found in peroxisomes.

In addition to catalase's ability to break down hydrogen peroxide, the enzyme can also use hydrogen peroxide to oxidize a wide variety organic compounds, including phenols, formic acid, formaldehyde, acetaldehyde, and alcohols, but with much lower efficiency.

Health

The importance of catalase for health is uncertain. Mice deficient in the enzyme appear healthy and humans with low levels of the enzyme display few problems. On the other hand, mice engineered to produce higher levels of catalase, in at least one study, lived longer. The ability of organisms to live with lower levels or no catalase may arise from another group of enzymes, the peroxiredoxins, which also act on hydrogen peroxide and may make up for lower quantities of catalase. Last, there is evidence that reduced levels of catalase with aging may be responsible for the graying of hair. Higher levels of H_2O_2 with

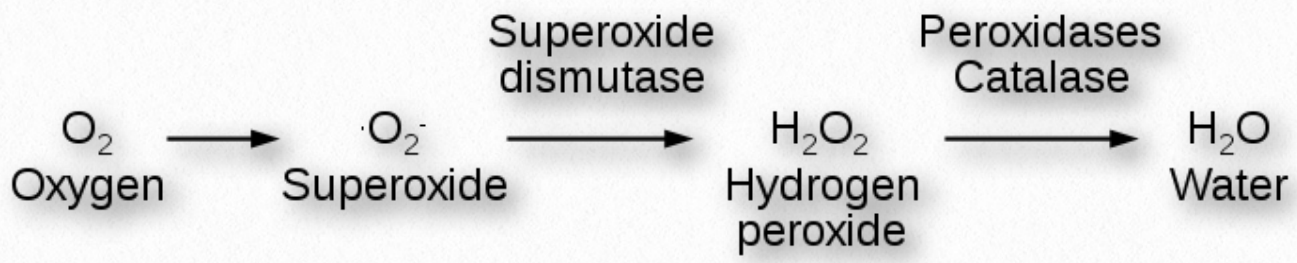


Figure 5.40 - Detoxifying reactive oxygen species

reduced catalase results in a bleaching of hair follicles.

Superoxide dismutase

Another important enzyme for protection against reactive oxygen species is superoxide dismutase (SOD), which is found, like catalase, in virtually all organisms living in an oxygen environment. Superoxide dismutase, also like catalase, has a very high K_{cat} value and, in fact, has the highest K_{cat}/K_m known for any known enzyme. It catalyzes the reactions at the top of the next column (superoxides shown in red):

The enzyme thus works by a ping-pong (double displacement) mechanism (see HERE), being converted between two different forms.

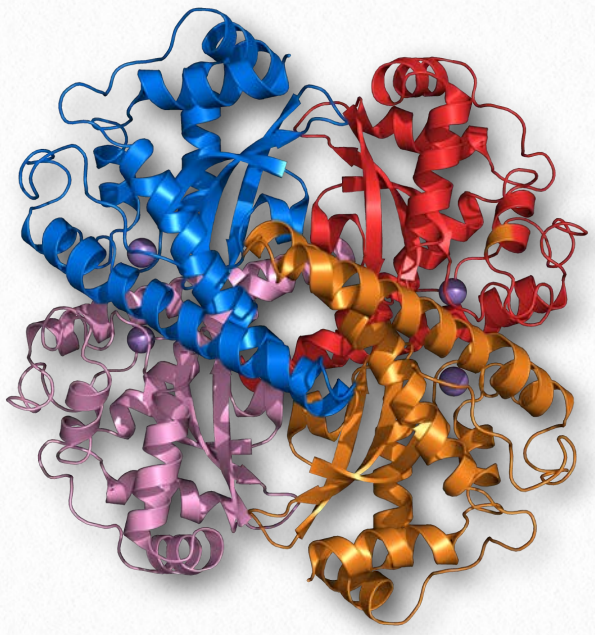


Figure 5.41 - SOD2 of humans

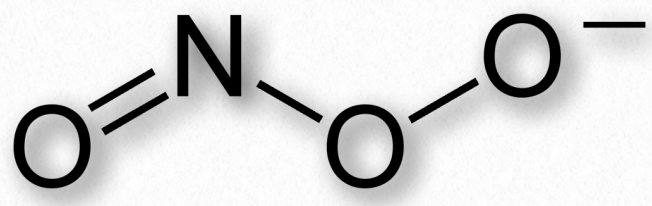


Figure 5.42 3 - Peroxynitrite Ion

1. O_2^- + Enzyme-Cu^{++}

$\rightleftharpoons$

O_2 + Enzyme-Cu^{+}

2. O_2^- + Enzyme-Cu^{+} + $2H^+$

$\rightleftharpoons$

H_2O_2 + Enzyme-Cu^{++}

The hydrogen peroxide produced in the second reaction is easily handled by catalase and is also less harmful than superoxide, which can react with nitric oxide (NO) to form very toxic peroxynitrite ions (Figure 5.43). Peroxynitrite has negative effects on cells, as shown in Figure 5.45.

In addition to copper, an ion of Zn^{++} is also bound by the enzyme and likely plays a role in the catalysis. Forms of superoxide dismutase that use manganese, nickel, or iron are also known and are mostly found in prokaryotes and protists, though a manganese SOD is found in most mitochondria. Copper/zinc enzymes are common in eukaryotes.

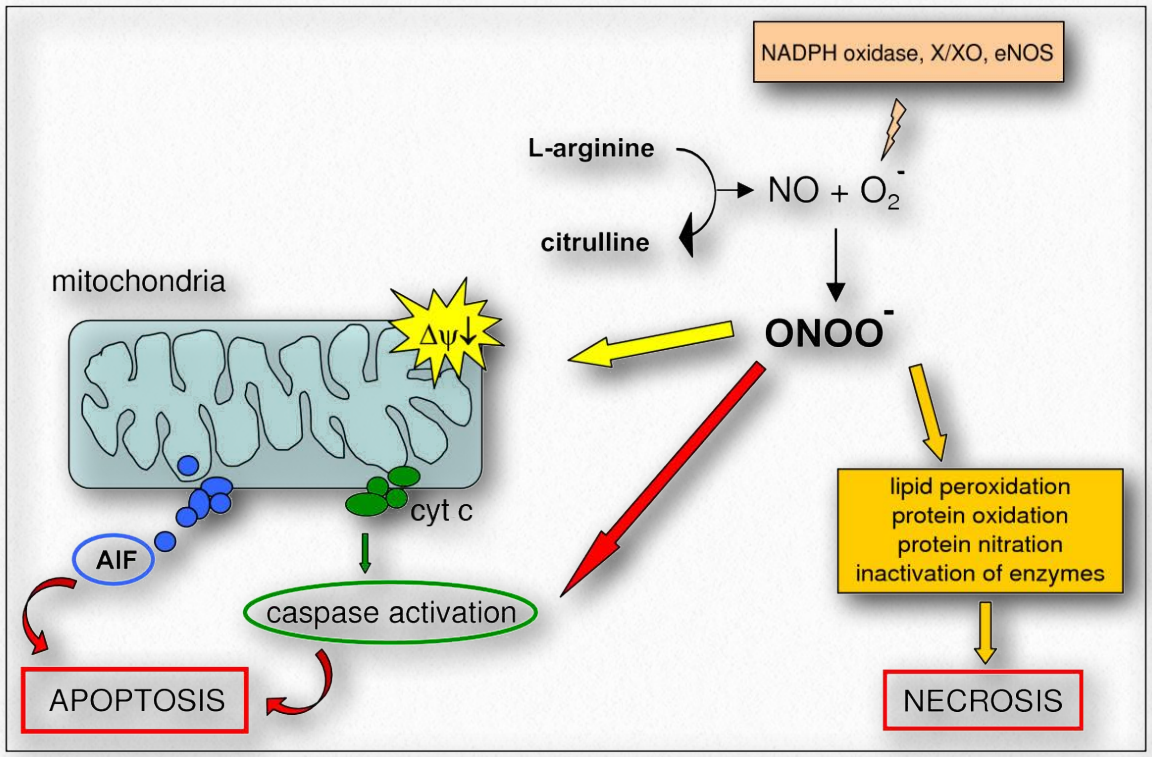


Figure 5.43 - Peroxynitrite's effects on cells lead to necrosis or apoptosis

Mixed function oxidases

Other enzymes catalyzing reactions involving oxygen include the mixed function oxidases. These enzymes use molecular oxygen for two different purposes in one reaction. The mixed function part of the name is used to indicate reactions in which two different substrates are being oxidized simultaneously.

Three forms of superoxide dismutase are found in humans and localized to the cytoplasm (SOD1 - Figure 5.45), mitochondria (SOD2 - Figure 5.46), and extracellular areas (SOD3 - Figure 5.47). Mice lacking any of the three forms of the enzyme are more sensitive to drugs, such as paraquat. Deficiency of SOD1 in mice leads to hepatocellular carcinoma and early loss of muscle tissue related to aging. *Drosophila* lacking SOD2 die before birth and those lacking SOD1 prematurely age.

In humans, superoxide dismutase mutations are associated with the genetically-linked form of Amyotrophic Lateral Sclerosis (ALS) and over-expression of the gene is linked to neural disorders associated with Down syndrome.

Wikipedia

Figure 5.44 - SOD1 of humans

Wikipedia

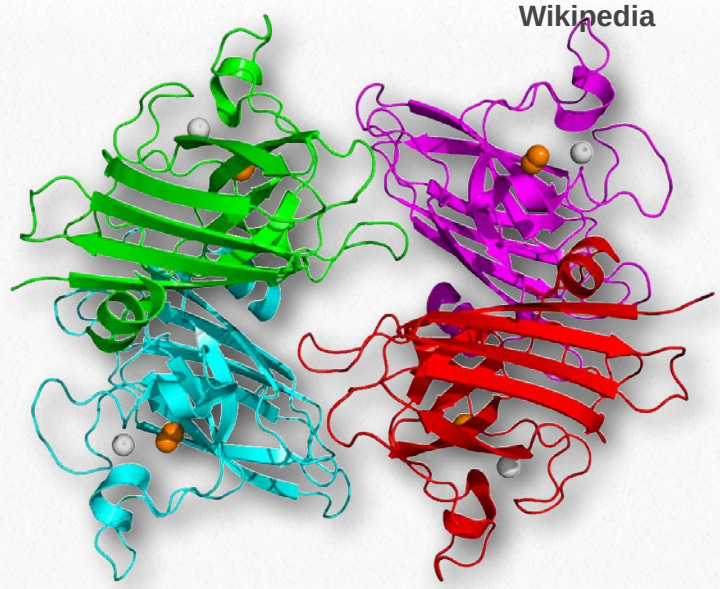


Figure 5.45 - SOD3 of humans

$$RH + O_2 + \mathbf{NADPH} + H^+ \rightleftharpoons ROH + H_2O + NADP^+$$

Monooxygenases are examples of mixed function oxidases. An example of a mixed function oxidase reaction is shown below.

$$AH + BH2 + O_2 <=> AOH + B + H_2O$$

In this case, the oxygen molecule has one atom serve as an electron acceptor and the other atom is added to the AH, creating an alcohol.

Cytochrome P_{450} enzymes

Cytochrome P_{450} enzymes (called CYPs) are family of heme-containing mixed function oxidase enzymes found in all domains of life. Over 21,000 CYP enzymes are known. The most characteristic reaction catalyzed by these enzymes follows

Monooxygenase reactions such as this are relatively rare in the cell due to their use of molecular oxygen. CYPs require an electron donor for reactions like the one shown here and frequently require a protein to assist in transferring electrons to reduce the heme iron. There are six different classes of P_{450} enzymes based on how they get electrons

1. Bacterial P_{450} - electrons from ferredoxin reductase and ferredoxin

2. Mitochondrial P_{450} - electrons from adrenodoxin reductase and adrenodoxin

3. CYB5R/cyb5 - electrons come from cytochrome b5

4. FMN/Fd - use a fused FMN reductase

5. Microsomal P_{450} - NADPH electrons come via cytochrome P_{450} reductase or from cytochrome b_5 and cytochrome b_5 reductase

6. P_{450} only systems - do not require external reducing power

The CYP genes are abundant in humans and catalyze thousand of reactions on both cellular and extracellular chemicals. There are 57 human genes categorized into 18 different families of enzymes. Some CYPs are specific for one or a few substrates, but others can act on many different substrates.

CYP enzymes are found in most body tissues and perform important functions in synthesis of steroids (cholesterol, estrogen, testosterone, Vitamin D, e.g.), breakdown of endogenous compounds (bilirubin), and in detoxification of toxic compounds including drugs. Because they act on many drugs, changes in CYP activity can produce unexpected results and cause problems with drug interactions.

Bioactive compounds, for example, in grapefruit juice, can inhibit CYP3A4 activity, lead-

ing to increased circulating concentrations of drugs that would normally have been acted upon by CYP3A4. This is the reason that patients prescribed drugs that are known to be CYP3A4 substrates are advised to avoid drinking grapefruit juice while under treatment. St. Johns Wort, an herbal treatment, on the other hand, induces CYP3A4 activity, but inhibits CYP1A1, CYP1B1, and CYP2D6. Tobacco smoke induces CYP1A2 and watercress inhibits CYP2E1.

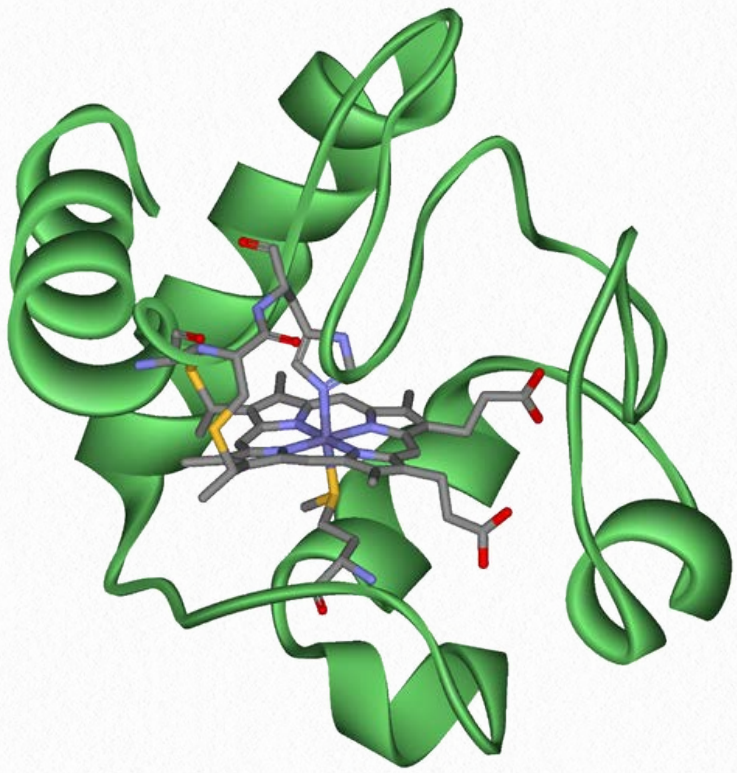


Figure 5.46 - Cytochrome c with its heme group

Cytochromes

Cytochromes are heme-containing proteins that play major roles in the process of electron transport in the mitochondrion and in photosynthesis in the chloroplast. They exist either as monomers (cytochrome c) or as subunits within large redox complexes (Complex III and Complex IV of electron transport. An atom of iron at the center of the heme group plays a central role in the process, flipping between the ferrous (Fe^{++}) and ferric (Fe^{+++}) states as a result of the movement of electrons through it.

There are several different cytochromes. Cytochrome c (Figure 5.47) is a soluble protein loosely associated with the mitochondrion. Cytochromes a and a_3 are found in Complex IV. Complex III has cytochromes b and c_1 and the plastoquinol-plastocyanin reductase of the chloroplast contains cytochromes b_6 and f. Another important class of enzymes containing cytochromes is the cytochrome P_{450} oxidase group (see above). They get their name from the fact that they absorb light at 450 nm when their heme iron is reduced.

Iron-Sulfur Proteins

Iron-sulfur proteins contain iron-sulfur clusters in a variety of formats, including sulfide-linked di-, tri-, and tetrairon centers existing in different oxidation states (Figures 5.48 & 5.49). The clusters play a variety of roles, but the best known ones are in electron transport where they function in the redox reactions involved in the movement of electrons.

Complexes I and Complex II contain multiple Fe-S centers. Iron-sulfur proteins, though, have many other roles in cells. Aconitase uses an iron-sulfur center in its catalytic ac-

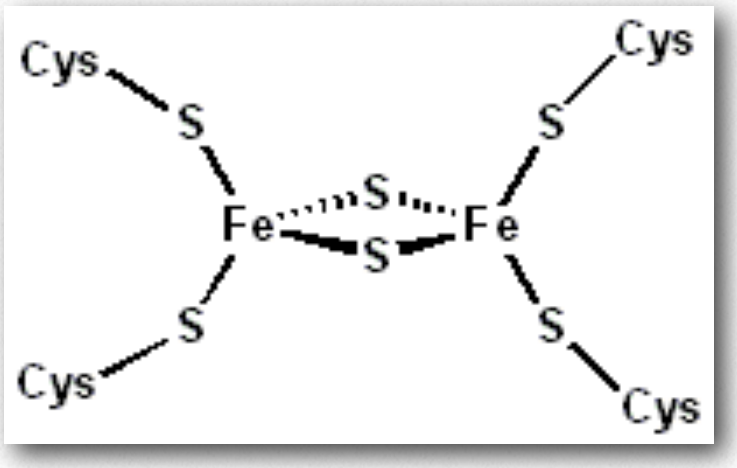


Figure 5.47 - Fe_2S_2 Cluster

tion and the ability of the enzyme to bind iron allows it to function as a barometer of iron concentration in cells. Iron-sulfur centers help to generate radicals in enzymes using S-Adenosyl Methionine (SAM) and can serve as a source of sulfur in the synthesis of biotin and lipoic acid. Some iron-sulfur proteins even help to regulate gene expression.

YouTube Lectures by Kevin HERE & HERE

Ferredoxin

Ferredoxins are iron-sulfur containing proteins performing electron transfer in a wide variety of biological systems and processes. They include roles in photosynthesis in chloroplasts. Ferredoxins are classified structurally by the iron-sulfur clustered centers they contain. Fe_2S_2 clusters (Figure 5.50) are found in chloroplast membranes and can donate electrons to glutamate synthase, nitrate reductase, and sulfite reductase and serve as electron carriers between reductase flavoproteins and bacterial dioxygenase systems. Adrenodoxin is a soluble human Fe_2S_2 ferredoxin (also called ferredoxin 1) serving as an electron carrier (to cytochrome P_{450}) in mitochondrial monooxygenase systems. Fe_4S_4 ferredoxins are subdivided as low and high potential ferredoxins, with the latter ones functioning in anaerobic electron transport chains.

Ferritin

Ferritin is an intracellular iron-storage protein found in almost all living organisms, from bacteria to higher plants and animals. It is a globular protein complex with 24 subunits

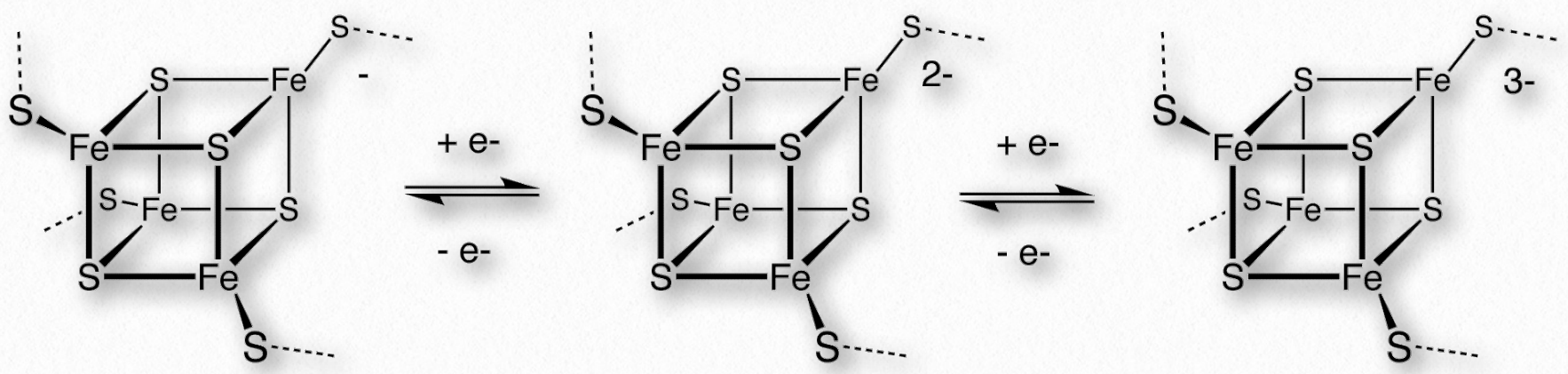


Figure 5.48 - Redox reactions for Fe_4S_4 clusters

and is the primary intracellular iron-storage protein in eukaryotes and prokaryotes. Ferritin functions to keep iron in a soluble and non-toxic form. Its ability to safely store iron and release it in a controlled fashion allow it to act like the prime iron buffer and solubilizer in cells - keeping the concentration of free iron from going to high or falling too low. Ferritin is located in the cytoplasm in most tissues, but it is also found in the serum acting as an iron carrier. Ferritin that doesn't contain any iron is known as apoferritin.

Monoamine oxidases

Monoamine oxidases are enzymes that catalyze the oxidative deamination of monoamines, such as serotonin, epinephrine, and dopamine. Removal of the amine with oxygen results in the production of an aldehyde and ammonia. The enzymes are found inside and outside of the central nervous system.

There are two types of monoamine oxidase enzymes - MAO-A and MAO-B. MAO-A is particularly important for oxidizing monoamines consumed in the diet. Both MAO-A and MAO-B play important roles in inactivating monoaminergic neurotransmitters. Both enzymes act on dopamine, tyramine (Figure 5.50), and tryptamine. MAO-A is the primary enzyme for metabolizing melatonin, serotonin, norepinephrine, and epinephrine, while MAO-B is the primary enzyme for phenethylamine (Figure 5.51) and benzylamine. MAO-B levels have been reported to be considerably reduced with tobacco usage.

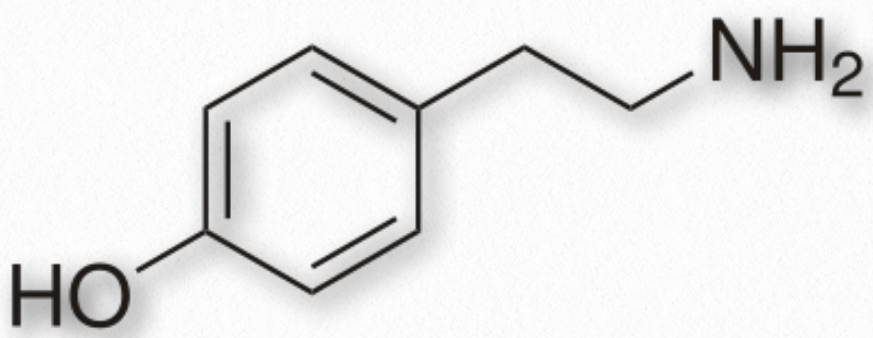


Figure 5.49 - Tyramine

Actions of monoamine oxidases thus affects levels of neurotransmitters and consequently are thought to play roles in neurological and/or psychiatric disorders. Aberrant levels of MAOs have been linked to numerous psychological problems, including depression, attention deficit disorder (ADD), migraines, schizophrenia, and substance abuse. Medications targeting MAOs are sometimes used to treat depression as a last resort - due to potential side effects. Excess levels of catecholamines, such as epinephrine, norepineph-

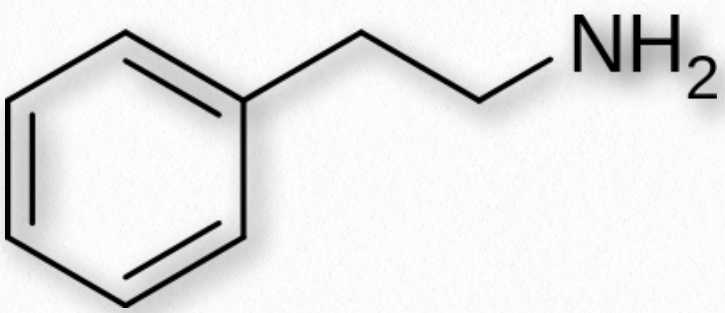


Figure 5.50 - Phenethylamine

rine, and dopamine, can result in dangerous hypertension events.

DNA damage theory of aging

The DNA Damage Theory of Aging is based on the observation that, over time, cells are subject to extensive oxidative events. As already noted, these afford opportunities for the formation of ROS that can damage cellular molecules, and it follows that accumulation of such damage, especially to the DNA would be deleterious to the cell. The build-up of DNA damage could, thus, be responsible for the changes in gene expression that we associate with aging.

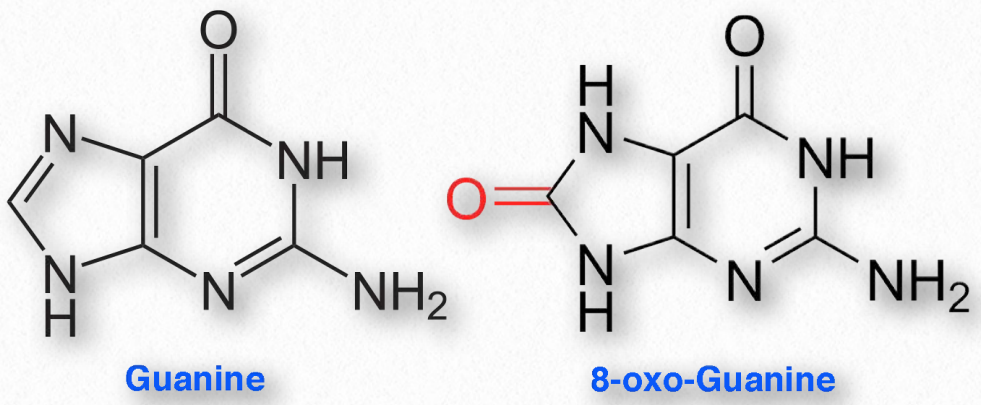


Figure 5.51 - Guanine and 8-oxo-guanine

Numerous damage events

The amount of DNA damage that can occur is considerable. In mice, for example, it is estimated that each cell experiences 40,000 to 150,000 damage events per day. The damage, which happens to nuclear as well as to mitochondrial DNA, can result in apoptosis and/or cellular senescence. DNA repair systems, of course, protect against damage to DNA, but over time, unrepairable damage may accumulate.

Oxidative damage

DNA damage can occur in several ways. Oxidation can damage nucleotides and alter their base-pairing tendencies. Oxidation of guanine by reactive oxygen species, for example, can produce 8-oxoguanine (Figures 5.52 and 5.53). This oxidized nucleobase commonly produced lesion in DNA arising from action of reactive oxygen species like superoxides. 8-oxoguanine is capable of forming a stable base pairing interaction within a DNA duplex with adenine, potentially giving rise to a mutation when DNA rep-

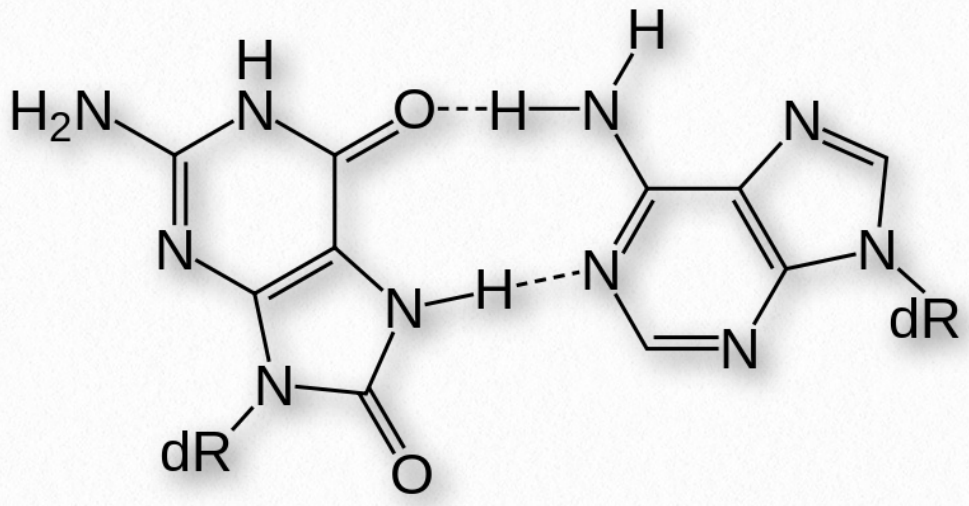


Figure 5.52 - Adenine-8-oxo-guanine base pair. dR = deoxyribose

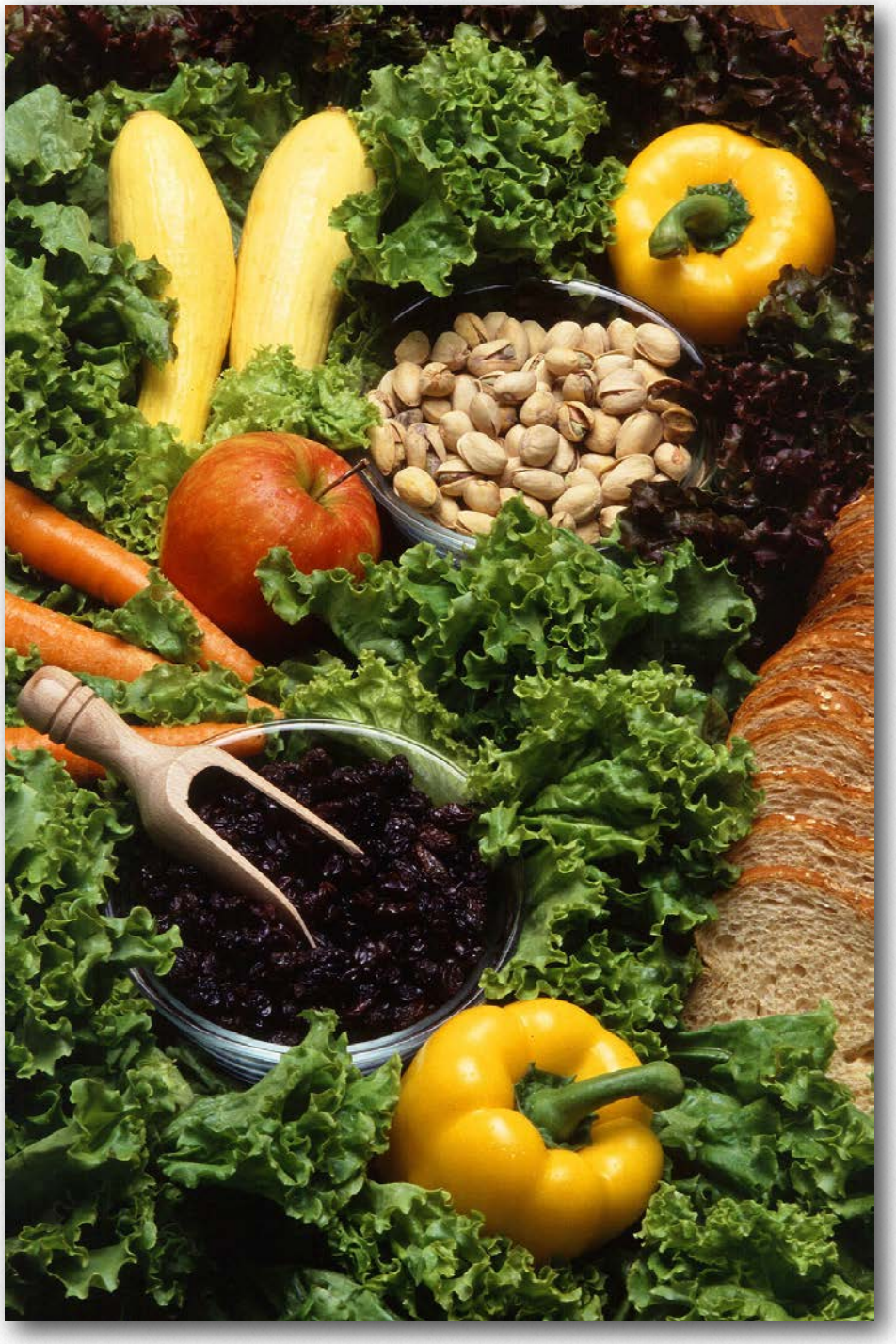


Figure 5.53 - Good antioxidant sources

lication proceeds. 8-oxoguanine can be repaired if recognized in time by a DNA glycosylase, which acts to clip out the damaged base and it can then be replaced by the proper one. Polycyclic aromatic hydrocarbons from cigarette smoke, diesel exhaust, or overcooked meat can covalently bind to DNA and, if unrepaired, lead to mutation. Chemical damage to DNA can result in broken or cross-linked DNAs.

Diseases of DNA repair

The importance of DNA repair in the aging process is made clear by diseases affecting DNA repair that lead to premature aging. These include Werner syndrome, for whom the life expectancy is 47 years. It arises as a result of loss of two enzymes in base excision repair. People suffering from Cockayne syndrome have a life expectancy of 13 years due to mutations that alter transcription-coupled nucleotide excision repair, which is an important system for fixing oxidative damage.

Further, the life expectancies of 13 species of mammalian organisms correlates with the level of expression of the PARP DNA repair-inducing protein. Interestingly, people who lived past the age of 100 had a higher level of PARP than younger people in the population.

Antioxidants

There is a growing interest in the subject of antioxidants because of health concerns raised by our knowledge of problems created as a result of spontaneous oxidation of biomolecules by Reactive Oxygen Species (ROS), such as superoxide. Antioxidants have the chemical property of protecting against oxidative damage by being readily oxidized themselves, preferentially to other biomolecules.

Biologically, cells have several lines of antioxidant defense. They include molecules, such

as vitamins C, A, and E, glutathione, and enzymes that destroy ROS such as superoxide dismutase, catalase, and peroxidases.

Health effects

Oxidation by ROS is mutagenic and has been linked to atherosclerosis. Nonetheless, randomized studies of oral supplementation of various vitamin combinations have shown no protective effect against cancer and supplementation of Vitamin E and selenium has revealed no decrease in the risk of cardiovascular disease. Further, no reduction in mortality rates as a result of supplementation with these materials has been found, so the protective effects, if any, of antioxidants on ROS in human health remain poorly understood.

Glutathione

The major endogenous antioxidant found in cells spanning most living systems, glutathione is a tripeptide protecting cells against damage caused by reactive oxygen species and heavy metals (Figures 5.55 & 5.56). The three amino acids in glutathione (glutamate, cysteine, and glycine) are joined in an unusual fashion.

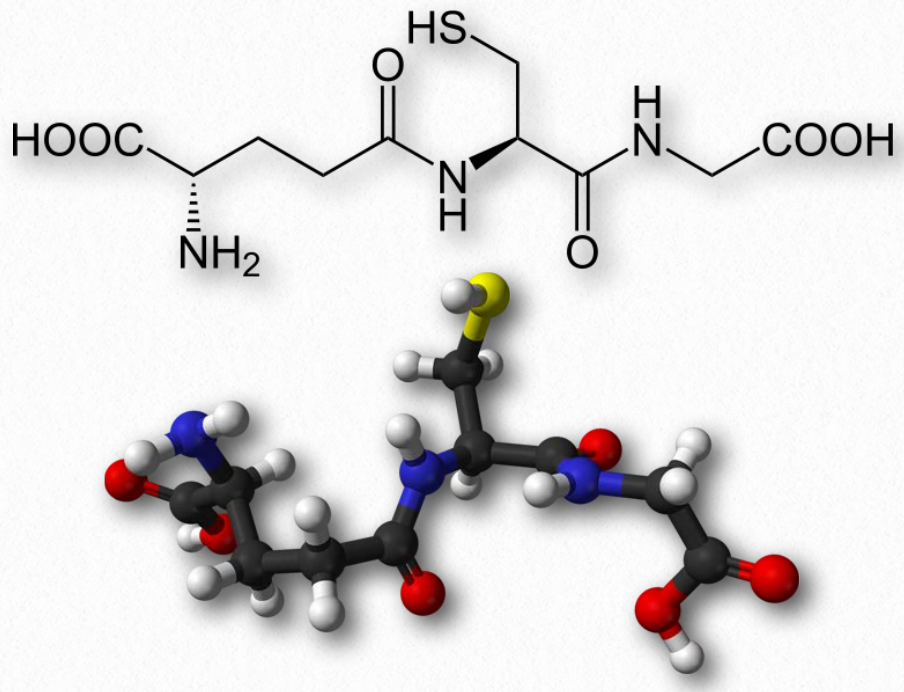


Figure 5.54 - Structure of reduced glutathione (GSH)

The glutamate is joined to the center cysteine by a peptide bond between the R-group carboxyl of glutamate and the α-amine of cysteine. The bond between cysteine and glycine is a normal peptide bond between the α-carboxyl of cysteine and the α-amine of glycine.

The thiol group of cysteine is a reducing agent that reduces disulfide bonds to sulfhydryls in cytoplasmic proteins. This, in turn, is the bridge when two glutathiones get oxidized and form a disulfide bond with each other (Figure 5.56). Glutathione's two oxidative states are abbreviated as follows: GSH (reduced) and GSSG (oxidized).

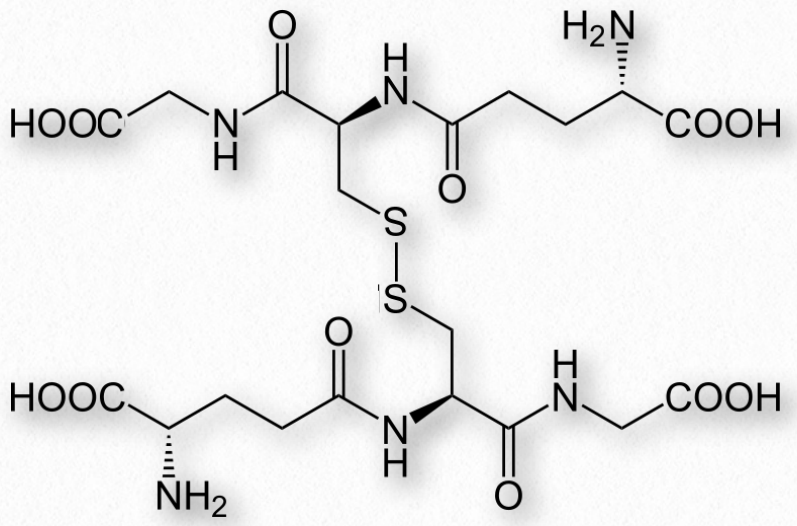


Figure 5.55 - Oxidized glutathiones (GSSG) joined by a disulfide bond

Wikipedia

Disulfide-joined glutathiones can be separated by reduction of their bonds with glutathione reductase, using electrons from NADPH for the reduction.

Non-ribosomal synthesis

Glutathione is not made by ribosomes. Rather, two enzymes catalyze its synthesis. The enzyme γ-glutamylcysteine synthetase catalyzes the joining of the glutamate to the cysteine and then glutathione synthetase catalyzes the peptide bond formation between the cysteine and the glycine. Each step requires energy from ATP.

YouTube Lectures by Kevin HERE & HERE

Essential for life

Glutathione is important for life. Mice lacking the first enzyme involved in its synthesis in the liver die in the first month after birth. In healthy cells, 90% of glutathione is in the GSH state. Higher levels of GSSG correspond to cells that are oxidatively stressed.

Besides reducing disulfide bonds in cells, glutathione is also important for the following:

• Neutralization of free radicals and reactive oxygen species.

• Maintenance of exogenous antioxidants such as vitamins C and E in their reduced forms.

• Regulation of the nitric oxide cycle

Resveratrol

Categorized as a stilbenoid, resveratrol (Figure 5.57) is a phenolic compound produced in the skin of plants such as grapes, raspberries, and blueberries, in response to injury or when they are being attacked by pathogens.

Numerous health benefits are claimed for the compound, though evidence of such benefits is in short supply. Resveratrol is metabolized rapidly in the body, so it is difficult to maintain levels of it.

Some data indicates resveratrol may improve the functioning of mitochondria. It also acts as an antioxidant and causes concentration of another anti-oxidant, glutathione, to increase. The compound appears to induce expression of manganese superoxide dis-

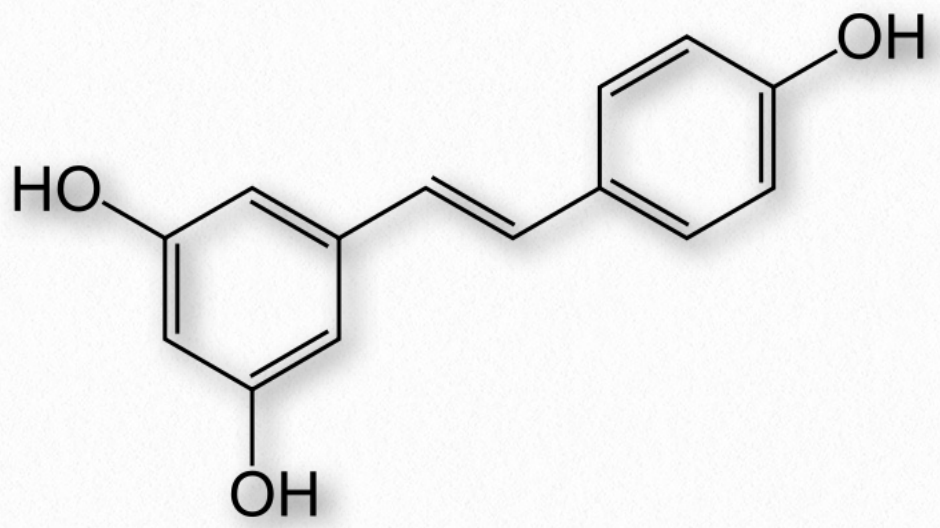


Figure 5.56 - Resveratrol

mutase (protects against reactive oxygen species) and inhibits several phosphodiesterases. This causes an increase in cAMP which results in increases in oxidation of fatty acids, mitochondria formation, gluconeogenesis, and glycogen breakdown. It has been claimed to be the cause of the French Paradox in which drinking of red wine is supposed to give protection for the cardiovascular system. Research data is lacking in support of the claim, however. Resveratrol is known to activate Sirtuin proteins, which play roles in gene inactivation.

Summary

In summary, energy is needed for cells to perform the functions that they must carry out in order to stay alive. At its most basic level, this means fighting a continual battle with entropy, but it is not the only need for energy that cells have.

References

1. Winge, D.R., Mol Cell Biol. 2012 Jul; 32(14): 2647–2652. doi: 10.1128/MCB.00573-12

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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I’m a Little Mitochondrion

To the tune of “*I’m a Lumberjack*”

Metabolic Melodies Website HERE

I'm a little mitochondrion
Who gives you energy
I use my proton gradient
To make the ATPs

He's a little mitochondrion
Who gives us energy
He uses proton gradients
To make some ATPs

Electrons flow through Complex II
To traffic cop Co-Q
Whenever they arrive there in
An FADH-two

Electrons flow through Complex II
To traffic cop Co-Q
Whenever they arrive there in
An FADH-two

Tightly coupled is my state
Unless I get a hole
Created in my membrane by
Some di-ni-tro-phe-nol

Yes tightly coupled is his state
Unless he gets a hole
Created in his membrane by
Some di-ni-tro-phenol

Both rotenone and cyanide
Stop my electron flow
And halt the calculation of
My "P" to "O" ratio

Recording by Tim Karplus
Lyrics by Kevin Ahern

N-A-D

To the tune of "*Penny Lane*"

Metabolic Melodies Website HERE

In the catabolic pathways that our cells employ
Oxidations help create the ATP
While they lower Gibbs free energy
Thanks to enthalpy

If a substrate is converted from an alcohol
To an aldehyde or ketone it is clear
Those electrons do not disappear
They just rearrange – very strange

N-A-D is in my ears and in my eyes
Help-ing mol-e-cules get oxidized
Making N-A-D-H then

And the latter is a problem anaerobically
'Cuz accumulations of it muscles hate
They respond by using pyruvate
To produce lactate

Catalyzing is essential for the cells to live
So the enzymes grab their substrates eagerly
If they bind with high affinity
Low K_m you see, just as me

N-A-D is in my ears and in my eyes
Help-ing mol-e-cules get oxidized
Making N-A-D-H then

Recorded by Tim Karplus
Lyrics by Kevin Ahern

Superoxide Dismutase

To the tune of "*Supercalifragilistiexpialidocious*"
Metabolic Melodies Website HERE

When oxygen's electrons all are in the balanced state
There's twelve of them for oh-two. The molecule is great
But problems sometimes happen on the route to complex IV
Making reactive species that the cell cannot ignore

Oh superoxide dismutase is super catalytic
Keeping cells from getting very peroxynitritic
Faster than a radical, its actions are terrific
Superoxide dismutase is super catalytic

Enzyme, enzyme deep inside
Blocking all the bad oxides

The enzyme's main advantage is it doesn't have to wait
By binding superoxide in a near-transition state
It turns it to an oxygen in mechanism one
Producing "h two oh two" when the cycle is all done

Oh superoxide dismutase you're faster than all them
You've got the highest ratio of kcat over KM
This means that superoxide cannot cause too much mayhem
Superoxide dismutase is faster than all them

Superoxide dismutase
Stopping superoxide's ways

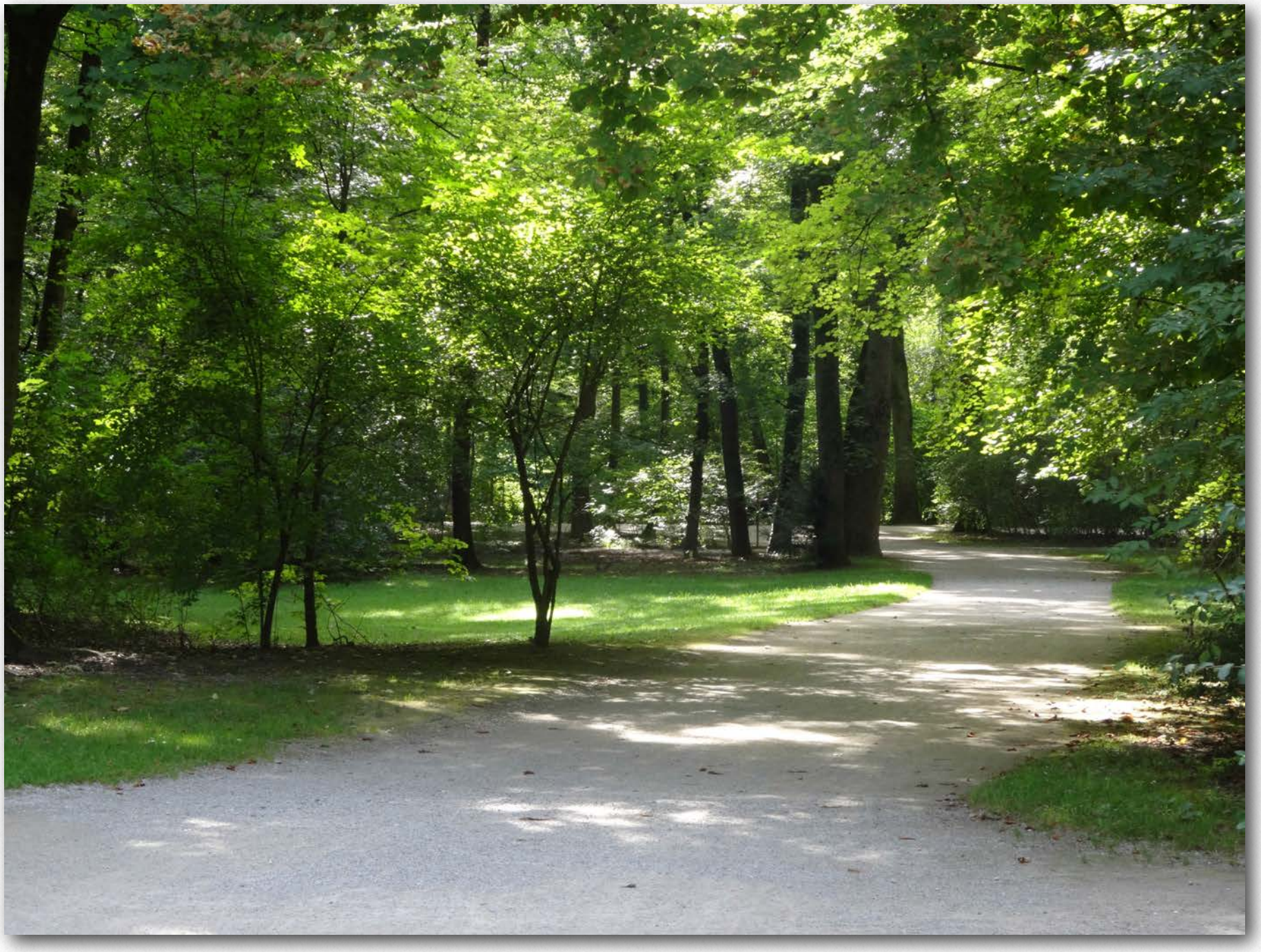
The enzyme's like a ping-pong ball that mechanistic-ly
Bounces between two copper states, plus one and two you see
So S-O-D behaves just like an anti-oxidant
Giving as much protection as a cell could ever want

Oh superoxide dismutase, the cell's in love with you
Because you let electron transport do what it must do
Without accumulation of a radical oh two
Superoxide dismutase - that's why a cell loves you

Lyrics by Kevin Ahern

No Recording Yet For This Song

Energy: Photophosphorylation



Photophosphorylation

The third type of phosphorylation to make ATP is found only in cells that carry out photosynthesis. This process is similar to oxidative phosphorylation in several ways. A primary difference is the ultimate source of the energy for ATP synthesis. In oxidative phosphorylation, the energy comes from electrons produced by oxidation of biological molecules. In photosynthesis, the energy comes from the light of the sun.

YouTube Lectures by Kevin HERE & HERE

Photons from the sun interact with chlorophyll molecules in reaction centers in the chloroplasts (Figures 5.58 & 5.59)of plants or membranes of photosynthetic bacteria.

The similarities of photophosphorylation to oxidative phosphorylation include:

• a membrane associated electron transport chain

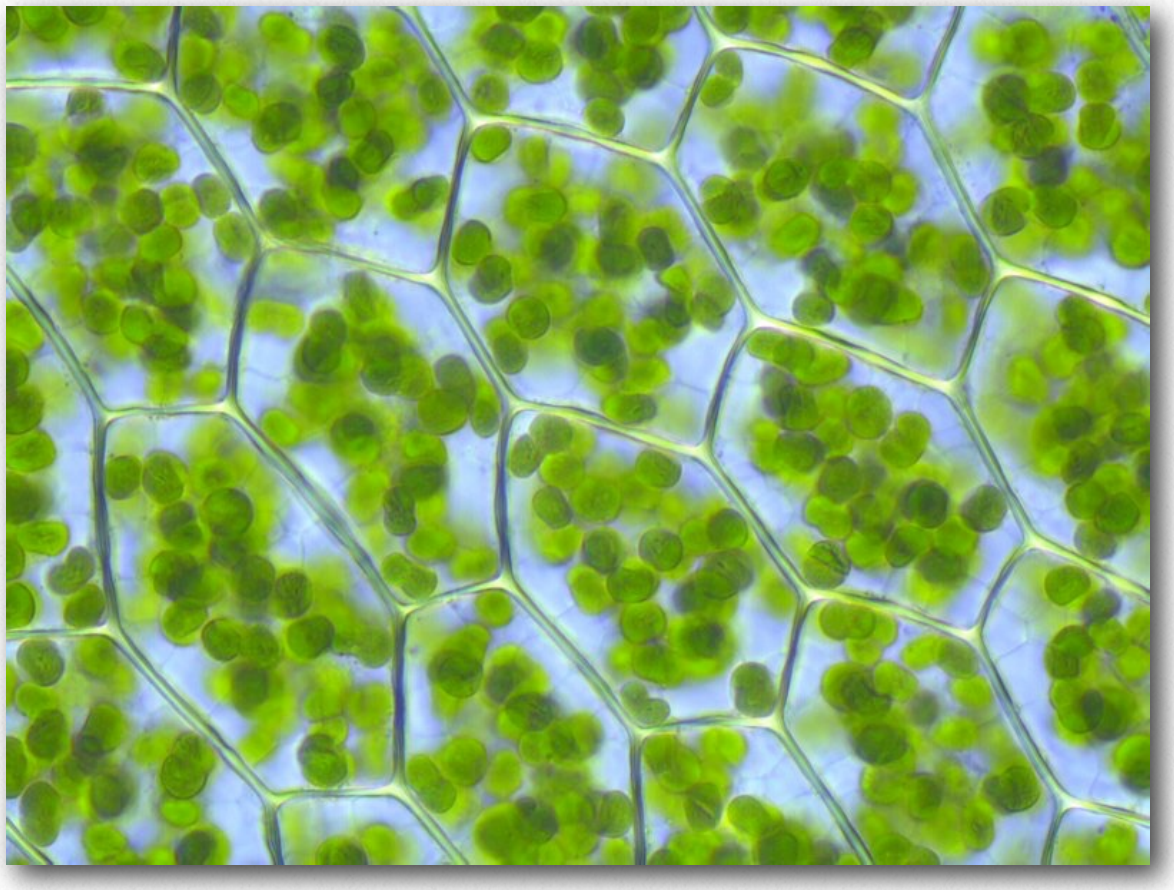


Figure 5.57 - Chloroplasts in moss cells

Wikipedia

- creation of a proton gradient
- harvesting energy of the proton gradient by making ATP with the help of an ATP synthase.

Differences

Some of the differences include :

- the source of the electrons – H_2O for photosynthesis versus NADH/$FADH_2$ for oxidative phosphorylation

- direction of proton pumping – into the thylakoid space of the chloroplasts versus outside the matrix of the mitochondrion

- movement of protons during ATP synthesis – out of the thylakoid space in photosynthesis versus into the mitochondrial matrix in oxidative phosphorylation

- nature of the terminal electron acceptor – $NADP^+$ in photosynthesis versus O_2 in oxidative phosphorylation.

Electron transport: chloroplasts *vs* mitochondria

In some ways, the movement of electrons in chloroplasts during photosynthesis is opposite that of electron transport in mitochondria. In photosynthesis, water is the source of

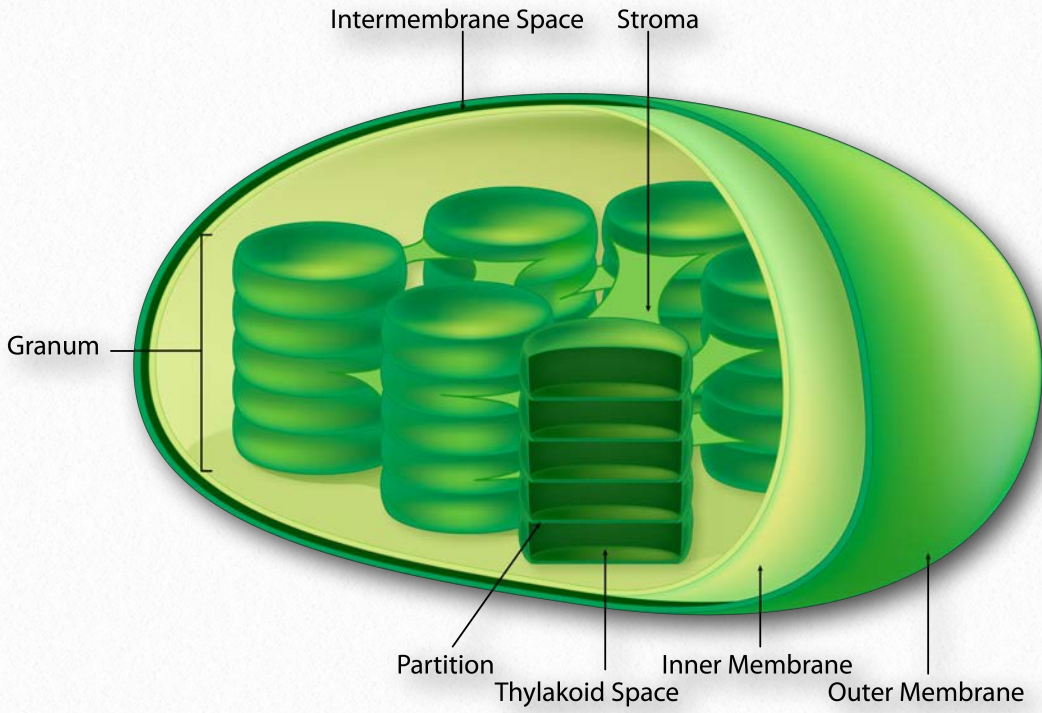


Figure 5.58 - The chloroplast

Image by Aleia Kim

electrons and their final destination is $NADP^+$ to make NADPH. In mitochondria, $NADH/FADH_2$ are electron sources and H_2O is their final destination. How do biological systems get electrons to go both ways? It would seem to be the equivalent of going to and from a particular place while always going downhill, since electrons will move according to potential.

Solar power

The answer is the captured energy of the photons from the sun (Figure 5.60), which elevates electrons to an energy where they move "downhill" to their NADPH destination in a Z-shaped scheme. The movement of electrons through this scheme in plants requires energy from photons in two places to "lift" the energy of the electrons sufficiently.

Last, it should be noted that photosynthesis actually has two phases, referred to as the light cycle (described above) and the dark cycle, which is a set of chemical reactions that captures CO_2 from the atmosphere and "fixes" it, ultimately into glucose. The dark cycle is also referred to as the Calvin Cycle and is discussed HERE.

Photosynthesis

Photosynthesis is an energy capture process found in plants and other organisms to harvest light energy and convert it into chemical energy. This photochemical energy is stored ultimately in carbohydrates which are made using ATP (from the energy harvesting), carbon dioxide and water. In most cases, a byproduct of the process is oxygen, which is released from water in the capture process. Photosynthesis is responsible for most of the oxygen in the atmosphere and it supplies the organic materials and most of the energy used by life on Earth.

Steps

The steps in the photosynthesis process varies slightly between organisms. In a broad overview, it always starts with energy capture from light by protein complexes, containing chlorophyll pigments, called reaction centers. Plants sequester these proteins in chlo-

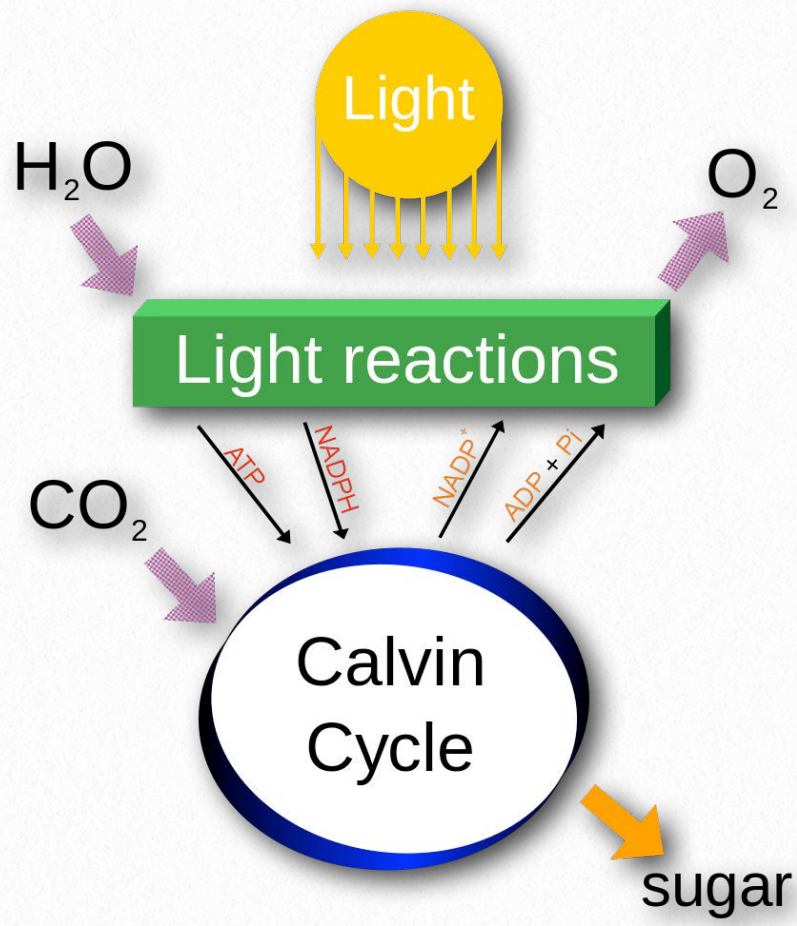


Figure 5.59 - Overview of photosynthesis
Wikipedia

roplasts, but bacteria, which don't have organelles, embed them in their plasma membranes.

Energy from the light is used to strip electrons away from electron donors (usually water) and leave a byproduct (oxygen, if water was used). Electrons are donated to a carrier and ultimately are accepted by $NADP^+$, to become NADPH. As electrons travel towards $NADP^+$, they generate a proton gradient across the thylakoid membrane, which is used to drive synthesis of ATP. Thus NADPH, ATP, and oxygen are the products of the first phase of photosynthesis called the light reactions. Energy from ATP and electrons from NADPH are used to reduce CO_2 and build sugars, which are the ultimate energy storage directly arising from photosynthesis.

Chloroplasts

Chloroplasts are found in almost all aboveground plant cells, but are primarily concentrated in leaves. The interior of a leaf, below the epidermis is made up of photosynthesis tissue called mesophyll, which can contain up to 800,000 chloroplasts per square millimeter.

The chloroplast's membrane has a phospholipid inner membrane, a phospholipid outer membrane, and a region between them called the intermembrane space (Figure 5.61). Within the inner chloroplast membrane is the stroma, in which the chloroplast DNA and the enzymes of the Calvin cycle are located. Also within the stroma are stacked, flattened disks known as thylakoids which are defined by their thylakoid membranes. The space within the thylakoid membranes are termed the thylakoid spaces or thylakoid lumen. The protein complexes containing the light-absorbing pigments, known as photosystems, are located on the thylakoid membrane. Besides chlorophylls, carotenes and xanthophylls are also present, allowing for absorption of light energy over a wider range. The same pigments are used by green algae and land plants.

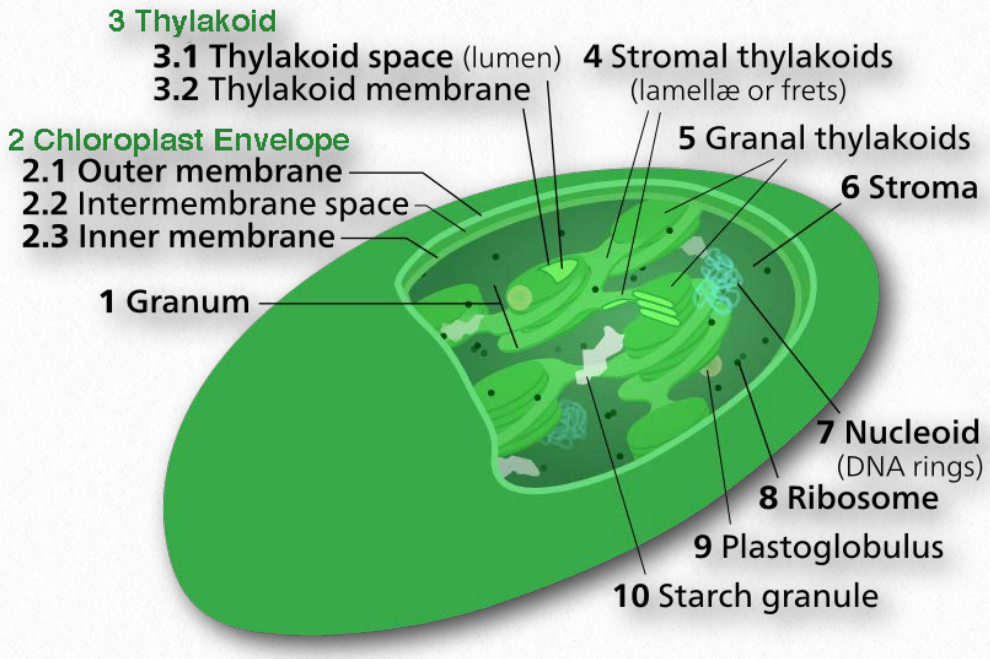


Figure 5.60 - Chloroplast anatomy

Wikipedia

Brown algae and diatoms add fucoxanthin (a xanthophyll) and red algae add phycoerythrin to the mix. In plants and algae, the pig-

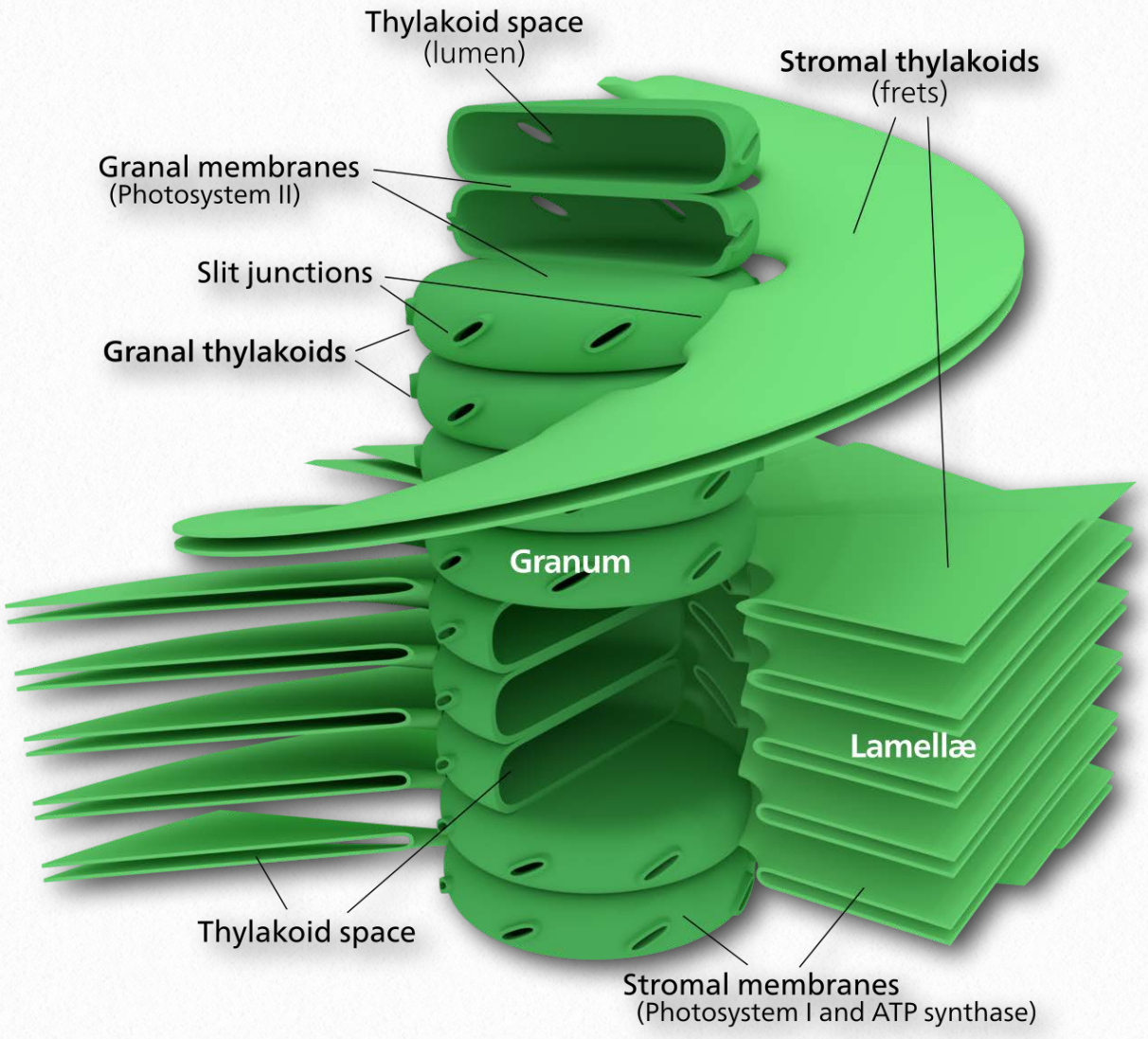


Figure 5.61 - Side view of thylakoids

Wikipedia

ments are held in a very organized fashion complexes called antenna proteins that help funnel energy, through resonance energy transfer, to the reaction center chlorophylls. A system so organized is called a light harvesting complex. The electron transport complexes of photosynthesis are also located on the thylakoid membranes.

YouTube Lectures by Kevin HERE & HERE

Light reactions of photosynthesis

In chloroplasts, the light reactions of photosynthesis involving electron transfer occur in the thylakoid membranes (Figure 5.62). Separate biochemical reactions involving the assimilation of carbon dioxide to make glucose are referred to as the Calvin cycle, also sometimes referred to as the "dark reactions". This will be discussed elsewhere in the section on metabolism (HERE).

The chloroplasts are where the energy of light is captured, electrons are stripped from water, oxygen is liberated, electron transport occurs, NADPH is formed, and ATP is generated. The thylakoid membrane corresponds to the inner membrane of the mitochondrion for transport of electrons and proton pumping (Figure 5.63).

The thylakoid membrane does its magic using four major protein complexes. These include Photosystem II (PS II), Cytochrome b6f complex (Cb6f), Photosystem I (PS I), and ATP synthase. The roles of these complexes, respectively, are to capture light energy, create a proton gradient from electron movement, capture light energy

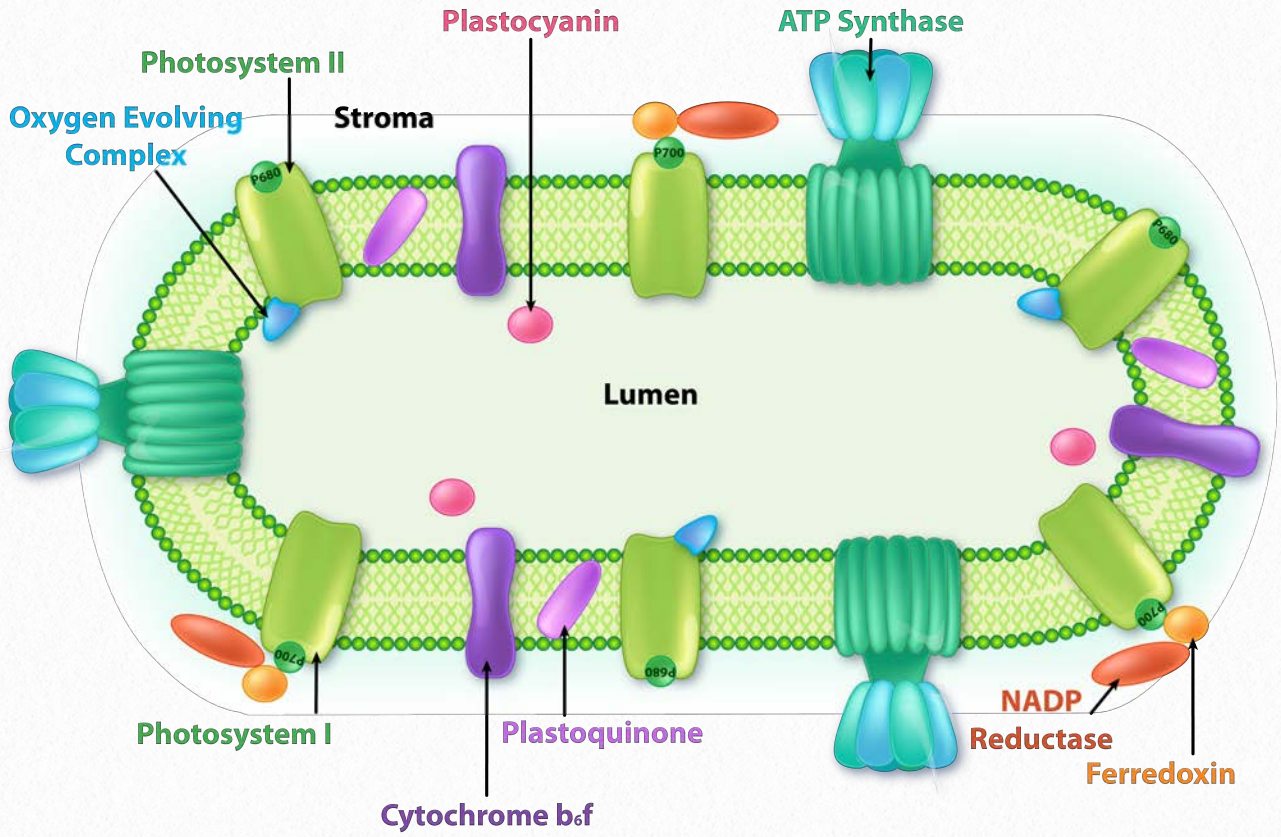


Figure 5.62 - Complexes in the thylakoid membrane

Image by Aleia Kim

(again), and use proton gradient energy from the overall process to synthesize ATP.

Light harvesting

Harvesting the energy of light begins in PS II with the absorption of a photon of light at a reaction center. PS II performs this duty best with light at a wavelength of 680 nm and it readily loses an electron to excitation when this occurs, leaving PS II with a positive charge. This electron must be replaced. The ultimate replacement source of electrons is water, but water must lose four electrons and PS II can only accept one at a time.

Interactive Learning Module HERE

Photosynthesis left me aghast
As electrons all went whizzing past
Leaving water at start
They trace the Z chart
In the membranes of each chloroplast

Manganese centers

An intermediate Oxygen Evolving Complex (OEC) contains four manganese centers that provide the immediate replacement electron that PSII requires. After four electrons have been donated by the OEC to PS II, the OEC extracts four electrons from two water molecules, liberating oxygen and dumping four protons into the thylakoid space, thus contributing to the proton gradient. The excited electron from PS II must be passed to another carrier very quickly, lest it decay back to its original state. It does this, giving its electron within picoseconds to pheophytin (Figure 5.64).

Pheophytin passes the electron on to protein-bound plastoquinones. The first is known as PQ_A. PQ_A hands the electron off to a second plastoquinone (PQ_B), which waits for a second electron and collects two protons to become PQH_2, also known as plastoquinol (Figure 5.65). PQH_2

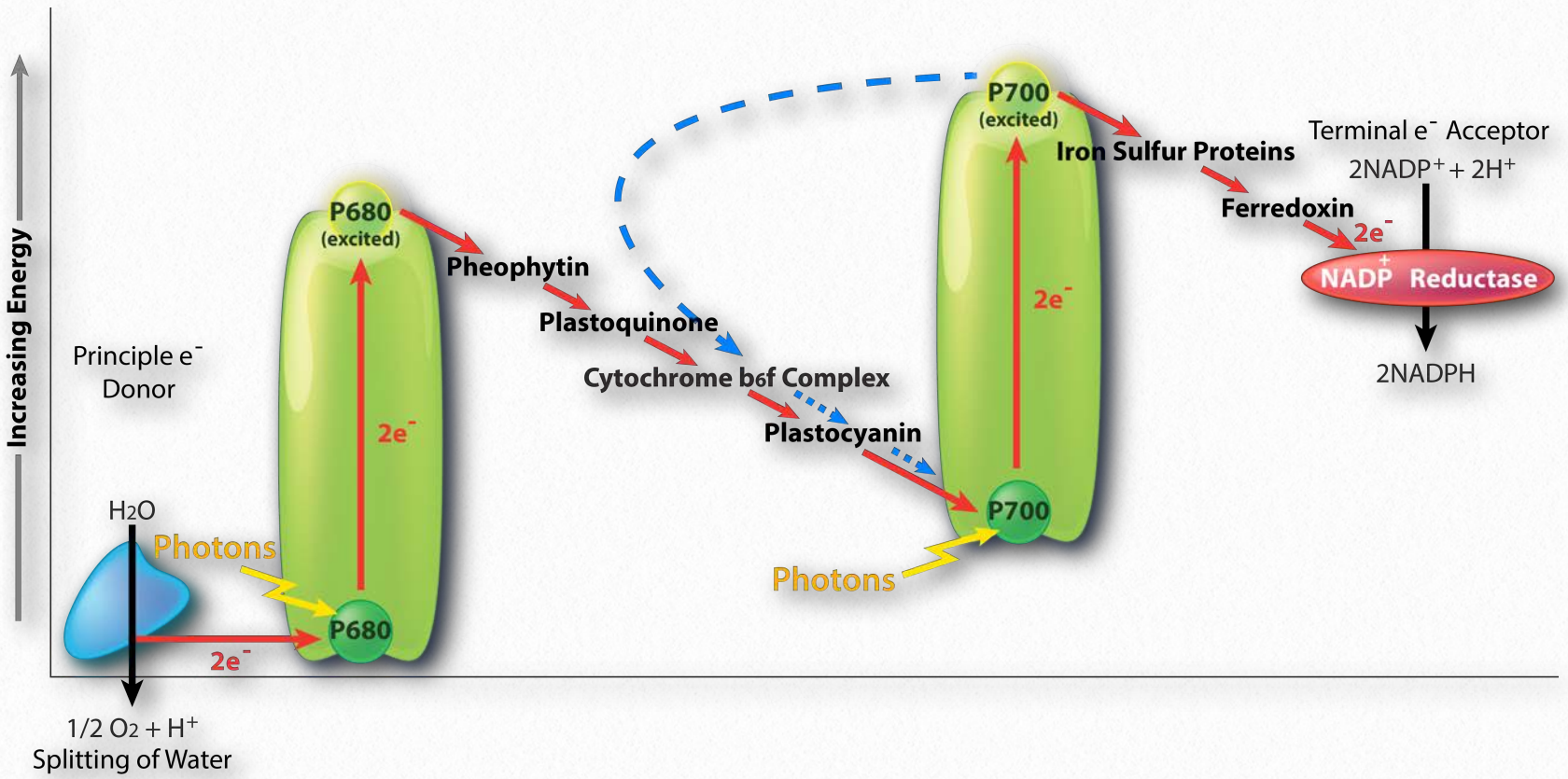


Figure 5.63 - Movement of electrons through photosystems. Cyclic photophosphorylation shown by blue dashed line

Image by Aleia Kim and Pehr Jacobson

passes these to the Cytochrome b_6f complex (Cb_6f) which uses passage of electrons through it to pump protons into the thylakoid space. ATP synthase makes ATP from the proton gradient created in this way. Cb6f drops the electron off at plastocyanin, which holds it until the next excitation process begins with absorption of another photon of light at 700 nm by PS I.

Absorption of light at PS I

With absorption of a photon of light by PS I, a process begins, that is similar to the process in PS II. PS I gains a positive charge as a result of the loss of an excited electron and pulls the electron in plastocyanin away from it. Meanwhile, the excited electron from PS I passes through an iron-sulfur protein, which gives the electron to ferredoxin (another iron sulfur protein). Ferredoxin then passes the electron off to the last protein in the system known as Ferredoxin:$NADP^+$ oxidoreductase, which gives the electron and a proton to $NADP^+$, creating NADPH.

Note that reduction of $NADP^+$ to NADPH requires two electrons and one proton, so the four electrons and two protons from oxidation of water will result in production of two molecules of NADPH. At this point, the light cycle is complete - water has been oxidized, ATP has been created, and NADPH has been made. The electrons have made their way from water to NADPH via carriers in the thylakoid membrane and their movement has released sufficient energy to make ATP. En-

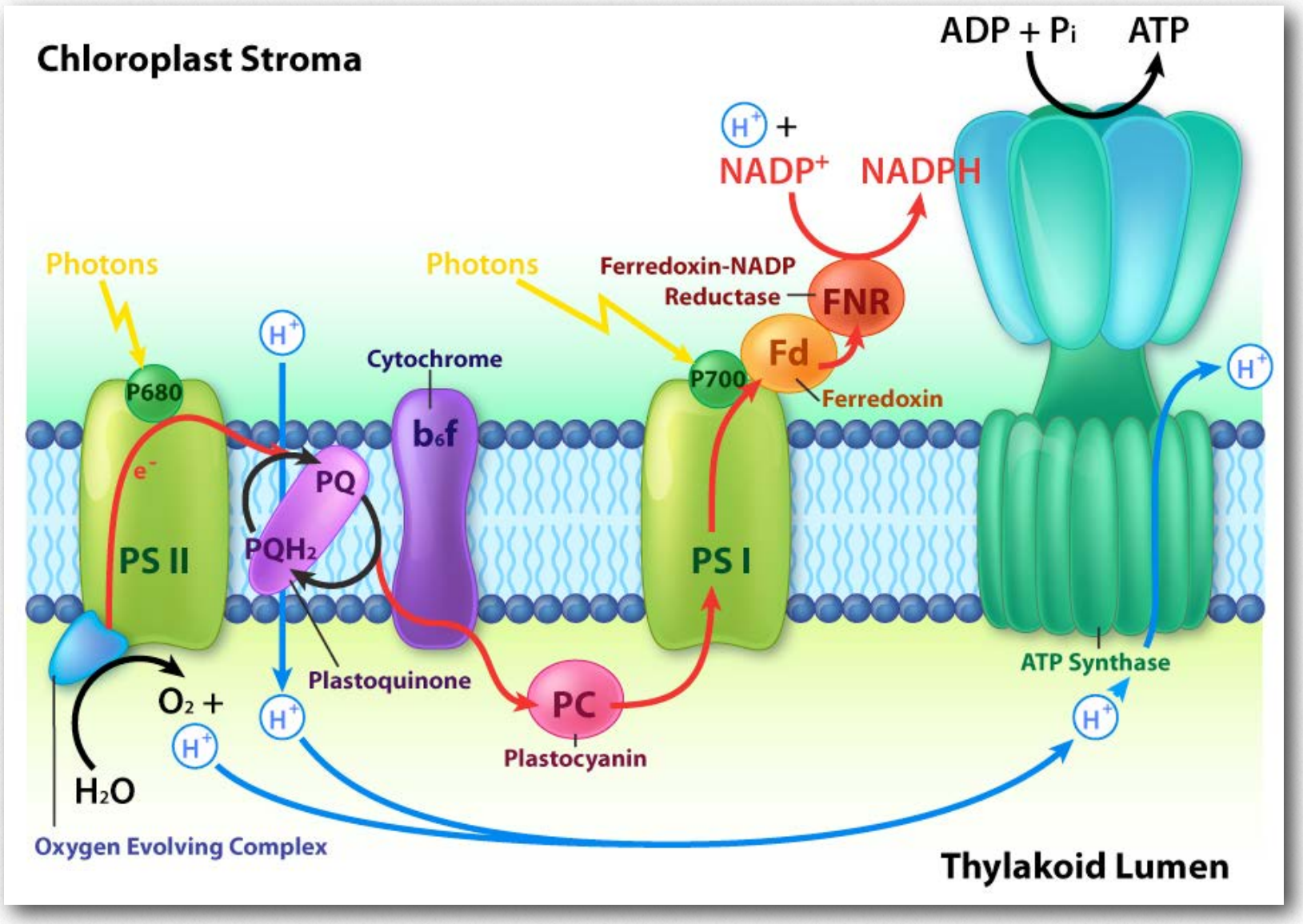


Figure 5.64 - Movement of electrons and protons through the thylakoid membrane

Image by Aleia Kim

ergy for the entire process came from four photons of light.

The two photosystems performing all of this magic are protein complexes that are similar in structure and means of operation. They absorb photons with high efficiency so that whenever a pigment in the photosynthetic reaction center absorbs a photon, an electron from the pigment is excited and transferred to another molecule almost instantaneously. This reaction is called photo-induced charge separation and it is a unique means of transforming light energy into chemical forms.

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Cyclic photophosphorylation

Besides the path described above for movement of electrons through PS I, plants have an alternative route that electrons can take. Instead of electrons going through ferredoxin to form NADPH, they instead take a backwards path through the the proton-pumping b6f complex. This system, called cyclic photophosphorylation (Figure 5.64) which generates more ATP and no

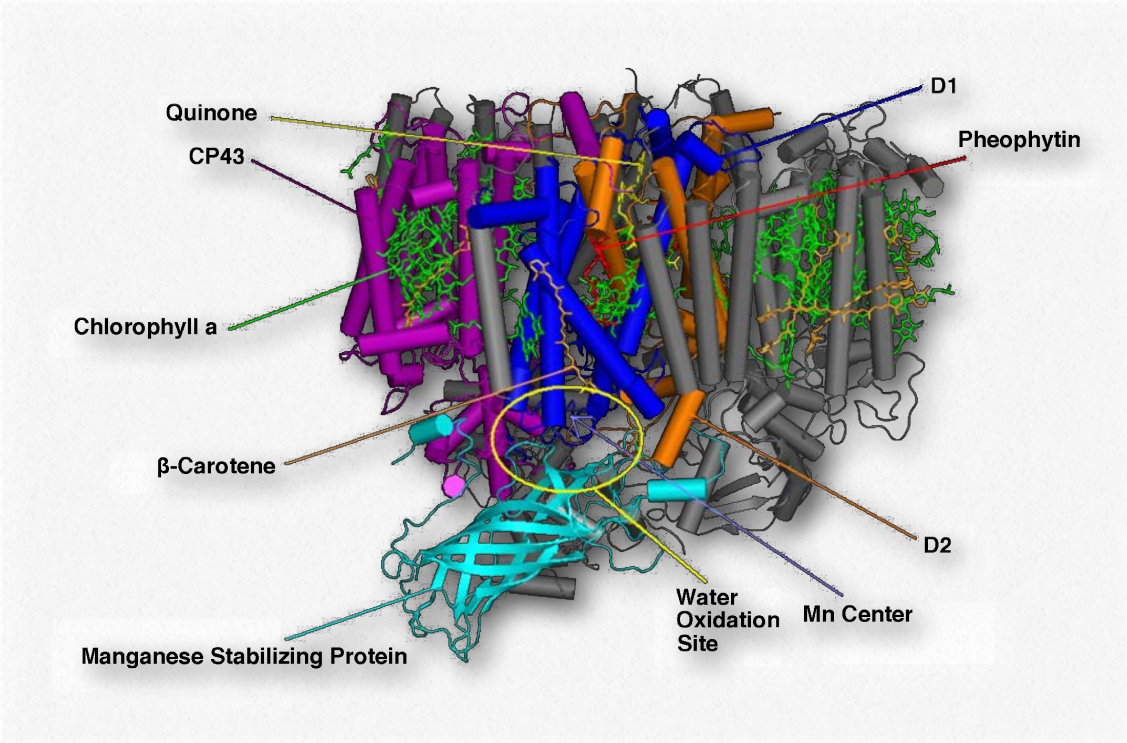

Figure 5.65 - Photosystem II of cyanobacteria

Wikipedia

NADPH, is similar to a system found in green sulfur bacteria. The ability of plants to switch between non-cyclic and cyclic photosystems allows them to make the proper ratio of ATP and NADPH they need for assimilation of carbon in the dark phase of photosynthesis. This ratio turns out to be 3 ATPs to 2 NADPHs.

Photosynthetic energy

The output of the photophosphorylation part of photosynthesis (O_2, NADPH, and ATP), of course, is not the end of the process of photosynthesis. For the growing plant, the NADPH and ATP are used to capture carbon dioxide from the atmosphere and convert it (ultimately) into glucose and other important carbon compounds. This, as noted previously, occurs in the Calvin Cycle (see HERE) in what is called the dark phase of the process. The oxygen liberated in the process is a necessary for respiration of all aerobic life forms on Earth. Indeed, it is believed that essentially all of the oxygen in the atmosphere today is the result the splitting of water in photosynthesis over the many eons that the process has existed.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

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Photosynthesis is Divine

To the tune of "*Scarborough Fair*"

Metabolic Melodies Website HERE

Photosynthesis is divine
Fixing carbon using sunshine
It's thanks to plants that we've got a prayer
They pull CO_2 from the air

Reaping energy from the sun
It's efficient second to none
You grab the photons almost at will
Protoporphyrin chlorophyll

Light reactions of System II
Split up water, making O_2
Electrons pass through schemes labeled 'Z'
Pumping protons gradiently

ATP's made due to a shift
Of the protons spinning quite swift

An enzyme turbine, cellular maze
You know as A-T-P synthase

Carbon's fixed onto a substrate
Ribulose-1,5-bisphosphate
Rubisco acts in-e-fficient-ly
Splitting it into 3PGs

If the enzyme grabs an O_2
It makes glycolate, it is true
The Calvin Cycle works in a wheel
Giving plants a sugary meal

So photosynthesis is divine
'Cause it happens all of the time
From dawn to dusk and times in between
Solar panels truly are green

Recording by David Simmons
Lyrics by Kevin Ahern

6

Metabolism

"The true sign of intelligence is not knowledge but imagination."

- Albert Einstein

The term 'metabolism' (from the Greek, to change) is defined as sum total of all the chemical processes occurring within a living cell or organism that are necessary for the maintenance of life. In metabolism some substances are broken down to yield energy for vital processes (catabolism) while other substances, necessary for life, are synthesized (anabolism).

Studying the entire set of chemical processes necessary for life may seem intimidating, but in fact, there are two factors that make the study of metabolism much simpler than might be expected. The first is the unity of biochemical processes across species. Carl Sagan noted that “when you look more generally at life on Earth, you find that it is all the same kind of life. There are not many different kinds; there's only one kind. It uses about fifty fundamental biological building blocks, organic molecules.” This means that what we learn in one organism will help us understand the biochemistry of all other organisms.

The second reassuring fact, in the words of Sir Frederick Gowland Hopkins, is that "in the study of the intermediate processes of metabolism we have to deal not with complex substances which elude ordinary chemical methods, but with the simple substances undergoing comprehensible reactions.

With that as our starting point . . . . . .

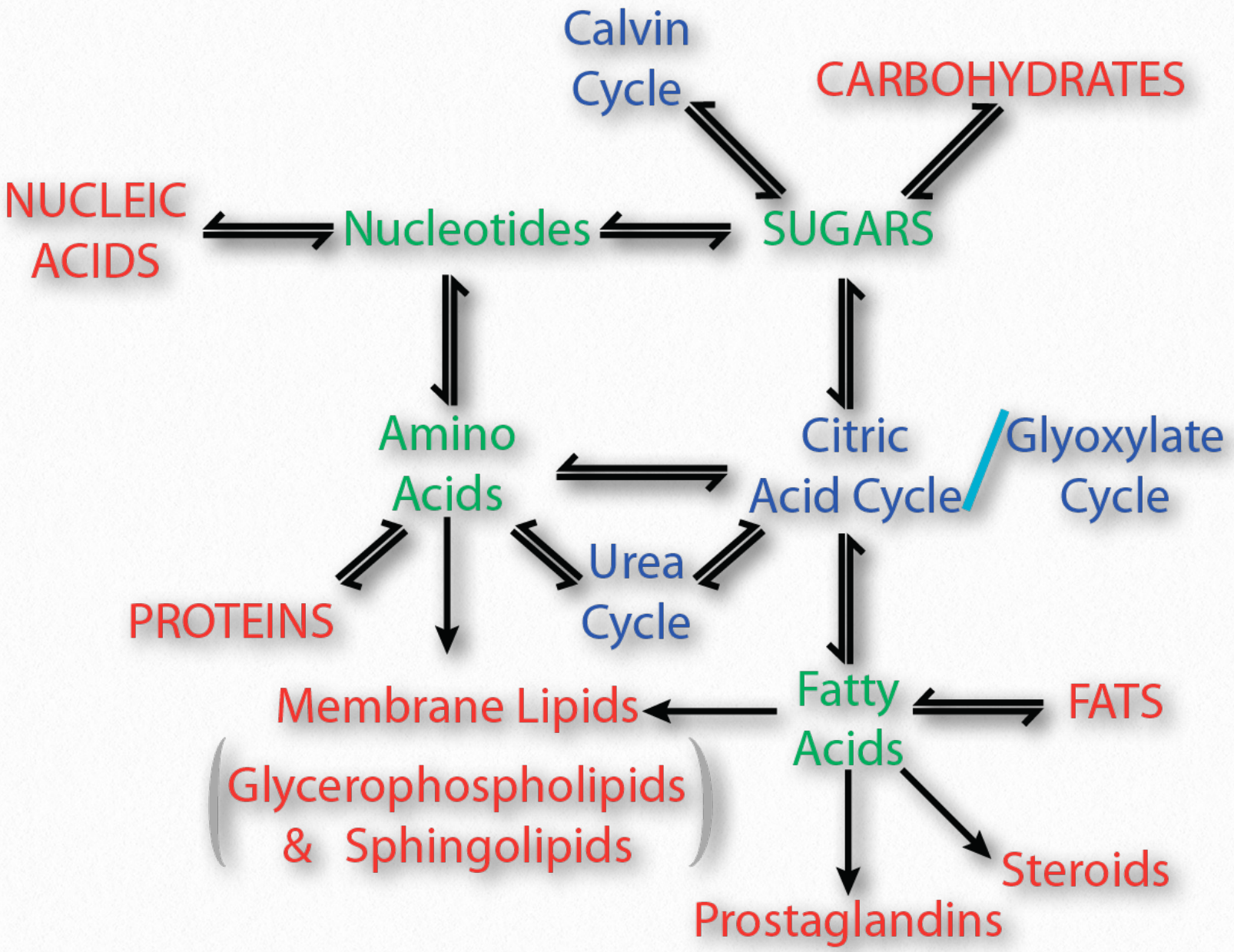

Figure 6.1 - Overview of metabolism

Image by Aleia Kim

Metabolism: Sugars

Glycolysis

Carbohydrates, whether synthesized by photosynthetic organisms, stored in cells as glycogen, or ingested by heterotrophs, must be broken down to obtain energy for the cell's activities as well as to synthesize other molecules required by the cell. Starch and glycogen, polymers of glucose, are the main energy storage forms of carbohydrates in plants and animals, respectively. To use these sources of energy, cells must first break down the polymers to yield glucose. The glucose is then taken up by cells through transporters in cell membranes. The metabolism of glucose, as well as other six carbon sugars (hexoses) begins with the catabolic pathway called glycolysis. In this pathway, sugars are oxidized and broken down into pyruvate molecules. The corresponding anabolic pathway by which glucose is synthesized is termed gluconeogenesis. Neither glycolysis nor gluconeogenesis is a major oxidative/reductive process, with one step in each one involving loss/gain of elec-

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Your cells may have a mounting crisis
Should they not go through glyco-lye-sis
No glucose energy releases
Until it's fractured into pieces

trons, but the product of glycolysis, pyruvate, can be completely oxidized to carbon dioxide (Figure 6.2). Indeed, without production of pyruvate from glucose in glycolysis, a major energy source for the cell would not be available.

Glucose is the most abundant hexose in nature and is traditionally used to illustrate the reactions of glycolysis, but fructose (in the form of fructose-6-phosphate) is also readily metabolized, while galactose can easily be converted into glucose for catabolism in the pathway as well. The end metabolic products of glycolysis are two molecules of ATP, two molecules of NADH and two molecules of pyruvate (Figure 6.3), which, in turn, can be oxidized further in the citric acid cycle.

Entry points for glycolysis

Glucose and fructose are the sugar 'funnels' serving as entry points to the glycolytic pathway. Other sugars must be converted to either of these forms to be metabolized in glycolysis. Some pathways, including the Calvin

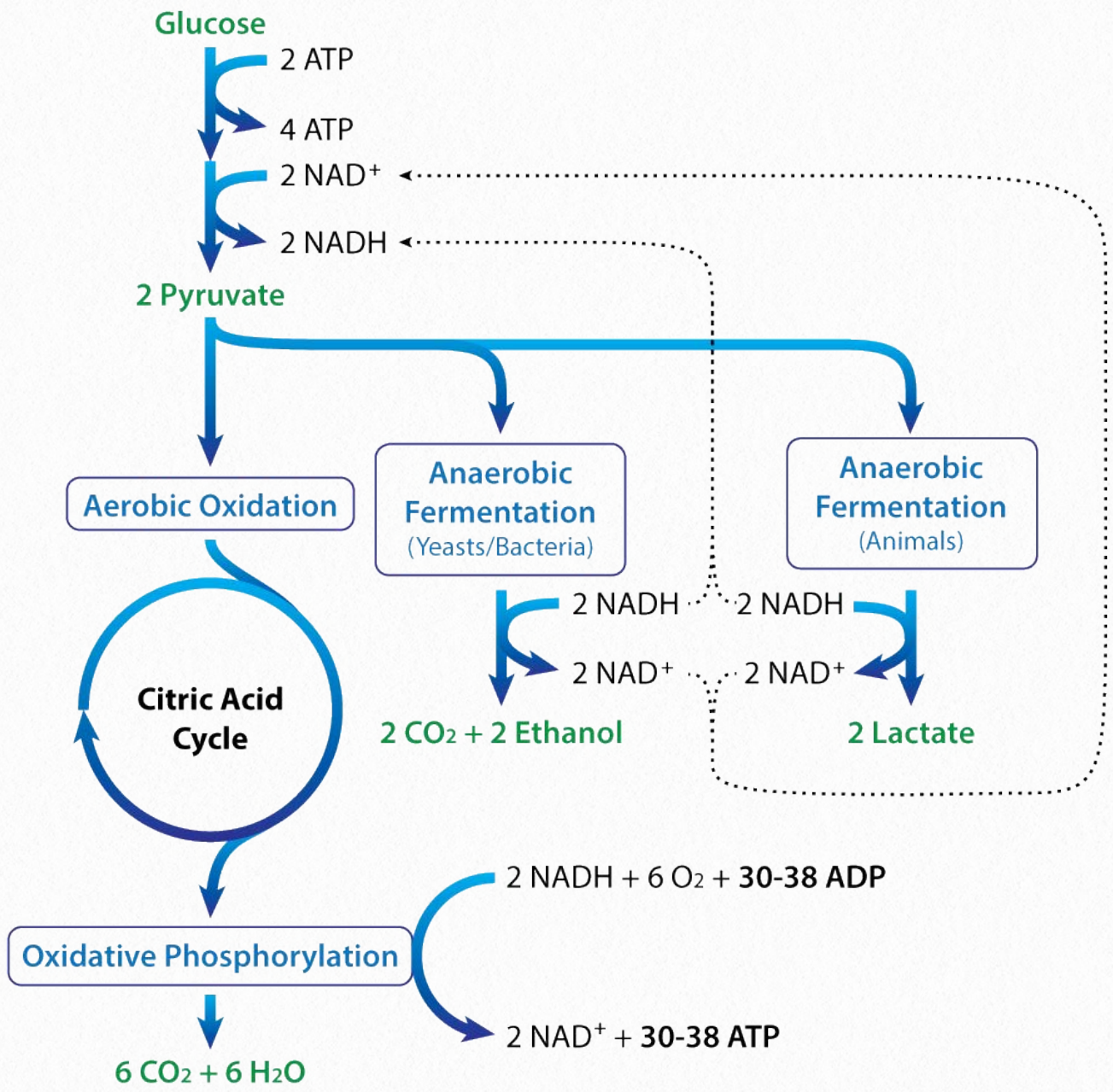

Figure 6.2 - Metabolic fates of glucose

Image by Aleia Kim

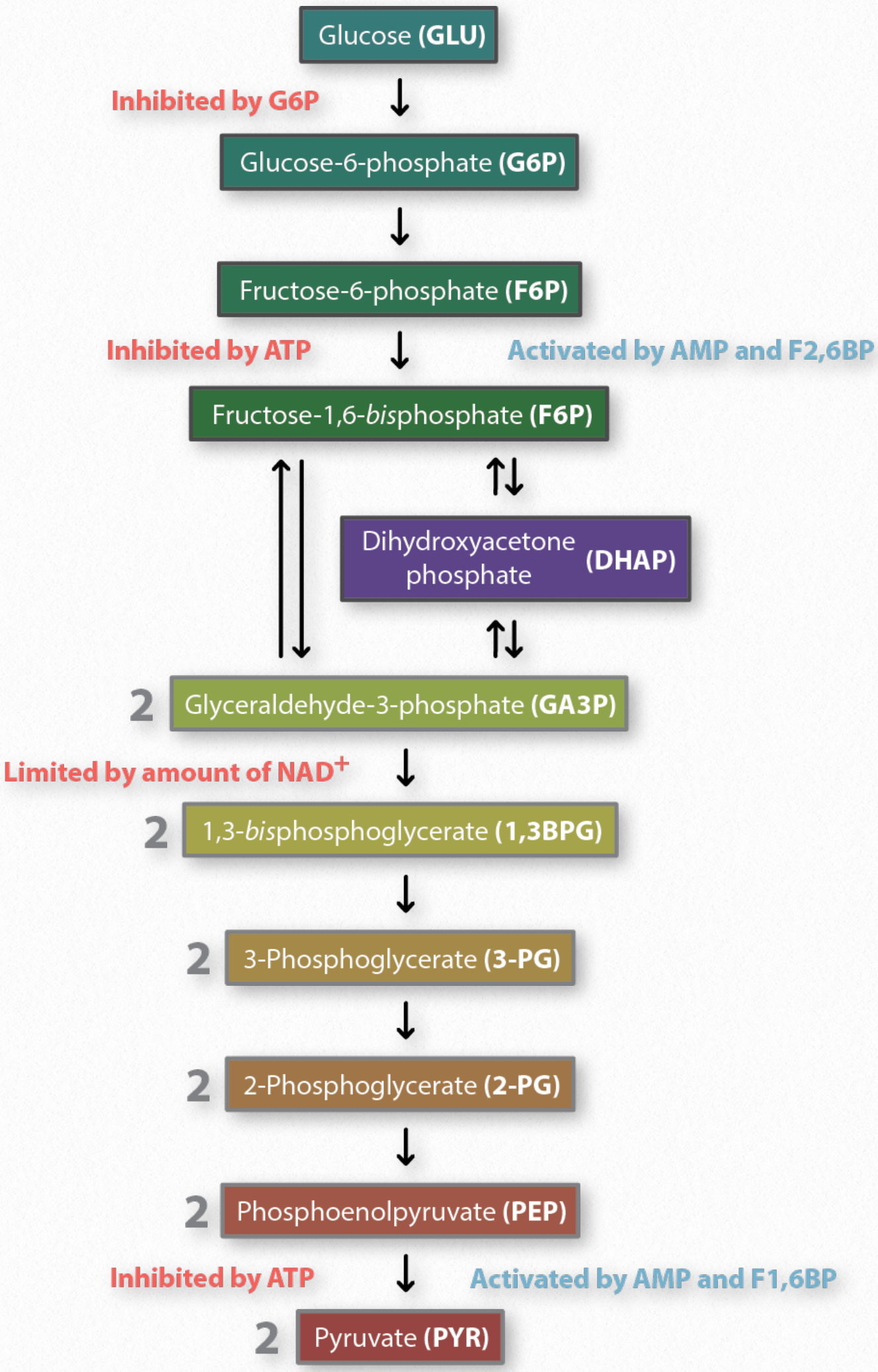

Figure 6.3 - Glycolysis and its Regulators

Image by Ben Carson

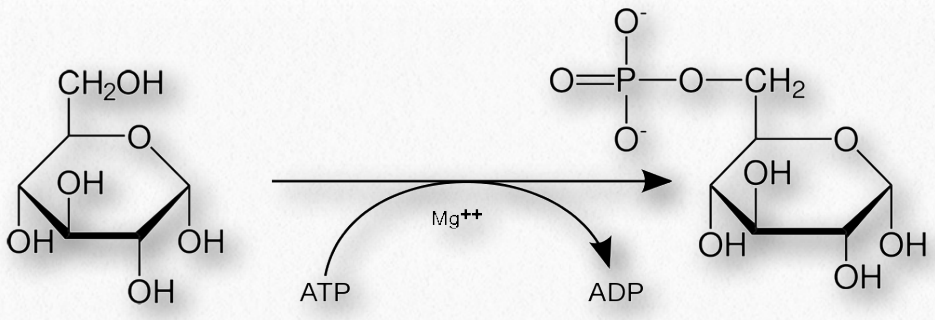

Figure 6.4 - Reaction #1 - Phosphorylation of glucose - catalyzed by hexokinase

Cycle and the Pentose Phosphate Pathway (PPP) contain intermediates in common with glycolysis, so in that sense, almost any cellular sugar can be metabolized here.

Other pathways

Intermediates of glycolysis and gluconeogenesis that are common to other pathways include glucose-6-phosphate (PPP, glycogen metabolism), Fructose-6-phosphate (Calvin Cycle, PPP), Glyceraldehyde-3-phosphate (Calvin Cycle, PPP), dihydroxyacetone phosphate (PPP, glycerol metabolism, Calvin Cycle), 3-phosphoglycerate (Calvin Cycle, PPP), phosphoenolpyruvate (C4 plant metabolism, Calvin Cycle), and pyruvate (fermentation, acetyl-CoA genesis, amino acid metabolism). It is worth noting that glycerol from the breakdown of fat can readily be metabolized to dihydroxyacetone phosphate (DHAP) and thus enter the glycolysis pathway. It is the only part of a fat that is used in these pathways.

Reaction 1

Glucose gets a phosphate from ATP to make glucose-6-phosphate (G6P) in a reaction catalyzed by the enzyme hexokinase, a transferase enzyme.

$$\text{Glucose} + \text{ATP} \rightleftarrows \text{G6P} + \text{ADP} + \text{H}^+$$

Hexokinase is one of three regulated enzymes in glycolysis and is inhibited by one of the products of its action - G6P. Hexokinase has flexibility in its substrate binding and is able to phosphorylate a variety of hexoses, including fructose, mannose, and galactose.

Why phosphorylate glucose?

Phosphorylation of glucose serves two important purposes. First, the addition of a phosphate group to glucose effectively traps it in the cell, as G6P cannot diffuse across the lipid bilayer. Second, the reaction decreases the concentration of free glucose, favoring additional import of the molecule. G6P is a substrate for the pentose phosphate pathway and can also be converted to glucose-1-phosphate (G1P) for use in glycogen synthesis and galactose metabolism (Figure 6.5).

It is worth noting that the liver has an enzyme like hexokinase called glucokinase, which

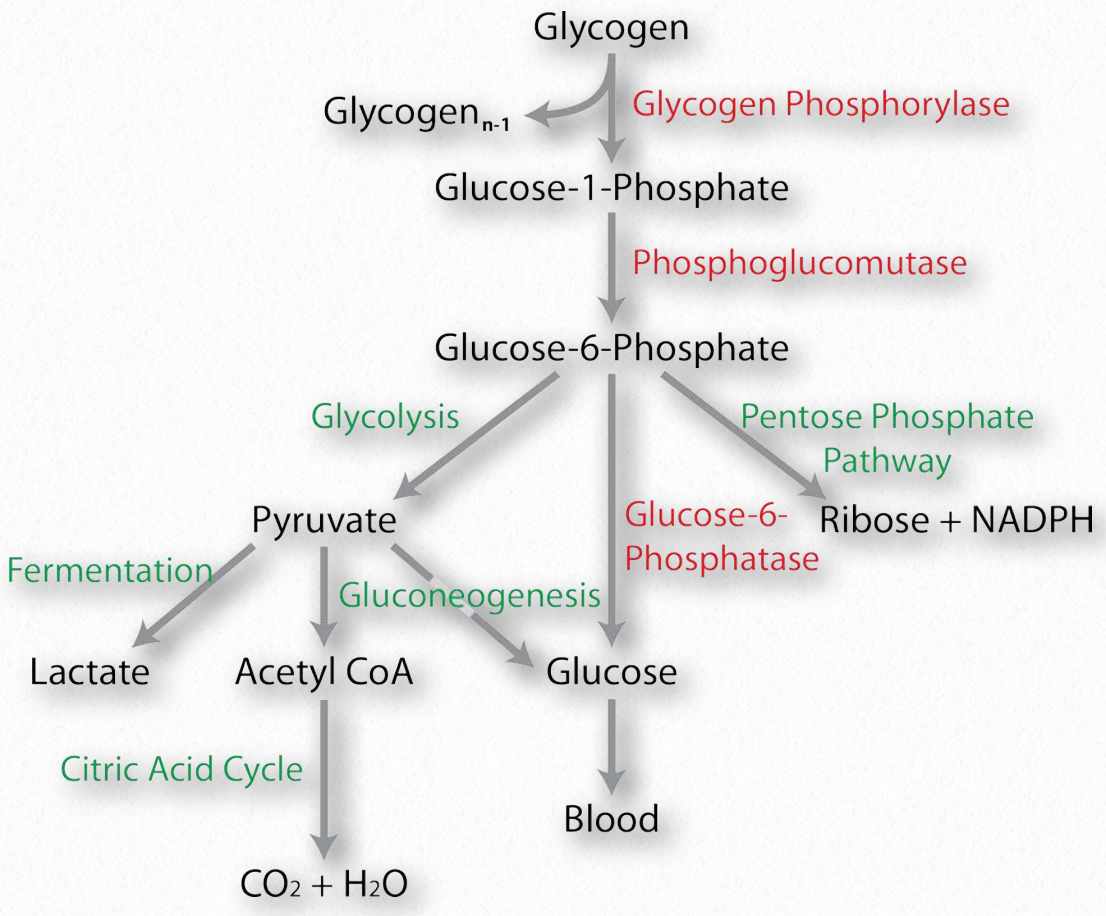

Figure 6.5 - The centrality of glucose-6-phosphate in metabolism

Image by Aleia Kim

where cellular concentrations of glucose can be relatively high. With a lower affinity glucose phosphorylating enzyme, glucose is not converted to G6P unless glucose concentrations get high, so the liver is able to release the glucose it makes into the bloodstream for the rest of the body to use.

Reaction 2

Next, G6P is converted to fructose-6-phosphate (F6P), in a reaction catalyzed by the enzyme phosphoglucoisomerase.

G6P ⇄ F6P

has a much higher K_m (lower affinity) for glucose. This is important, because the liver is a site of glucose synthesis (gluconeogenesis)

The reaction has a low $\Delta G°'$, so it is readily favorable in either direction with

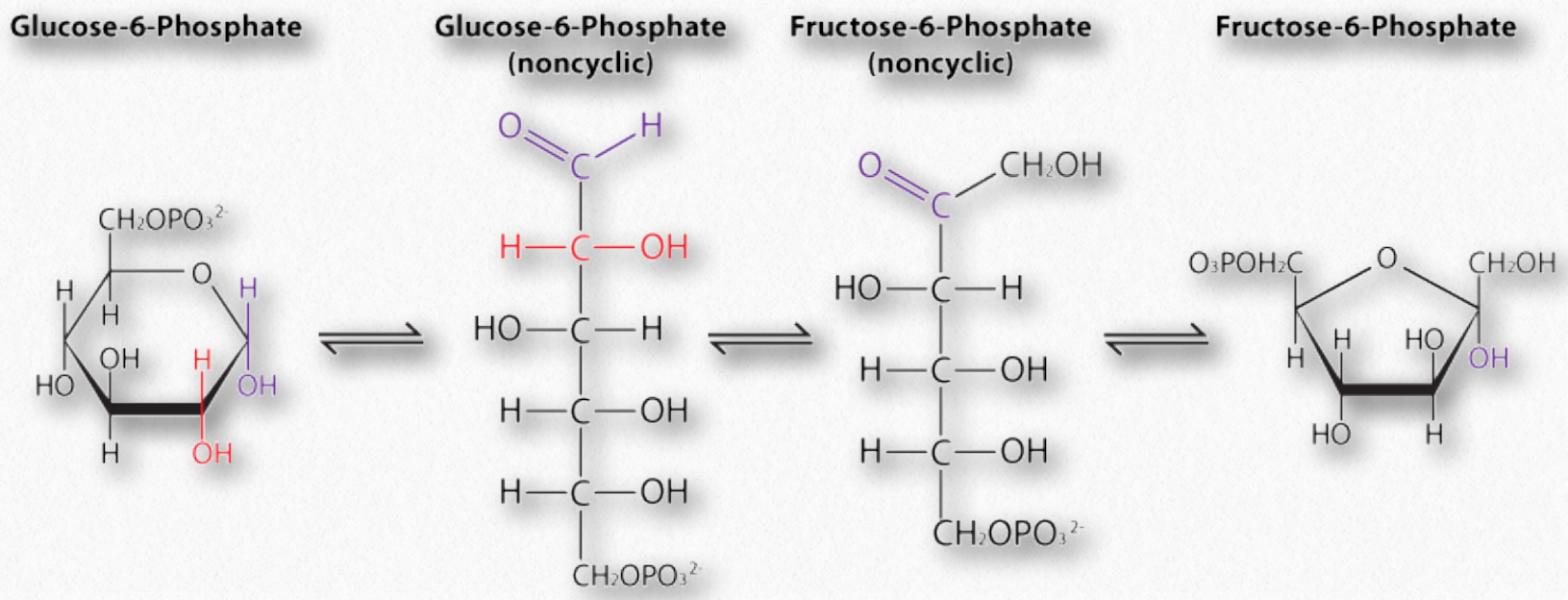

Figure 6.6 - Mechanism of conversion of G6P to F6P in reaction #2

only slight changes in concentration of reactants.

Reaction 3

F6P + ATP ⇄ F1,6BP + ADP + H^+

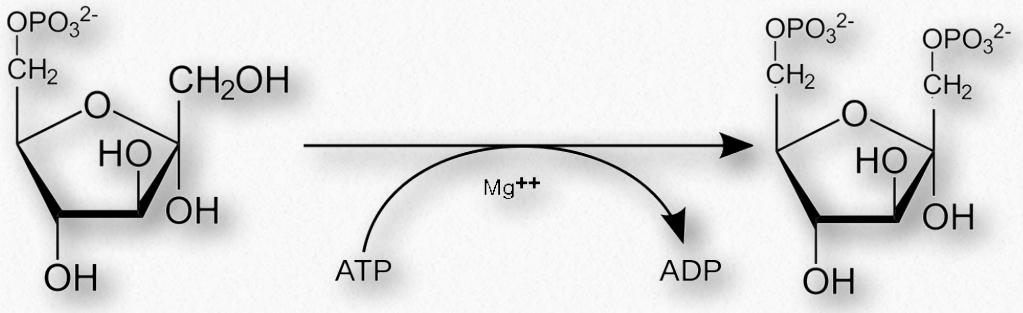

Figure 6.7 - Reaction #3 - Conversion of F6P to F1,6BP by PFK

Wikipedia

The second input of energy occurs when F6P gets another phosphate from ATP in a reaction catalyzed by the enzyme phosphofructokinase-1 (PFK-1 - another transferase) to make fructose-1,6-bisphosphate (F1,6BP). PFK-1 is a very important enzyme regulating glycolysis, with several allosteric activators and inhibitors (see HERE).

YouTube Lectures by Kevin HERE & HERE

Like the hexokinase reaction the energy from ATP is needed to make the reaction energetically favorable.

PFK-1 is the most important regulatory enzyme in the pathway and this reaction is the rate-limiting step. It is also one of three essentially irreversible reactions in glycolysis.

A variant enzyme found in plants and some bacterial uses pyrophosphate rather than ATP as the energy source and due to the lower energy input from hydrolysis of the pyrophosphate, that reaction is reversible.

Reaction 4

F1,6BP ⇄ D-GLYAL3P + DHAP

With the glycolysis pump thus primed, the pathway proceeds to split the F1,6BP into two 3-carbon intermediates. This reaction catalyzed by the lyase known as aldolase is energetically a “hump” to overcome in the glycolysis direction ($\Delta G^{\circ\prime}$ = +24 kJ/mol

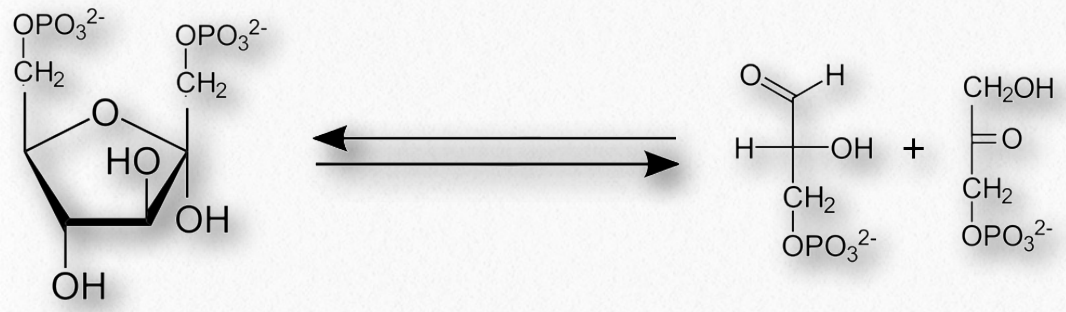

Figure 6.8 - Reaction #4 - Breakdown of F1,6BP into GLYAL3P (left) and DHAP (right) by aldolase

°K) so to get over the energy hump, cells must increase the concentration the reactant (F1,6BP) and decrease the concentration of the products, which are D-glyceraldehyde-3-phosphate (D-GLYAL3P) and dihydroxyacetone phosphate (DHAP).

A novel scheme facilitates decreasing concentration of the products (see below). Aldolases cut the ketose ring by two different mechanisms and these enzymes are grouped as Class I (in animals and plants) and Class II (in fungi and bacteria).

Reaction 5

DHAP ⇄ D-GLYAL3P

In the next step, DHAP is converted to D-GLYAL3P in a reaction catalyzed by the enzyme triosephosphate isomerase. At this point, the six carbon glucose molecule has been broken down to two units of three carbons each - D-GLYAL3P. From this point forward each reaction of glycolysis contains two of each molecule. Reaction #5 is fairly readily reversible in cells.

The enzyme is of note because it is one example of a "perfect enzyme." Enzymes in this category have very high ratios of K_{cat}/K_m that approach a theoretical maximum limited only by the diffusion of substrate into the active site of the enzyme. The apparent reason for the enzyme evolving in this way is that the mechanism of the reaction produces an unstable, toxic intermediate (Figure 6.9). With the reaction proceeding as rapidly as it does, there is less chance of the intermediate escaping and causing damage in the cell.

Reaction 6

D-GLYAL3P + NAD^+ + P_i ⇅ D-1,3BPG + NADH + H^+

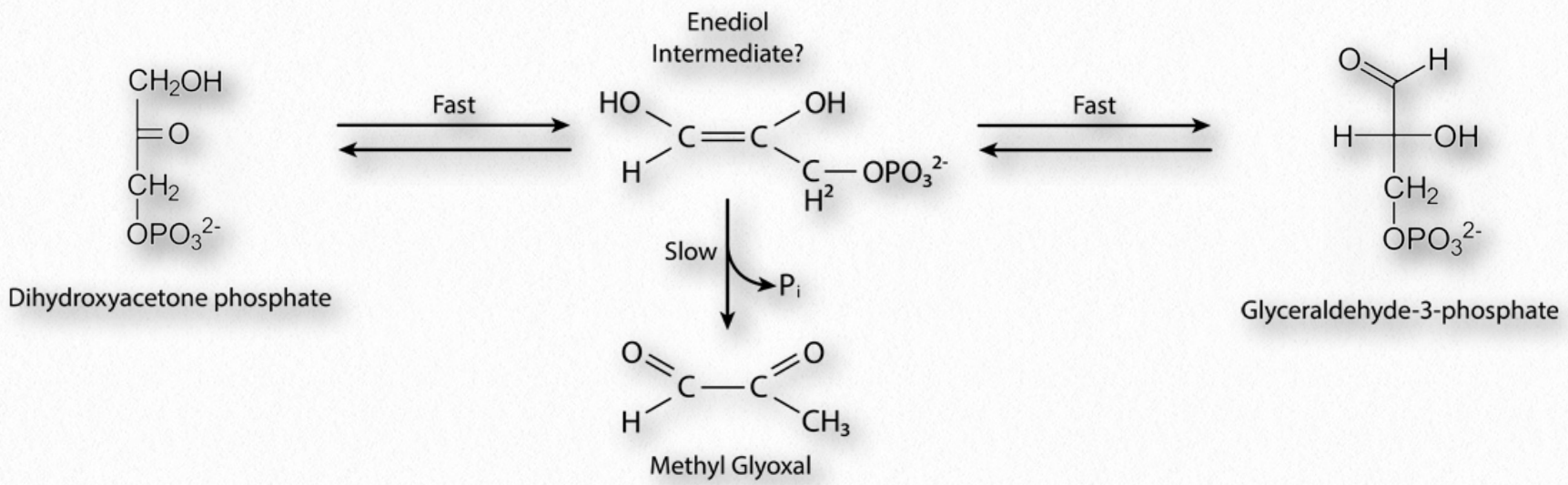

Figure 6.9 - Reaction #5 - Triose phosphate isomerase with unstable, toxic intermediate (methyl glyoxal)

Image by Ben Carson

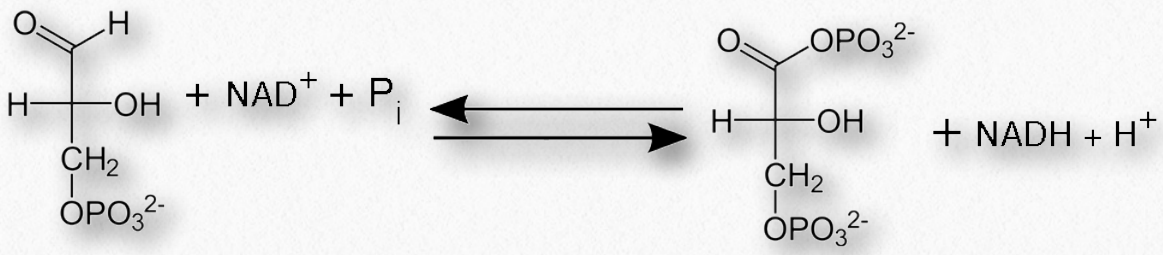

Figure 6.10 - Reaction #6 - Oxidation of GLYAL3P, catalyzed by glyceraldehyde-3-phosphate dehydrogenase

In this reaction, D-GLYAL3P is oxidized in the only oxidation step of glycolysis catalyzed by the enzyme glyceraldehyde-3-phosphate dehydrogenase, an oxidoreductase. The aldehyde in this reaction is oxidized, then linked to a phosphate to make an ester - D-1,3-bisphospho-glycerate (D-1,3BPG). Electrons from the oxidation are donated to NAD^+, creating NADH.

NAD^+ is a critical constituent in this reaction and is the reason that cells need a fermentation option at the end of the pathway (see below).

Note here that ATP energy was not required to put the phosphate onto the oxidized D-GLYAL3P. The reason for this is because the energy provided by the oxidation reaction is sufficient for adding the phosphate.

Reaction 7

D-1,3BPG + ADP ⇄ 3PG + ATP

The two phosphates in the tiny 1,3BPG molecule repel each other and give the molecule high potential energy. This energy is utilized by the enzyme phosphoglycerate kinase (another transferase) to phosphorylate ADP and make ATP, as well as the product, 3-phosphoglycerate (3-PG). This is an example of a substrate-level phosphorylation. Such mechanisms for making ATP require an intermediate with a high enough energy to phosphorylate ADP to make ATP.

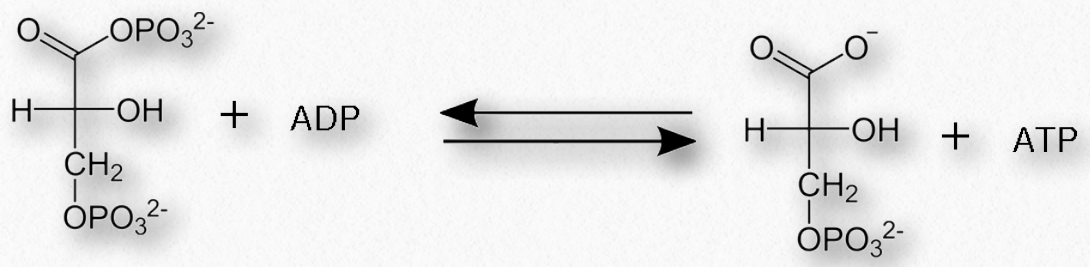

Figure 6.11 - Reaction #7 - Substrate-level Phosphorylation by 1,3-BPG

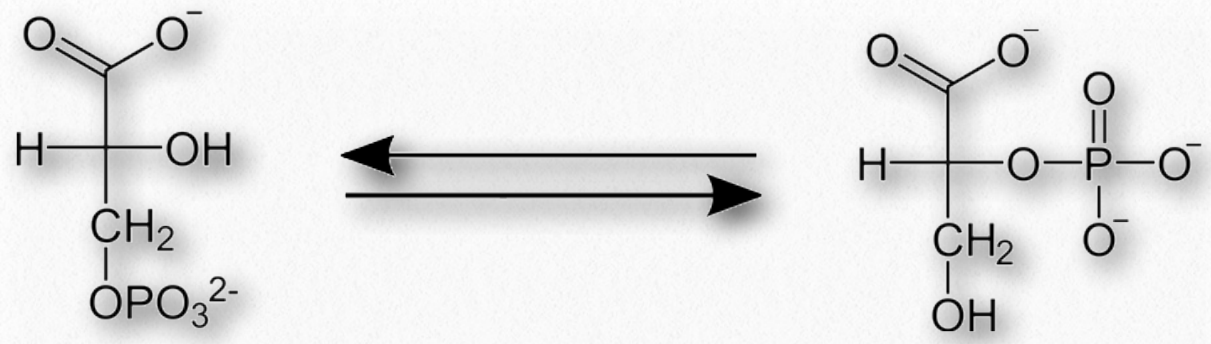

Figure 6.12 - **Reaction #8 - Conversion of 3-PG to 2-PG**

Reaction 8

3-PG ⇄ 2-PG

Conversion of the 3-PG intermediate to 2-PG (2-phosphoglycerate) occurs by an important mechanism. An intermediate in this readily reversible reaction (catalyzed by phosphoglycerate mutase - a mutase enzyme) is 2,3-BPG. This intermediate, which is stable, is released with low frequency by the enzyme instead of being con-

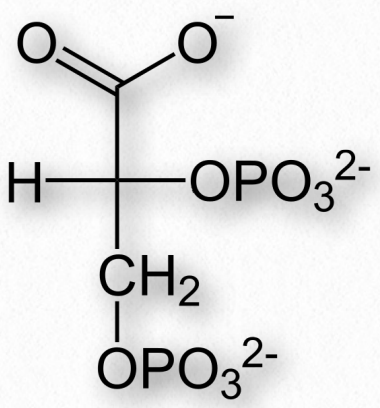

Figure 6.14 - **2,3-Bisphosphoglycerate (2,3-BPG)**

Though there are a few substrate level phosphorylations in cells (including another one at the end of glycolysis), the vast major of ATP is made by oxidative phosphorylation in the mitochondria (in animals). In addition to oxidative phosphorylation, plants also make ATP by photophosphorylation in their chloroplasts. Since there are two 1,3 BPGs produced for every glucose, the two ATPs produced in this reaction replenish the two ATPs used to start the cycle and the net ATP count at this point of the pathway is zero.

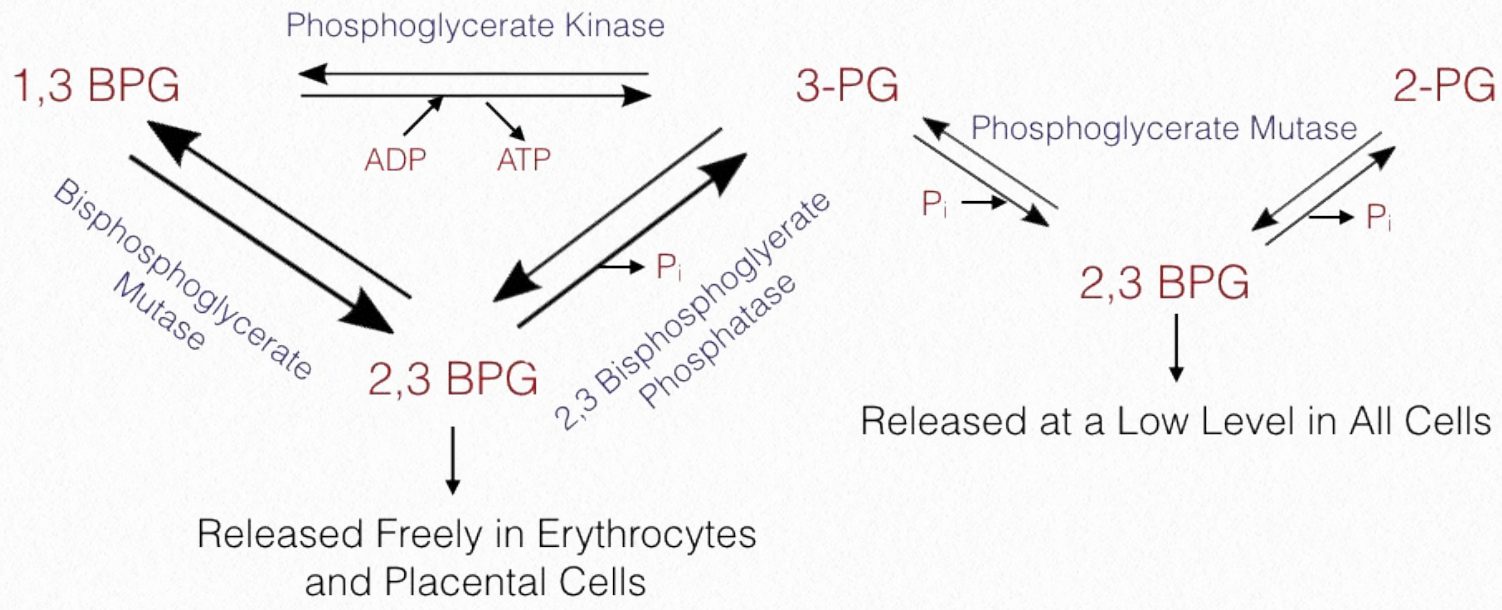

Figure 6.13 - **Two routes to formation of 2,3-BPG**

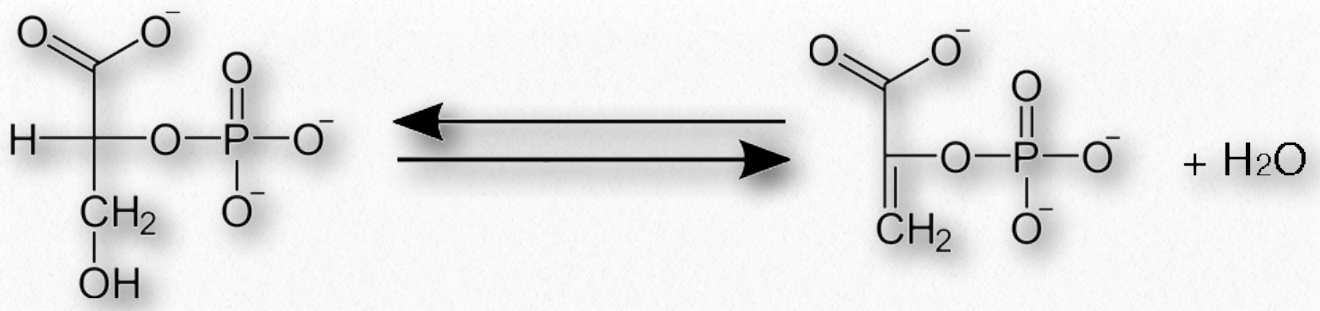

Figure 6.15 - **Reaction #9 - Enolase-catalyzed removal of water**

Wikipedia

verted to 2-PG.

2,3BPG is important because it binds to hemoglobin and stimulates release of oxygen. The molecule can also be made from 1,3-BPG as a product of a reaction catalyzed by bisphophglycerate mutase (Figure 6.13). Cells which are metabolizing glucose rapidly release more 2,3-BPG and, as a result, get more oxygen, supporting their needs. Notably, cells which are metabolizing rapidly are using oxygen more rapidly and are more likely to be deficient in it.

Reaction 9

$$\text{2-PG} \rightleftarrows \text{PEP} + H_2O$$

2-PG is converted by enolase (a lyase) to phosphoenolpyruvate (PEP) by removal of water, creating a very high energy intermediate. The reaction is readily reversible, but with PEP, the cell has one of its highest energy molecules and that is important for the next reaction.

Reaction 10

$$\text{PEP} + \text{ADP} + H+ \rightleftarrows \text{PYR} + \text{ATP}$$

Conversion of PEP to pyruvate by pyruvate kinase is the second substrate level phosphorylation of glycolysis, creating ATP. This reaction is what some refer to as the “Big Bang” of glycolysis because there is almost enough energy in PEP to stimulate production of a second ATP ($\Delta G°’ = 31.6$ kJ/mol), but it is not used. Consequently, this energy is lost as heat. If you wonder why you get hot when you exercise, the heat produced in the breakdown of glucose is a prime contributor and the pyruvate kinase reaction is a major source.

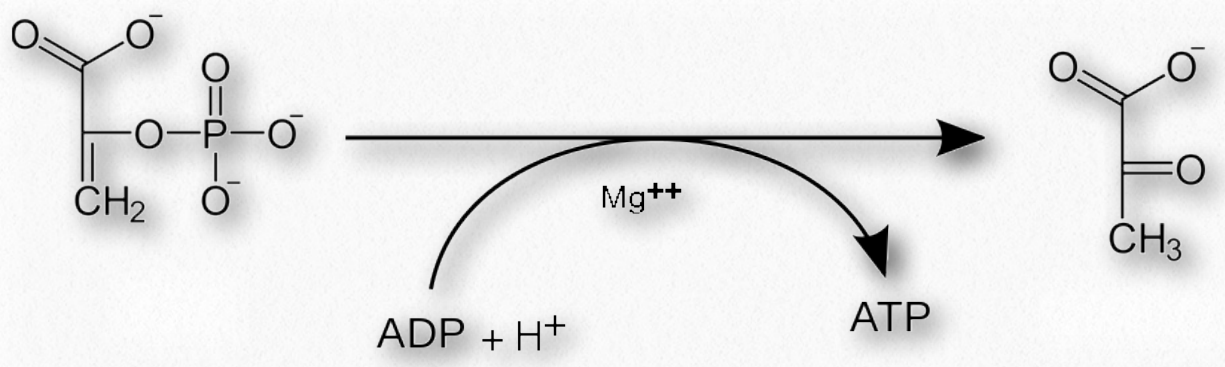

Figure 6.16 - **Reaction #10 - The big bang - PEP phosphorylates ADP with a lot of energy to spare**

Wikipedia

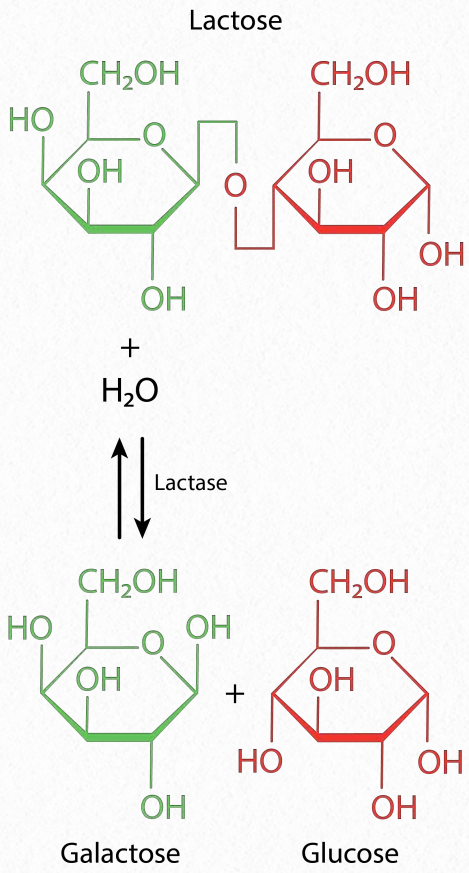

Figure 6.17 - Breakdown of lactose to glucose and galactose by lactase

Image by Pehr Jacobson

Pyruvate kinase is the third and last enzyme of glycolysis that is regulated (see below). The primary reason this is the case is to be able to prevent this reaction from occurring when cells are making PEP while going through gluconeogenesis (see more HERE).

Catabolism of other sugars

Though glycolysis is a pathway focused on the metabolism of glucose and fructose, the fact that other sugars can be readily metabolized into glucose means that glycolysis can be used for extracting energy from them as well. Galactose is a good example. It is commonly produced in the produced in the body as a result of hydrolysis of lactose, catalyzed by the enzyme known as lactase (Figure 6.17). Deficiency of lactase is the cause of lactose intolerance.

Galactose begins preparation for entry into glycolysis by being converted to galactose-1-phosphate (catalyzed by galactokinase - Figure 6.18). Galactose-1-phosphate swaps with glucose-1-phosphate from UDP-glucose to make UDP-galactose (Figure 6.19). An epimerase converts UDP-galactose back to UDP-glucose and the cycle is complete. Each turn of the cycle thus takes in one galactose-1-phosphate and releases one glucose-1-phosphate.

Deficiency of galactose conversion enzymes results in accumulation of galactose (from breakdown of lactose). Excess galactose is converted to galactitol, a sugar alcohol. Galactitol in the human eye lens causes it to absorb water and this may be a factor in formation of cataracts.

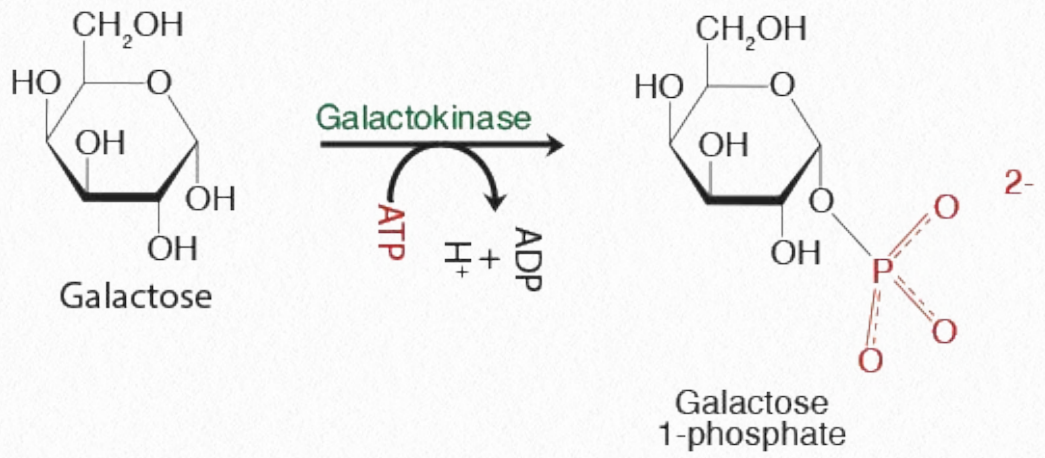

Figure 6.18 - Galactokinase Reaction

Image by Penelope Irving

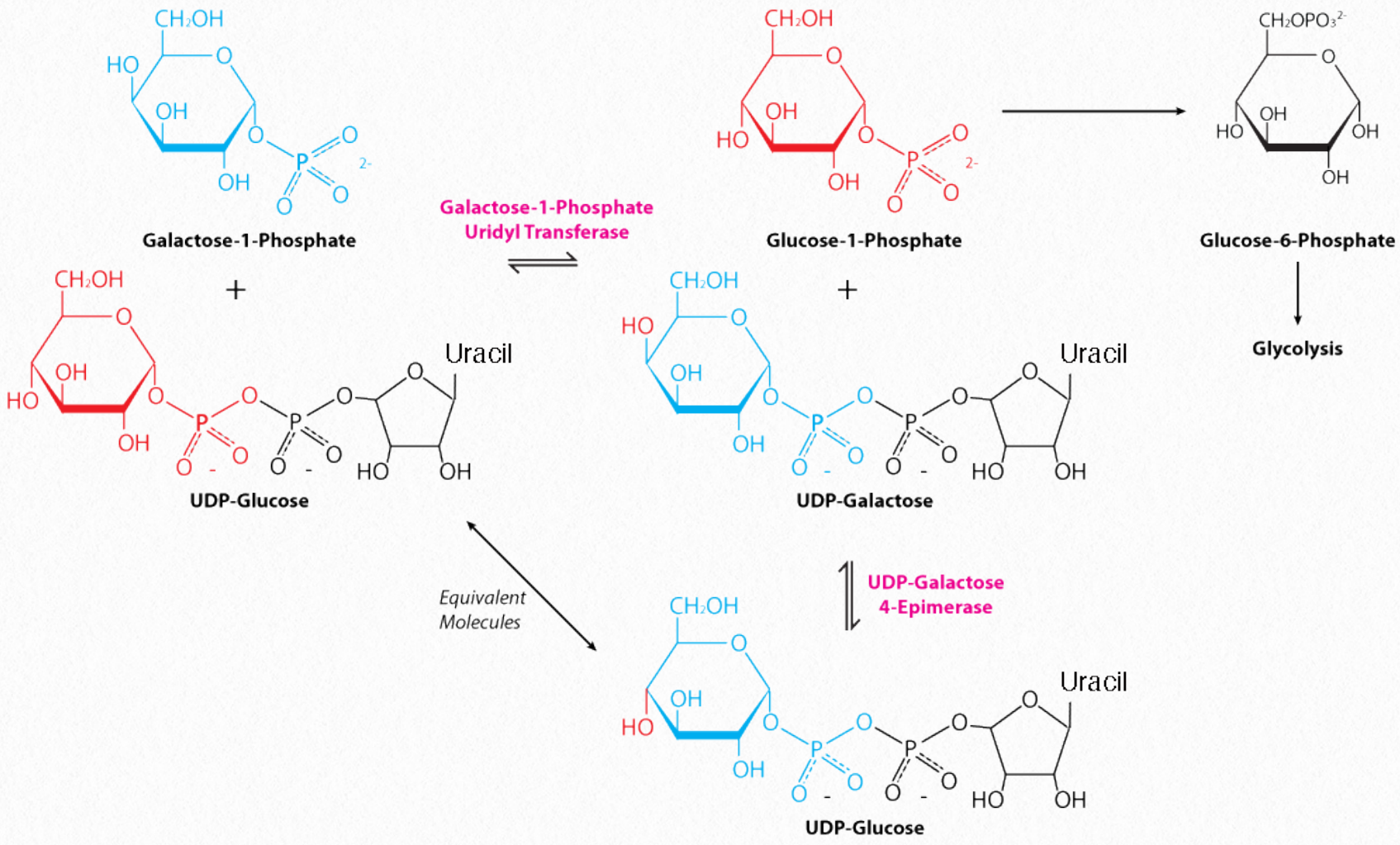

Figure 6.19 - Conversion of galactose-1-phosphate into glucose-6-phosphate

Image by Aleia Kim

Free fructose can also enter glycolysis by two mechanisms. First, it can be phosphorylated to fructose-6-phosphate by hexokinase. A more interesting alternate entry point is that shown in Figure 6.20. Phosphorylation of fructose by fructokinase produces fructose-1-phosphate and cleavage of that by fructose-1-phosphate aldolase yields DHAP and glyceraldehyde.

Phosphorylation of glyceraldehyde by triose kinase yields GLYAL3P. This alternative entry means for fructose may have important implications because DHAP and GLYAL3P are introduced into the glycolysis pathway while bypassing PFK-1 regulation. Some have proposed this may be important when considering metabolism of high fructose corn syrup, since it forces production of pyruvate, a precursor of acetyl-CoA, which is itself a precursor of fatty acids when ATP levels are high.

YouTube Lectures by Kevin HERE & HERE

Mannose metabolism

Mannose can also be metabolized in glycolysis. In this case, it enters via fructose by the following two-step process - 1) phosphoryla-

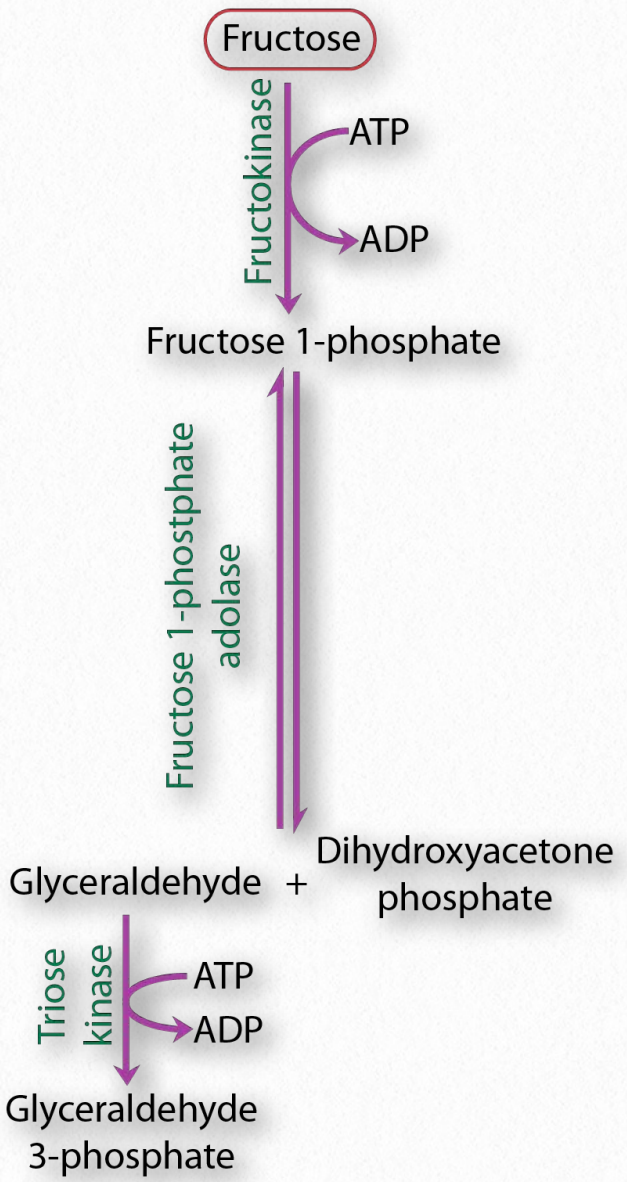

Figure 6.20 - Entry of fructose into glycolysis, bypassing PFK-1

Image by Penelope Irving

tion by hexokinase to make mannose-6-phosphate followed by its conversion to fructose-6-phosphate, catalyzed by phosphomannoisomerase (Figure 6.21).

Glycerol metabolism

Glycerol is an important molecule for the synthesis of fats, glycerophospholipids, and other membrane lipids. Most commonly it is made into glycerol-3-phosphate (Figure 6.22) and the glycolysis/gluconeogenesis pathways are important both for producing the compound and for metabolizing it. The relevant intermediate in these pathways both for producing and for using glycerol-3-phosphate is DHAP. The enzyme glycerol-3-phosphate dehydrogenase reversibly converts glycerol-3-phosphate into DHAP (Figure 6.22).

This reaction, which is an oxidation, transfers electrons to NAD^+ to produce NADH. In the reverse reaction, production of glycerol-3-phosphate from DHAP, of course, requires electrons from NADH for the reduction. Both glycolysis and gluconeogenesis are sources DHAP, meaning when the cell needs glycerol-3-phosphate that it can use sugars (glucose, fructose, mannose, or galactose) as sources in glycolysis. For gluconeogenesis, sources include pyruvate, alanine and

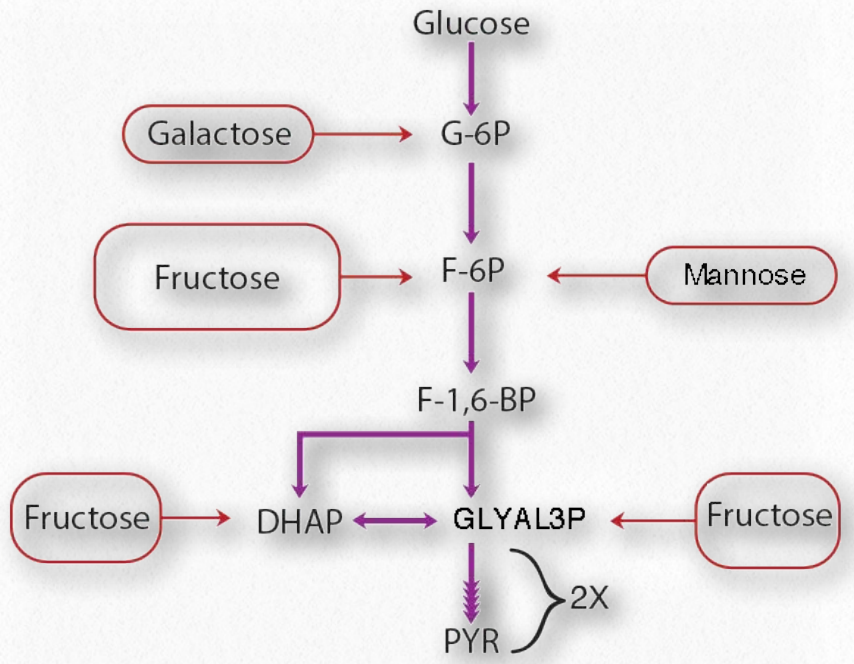

Figure 6.21 - Entry of other sugars into glycolysis

Image by Penelope Irving

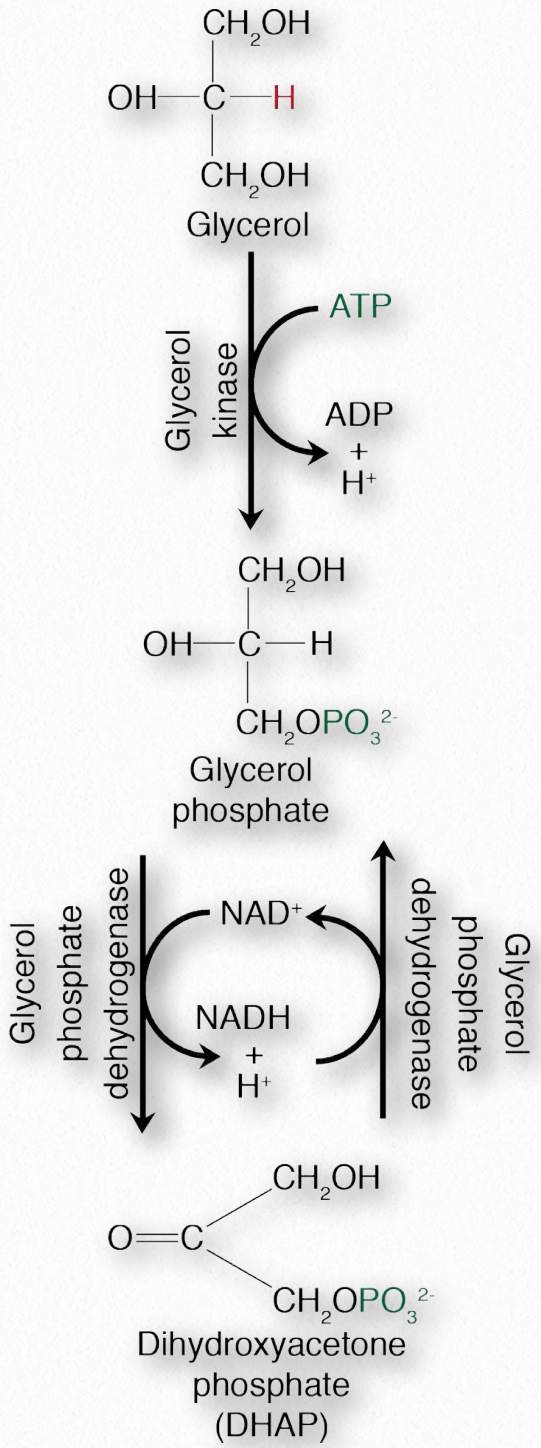

Figure 6.22 - Reactions in glycerol metabolism

Image by Penelope Irving

lactate (both can easily be made into pyruvate), oxaloacetate, aspartic acid (which can be made into oxaloacetate by transamination), and others. All of the intermediates of the citric acid cycle (and glyoxylate cycle) can be converted ultimately to oxaloacetate, which is a gluconeogenesis intermediate, as well.

It is worth noting that animals are unable to use fatty acids as materials for gluconeogenesis in net amounts, but they can, in fact, use glycerol in both glycolysis and gluconeogenesis. It is the only part of the fat molecule that can be so used.

Pyruvate metabolism

As noted, pyruvate produced in glycolysis can be oxidized to acetyl-CoA, which is itself oxidized in the citric acid cycle to carbon dioxide. That is not the only metabolic fate of pyruvate, though (Figure 6.23).

Pyruvate is a "starting" point for gluconeogenesis, being converted to oxaloacetate in the mitochondrion in the first step. Pyruvate in animals can also be reduced to lactate by adding electrons from NADH (Figure 6.24). This reaction produces NAD^+ and is critical for generating the latter molecule to keep the glyceraldehyde-3-phosphate dehydrogenase reaction of glycolysis (reaction #6) going under conditions when there is no oxygen.

This is because oxygen is necessary for the electron transport system (ETS) to operate and it performs the important function of converting NADH back to NAD^+. When the ETS is running, NADH donates electrons to Complex I and is oxidized to NAD^+ in the process, generating the intermediate needed for oxidizing GLYAL-3P. In the absence of oxygen, however, NADH cannot be converted to

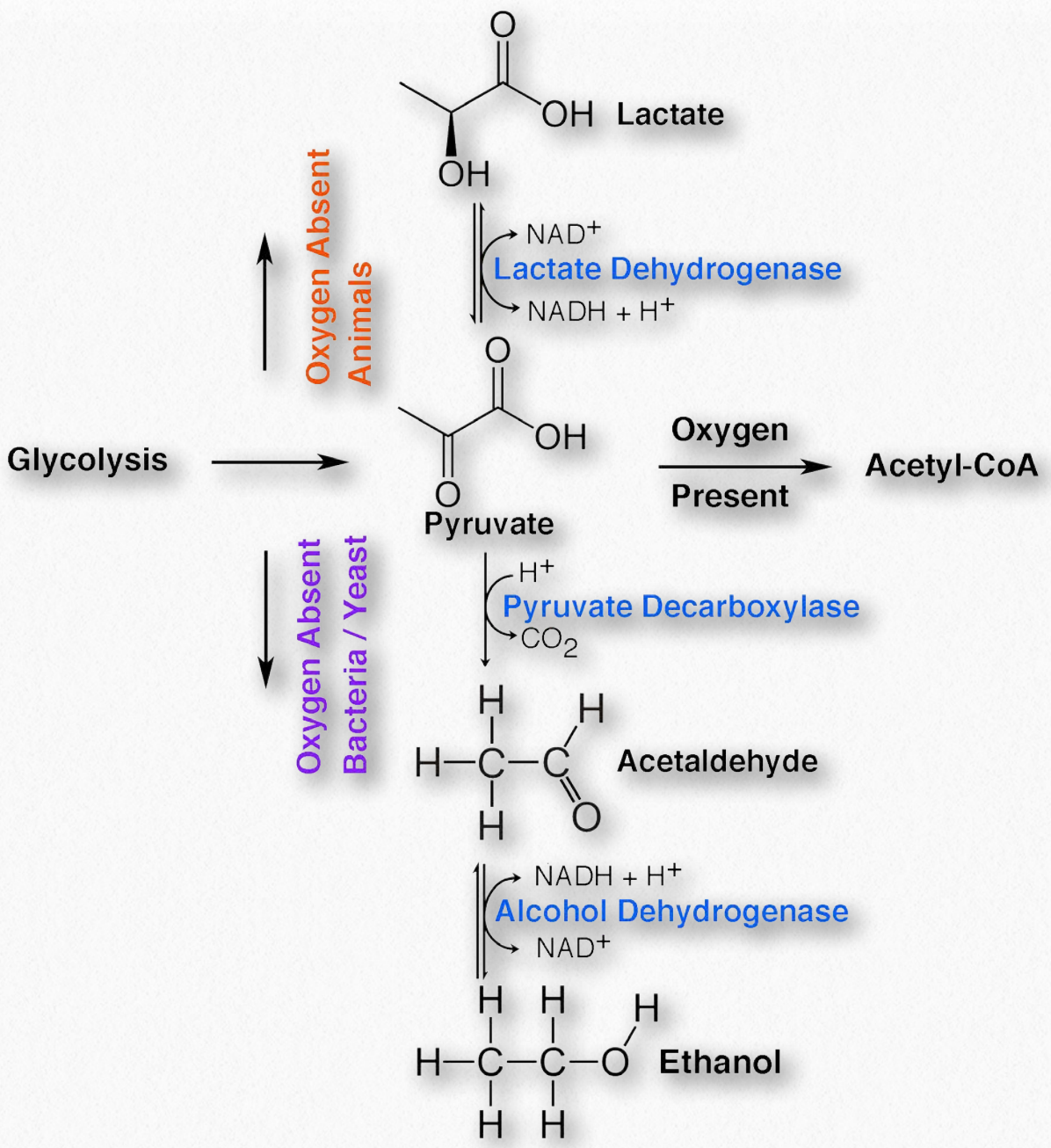

Figure 6.23 - Pyruvate metabolism. When oxygen is absent, pyruvate is converted to lactate (animals) or ethanol (bacteria and yeast). When oxygen is present, pyruvate is converted to acetyl-CoA. Not shown - Pyruvate transamination to alanine or carboxylation to form oxaloacetate.

NAD^+ by the ETS, so an alternative means of making NAD^+ is necessary for keeping glycolysis running under low oxygen conditions (fermentation).

Bacteria and yeast generate NAD^+ under oxygen deprived conditions by doing fermentation in a different way (Figure 6.25). They use NADH-requiring reactions that regenerate NAD^+ while producing ethanol from pyruvate instead of making lactate. Thus, fermentation of pyruvate is essential to keep glycolysis operating when oxygen is limiting. It is also for these reasons that brewing of beer (using yeast) involves depletion of oxygen and muscles low in oxygen produce lactic acid (animals).

Pyruvate is a precursor of alanine which can be easily synthesized by transfer of a nitrogen from an amine donor, such as glutamic acid. Pyruvate can also be converted into oxaloacetate by carboxylation in the process of gluconeogenesis (see below).

The enzymes involved in pyruvate metabolism include pyruvate dehydrogenase (makes acetyl-CoA), lactate dehydrogenase (makes lactate), transaminases (make alanine), pyruvate carboxylase (makes ox-

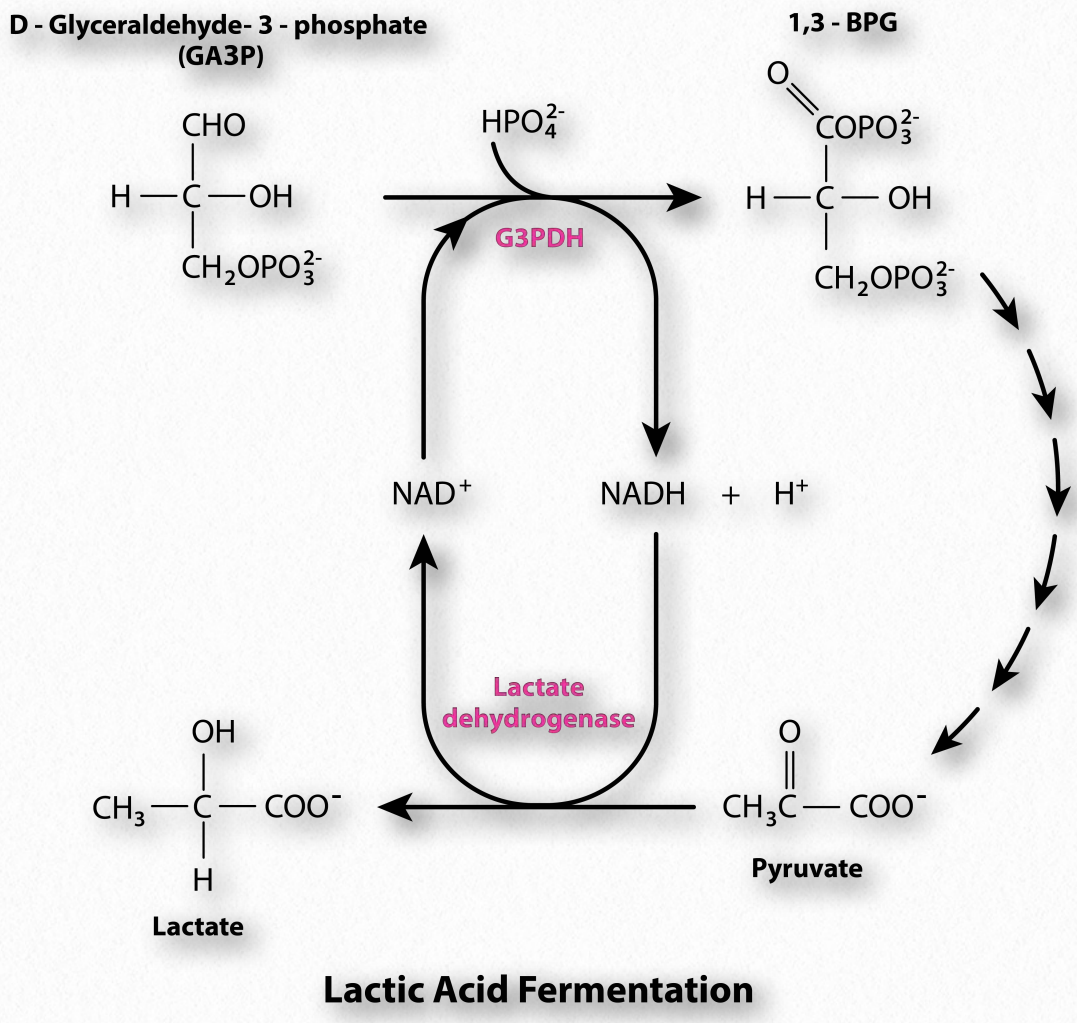

Figure 6.24 - Formation of lactate in animal fermentation produces NAD⁺ for G3PDH

Image by Ben Carson

aloacetate), and pyruvate decarboxylase (a part of pyruvate dehydrogenase that makes acetaldehyde in bacteria and yeast).

Catalytic action and regulation of the pyruvate dehydrogenase complex is discussed in the section on the citric acid cycle (HERE).

Gluconeogenesis

The anabolic counterpart to glycolysis is gluconeogenesis (Figure 6.26), which occurs mostly in the cells of the liver and kidney and virtually no other cells in the body. In seven of the eleven reactions of gluconeogenesis (starting from pyruvate), the same enzymes are used as in glycolysis, but the reaction directions are reversed. Notably, the ΔG values of these reactions in the cell are typically near zero, meaning their direction can be readily controlled by changing substrate and product concentrations by small amounts.

The three regulated enzymes of glycolysis all catalyze reactions whose cellular ΔG values are not close to zero, making manipulation of reaction direction for their reac-

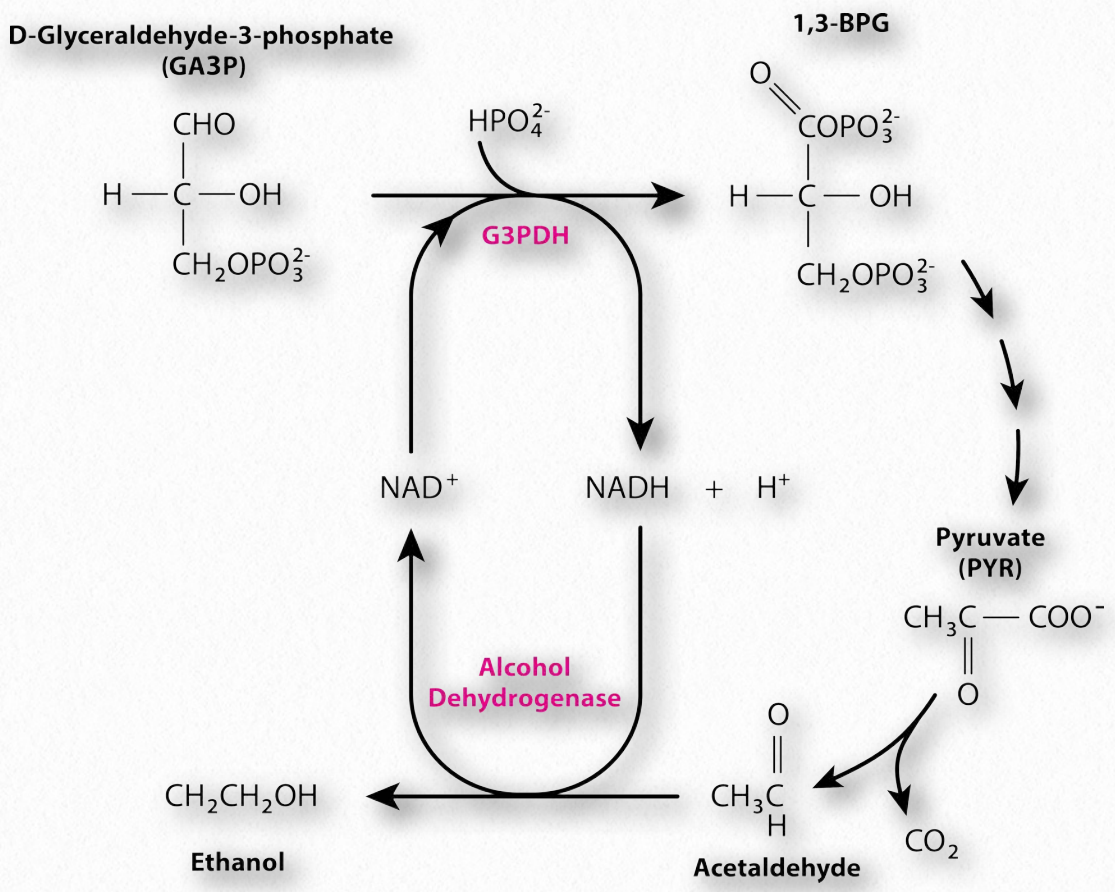

Figure 6.25 - Formation of ethanol in microbial fermentation produces NAD⁺ for G3PDH

Image by Ben Carson

tions non-trivial. Consequently, cells employ "work-around" reactions catalyzed by four different enzymes to favor gluconeogenesis, when appropriate.

Bypassing pyruvate kinase

Two of the enzymes (pyruvate carboxylase and PEP carboxykinase - PEPCK) catalyze reactions that bypass pyruvate kinase. F1,6BPase bypasses PFK-1 and G6Pase bypasses hexokinase. Notably, pyruvate carboxylase and G6Pase are found in the mitochondria and endoplasmic reticulum, respectively, whereas the other two are found in the cytoplasm along with all of the enzymes of glycolysis.

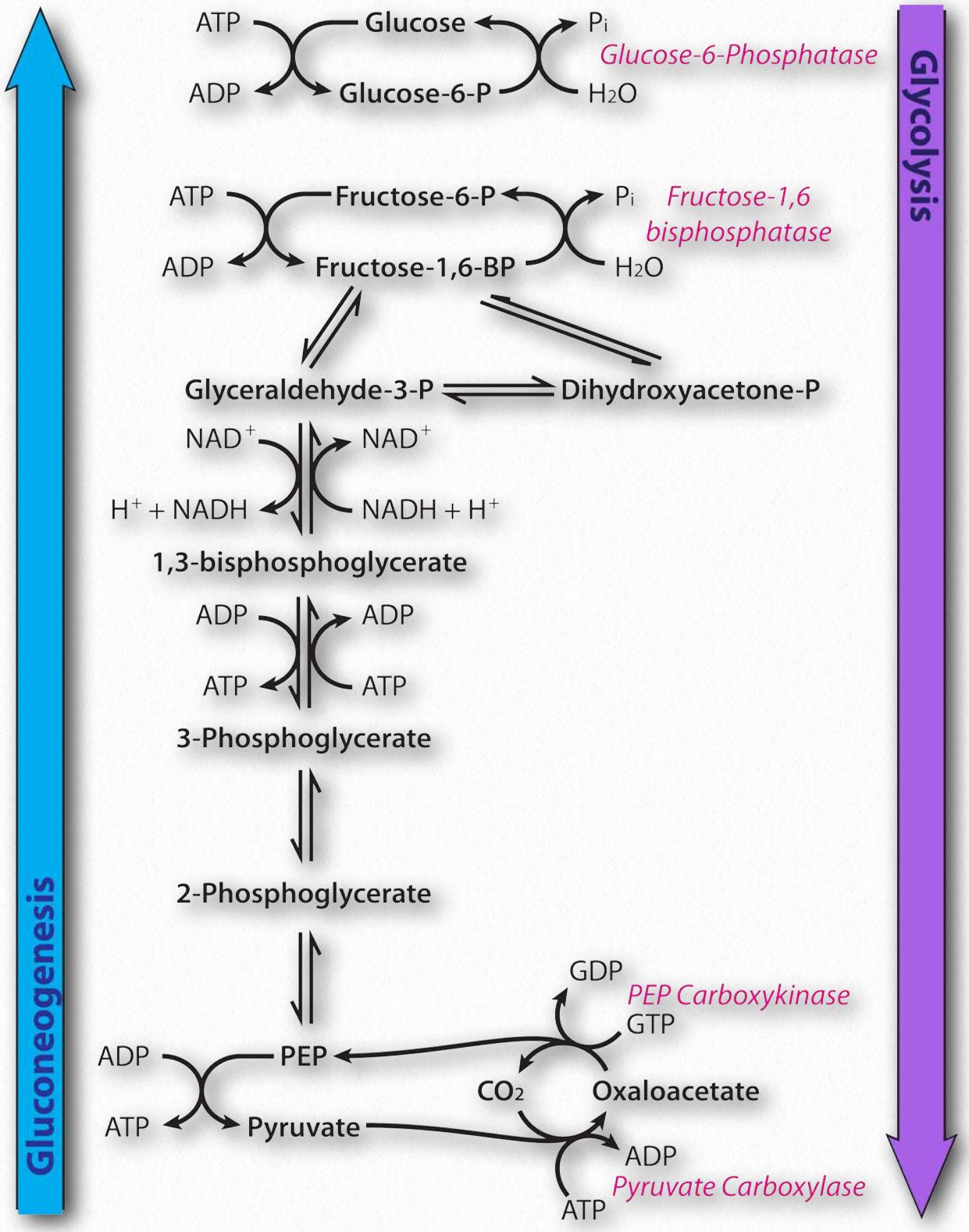

Figure 6.26 - Gluconeogenesis and glycolysis. Only the enzymes differing in gluconeogenesis are shown

Image by Aleia Kim

Biotin

An important coenzyme used by pyruvate carboxylase is biotin (Figure 6.27). Biotin is commonly used by carboxylases to carry CO_2 to incorporate into the substrate.

YouTube Lectures by Kevin HERE & HERE

Also known as vitamin H, biotin is a water soluble B vitamin (B_7) needed for many metabolic processes, including fatty acid synthesis, gluconeogenesis, and amino acid metabolism. Deficiency of the vitamin is rare, since it is readily produced by gut bac-

teria. There are many claims of advantages of taking biotin supplements, but there is no strong indication of benefits in most cases. Deficiencies are associated with inborn genetic errors, alcoholism, burn patients, and people who have had a gastrectomy. Some pregnant and lactating women may have reduced levels due to increased biotin catabolism.

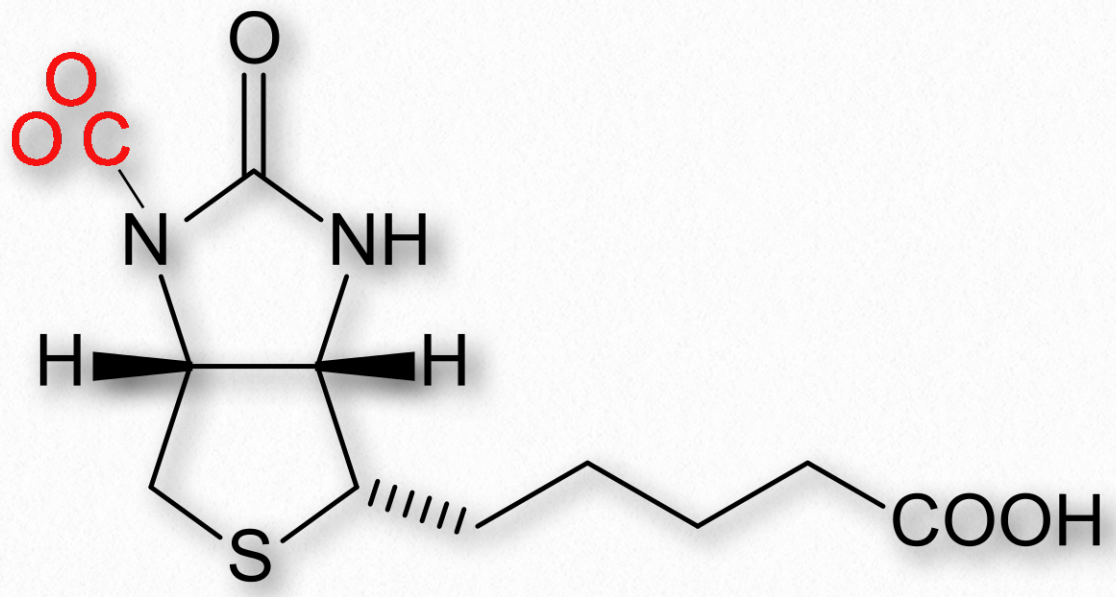

Figure 6.27 - Biotin carrying carbon dioxide (red)
Wikipedia

Reciprocal regulation

All of the enzymes of glycolysis and nine of the eleven enzymes of gluconeogenesis are all in the cytoplasm, necessitating a coordinated means of controlling them. Cells generally need to minimize the extent to which paired anabolic and catabolic pathways are occurring simultaneously, lest they produce a futile cycle, resulting in wasted energy with no tangible product except heat. The mechanisms of controlling these pathways have opposite effects on catabolic and anabolic processes. This method of control is called reciprocal regulation (see above).

Reciprocal regulation is a coordinated means of simultaneously controlling metabolic pathways that do opposite things. In reciprocal regulation, a single molecule (allosteric regulation) or a single covalent modification (phosphorylation/dephosphorylation,

Allosteric Regulation of Glycolysis & Gluconeogenesis

Reciprocal Regulation

AMP - Activates PFK-1, Inhibits F1,6BPase
F2,6BP - Activates PFK-1, Inhibits F1,6BPase
Citrate - Activates PFK-1, Inhibits F1,6BPase

Glycolysis Only

ATP - Inhibits PFK-1 and Pyruvate Kinase
Alanine - Inhibits Pyruvate Kinase

Gluconeogenesis Only

ADP - Inhibits Pyruvate Carboxylase and PEPCK
Acetyl-CoA - Activates Pyruvate Carboxylase

for example) has opposite effects on the different pathways.

> Directional velocity
> Inverts with reciprocity
> If glycolysis is flowing
> Glucose synthesis awaits
> But when the latter is a-going
> Sugar breakdown then abates

Reciprocal allosteric effects

For example, in glycolysis, the enzyme known as phosphofructokinase (PFK-1) is allosterically activated by AMP and a molecule known as F2,6BP (Figure 6.28). The corresponding enzyme from gluconeogenesis catalyzing a reversal of the glycolysis reaction is known as F1,6BPase. F1,6BPase is inhibited by both AMP and F2,6BP.

Reciprocal covalent effects

In glycogen metabolism, the enzymes phosphorylase kinase and glycogen phosphorylase catalyze reactions important for the breakdown of glycogen. The enzyme glycogen synthase catalyzes the synthesis of glyco-

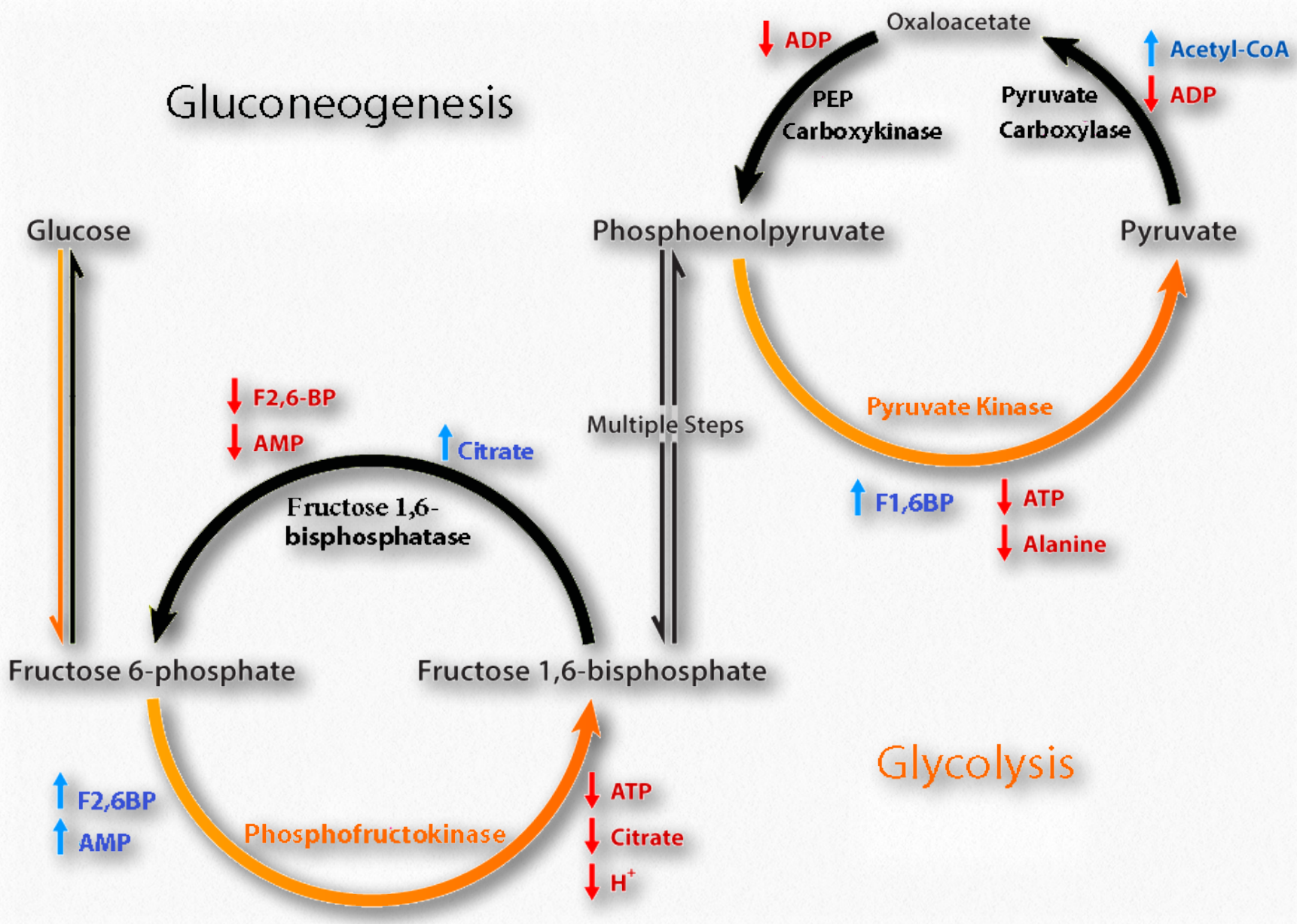

Figure 6.28 - Regulation of glycolysis (orange path) and gluconeogenesis (black path)

Image by Aleia Kim

gen. Each of these enzymes is, at least partly, regulated by attachment and removal of phosphate.

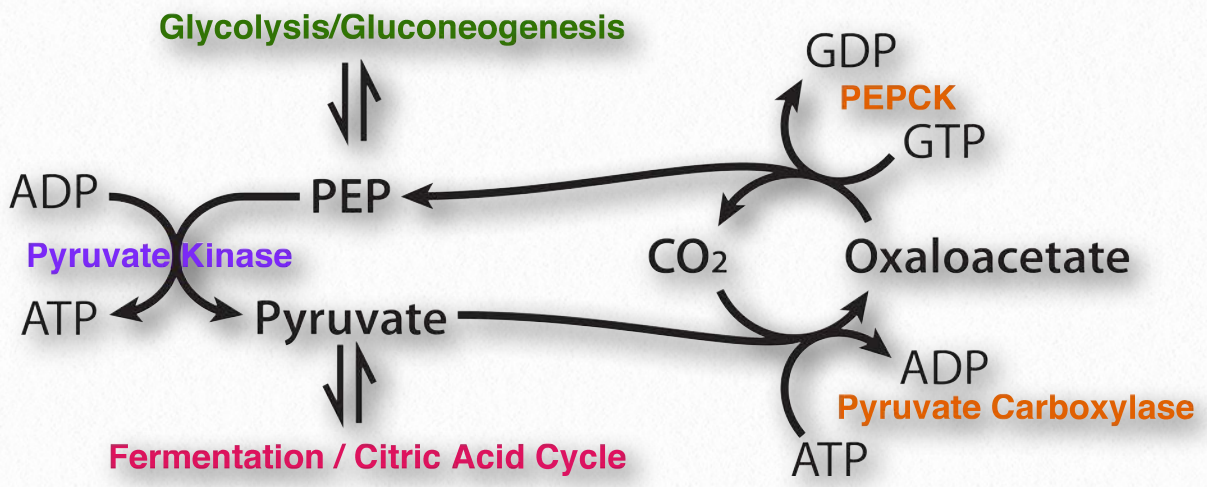

Figure 6.29 - A simple futile cycle - follow the black lines

Image by Aleia Kim

Phosphorylation of phosphorylase kinase and glycogen phosphorylase has the effect of making them more active, whereas phosphorylation of glycogen synthase makes it less active. Conversely, dephosphorylation has the reverse effects on these enzymes - phosphorylase kinase and glycogen phosphorylase become less active and glycogen synthase becomes more active.

Interactive Learning Module HERE

Simple and efficient

The advantage of reciprocal regulation schemes is that they are very efficient. It doesn't take separate molecules or separate treatments to control two pathways simultaneously. Further, its simplicity ensures that when one pathway is turned on, the other is turned off.

This is especially important with catabolic/anabolic regulation, because having both pathways going on simultaneously in a cell is not very productive, leading only to production of heat in a futile cycle. A simple futile cycle is shown on Figure 6.29. If unregulated, the cyclic pathway in the figure (shown in black) will make ATP in creating pyruvate from PEP and will use ATP to make oxaloacetate from pyruvate.

It will also use GTP to make PEP from oxaloacetate. Thus, each turn of the cycle will make one ATP, use one ATP and use one GTP for a net loss of energy. The process will start with pyruvate and end with pyruvate, so there is no net production of molecules. (see HERE for one physiological use of a futile cycle).

Specific gluconeogenesis controls

Besides reciprocal regulation, other mechanisms help control gluconeogenesis. First, PEPCK is controlled largely at the level of synthesis. Overexpression of PEPCK (stimulated by glucagon, glucocorticoid hormones, and cAMP and inhibited by insulin) produces symptoms of diabetes.

Pyruvate carboxylase is sequestered in the mitochondrion (one means of regulation)

and is sensitive to acetyl-CoA, which is an allosteric activator. Acetyl-CoA concentrations increase as the citric acid cycle activity decreases. Glucose-6-phosphatase is present in low concentrations in many tissues, but is found most abundantly and importantly in the major gluconeogenic organs – the liver and kidney cortex.

Specific glycolysis controls

Control of glycolysis and gluconeogenesis is unusual for metabolic pathways, in that regulation occurs at multiple points. For glycolysis, this involves three enzymes:

1. Hexokinase (Glucose ⇄ G6P)

2. Phosphofructokinase-1 (F6P ⇄ F1,6BP)

3. Pyruvate kinase (PEP ⇄ Pyruvate).

Regulation of hexokinase is the simplest of these. The enzyme is unusual in being inhibited by its product, glucose-6-phosphate. This ensures when glycolysis is slowing down hexokinase is also slowing down to reduce feeding the pathway.

Pyruvate kinase

It might also seem odd that pyruvate kinase, the last enzyme in the pathway, is regulated (Figure 6.30), but the reason is simple. Pyruvate kinase catalyzes the most energetically rich reaction of glycolysis. The reaction is favored so strongly in the forward direction that cells must do a 'two-step' around it in the reverse direction when making glucose in the gluconeogenesis pathway.

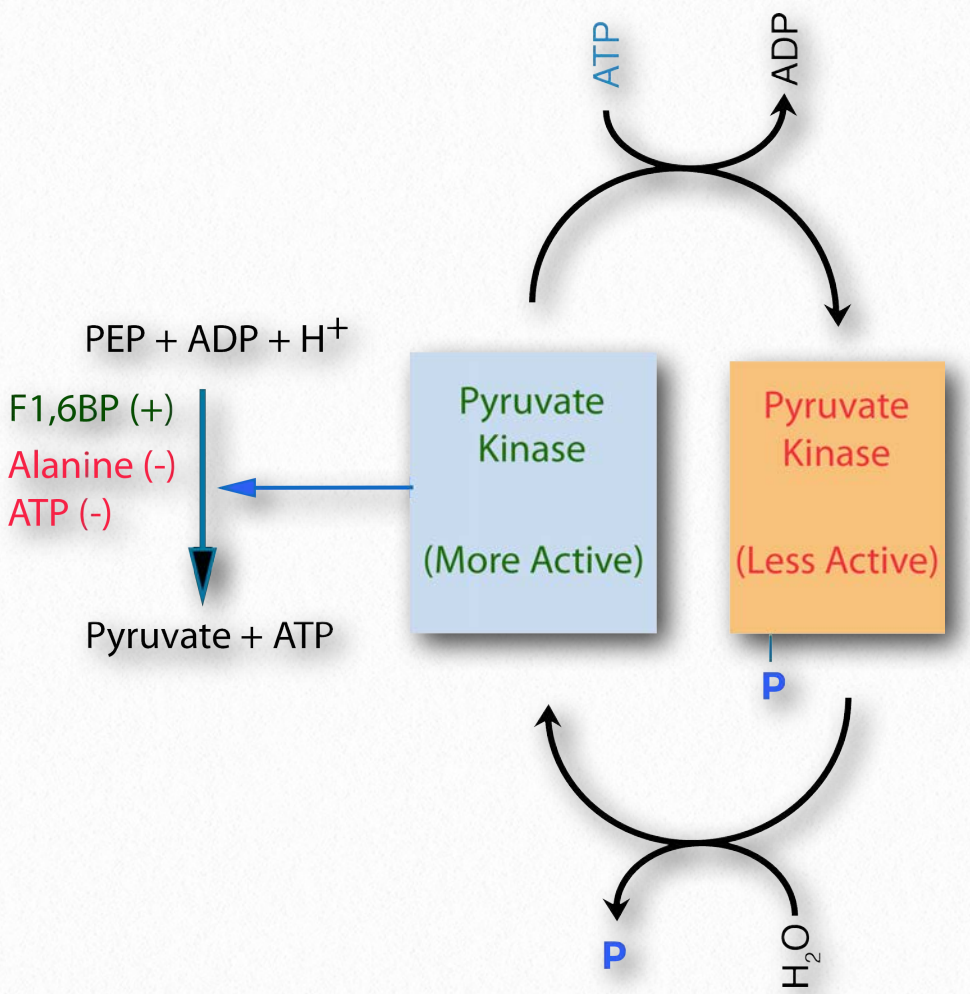

Figure 6.30 - Regulation of pyruvate kinase

For cells a glucose cycling's cost
Is energy in reams
Four ATPs each time is lost
From breaking/making schemes

So use for metabolic heat
To make it warm inside your feet
Else it's of no utility
To practice such futility

In other words, it takes two enzymes, two reactions, and two triphosphates (ATP and GTP) to go from one pyruvate back to one PEP in gluconeogenesis. When cells are needing to make glu-

cose, they can't be sidetracked by having the PEP they have made in gluconeogenesis be converted directly back to pyruvate by pyruvate kinase. Consequently, pyruvate kinase must be inhibited during gluconeogenesis or a futile cycle will occur and no glucose will be made.

Another interesting control mechanism called feedforward activation involves pyruvate kinase. Pyruvate kinase is activated allosterically by the glycolysis intermediate, F1,6BP. This molecule is a product of the PFK-1 reaction and a substrate for the aldolase reaction.

Reactions pulled

As noted above, the aldolase reaction is energetically unfavorable (high positive $\Delta G°'$), thus allowing F1,6BP to accumulate. When this happens, some of the excess F1,6BP binds to pyruvate kinase, which activates and jump-

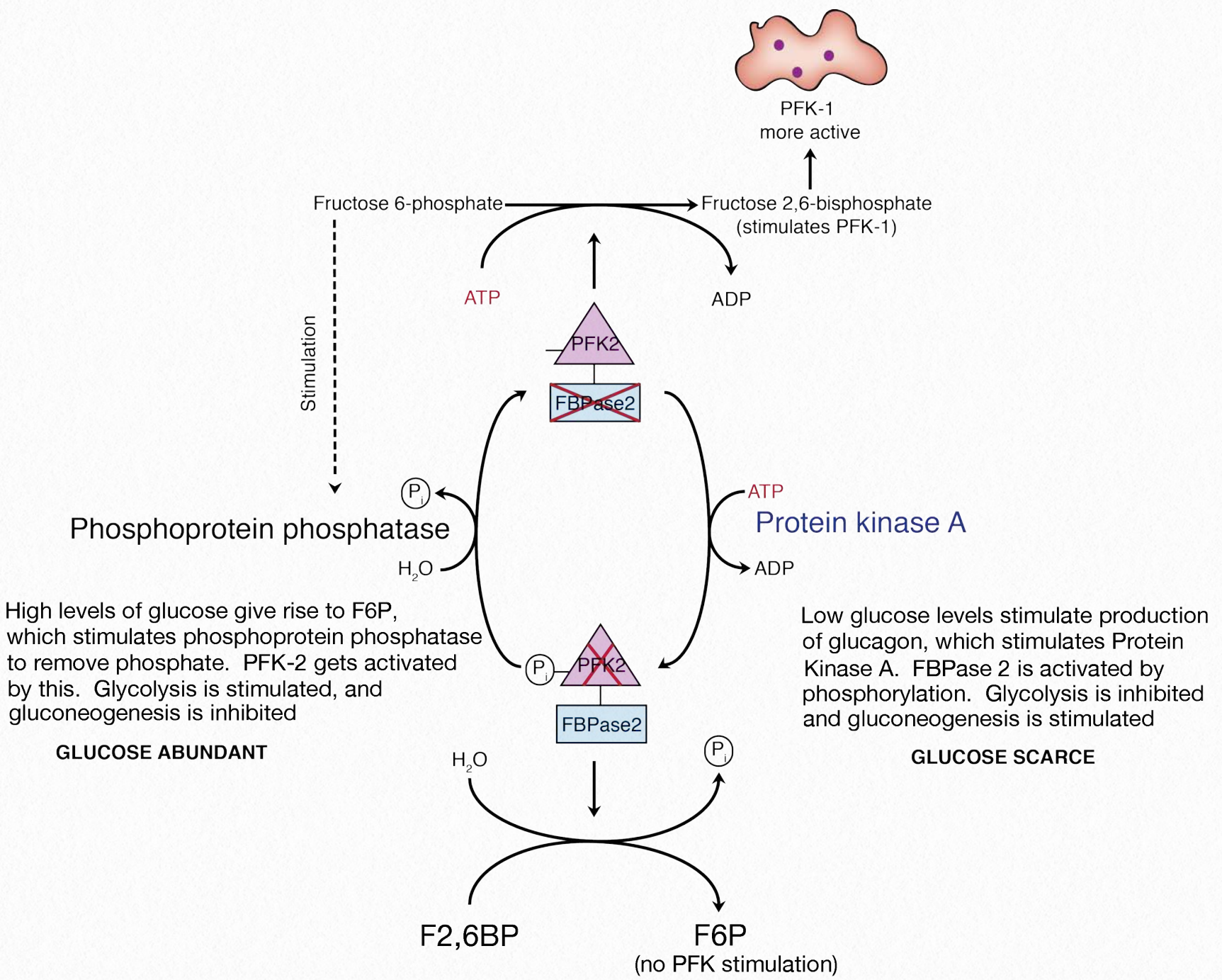

Figure 6.31 - Regulation of Synthesis and Breakdown of F2,6BP

Image by Penelope Irving

starts the conversion of PEP to pyruvate. The resulting drop in PEP levels has the effect of "pulling" on the reactions preceding pyruvate kinase. As a consequence, the concentrations of GLYAL3P and DHAP fall, helping to pull the aldolase reaction forward.

YouTube Lectures by Kevin HERE & HERE

PFK-1 regulation

PFK-1 has a complex regulation scheme. First, it is reciprocally regulated (relative to F1,6BPase) by three molecules. F2,6BP activates PFK-1 and inhibits F1,6BPase. PFK-1 is also allosterically activated by AMP, whereas F1,6BPase is inhibited. On the other hand, citrate inhibits PFK-1, but activates F1,6BPase.

PFK-1 is also inhibited by ATP and is exquisitely sensitive to proton concentration, easily losing activity when the pH drops only slightly. PFK-1's inhibition by ATP is noteworthy and odd at first glance because ATP is also a substrate whose increasing concentration should favor the reaction instead of inhibit it. The root of this conundrum is that PFK-1 has two ATP binding sites - one at an allosteric site that binds ATP relatively inefficiently and one that the active site that binds ATP with high affinity. Thus, only when ATP concentration is high is binding at the allosteric site favored and only then can ATP turn off the enzyme.

F2,6BP regulation

Regulation of PFK-1 by F2,6BP is simple at the PFK-1 level, but more complicated at the level of synthesis of F2,6BP. Despite having a name sounding like a glycolysis/gluconeogenesis intermediate (F1,6BP), F2,6BP is not an intermediate in either pathway. Instead, it is made from fructose-6-phosphate and ATP by the enzyme known as phosphofructokinase-2 (PFK-2 - Figure 6.31).

Cori cycle

With respect to energy, the liver and muscles act complementarily. The liver is the major or-

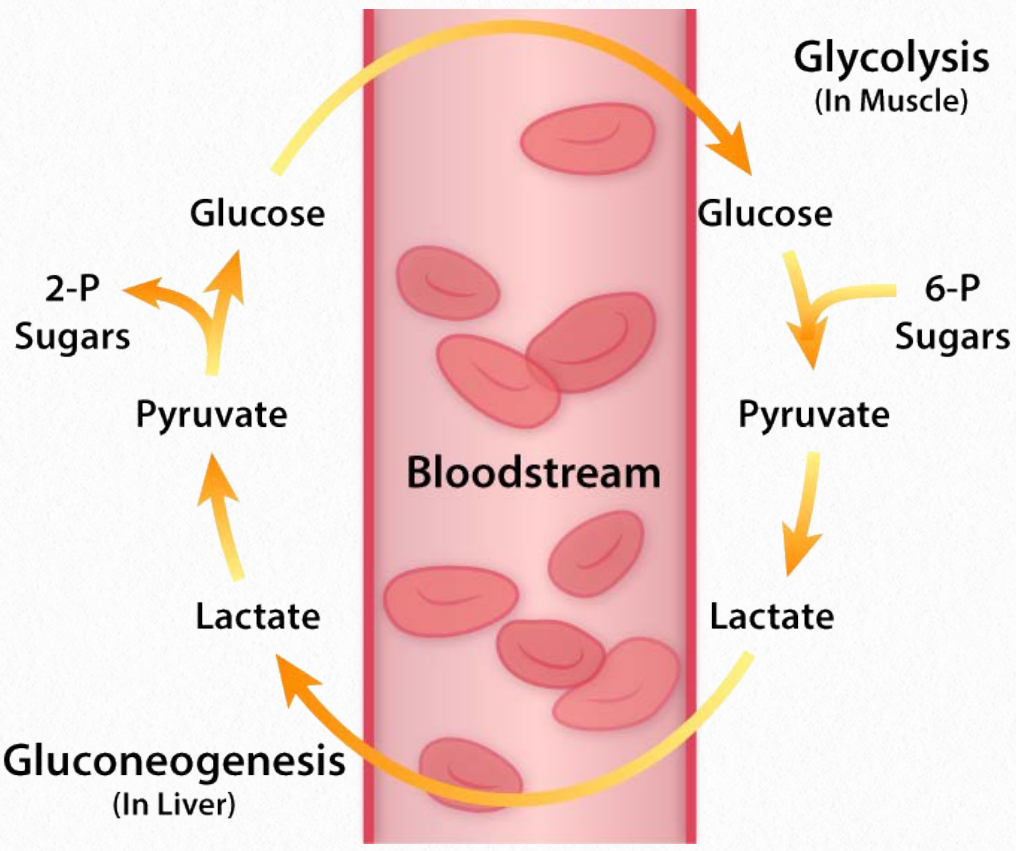

Figure 6.32 - The Cori cycle

Image by Aleia Kim

gan in the body for the synthesis of glucose. Muscles are major users of glucose to make ATP. Actively exercising muscles use oxygen faster than the blood can deliver it. As a consequence, the muscles go anaerobic and produce lactate. This lactate is of no use to muscle cells, so they dump it into the blood. Lactate travels in the blood to the liver, which takes it up and reoxidizes it back to pyruvate, catalyzed by the enzyme lactate dehydrogenase (Figure 6.32).

Pyruvate in the liver is then converted to glucose by gluconeogenesis. The glucose thus made by the liver is dumped into the bloodstream where it is taken up by muscles and used for energy, completing the important intercellular pathway known as the Cori cycle.

Glucose alanine cycle

The glucose alanine cycle (also known as the Cahill Cycle), has been described as the amine equivalent of the Cori cycle (Figure 6.33). The Cori cycle, of course, exports lac-

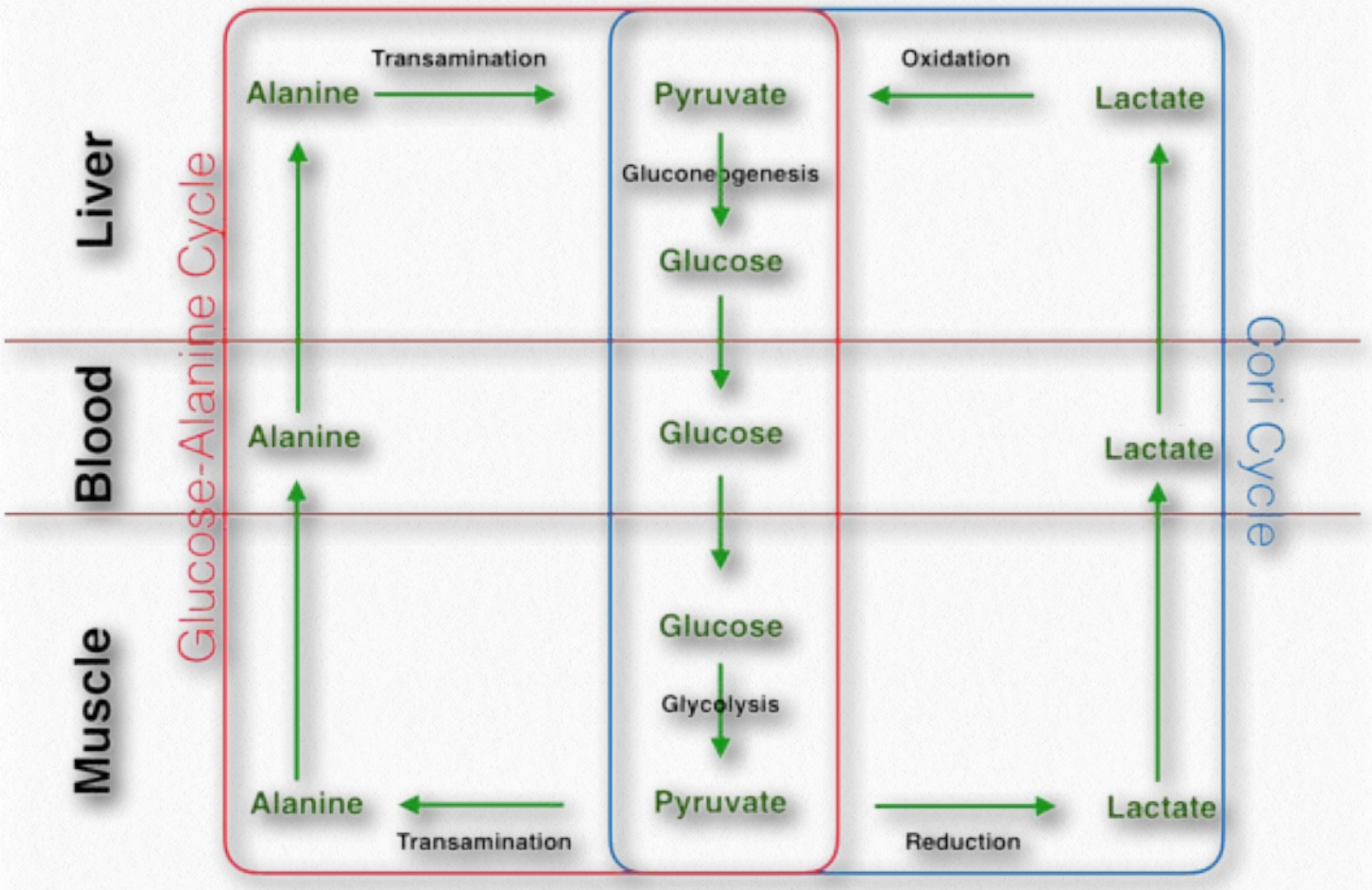

Figure 6.33 - Overlap between the Cori cycle and the glucose alanine cycle

tate from muscles (when oxygen is limiting) to the liver via the bloodstream. The liver, in turn, converts lactate to glucose, which it ships back to the muscles via the bloodstream. The Cori Cycle is an essential source of glucose energy for muscles during periods of exercise when oxygen is used faster than it can be delivered.

In the glucose-alanine cycle, cells are generating toxic amines and must export them. This is accomplished by transaminating pyruvate (the product of glycolysis) to produce the amino acid alanine.

The glucose-alanine process requires the enzyme alanine aminotransferase, which is found in muscles, liver, and intestines. Alanine is exported in the process to the blood and picked up by the liver, which deaminates it to release the amine for synthesis of urea and excretion. The pyruvate left over after the transamination is a substrate for gluconeogenesis. Glucose produced in the liver is then exported to the blood for use by cells, thus completing the cycle.

Polysaccharide metabolism

Sugars are metabolized rapidly in the body and that is one of the primary reasons they are used. Managing levels of glucose in the body is very important - too much leads to complications related to diabetes and too little gives rise to hypoglycemia (low blood sugar). Sugars in the body are maintained by three processes - 1) diet; 2) synthesis (gluconeogenesis); and 3) storage. The storage forms of sugars are, of course, the polysaccharides and their metabolism is our next topic of discussion.

Amylose and amylopectin

The energy needs of a plant are much less dynamic than those of animals. Muscular contraction, nervous systems, and information processing in the brain require large amounts of quick energy. Because of this, the polysaccharides stored in plants are somewhat less complicated than those of animals. Plants store glucose for energy in the form of amylose (Figure 6.34 and see HERE) and amylopectin and for structural integrity in the form of cellulose (see HERE). These structures differ in that cellulose contains glucose units solely joined by β-1,4 bonds, whereas amylose has only α-1,4 bonds and amylopectin has α-1,4 and α-1,6 bonds.

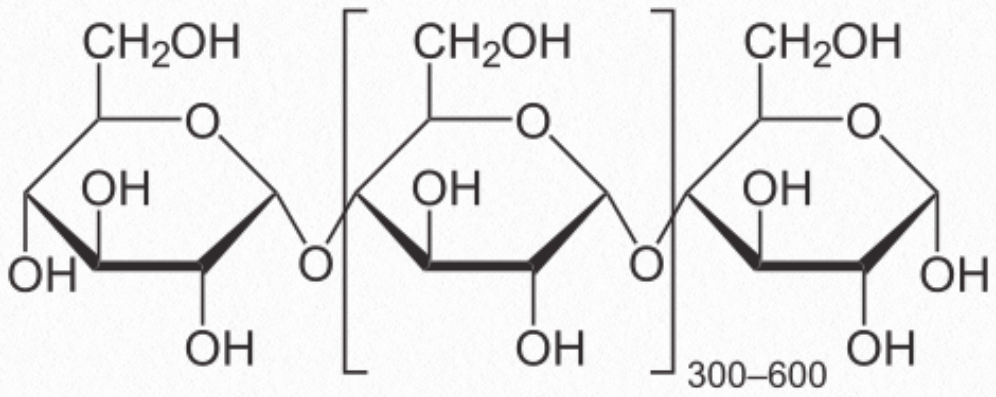

Figure 6.34 Amylose, a polymer of glucose in plants

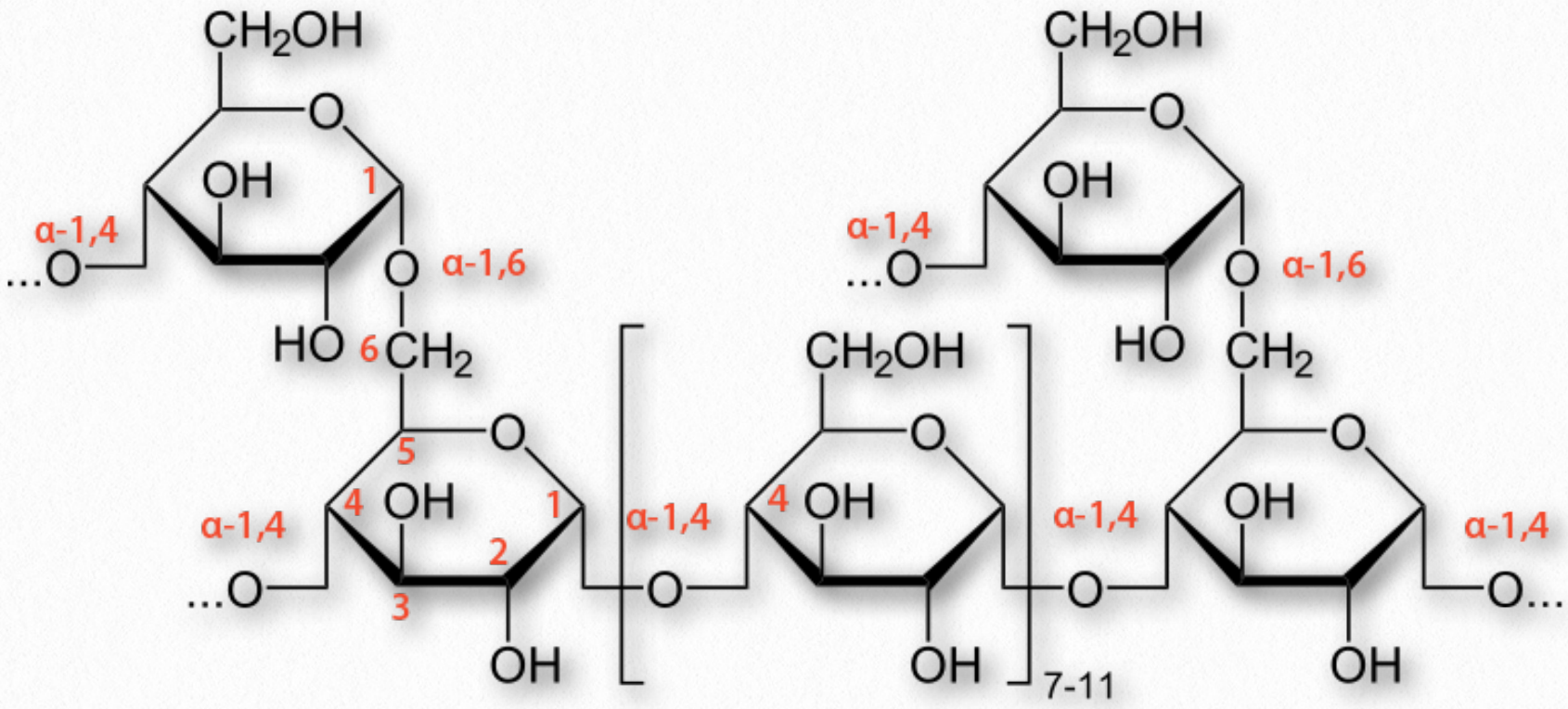

Figure 6.35 - Glycogen Structure - α-1,4 links with α-1,6 branches every 7-10 residues

Glycogen

Animals store glucose primarily in liver and muscle in the form of a compound related to amylopectin known as glycogen. The structural differences between glycogen and amylopectin are solely due to the frequency of the α-1,6 branches of glucoses. In glycogen they occur about every 10 residues instead of every 30-50, as in amylopectin (Figure 6.35).

Glycogen provides an additional source of glucose besides that produced *via* gluconeogenesis. Because glycogen contains so many glucoses, it acts like a battery backup for the body, providing a quick source of glucose when needed and providing a place to store excess glucose when glucose concentrations in the blood rise.

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The branching of glycogen is an important feature of the molecule metabolically as well. Since glycogen is broken down from the "ends" of the molecule, more branches translate to more ends, and more glucose that can be released at once.

Just as in gluconeogenesis, the cell has a separate mechanism for glycogen synthesis that is distinct from glycogen breakdown. As noted previously, this allows the cell to separately control the reactions, avoiding futile cycles, and enabling a process to occur efficiently (synthesis of glycogen) that would not occur if

it were simply the reversal of glycogen breakdown.

Glycogen breakdown

Breakdown of glycogen involves 1) release of glucose-1-phosphate (G1P), 2) rearranging the remaining glycogen (as necessary) to permit continued breakdown, and 3) conversion of G1P to G6P for further metabolism. G6P can be 1) used in glycolysis, 2) converted to glucose by gluconeogenesis, or 3) oxidized in the pentose phosphate pathway.

Glycogen phosphorylase (sometimes simply called phosphorylase) catalyzes breakdown of glycogen into glucose-1-Phosphate (G1P - Figure 6.36). The reaction that produces G1P from glycogen is a phosphorolysis, not a hydrolysis reaction. The distinction is that hydrolysis reactions use water to cleave bigger molecules into smaller ones, but phosphorolysis reactions use phosphate instead for the same purpose. Note that the phosphate is just that - it does NOT come from ATP. Since ATP is *not* used to put phosphate on G1P, the reaction saves the cell energy.

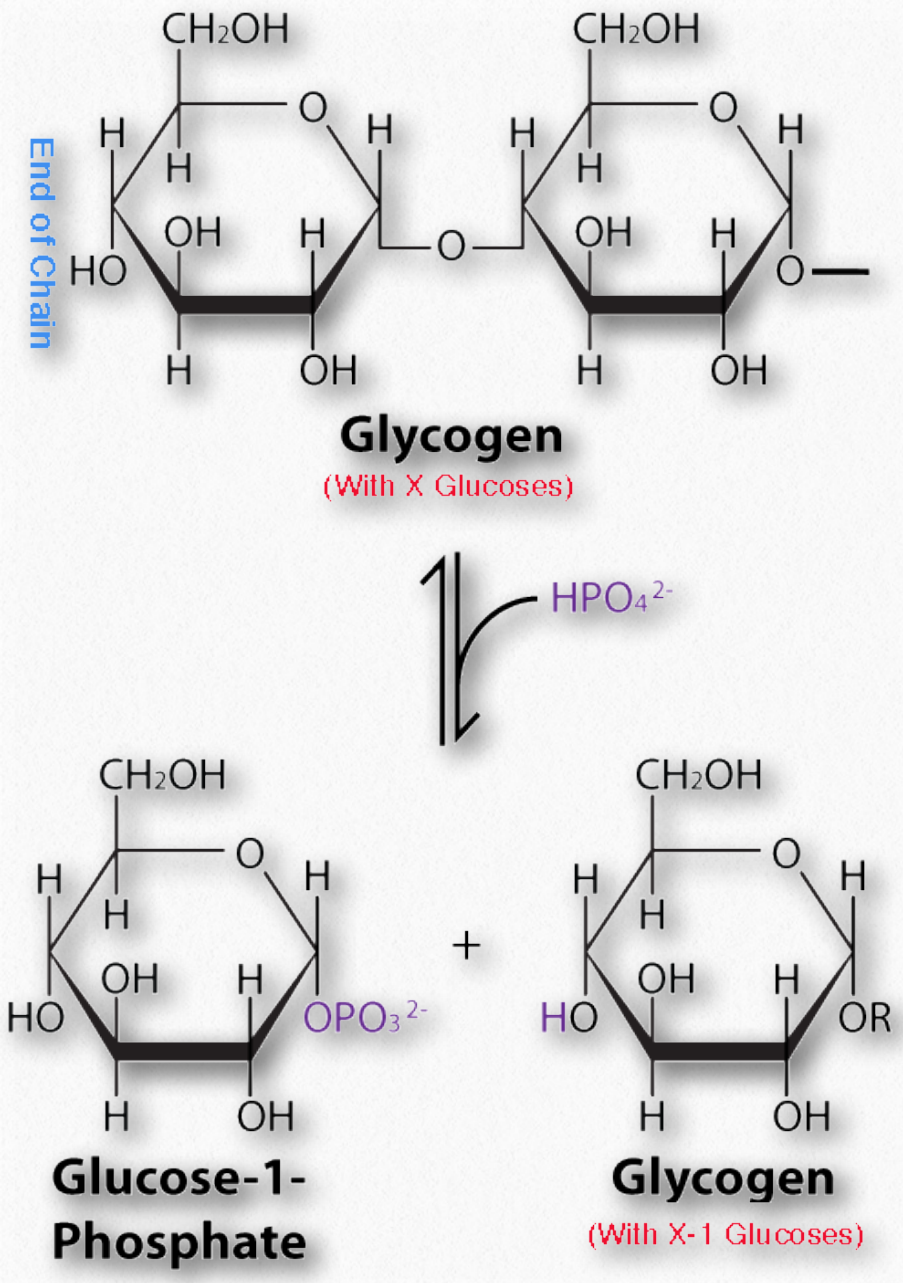

Figure 6.36 - Breaking of α-1,4 bonds of glycogen by glycogen phosphorylase

Image by Aleia Kim

Glycogen debranching enzyme

Glycogen phosphorylase will only act on non-reducing ends of a glycogen chain that are at least 5 glucoses away from a branch point. A second enzyme, Glycogen Debranching Enzyme (GDE) (also called debranching enzyme), is therefore needed to convert α (1-6) branches to α (1-4) branches. GDE acts on glycogen branches that have reached their limit of phosphorylysis with glycogen phosphorylase.

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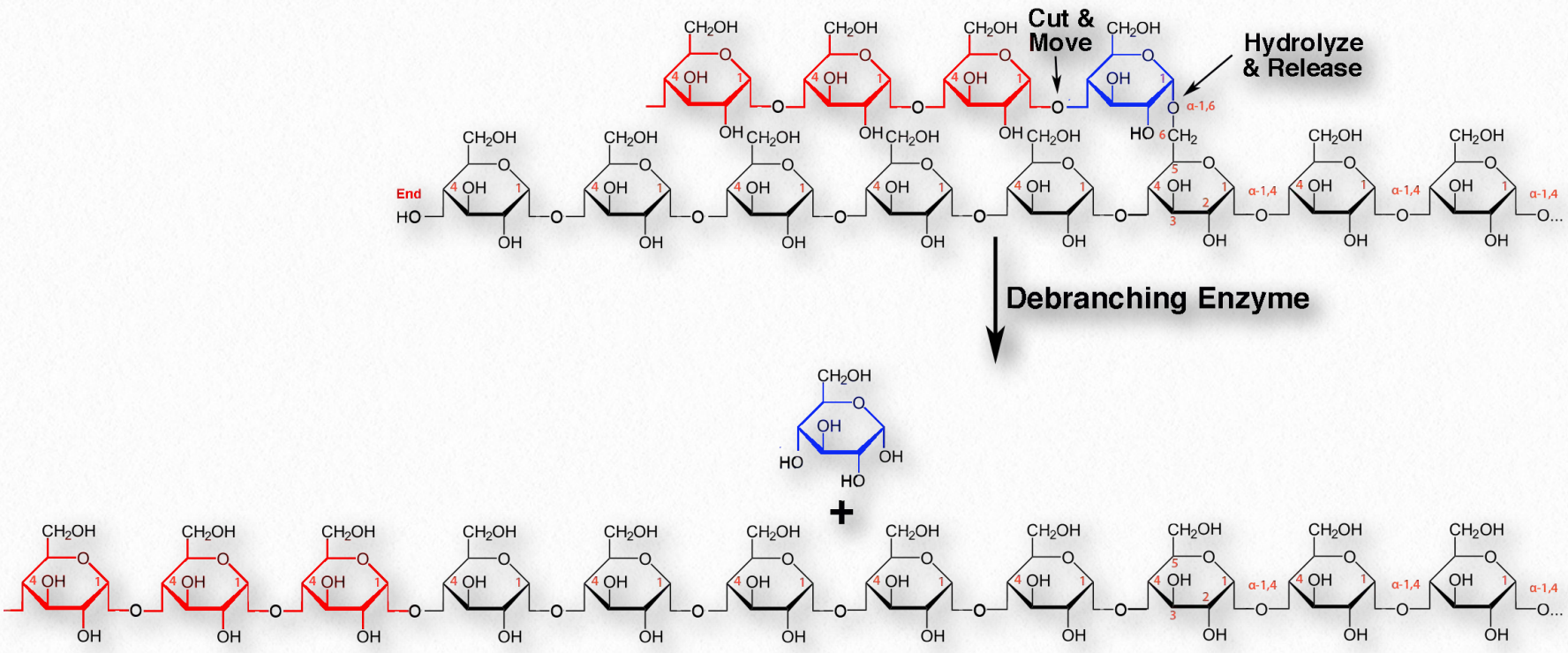

Figure 6.37 - Catalytic activity of debranching enzyme

GDE acts to transfer a trisaccharide from an α-1,6 branch onto an adjacent α-1,4 branch, leaving a single glucose at the 1,6 branch. Note that the enzyme also catalyzes the hydrolysis of the remaining glucose at the 1,6 branch point (Figure 6.37). Thus, the breakdown products from glycogen are G1P and glucose (mostly G1P). Glucose can, of course, be converted to Glucose-6-Phosphate (G6P) as the first step in glycolysis by either hexokinase or glucokinase.

G1P can be converted to G6P by action of an enzyme called phosphoglucomutase. This reaction is readily reversible, allowing G6P and G1P to be interconverted as the concentration of one or the other increases. This is important, because phosphoglucomutase is needed to form G1P for glycogen synthesis.

Regulation of glycogen metabolism

Regulation of glycogen metabolism is complex, occurring both allosterically and *via* hormone-receptor controlled events that result in protein phosphorylation or dephosphorylation. In order to avoid a futile cycle of glycogen synthesis and breakdown simultaneously, cells have evolved an elaborate set of controls that ensure only one pathway is primarily active at a time.

Regulation of glycogen metabolism is managed by the enzymes glycogen phosphorylase and glycogen synthase. Glycogen phosphorylase is regulated by both allosteric factors (ATP, G6P, AMP, and glucose) and by covalent modification (phosphorylation / dephosphorylation). Its regulation is consistent with the energy needs of the cell. High energy molecules (ATP, G6P, glucose) al-

losterically inhibit glycogen phosphorylase, while the low energy molecule AMP allosterically activates it.

GP_a/GP_b allosteric regulation

Glycogen phosphorylase exists in two different covalent forms – one form with phosphate (called GP_a here) and one form lacking phosphate (GP_b here). GP_b is converted to GP_a by phosphorylation by an enzyme known as phosphorylase kinase. GP_a and GP_b can each exist in an 'R' state and a 'T' state (Figure 6.38). For both GP_a and GP_b, the R state is the more active form of the enzyme. GP_a's negative allosteric effector (glucose) is usually not abundant in cells, so GP_a does not flip into the T state often. There is no positive allosteric effector of GP_a. When glucose is absent, GP_a automatically flips into the R (more active) state (Figure 6.39). It is for this reason that people tend to think of GP_a as being the more active covalent form of the enzyme.

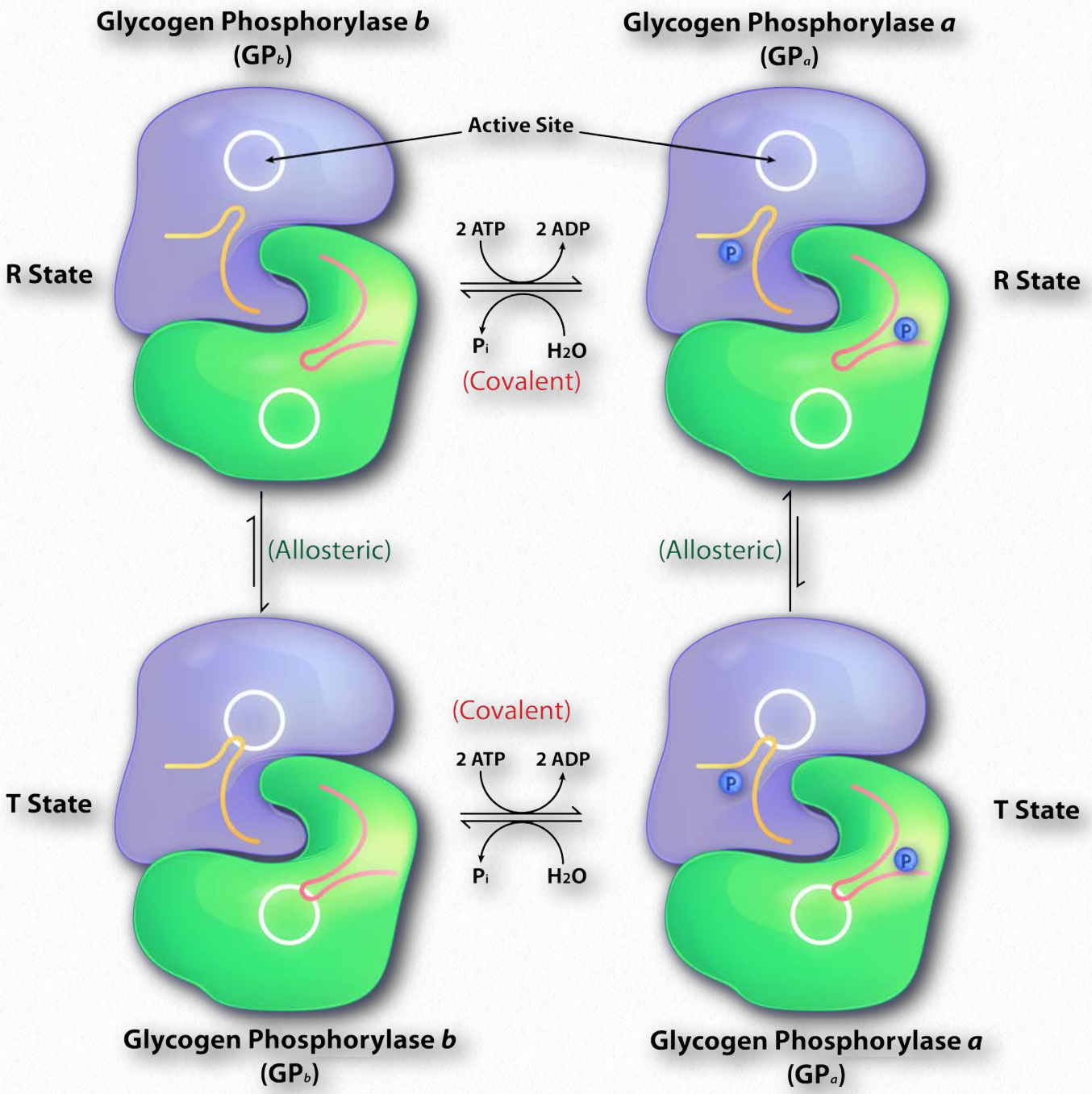

Figure 6.38 - Glycogen phosphorylase regulation - covalent (horizontal) and allosteric (vertical)

Image by Aleia Kim

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GP_b can convert from the GP_b T state to the GP_b R state by binding AMP. Unless a cell is low in energy, AMP concentration is low. Thus GP_b is not converted

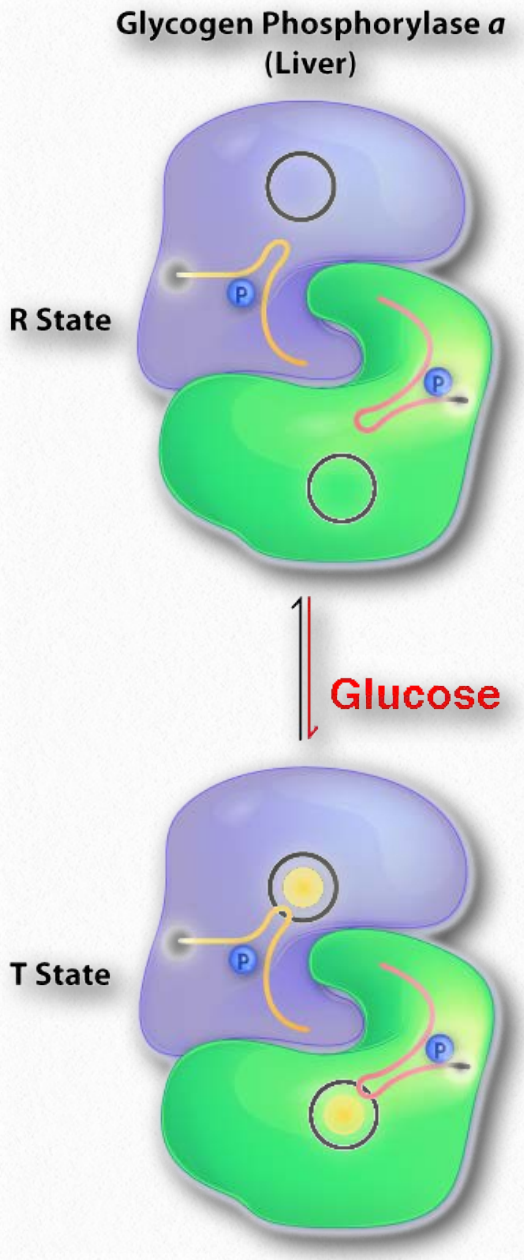

Figure 6.39 - Allosteric regulation of GP_a

Image by Aleia Kim

to the R state very often. This is why people think of the GP_b form as less active than GP_a. On the other hand, ATP and/or G6P are usually present at high enough concentration in cells that GP_b is readily flipped into the T state (Figure 6.40).

GP_a/GP_b covalent regulation

The relative amounts of GP_a and GP_b largely govern the overall process of glycogen breakdown, since GP_a tends to be active more often than GP_b. It is important, therefore, to understand the controls on the enzymes that interconvert GP_a and GP_b. This is accomplished by the enzyme phosphorylase kinase, which transfers phosphates from 2 ATPs to GP_b to form GP_a.

Phosphorylase kinase itself has two covalent forms – phosphorylated (active) and dephosphorylated (inactive). It is phosphorylated by the enzyme Protein Kinase A (PKA -). Another way to activate the enzyme is allosterically with calcium (Figure 6.41). Phosphory-

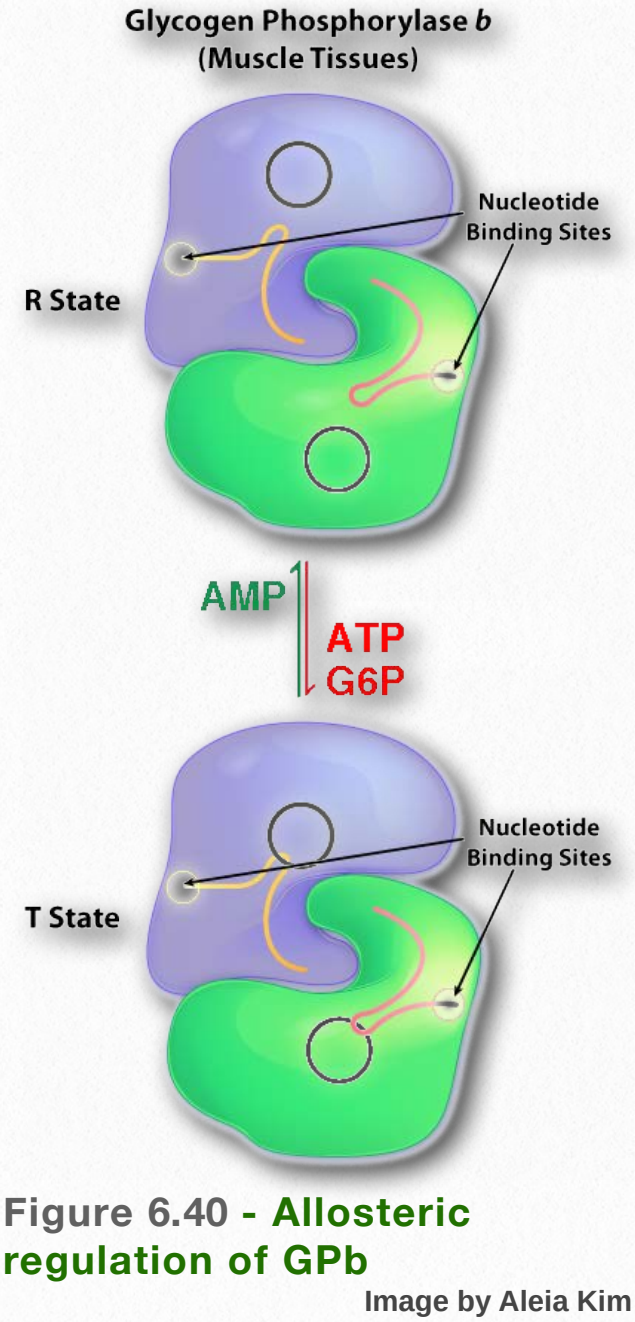

Figure 6.40 - Allosteric regulation of GPb

Image by Aleia Kim

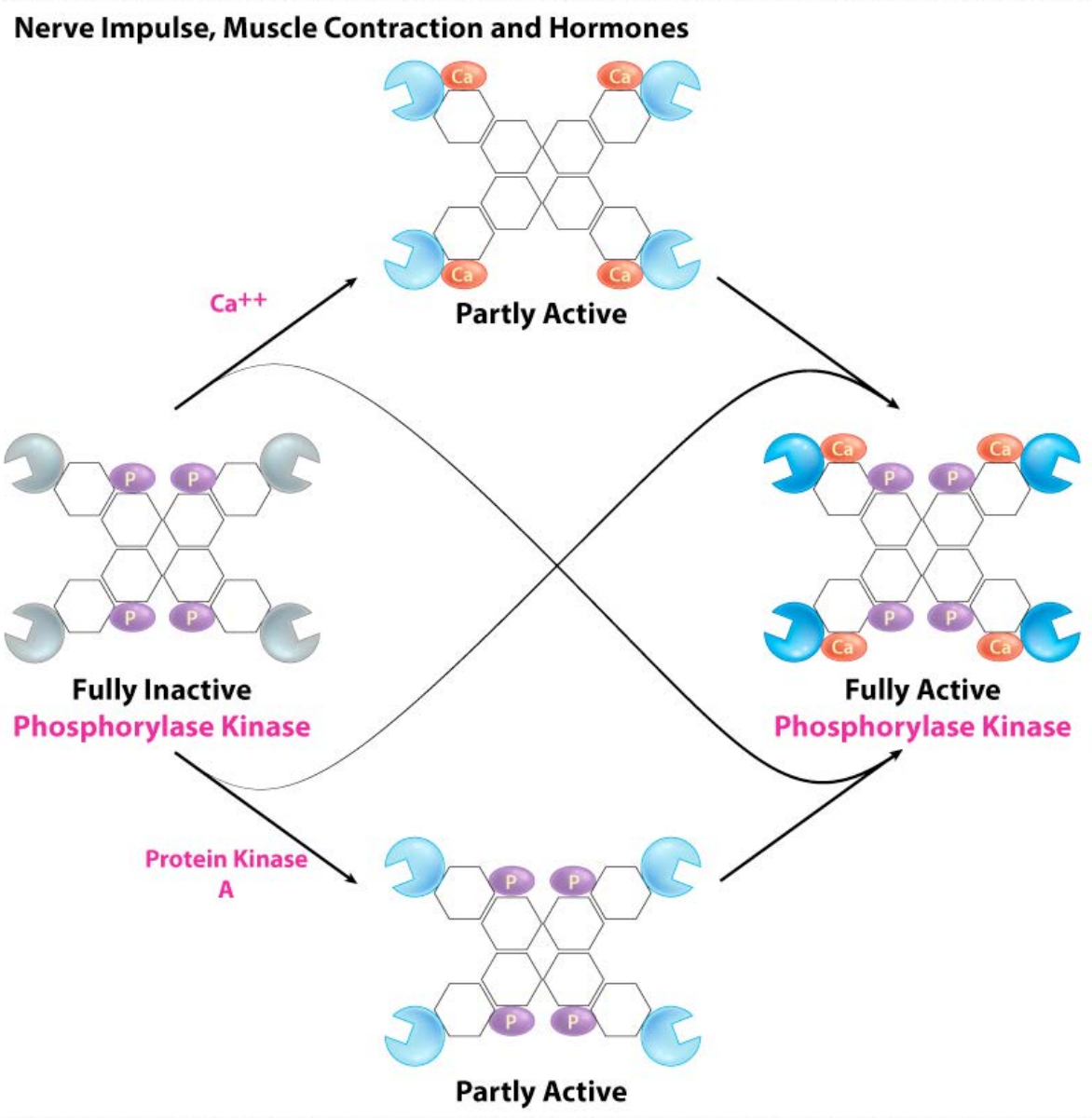

Figure 6.41 - Activation of phosphorylase kinase

Image by Aleia Kim

lase kinase is dephosphorylated by phosphoprotein phosphatase, the same enzyme that removes phosphate from GP_a.

PKA and cAMP

PKA is activated by cAMP, which is, in turn, produced by adenylate cyclase after activation by a G-protein (See HERE for overview). G-proteins are activated ultimately by binding of ligands to specific membrane receptors called 7-TM receptors, also known as G-protein coupled receptors. These are discussed in greater detail HERE. Common ligands for 7-TM receptors include epinephrine (binds β-adrenergic receptor) and glucagon (binds glucagon receptor). Epinephrine exerts its greatest effects on muscle and glucagon works preferentially on the liver. Thus, epinephrine and glucagon can activate glycogen breakdown by stimulating synthesis of cAMP followed by the cascade of events described above.

Turning off glycogen breakdown

Turning off signals is as important, if not more so, than turning them on. Glycogen is a precious resource. If its breakdown is not controlled, a lot of energy used in its synthesis is wasted. The steps in the glycogen breakdown regulatory pathway can be reversed at every level. First, the ligand (epinephrine or glucagon) can leave the receptor, turning off the stimulus. Second, the G-proteins have an inherent GTPase activity. GTP, of course, is what activates G-proteins, so a GTPase activity converts the GTP it is carrying to GDP and the G-protein becomes inactive. Thus, G-proteins turn off

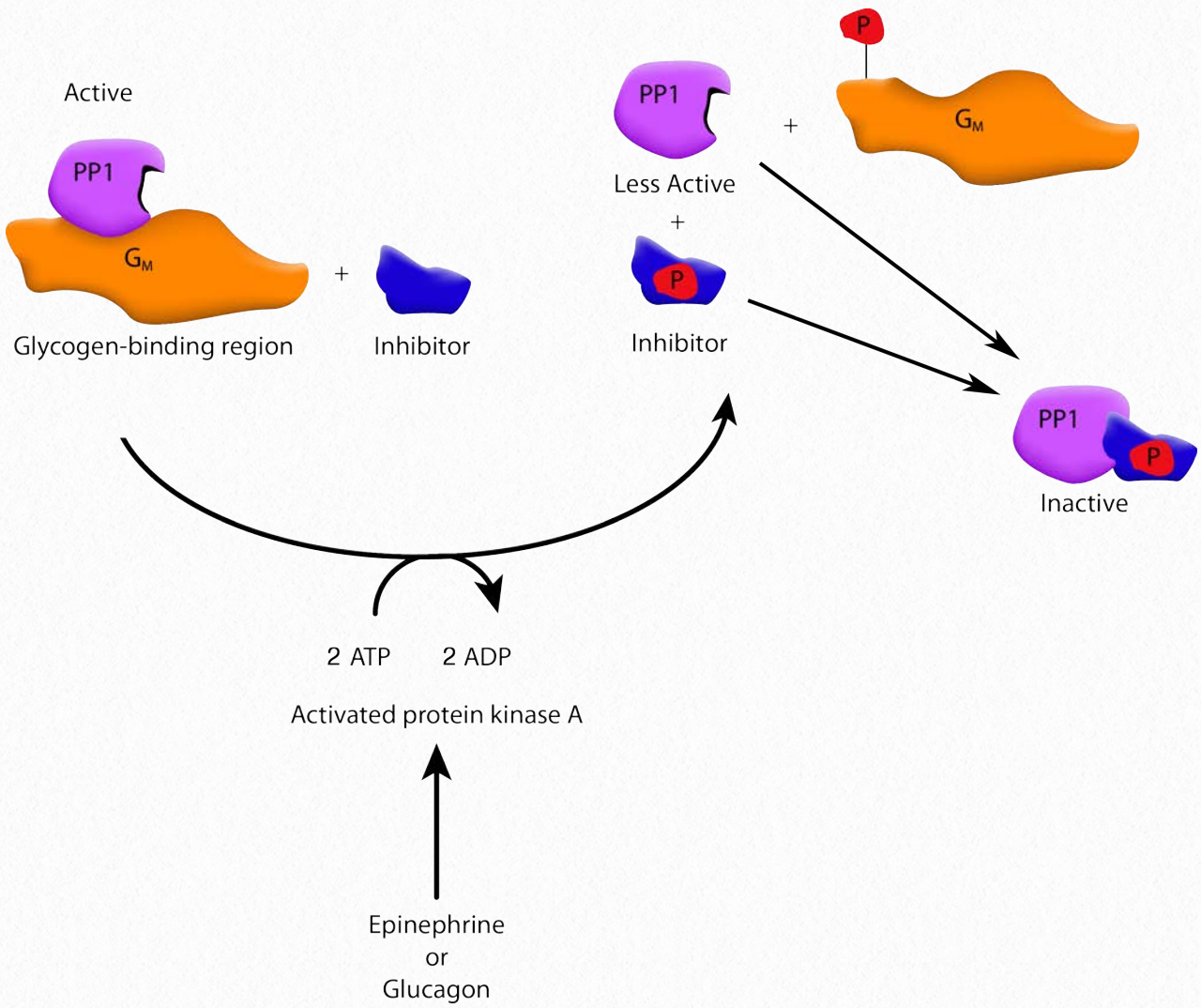

Figure 6.42 - Inactivation of phosphoprotein phosphatase by protein kinase A via phosphorylation of PI-1 (Inhibitor) and the G_M binding protein

Image by Pehr Jacobson

their own activity. Interfering with their ability to convert GTP to GDP can have dire consequences, including cancer in some cases.

Third, cells have phosphodiesterase enzymes (inhibited by caffeine) for breaking down cAMP. cAMP is needed to activate PKA, so breaking it down stops PKA from activating phosphorylase kinase. Fourth, the enzyme known as phosphoprotein phosphatase (also called PP1) plays a major role. It can remove phosphates from phosphorylase kinase (inactivating it) and form GP_a, converting it to the less likely to be active GP_b. Regulation of phosphoprotein phosphatase activity occurs at several levels. Two of these are shown in Figures 6.42 & 6.43.

In Figure 6.42, phosphoprotein phosphatase is shown being inactivated by phosphorylation of an inhibitor (called PI-1 - see below). This happens as a result of cascading actions from binding of epinephrine (or glucagon) to a cell's β-adrenergic receptor. Reversal of these actions occurs when insulin binds to the cell's insulin receptor, resulting in activation of phosphoprotein phosphatase.

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PI-1

The inhibitor PI-1 can block activity of phosphpoprotein phosphatase only if it (PI-1) is phosphorylated. When PI-1 gets dephosphorylated, it no longer functions as an inhibitor, so phosphoprotein phosphatase be-

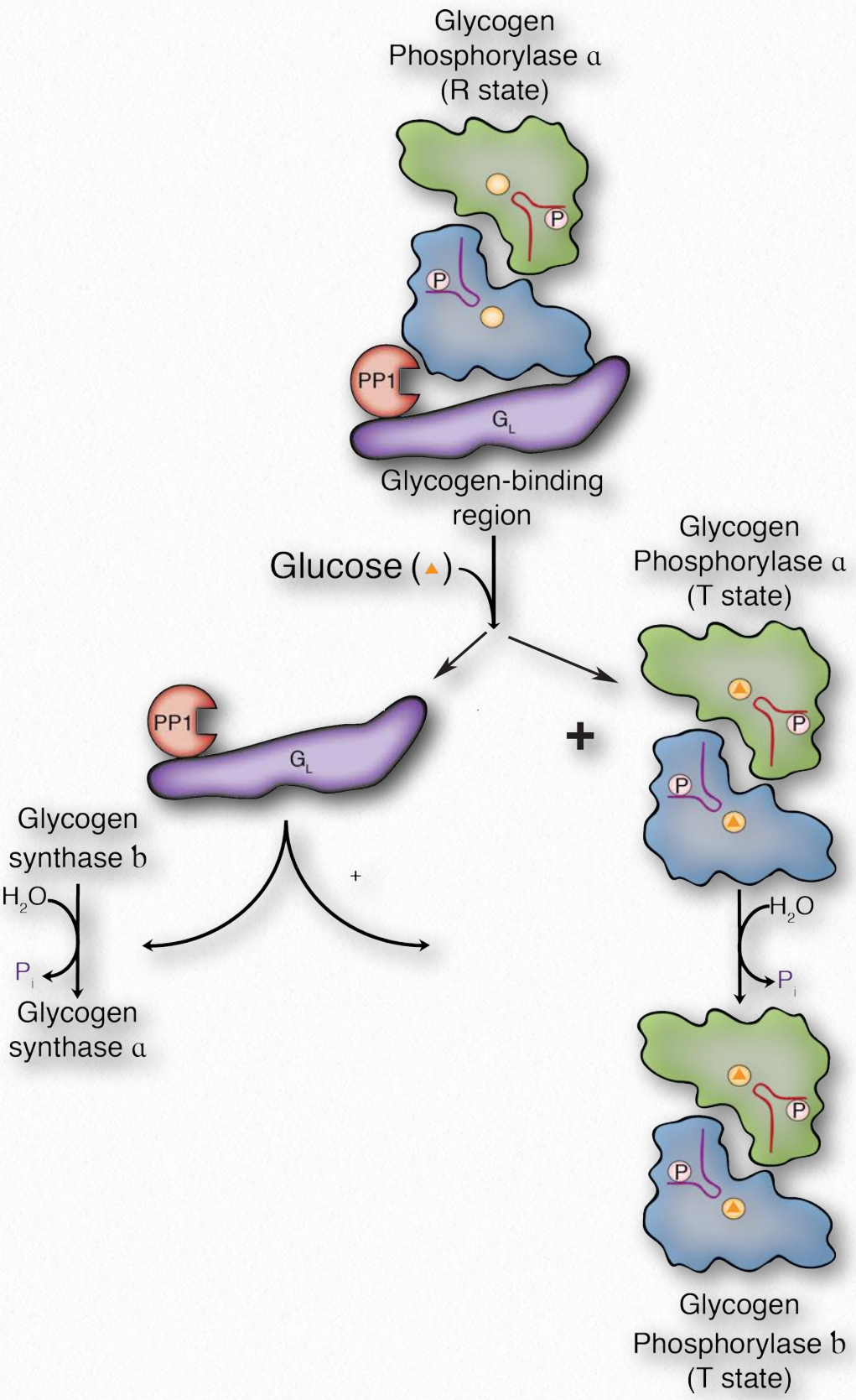

Figure 6.43 - Regulation of phosphoprotein phosphatase (PP-1) activity by GPa

Image by Penelope Irving

comes active. Now, here is the clincher - PI-1 gets phosphorylated by PKA (thus, when epinephrine or glucagon binds to a cell) and gets dephosphorylated when insulin binds to a cell.

Another regulatory mechanism

Another way to regulate phosphoprotein phosphatase in the liver involves GP_a directly (Figure 6.43). In liver cells, phosphoprotein phosphatase is bound to a protein called G_L. GL can also bind to GPa. As shown in the figure, if the three proteins are complexed together (top of figure), then PP1 (phosphoprotein phosphatase) is inactive. When glucose is present (such as when the liver has made too much glucose), then the free glucose binds to the GP_a and causes GP_a to be released from the G_L.

This has the effect of activating phosphoprotein phosphatase, which begins dephosphorylating enzymes. As shown in the figure, two such enzymes are GP_a (making GP_b) and glycogen synthase b, making glycogen synthase a. These dephosphorylations have opposite effects on the two enzymes, making GP_b, which is less active and glycogen synthase a, which is much more active.

Glycogen synthesis

The anabolic pathway opposing glycogen breakdown is that of glycogen synthesis. Just

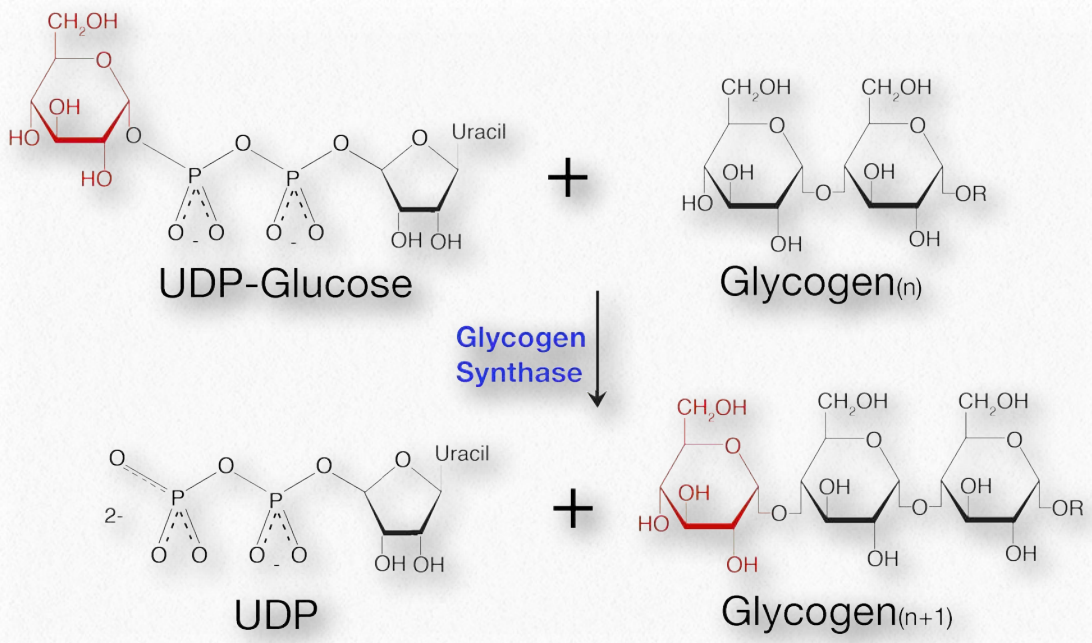

Figure 6.44 - Catalytic activity of glycogen synthase
Image by Penelope Irving

Synthesis of glycogen starts with G1P, which is converted to an 'activated' intermediate, UDP-glucose. This activated intermediate is what 'adds' the glucose to the growing glycogen chain in a reaction catalyzed by the enzyme known as glycogen synthase (Figure 6.44). Once the glucose is added to glycogen, the glycogen molecule may need to have branches inserted in it by the enzyme known as branching enzyme (Figure 6.45).

as cells reciprocally regulate glycolysis and gluconeogenesis to prevent a futile cycle between these pathways, so too do cells use reciprocal schemes to regulate glycogen breakdown and synthesis.

Steps

Let us first consider the steps in glycogen synthesis. 1) Glycogen synthesis from glucose involves phosphorylation to form G6P, and isomerization to form G1P (using phospho-

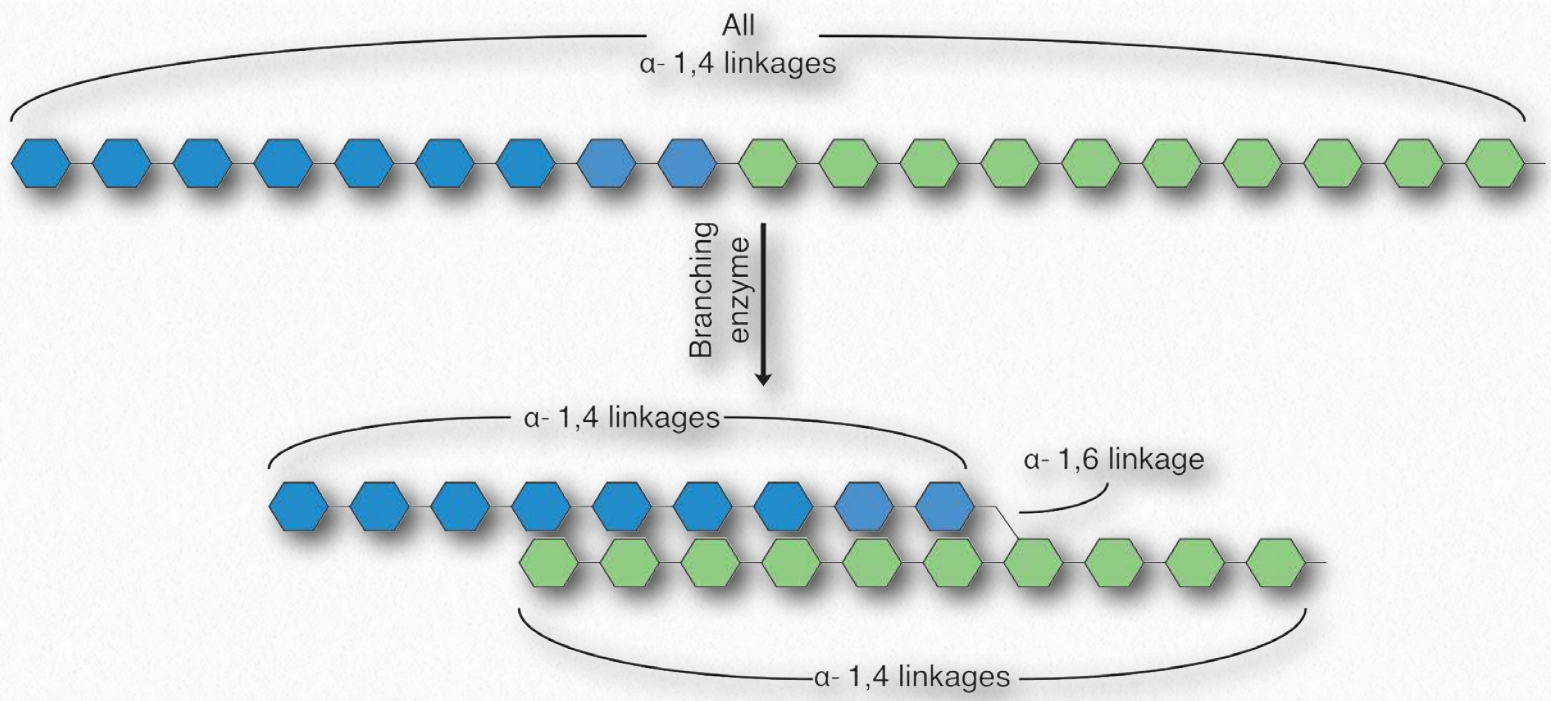

Figure 6.45 - Branch formation in glycogen by branching enzyme
Image by Penelope Irving

glucomutase, common to glycogen breakdown). G1P is reacted with UTP to form UDP-glucose in a reaction catalyzed by UDP-glucose pyrophosphorylase. Glycogen synthase catalyzes synthesis of glycogen by joining carbon #1 of the UDP-derived glucose onto the carbon #4 of the non-reducing end of a glycogen chain, to form the familiar α(1,4) glycogen links. Another product of the reaction is UDP.

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"Primer" requirements

It is also worth noting, in passing, that glycogen synthase will only add glucose units from UDP-Glucose onto a preexisting glycogen chain that has at least four glucose residues. Linkage of the first few glucose units to form the minimal "primer" needed for glycogen synthase recognition is catalyzed by a protein called glycogenin, which attaches to the first glucose and catalyzes linkage of the first eight glucoses by α(1,4) bonds. 3) The characteristic α(1,6) branches of glycogen are the products of the enzyme known as branching enzyme. Branching enzyme breaks α(1,4) chains and carries the broken chain to the carbon #6 and forms an α(1,6) linkage (Figure 6.45).

Regulation of glycogen synthesis

The regulation of glycogen biosynthesis is reciprocal to that of glycogen breakdown. It also has a cascading covalent modification system similar to the glycogen breakdown system described above. In fact, part of the system is identical to glycogen breakdown. Epinephrine or glucagon signaling stimulates adenylate cyclase to make cAMP, which activates PKA.

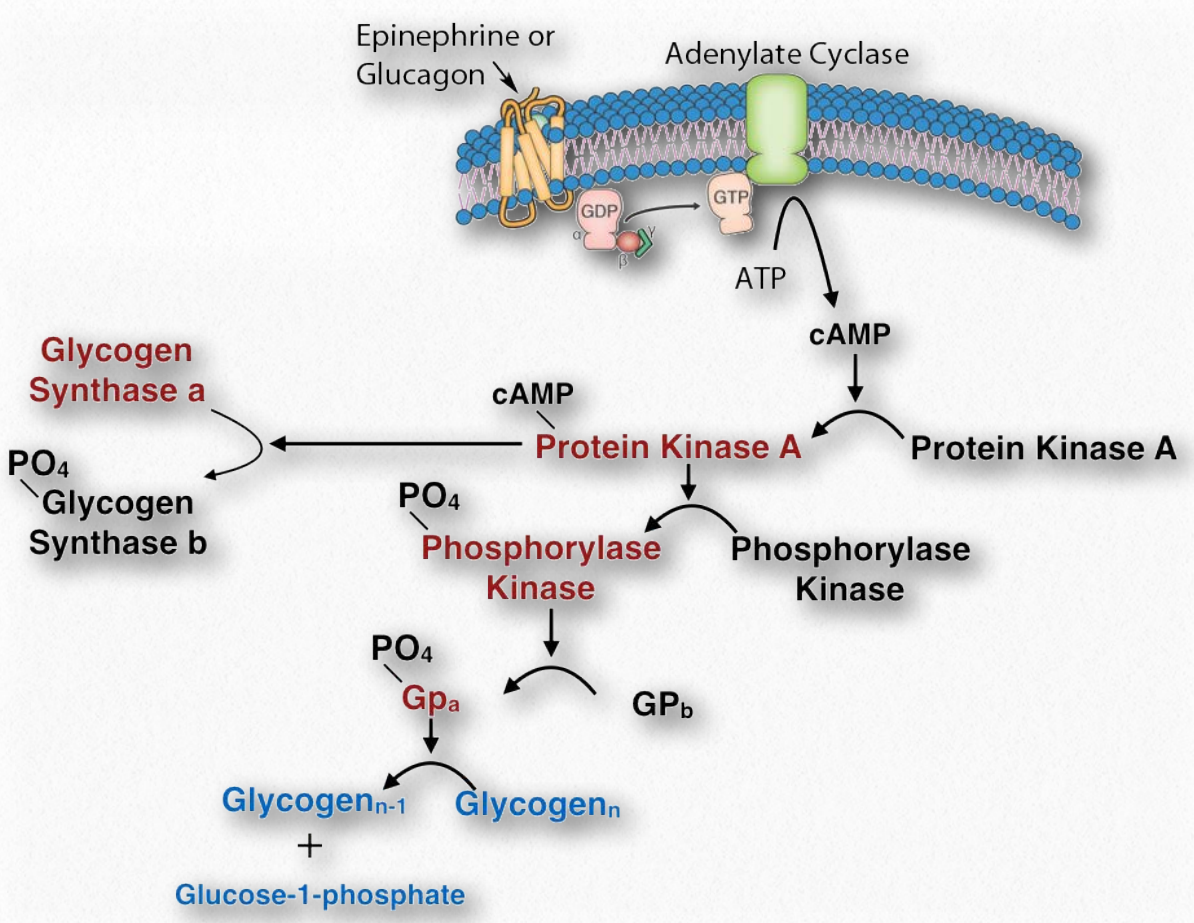

Figure 6.46 - Reciprocal regulation by the phosphorylation cascade - glycogen breakdown activated / glycogen synthesis inhibited

Image by Penelope Irving

Effect of phosphorylation

In glycogen synthesis, protein kinase A phosphorylates the active form of glycogen synthase (GS_a), and converts it into the usually inactive b form (called GS_b).

Note the conventions for glycogen synthase and glycogen phosphorylase. For both enzymes, the more active forms are called the 'a' forms (GP_a and GS_a) and the less active forms are called the 'b' forms (GP_b and GS_b). The *major* difference, however, is that GP_a has a phosphate, but GS_a does not and GP_b has no phosphate, but GS_b does.

Thus phosphorylation and dephosphorylation have *opposite effects* on the enzymes of glycogen metabolism (Figure 6.46). This is the hallmark of reciprocal regulation. It is of note that the less active glycogen synthase form, GS_b, can be activated by G6P. Recall that G6P had the exactly opposite effect on GP_b.

Glycogen synthase, glycogen phosphorylase (and phosphorylase kinase) can all be dephosphorylated by the same enzyme - phosphoprotein phosphatase - and it is activated when insulin binds to its receptor in the cell membrane.

Big picture

In the big picture, binding of epinephrine or glucagon to appropriate cell receptors stimulates a phosphorylation cascade which simultaneously activates breakdown of glycogen by glycogen phosphorylase and inhibits its synthesis of glycogen by glycogen synthase. Epinephrine, is also known as adrenalin, and the properties that adrenalin gives arise from a large temporary increase of blood glucose, which powers muscles.

Figure 6.47 - Cotton - the purest natural form of cellulose

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On the other hand, insulin stimulates dephosphorylation by activating phosphoprotein phosphatase. Dephosphorylation reduces action of glycogen phosphorylase (less glycogen breakdown) and activates glycogen synthase (starts glycogen synthesis). Our bodies make glycogen when blood glucose levels rise. Since high blood glucose levels are harmful, insulin stimulates cells to take up glucose. In the liver and in muscle cells, the uptaken glucose is made into glycogen.

Cellulose synthesis

Cellulose is synthesized as a result of catalysis by cellulose synthase. Like glycogen synthesis it requires an activated intermediate to add glucose residues and there are two possible ones - GDP-glucose and UDP-glucose, depending on which cellulose synthase is involved. In plants, cellulose provides support to cell walls.

The reaction catalyzed is shown next where $Cellulose_n$ = a polymer of [(1→4)-β-D-glucosyl] n units long.

UDP-glucose + $Cellulose_n$

⇅

UDP + $Cellulose_{n+1}$

The GDP-glucose reaction is the same except with substitution of GDP-glucose for UDP-

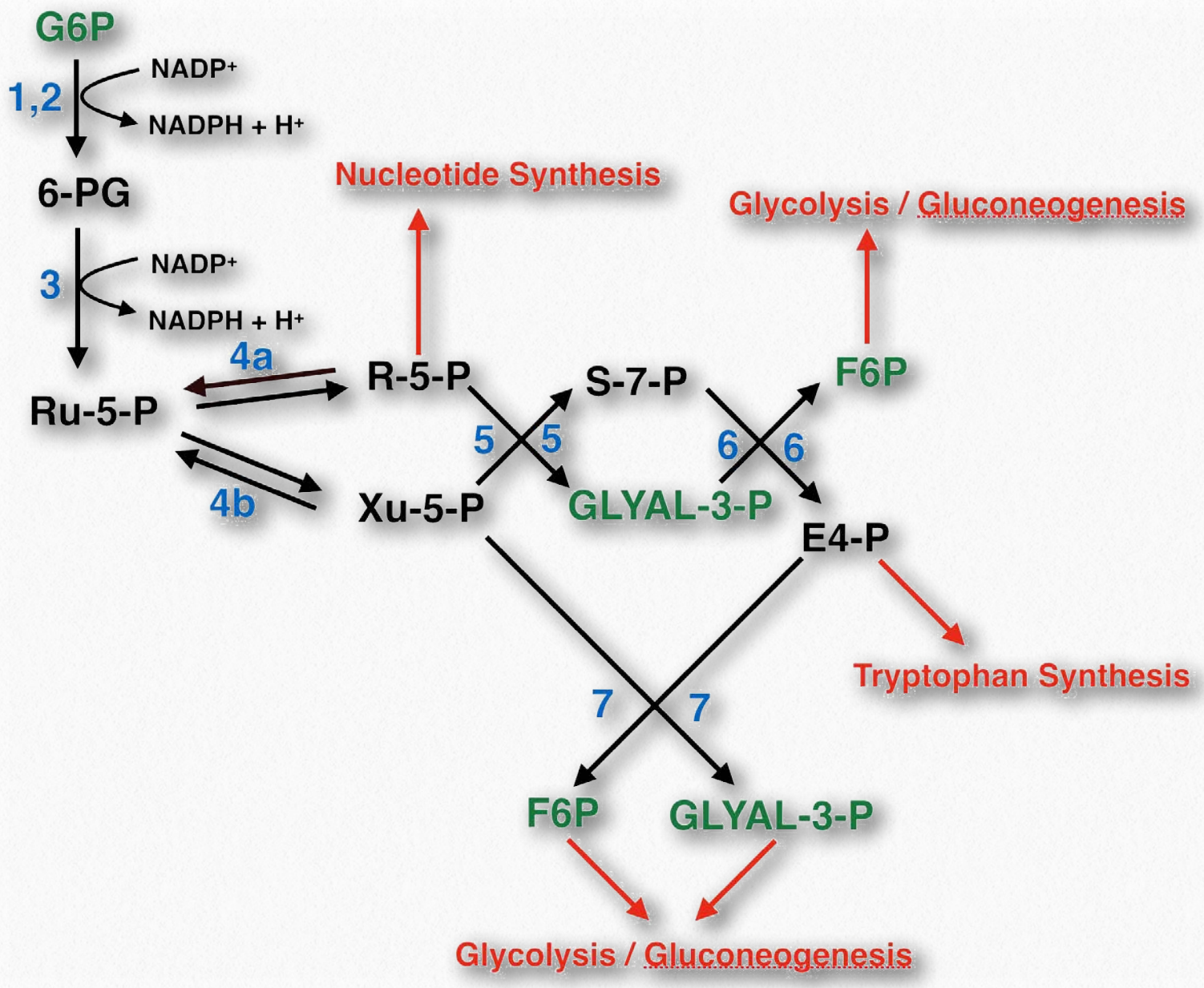
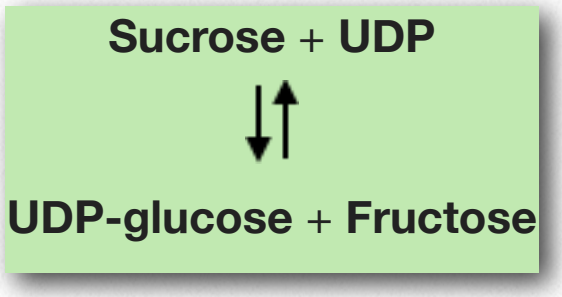


Figure 6.48 - The Pentose Phosphate Pathway - Enzymes - 1 = G6P dehydrogenase / 2 = 6-Phosphogluconolactonase / 3 = 6-PG dehydrogenase / 4a = Ribose 5-phosphate isomerase / 4b = Ribulose 5-phosphate 3-epimerase / 5,7 = Transketolase / 6 = Transaldolase

glucose. UDP-glucose for the reaction is obtained by catalysis of sucrose synthase.



The enzyme is named for the reverse reaction.

Pentose phosphate pathway

The pentose phosphate pathway (PPP - also called the hexose monophosphate shunt) is an oxidative pathway involving sugars that is sometimes described as a parallel pathway to glycolysis. It is, in fact, a pathway with multiple inputs and outputs (Figure 6.48). PPP is also a major source of NADPH for biosynthetic reactions and can provide ribose-5-phosphate for nucleotide synthesis.

Though when drawn out, the pathway's "starting point" is often shown as glucose-6-phosphate (G6P), in fact there are multiple entry points including other glycolysis intermediates, such as fructose-6-phosphate (F6P) and glyceraldehyde-3-phosphate (GLYAL-3-P), as well as less common sugar compounds with 4,5, and 7 carbons.

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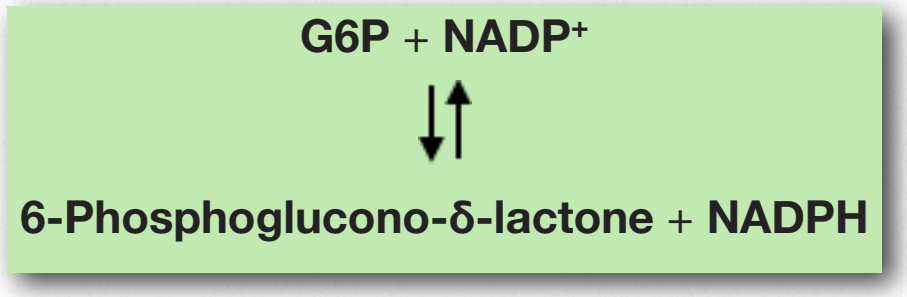
The multiple entry points and multiple outputs gives the cell tremendous flexibility to meet its needs by allowing it to use a variety of materials to make any of these products.

Oxidation #1

Beginning with G6P, PPP proceeds through its oxidative phase as follows:



The enzyme catalyzing the reaction is G6P dehydrogenase. It is the rate limiting step of the pathway and the enzyme is inhibited both by NADPH and acetyl-CoA. NADPH is important for anabolic pathways, such as fatty acid synthesis and also for maintaining glutathione in a reduced state. The latter is important in protection against damage from reactive oxygen species.

Deficiency of the G6P dehydrogenase enzyme is not rare, leading to acute hemolytic anemia, due to reduced NADPH concentration, and a reduced ability of the cell to disarm reactive oxygen species with glutathione. Reduced activity of the enzyme appears to have a protective effect against malarial infection, likely due to the increased fragility of the red blood cell membrane, which is then unable to sustain an infection by the parasite.

Hydrolysis

Reaction #2 is a hydrolysis and it is catalyzed by 6-phosphogluconolactonase. The reac-

tion converts the circular 6-phosphoglucono-δ-lactone into the linear 6-phosphogluconate (6-PG) in preparation for oxidation in the next step.

6-Phosphoglucono-δ-lactone + H_2O

⇅

6-phosphogluconate (6-PG) + H^+

Decarboxylation

Reaction #3 is the only decarboxylation in the PPP and the last oxidative step. It is catalyzed by 6-phosphogluconate dehydrogenase.

6-PG + **$NADP^+$**

⇅

Ribulose-5-phosphate (Ru-5-P) + **NADPH** + **CO_2**

Mutations disabling the protein made from this gene negatively impact red blood cells. At this point, the oxidative phase of PPP is complete and the remaining reactions involve molecular rearrangements. Ru5P has two possible fates and these are each described below.

Isomerization

Reaction 4a: The enzyme catalyzing this reversible reaction is Ru5P isomerase (top of next column). It is important because this is the way cells make R-5-P for nucleotide synthesis. The R-5-P can also be used in other PPP reactions shown elsewhere.

Ru-5-P

⇅

Ribose-5-phosphate (R-5-P)

Epimerization

Reaction 4b (catalyzed by Ru-5-P epimerase) is another source of a pentose sugars and provides an important substrate for subsequent reactions.

Ru-5-P

⇅

Xylulose-5-phosphate (Xu-5-P)

Transketolase reactions

The other reactions don't really have an order to them and whether they occur or not depends on cellular needs. The first enzyme, transketolase, is flexible in terms of its substrate/product combinations and is used not only in PPP, but also in the Calvin cycle of plants. It catalyzes the next two reactions

Xu-5-P + R-5-P

⇅

GLYAL-3-P + Sedoheptulose-7-phosphate (S-7-P)

In the first reaction (above), two phosphorylated sugars of 5 carbons each are converted into one phosphorylated sugar of 3 carbons and one of 7 carbons. In the second (next page), a five carbon sugar phosphate and a

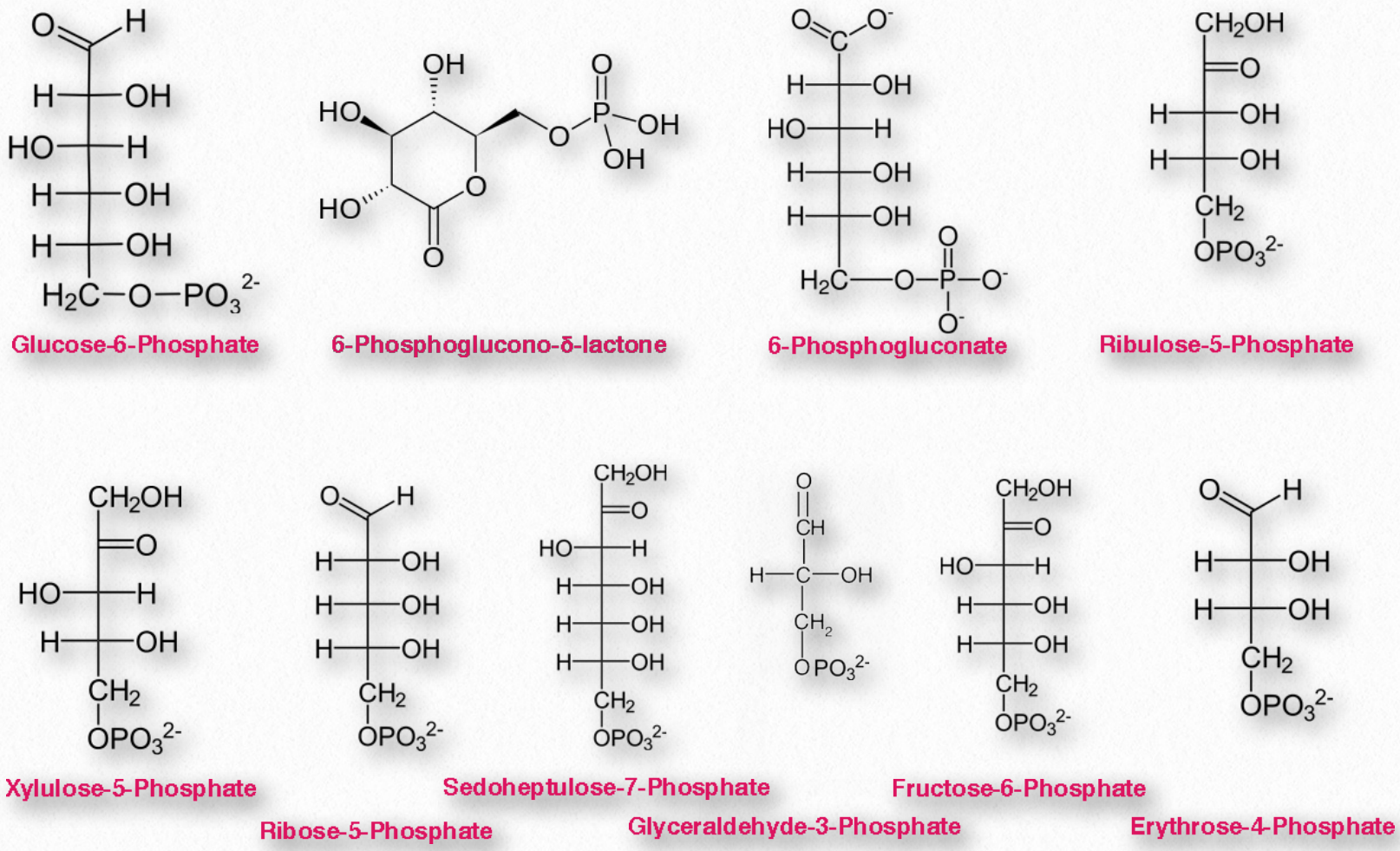


Figure 6.49 - Intermediates of the pentose phosphate pathway

four carbon sugar phosphate are rearranged into sugar phosphates with 3 and 6 carbons.

Xu-5-P + Erythrose-4-phosphate (E-4-P)

⇅

GLYAL-3-P + F6P

Glycolysis intermediates

In the reversible reactions of the pentose phosphate pathway, one can see how glycolysis intermediates can easily be rearranged and made into other sugars. Thus, GLYAL-3-P and F6P can be readily made into Ribose-5-phosphate for nucleotide synthesis.

Involvement of F6P in the pathway permits cells to continue making nucleotides (by making R-5-P) or tryptophan (by making E-4-P) even if the oxidative reactions of PPP are inhibited.

The last reaction is catalyzed by the enzyme known as transaldolase.

GLYAL-3-P + S-7-P

⇅

E-4-P + F6P

TPP co-factor

Transketolase uses thiamine pyrophosphate (TPP) to catalyze reactions. TPP's thia-

zole ring's nitrogen and sulfur atoms on either side of a carbon, allow it to donate a proton and act as an acid, thus forming a carbanion, which gets stabilized by the adjacent tetravalent nitrogen (Figures 6.50 & 6.51)).

The stabilized carbanion plays important roles in the reaction mechanism of enzymes, such as transketolase that use TPP as a co-

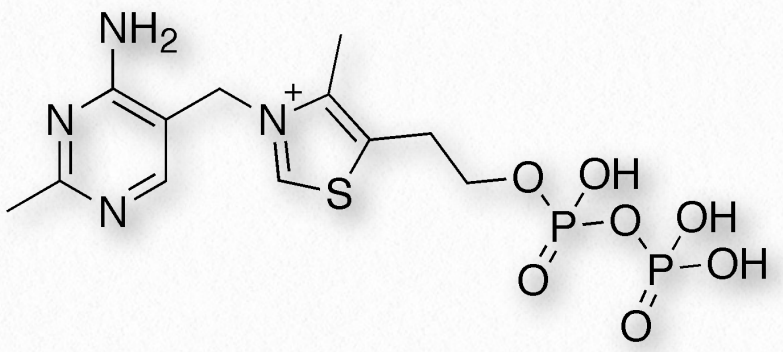


Figure 6.50 - Thiamine pyrophosphate

factor. Commonly, the carbanion acts as a nucleophile that attacks the carbonyl carbon of the substrate. Such is the case with transketolase. Attack by the carbanion breaks the carbonyl bond on the substrate and covalently links it to the ionized carbon of TPP, thus allowing it to "carry" the carbonyl group to the other substrate for attachment. In this way, two carbons are moved from Xu-5-P to E-4-P to make F6P (from E-4-P) and GLYAL-3-P (from Xu-5-P). Similarly, S-7-P and GLYAL-3-P are made from R-5-P and Xu-5-P, respectively.

Thiamines

Thiamines are a class of compounds involved in catalysis of important respiration-related

The Pentose Phosphate Pathway

by Kevin Ahern

I need erythrose phosphate
And don't know what to do
My cells are full of G-6-P
And NADP too

But I just hit upon a plan
As simple as can be
I'll run reactions through the path
That's known as PPP

In just two oxidations
There's ribulose-5P
Which morphs to other pentoses
Each one attached to P

The next step it is simple
Deserving of some praise
The pentose carbons mix and match
Thanks to transketolase

Glyceraldehyde's a product
Sedoheptulose is too
Each with a trailing phosphate
But we are not quite through

Now three plus seven is the same
As adding six and four
By swapping carbons back and forth
There's erythrose-P and more

At last I've got the thing I need
From carbons trading places
I'm happy that my cells are full
Of some transaldolases

reactions in the citric acid cycle, pyruvate metabolism, the pentose phosphate pathway, and the Calvin cycle. Thiamine was the first water-soluble vitamin (B_1) to be discovered via association with the peripheral nervous system disease known as Beriberi. Thiamine pyrophosphate (TPP) is an enzyme cofactor found in all living systems derived from thiamine by action of the enzyme thiamine diphosphokinase. TPP facilitates catalysis of several biochemical reactions essential for tissue respiration.

YouTube Lectures by Kevin HERE & HERE

Deficiency of the vitamin is rare today, though people suffering from Crohn's disease, anorexia, alcoholism or undergoing kidney dialysis may develop deficiencies. TPP is required for the oxidative decarboxylation of pyruvate to form acetyl-CoA and similar reactions. Transketolase, an important enzyme in the pentose phosphate pathway, also uses it as a coenzyme. Besides these reactions, TPP is also required for oxidative decarboxylation of α-keto acids like α-ketoglutarate and branched-chain α-keto acids arising from metabolism of valine, isoleucine, and leucine.

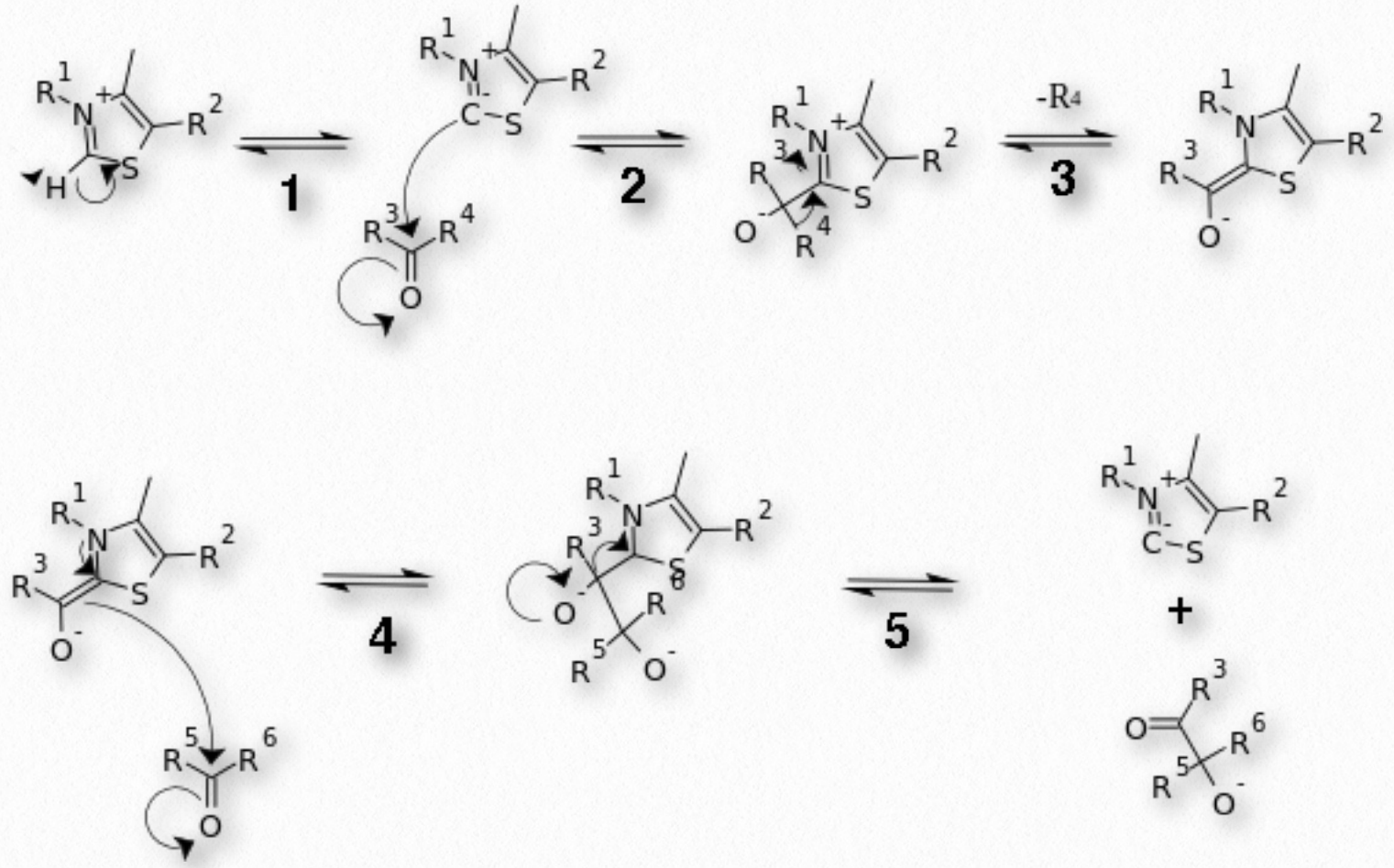


Figure 6.51 - Mechanism of action of thiamine pyrophosphate (TPP) - 1) Carbanion formation; 2) Nucleophilic attack; 3) Covalent attachment of carbonyl; 4) Transfer to second group; 5) Release of product and regeneration of TPP

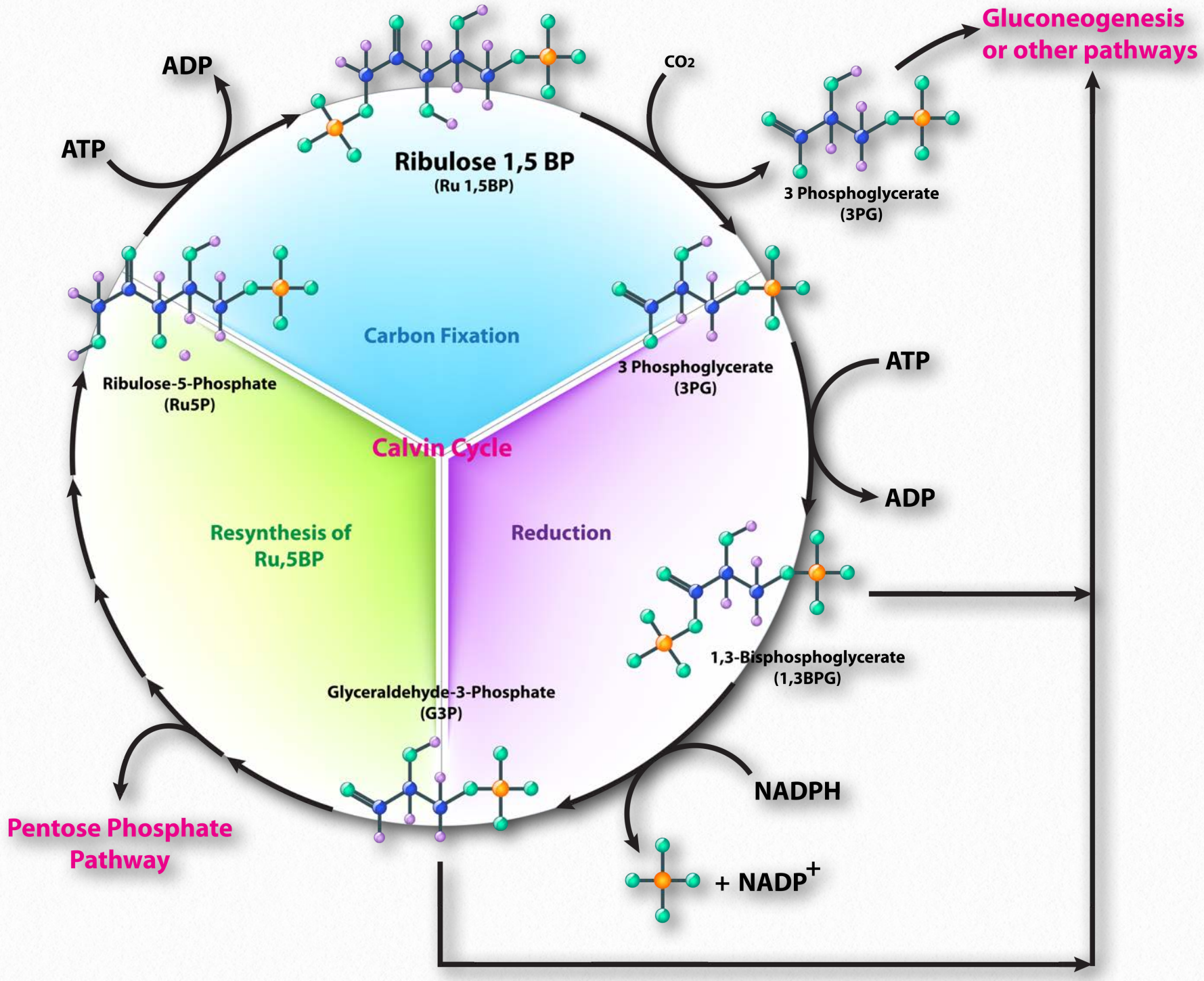


Figure 6.52 - The Calvin cycle - The resynthesis phase has multiple steps and is described below.

Image by Aleia Kim

TPP acts in the pyruvate dehydrogenase complex to assist in decarboxylation of pyruvate and "carrying" the activated acetaldehyde molecule to its attachment (and subsequent oxidation) to lipoamide. Central to TPP's function is the thiazolium ring, which stabilizes carbanion intermediates (through resonance) by acting as an electron sink (Figure 6.51). Such action facilitates breaking of carbon-carbon bonds such as occurs during decarboxylation of pyruvate to produce the activated acetaldehyde.

Thiamine deficiency

Thiamine is integral to respiration and is needed in every cell. Acute deficiency of thiamine leads to numerous problems - the best known condition is beriberi, whose symptoms include weight loss, weakness, swelling, neurological issues, and irregular heart rhythms.

Causes of deficiency include poor nutrition, significant intake of foods containing the enzyme known as thiaminase, foods with compounds that counter thiamine action (tea, coffee), and chronic diseases, including diabetes, gastrointestinal diseases, persistent vomiting. People with severe alcoholism often are deficient in thiamine.

Calvin cycle

The Calvin cycle (Figure 6.52) is a metabolic pathway occurring exclusively in photosynthetic organisms. Commonly referred to as the "Dark Cycle" or the Light-Independent Cycle, the Calvin cycle does not actually occur in the dark. The cell/chloroplast simply is not directly using light energy to drive it.

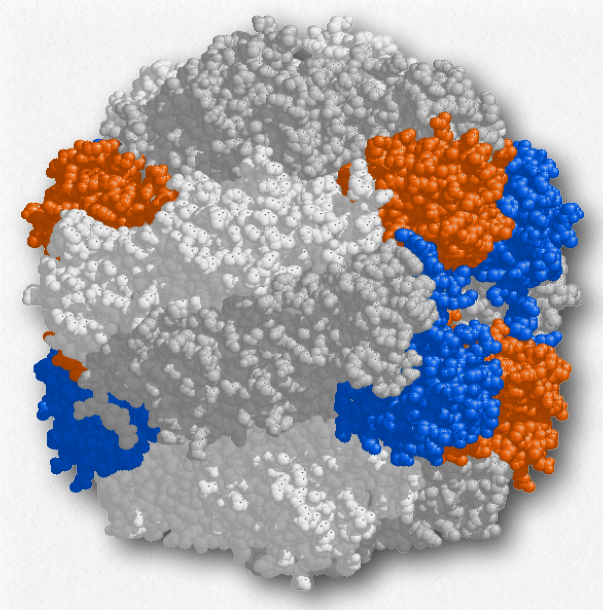


Figure 6.53 - Rubisco, the most abundant enzyme on Earth

Assimilation

It is in the Calvin cycle of photosynthesis that carbon dioxide is taken from the atmosphere and ultimately built into glucose (or other sugars). Reactions of the Calvin cycle take place in regions of the chloroplast known as the stroma, the fluid areas outside of the thylakoid membranes. The cycle can be broken into three phases

1) assimilation of CO_2

2) reduction reactions

3) regeneration of the starting material, ribulose 1,5 bisphosphate (Ru1,5BP).

Though reduction of carbon dioxide to glucose ultimately requires electrons from twelve molecules of NADPH (and 18 ATPs), it is confusing because one reduction occurs 12 times (1,3 BPG to GLYAL-3P) to input the overall reduction necessary to make one glucose.

Carbon dioxide

Another reason students find the pathway confusing is because the carbon dioxide molecules are absorbed one at a time into six different molecules of Ru1,5BP. At no point are the six carbons ever together in the same molecule to make a single glucose.

Instead, six molecules of Ru1,5BP (30 carbons) gain six more carbons via carbon dioxide and then split into 12 molecules of 3-phosphoglycerate (36 carbons). The gain of six carbons allows two three carbon molecules to be produced in excess for each turn of the cycle. These two molecules molecules are then converted into glucose using the enzymes of gluconeogenesis. The other ten molecules of 3-PG are used to regenerate the six molecules of Ru1,5BP.

Cyclic pathway

Like the citric acid cycle, the Calvin cycle doesn't really have a starting or ending point, but can we think of the first reaction as the fixation of carbon dioxide to Ru1,5BP. This reaction is catalyzed by the enzyme known as ribulose-1,5 bisphosphate carboxylase (RUBISCO - Figure 6.53). The resulting six carbon intermediate is unstable and is rapidly converted to two molecules of 3-phosphoglycerate.

As noted, if one starts with 6 molecules of Ru1,5BP and makes 12 molecules of 3-PG, the extra 6 carbons that are a part of the cycle can be shunted off as two three-carbon molecules of glyceraldehyde-3-phosphate (GLYAL3P) to gluconeogenesis, leaving behind 10 molecules to be reconverted into 6 mole-

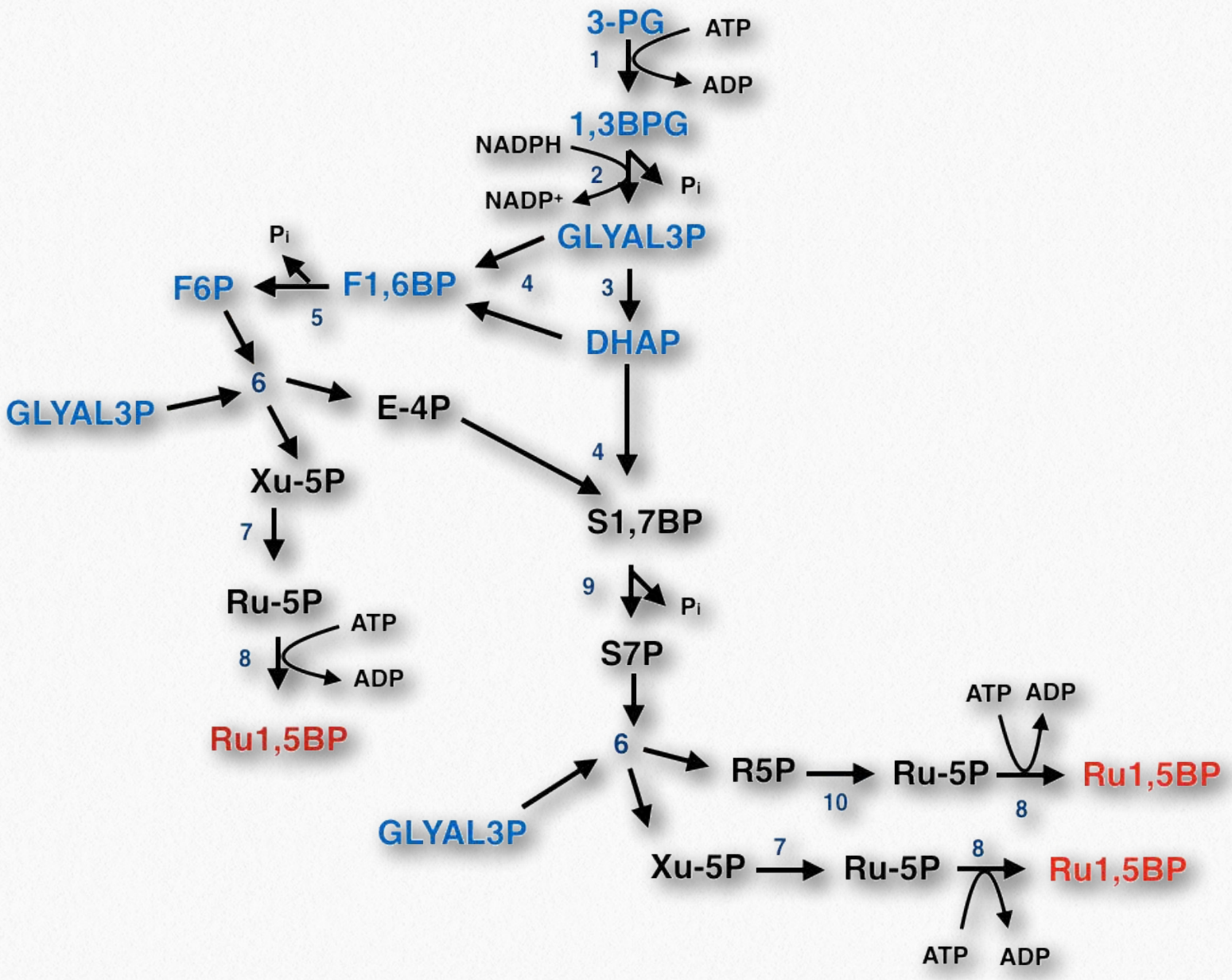


Figure 6.54 - Resynthesis phase of the Calvin cycle - All paths lead to regenerating Ru1,5BP, which is the aim of the resynthesis phase. Glycolysis/gluconeogenesis intermediates shown in blue. Enzyme numbers explained in text.

cules of Ru1,5BP. This occurs in what is called the resynthesis phase.

Resynthesis phase

The resynthesis phase (Figure 6.54) requires multiple steps, but only utilizes two enzymes unique to plants - sedoheptulose-1,7 bisphosphatase and phosphoribulokinase. RUBISCO is the third (and only other) enzyme of the pathway that is unique to plants.

All of the other enzymes of the pathway are common to plants and animals and include some found in the pentose phosphate pathway and gluconeogenesis. Enzymes shown as numbers in Figure 6.54 are as follows (enzymes unique to plants in green):

1 - Phosphoglycerate kinase
2 - G3PDH
3 - Triosephosphate Isomerase
4 - Aldolase
5 - Fructose 1,6 bisphosphatase
6 - Transketolase
7 - Phosphopentose Epimerase
8 - Phosphoribulokinase
9 - Sedoheptulose 1,7 bisphosphatase
10 - Phosphopentose Isomerase

Reactions

The resynthesis phase begins with conversion of the 3-PG molecules into GLYAL3P (there are actually 10 GLYAL3P molecules involved in resynthesis, as noted above, but we are omitting numbers to try to help students to see the bigger picture. Suffice it to say that there are sufficient quantities of all of the molecules to complete the reactions described). Some GLYAL3P is converted to DHAP by triose phosphate isomerase. Some DHAPs are converted (via gluconeogenesis) to F6P (one phosphate is lost for each F6P).

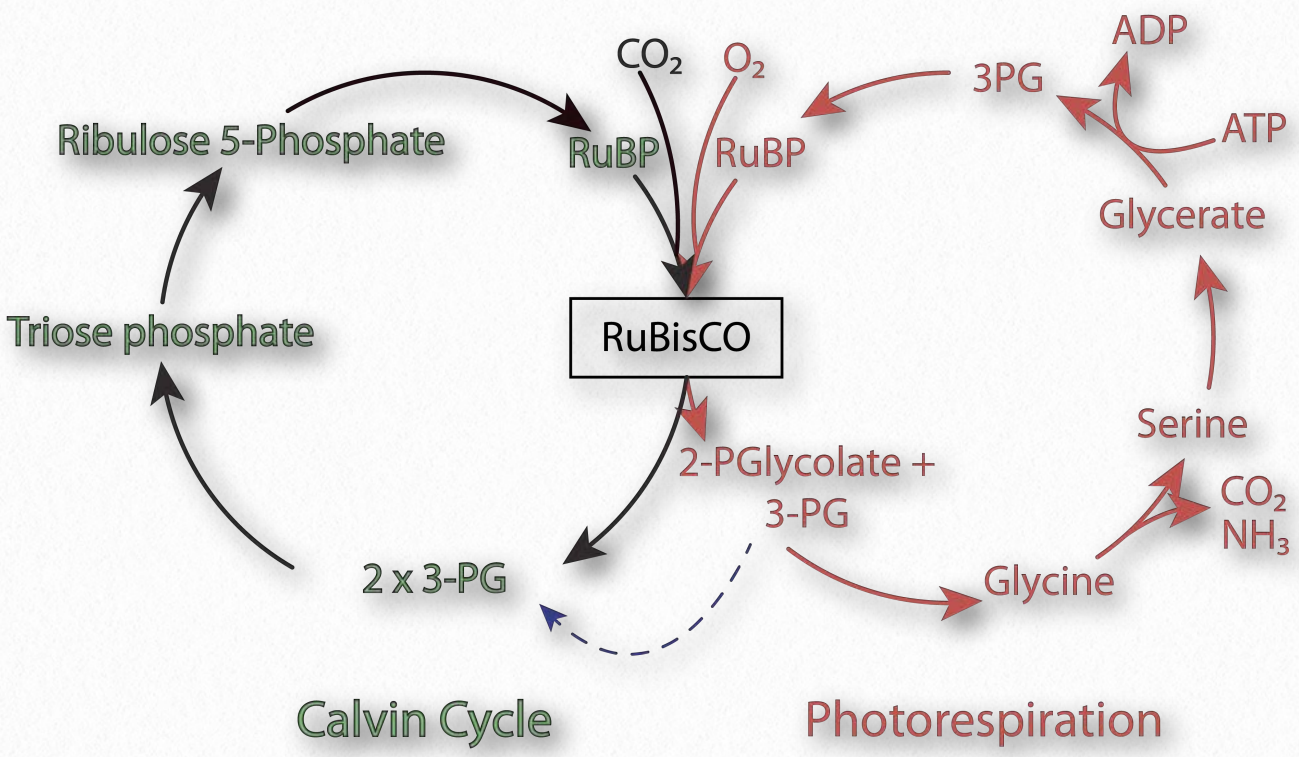


Figure 6.55 - Use of CO_2 (Calvin cycle) vs. O_2 (photorespiration) by RUBISCO.

Image by Pehr Jacobson

Two carbons from F6P are given to GLYAL3P to create E-4P and Xu-5P (reversal of PPP reaction). E-4P combines with DHAP to form sedoheptulose-1,7 bisphosphate (S1,7BP). The phosphate at position #1 is

cleaved by sedoheptulose-1,7 bisphosphatase to yield S-7-P. Transketolase (another PPP enzyme) catalyzes transfer to two carbons from S-7-P to GLYAL3P to yield Xu-5P and R5P.

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Phosphopentose isomerase catalyzes conversion of R5P to Ru5P and phosphopentose epimerase similarly converts Xu-5P to Ru5P. Finally, phosphoribulokinase transfers a phosphate to Ru5P (from ATP) to yield Ru1,5BP.

Photorespiration

In the Calvin cycle of photosynthesis, the enzyme ribulose-1,5-bisphosphate carboxylase (RUBISCO) catalyzes the addition of carbon dioxide to ribulose-1,5-bisphosphate (Ru1,5BP) to create two molecules of 3-phosphoglycerate. Molecular oxygen (O_2), however, competes with CO_2 for this enzyme, so about 25% of the time, the molecule that gets added is not CO_2, but rather O_2 (Figure 6.55). When this happens, the following reaction occurs

$$\text{Ru1,5BP} + O_2 \rightleftharpoons \text{Phosphoglycolate} + \text{3-phosphoglycerate} + 2H^+$$

This is the first step in the process known as photorespiration. The process of photorespiration is inefficient relative to the carboxylation of Ru1,5BP. Phosphoglycolate is converted to glyoxylate in the glyoxysome and then transamination of that yields glycine. Two glycines can combine in a complicated coupled set of reactions in the mitochondrion shown next.

$$2\ \text{Glycine} + NAD^+ + H_2O \rightleftharpoons \text{Serine} + CO_2 + NH_3 + NADH + H^+$$

Figure 6.56 - Maize - a C_4 plant

Deamination and reduction of serine yields pyruvate, which can be then be converted back to 3-phosphoglycerate. The end point of oxygenation of Ru1,5BP is the same as the carboxylation of Ru1,5BP reactions, but there are significant energy costs associated with it, making the process less efficient.

C_4 plants

The Calvin cycle is the means by which plants assimilate carbon dioxide from the atmosphere, ultimately into glucose. Plants use two general strategies for doing so. The first is employed by plants called C_3 plants (most plants) and it simply involves the pathway described above. They are called C_3 plants because the first stable intermediate after absorbing carbon dioxide contains three carbons - 3-phosphoglycerate. Another class of plants, called C_4 plants (Figure 6.56) employ a novel strategy for concentrating the

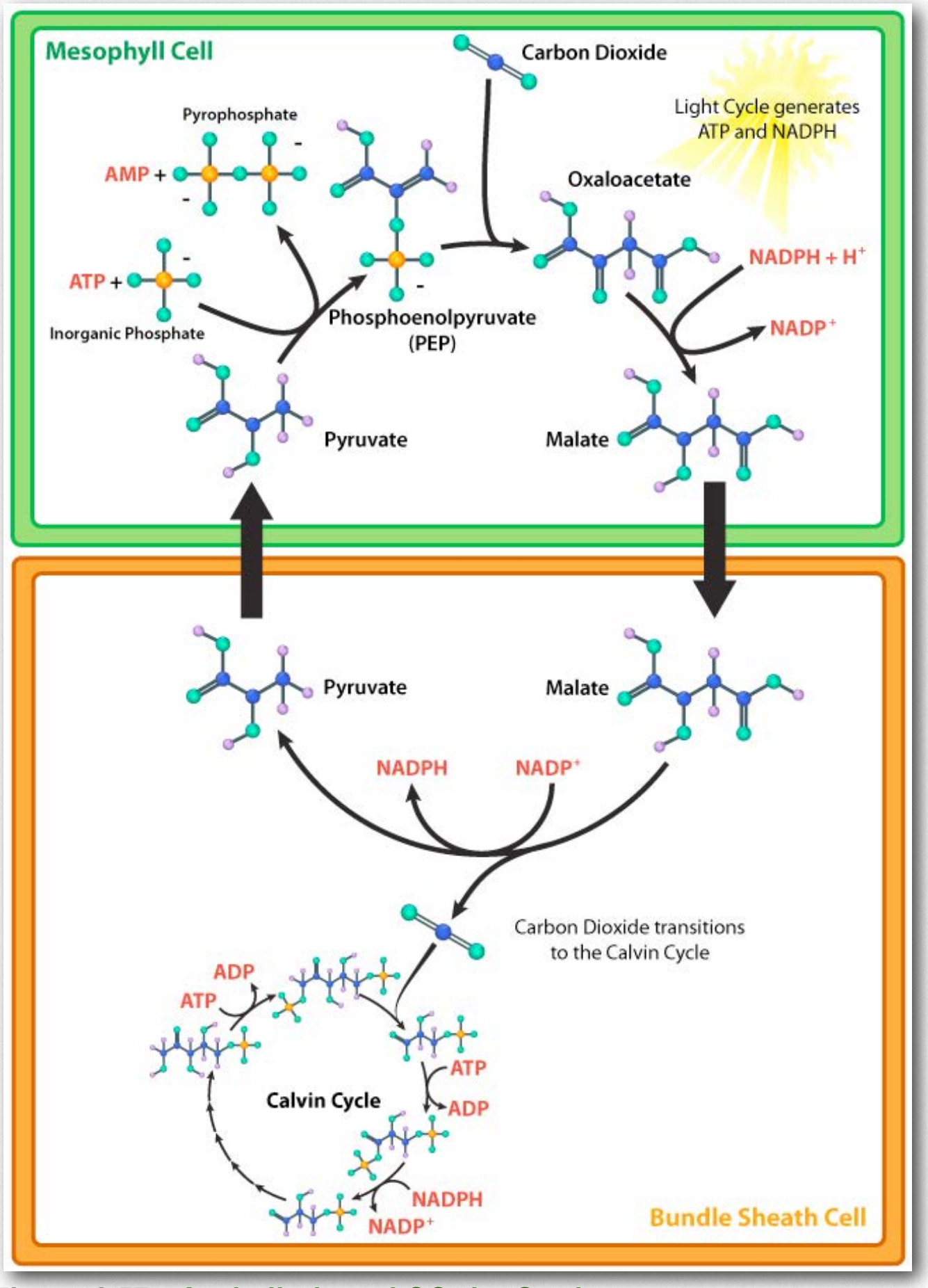

Figure 6.57 - Assimilation of CO_2 by C_4 plants

Image by Aleia Kim

CO_2 prior to assimilation. C_4 plants are generally found in hot, dry environments where conditions would otherwise favor the wasteful photorespiration reactions of RUBISCO and loss of water.

Capture by PEP

In C_4 plants, carbon dioxide is captured in special mesophyll cells first by phosphoenolpyruvate (PEP) to make oxaloacetate (contains four carbons and gives the C_4 plants their name - Figure 6.57). The oxaloacetate is converted to malate and transported into bundle sheath cells where the carbon dioxide is released and captured by Ru1,5BP, as in C_3 plants. The Calvin cycle proceeds from there. The advantage of the C_4 plant scheme is that it allows concentration of carbon dioxide while minimizing loss of water and photorespiration.

Peptidoglycan synthesis

Bacterial cell walls contain a layer of protection known as the peptidoglycan layer. Assembly of the layer begins in the cytoplasm. Steps in the process follow

1. Donation of an amine from glutamine to fructose-6-phosphate and isomerization to make glucosamine-6-phosphate.

2. Donation of an acetyl group from acetyl-CoA to make N-acetyl-glucosamine-6-phosphate

3. Isomerization of N-acetyl-glucosamine-6-phosphate makes N-acetyl-glucosamine-1-phosphate

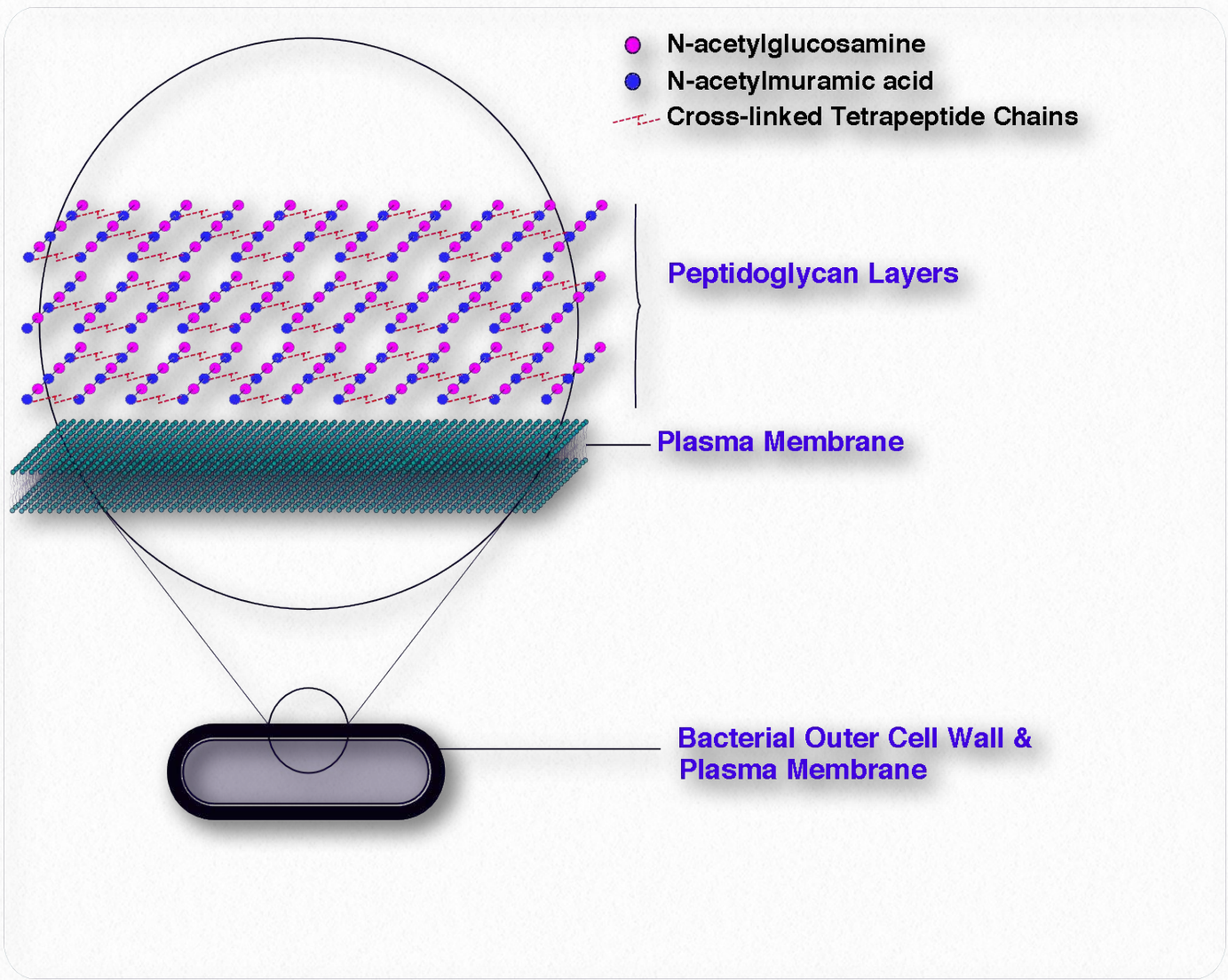

Figure 6.58 - Peptidoglycan layer in a bacterial outer cell wall
Wikipedia

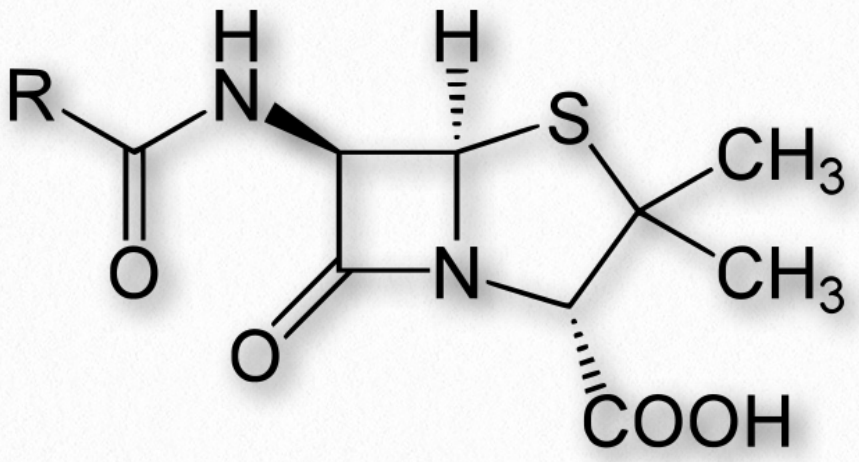

Figure 6.59 - Penicillin

4. UTP combines with N-acetyl-glucosamine-1-phosphate to make UDP-N-acetyl-glucosamine-1-phosphate

5. Addition of PEP and electrons from NADPH yields UDP-N-acetylmuramic acid

6. A pentapeptide or tetrapeptide chain is attached to the UDP-N-acetylmuramic acid. The sequence varies a bit between species, but commonly is L-Ala - D-Glu - L-Lys - D-Ala - D-Ala

7. Dolichol phosphate replaces UMP on the UDP-N-acetylmuramic acid-pentapeptide.

8. UDP-N-acetyl-glucosamine donates a glucose to the N-acetylmuramic acid part of the Dolichol-PP-N-acetylmuramic acid-pentapeptide

9. A pentapeptide chain of glycines (penta-glycine) is linked to lysine of the pentapeptide chain to create a Dolichol-PP-N-acetylmuramic acid-N-acetylglucosamine-decapeptide. The pentaglycine serves as cross links in the overall structure.

10. Dolichol-PP is removed to yield N-acetylmuramic acid-N-acetylglucosamine-decapeptide

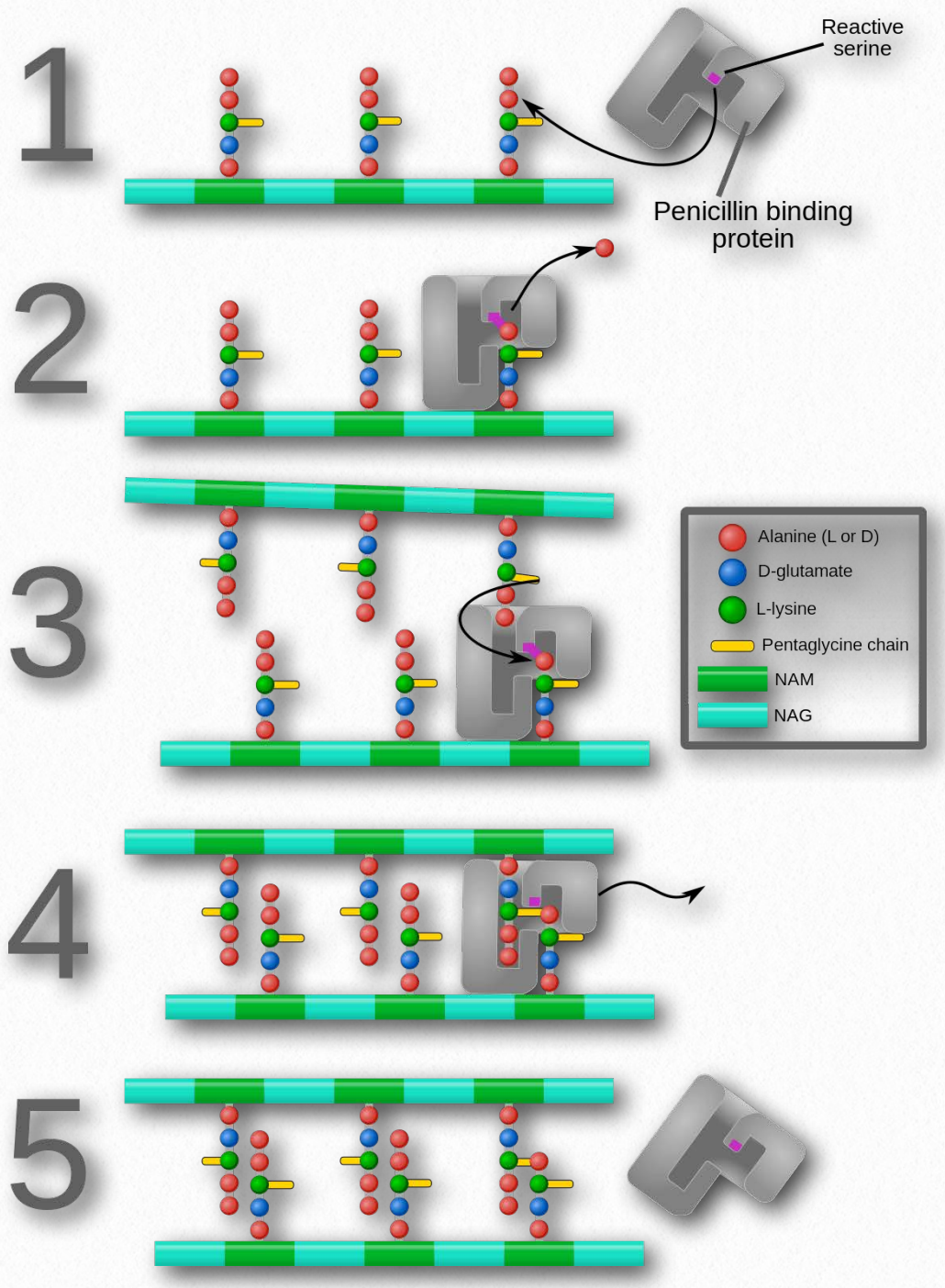

Figure 6.60 - Catalytic activity of DD-transpeptidase

Wikipedia

11. This last group is added to the growing peptidoglycan network by joining the pentaglycine of one chain to the tetrapeptide/pentapeptide of another.

YouTube Lectures by Kevin HERE & HERE

The enzyme catalyzing the addition of the N-acetylmuramic acid-N-acetylglucosamine-decapeptide to the network in the last step is DD-transpeptidase. This is the cellular enzyme targeted by penicillin and its derivatives. One reason penicillin is so effective is because synthesis of a peptidoglycan cell wall for a single bacterium requires millions of cycles of reactions above. Even slowing down the process can have a major effect on bacterial growth. On the flip side, resistance to penicillin and derivatives arises as a result of mutations in one enzyme - the transpeptidase.

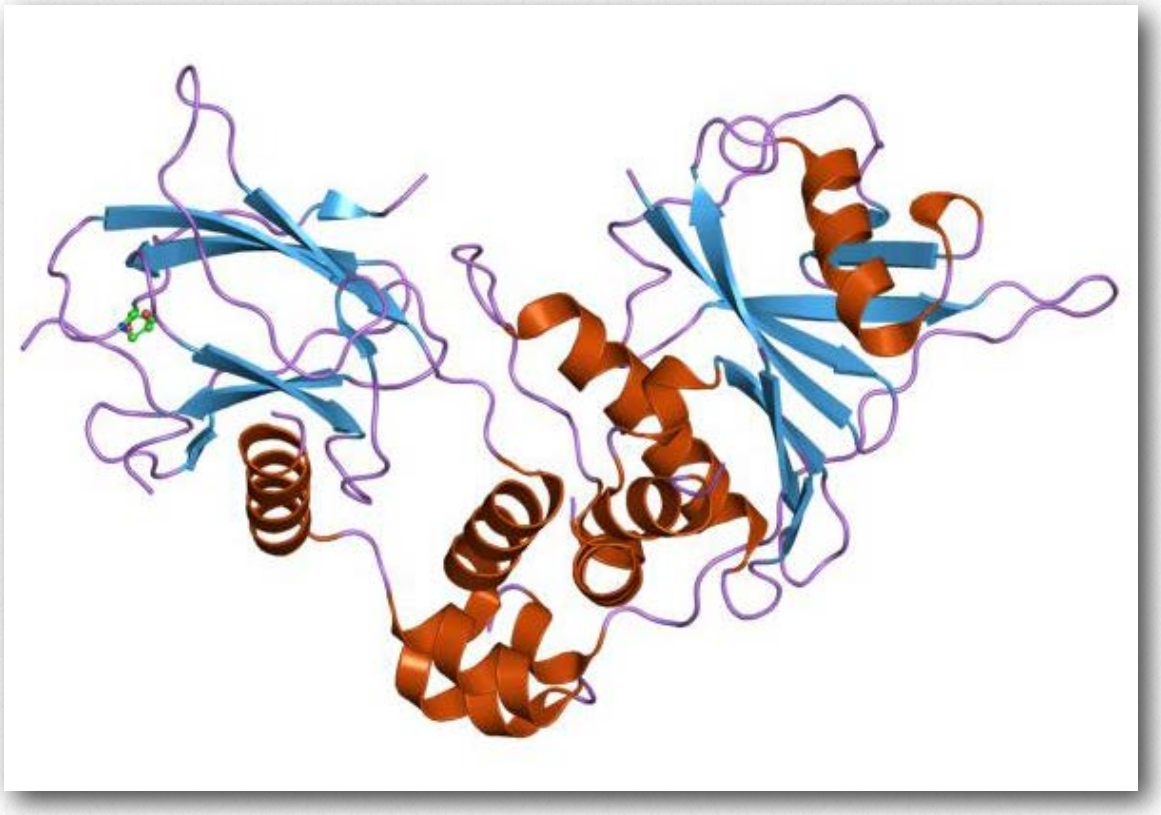

Figure 6.61 - Hypoxia inducible factor

Metabolons

At this point, it is appropriate to bring up the concept of metabolons. Metabolons are cellular complexes containing multiple enzymes of a metabolic pathway that appear to be arranged so that the product of one enzymatic reaction is passed directly as substrate to the enzyme that catalyzes the next reaction in the metabolic pathway. The structural complexes are temporary and are held together by non-covalent forces.

Metabolons appear to offer advantages of reducing the amount of water needed to hydrate enzymes. Activity of enzymes in the complex is increased. Most of the basic metabolic pathways are thought to use metabolons. They include glycolysis, the citric acid cycle, nucleotide metabolism, glycogen synthesis, steroid synthesis, DNA synthesis, RNA synthesis, the urea cycle, and the process of electron transport.

Hypoxia

Hypoxia occurs when the body or a region of it has an insufficient oxygen supply. Varia-

GLUT 1
GLUT 3
Aldolase
Enolase
GLYAL3P dehydrogenase
Hexokinase
PFK-1
Phosphoglycerate kinase
Pyruvate Kinase

Figure 6.62 - Proteins induced by HIF-1. Glycolysis enzymes in blue

tions in arterial oxygen concentrations in normal physiology may lead to hypoxia, for example, during hypoventilation training or strenuous physical exercise. Generalized hypoxia may appear in healthy people when at high altitudes. Cancer cells, which may be undergoing faster respiration than surrounding tissues may also tend to be hypoxic. Hypoxia is an important consideration for sugar metabolism due to the ability of cells to change their sugar metabolism (fermentation) when these conditions exist.

The body's response to hypoxia is to produce Hypoxia-Inducible Factors (HIFs), which are transcription factors that induce expression of genes to help cells adapt to the hypoxic conditions. Many of the genes activated by HIFs are enzymes of glycolysis and GLUTs (glucose transport proteins). The combination of these gene products allows cells to 1) import more glucose and 2) metabolize it more rapidly when it arrives. This is to be expected because anaerobic sugar metabolism is only about 1/15th as efficient as aerobic metabolism. Consequently, it requires much more sugar metabolism to keep the cancer cells alive. A recently discovered protein called cytoglobin is believed to help assist in hypoxia by facilitating transfer of oxygen from arteries to the brain.

Covalent modification

HIFs are regulated partly by an interesting covalent modification. When oxygen concentration is high, the enzyme prolyl hydroxylase will hydroxylate proline residues in HIFs. This stimulates the protein degradation system (proteasome) to degrade them. When oxygen concentration is low, the hydroxylation occurs to a much lower extent (or does not occur at all), reducing/stopping degradation of HIFs and allowing them to activate genes. In this way, the concentration of HIFs is kept high under low oxygen concentration (to activate HIF genes) and low under high oxygen concentrations (to stop synthesis of HIF genes).

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

Click HERE for Penelope Irving's Web Page

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Gluconeogenesis

To the tune of "*Supercalifragelisticexpialidocious*"
Metabolic Melodies Website HERE

When cells have lots of ATP and NADH too
They strive to store this energy as sugar yes they do
Inside of mitochondria they start with pyruvate
(*slow*) Carboxylating it to make oxaloacetate

Oh gluconeogenesis is so exhilarating
Memorizing it can really be exasperating
Liver cells require it so there's no need for debating
Gluconeogenesis is so exhilarating

Oh, glucose, glucose come to be
Glucose, glucose come to be

Oxaloacetate has got to turn to PEP
Employing energy that comes from breaking GTP
From there it goes to make a couple phosphoglycerates
(*slow*) Exploiting ee-nolase and mutase' catalytic traits

Oh gluconeogenesis is liver's specialty
Producing sugar for the body most admirably
Six ATPs per glucose is the needed energy*
Gluconeogenesis is liver's specialty

Oh glucose, glucose joy to me
Glucose, glucose joy to me

Converting phosphoglycerate to 1,3BPG
Requires a phosphate that includes A-T-P energy
Reduction with electrons gives us all an N-A-D
(*slow*) And G3P's isomerized to make D-H-A-P

Oh gluconeogenesis is anabolic bliss
Reversing seven mechanisms of glycolysis
To do well on the final students have to learn all this
Gluconeogenesis is anabolic bliss

Oh, glucose, glucose factory
Glucose, glucose factory

The aldolase reaction puts together pieces so
A fructose molecule is made with two phosphates in tow
And one of these gets cleaved off by a fructose phosphatase
(*slow*) Unless F2,6BP's acting blocking path-a-ways

Oh gluconeogenesis a pathway to revere
That makes a ton of glucose when it kicks into high gear
The cell's a masterminding metabolic engineer
Gluconeogenesis a pathway to revere

Oh glucose, glucose jubilee
Glucose, glucose jubilee

From F6P to G6P, that is the final phase
The enzyme catalyzing it is an isomerase
Then G6P drops phosphate and a glucose it becomes
(*slow*) Inside the tiny endoplasmic-al reticulums

Oh gluconeogenesis is not so very hard
I know that on the final we will not be caught off guard
Cuz our professor lets us use a filled out index card
Gluconeogenesis is not so very hard

*Actually, you need two NADHs too, but that wouldn't fit the rhyme :-)

Recording by Tim Karplus
Lyrics by Kevin Ahern

The Sound of Glucose

To the tune of "*A Few of My Favorite Things*"

Metabolic Melodies Website HERE

Aldehyde sugars are always aldoses and
If there's a ketone we call them ketoses
Some will form structures in circular rings
Saccharides do some incredible things

Onto a glucose we add a 'P' to it
ATP energy ought to renew it
Quick rearranging creates F6P
Without requiring input energy

At a high rate
Add a phosphate
With PFK
F1,6BP is made up this way
So we can run and play

Aldolase breaks it and then it releases
DHAP and a few G-3-Pieces
These both turn in to 1,3 BPG
Adding electrons onto NAD

Phosphate plus ADP makes ATP
While giving cells what they need - en-er-gy
Making triphosphate's a situa-shun
Of substrate level phosphoryla-shun

3-B-P-G
2-B-P-G
Lose a water
PEP gets a high energy state
Just to make py-ru-vate

So all the glucose gets broken and bent
If there's no oxygen cells must ferment
Pyruvate / lactate our cells hit the wall
Some lucky yeast get to make ethanol

This is the end of your glucose's song
Unless you goof up and get it all wrong
Break it, don't make it to yield ATP
You'll save your cells from fu-til-i-ty

Recording by Tim Karplus
Lyrics by Kevin Ahern

In My Liver

To the tune of "*And I Love Her*"

Metabolic Melodies Website HERE

If I am missing meals
On busy days
That's when my body steals
Glucose away
From my liver

It starts with glucagon
When I'm weak kneed
The hormone acts to spawn
New energy
In my liver

Bridge
The signaling
Acts rapidly
c-A-M-P's
Fire up kinase

Phosphorylase then gets
Re-activated
So glycogen begets
Glucose phosphated
In my liver

Instrumental

Then in the last step here
A phosphatase
Makes phosphate disappear
With no delays
In my liver

Recording by David Simmons
Lyrics by Kevin Ahern

It Flows, Then My Glycogen Grows

To the tune of "*Love Grows Where My Rosemary Goes*"

Metabolic Melodies Website HERE

When I'm exercisin'
It is not surprisin'
That insulin is absentee
But when it flows
Then my glycogen grows
And nobody knows like me

During all the flexing
It may seem perplexing
The liver's working easily
Turning lactate
Into glucose is great
And it is first rate to me

There's something about an insulin high
That is hard to deny
And I shouldn't suppress, Yes!
It gets the sugar into the cells
More than anything else
Easing cellular stress

Epinephrine's crazy
Absent when I'm lazy
Made when I am scared you see
Then when it flows, all my glycogen goes
And G1P grows in me

My hormones they are treating my fine
Working all of the time
Don't know what I would do - ooh!
Activating protein kinase
So my phosphorylase
Does a glycogen chew

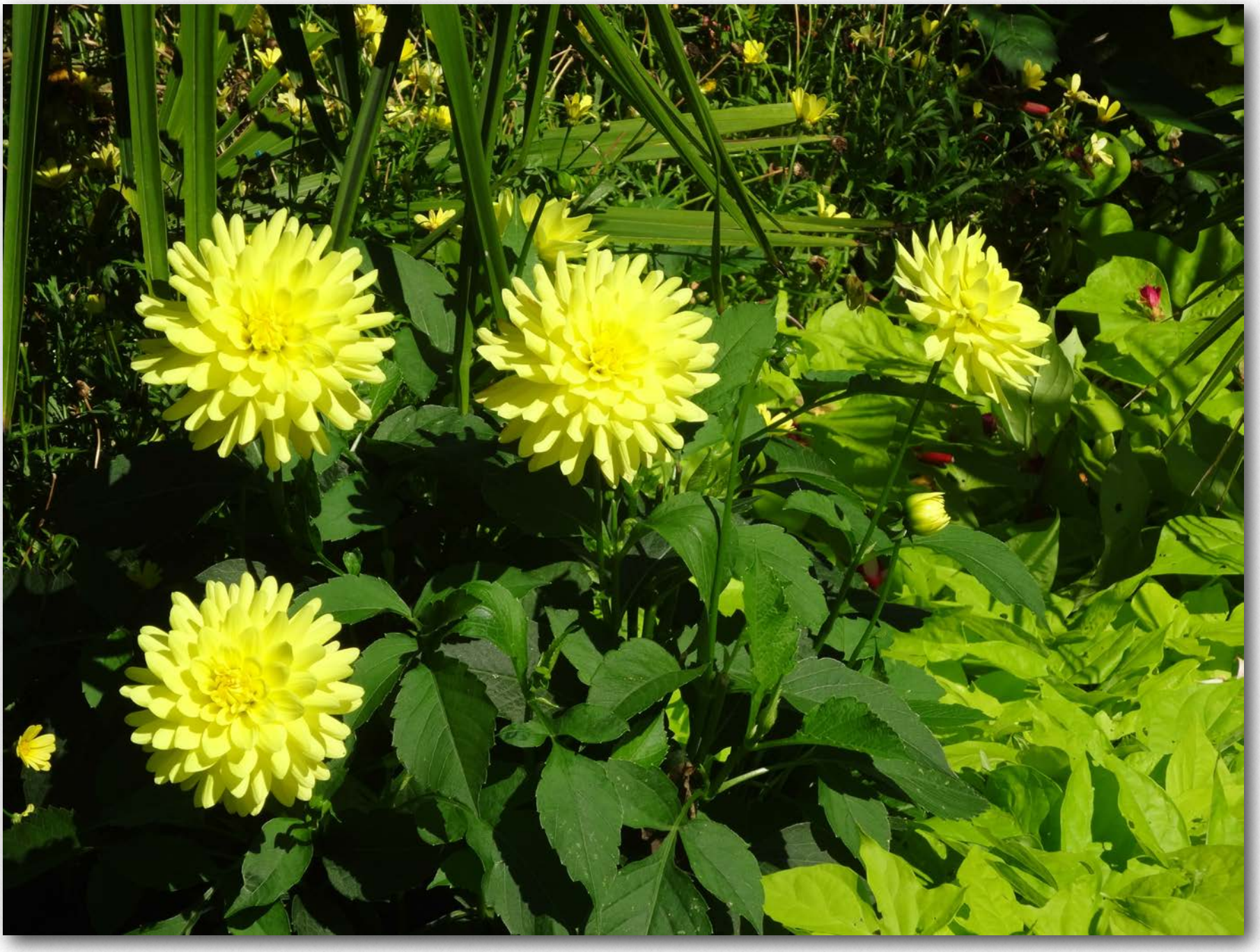
There is such a balance
Thanks to hormones' talents
Managing the energy
Making glucose from my head to my toes
So evenly flow in me

It keeps working every night and day
And nobody knows like me
I just love it but never think of it
And nobody knows like me

Lyrics by Kevin Ahern

No Recording Yet For This Song

Metabolism: Citric Acid Cycle & Related Pathways



Citric acid cycle

The primary catabolic pathway in the body is the citric acid cycle because it is here that oxidation to carbon dioxide occurs for breakdown products of the cell's major building blocks - sugars, fatty acids, and amino acids. The pathway is cyclic (Figure 6.63) and thus, doesn't really have a starting or ending point. All of the reactions occur in mitochondria, though one enzyme is embedded in the organelle's inner membrane. As needs change, cells may use a subset of the reactions of the cycle to produce a desired molecule rather than to run the entire cycle (see HERE).

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Acetyl-CoA

The molecule "feeding" the citric acid cycle is acetyl-CoA and it can be obtained from pyruvate (from glycolysis), from fatty acid β-oxidation, from ketone bodies, and from amino acid metabolism. Molecules from other pathways feeding into the citric acid cycle for catabolism make the

citric acid cycle 'cataplerotic'. It is worth noting that acetyl-CoA has very different fates, depending on the cell's energy status/needs (see HERE). The description below describes oxidation (catabolism) in citric acid cycle.

Anabolically, acetyl-CoA is also very important for providing building blocks for synthesis of fatty acids, ketone bodies, amino acids and cholesterol. Other citric acid cycle intermediates are also important in amino acid metabolism (Figure 6.63), heme synthesis, electron shuttling, and shuttling of acetyl-CoA across the mitochondrial inner membrane. The ability of the citric acid cycle to supply intermediates to pathways gives rise to the term 'anaplerotic.' It means 'to fill up.' Before discussing the citric acid cycle, it is important to first describe one important enzyme complex that is a major source of acetyl-CoA for the cycle.

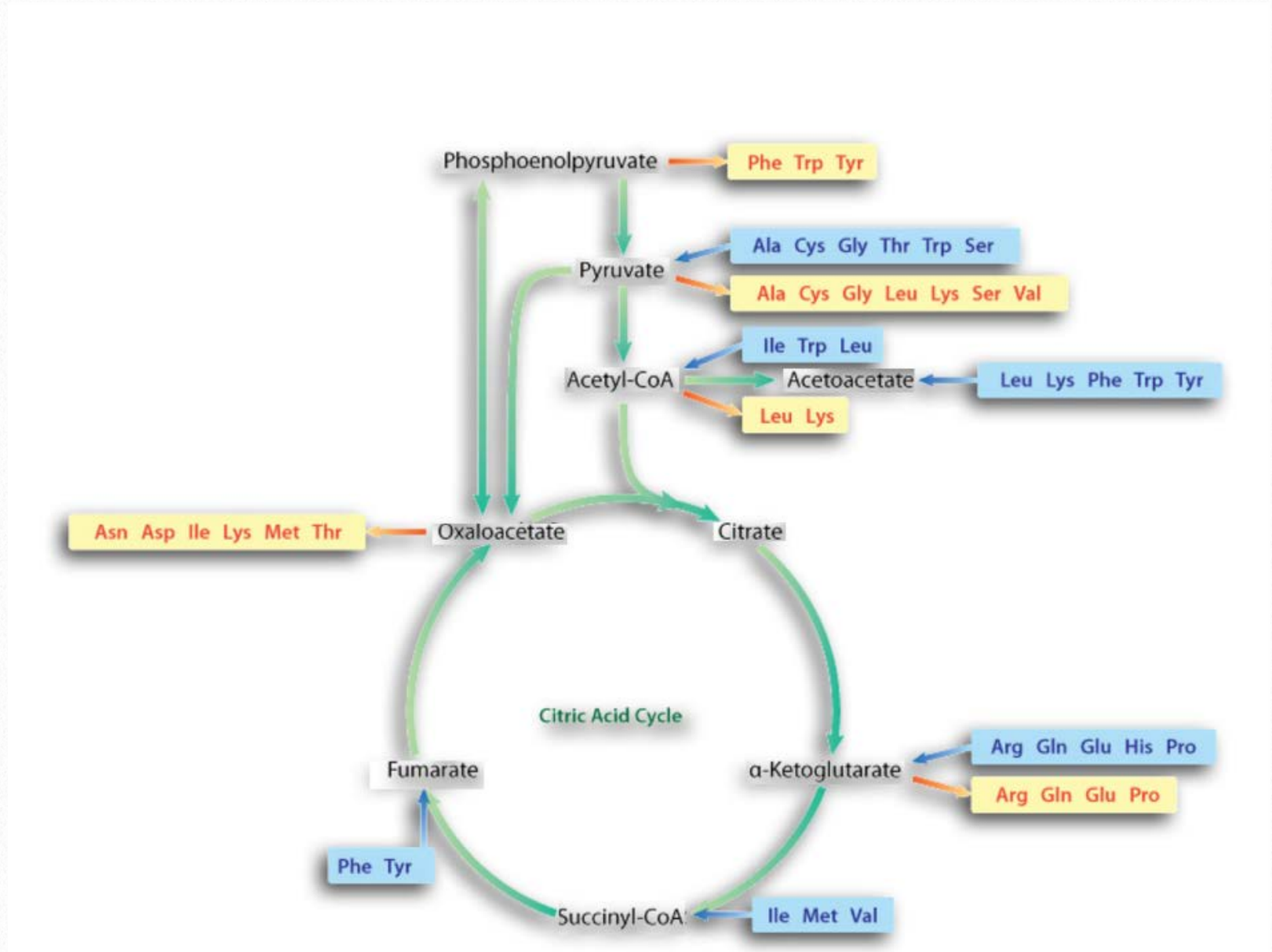

Figure 6.63 - Amino acid metabolism and the citric acid cycle. Amino acids boxed in yellow are made from the indicated intermediate. Amino acids in blue are made into the intermediate in catabolism.

Image by Aleia Kim

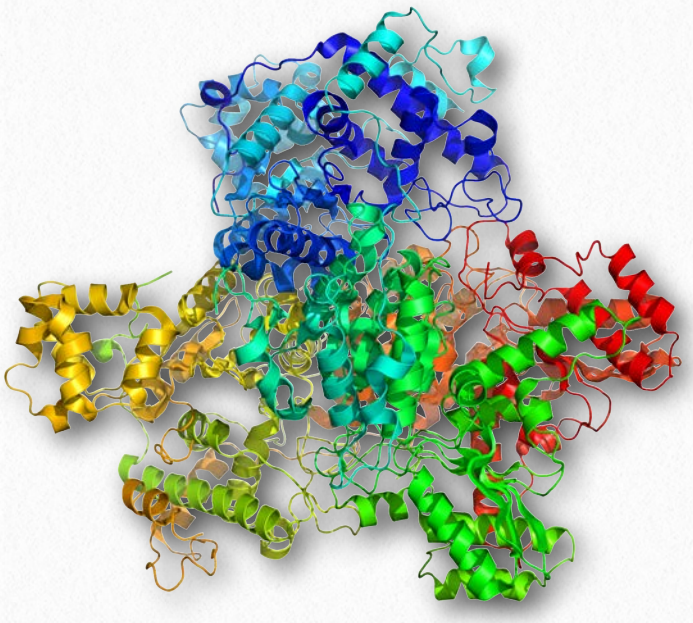

Figure 6.64 - E1 Subunit of Pyruvate Dehydrogenase

Wikipedia

Pyruvate decarboxylation

The pyruvate dehydrogenase enzyme is a complex of multiple copies of three subunits that catalyze the decarboxylation of pyruvate to form acetyl-CoA. The reaction mechanism requires use of five coenzymes. Pyruvate dehydrogenase is an enormous complex in mammals with a size five times greater than ribosomes.

Subunits

The three subunits are designated by E_1, E_2, and E_3. E_2 is also referred to as dihydrolipoamide acetyltransferase and E_3 is more precisely called dihydrolipoyl dehydroge-

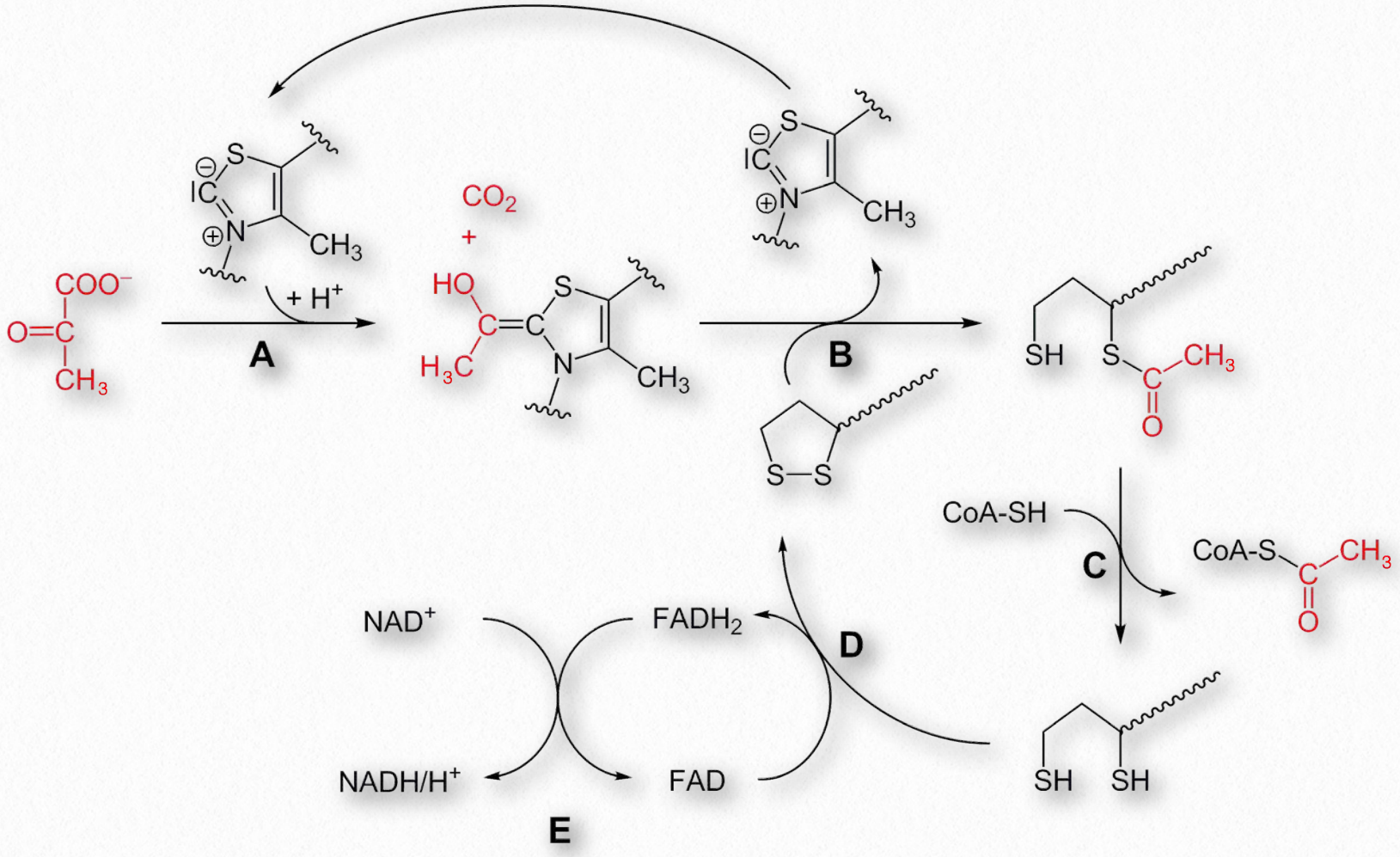

Figure 6.65 - Mechanism of action of pyruvate decarboxylation and oxidation by pyruvate dehydrogenase.

nase. Confusion arises with the name for E_1. Some call it pyruvate dehydrogenase and others give it the name pyruvate decarboxylase. We will use pyruvate decarboxylase solely to refer to E_1 and pyruvate dehydrogenase only to refer to the complex of E_1, E_2, and E_3.

The catalytic actions of pyruvate dehydrogenase can be broken down into three steps, each taking place on one of the subunits. The steps, sequentially occurring on E_1, E_2, and E_3, are 1) decarboxylation of pyruvate; 2) oxidation of the decarboxylated product; and 3) transfer of electrons to ultimately form NADH (Figure 6.65).

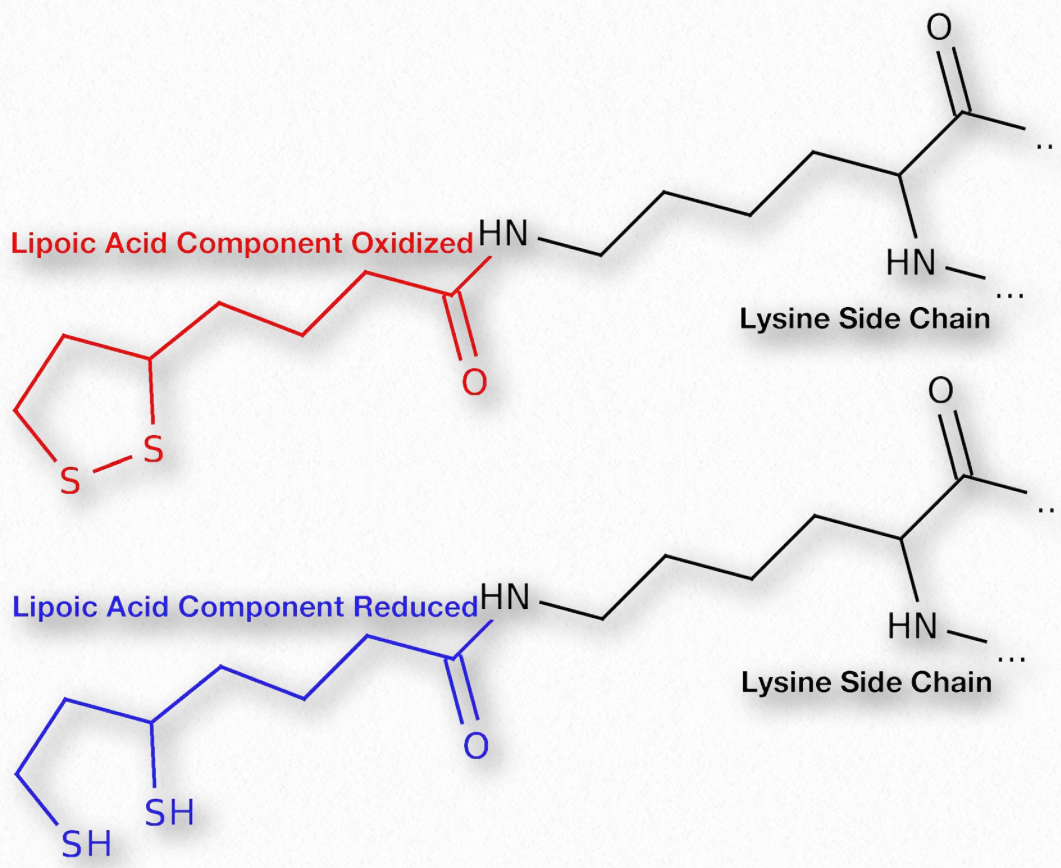

Figure 6.66 - Oxidized and reduced structures of lipoamide (lipoic acid linked to lysine)

Catalysis

The catalytic process begins after binding of the pyruvate substrate with activation of the thiamine pyrophosphate coenzyme through formation of an ylide intermediate. The nucleophilic carbanion of the ylide attacks the electrophilic ketone carbon on the pyruvate, releasing carbon dioxide and creating an enol that loses a proton on the carbon to become a 1,3 dipole that includes the positively charged nitrogen of the thiamine. The reaction (step A in Figure 6.65) is a non-oxidative decarboxylation. Oxidation of the two carbon hydroxyethyl unit occurs in the transfer to the lipoamide.

Reductive acetylation

Reductive acetylation occurs next (Step B) as the 2-carbon hydroxyethyl unit is transferred to lipoamide on E_2. (Lipoamide is the name for a molecule of lipoic acid covalently attached to a lysine side chain in the E_2 subunit). In prokaryotes in the absence of oxygen, the hydroxyethyl group is not passed to lipoamide, but instead is released as free acetaldehyde , which can accept electrons from NADH (catalyzed by alcohol dehydrogenase) and become ethanol in the process of fermentation. In the presence of oxygen in almost all aerobic organ-

isms, the process continues with transfer of the hydroxyethyl unit to E_2 and continuation of the cycle below.

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Oxidation step

Transfer of the hydroxyethyl group from E_1 to the lipoamide coenzyme in E_2 is an oxidation, with transfer of electrons from the hydroxyethyl group to lipoamide's disulfide (reducing it) and formation on the lipoamide of an acetyl-thioester (oxidizing it).

The acetyl group is then transferred from lipoamide to coenzyme A in E_2 (Step C in Figure 6.65), forming acetyl-CoA, which is released and leaving reduced sulfhydryls on the lipoamide. In order for the enzyme to return to its original state, the disulfide bond on lipoamide must be re-formed. This occurs with transfer of electrons from reduced lipoamide to an FAD covalently bound to E_3 (Step D). This reduces FAD to $FADH_2$.

Formation of NADH

In the last step in the process, electrons from $FADH_2$ are transferred to external NAD^+, forming NADH (Step E) and completing the overall cycle. Then enzyme can then begin another catalytic round by binding to a pyruvate.

Pyruvate dehydrogenase regulation

Pyruvate deyhdrogenase is regulated both allosterically and by covalent modification - phosphorylation / dephosphorylation.

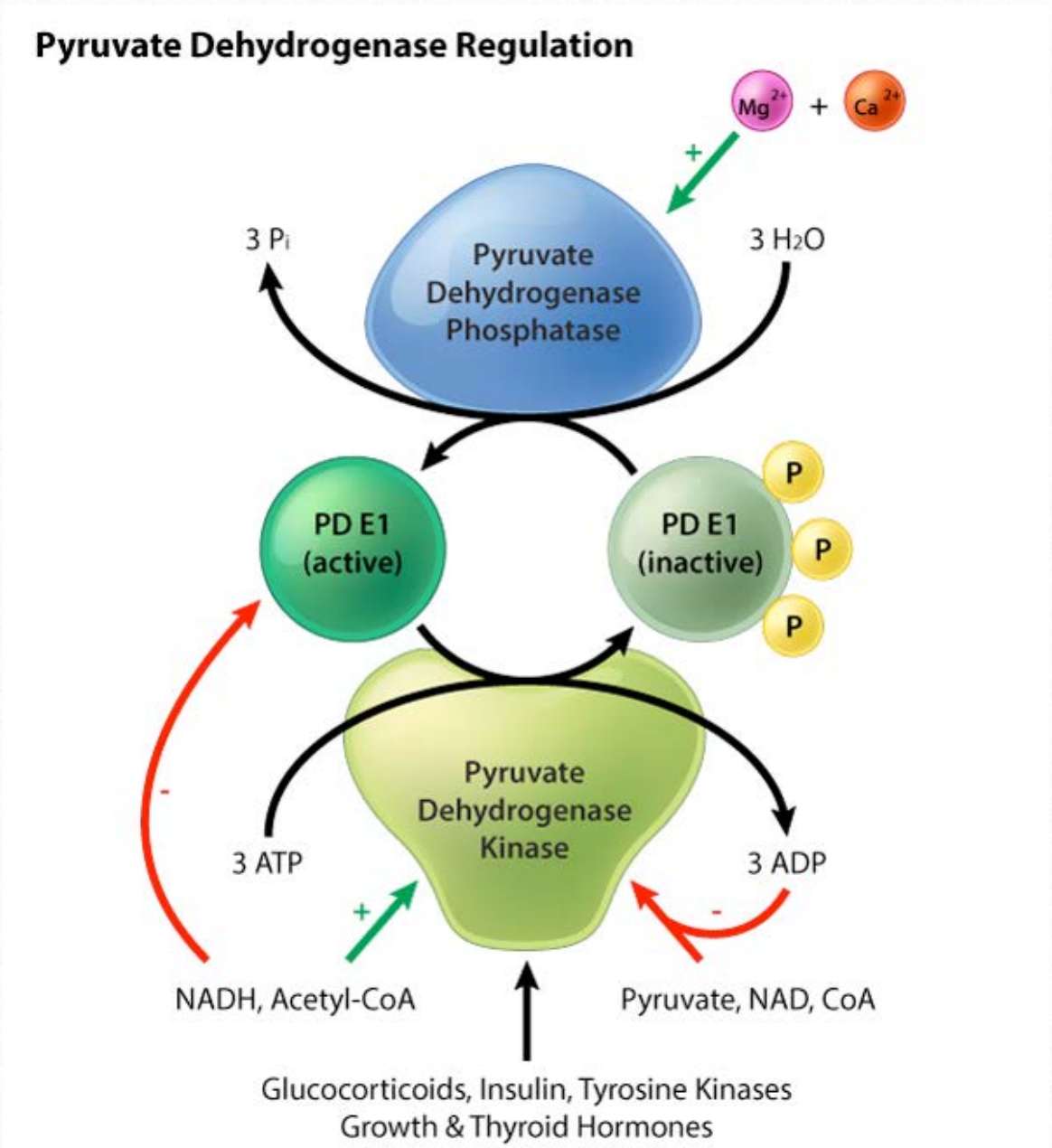

Figure 6.67 - Regulation scheme for pyruvate dehydrogenase (PD)

Image by Aleia Kim

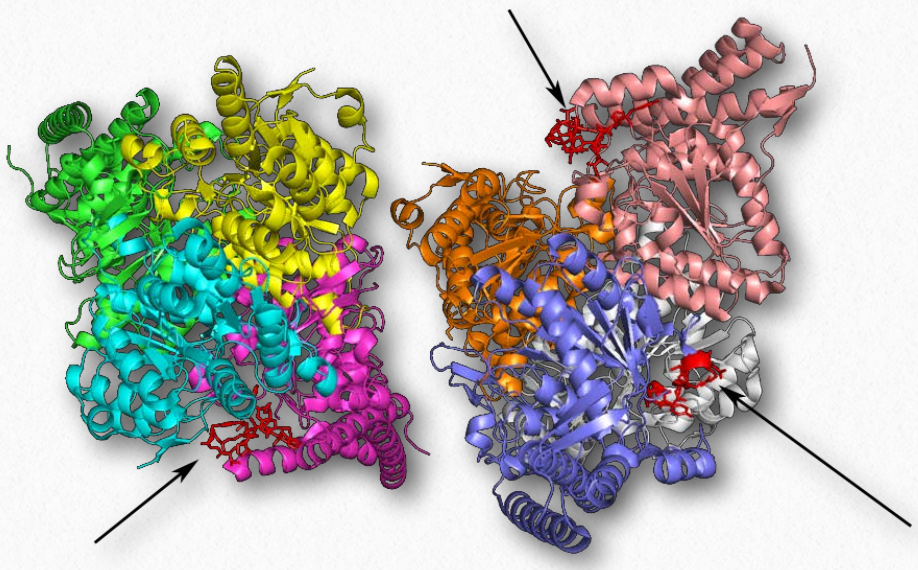

Figure 6.68 - Pyruvate dehydrogenase complex with three phosphorylation sites in red marked by arrows.

Wikipedia

tion. Regulation of pyruvate dehydrogenase, whether by allosteric or covalent mechanisms has the same strategy. Indicators of high energy shut down the enzyme, whereas indicators of low energy stimulate it. For allosteric regulation, the high energy indicators affecting the enzyme are ATP, acetyl-CoA, NADH, and fatty acids, which inhibit it. AMP, Coenzyme A, NAD^+, and calcium, on the other hand, stimulate it (Figure 6.67).

Covalent modification

Covalent modification regulation of pyruvate dehydrogenase is a bit more complicated. It occurs as a result of phosphorylation by pyruvate dehydrogenase kinase (PDK - Figure 6.67) or dephosphorylation by pyruvate dehydrogenase phosphatase (PDP).

PDK puts phosphate on any one of three serine residues on the E_1 subunit, which causes pyruvate kinase to not be able to perform its first step of catalysis - the decarboxylation of pyruvate. PDP can remove those phosphates. PDK is allosterically activated in the mitochondrial matrix when NADH and acetyl-CoA concentrations rise.

Product inhibition

Thus, the products of the pyruvate dehydrogenase reaction inhibit the production of more products by favoring its phosphorylation by PDK. Pyruvate, a substrate of pyruvate dehydrogenase, inhibits PDK, so increasing concentrations of substrate activate pyruvate dehydrogenase by reducing its phosphorylation by PDK. As concentrations of NADH and acetyl-CoA fall, PDP associates with pyruvate kinase and removes the phosphate on the serine on the E_1 subunit.

Low concentrations of NADH and acetyl-CoA are necessary for PDP to remain on the enzyme. When those concentrations rise, PDP dissociates and PDK gains access to the serine for phosphorylation. Insulin and calcium can also activate the PDP. This is very impor-

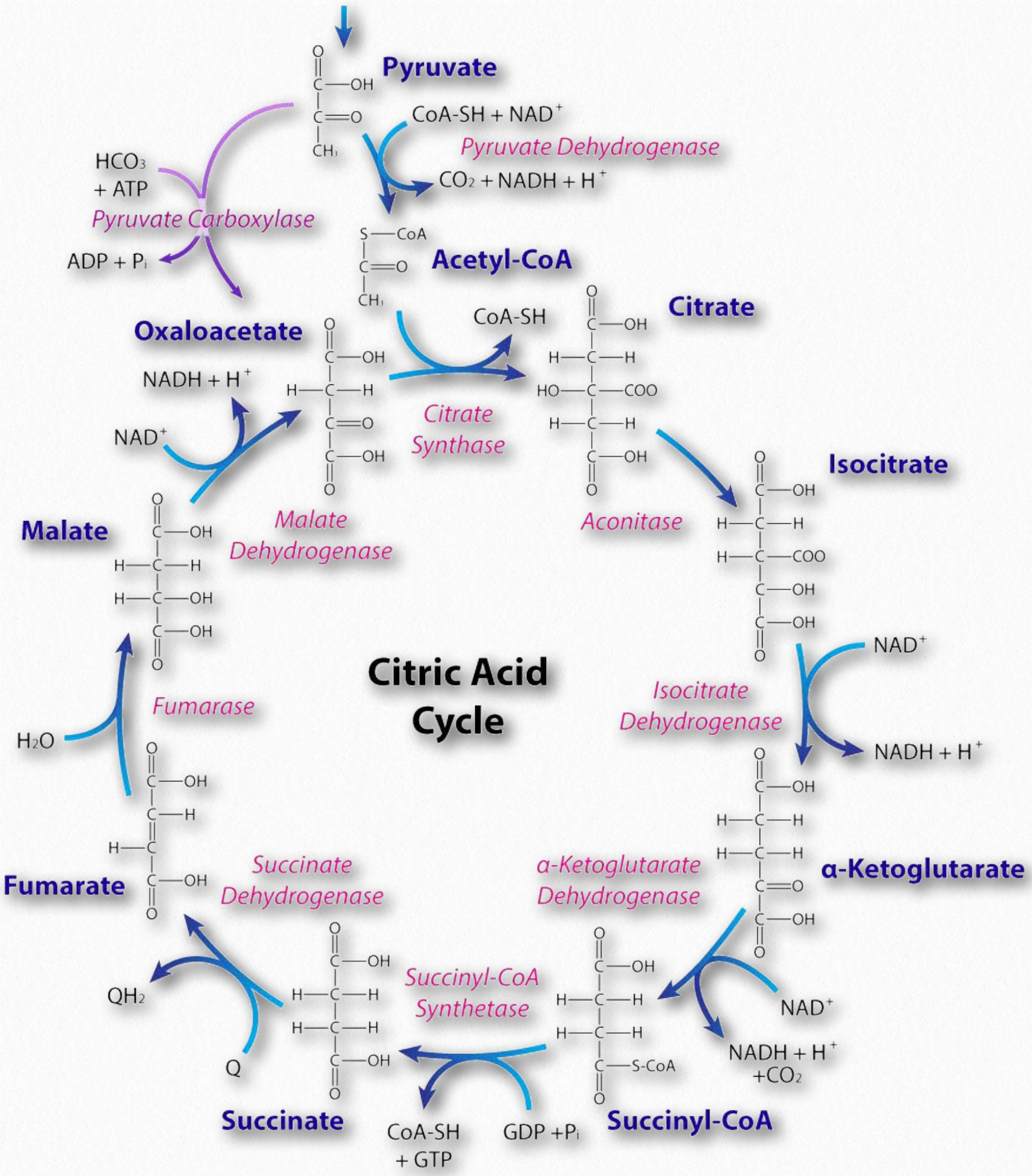

Figure 6.69 - The citric acid cycle

image by Aleia Kim

tant in muscle tissue, since calcium is a signal for muscular contraction, which requires energy.

Insulin also also activates pyruvate kinase and the glycolysis pathway to use internalized glucose. It should be noted that the cAMP phosphorylation cascade from the β-adrenergic receptor has no effect on pyruvate kinase, though the insulin cascade does, in fact, affect PDP and pyruvate kinase.

Citric acid cycle reactions

Focusing on the pathway itself (Figure 6.69), the usual point to start discussion is addition of acetyl-CoA to oxaloacetate (OAA) to form citrate.

Acetyl-CoA for the pathway can come from a variety of sources. The reaction joining it to OAA is catalyzed by citrate synthase and the $\Delta G^{\circ\prime}$ is fairly negative. This, in turn, helps to "pull" the malate dehydrogenase reaction preceding it in the cycle.

Acetyl-CoA + Oxaloacetate

⇅

Citrate + CoA-SH

In the next reaction, citrate is isomerized to isocitrate by action of the enzyme called aconitase.

Citrate

⇅

Isocitrate

Isocitrate is a branch point in plants and bacteria for the glyoxylate cycle (see HERE). Oxidative decarboxylation of isocitrate by

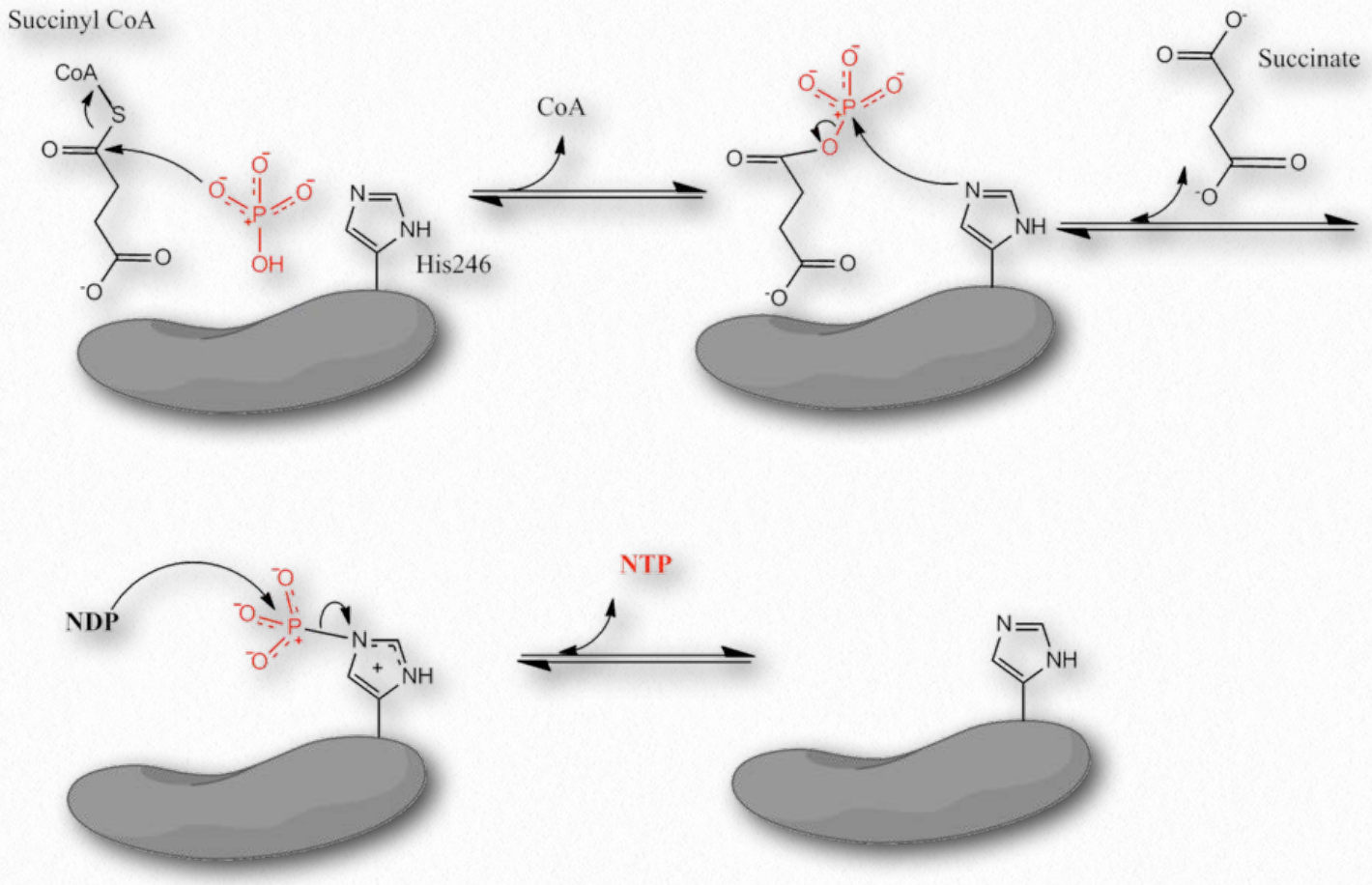

Figure 6.70 - Succinyl-CoA synthetase mechanism

isocitrate dehydrogenase produces the first NADH and yields α-ketoglutarate.

Isocitrate + NAD^+

⇅

α-ketoglutarate + NADH + CO_2

This five carbon intermediate is a branch point for synthesis of the amino acid glutamate. In addition, glutamate can also be made easily into this intermediate in the reverse reaction. Decarboxylation of α-ketoglutarate produces succinyl-CoA and is catalyzed by α-ketoglutarate dehydrogenase.

α-ketoglutarate + NAD^+ + CoA-SH

⇅

Succinyl-CoA + NADH + CO_2

The enzyme α-ketoglutarate dehydrogenase is structurally very similar to pyruvate dehydrogenase and employs the same five coenzymes – NAD^+, FAD, CoA-SH, thiamine pyrophosphate, and lipoamide.

Regeneration of oxaloacetate

The remainder of the citric acid cycle involves conversion of the four carbon succinyl-CoA into oxaloacetate. Succinyl-CoA is a branch point for the synthesis of heme (see HERE). Succinyl-CoA is converted to succinate in a reaction catalyzed by succinyl-CoA synthetase (named for the reverse reaction) and a GTP is produced, as well – the only substrate level phosphorylation in the cycle.

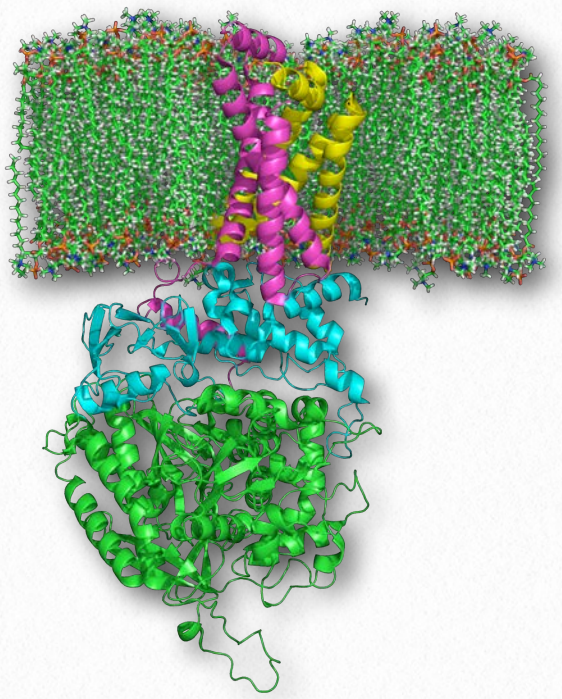

Figure 6.71 - Succinate dehydrogenase embedded in the mitochondrial inner membrane (top)
Wikipedia

Succinyl-CoA + GDP + P_i

⇅

Succinate + GTP + CoA-SH

The energy for the synthesis of the GTP comes from hydrolysis of the high energy thioester bond between succinate and the CoA-SH. Evidence for the high energy of a thioester bond is also evident in the citrate synthase reaction, which is also very energetically favorable. Succinate is also produced by metabolism of odd-chain fatty acids (see HERE).

Succinate Oxidation

Oxidation of succinate occurs in the next step, catalyzed by succinate dehydrogenase.

Succinate + FAD

⇅

Fumarate + $FADH_2$

This interesting enzyme both catalyzes this reaction and participates in the electron transport system, funneling electrons from the $FADH_2$ it gains in the reaction to coenzyme Q. The product of the reaction, fumarate, gains a water across its *trans* double bond in the next reaction, catalyzed by fumarase to form malate.

Fumarate + H_2O

⇅

L-Malate

Fumarate is also a byproduct of nucleotide metabolism and of the urea cycle. Malate is important also for transporting electrons across membranes in the malate-aspartate shuttle (see HERE) and in ferrying carbon dioxide from mesophyll cells to bundle sheath cells in C_4 plants (see HERE).

YouTube Lectures by Kevin HERE & HERE

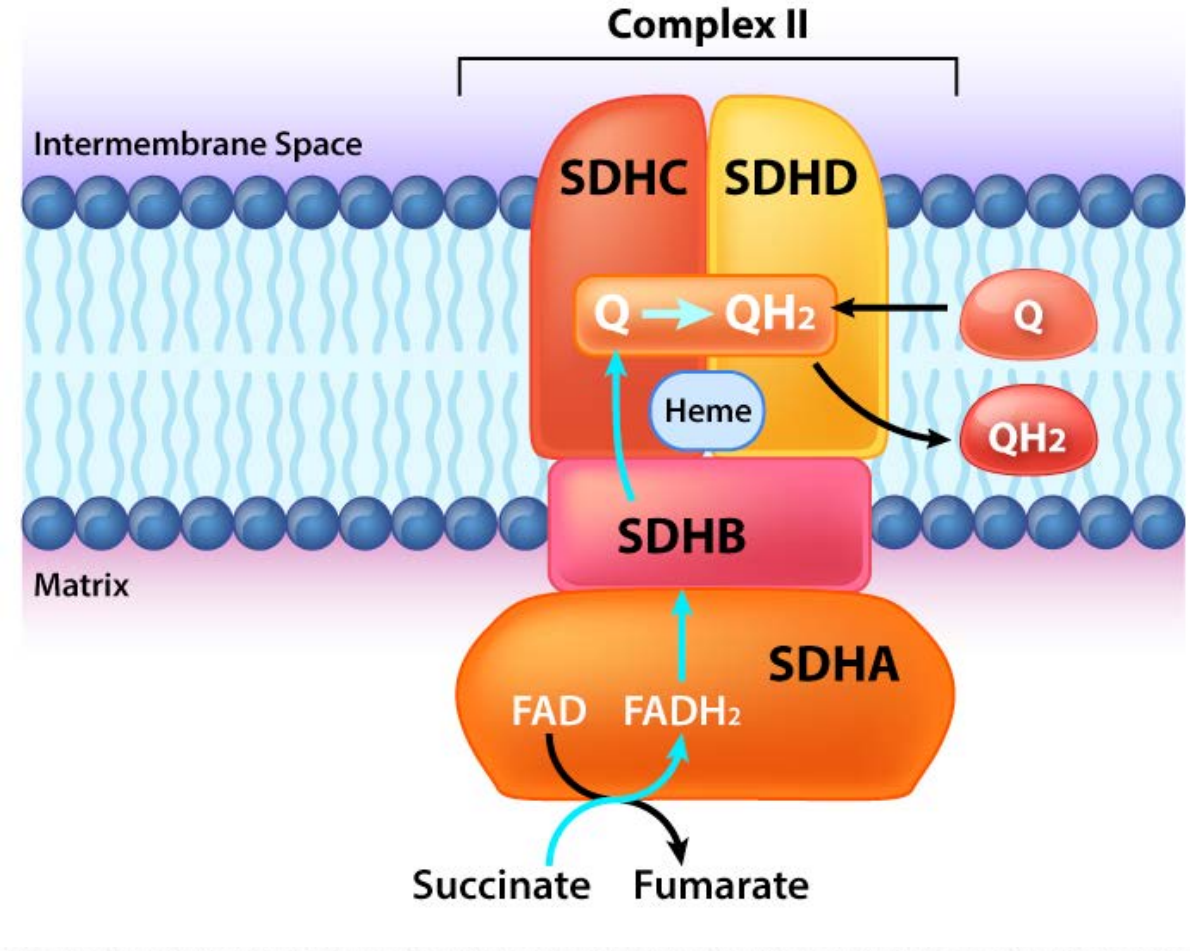

Figure 6.72 - Succinate dehydrogenase reaction

Image by Aleia Kim

Rare oxidation

Conversion of malate to oxaloacetate by malate dehydrogenase is a rare biological oxidation that has a $\Delta G°'$ with a positive value (29.7 kJ/mol).

L-Malate + NAD^+

⇅

Oxaloacetate + NADH

The reaction is 'pulled' by the energetically favorable conversion of oxaloacetate to citrate in the citrate

synthase reaction described above. Oxaloacetate intersects other important pathways, including amino acid metabolism (readily converted to aspartic acid), transamination (nitrogen movement) and gluconeogenesis.

It is worth noting that reversal of the citric acid cycle theoretically provides a mechanism for assimilating CO_2. In fact, this reversal has been noted in both anaerobic and microaerobic bacteria, where it is called the Arnon-Buchanan cycle (Figure 6.73).

Regulation of the citric acid cycle

Allosteric regulation of the citric acid cycle is pretty straightforward. The molecules involved are all substrates/products of the pathway or molecules involved in energy transfer. Substrates/products that regulate or affect the pathway include acetyl-CoA and succinyl-CoA .

Inhibitors and activators

High energy molecular indicators, such as ATP and NADH will tend to inhibit the cycle and low energy indicators (NAD^+, AMP, and ADP) will tend to activate the cycle. Pyruvate dehydrogenase, which catalyzes formation of acetyl-CoA for entry into the cycle is allosterically inhibited by its product (acetyl-CoA), as well as by NADH and ATP.

Regulated enzymes

Regulated enzymes in the cycle include citrate synthase (inhibited by NADH, ATP, and succinyl-CoA), isocitrate dehydrogenase (inhibited by ATP, activated by ADP and

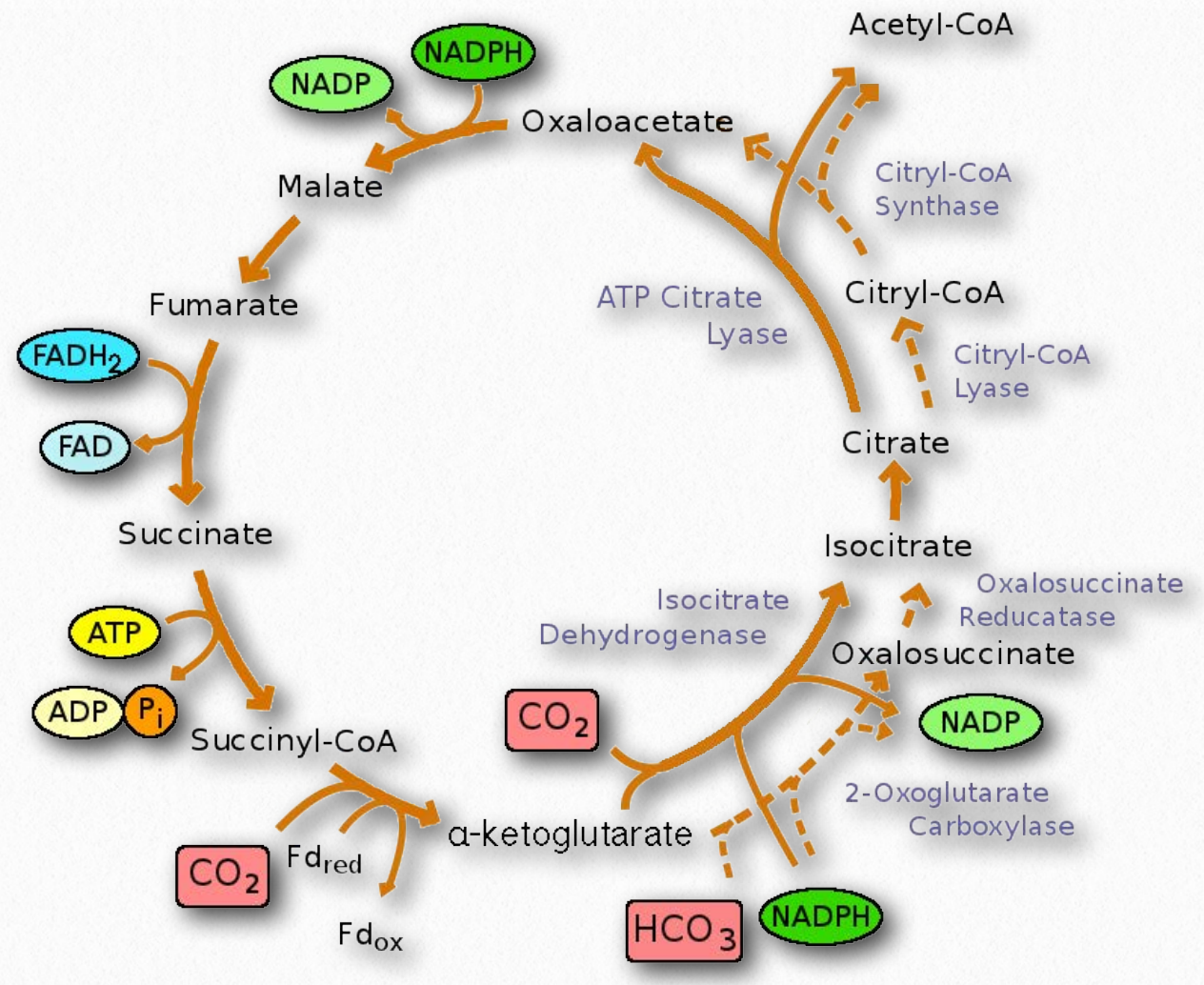

Figure 6.73 - Arnon-Buchanon cycle. Alternative enzymes shown on right in lavender. Fd = ferredoxin

Wikipedia

NAD^+), and α-ketoglutarate dehydrogenase (inhibited by NADH and succinyl-CoA and activated by AMP).

Anaplerotic/ cataplerotic pathway

The citric acid cycle is an important catabolic pathway oxidizing acetyl-CoA into CO_2 and generating ATP, but it is also an important source of molecules needed by cells and a mechanism for extracting energy from amino acids in protein breakdown and other breakdown products. This ability of the citric acid cycle to supply molecules as needed and to absorb metabolic by-products gives great flexibility to cells. When citric acid cycle intermediates are taken from the pathway to make other molecules, the term used to describe this is cataplerotic, whereas when molecules are added to the pathway, the process is described as anaplerotic.

I love my citrate synthase
It really is first rate
Adds O-A-A to Ac-Co-A
Producing one citrate

Aconitase is picky
Binds substrates specially
Creating isocitrate
Which has no symmetry

Then CO_2 gets lost from it
Released in the next phase
The secret weapon - Isocitrate
Dehydrogenase

The alpha K–D-H is next
It gets my admiration
For clipping CO_2 in one more
Decarboxylation

Succ-CoA synthetase steps up
Reacting most absurd
It's named for a catalysis
That simply runs backward

Suc -CIN-ate de-hyd-ROG-en-ase
Pulls H from succinate
Creating $FADH_2$
As well as fumarate

The fumarate gains water
O-H configured L
The fumarase's product?
Some malate for the cell

With one last oxidation
Malate de-hyd-ROG-en-ase
Expels its two creations
N-A-D-H / O-A-A

Kevin Ahern

Cataplerotic molecules

The citric acid cycle's primary cataplerotic molecules include **α**-ketoglutarate, succinyl-CoA, and oxaloacetate. Transamination of α-ketoglutarate and oxaloacetate produces the amino acids glutamate and aspartic acid, respectively. Oxaloacetate is important for the production of glucose in gluconeogenesis.

Glutamate plays a very important role in the movement of nitrogen through cells via glutamine and other molecules and is also needed for purine synthesis. Aspartate is a precursor of other amino acids and for production of pyrimidine nucleotides. Succinyl-CoA is necessary for the synthesis of porphyrins, such as the heme groups in hemoglobin, myoglobin and cytochromes.

Citrate is an important source of acetyl-CoA for making fatty acids. When the citrate concentration is high (as when the citric acid cycle is moving slowly or is stopped), it gets shuttled across the mitochondrial

membrane into the cytoplasm and broken down by the enzyme citrate lyase to oxaloacetate and acetyl-CoA. The latter is a precursor for fatty acid synthesis in the cytoplasm.

Anaplerotic molecules

Anaplerotic molecules replenishing citric acid cycle intermediates include acetyl-CoA (made in many pathways, including fatty acid oxidation, pyruvate decarboxylation, amino acid catabolism, and breakdown of ketone bodies), α-ketoglutarate (from amino acid metabolism), succinyl-CoA (from propionic acid metabolism), fumarate (from the urea cycle and purine metabolism), malate (carboxylation of PEP in plants), and oxaloacetate (many sources, including amino acid catabolism and pyruvate carboxylase action on pyruvate in gluconeogenesis)

Glyoxylate cycle

A pathway related to the citric acid cycle found only in plants and bacteria is the glyoxylate cycle (Figures 6.74 & 6.75). The glyoxylate cycle, which bypasses the decarboxylation reactions while using most of the non-decarboxylation reactions of the citric acid cycle, does not operate in animals, because they lack two enzymes necessary for it – isocitrate

I'm thinking I could lose some weight
If I could make glyoxylate
Combined with acetyl-CoA
Malate would then form OAA
The excess OAA in turn
Would give more glucose to be burned
Converting fat to glucose, see
Expends it glycolytically

lyase and malate synthase. The cycle occurs in specialized plant peroxisomes called glyoxysomes. Isocitrate lyase catalyzes the conversion of isocitrate into succinate and

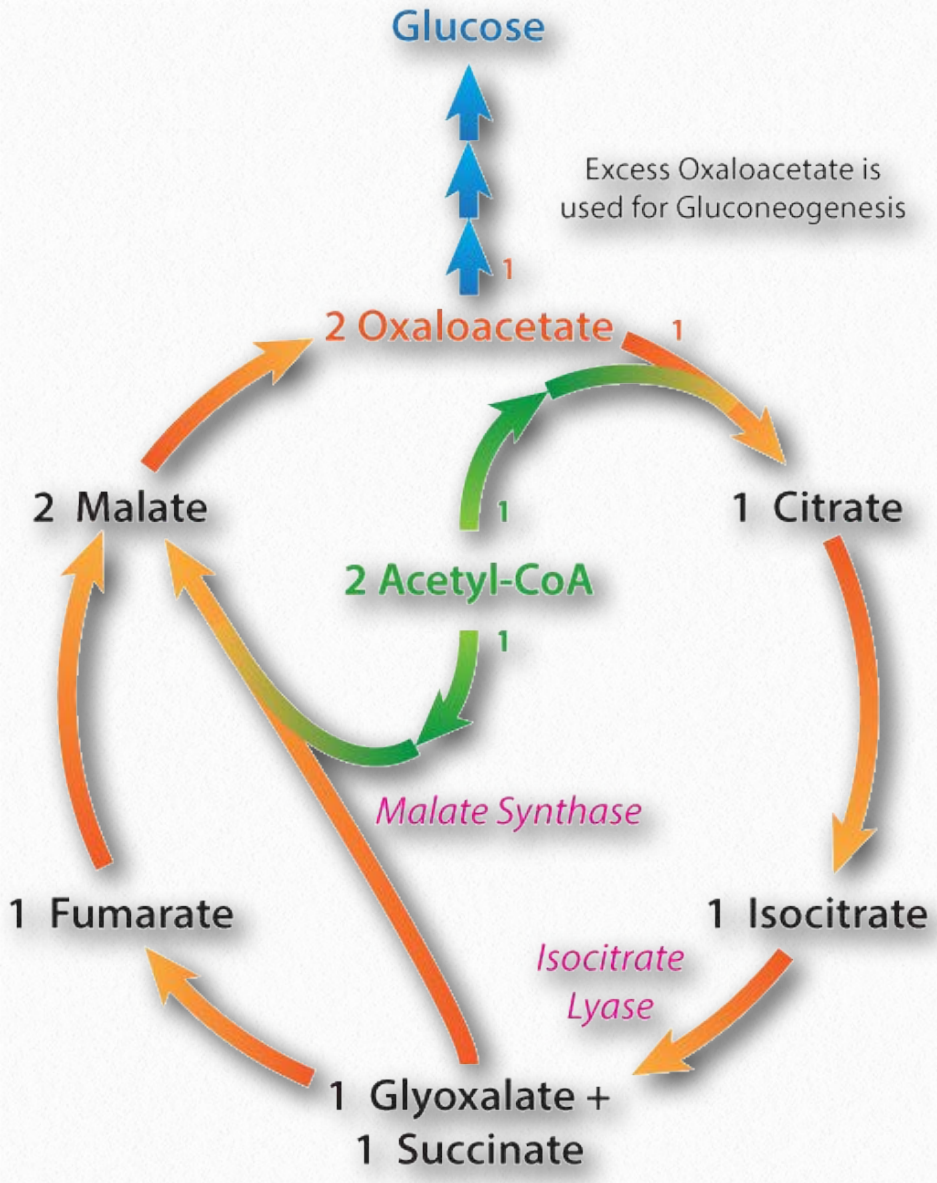

Figure 6.74 - Overview of the glyoxylate cycle
Image by Aleia Kim

glyoxylate. Because of this, all six carbons of the citric acid cycle survive each turn of the cycle and do not end up as carbon dioxide.

YouTube Lectures by Kevin HERE & HERE

Succinate continues through the remaining reactions to produce oxaloacetate. Glyoxylate combines with another acetyl-CoA

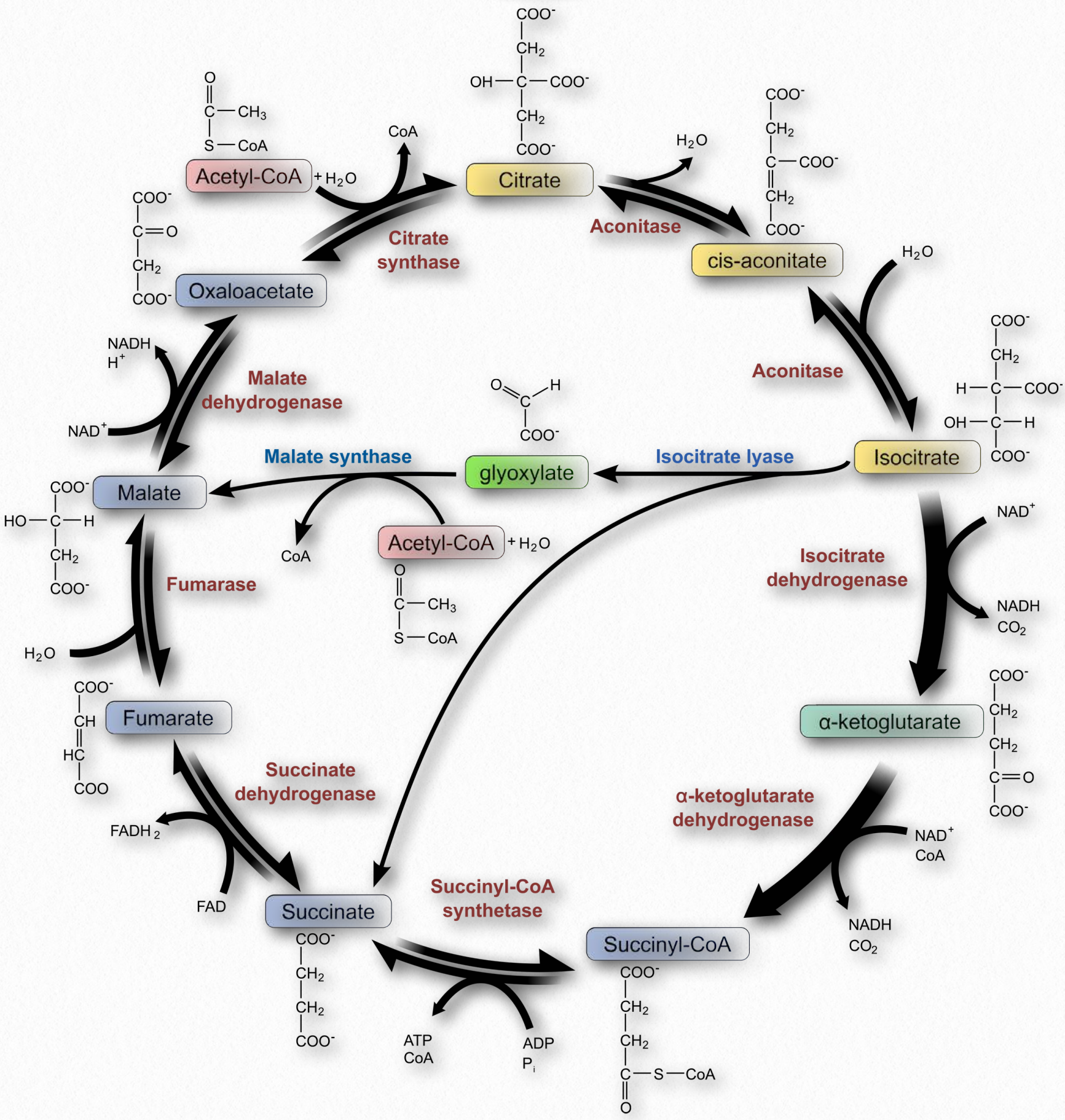

Figure 6.75 - Reactions of the glyoxylate cycle

Wikipedia

Figure 6.76 - A gingko seed embryo
Wikipedia

(one acetyl-CoA was used to start the cycle) to create malate (catalyzed by malate synthase). Malate can, in turn, be oxidized to oxaloacetate.

It is at this point that the glyoxylate pathway's contrast with the citric acid cycle is apparent. After one turn of the citric acid cycle, a single oxaloacetate is produced and it balances the single one used in the first reaction of the cycle. Thus, in the citric acid cycle, there is no net production of oxaloacetate in each turn of the cycle.

Net oxaloacetate production

On the other hand, thanks to assimilation of carbons from two acetyl-CoA molecules, each turn of the glyoxylate cycle results in two oxaloacetates being produced, after starting with one. The extra oxaloacetate of the glyoxylate cycle can be used to make other molecules, including glucose in gluconeogenesis. This is particularly important for plant seed germination (Figure 6.76), since the seedling is not exposed to sunlight. With the glyoxylate cycle, seeds can make glucose from stored lipids.

Because animals do not run the glyoxylate cycle, they cannot produce glucose from acetyl-CoA in net amounts, but plants and bacteria can. As a result, plants and bacteria can turn acetyl-CoA from fat into glucose, while animals can't. Bypassing the oxidative decarboxylations (and substrate level phosphorylation) has energy costs, but, there are also benefits. Each turn of the glyoxylate cycle produces one $FADH_2$ and one NADH instead of the three NADHs, one $FADH_2$, and one GTP made in each turn of the citric acid cycle.

Carbohydrate needs

Organisms that make cell walls, such as plants, fungi, and bacteria, need large quantities of carbohydrates as they grow to support the biosynthesis of the complex structural polysaccharides of the walls. These include cellulose, glucans, and chitin. Notably, each of the organisms can operate the glyoxylate cycle using acetyl-CoA from β-oxidation.

Coordination of the glyoxylate cycle and the citric acid cycle

The citric acid cycle is a major catabolic pathway producing a considerable amount of

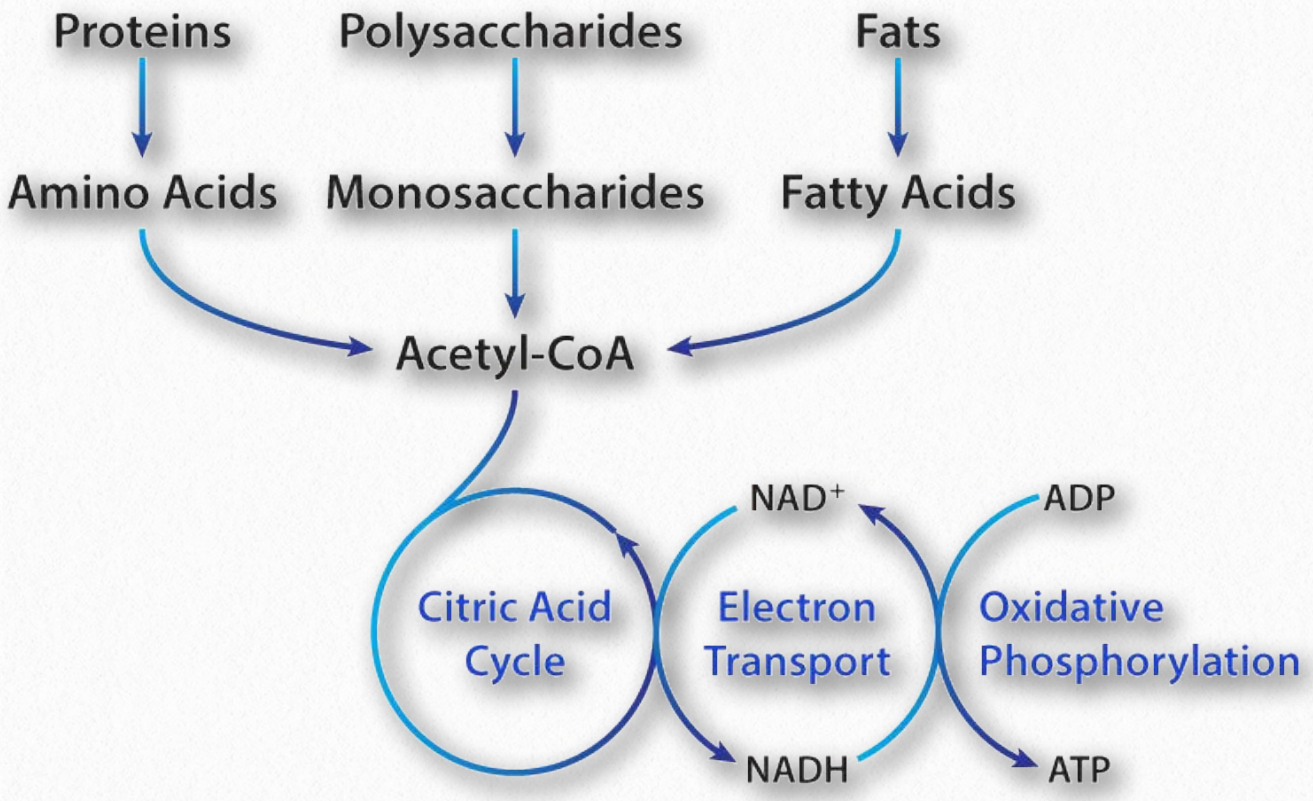

Figure 6.77 - Acetyl-CoA metabolism

Image by Aleia Kim

energy for cells, whereas the glyoxylate cycle's main function is anabolic - to allow production of glucose from fatty acids in plants and bacteria. The two pathways are physically separated from each other (glyoxylate cycle in glyoxysomes / citric acid cycle in mitochondria), but nonetheless a coordinated regulation of them is important.

The enzyme that appears to provide controls for the cycle is isocitrate dehydrogenase. In plants and bacteria, the enzyme can be inactivated by phosphorylation by a kinase found only in those cells. Inactivation causes isocitrate to accumulate in the mitochondrion and when this happens, it gets shunted to the glyoxysomes, favoring the glyoxylate cycle.

Removal of the phosphate from isocitrate dehydrogenase is catalyzed by an isocitrate dehydrognease-specific phosphoprotein phosphatase and restores activity to the enzyme.

When this happens, isocitrate oxidation resumes in the mitochondrion along with the rest of the citric acid cycle reactions.

In bacteria, where the enzymes for both cycles are present together in the cytoplasm, accumulation of citric acid cycle intermediates and glycolysis intermediates will tend to favor the citric acid cycle by activating the phosphatase, whereas high energy conditions will tend to favor the glyoxylate cycle by inhibiting it.

Acetyl-CoA metabolism

Acetyl-CoA is one of the most "connected" metabolites in biochemistry, appearing in fatty acid oxidation/synthesis, pyruvate oxidation, the citric acid cycle, amino acid anabolism/catabolism, ketone body metabolism, steroid/bile acid synthesis, and (by extension from fatty acid metabolism) prostaglandin synthesis . Most of these pathways

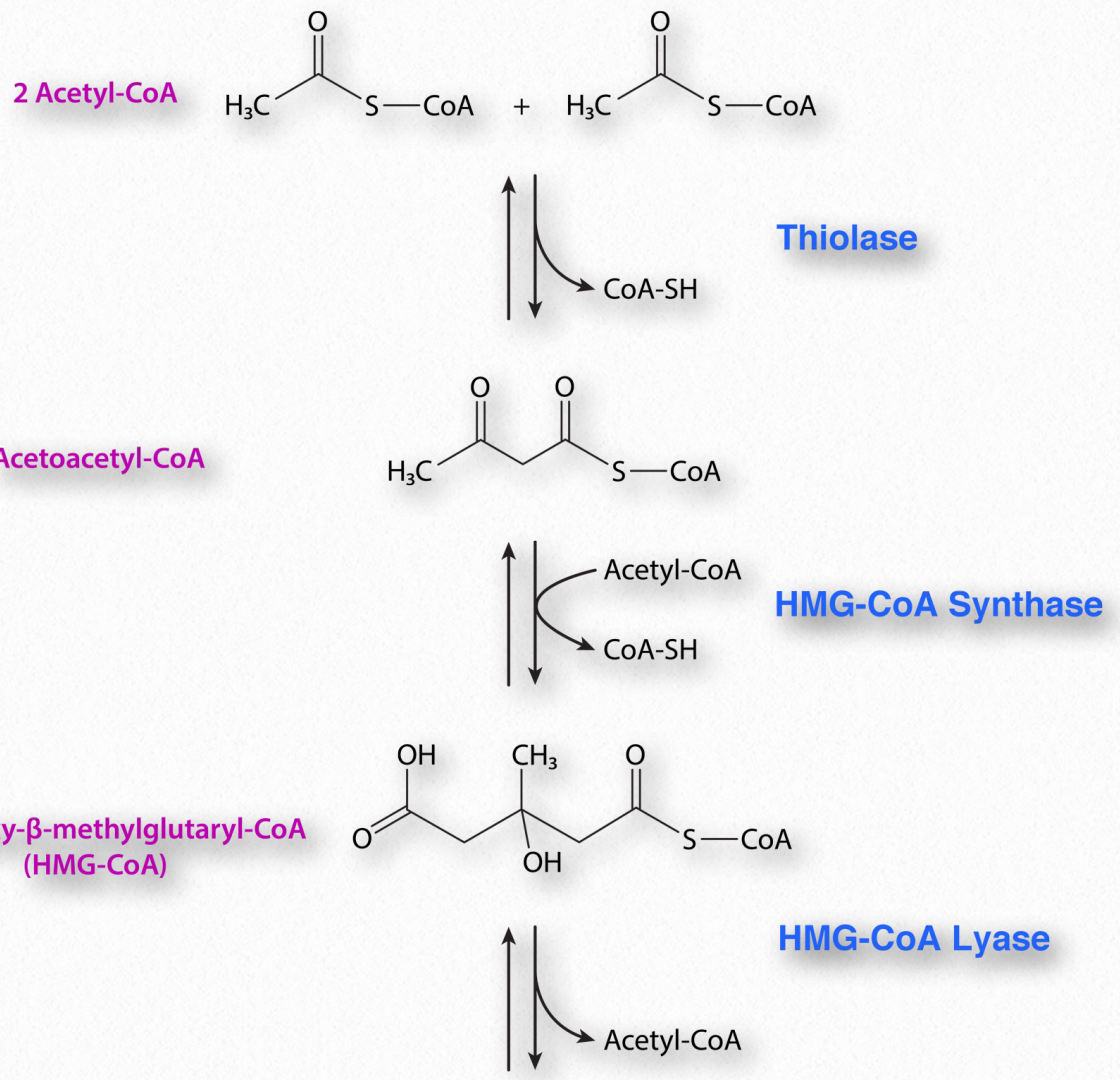

Figure 6.78 Ketone body metabolism

Image by Pehr Jacobson

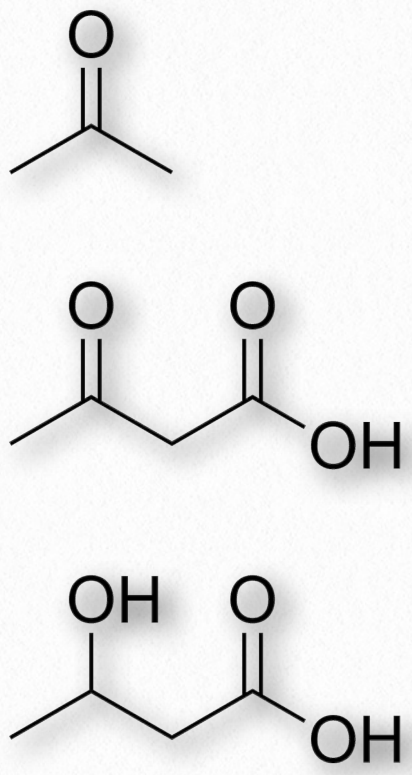

Figure 6.79 - Three ketone bodies - acetone (top), acetoacetic acid (middle), and β-hydroxybutyrate (bottom)

will be dealt with separately. Here we will cover ketone body metabolism.

Ketone body metabolism

Ketone bodies are molecules made when the blood levels of glucose fall very low. Ketone bodies can be converted to acetyl-CoA by reversing the reaction of the pathway that makes them (Figure 6.78). Acetyl CoA, of course, can be used for ATP synthesis via the citric acid cycle. People who are very hypoglycemic (including some diabetics) will produce ketone bodies (Figure 6.79) and these are often first detected by the smell of acetone on their breath.

Overlapping pathways

The pathways for ketone body synthesis and cholesterol biosynthesis (Figure 6.80

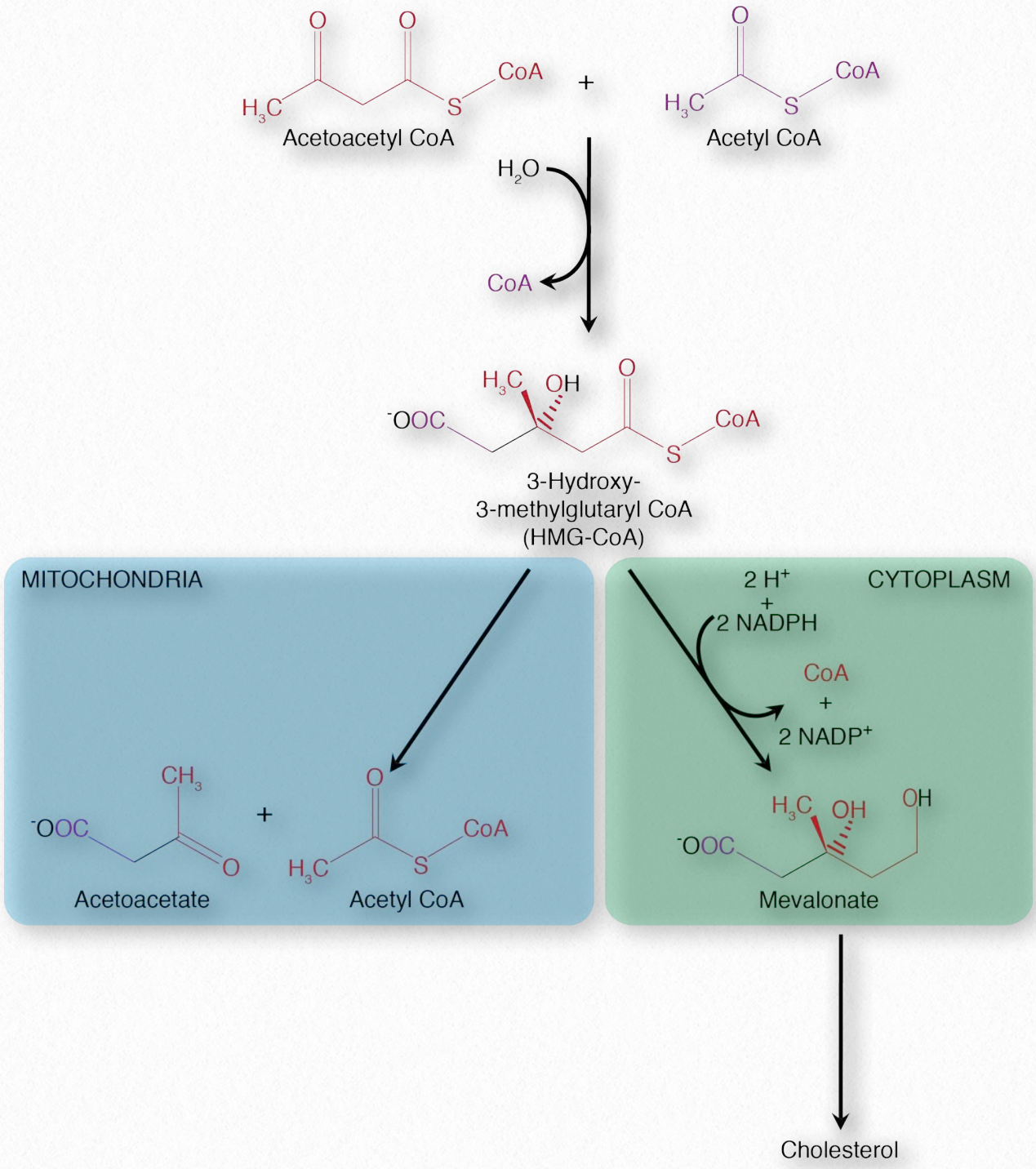

Figure 6.80 - Diverging biosynthetic pathways for ketone bodies (left) and cholesterol biosynthesis (right)

Image by Penelope Irving

and see HERE) overlap at the beginning. Each of these starts by combining two acetyl-CoAs together to make acetoacetyl-CoA. Not coincidentally, that is the next to last product of β-oxidation of fatty acids with even numbers of carbons (see HERE for fatty acid oxidation). In fact, the enzyme that catalyzes the joining is the same as the one that catalyzes its breakage in fatty acid oxidation – thiolase. Thus, these pathways start by reversing the last step of the last round of fatty acid oxidation.

YouTube Lectures by Kevin HERE & HERE

HMG-CoA formation

Both pathways also include addition of two more carbons to acetoacetyl-CoA from a third acetyl-CoA to form hydroxy-methyl-glutaryl-CoA, or HMG-CoA, as it is more commonly known. It is at this point that the two pathways diverge. HMG-CoA is a branch point between the two pathway and can either go on to become cholesterol or ketone bodies. In the latter pathway, HMG-CoA is broken down into acetyl-CoA and acetoacetate.

Acetoacetate is itself a ketone body and can

be reduced to form another one, D-β-hydroxybutyrate (not actually a ketone, though). Alternatively, acetoacetate can be converted into acetone. This latter reaction can occur either spontaneously or via catalysis by acetoacetate decarboxylase. Acetone can be converted into pyruvate and pyruvate can be made into glucose.

D-β-hydroxybutyrate travels readily in the blood and crosses the blood-brain barrier. It can be oxidized back to acetoacetate, converted to acetoacetyl-CoA, and then broken down to two molecules of acetyl-CoA for oxidation in the citric acid cycle.

Ketosis

When a body is producing ketone bodies for its energy, this state in the body is known as ketosis. Formation of ketone bodies in the liver is critical. Normally glucose is the body's primary energy source. It comes from the diet, from the breakdown of storage carbohydrates, such as glycogen, or from glucose synthesis (gluconeogenesis). Since the primary stores of glycogen are in muscles and liver and since gluconeogenesis occurs only in liver, kidney, and gametes, when the supply of glucose is interrupted for any reason, the liver must supply an alternate energy source.

From fatty acid breakdown

In contrast to glucose, ketone bodies can be made in animals from the breakdown of fat/fatty acids. Most cells of the body can use ketone bodies as energy sources. Ketosis may arise from fasting, a very low carbohydrate diet or, in some cases, diabetes.

Acidosis

The term acidosis refers to conditions in the body where the pH of arterial blood drops be-

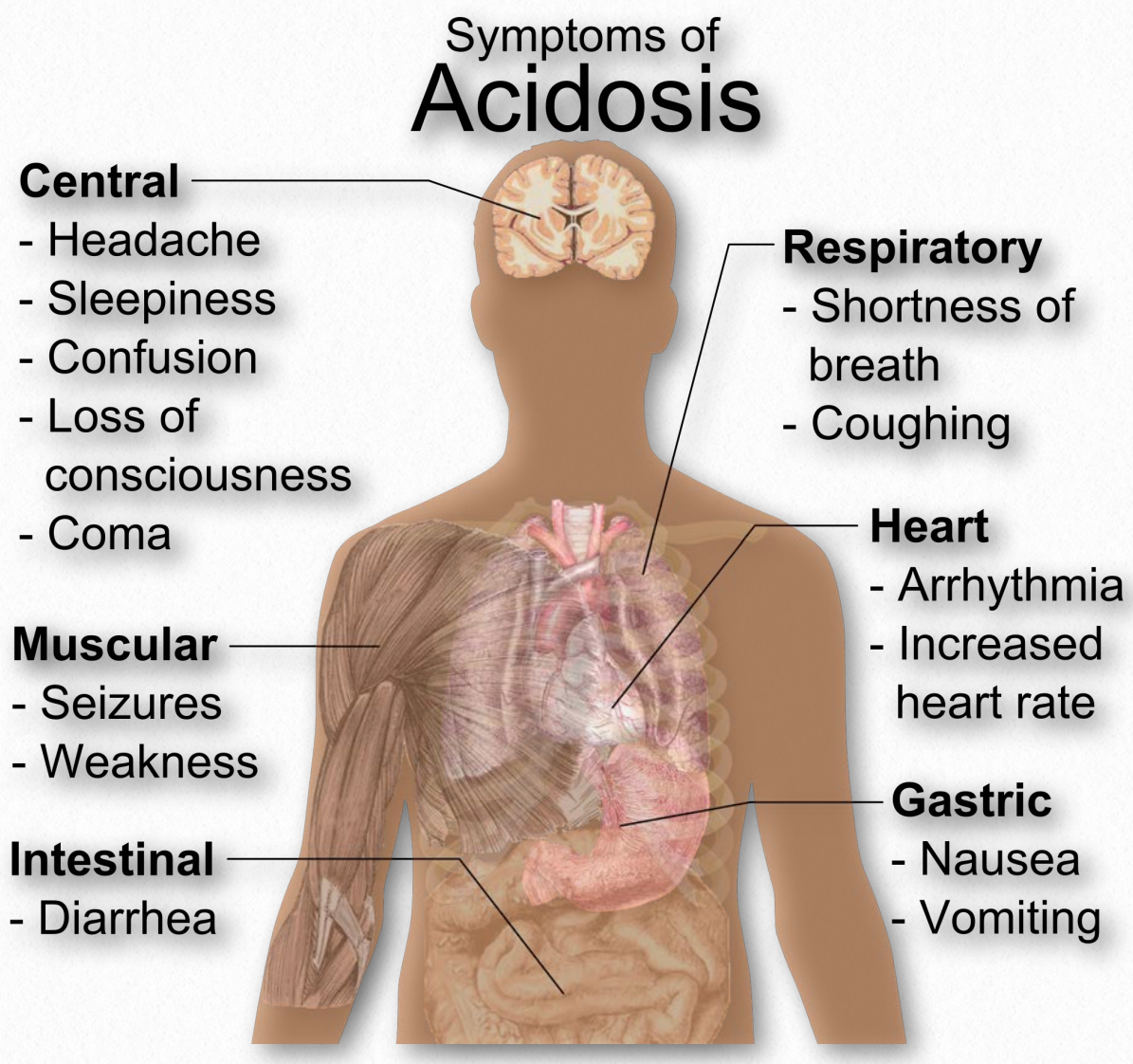

Figure 6.81 - Symptoms of acidosis

low 7.35. It is the opposite of the condition of alkalosis, where the pH of the arterial blood rises above 7.45. Normally, the pH of the blood stays in this narrow pH range. pH values of the blood lower than 6.8 or higher than 7.8 can cause irreversible damage and may be fatal. Acidosis may have roots in metabolism (metabolic acidosis) or in respiration (respiratory acidosis).

There are several causes of acidosis. In metabolic acidosis, production of excess lactic acid or failure of the kidneys to excrete acid can cause blood pH to drop. Lactic acid is produced in the body when oxygen is limiting, so anything that interferes with oxygen delivery may create conditions favoring production of excess lactic acid. These may include restrictions in the movement of blood to target tissues, resulting in hypoxia (low oxygen conditions) or decreases in blood volume. Issues with blood movement can result from heart problems, low blood pressure, or hemorrhaging.

Strenuous exercise can also result in production of lactic acid due to the inability of the blood supply to deliver oxygen as fast as tissues require it (hypovolemic shock). At the end of the exercise, though, the oxygen supply via the blood system quickly catches up.

Respiratory acidosis arises from accumulation of carbon dioxide in the blood. Causes include hypoventilation, pulmonary problems, emphysema, asthma, and severe pneumonia.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

Click HERE for Penelope Irving's Web Page

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The Citric Acid Cycle

To the tune of "*When Irish Eyes Are Smiling*"

Metabolic Melodies Website HERE

(This song uses only the chorus of the original song)

The citric acid cycle
Is a source of energy
It gets electrons moving
While reducing NAD

It starts with citric acid
Turning to aconitate
Which becomes an isocitrate
On the way to glutarate

The loss of one more carbon
Gives succinyl-CoA
And then succinic acid
When the CoA goes away

A further oxidation
Gives one *trans* fumarate
Which gains a water on the
Next step to make malate

One simple oxidation
Makes O-A-A you see
Which combined with Ac-Co-A
Returns us cyclically

Recording by David Simmons
Lyrics by Kevin Ahern

The Mellow Woes of Testing

To the tune of "*Yellow Rose of Texas*"

Metabolic Melodies Website HERE

The term is almost at an end
Ten weeks since it began
I worried how my grade was cuz
I did not have a plan

The first exam went not so well
I got a sixty three
'Twas just about the average score
In biochemistry

I buckled down the second time
Did not sow my wild oats
I downloaded the videos
And took a ton of notes

I learned about free energy
And Delta Gee Naught Prime
My score increased by seven points
A C-plus grade was mine

I sang the songs, I memorized
I played the mp_3s
I learned the citrate cycle
And I counted ATPs

I had electron transport down
And all of complex vee
I gasped when I saw my exam
It was a ninety three

So heading to the final stretch
I crammed my memory
And came to class on sunny days
For quizzing comedy

I packed a card with info and
My brain almost burned out
'Twas much to my delight I
Got the 'A' I'd dreamed about

So here's the moral of the song
It doesn't pay to stew
If scores are not quite what you want
And you don't have a clue

The answers get into your head
When you know what to do
Watch videos, read highlights and
Re-

Recording by David Simmons
Lyrics by Kevin Ahern

Metabolism: Fats and Fatty Acids

In the modern Western world, which is fat and getting fatter, there is a tremendous amount of interest in the metabolism of fat and fatty acids. Fat is the most important energy storage form of animals, storing considerably more energy per carbon than carbohydrates, but its insolubility in water requires the body to package it specially for transport. Surprisingly, fat/fatty acid metabolism is not nearly as tightly regulated as that of carbohydrates. Neither are the metabolic pathways of breakdown and synthesis particularly complicated, either.

YouTube Lectures by Kevin
HERE & HERE

Movement of dietary fat

Before we discuss the breakdown and synthesis of fat, let us first discuss the movement of dietary fat and oil (triglycerides - Figure 6.82) in the body. Upon consumption of triglycerides in the diet, they first are solubilized in the digestive system by the churning action of the stomach and the emulsifying properties of the bile acids.

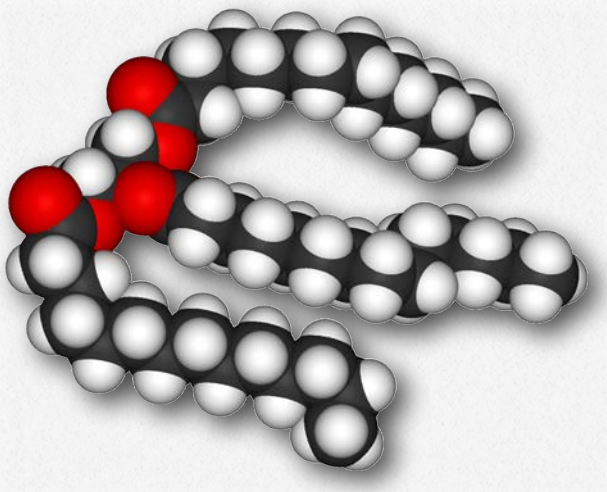

Figure 6.82 - Trimyristin - A triacylglyceride

Upon passing into the lumen of the intestine, the triglycerides are acted on first by enzymes known as lipases that use water twice on each triglyceride to release two fatty acids, leaving behind a monoacylglyceride. As shown in Figure 6.83, the fatty acids and the monoacylglyceride are moved across the intestinal wall into the lymph system where they are reassembled back into a triglyceride. In the lymph system triglycerides and other insoluble lipids are packaged into lipoprotein complexes called chylomicrons that enter the blood stream and travel to target cells. The journey of lipids in the body after leaving the digestive system is long and is discussed in more depth HERE.

In the body, fat is stored in specialized cells known as adipocytes. When these cells receive appropriate signals, they begin the breakdown of fat into glycerol and fatty acids.

Breakdown of fat

Breakdown of fat in adipocytes requires catalytic action of three enzymes. The first

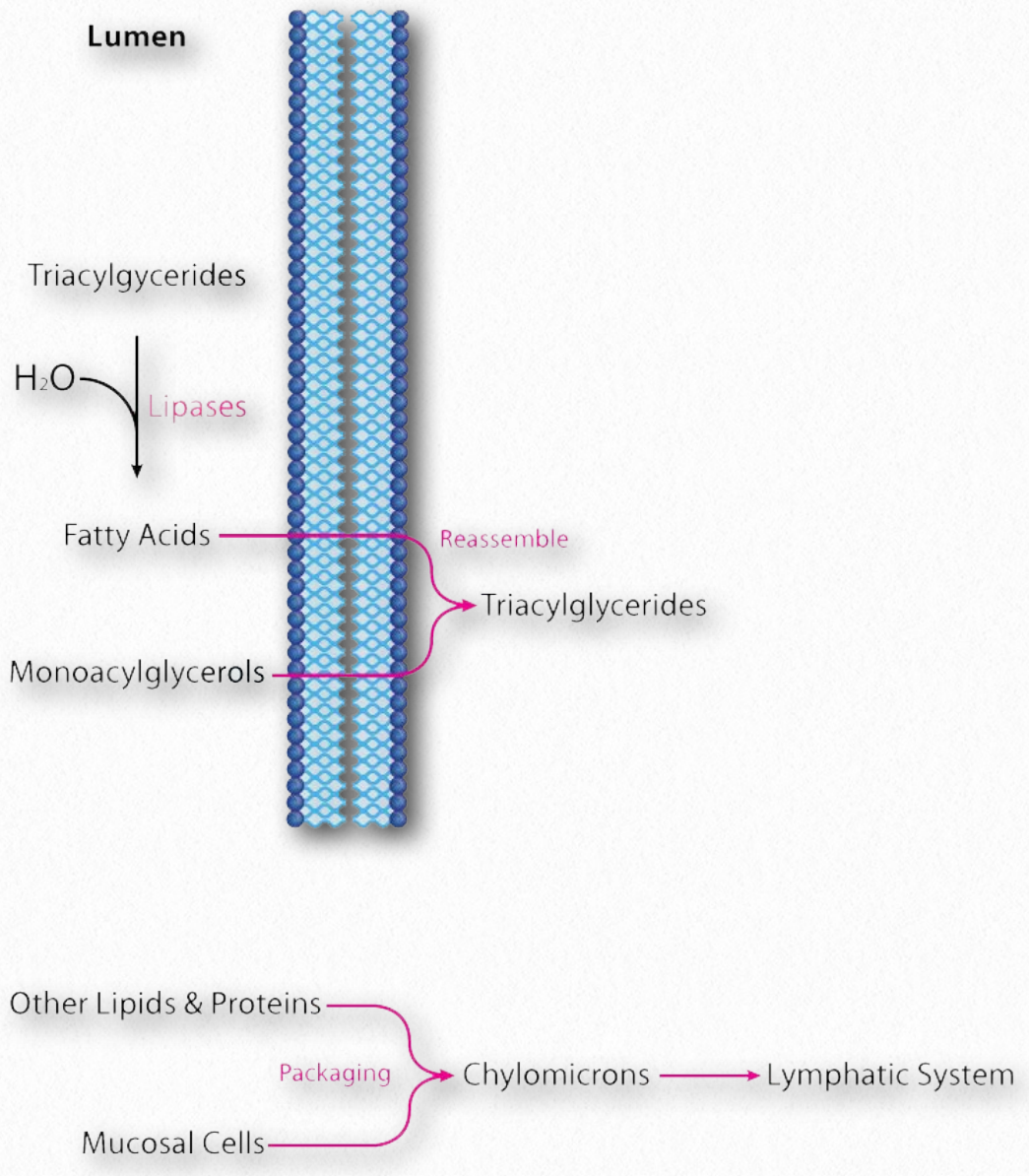

Figure 6.83 - Movement of dietary triglycerides

Image by Aleia Kim

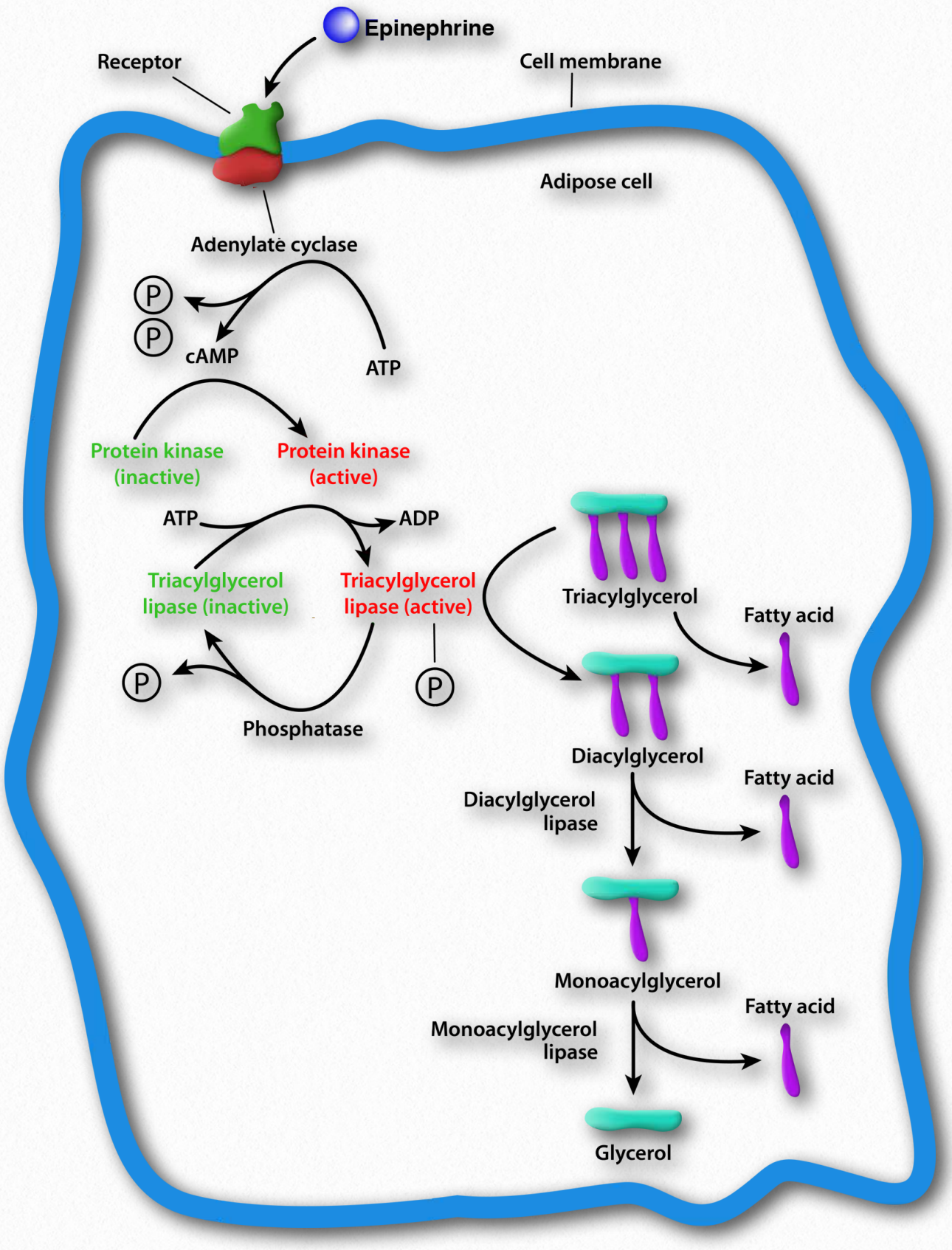

Figure 6.84 - Breakdown of fat in adipocytes

Image by Pehr Jacobson

of these is controlled by binding of hormones to the cell membrane (Figure 6.84). It is the only regulated enzyme of fat breakdown and is known as hormone sensitive triacylglycerol lipase. It removes the first fatty acid from the fat. Diacylglyceride lipase removes the second one and monoacylglyceride lipase removes the third. As noted, only the first one is regulated and it appears to be the rate limiting reaction when active.

Epinephrine activation

As shown in Figure 6.84, activation of hormone sensitive triacylglycerol lipase (HSTL) is accomplished by epinephrine stimulation process and that it overlaps with the same activation that stimulates glycogen breakdown and gluconeogenesis.

This coordination is very important. Each of the pathways stimulated by the epinephrine signaling system aims to provide the body with more materials to catabolize for energy - sugars and fatty acids. The HSTL is inhibited

Synthesis of Phosphatidic Acid from Glycerol-3-phosphate

1. **Glycerol-3-phosphate** + Acyl-CoA <=> Monoacylglycerol phosphate + CoA-SH

2. Monoacylglycerol phosphate + Acyl-CoA <=> **Phosphatidic acid** + CoA-SH

by dephospohrylation and this is stimulated by binding of insulin to its cell membrane receptor.

Perilipin

A protein playing an important roles in regulation of fat breakdown is perilipin. Perilipin associates with fat droplets and helps regulate action of HSTL, the enzyme catalyzing the first reaction in fat catabolism. When perilipin is not phosphorylated, it coats the fat droplet and prevents HSTL from getting access to it. Activation of protein kinase A in the epinephrine cascade, however, results in phosphorylation of both perilipin and HSTL. When this occurs, perilipin loosens its tight binding to the fat droplet, allowing digestion of the fat to begin by HSTL.

Perilipin expression is high in obese organisms and some mutational variants have been associated with obesity in women. Another mutation reduces perilipin expression and is associated with greater lipolysis (fat breakdown) in women. Mice lacking perilipin eat more food than wild-type mice, but gain 1/3 less weight when on the same diet.

Fat synthesis

Synthesis of fat requires action of acyl transferase enzymes, such as glycerol-3 O-phosphate acyl transferase, which catalyzes addition of fatty acids to the glycerol backbone (reaction #1 above). The process requires glycerol-3-phosphate (or DHAP) and three fatty acids. In the first reaction, glycerol-3-phosphate is esterified at position 1 with a fatty acid, followed by a duplicate re-

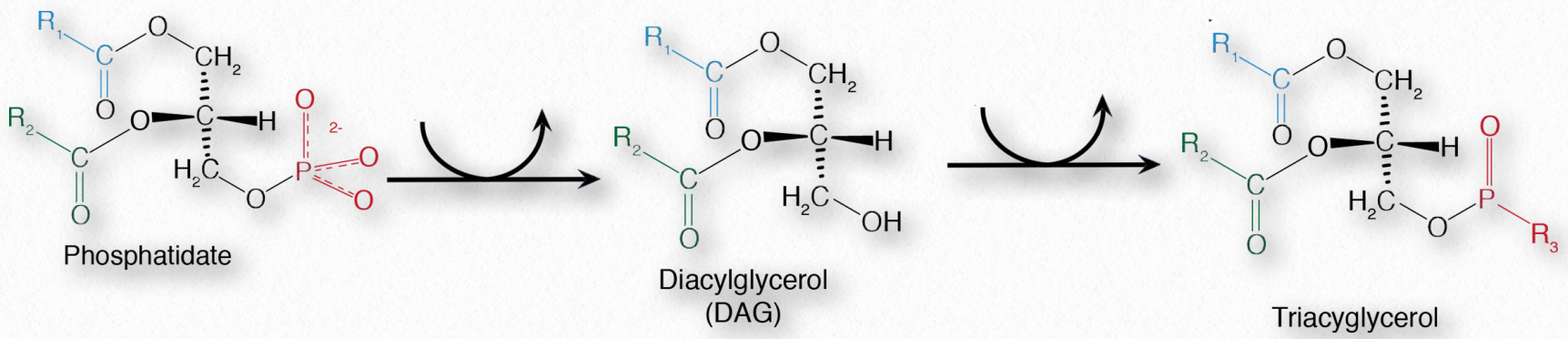

Figure 6.85 - Synthesis of fat from phosphatidic acid (phosphatidate)

Image by Penelope Irving

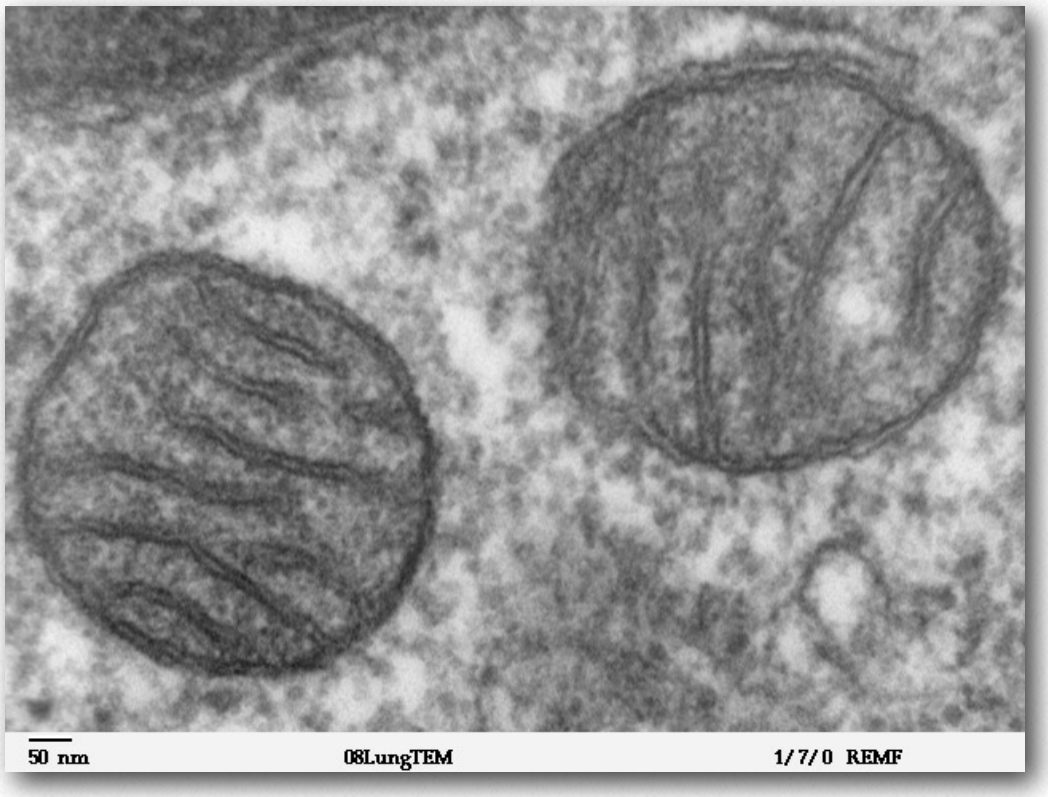

Figure 6.86 - Mitochondria - site of β-oxidation

action at position 2 to make phosphatidic acid (diacylglycerol phosphate). This molecule, which is an intermediate in the synthesis of both fats and phosphoglycerides, gets dephosphorylated to form diacylglycerol before the esterification of the third fatty acid to the molecule to make a fat.

Fatty acids released from adipocytes travel in the bloodstream bound to serum albumin. Arriving at target cells, fatty acids are taken up by membrane-associated fatty acid binding proteins, which help control cellular fatty acid uptake by transport proteins. Players in this process include CD36, plasma membrane-associated fatty acid-binding protein, and a family of fatty acid transport proteins (called FATP1-6).

Fatty acid oxidation

Upon arrival inside of target cells, fatty acids are oxidized in a process that chops off two carbons at a time

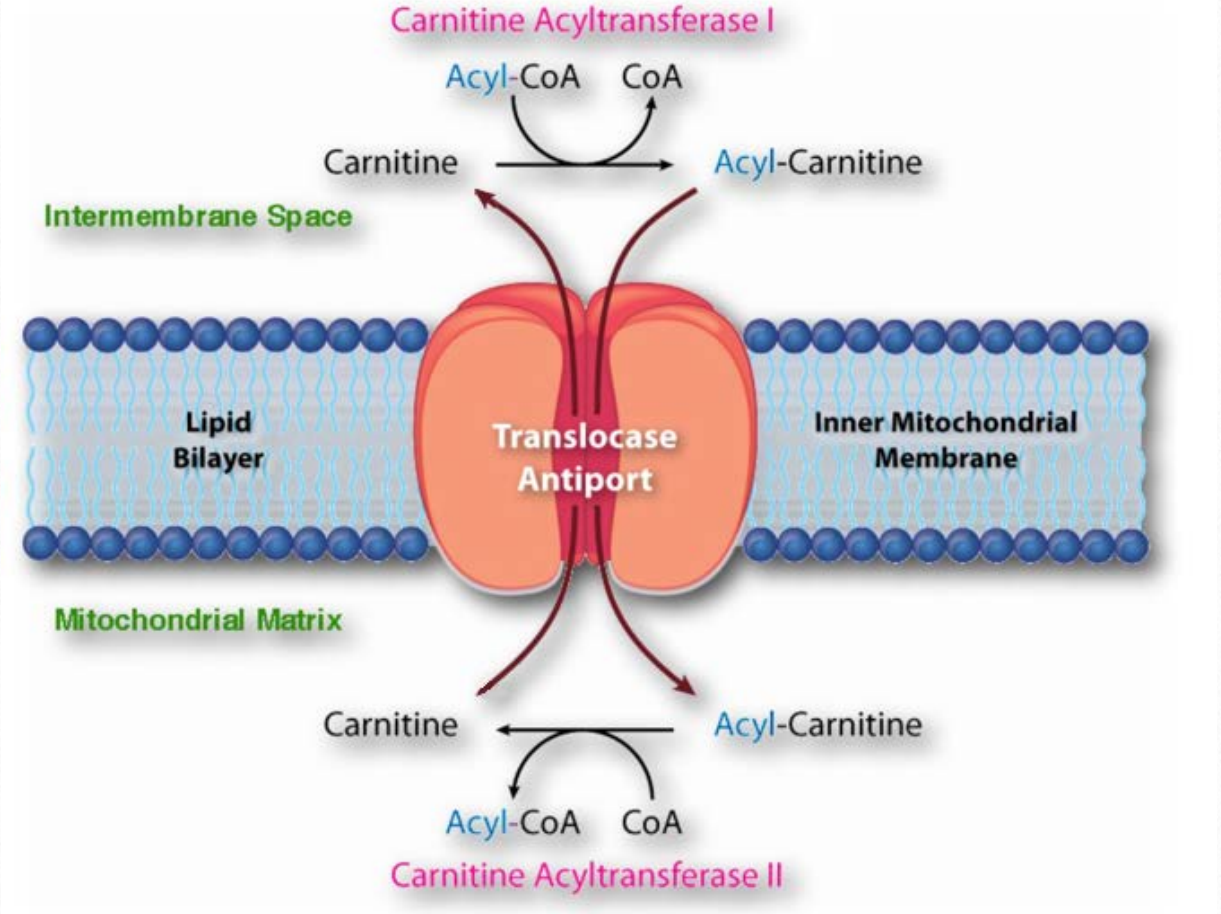

Figure 6.87 - Transport of fatty acid (acyl group) across mitochondrial inner membrane

Image by Aleia Kim

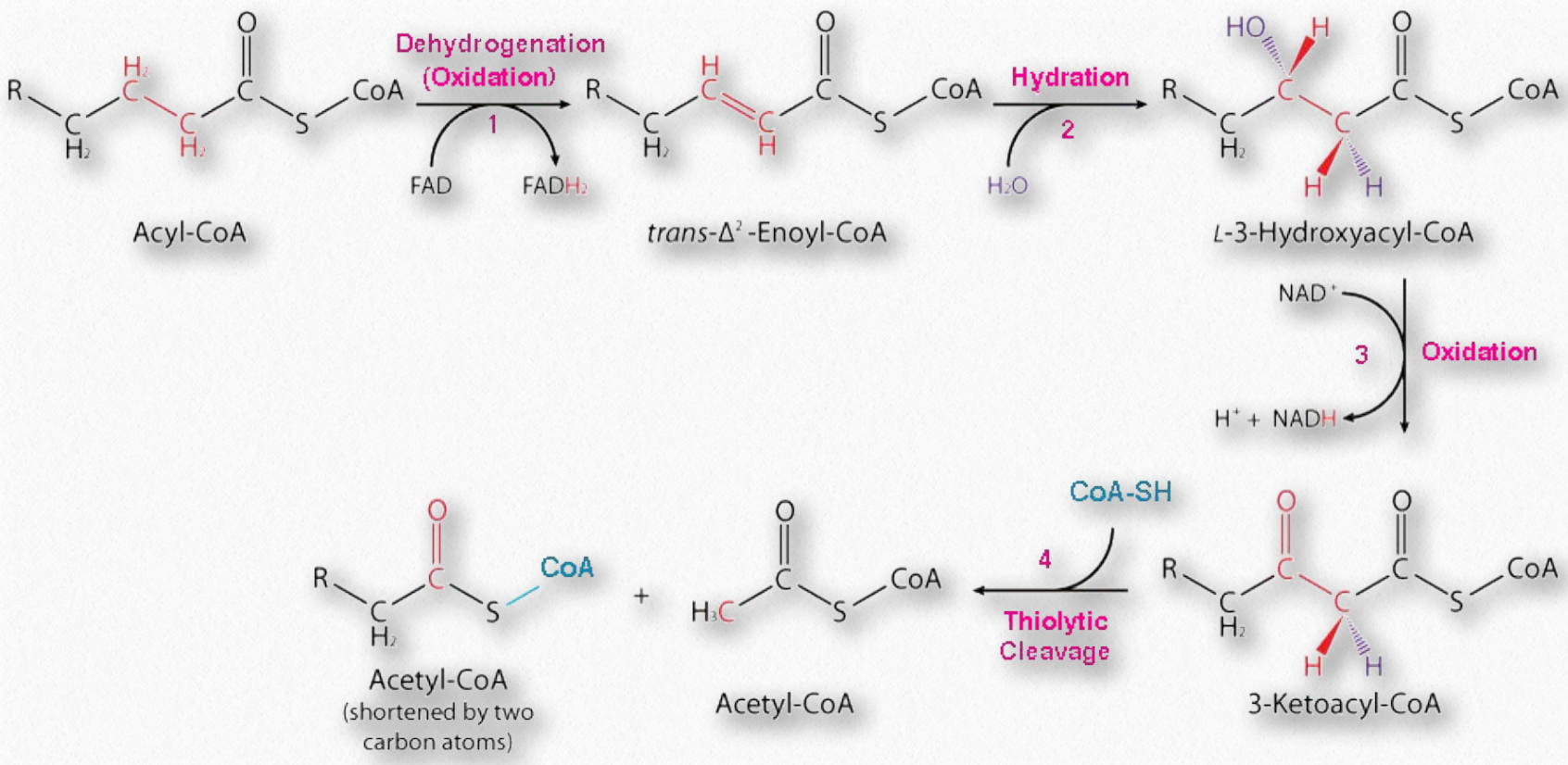

Figure 6.88 - Four reactions in β-oxidation

Image by Aleia Kim

to make acetyl-CoA, which is subsequently oxidized in the citric acid cycle. Depending on the size of the fatty acid, this process (called β-oxidation) will begin in either the mitochondrion (Figure 6.86) or the peroxisomes (see HERE).

Transport

To be oxidized in the mitochondrion, fatty acids must first be attached to coenzyme A (CoA-SH or CoA) and transported through the cytoplasm and the outer mitochondrial membrane. In the mitochondrion's intermembrane space, the CoA on the fatty acid is replaced by a carnitine (Figure 6.87) in order to be moved into the matrix. After this is done, the fatty acid linked to carnitine is transported into the mitochondrial matrix and in the matrix the carnitine is replaced again by coenzyme A. It is in the mitochondrial matrix where the oxidation occurs. The fatty acid linked to CoA (called an acyl-CoA) is the substrate for fatty acid oxidation.

YouTube Lectures by Kevin HERE & HERE

Steps

The process of fatty acid oxidation (Figure 6.88) is fairly simple. The reactions all occur between carbons 2 and 3 (with #1 being the one linked to the CoA) and sequentially include the following steps 1) dehydrogenation to create $FADH_2$ and a fatty acyl group with a double bond between carbons 2 and 3 in the *trans* configuration; 2) hydration across the double bond to put a hydroxyl group on carbon 3 in the L configuration; 3) oxidation of the

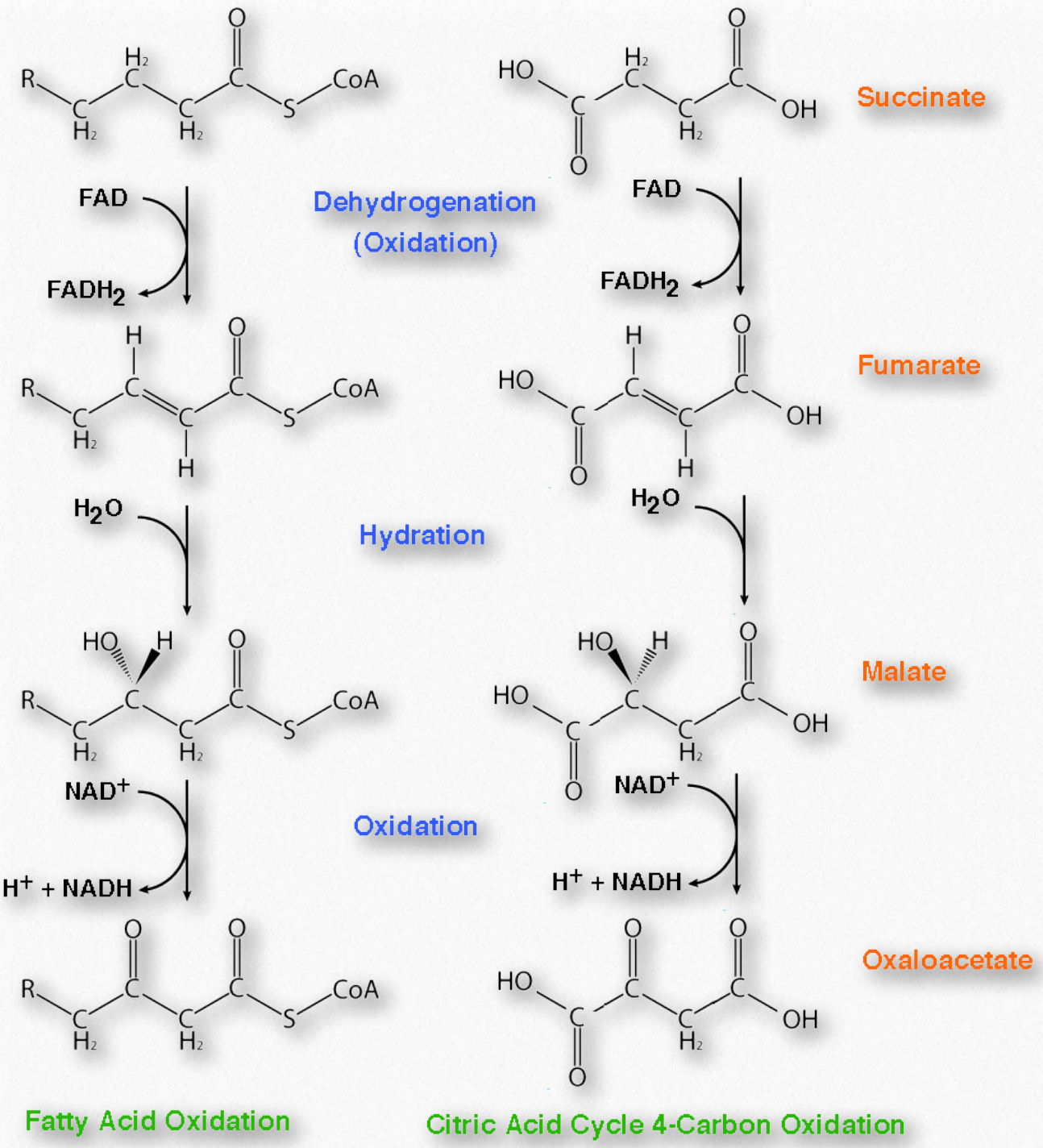

Figure 6.89 - Similar reactions for fatty acid oxidation and oxidation of 4-carbon compounds in the citric acid cycle

Image by Aleia Kim

which catalyzes the dehydrogenation in the first reaction and yields $FADH_2$. The enzyme comes in three different forms – ones specific for long, medium, or short chain length fatty acids. The first of these is sequestered in the peroxisomes of animals (see below) whereas the ones that work on medium and shorter chain fatty acids are found in the mitochondria. Action of all three enzymes is typically needed to oxidize a fatty acid. Plants and yeast perform β-oxidation exclusively in peroxisomes.

hydroxyl group to make a ketone; and 4) thiolytic cleavage to release acetyl-CoA and a fatty acid two carbons shorter than the starting one.

Enzymes of β-oxidation

Two of the enzymes of β-oxidation are notable. The first is acyl-CoA dehydrogenase, The most interesting of the acyl-CoA dehydrogenases is the one that works on medium length fatty acids. This one, which is the one most commonly deficient in animals, has been associated with sudden infant death syndrome. Reactions two and three in β-oxidation are catalyzed by enoyl-CoA hy-

dratase and 3-hydroxyacyl-CoA dehydrogenase, respectively. The latter reaction yields an NADH.

Thiolase

The second notable enzyme of β-oxidation is thiolase because this enzyme not only catalyzes the formation of acetyl-CoAs in **β**-oxidation, but also the joining of two acetyl-CoAs (essentially the reversal of the last step of β-oxidation) to form acetoacetyl-CoA – essential for the pathways of ketone body synthesis and cholesterol biosynthesis.

Similarity to citric acid cycle oxidation

It is worth noting that oxidation of fatty acids is chemically very similar to oxidation of the four carbon compounds of the citric acid cycle (Figure 6.89). In fatty acid oxidation, dehydrogenation between carbons 2 and 3 generates electrons which are donated to FAD to make $FADH_2$ and a *trans*-bonded intermediate is formed.

The same thing happens in the citric acid cycle reaction catalyzed by succinate dehydrogenase - the *trans*-bonded molecule is fumarate. Addition of water in the second step of fatty acid oxidation occurs also in the next step of the citric acid cycle catalyzed by fumarase to create malate. Oxidation of the hydroxyl on carbon 3 in β-oxidation is repeated in the citric acid cycle reaction catalyzed by malate dehydrogenase yielding oxaloacetate.

Oxidation of odd chain fatty acids

Though most fatty acids of biological origin have even numbers of carbons, not all of them do. Oxidation of fatty acids with odd numbers of carbons ultimately produces an intermediate with three carbons called

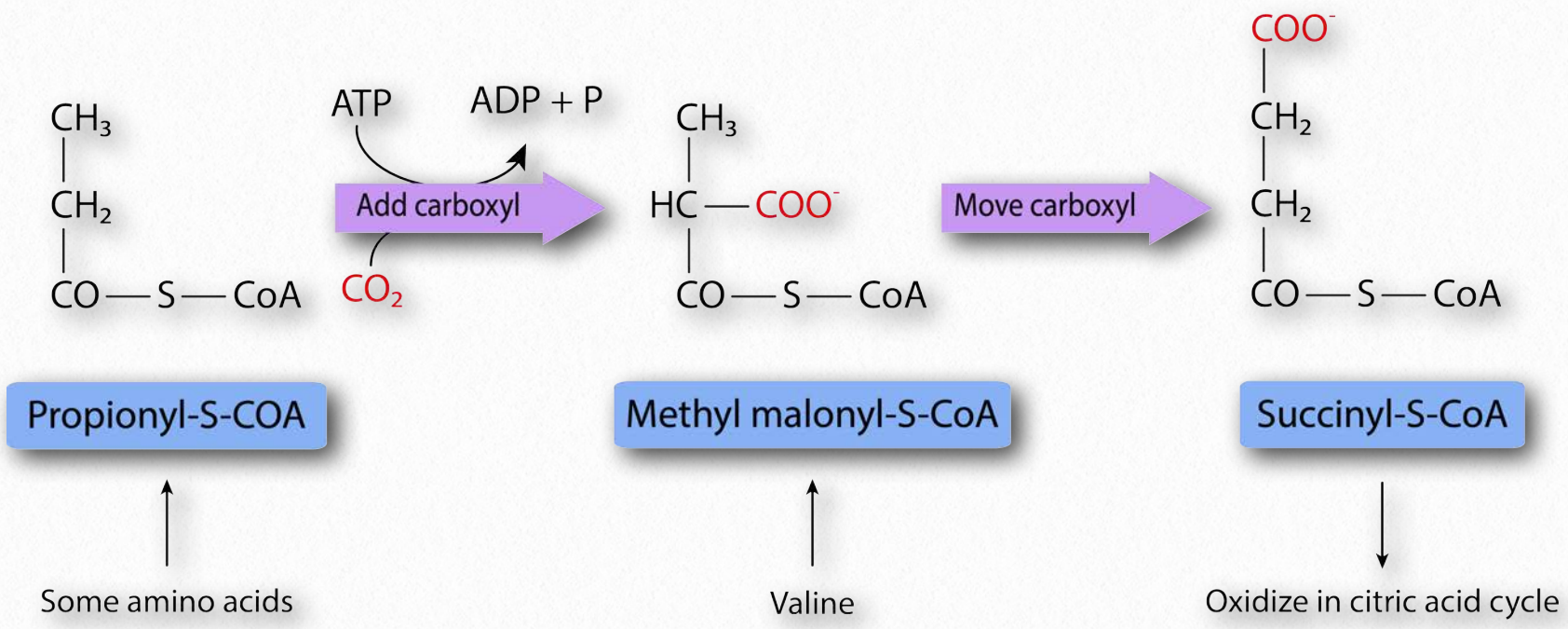

Figure 6.90 - Metabolism of propionyl-CoA

Image by Pehr Jacobson

In beta oxidation, it just occurred to me
The process all takes place 'tween carbons two and three
Some hydrogens are first removed to $FADH_2$
Then water adds across the bond, the H to carbon two
Hydroxyl oxidation's next, a ketone carbon three
Then thiolase catalysis dissects the last two C's
The products of the path, of course, are acetyl-CoAs
Unless there were odd carbons, hence propionyl-CoA

propionyl-CoA, which cannot be oxidized further in the β-oxidation pathway.

Metabolism of this intermediate is odd. Sequentially, the following steps occur (Figure 6.90) – 1) carboxylation to make D-methylmalonyl-CoA; 2) isomerization to L-methylmalonyl-CoA; 3) rearrangement to form succinyl-CoA. The last step of the process utilizes the enzyme methylmalonyl-CoA mutase, which uses the B_{12} coenzyme in its catalytic cycle. Succinyl-CoA can be metabolized in the citric acid cycle.

Peroxisomal oxidation

Long chain fatty acids (typically 22 carbons or more - Figure 6.91) have their oxidation initiated in the peroxisomes, due to the localization of the long acyl-CoA dehydrogenase in that organelle. Peroxisomal fatty acid oxidation is chemically similar to β-oxidation of mitochondria, but there are some differences in the overall process.

Differences

First, since there is no electron transport system in peroxisomes, the reduced electron carriers produced in oxidation there must have their own recycling process. Peroxisomes accomplish this by transferring electrons and protons from $FADH_2$ to O_2 to form hydrogen peroxide (H_2O_2). As a result of this, the lack of electron transport means no proton pump and, consequently, no ATP produced from $FADH_2$ for peroxisomal fatty acid oxidation, making it less efficient that mitochondrial β-oxidation.

Electrons from NADH produced in the third step of the fatty acid oxidation must be shuttled to the cytoplasm and ultimately to the mitochondrion for ATP generation. Peroxisomal oxidation is increased for individuals on a high fat diet. In addition to long chain fatty acids, peroxisomes are also involved in

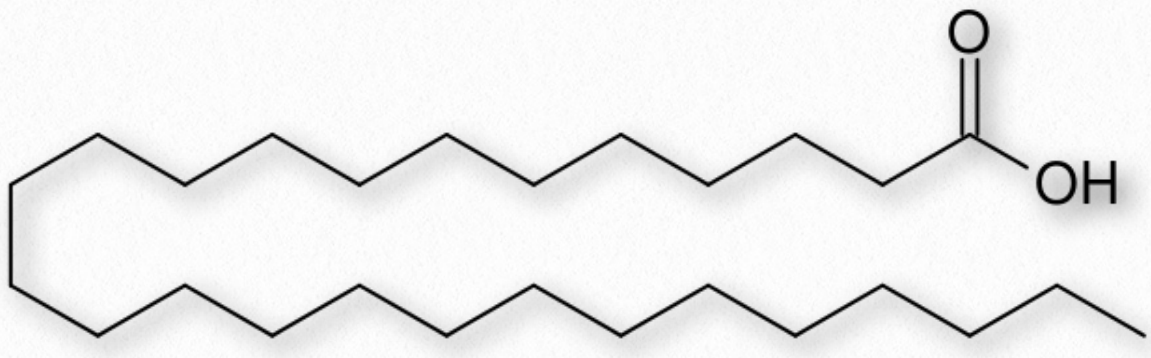

Figure 6.91 - Cerotic acid - A long chain fatty acid with 26 carbons

oxidation of branched chain fatty acids, leukotrienes, and some prostaglandins.

Unsaturated fatty acid oxidation

Unsaturated fatty acids complicate the oxidation process a bit (see below), primarily because they have *cis* bonds, for the most part, if they are of biological origin, and these must be converted to the relevant *trans* intermediates for β-oxidation. Sometimes the bond must be moved down the chain, as well, in order to be positioned properly. Two enzymes (described below) handle all the necessary isomerizations and moves necessary to oxidize all of the unsaturated fatty acids (Figure 6.92).

YouTube Lectures by Kevin
HERE & HERE

Extra enzymes

As noted above, oxidation of unsaturated fatty acids requires two additional enzymes to the complement of enzymes for β-oxidation. If the β-oxidation of the fatty acid produces an intermediate with a *cis* bond between carbons three and four, *cis*-Δ3-enoyl-CoA isomerase will convert the bond to a *trans* bond between carbons two and three and β-oxidation can proceed as normal.

On the other hand, if β-oxidation produces an intermediate with a *cis* double bond between carbons four and five, the first step of β-oxidation (dehydrogenation between car-

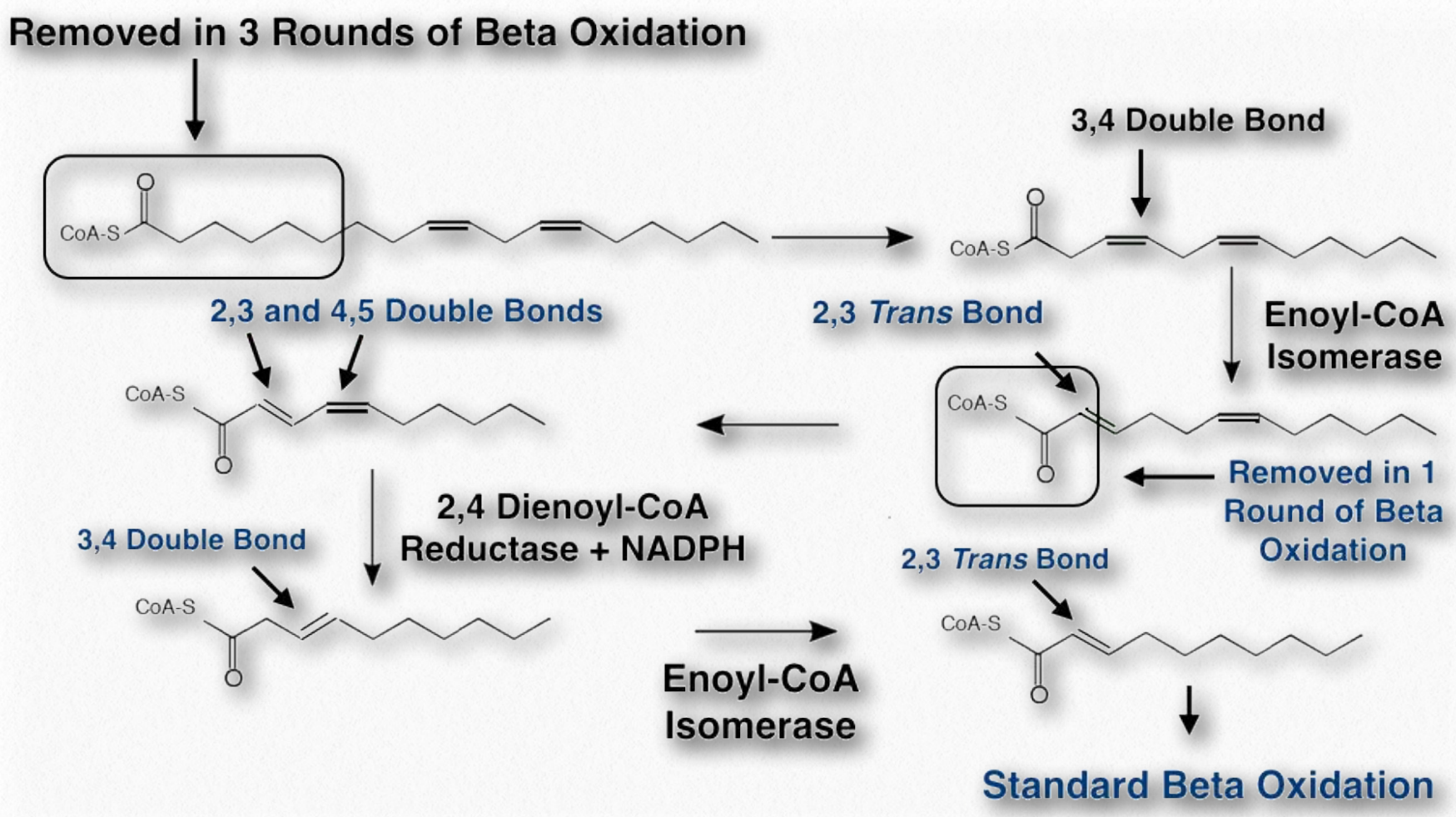

Figure 6.92 - Unsaturated fatty acid oxidation

bons two and three) occurs to produce an intermediate with a *trans* double bond between carbons two and three and a *cis* double bond between carbons four and five.

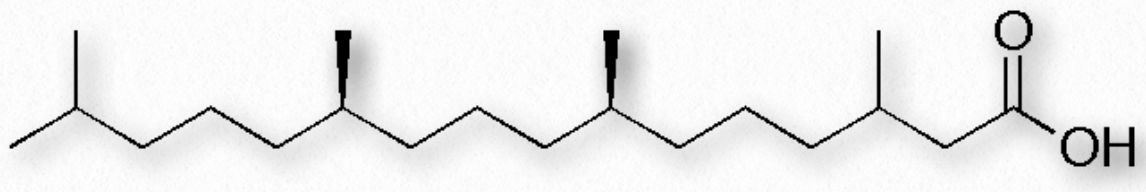

Figure 6.93 - Phytanic acid

2,4 dienoyl-CoA reductase

The enzyme 2,4 dienoyl CoA reductase reduces this intermediate (using NADPH) to one with a single *cis* bond between carbons three and four. The newly created *cis*-bonded molecule is then identical to the one acted on by *cis*-Δ3-enoyl-CoA isomerase above, which converts it into a regular **β**-oxidation intermediate, as noted above.

α-oxidation

Yet another consideration for oxidation of fatty acids is **α**-oxidation. This pathway, which occurs in peroxisomes, is necessary for catabolism of fatty acids that have branches in their chains. For example, breakdown of chlorophyll's phytol group yields phytanic acid (Figure 6.93), which undergoes hydroxylation and oxidation on carbon number two (in contrast to carbon three of β-oxidation), followed by decarboxylation and production of an unbranched intermediate that can be further oxidized by the β-oxidation pathway. Though **α**-oxidation is a relatively minor metabolic pathway, the inability to perform the reactions of the pathway leads to Refsum's disease where accumulation of phytanic acid leads to neurological damage.

ω-oxidation of fatty acids

In addition to **β**-oxidation and **α**-oxidation of fatty acids, which occur in the mitochondria and peroxisomes of eukaryotic cells respectively, another fatty acid oxidation pathway known as **ω**-oxidation also occurs in the smooth endoplasmic reticulum of liver and kidney cells. It is normally a minor oxidation pathway operating on medium chain fatty acids (10-12 carbons), but gains importance 1) when **β**-oxidation is not functional or 2) for production of long chain intermediates, such as 20-HETE (20-hydroxyeicosatetraenoic acid), that can function in signaling.

Steps in the process involve 1) oxidation of the terminal methyl group of the fatty acid to an alcohol; 2) oxidation of the alcohol to an aldehyde, and 3) oxidation of the aldehyde group to a carboxylic acid (Figure 6.94). The first oxidation is catalyzed by a mixed function oxidase, and yields 20-HETE if the starting material is arachidonic acid.

The last two reactions are catalyzed by alcohol dehydrogenase and each requires NAD^+. After the last oxidation, the fatty acid has carboxyl groups at each end and can be attached to coenzyme A at either end and subsequently oxidized, ultimately yielding succinate.

Regulation of fatty acid oxidation

Breakdown of fatty acids is controlled at different levels. The first is by control of the availability of fatty acids from the breakdown of fat. As noted above, this process is by regulating the activity of hormone-sensitive triacylglycerol lipase (HSTL) activity by epinephrine (stimulates) and insulin (inhibits).

A second level of control of fatty acid availability is by regulation of carnitine acyl transferase (Figure 6.87 - see HERE). This enzyme controls the swapping of CoA on an acyl-CoA molecule for carnitine, a necessary step for the fatty acid to be imported into the mitochondrion for oxidation.

The enzyme is inhibited by malonyl-CoA, an intermediate in fatty acid synthesis. Thus, when fatty acids are being synthesized, import of them into the mitochondrion for oxidation is inhibited. Last, the last enzyme in the β-oxidation cycle, thiolase, is inhibited by acetyl-CoA.

Fatty acid synthesis

Synthesis of fatty acids occurs in the cytoplasm and endoplasmic reticulum of the cell and is chemically similar to the reverse of the β-oxidation process, but with a couple of key differences (Figure 6.95). The first of these occur in preparing substrates for the reactions that grow the fatty acid. Fatty acid synthesis occurs in the cytoplasm of eukary-

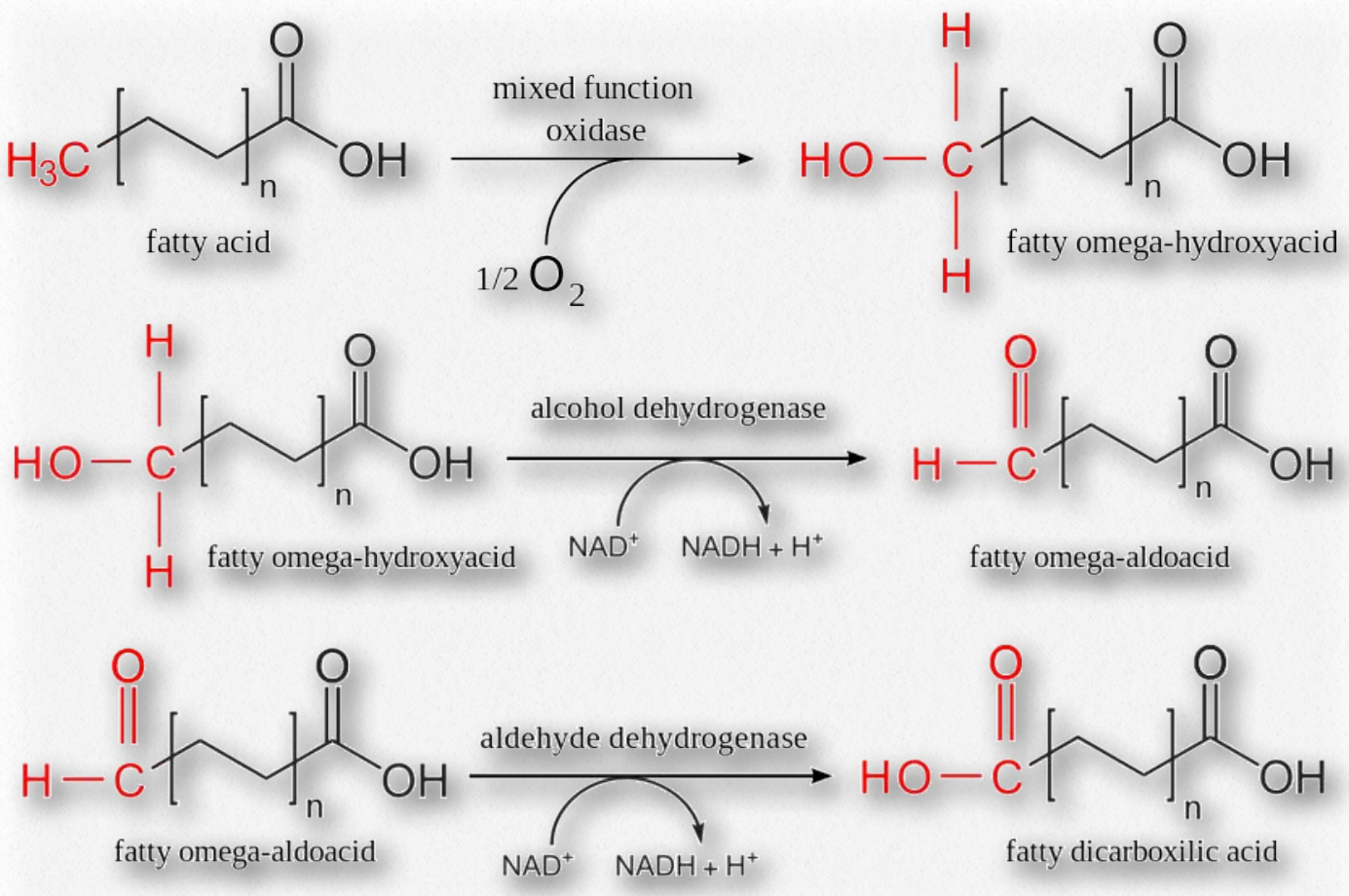

Figure 6.94 - ω Oxidation

Wikipedia

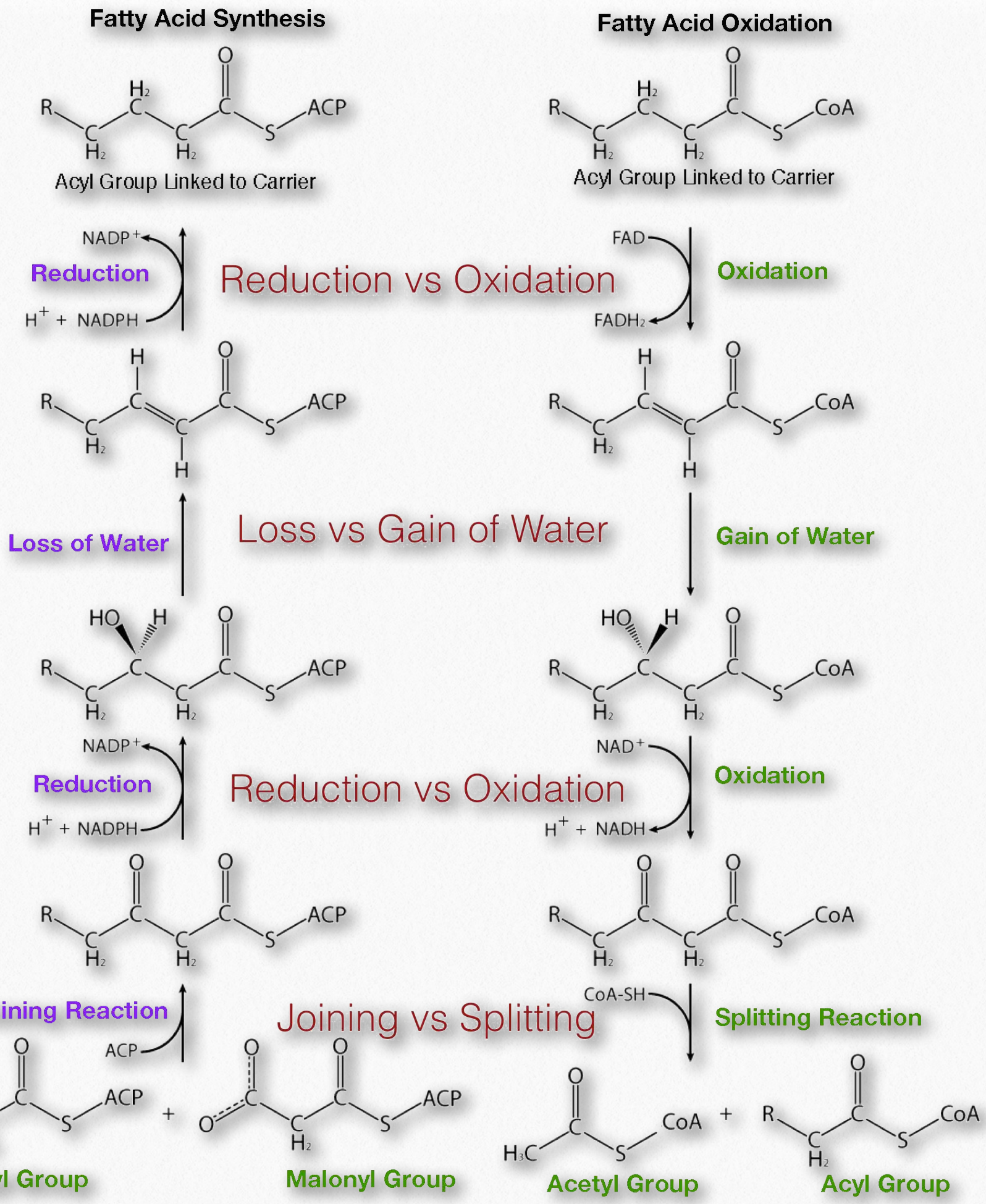

Figure 6.95 - Fatty acid synthesis is the reverse of fatty acid oxidation chemically

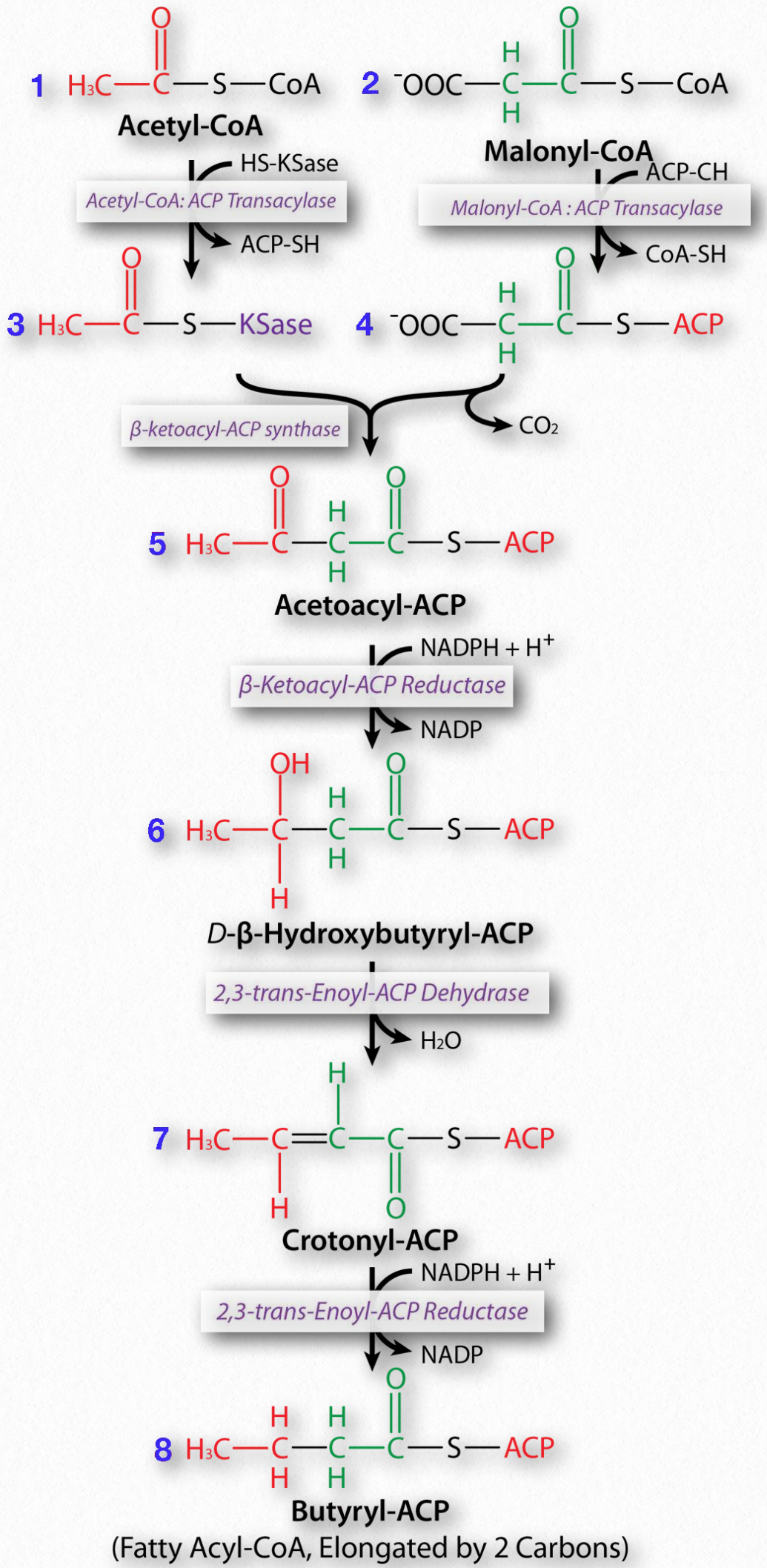

Figure 6.96 - One round of fatty acid synthesis

image by Aleia Kim

otic cells. Transport of acetyl-CoA from the mitochondrial matrix occurs when it begins to build up. This happens when the citric acid cycle slows or stops from lack of exercise.

Two molecules can play roles in moving acetyl-CoA to the cytoplasm – citrate and acetylcarnitine. Joining of oxaloacetate with acetyl-CoA in the mitochondrion creates citrate which gets transported across the membrane, followed by action of citrate lyase in the cytoplasm of the cell to release acetyl-CoA and oxaloacetate. Additionally, when free acetyl-CoA accumulates in the mitochondrion, it may combine with carnitine and be transported out to the cytoplasm.

Fatty acid synthase

In animals, six different catalytic activities necessary to fully make palmitoyl-CoA are contained in a single complex called Fatty Acid Synthase. As shown in Figures 6.96 and 6.97, these include 1) transacylases (MAT) for swapping CoA-SH with ACP-SH on acetyl-CoA and malonyl-CoA; 2) a synthase (KS) to catalyze addition of the two carbon unit from the three carbon malonyl-ACP in the first step of the elongation process; 3) a reductase (KR) to

reduce the ketone; 4) a dehydrase (DH) to catalyze removal of water; 5) a reductase (ER) to reduce the *trans* double bond and 6) a thioesterase (TE) to cleave the finished palmitoyl-CoA into palmitic acid and CoA-SH.

In the middle of the complex is a site for binding the ACP portion of the growing fatty acid chain to hold it as the other part of the fatty acid is rotated into positions around the enzyme complex for each catalysis. In bacteria, these six activities are found on separate enzymes and are not part of a complex.

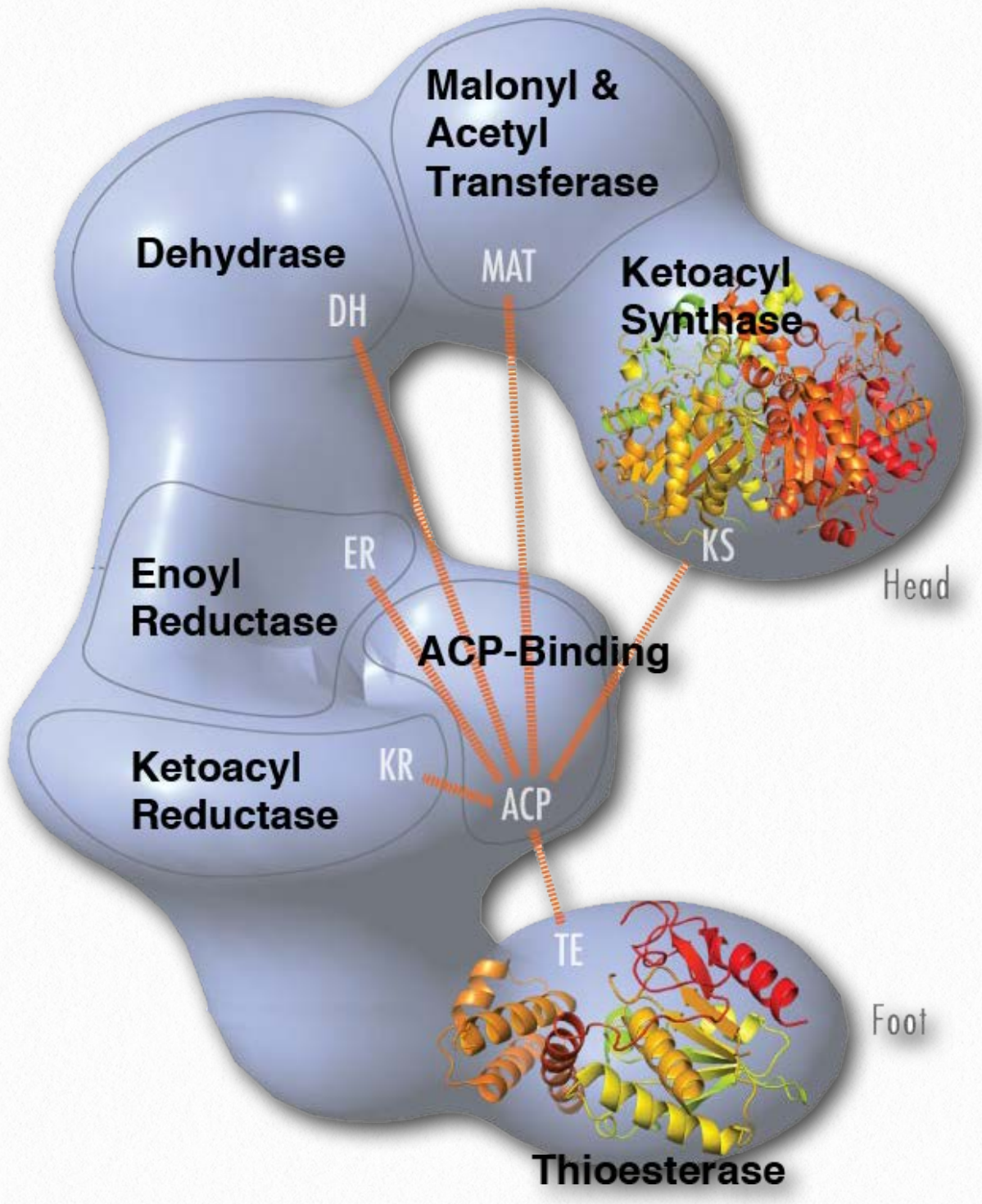

Figure 6.97 - Fatty acid synthase complex

Cytoplasmic reactions

The process of making a fatty acid in the cytoplasm starts with two acetyl-CoA molecules. One is converted to malonyl-CoA by adding a carboxyl group. This reaction is catalyzed by the enzyme acetyl-CoA carboxylase (ACC), the only regulated enzyme of fatty acid synthesis (see below) and the only one separate from the fatty acid synthase. Next, both acetyl-CoA and malonyl-CoA have their CoA portions replaced by a carrier protein known as ACP (acyl-carrier protein) to form acetyl-ACP (catalyzed by acetyl-CoA : ACP transacylase - MAT in Figure 6.97) and malonyl-ACP (catalyzed by malonyl-CoA : ACP transacylase - MAT in Figure 6.97). Joining of a fatty acyl-ACP (in this case, acetyl-ACP) with malonyl-ACP splits out the car-

For fatty acid synthesis, I must reverse the path
Of breaking fatty acids, though you'll wonder 'bout the math

Each cycle of addition starts with carbons one two three
Yet products of reactions number carbons evenly

The reason is that CO_2 plays peek-a-boo like games
By linking to an Ac-CoA then popping off again

Reactions are like oxidations 'cept they're backwards here
Reduction, dehydration, then two hydrogens appear

The product of the process is a 16 carbon chain
The bonds are saturated. No double ones remain

For them desaturases toil to put in links of *cis*
In animals to delta nine, but no more go past this

And last there's making longer ones eicosanoidic fun
They're made by elongases in the *e. reticulum*

Kevin Ahern

boxyl group from malonyl-ACP that was added to it and creates the acetoacyl-ACP intermediate (catalyzed by **β**-ketoacyl-ACP synthase - KS on Figure 6.97) .

From this point forward, the chemical reactions resemble those of β-oxidation reversed. First, the ketone is reduced to a hydroxyl using NADPH (catalyzed by **β**-ketoacyl-ACP reductase - KR on Figure 6.97). In contrast to the hydroxylated intermediate of **β**-oxidation, the intermediate here (D-β- hydroxybutyryl-ACP) is in the D-configuration.

Dehydration

Next, water is removed from carbons 2 and 3 of the hydroxyl intermediate in a reaction catalyzed by 2,3-*trans*-enoyl-ACP dehydrase - DH on Figure 6.97. This yields a *trans* doubled-bonded molecule. Last, the double bond is hydrogenated to yield a saturated intermediate by 2,3-trans-enoyl-ACP reductase - ER on Figure 6.97. This completes the first cycle of synthesis.

Additional cycles involve addition of more two-carbon units from malonyl-ACP to the growing chain until ultimately an intermediate with 16 carbons is produced (palmitoyl-ACP). At this point, a thioesterase cleaves the ACP from the palmitoyl-ACP to yield palmitic acid and the cytoplasmic synthesis ceases.

Regulation of fatty acid synthesis

Acetyl-CoA carboxylase, which catalyzes synthesis of malonyl-CoA, is the only regulated enzyme in fatty acid synthesis. Its regulation involves both allosteric control and covalent modification. The enzyme is known to be phosphorylated

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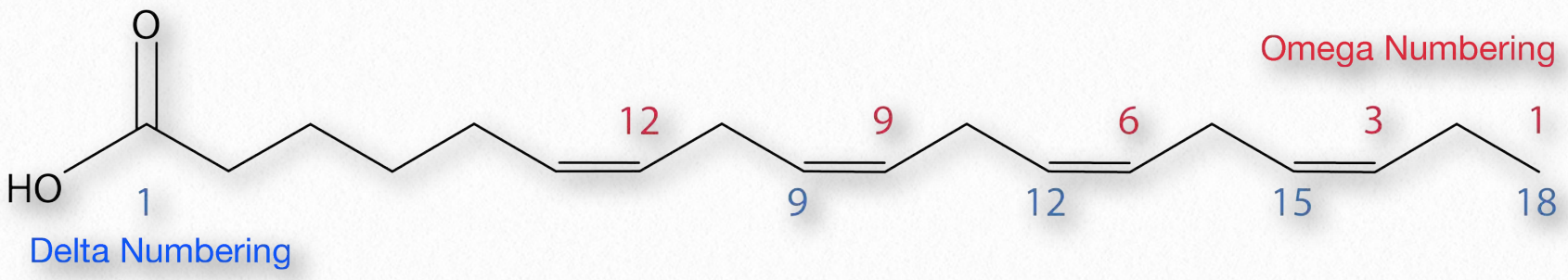


Figure 6.98 - Carbon numbering schemes for fatty acids

Image by Pehr Jacobson

by both AMP Kinase and Protein Kinase A.

Dephosphorylation is stimulated by phosphatases activated by insulin binding. Dephosphorylation activates the enzyme and favors its assembly into a long polymer, while phosphorylation reverses the process. Citrate acts as an allosteric activator and may also favor polymerization. Palmitoyl-CoA allosterically inactivates it.

Elongation past 16 carbons

Elongation to make fatty acids longer than 16 carbons occurs in the endoplasmic reticulum and is catalyzed by enzymes described as elongases. Mitochondria also can elongate fatty acids, but their starting materials are generally longer than 16 carbons long.

The mechanisms in both environments are similar to those in the cytoplasm (a malonyl group is used to add two carbons, for example), but CoA is attached to the intermediates, not ACP. Further, whereas cytoplasmic synthesis employs the fatty acid synthase complex, the enzymes in these organelles are separable and not part of a complex.

Desaturation of fatty acids

Fatty acids are synthesized in the saturated form and desaturation occurs later - in the endoplasmic reticulum. Reactions to elongate the fatty acid (with elongases) may also occur to make unsaturated fatty acids of varying lengths. Desaturases are named according to the location of the double bonds they introduce in fatty acids. The delta (Δ) system numbers the carbon at the carboxyl end as number 1 and the omega (ω) number system numbers the carbon at the methyl end as number 1 (Figure 6.98). Humans have desaturases named as Δ5, Δ6, and Δ9. A Δ9 desaturase, for example, could convert stearic acid into oleic acid, because stearic acid (see HERE) is a saturated 18 carbon fatty acid and oleic acid is an 18 carbon fatty acid with only one double bond - at position Δ9.

Polyunsaturated fatty acids

Polyunsaturated fatty acids require the action of multiple enzymes and (in some cases)

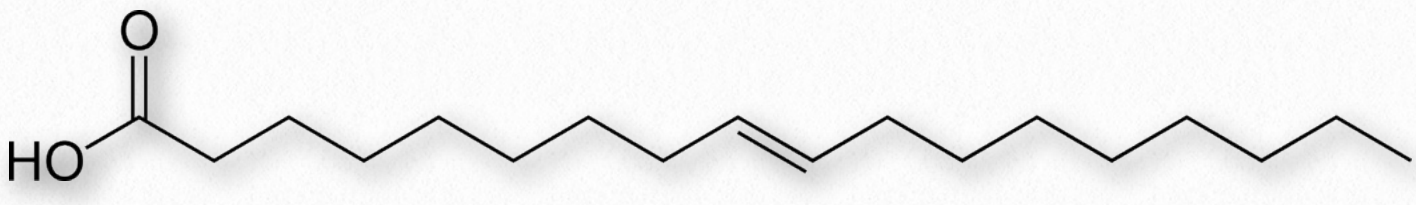


Figure 6.99 - Elaidic acid - A rare *trans* fatty acid in biology

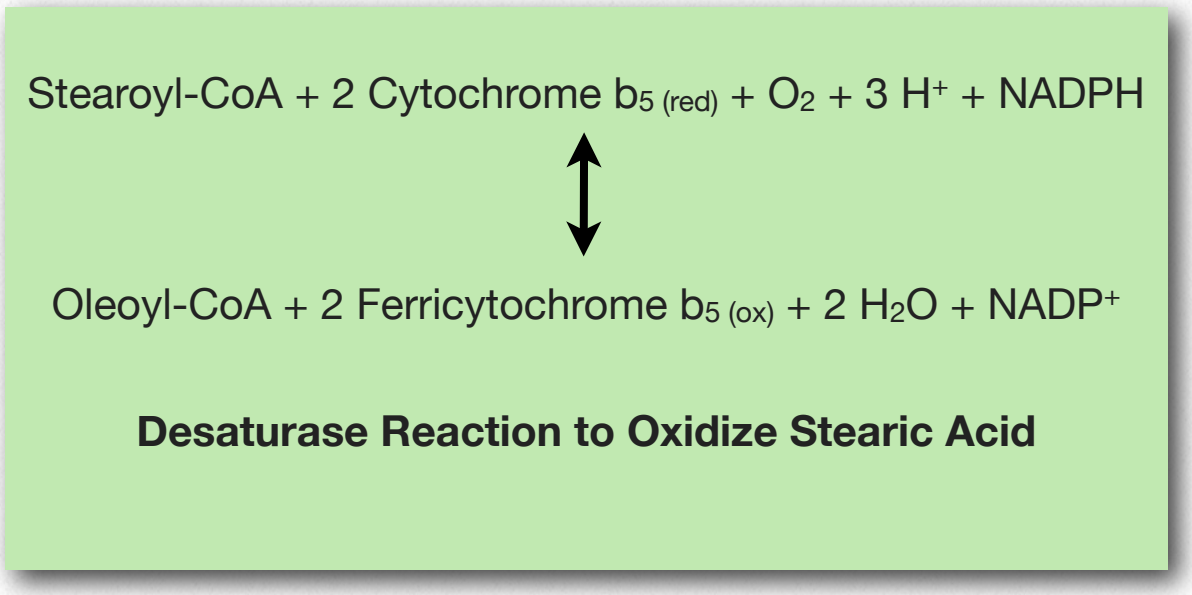
the action of elongases. Arachidonic acid, for example, is a 20 carbon fatty acid with four double bonds and its synthesis requires both an elongase (to increase the length of the fatty acid from 16 to 20) and multiple desaturases - one for each desaturated double bond.

Animals are limited in the fatty acids they can make, due to an inability of their desaturases to catalyze reactions beyond carbons Δ9. Thus, humans can make oleic acid, but cannot synthesize linoleic acid (Δ9,12) or linolenic acid (Δ9,12,15). Consequently, these two must be provided in the diet and are referred to as essential fatty acids.

Almost all desaturases make *cis*, not *trans* double bonds. There are a few minor exceptions to this, in cattle, for example (Figure 6.99). The *trans* fatty acids found in *trans* fat of prepared food are produced not by biological processes, but rather by the process of partial hydrogenation of unsaturated fats.

Unusual oxidation reaction

Removal of electrons and protons from a fatty acid to create a double bond is an oxidation reaction and these electrons, must have a destination. The path they take is a bit complex. It involves NAD(P)H, O_2, two membrane-bound cytochromes, the membrane bound desaturase, and the fatty acid.



Desaturase Reaction to Oxidize Stearic Acid

In the electron transfer, the O_2 is reduced to two molecules of H_2O. This reduction requires four electrons and four protons. Two electrons and two protons come from the fatty acid to form the double bond on it. Two electrons come from the NAD(P)H via the cytochromes and two protons come from the aqueous solution.

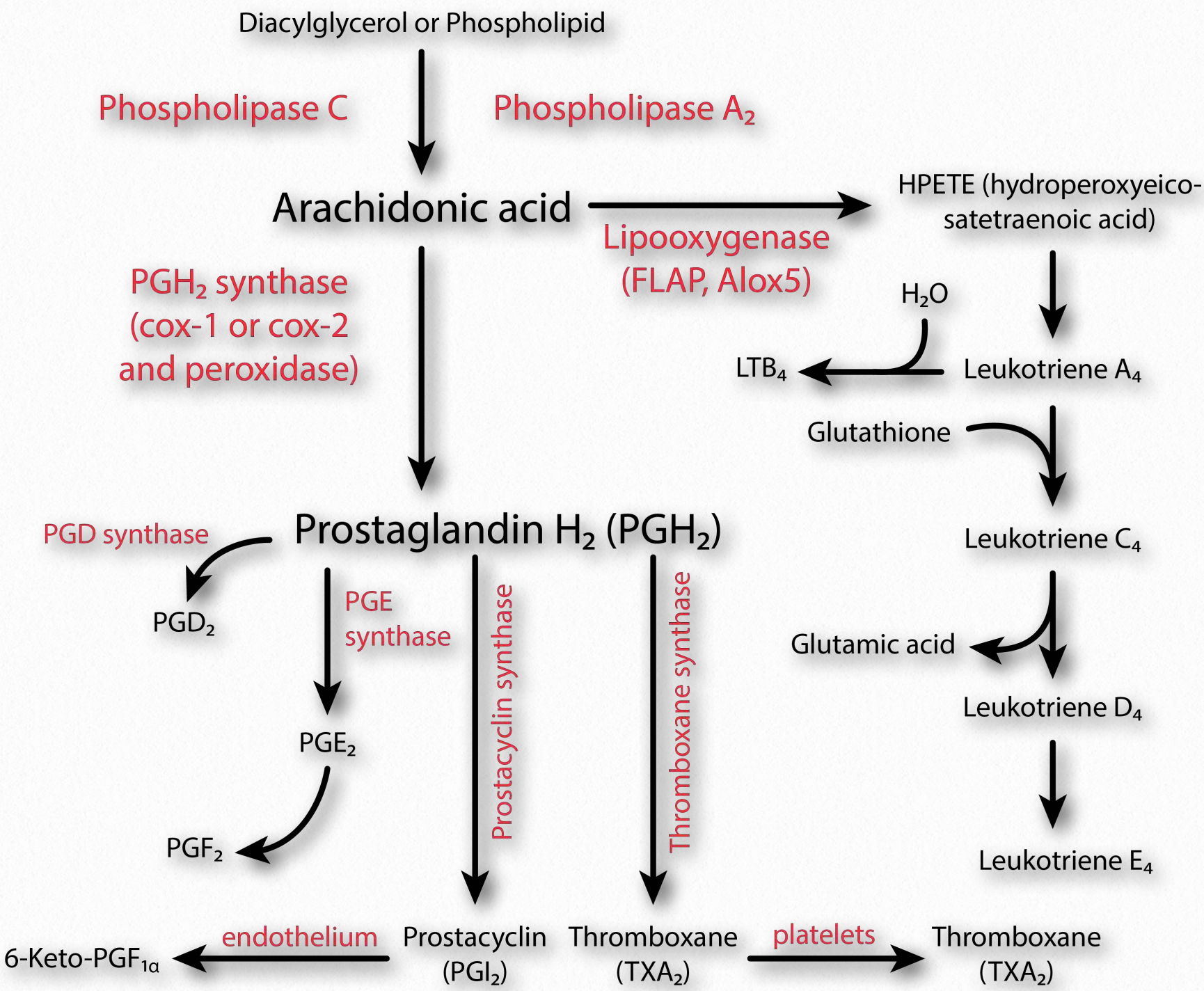


Figure 6.100 - Eicosanoid synthesis pathways

Image by Pehr Jacobson

Prostaglandin synthesis

The pathway for making prostaglandins and related molecules, such as the leukotrienes, prostacyclin, and thromboxanes is an extension of the synthesis of fatty acids (Figure 6.100).

Prostaglandins, known as eicosanoids because they contain 20 carbons, are synthesized in cells from arachidonic acid whenever it has been cleaved from membrane lipids. Prostaglandins are important for many physiological phenomena in the body, including swelling and pain and reduction of their levels is a strategy of some painkillers, such as aspirin (see below). Inflammation arising from bee stings, for example, occurs because bee (and snake) venom contains mellitin, an activator of PLA2 activity (Figure 6.100). There are two strategies for reducing prosta-

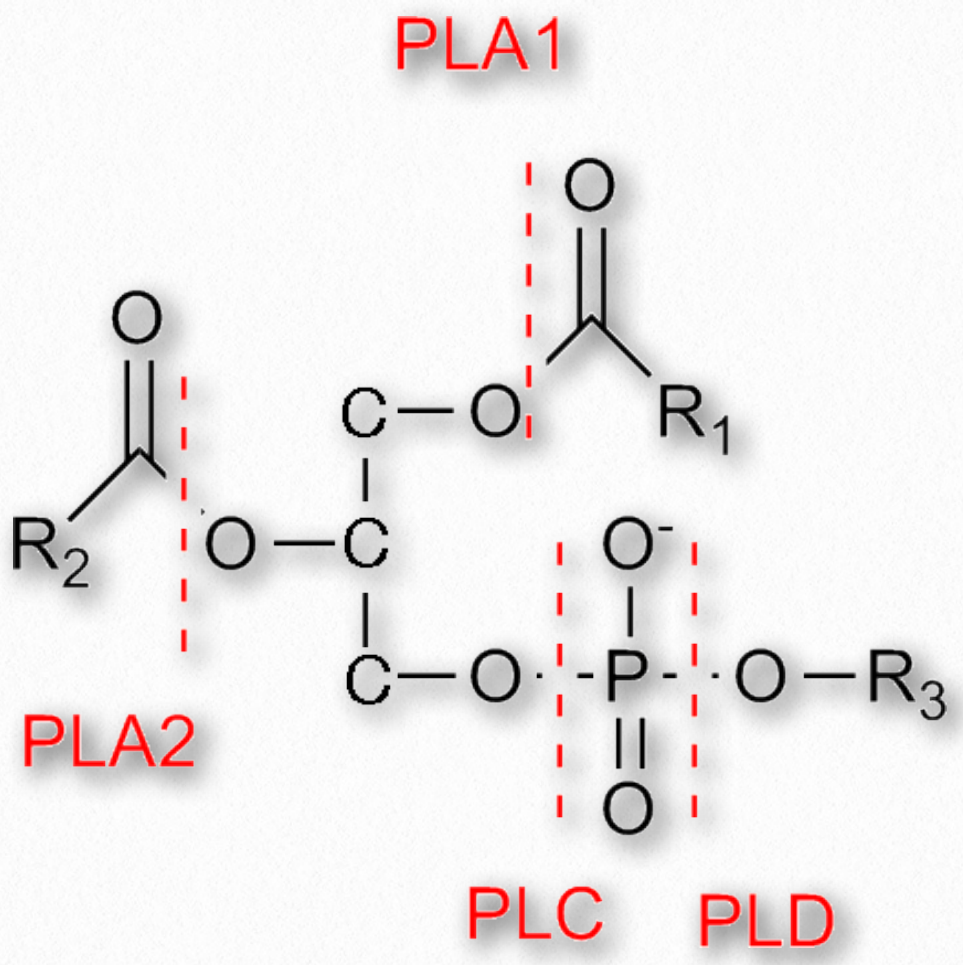


Figure 6.101 - Cleavage sites for four phospholipiases on a glycerophospholipid - phospholipases A_1 (PLA1), A_2 (PLA2), C (PLC), and D (PLD)

glandin production and the pain associated with it.

Phospholipase A_2

Action of phospholipase enzymes on glycerophospholipids produces fatty acids and either glycerol-3-phosphate or other substances. Figure 6.101 shows cleavage sites on phospholipids that are targeted by different phospholipases. Phospholipase A_1 (PLA1), for example, cleaves the fatty acid from position one of the glycerophospholipid and phospholipiase D (PLD) cleaves the R group from the phosphate part of the molecule.

Since the fatty acid on position #2 (where PLA_2 cuts) is most commonly unsaturated, PLA_2 is an important phosopholipase for hydrolyzing the unsaturated fatty acid known as arachidonic acid from glycerophospholipids. Release of arachidonic acid from membranes is necessary for synthesis of prostaglandins.

Inhibition of the release of arachidonic acid from membranes is the mechanism of action of steroidal anti-inflammatory drugs. They block action of phospholipase A_2 (PLA2 - Figure 6.101) which cleaves arachidonic acid from membrane lipids.

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Lipocortin

Lipocortin (also called annexin) is a protein that inhibits action of PLA2. Synthesis of lipocortin is stimulated by glucocorticoid hormones, such as cortisol, and is used in some treatments to reduce swelling/inflammation when it is severe and untreatable by non-steroidal drugs.

Second strategy

Synthesis of the prostanoid compounds (prostaglandins, prostacyclin, and thromboxanes) depends on conversion of arachi-

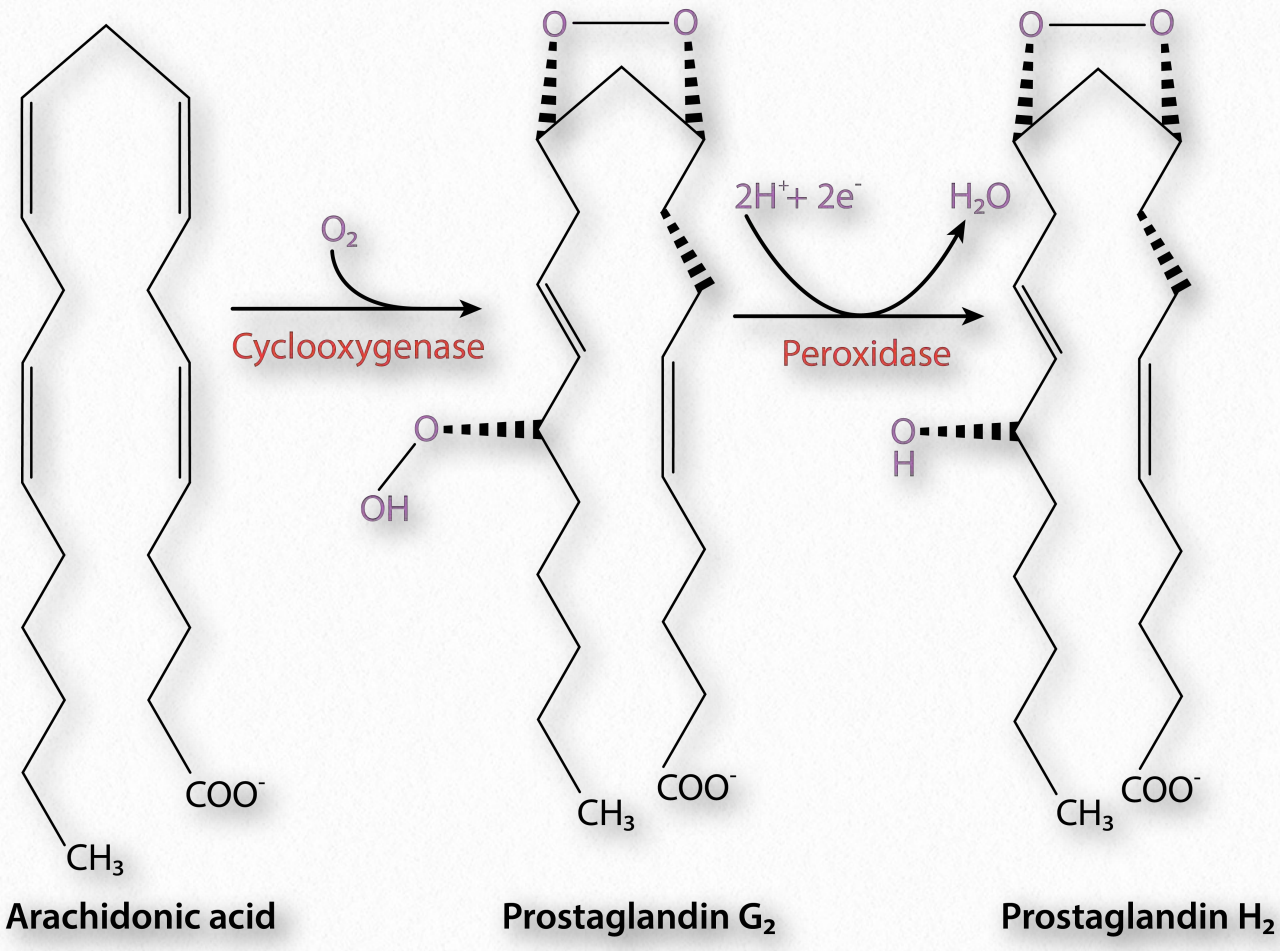


Figure 6.102 - Catalytic activity of cyclooxygenase and peroxidase in making prostaglandins

Image by Pehr Jacobson

donic acid to prostaglandins G_2 and H_2 by COX enzymes. A non-steroidal strategy for decreasing production of prostaglandins then is to inhibit the enzyme that catalyzes their synthesis from arachidonic acid (Figure 6.102). This enzyme is known as prostaglandin synthase, but is more commonly referred to as a cyclooxygenase (or COX) enzyme.

COX enzymes come in at least two forms in humans - COX-1, COX-2. A third form known as COX-3 has been reported as a splice variant of COX-1, but information about it is unclear. COX-1 and COX-2 are very similar in structure (70 kD and 72 kD, respectively, and 65% amino acid sequence homology), but coded by different genes.

COX-1 is synthesized constitutively whereas COX-2 displays inducible expression behavior and has a more specific pattern of tissue expression. COX-2 enzymes are expressed in increasing amounts in areas of growth and inflammation.

Non-steroidal drugs

Molecules inhibiting cyclooxygenases are known as non-steroidal anti-inflammatory drugs (NSAIDs). Molecules in this class include aspirin, ibuprofen, vioxx, and celebrex.

Targeting inhibitors

Some NSAID inhibitors, such as aspirin, bind to all types of COX enzymes. Newer COX inhibitors target the COX-2 enzyme specifically because it was believed to be a better target for relief of joint pain than COX-1 enzymes which are synthesized by most cells. COX-2 enzymes are found more specifically in joints so the thinking was that specific inhibition of them would not affect the COX-1 enzymes

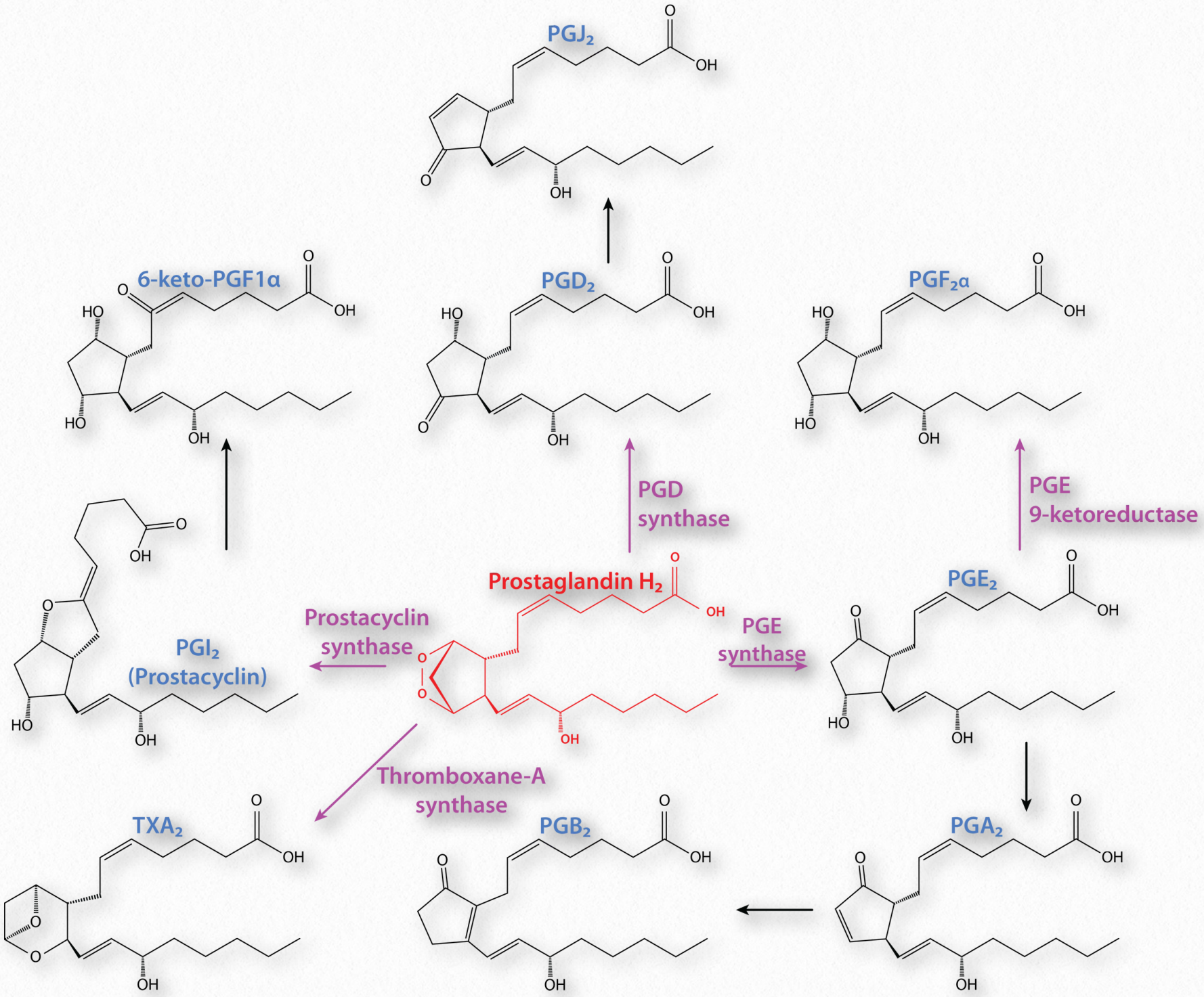


Figure 6.103 - Synthesis of prostaglandins from prostaglandin H_2 (red)

Image by Pehr Jacobson

which are important for producing prostaglandins that help maintain gastric tissue.

Numerous COX-2 - specific inhibitors were developed - celecoxib, etoricoxib, and rofecoxib (Vioxx), for example. Unfortunately, the COX-2 specific inhibitors are associated with some serious side effects, including a 37% increase in incidence of major cardiovascular events in addition to some of the gastrointestinal problems of NSAIDs.

Imbalance

The increased risk of heart attack, thrombosis, and stroke are apparently due to an imbalance between prostacyclin (reduced by inhibitors) and thromboxanes (not reduced by the inhibitors). Prostacyclin (made from

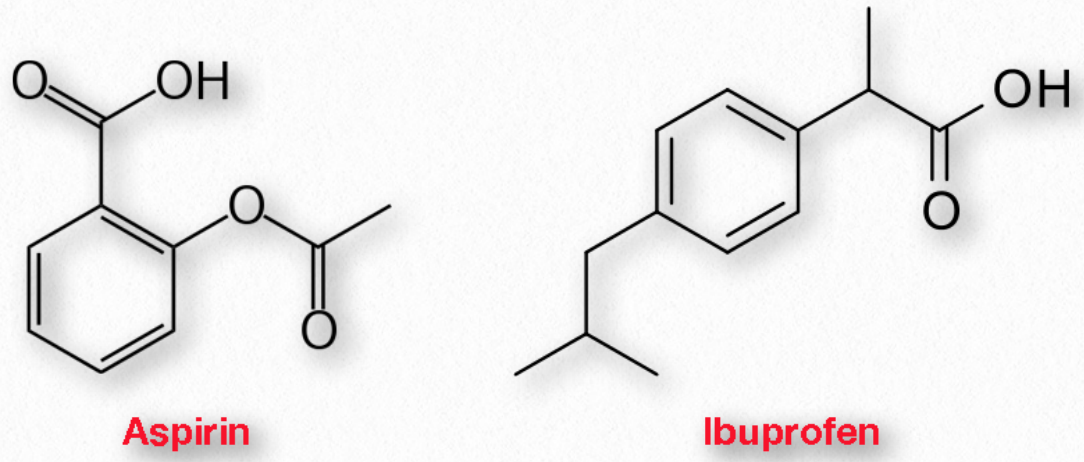


Figure 6.104 - Two NSAIDs

prostaglandin H_2 by prostacyclin synthase) is a special prostaglandin that inhibits activation of blood platelets in the blood clotting process and acts as a vasodilator. Thromboxanes counter prostacyclin, causing vasoconstriction and activating blood platelets for clotting. Due to imbalances in these opposite acting molecules resulting from COX-2-specific inhibition, Vioxx, was withdrawn from the market in September, 2004, due to health concerns.

Other compounds known to inhibit COX enzymes include some flavonoids, some components of fish oil, hyperforin, and vitamin D.

Connections to other pathways

There are several connections between fats and fatty acid metabolism and other metabolic pathways. Diacylglycerol (DAG - Figure 6.105), which is produced by removal of a phosphate from phosphatidic acid, is an intermediate in fat synthesis and also a messenger in some signaling systems. Phosphatidic acid, of course, is a branch intermediate in the synthesis of triacylglycerols and other lipids, including phosphoglycerides.

Fatty acids twenty carbons long based on arachidonic acid (also called eicosanoids) are precursors of the leukotrienes, prostaglandins, thromboxanes, and endocannabinoids.

Acetyl-CoA from β-oxidation can be assembled by the enzyme thiolase to make acetoacetyl-CoA, which is a precursor of both ketone bodies and the isoprenoids, a broad category of compounds that include steroid hormones, cholesterol, bile acids, and the fat soluble vitamins. In plants, acetyl-CoA can be made into carbohy-

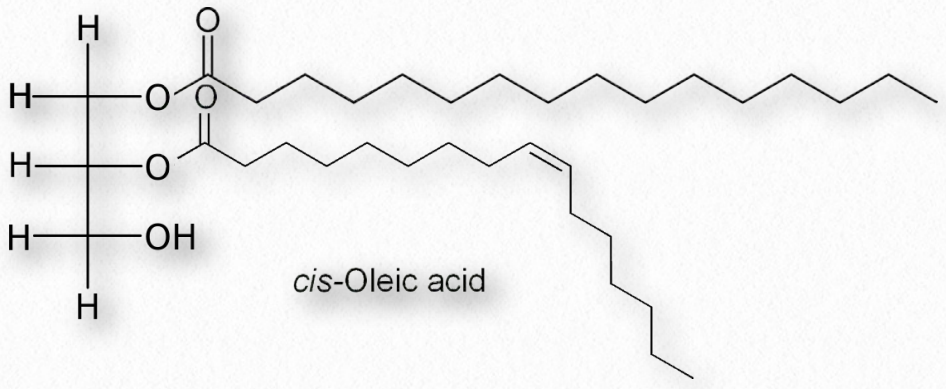


Figure 6.105 - Diacylglycerol

drates in net amounts via the glyoxylate cycle.

Fat, obesity, and hunger

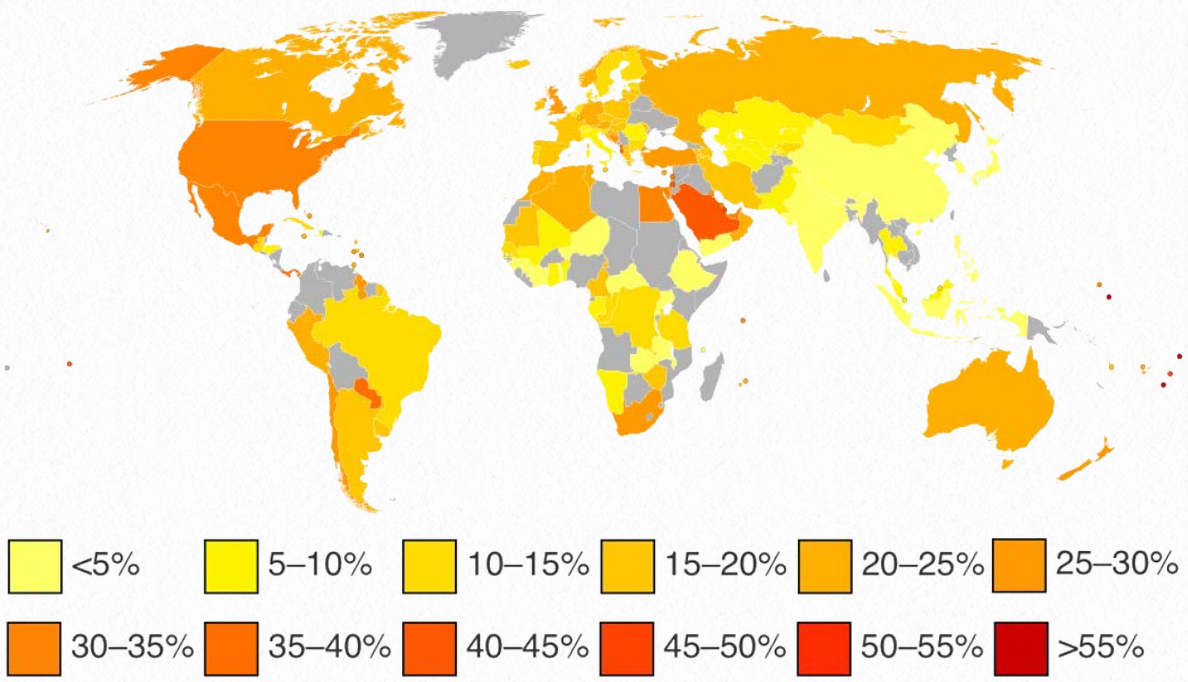
Obesity is an increasing problem in the western world. It is, in fact, the leading preventable cause of death worldwide. In 2014, over 600 million adults and 42 million children in the world were classified as obese, a condition when their body mass index is over 30 kg/m^2 (Figure 6.106). The body mass index of a person is obtained by dividing a person's weight by the square of their height. At a simple level, obesity arises from consumption of calories in excess of metabolic need, but there are many molecular factors to consider.

Adipokines

Adipokines are adipose tissue-synthesized cytokines. The class of molecules includes leptin (first discovered adipokine) and hundreds of other such compounds. These include adiponectin (regulates glucose levels and fatty acid oxidation), apelin (control of blood pressure, angiogenesis promotion, vasodilator release, increased water intake), chemerin (stimulation of lipolysis, adipocyte differentiation, link to insulin resistance), and resistin (links to obesity, type II diabetes, LDL production in liver), among others.

Resistin

Resistin is an adipokine peptide hormone with numerous associated negative health effects. Injection of the hormone into



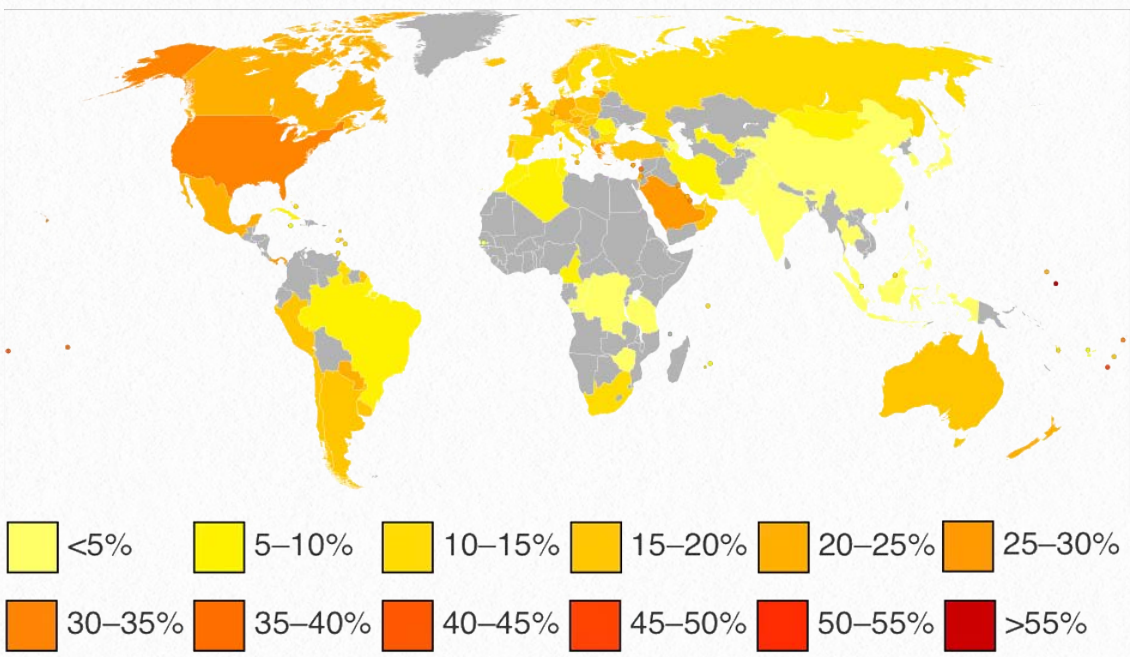


Figure 6.106 - Obesity worldwide - females (top) and males (bottom)

Wikipedia

mice results in increased resistance to insulin, a phenomenon of type 2 diabetes.

Resistin is linked to increased inflammation and serum levels of it correlate with increased obesity, though direct linkage of it to obesity is controversial. Resistin stimulates production of LDLs in the liver, supporting increased levels in the arteries. Resistin also adversely impacts the effects of statin drugs used to control levels of cholesterol in the body.

YouTube Lectures by Kevin HERE & HERE

Leptin

Leptin is a peptide hormone (adipokine) made in adipose cells that negatively impacts hunger and regulates energy balance. It is countered by ghrelin, also known as the hunger hormone. Both hormones act in the hypothalamus where hunger is controlled. When leptin levels are higher due to higher levels of body fat, hunger is suppressed, but when levels of leptin are lower (less body fat), then appetite increases.

Notably, leptin is also made in places besides adipose tissue and leptin receptors are found in places besides the hypothalamus, so the hormone has other effects in the body. When sensitivity to leptin changes, increased obesity can result. In mice, deletion of leptin function by mutation results in mice with voracious appetites and extreme obesity. Deletion of the leptin receptor gene in mice results in the same phenotype. Eight humans with leptin mutations all suffer from extreme obesity in infancy.

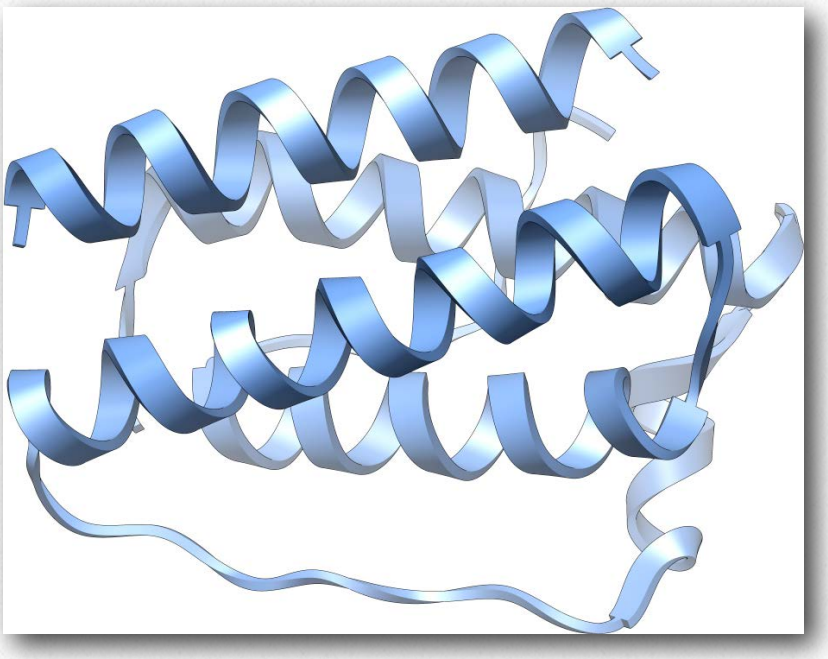


Figure 6.107 Leptin

Wikipedia

Physiology

Leptin is produced primarily by cells in white adipose tissue, but is also made in brown adipose tissue, ovaries, skeletal muscle, stomach, mammary epithelial cells and bone marrow.

Leptin levels

Leptin levels in the body are highest between midnight and early morning, presumably to suppress appetite. Though it is produced by fat cells, levels of leptin in humans do not strictly reflect levels of fat. For example, early in fasting, leptin levels fall before fat levels fall. Sleep deprivation can reduce leptin levels, as can increasing levels of testosterone and physical exercise.

Increasing estrogen, however, increases leptin levels. Emotional stress and insulin can increase leptin levels. Obesity increases leptin levels, but doesn't fully suppress appetite. Leptin resistance in these individuals is an important consideration, lessening the effects of the hormone on appetite.

Blocking leptin action

In the medial hypothalamus, leptin stimulates satiety and in the lateral hypothalamus, leptin inhibits hunger. Lesions in the lateral hypothalamus that block the ability to sense hunger result in anorexia (there are other causes of anorexia, though) and lesions in the medial hypothalamus cause excess hunger (no satiety). Neuropeptide Y is a potent hunger promoter whose receptors in the arcuate nucleus can be bound and blocked by leptin. Leptin levels are more sensitive to decreasing food intake than increasing food intake meaning that in humans the hormone plays a bigger role with respect to appetite than to levels of fat in the body.

At the molecular level, binding of leptin to the Ob-Rb receptor causes down-regulation of synthesis of endocannabinoids, whose normal function is to increase hunger. High fructose diets have been associated with reduced levels of leptin and of leptin receptor.

Ghrelin

Ghrelin is a peptide hormone made by cells in the gastrointestinal tract when the stomach is empty. Stretching of the stomach reduces the expression of the hormone. Ghrelin exerts its effects on the central nervous system to increase appetite and it is an unusual peptide in being able to cross the blood-brain barrier. The ghrelin receptor in the brain is found on the same cells as the leptin receptor (arcuate nucleus). Leptin can counter the ghrelin effect by decreasing hunger.

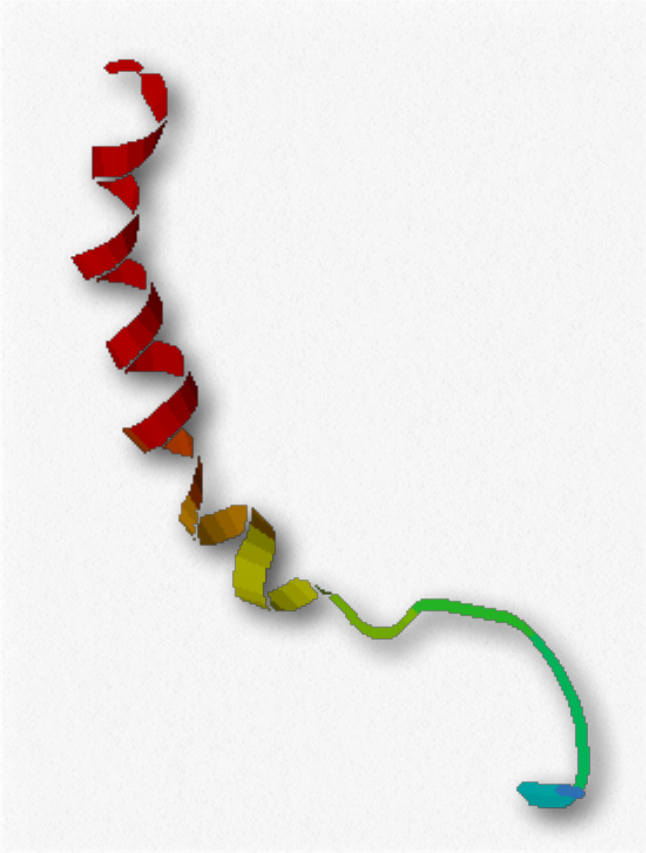


Figure 6.108 **Neuropeptide Y**

Behavioral effects

Activation of ghrelin occurs after processing the zymogen form of the hormone (preproghrelin) followed by linkage of an octanoic acid to a serine at position 3. Circulating levels of ghrelin increase before eating and decrease afterwards. There appears to be a

dose dependence for ghrelin on the amount of food consumed. Ghrelin increases food seeking behavior and there is a negative correlation between levels of ghrelin and weight.

Neuropeptide Y

Neuropeptide Y is a neuropeptide neurotransmitter produced by neurons of the sympathetic nervous system. It acts as a vasoconstrictor and favors growth of fat tissue. It appears to stimulate food intake, fat storage, relieve anxiety/stress, reduce pain perception, and lower blood pressure. Blockage of neuropeptide Y receptors in the brain of rats decreases food intake.

Stress effects

In mice and monkeys, repeated stress and high fat, high sugar diets stimulate neuropeptide Y levels and cause abdominal fat to increase.

High levels of neuropeptide Y may also help individuals to recover from post-traumatic stress disorder and to reduce the fear response. It may also protect against alcoholism. Mice lacking the ability to make neuropeptide Y have a higher voluntary consumption of alcohol and are less sensitive to its effects. The neuropeptide Y receptor is a G-protein-coupled receptor in the 7-transmembrane domain family.

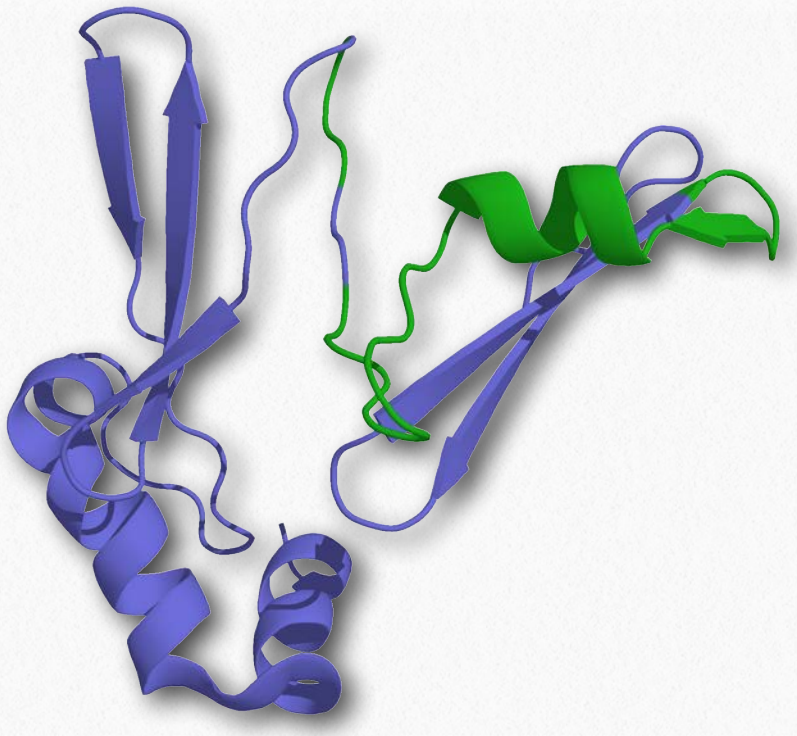


Figure 6.109 - Pre-proghrelin

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When Acids Get Oxidized

To the tune of "*When Johnny Comes Marching Home*"

Metabolic Melodies Website HERE

The fatty acids carried by
CoA, CoA
Are oxidized inside the
mi-to-chon-dri-ay

They get to there as you have seen
By hitching rides on carnitine
Then it goes away
When acids get oxidized

Electrons move through membranes, yes
It's true, it's true
They jump from complex I onto
Co-Q, Co-Q

The action can be quite intense
When building proton gradients
And its good for you
When acids get oxidized

The protons pass through complex V
You see, you see
They do this to make lots of
A-TP, TP

The mechanism you should know
Goes through the stages L-T-O
So there's energy
When acids get oxidized

Recording by Tim Karplus
Lyrics by Kevin Ahern

When Acids Are Synthesized

To the tune of "*When Johnny Comes Marching Home*"

Metabolic Melodies Website HERE

The 16 carbon fatty acid, palmitate
Gets all the carbons that it needs from acetate
Which citric acid helps release
From mitochondri - matrices
Oh a shuttle's great
When acids are synthesized

Carboxylase takes substrate and it puts within
Dioxy carbon carried on a biotin
CoA's all gain a quick release
Replaced by larger ACPs
And it all begins
When acids are synthesized

A malonate contributes to the growing chain
Two carbons seven times around again, again
For saturated acyl-ates
There's lots of N-A-DPH
That you must obtain
When acids are synthesized

Palmitic acid made this way all gets released
Desaturases act to make omega-threes
The finished products big and small
Form esters with a glycerol
So you get obese
When acids are synthesized

Recording by Tim Karplus
Lyrics by Kevin Ahern

Metabolism: Other Lipids

Sugars are the building blocks of carbohydrates, amino acids are the building blocks of proteins and nucleotides are the building blocks of the nucleic acids - DNA and RNA. Another crucial building block is acetyl-CoA, which is used to build many lipid substances, including fatty acids, cholesterol, fat soluble vitamins, steroid hormones, prostaglandins, endocannabinoids, and the bile acids. Indeed, acetyl-CoA goes into more different classes of molecule than any other building block.

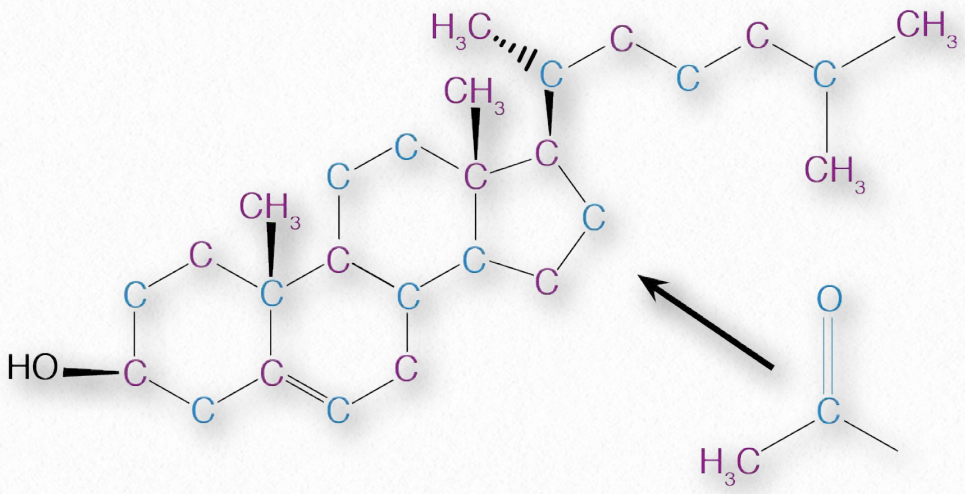


Figure 6.110 - Acetyl-CoA's carbons mapped onto cholesterol

Image by Penelope Irving

Mevalonate pathway

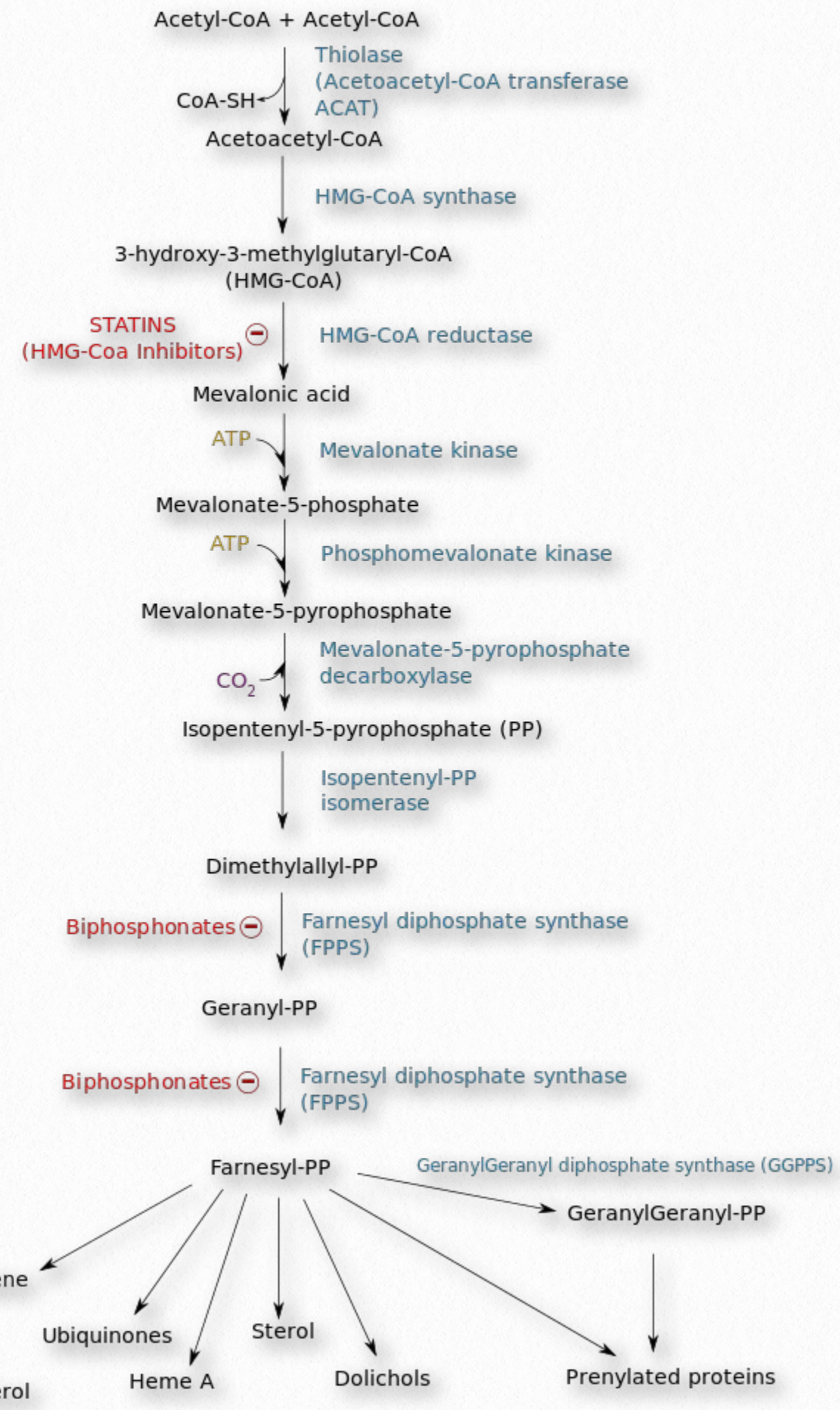


Figure 6.111 - Synthesis of isoprenoids from acetyl-CoA

Isoprenoids

We focus our attention here on a group of molecules made from acetyl-CoA that are known as as the isoprenoids. Isoprenoids are a large, diverse and ancient group of molecules that are found in all three domains of life. As noted earlier, they are components of membrane lipids in the cell membranes of archaebacteria, but beyond this, they serve an astonishing variety of functions. From photosynthetic pigments to plant defense compounds, from flavor compounds in cinnamon, mint, ginger and cloves to plant and animal hormones, from the cannabinoids in marijuana to the lycopene that gives tomatoes their color, and from heme to the quinones in the electron transport chain, isoprenoids are ubiquitous in cells. Isoprenoids derive their name from the fact that they are, in fact, made from five carbon building blocks called isoprenes that are derived from acetyl-CoA. The synthesis of the two isoprene units - isopentenyl pyrophosphate and dimethylallyl pyrophosphate is shown in Figure 6.111 and Figure 6.112.

YouTube Lectures by Kevin HERE & HERE

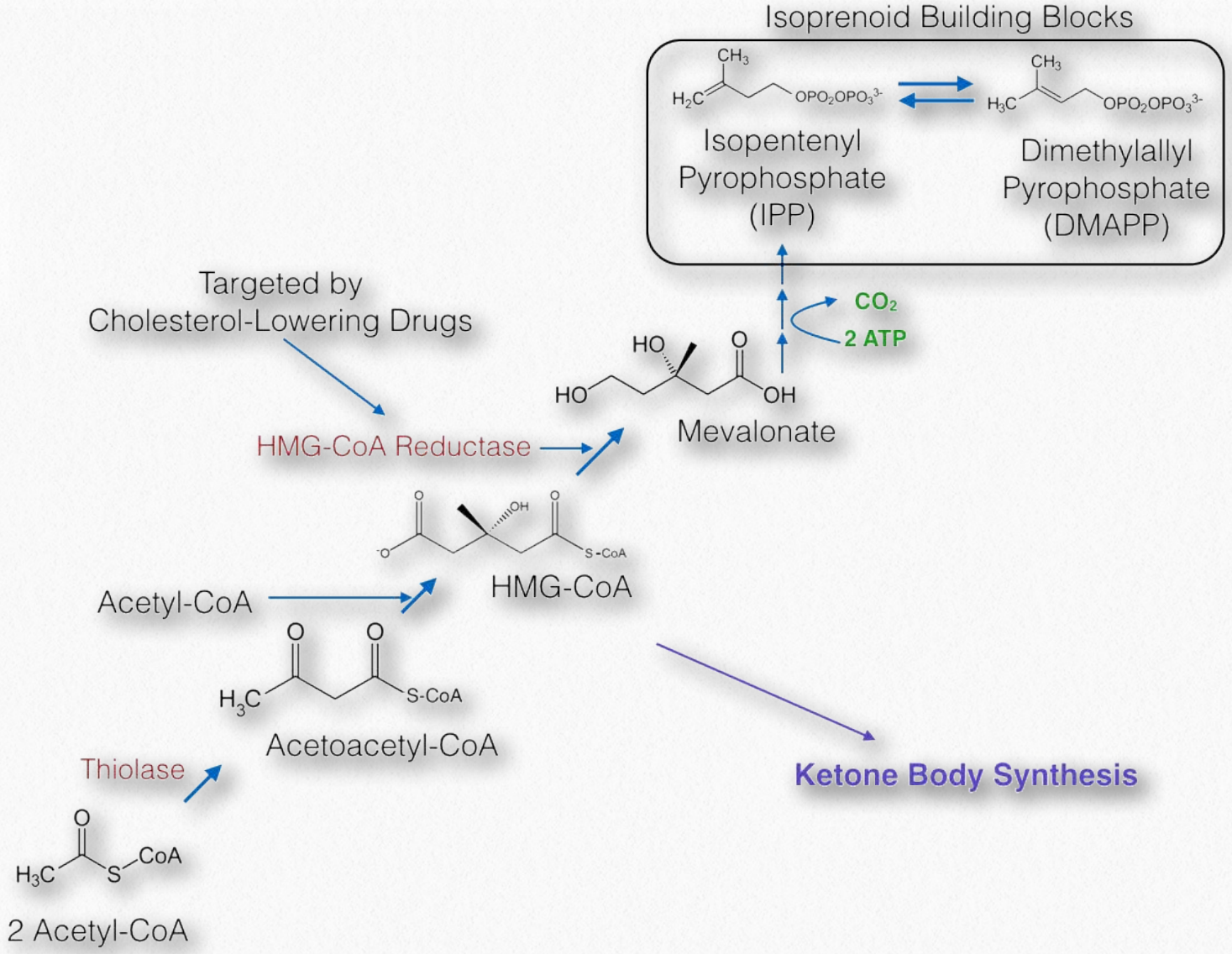


Figure 6.112 - Reactions to make isoprenes from acetyl-CoA

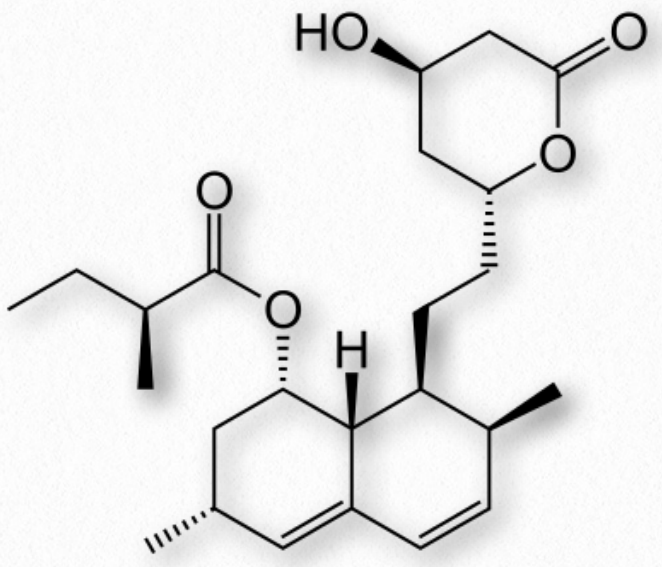


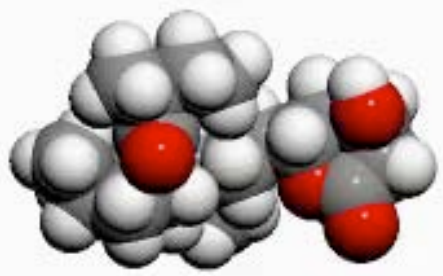
Figure 6.113 - Lovastatin

Wikipedia

The pathway leading up to isoprene synthesis overlaps with that of ketone body synthesis, for the two reactions (Figure 6.112), as has been discussed earlier in this book (see HERE). Thiolase catalyzes the initial reaction, joining together two acetyl-CoA molecules to make acetoacetyl-CoA. In the second reaction catalyzed by HMG-CoA synthase, a third acetyl-CoA is joined to form the six carbon compound known as hydroxymethyl glutaryl-CoA (HMG-CoA). Reaction three is an important one biologically and medically because of the enzyme catalyzing it - HMG-CoA reductase.

Statins

Medically, HMG-CoA reductase is the target of a class of drugs known as statins (Figure 6.113 & Movie 6.1), which are used to reduce cholesterol levels in people. These competitive inhibitors, which compete with HMG-CoA for binding have two effects. First, they reduce the production of mevalonate, which restricts the amount of substrate available to make cholesterol. Second, and perhaps more importantly, they increase production of LDL receptors in the liver, which favors uptake and destruction of LDLs, thus lowering serum cholesterol levels.



Movie 6.1 - Lovastatin

Wikipedia

Regulation

Biologically, the HMG-CoA reductase enzyme is also of importance because it is the primary regulatory point in cholesterol synthesis. Control of it is complex. First, it is feedback inhibited by cholesterol itself. High levels of glucose in the blood activate the enzyme. Phosphorylation by AMP-activated protein kinase inhibits its activity. Interestingly, the same enzyme phosphorylates and inactivates acetyl-CoA carboxylase - the only regulatory enzyme controlling fatty acid synthesis. Transcription of the gene encoding HMG-CoA reductase

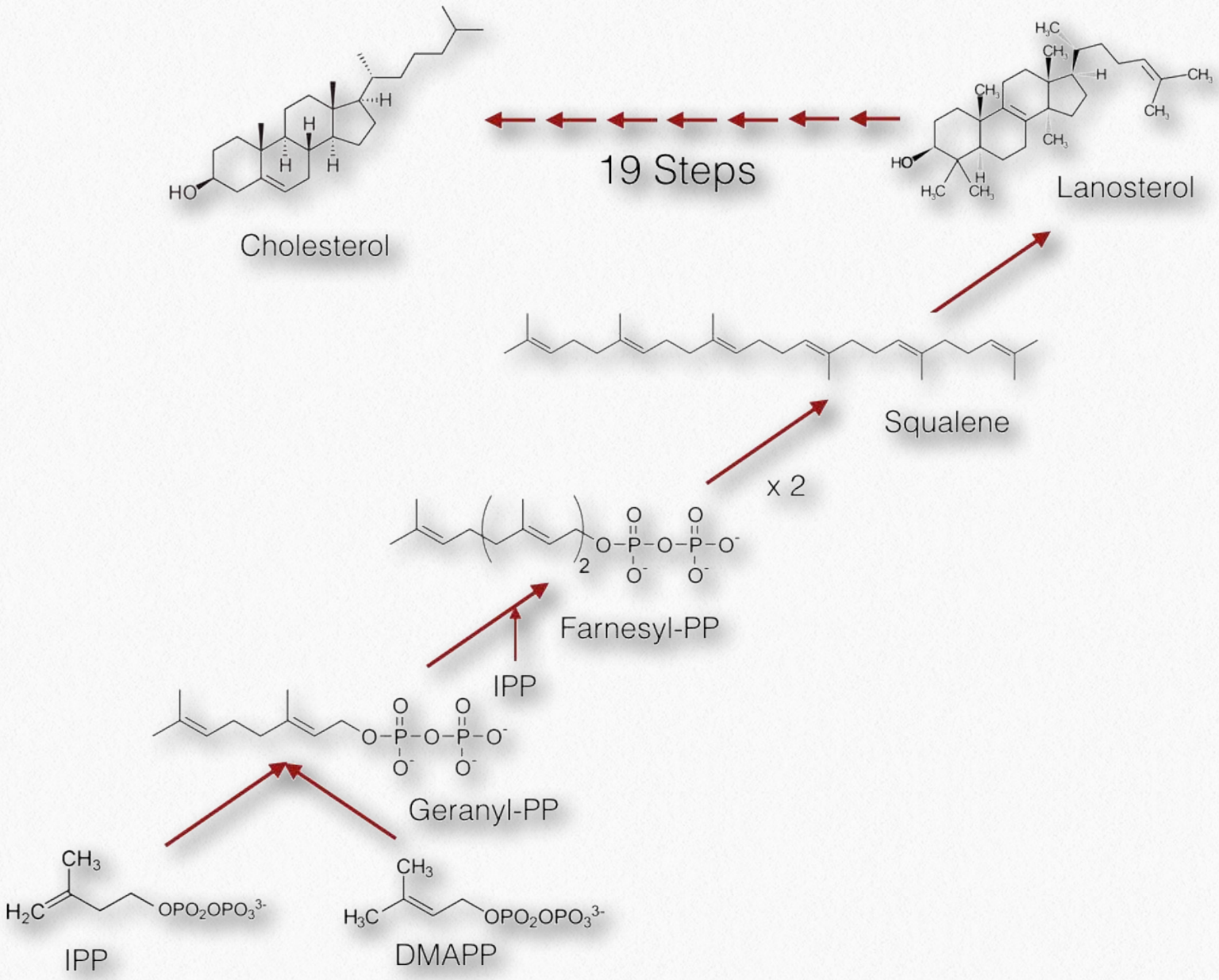


Figure 6.114 - Synthesis of cholesterol from isoprene units - isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP)

is enhanced by binding of the sterol regulatory element binding protein (SREBP) to the sterol recognition element (SRE) located near the gene coding sequence. As cholesterol levels rise, SREBP is proteolytically cleaved and transcription stops.

From HMG-CoA, the enzyme HMG-CoA reductase catalyzes the formation of mevalonate. This reaction requires NADPH and results in release of coenzyme A. Mevalonate gets phosphorylated twice and then decarboxylated to yield the five carbon intermediate known as isopentenyl-pyrophosphate (IPP). IPP is readily converted to the other important isoprenoid unit, dimethylallylpyrophosphate (DMAPP).

Isoprenes

These two five carbon compounds, IPP and DMAPP, are also called isoprenes (Figure 6.115) and are the building blocks for the syn-

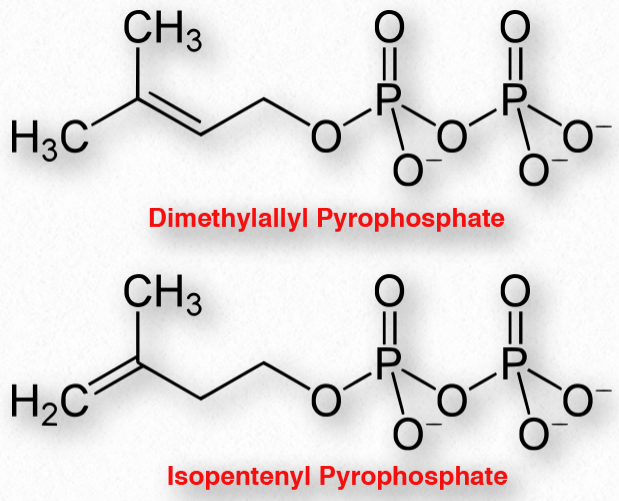


Figure 6.115 - Isoprene building blocks

thesis of cholesterol and related compounds. This pathway proceeds in the direction of cholesterol starting with the joining of IPP and DMAPP to form geranyl-pyrophosphate. Geranyl-pyrophosphate combines with another IPP to make farnesyl-pyrophosphate, a 15-carbon compound.

Squalene

Two farnesyl-pyrophosphates join to create the 30-carbon compound known as squalene. Squalene, in a complicated rearrangement involving reduction and molecular oxygen forms a cyclic intermediate known as lanosterol (Figure 6.116) that resembles cholesterol. Conversion of lanosterol to cholesterol is a lengthy process involving 19 steps that occur in the endoplasmic reticulum.

The cholesterol biosynthesis pathway from lanosterol is a long one and requires significant amounts of reductive and ATP energy. As noted earlier (see HERE), cholesterol has

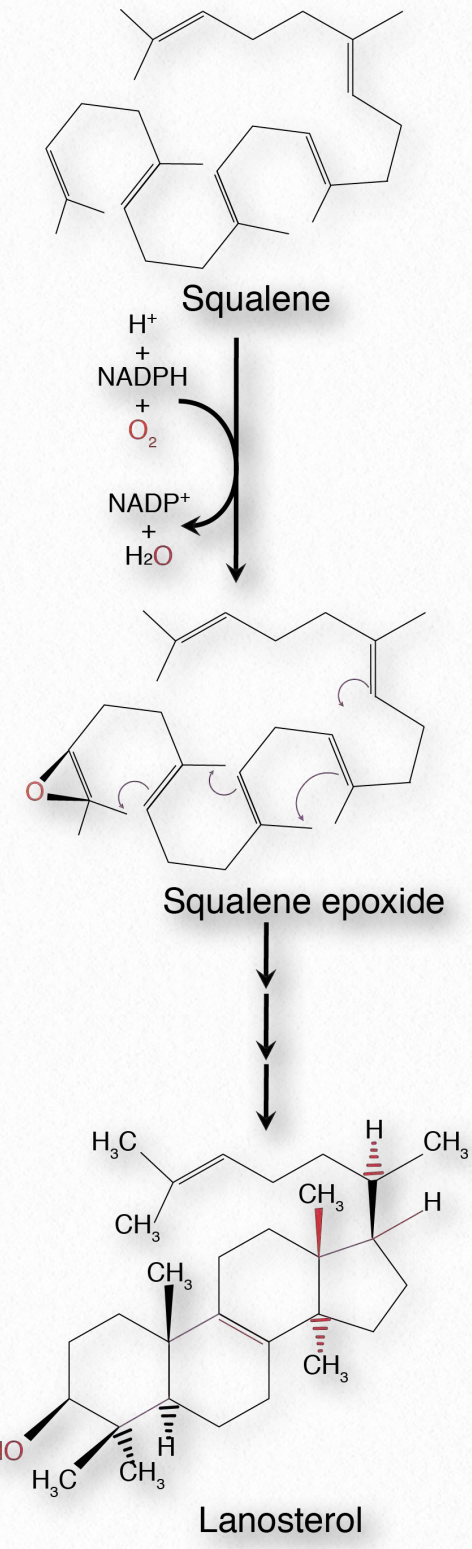


Figure 6.116 - Synthesis of lanosterol from squalene

Image by Penelope Irving

an important role in membranes. It is also a precursor of steroid hormones and bile acids and its immediate metabolic precursor, 7-dehydrocholesterol (Figure 6.117), branches to form vitamin D (Figure 6.118).

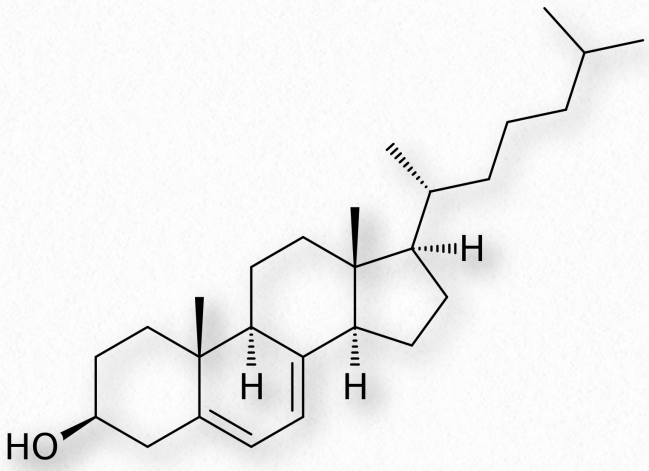
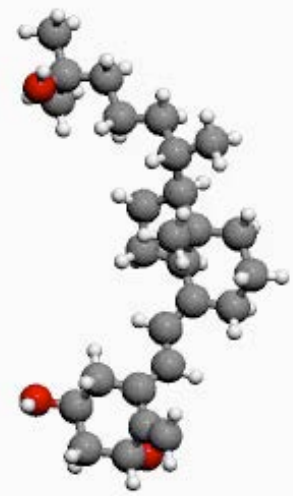


Figure 6.117 - 7-Dehydrocholesterol - A precursor of cholesterol and vitamin D

All steroid hormones in animals are made from cholesterol and include the progestagens, androgens, estrogens, mineralocorticoids, and the glucocorticoids. The branch molecule for all of the steroid hormones is the cholesterol metabolite (and progestagen) known as pregnenalone (Figure 6.119). The progestagens are thus precursors of all of the other classes of steroid hormones.



Movie 6.2 - Calcitriol - The active form of vitamin D

Wikipedia

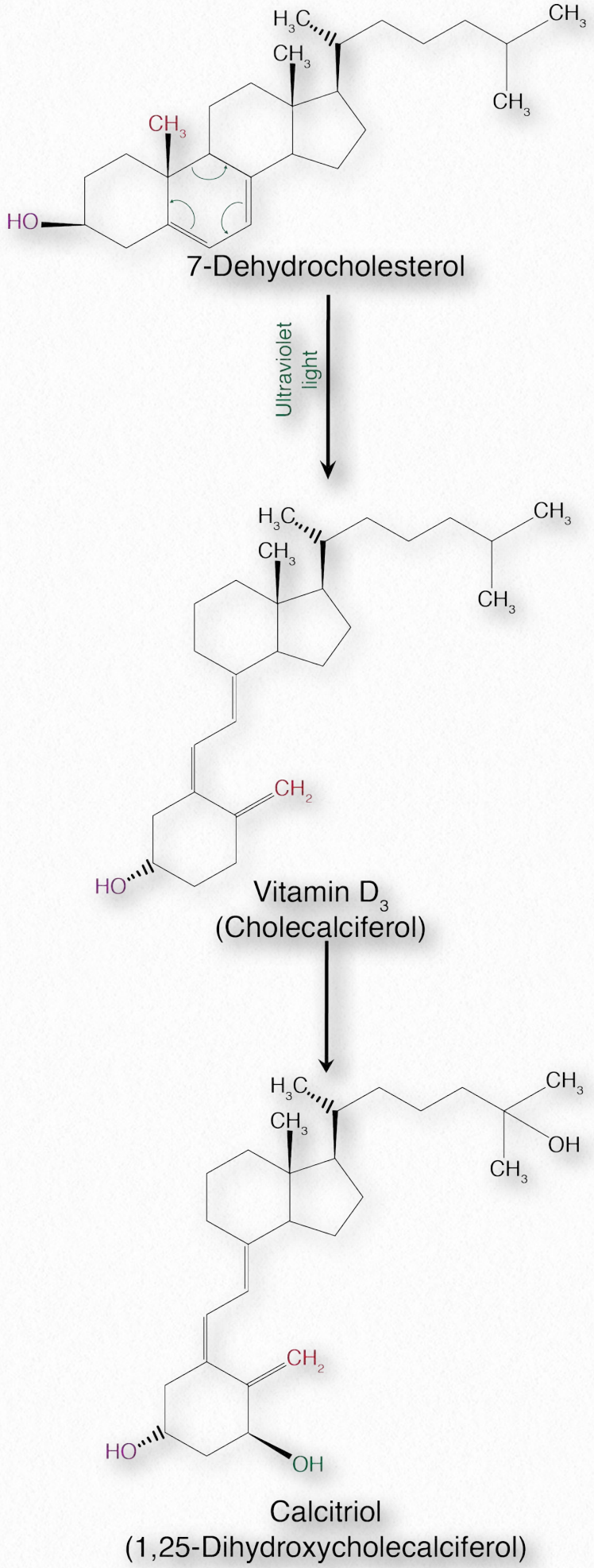


Figure 6.118 - Synthesis of the active form of vitamin D

Image by Penelope Irving

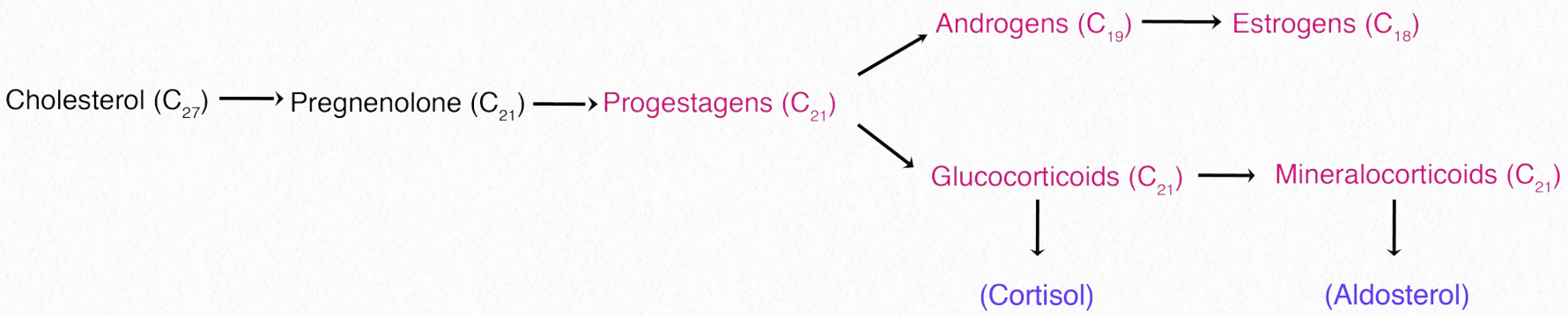


Figure 6.119 - Synthesis of steroid hormones from cholesterol. Example glucocorticoids and mineralocorticoids shown in blue.

Image by Penelope Irving

The estrogens are derived from the androgens in an interesting reaction that required formation of an aromatic ring (Figure 6.120). The enzyme catalyzing this reaction is known as an aromatase and it is of medical significance. The growth of some tumors is stimulated by estrogens, so aromatase inhibitors are prescribed to prevent the formation of estrogens and slow tumor growth. Two commonly used inhibitors include exemestane (a suicide inhibitor - Figure 6.121) and anastrozole (a competitive inhibitor).

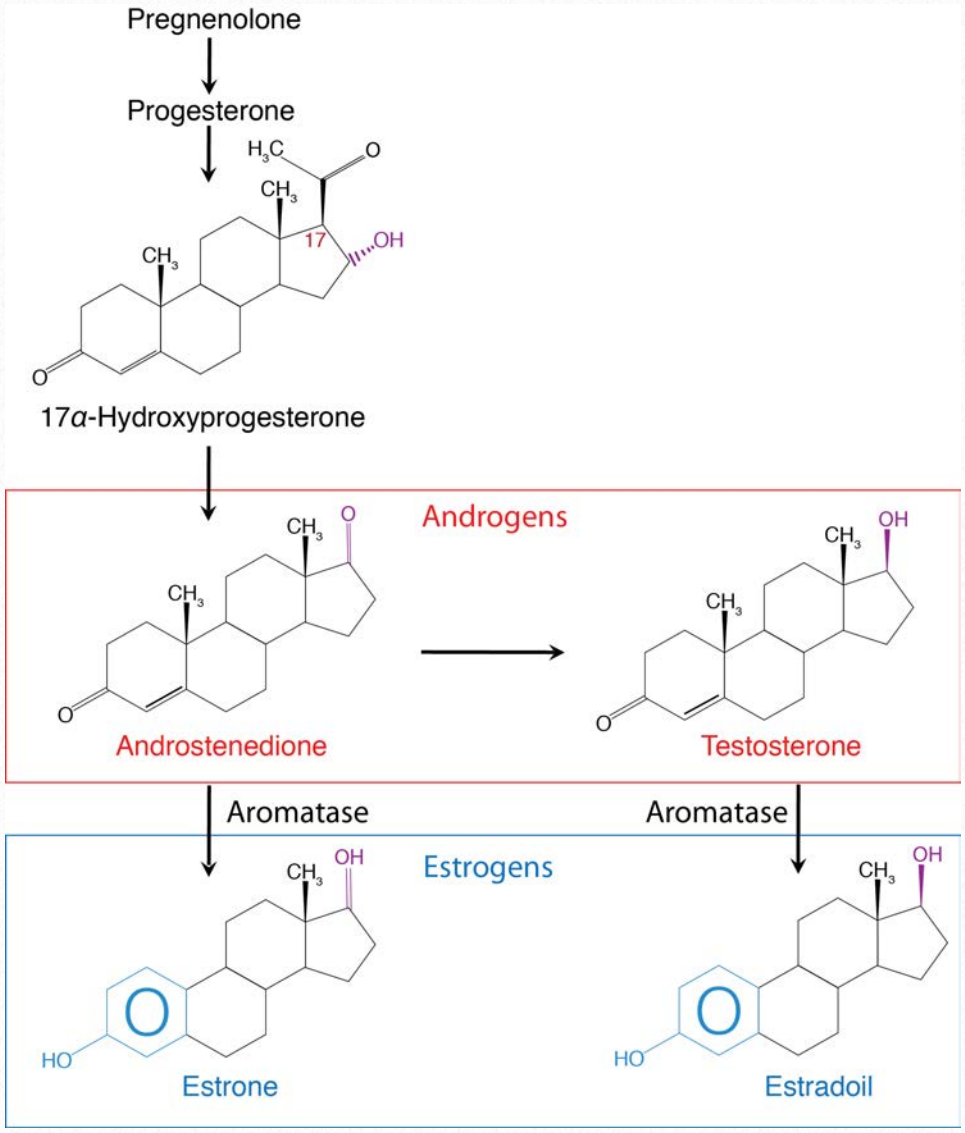


Figure 6.120 - Synthesis of Estrogens from Androgens

Image by Penelope Irving

Other fat-soluble vitamins

Synthesis of other fat soluble vitamins and chlorophyll also branches from the isoprenoid synthesis pathway at geranyl pyrophosphate. Joining of two geranylgeranyl pyrophosphates oc-

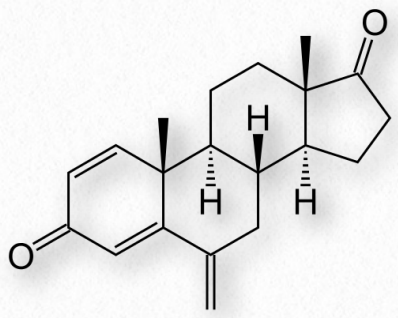


Figure 6.121 - Exemestane - A suicide inhibitor of aromatase

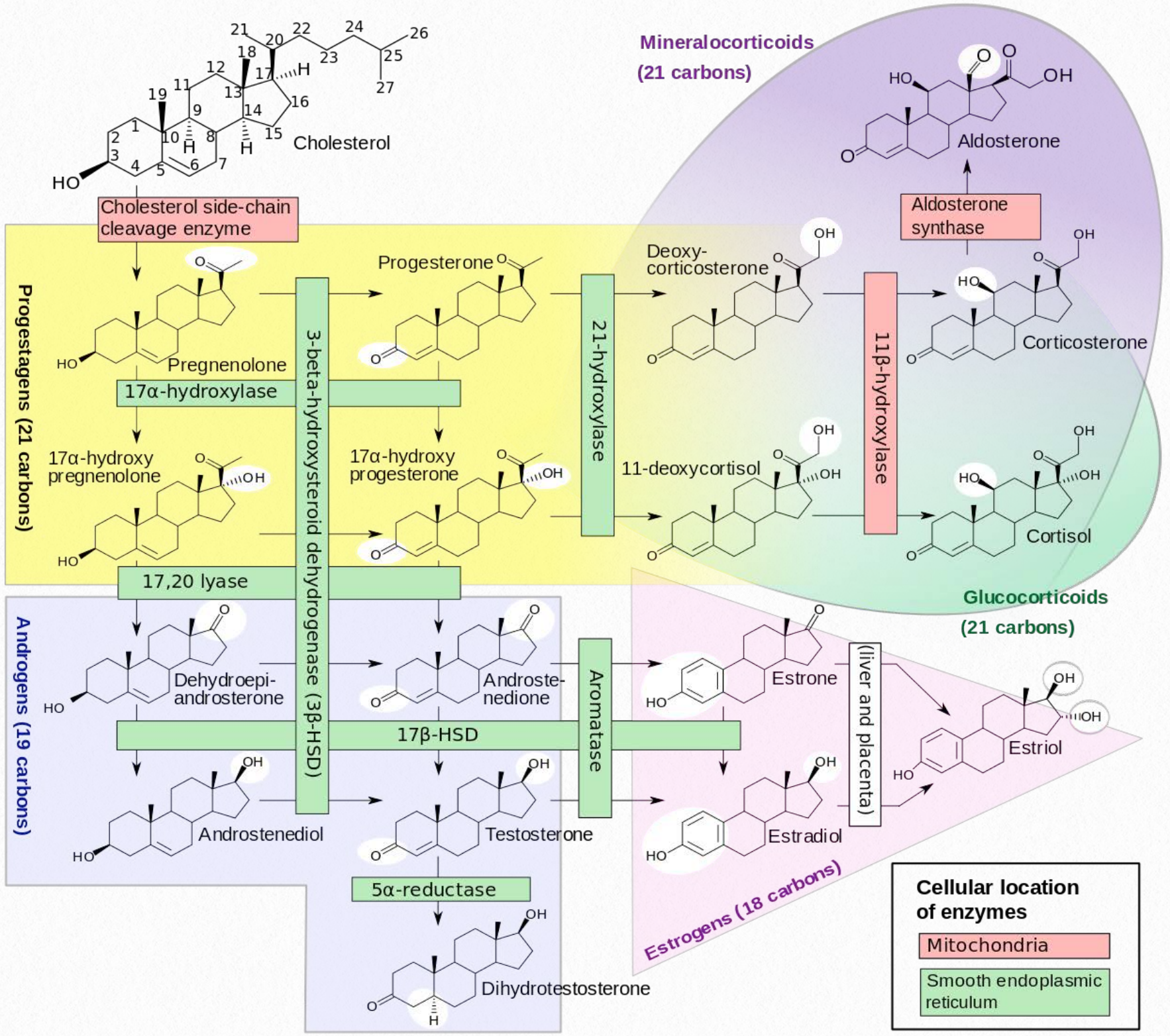


Figure 6.122 - Synthesis of steroid hormones from cholesterol

Wikipedia

curs in plants and bacteria and leads to synthesis of lycopene, which, in turn is a precursor of β-carotene, the final precursor of Vitamin A (see below also). Vitamins E and K, as well as chlorophyll are all also synthesized from geranylgeranyl pyrophosphate.

YouTube Lectures by Kevin HERE & HERE

Bile acid metabolism

Another metabolic pathway from cholesterol leads to the polar bile acids, which are important for the solubilization of dietary fat

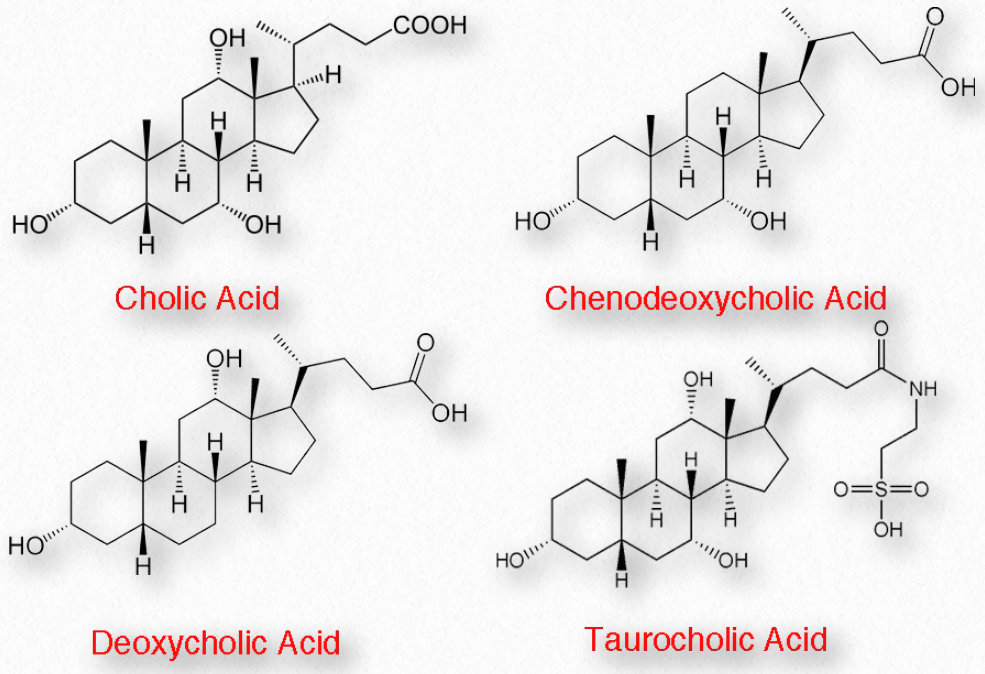


Figure 6.123 - Four bile acids

during digestion. Converting the very non-polar cholesterol to a bile acid involves oxidation of the terminal carbon on the side chain off the rings. Other alterations to increase the polarity of these compounds include hydroxylation of the rings and linkage to other polar compounds.

Common bile acids include cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, and deoxycholic acid (Figure 6.123). Another important consideration about bile acids is that their synthesis reduces the amount of cholesterol available and promotes uptake of LDLs by the liver. Normally bile acids are recycled efficiently resulting in limited reduction of cholesterol levels. However, inhibitors of the recycling promote reduction of cholesterol levels.

Vitamin A Synthesis

Vitamin A is important for many cellular functions related to growth, differentiation and organogenesis during embryonic development, tissue maintenance, and vision, to name a few.

There are three main active forms of the vitamin, retinal, retinol and retinoic acid, each with its own set of functions. Retinal, complexed with the protein, opsin, is found in the rod cells of the retina and is necessary for vision. Retinol and retinoic acid both function as signaling molecules that can modulate gene expression during development.

Synthesis of vitamin A occurs as a branch in synthesis of isoprenoids. Addition of isopentenyl pyrophosphate to farnesyl pyrophosphate creates a 20-carbon intermediate, geranylgeranyl pyrophosphate (GGPP - Figure 6.124).

Joining of two GGPPs creates a 40 carbon intermediate that is unstable and decomposes to phytoene. Desaturases oxidize two single bonds in phytoene, creating lycopene.

Lycopene is a linear 40 carbon unsaturated molecule found in tomatoes and other red vegetables and it gives them their color. Cyclization of end portions of lycopene give rise to β-carotene, the precursor of vitamin A (retinal/retinol - Figure 6.124).

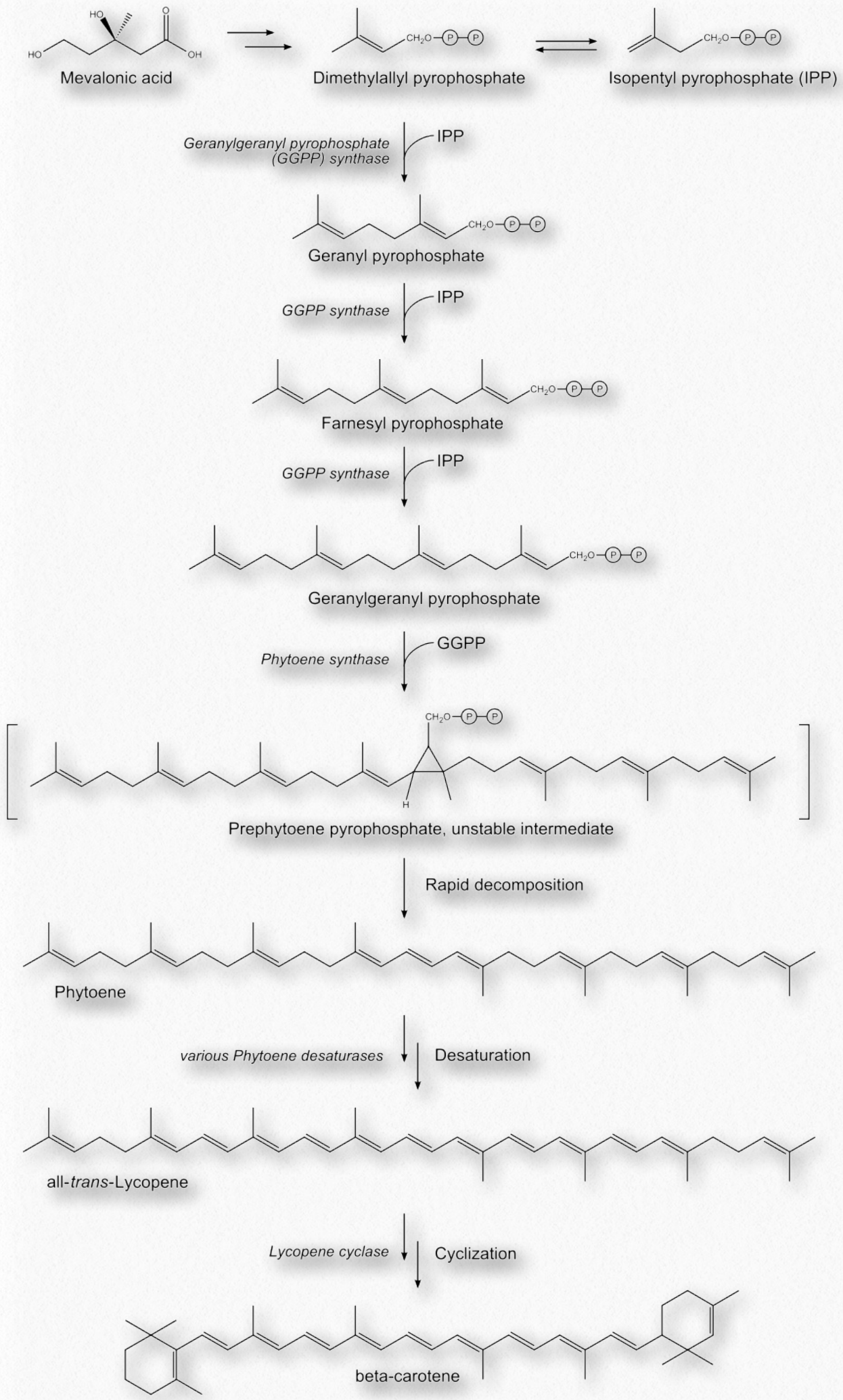


Figure 6.124 - Synthesis of β-carotene from mevalonate

Wikipedia

β-carotene is found in carrots and other orange vegetables, and is converted in the body to vitamin A. Catalytic action by β-Carotene 15,15' monooxygenase cleaves β-carotene to form retinal (the aldehyde form used in vision).

The enzyme retinol dehydrogenase catalyzes reduction of retinal to retinol (storage form). Oxidation of retinal creates another important retinoid known as retinoic acid. This form of vitamin A cannot be reduced back to retinal and thus cannot be used for vision or storage.

Instead, retinoic acid has roles in embryonic development. Retinoic acid acts through binding to the Retinoic Acid Receptor (RAR).

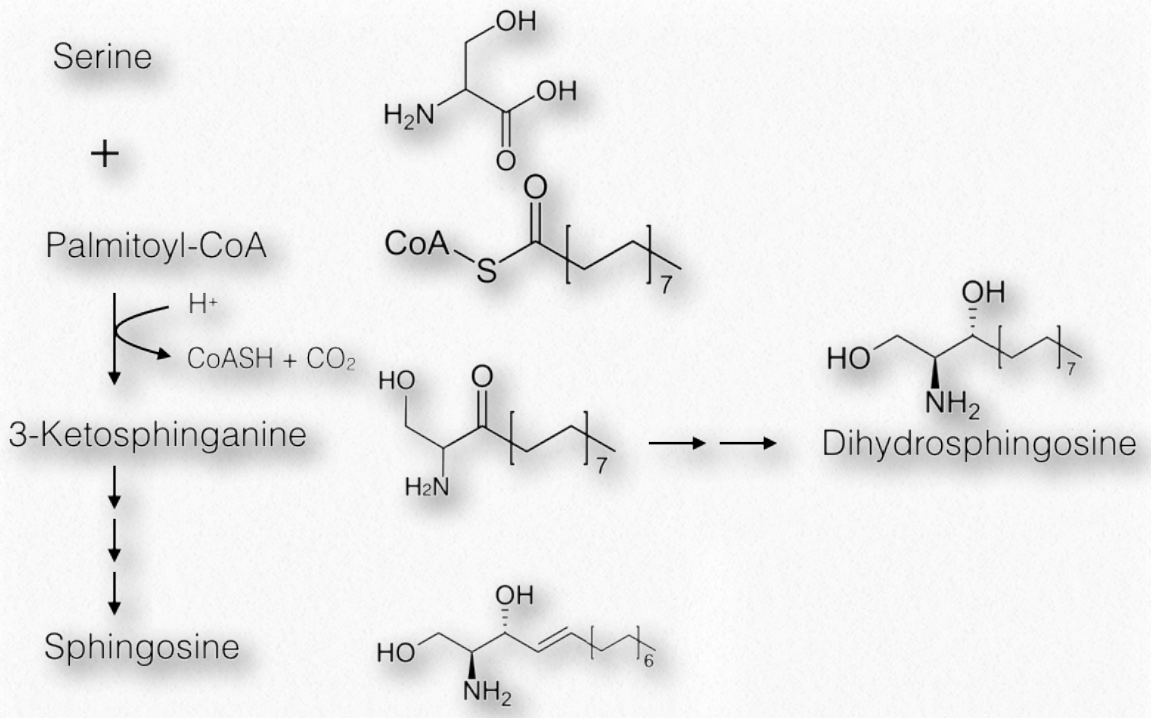


Figure 6.125 - Synthesis of dihydrosphingosine from serine and palmitoyl-CoA

RAR binds to DNA and affects transcription of several important sets of genes important for differentiation. These include the Hox genes, which control anterior/posterior patterning in early embryonic development.

Sphingolipid synthesis

Synthesis of sphingolipids, which are found primarily in brain and nerve tissue, begins with palmitoyl-CoA and serine that combine to make an 18-carbon amine called 3-keto-sphinganine (Figure 6.125). Reduction of that by NADPH yields dihydrosphingosine and addition of a fatty acid from an acyl-CoA yields N-acylsphinganine, which is a ceramide (Figure 6.126). A ceramide can be converted into a cerebroside by addition of a glucose from UDP-glucose (Figure 6.127).

If a few other simple sugars are added to the cerebroside, a globoside is created. If, instead of adding sugar, a phosphocholine is added from phosphatidylcholine, then sphingomyelin is created (Figure 6.127). If a complex set of sugars are added to to a cerebroside, then a ganglioside results (Figure 6.127).

Sphingolipid breakdown

In the overall metabolism of sphingolipids, the greatest problems arise with their catabolism. Figure 6.128 illustrates the nu-

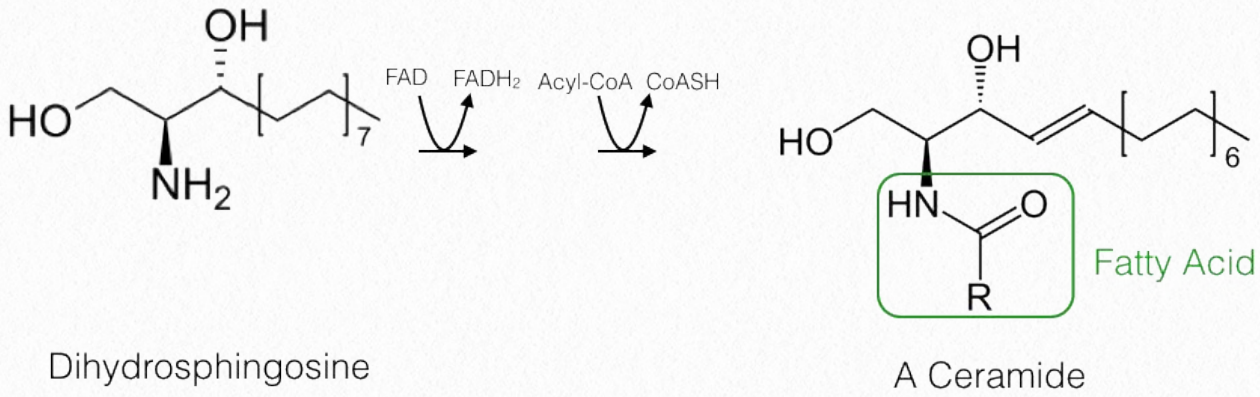


Figure 6.126 - Conversion of dihydrosphingosine to a ceramide

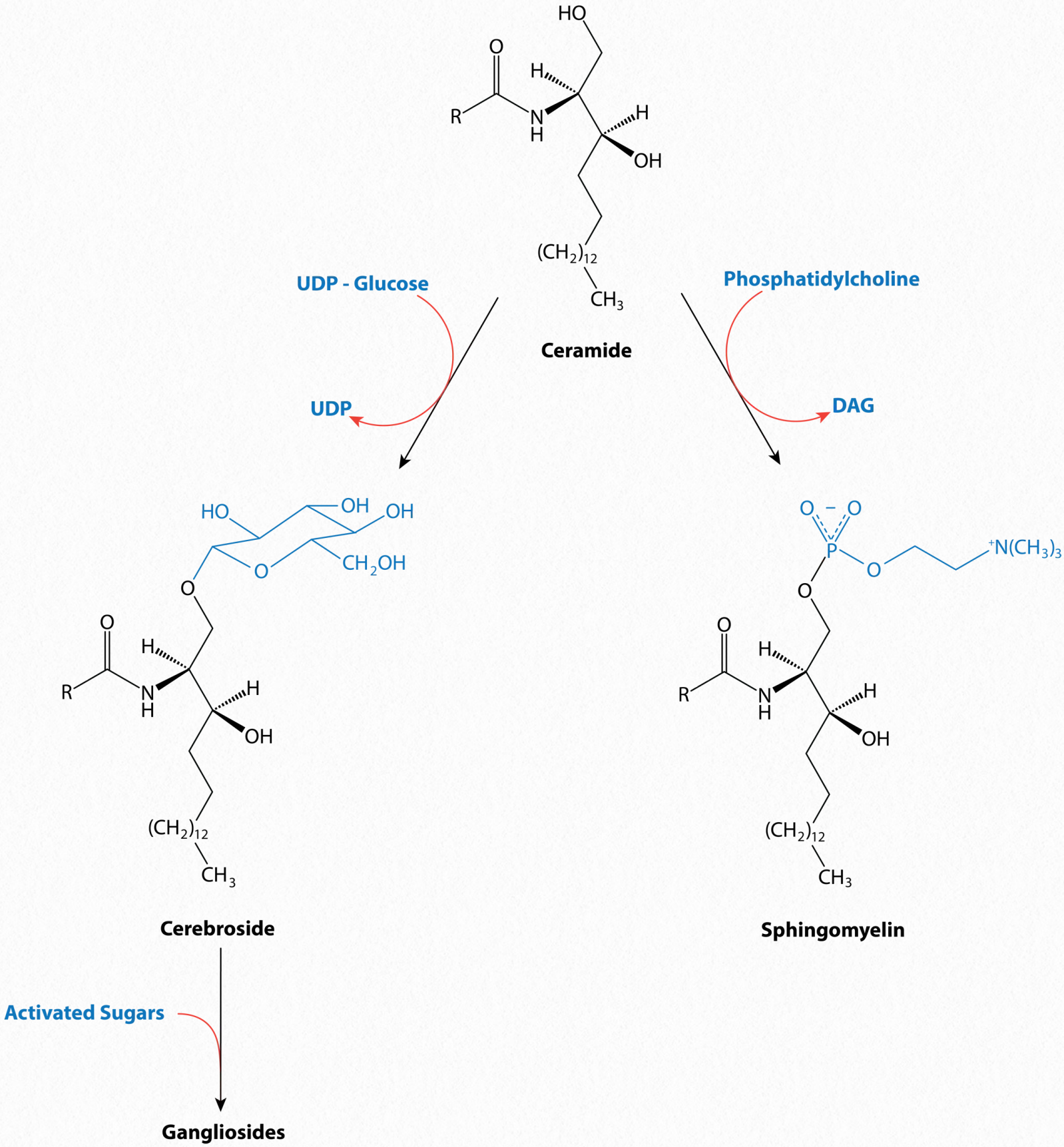


Figure 6.127 - Conversion of a ceramide into other sphingolipids

Image by Ben Carson

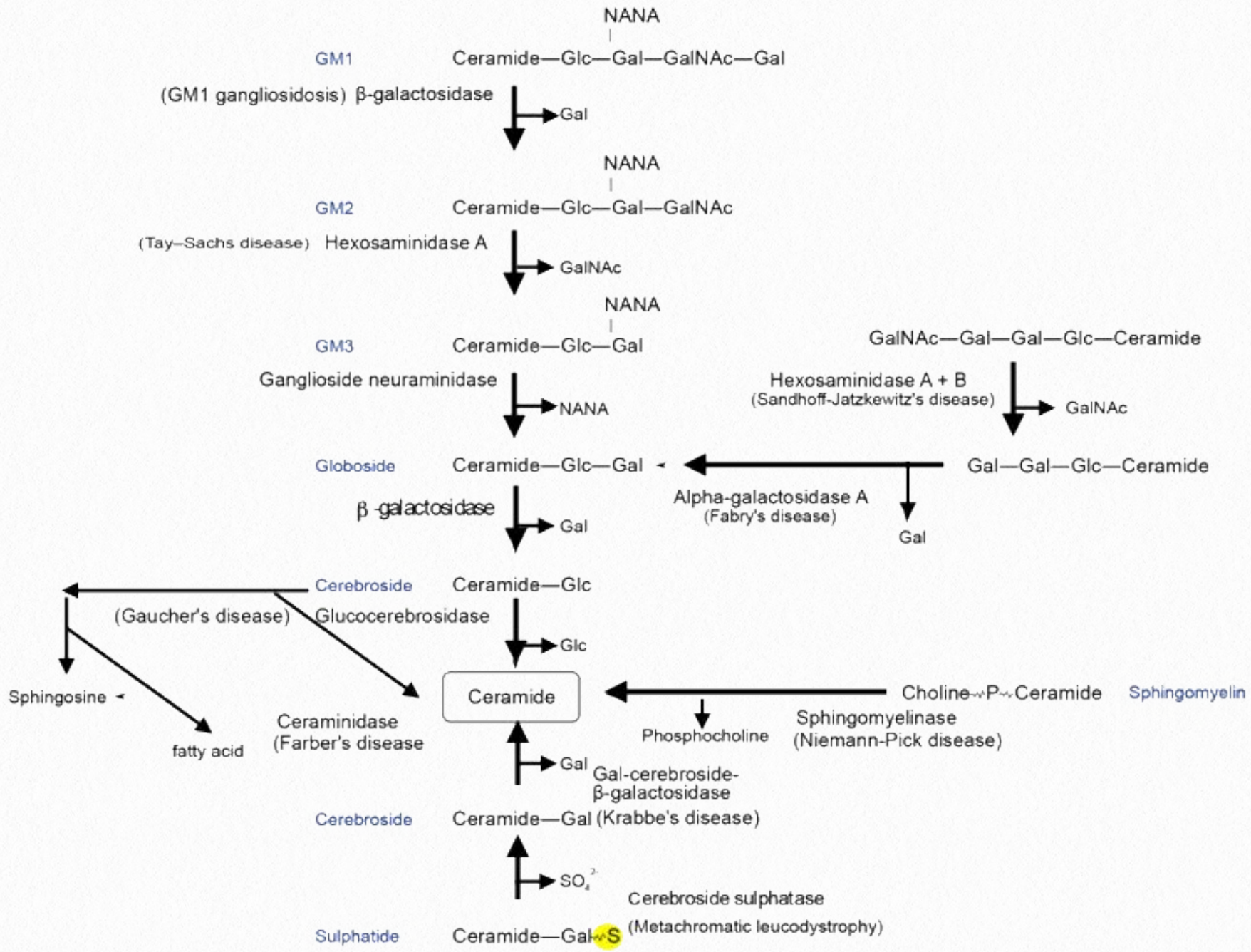


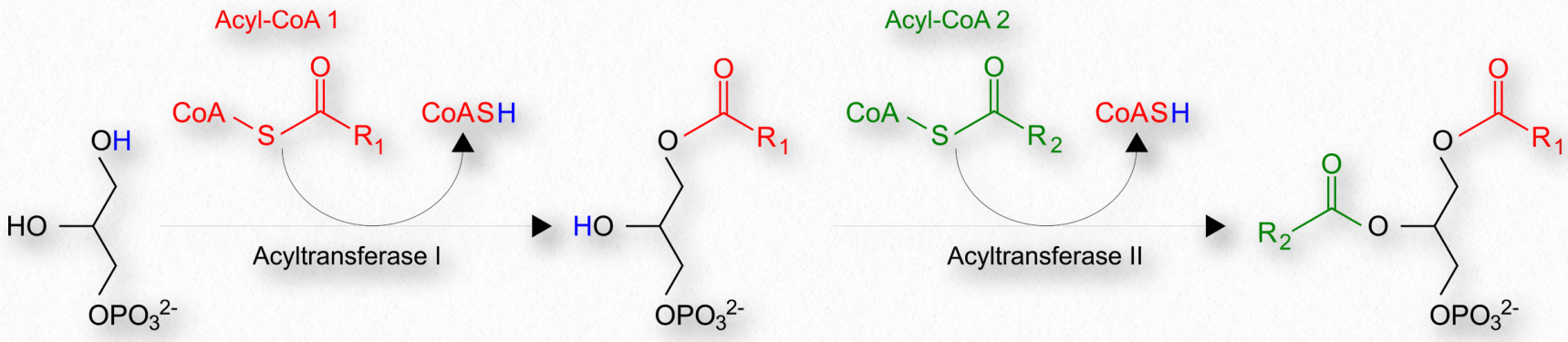
Figure 6.128 - Enzymes involved in sphingolipid breakdown and the diseases associated with their absence in parentheses. NANA = N-acetyl-neuraminic Acid / Glc = glucose / Gal = galactose / GalNAc = N-acetyl-galactosamine

Wikipedia

merous genetic diseases arising from mutations in DNA coding for some of these enzymes. All are lysosomal storage diseases and many of these are quite severe. GM1 glandiosidoses (arising from inability to breakdown GM1 gangliosides) cause severe neurodegeneration and seizures. Individuals suffering from them typically die by age 3. Tay-Sachs disease usually causes death by age 4, though late-onset forms of the disease in adults are known.

YouTube Lectures by Kevin HERE & HERE

With Gaucher's disease, three different types have been described with widely varying effects. In some, the disease is fatal by age four and in others, it does not manifest until teens



Glycerol 3-phosphate Lysophosphatidic acid Phosphatidic acid

Figure 6.129 - Phosphatidic acid synthesis

Wikipedia

or even adulthood. Fabry's disease patients can live into their 50s, on average.

Glycerophospholipid metabolism

Glycerophospholipids are the major components of membranes. Synthesis of glycerophospholipids begins with glycerol-3-phosphate. In the first reaction, glycerol-3-phosphate gains a fatty acid at position one from an acyl-CoA, followed by a duplicate reaction at position two to make phosphatidic acid (Figure 6.129). This molecule, which can branch to other reactions to form fats, is an important intermediate in the synthesis of many glycerophospholipids. Glycerophospholipid compounds can often be made by more than one pathway. The nucleotide CDP plays an important role in glycerophospholipid synthesis, serving as part of an activated intermediate for synthesis of phosphatidyl compounds. This is necessary, because formation of the phosphodiester bonds of these compounds requires higher energy input.

Cells use two strategies to accomplish this. Both involve CDP. In the first, CTP combines with phosphatidic acid to make CDP-diacylglcyerol with release of a pyrophosphate. The reaction is catalyzed by phosphatidate cytidylyltransferase.

CTP + Phosphatidic acid ⇅ **CDP-diacylglycerol + PP_i**

CDP-diacylglycerol then serves as an activated intermediate to donate the phosphotidate part of itself to another molecule. The reaction below illustrates one example

CDP-diacylglycerol + Serine ⇅ **Phosphatidylserine + CMP**

The second strategy is to make a CDP derivative of the group being added to phosphatidic acid. An example is shown next

Phosphocholine + **CTP**

⇅

CDP-choline + **PPi**

Then the CDP donates the phosphocholine to a diacylglycerol to made phosphatidylcholine and CMP

CDP-choline + **Diacylglycerol**

⇅

Phosphatidylcholine + **CMP**

Synthesis of other important glycerophospholipids follows from these basic strategies. Phosphatidylethanolamine can be easily made from phosphatidylserine by decarboxylation.

Phosphatidylserine

⇅

Phosphatidylethanolamine + **CO_2**

Phosphatidylethanolamine can serve as a precursor in an alternative pathway for making phosphatidylcholine (SAM = S-Adenosyl Methioinine / SAH = S-Adenosyl Homocysteine)

Phosphatidylethanolamine + 3 **SAM**

⇅

Phosphatidylcholine + 3 **SAH**

Phosphatidylserine and phosphatidylethanolamine can swap groups reversibly in the reaction below

Phosphatidylethanolamine + **Serine**

⇅

Phosphatidylserine + **Ethanolamine**

Similarly, phosphatidylserine and phosphatidylcholine can be interchanged as follows:

Phosphatidylserine + **Choline**

⇅

Phosphatidylcholine + **Serine**

Phosphatidylglycerol can be made from glycerol-3-phosphate and CDP-diacylglycerol

CDP-diacylglycerol + **Glycerol-3-phosphate**

⇅

Phosphatidylglycerol + **CMP**

Cardiolipin, which is essentially a diphosphatidyl compound can be made by joining CDP-diacylglyerol with phosphatidylglycerol

Phosphatidylglycerol + **CDP-diacylglycerol**

⇅

Cardiolipin + CMP

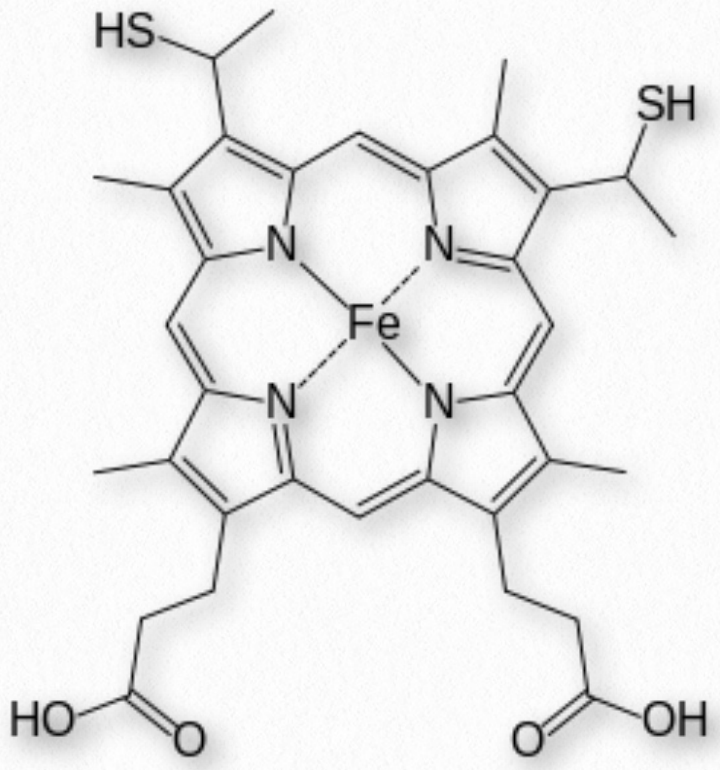


Figure 6.130 - Heme C

Phosphtidylinositol can be made from CDP-diacylglycerol and inositol.

CDP-diacylglycerol + **Inositol**

⇅

Phosphatidylinositol + **CMP**

Heme synthesis

The porphyrin ring found in the hemes of animals, fungi, and protozoa (Figure 6.130) is synthesized starting from very simple compounds (Figure 6.131). The process is a bit complicated, occurring between the cytoplasm and the mitochondrion. The first step is the creation of δ-aminolevulinic acid (also called aminolevulinic acid or dALA) from glycine and Succinyl-CoA.

Glycine + **Succinyl-CoA**

⇅

δ-aminolevulinic acid

Joining of two δ-aminolevulinic acid molecules together with splitting out of two molecules of water yields porphobilinogen.

2 **δ-aminolevulinic acid**

⇅

Porphobilinogen + $2H_2O$

Joining of four molecules of porphobilinogen together yields hydroxylmethylbilane (Figure 6.132).

4 **Porphobilinogen**

⇅

Hydroxymethylbilane

Next, a series of reactions involving 1) loss of water; 2) loss of four molecules of carbon dioxide; 3) loss of two more carbon dioxides, loss of six protons and electrons and (finally) 4) addition of Fe^{++} with loss of two protons yields heme. Individual heme molecules may be further processed.

Two enzymes in heme synthesis are sensitive to the presence of lead, and this is one of the primary causes of lead toxicity in humans. Inhibition of the enzymes leads to 1) anemia and 2) accumulation of δ-aminolevulinic acid,

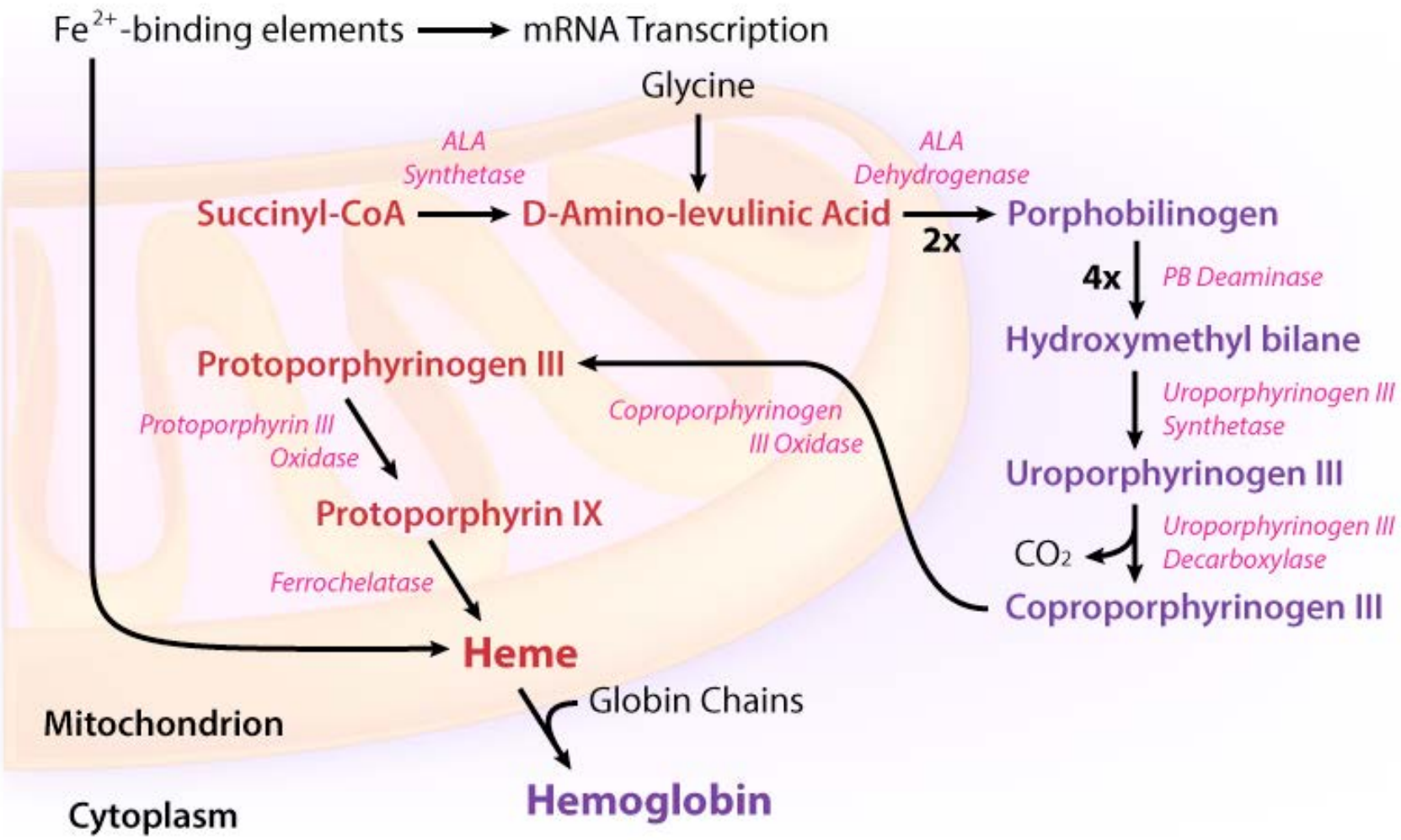


Figure 6.131 - Heme synthesis

Image by Aleia Kim

which can be harmful to neurons in development, resulting in learning deficiencies in children.

Porphyria

Defects in enzymes of the pathway can also lead to porphyrias, diseases in which one or more of the intermediates in the heme synthesis pathway accumulate due to deficiency of the enzyme necessary to convert the accumulating material into the next molecule in the pathway. The accumulation of purplish intermediates gave the diseases the name porphyria from the Greek word for purple.

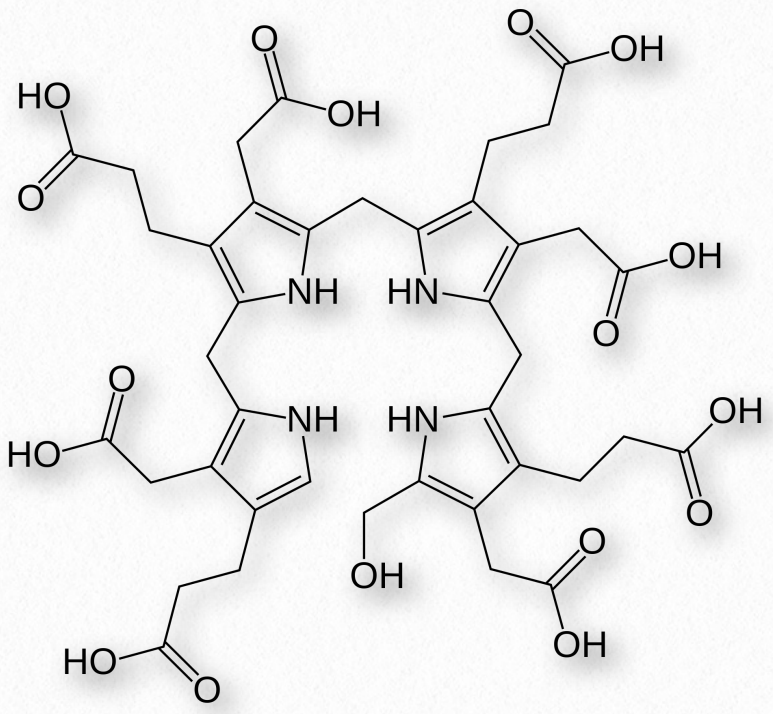


Figure 6.132 - Hydroxylmethylbilane - A precursor of heme

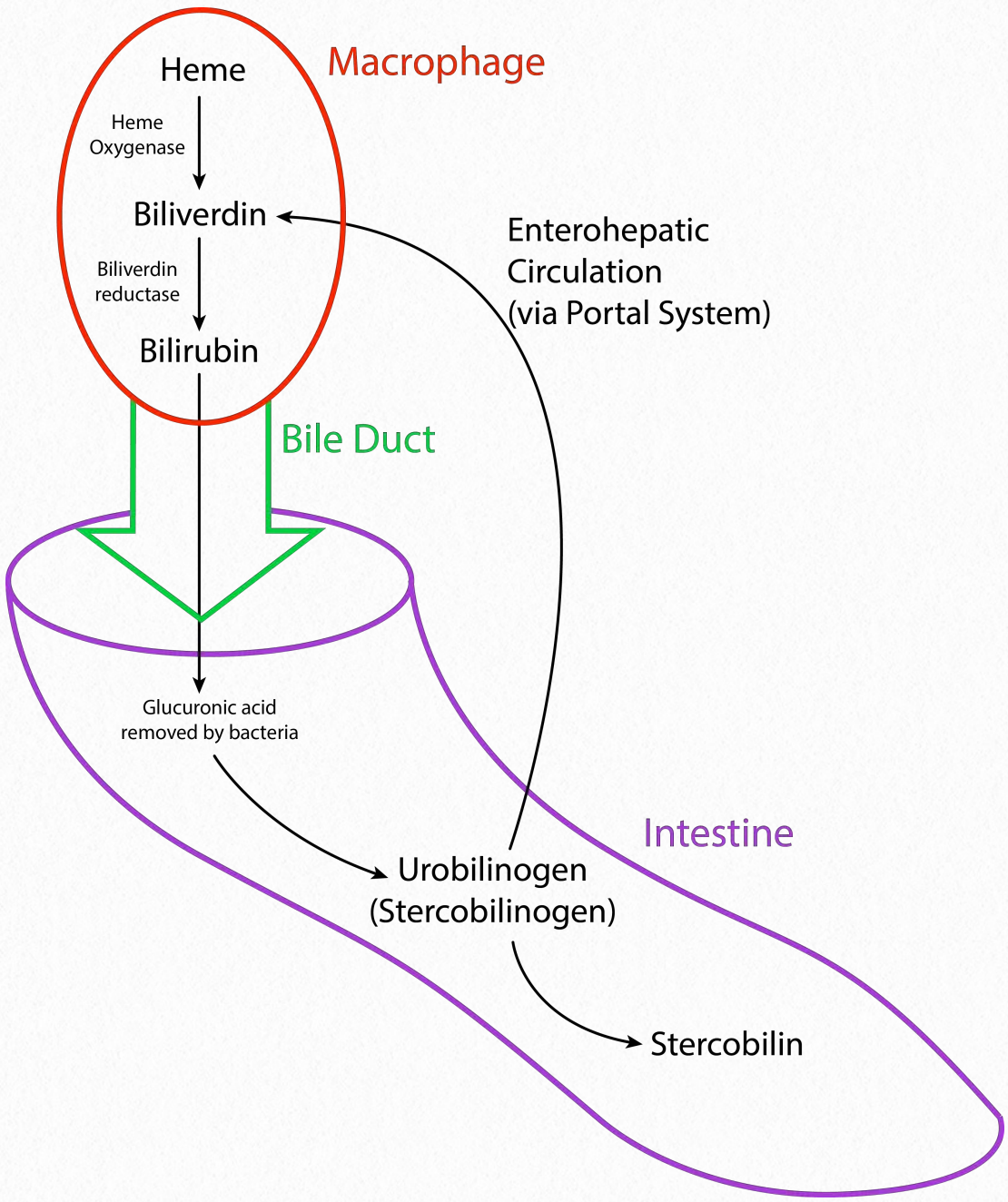


Figure 6.133 - Catabolism of heme

Image by Pehr Jacobson

Severe porphyrias can lead to brain damage, nerve damage, and mental disturbances. The "madness" of King George III may have been due to a form of porphyria. In other manifestations of the disease, cutaneous porphyrias cause skin problems on exposure to light. This need, for patients with certain forms of porphyria, to avoid light, coupled with the fact that porphyrias can be treated by blood tranfusions, may have led to the legend of vampires.

YouTube Lectures by Kevin HERE & HERE

Breakdown of heme

Catabolism of heme (Figure 6.133) begins in macrophages within the spleen . Targets for degradation are hemes within damaged red blood cells, which get removed from the blood supply due to their appearance. It is because of this system, for example, that sickle cell anemia is classified as an anemia (decrease in red blood cells or hemoglobin in the blood). After cells have sickled, they lose their shape and are more likely to be removed from the blood by this process, leaving the patient weakened from low blood cell counts.

The first biochemical step in catabolism is conversion of heme to biliverdin. This reaction is catalyzed by heme oxygenase and requires electrons from NADPH. In the process, Fe^{++} is released. Interestingly, carbon monoxide is also produced and it acts as a vasodilator.

Next, biliverdin is converted to bilirubin by biliverdin reductase and is secreted from the liver into bile. Bacteria in the

intestine convert bilirubin to urobilinogens, some of which is absorbed intestinal cells and transported into kidneys and excreted. The yellow color of urine arises from the compound known as urobilin, which is an oxidation product of urobilinogen. The remainder of the urobilinogens are converted in the intestinal tract to stercobilinogen whose oxidation product is stercobilin and it gives the color associated with feces.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

Click HERE for Penelope Irving's Web Page

Click HERE for Martha Baker's Web Page

Problem set related to this section **HERE**

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To Make a Cholesterol

To the tune of "*When Johnny Comes Marching Home*"

Metabolic Melodies Website HERE

Some things that you can build with acetyl-CoAs
Are joined together partly thanks to thiolase
They come together 1-2-3
Six carbons known as H-M-G
And you're on your way
To make a cholesterol

To synthesize a mevalonate in the cell
Requires reducing HMG-CoA, as well
The enzyme is a RE-ductase
Controlled in allosteric ways
When the cell's impelled
To make a cholesterol

The mevalonate made in metabolic schemes
Gets decarboxylated down to isoprenes
They're linked together willy-nil
To build a PP-geranyl
In the cells' routines
To make a cholesterol

A single step links farnesyls but that's not all
The squalene rearranges to lanosterol
From that there's nineteen steps to go
Before the sterol's apropos
Which you must recall
To make a cholesterol

The regulation of the scheme's complex in ways
Inhibited by feedback of the RE-duc-tase
And statins mimic so they say
The look of HMG-CoA
So we sing their praise
And not make cholesterol

Recording by David Simmons
Lyrics by Kevin Ahern

The Dieter's Song

To the tune of "*Story of Love*"

Metabolic Melodies Website HERE

You better lose your middle
Run a little
Get yourself fit as a fiddle
You must break a sweat
You will truly get
Fit

You need to change your diet
Don't deny it
Reducing intake you should try it
Hold off on the cheese
Count the calories,
Love

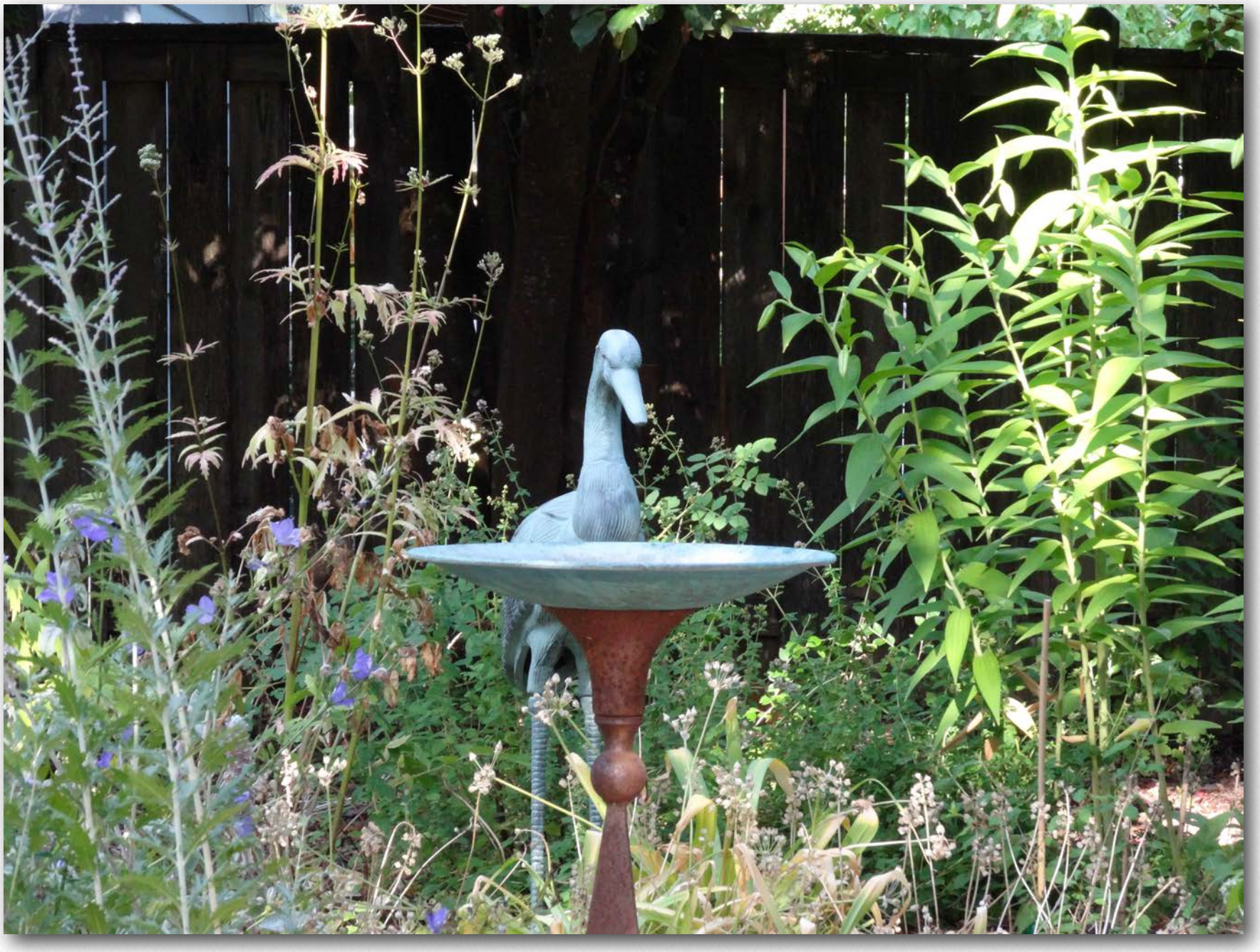
Bridge
Whenever there is juicy stuff
You need to ponder on the cost
Cuz just a little is enough
Or else your diet's lost

You wanna move your waistline
To the baseline
Give those legs a bit of racetime
It is worth the sweat
When you truly get
Fit

It is worth the sweat
When you truly get
Fit

Recording by David Simmons
Lyrics by Kevin Ahern

Metabolism: Amino Acids and the Urea Cycle



Amino acid metabolism

In contrast to some of the metabolic pathways described to this point, amino acid metabolism is not a single pathway. The 20 amino acids have some parts of their metabolism that overlap with each other, but others are very different from the rest. In discussing amino acid metabolism, we will group metabolic pathways according to common metabolic features they possess (where possible). First, we shall consider the anabolic pathways.

YouTube Lectures by Kevin
HERE & HERE

Transamination

Before beginning discussion of the pathways, it is worthwhile to discuss a reaction common to the metabolism of most of the amino acids and other nitrogen-containing compounds and that is transamination.

In cells, nitrogen is a nutrient that moves from one molecule to another in a sort of hand-off process. A common transamination reaction is shown on the next page.

α-ketoacid + **Glutamate**

⇅

Amino acid + **α-ketoglutarate**

A specific reaction of this type is shown in Figure 6.134.

Glutamate and glutamine play central roles in transamination, each containing one more amine group than **α**-ketoglutarate and glutamate, respectively. Transamination reactions, as noted earlier, occur by a ping-pong mechanism and involve swaps of amines and oxygens in Schiff base reactions. Two amino acids, glutamine and asparagine are the products of gaining an amine in their respective R-groups in reactions involving ammonium ion.

Synthesis varies

It is also important to recognize that organisms differ considerably in the amino acids that they can synthesize. Humans, for example, cannot make 9 of the 20 amino acids needed to make proteins, and the number of these that can be synthesized in needed amounts varies between adults and children.

Amino acids that cannot be made by an organism must be in the diet and are called essential amino acids. Non-essential amino acids are those an organism can make in sufficient quantities (Figure 6.135). Though amino acids do not have a common pathway of metabolism, they are often organized in "families" of amino acids with overlapping metabolic reactions common to members of each group. To designate amino acid families in the text we will use a blue font for headings to distinguish them.

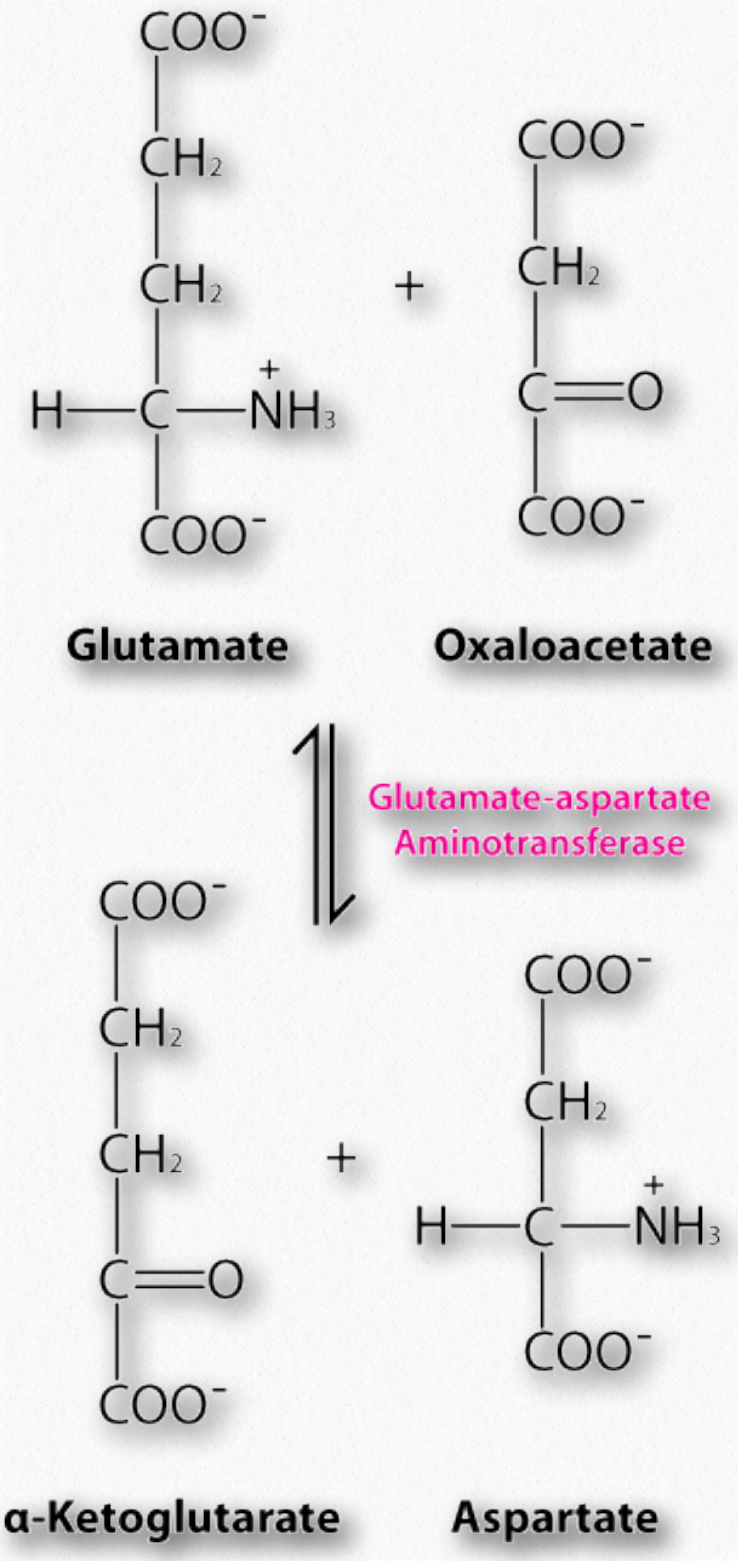


Figure 6.134 - Example of a transaminase (aminotransferase) reaction

Image by Aleia Kim

α-ketoglutarate family

This family of amino acids arises from α-ketoglutarate of the citric acid cycle. It includes the amino acids glutamic acid, glutamine, proline, and arginine. It is also called the glutamate family, since all the amino acids in it derive from glutamate.

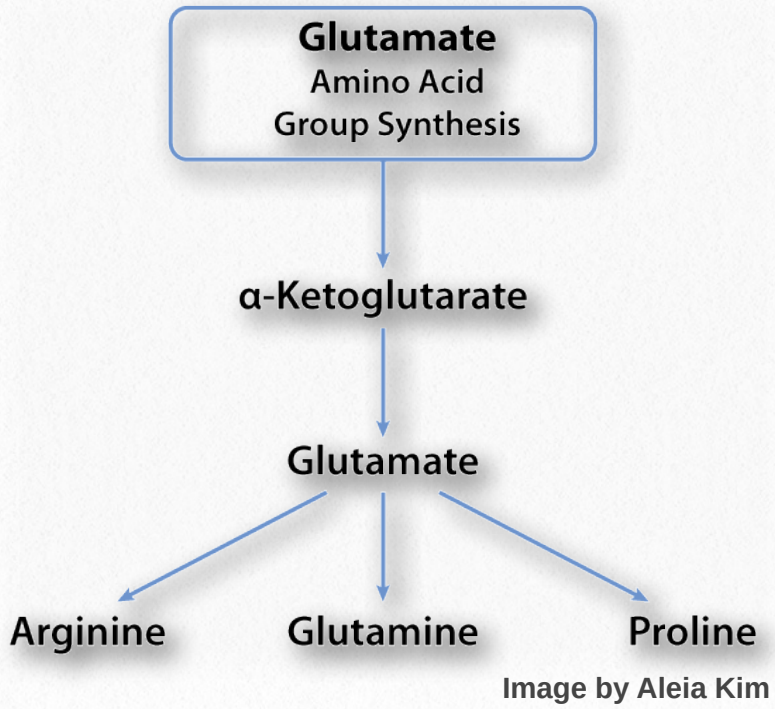


Image by Aleia Kim

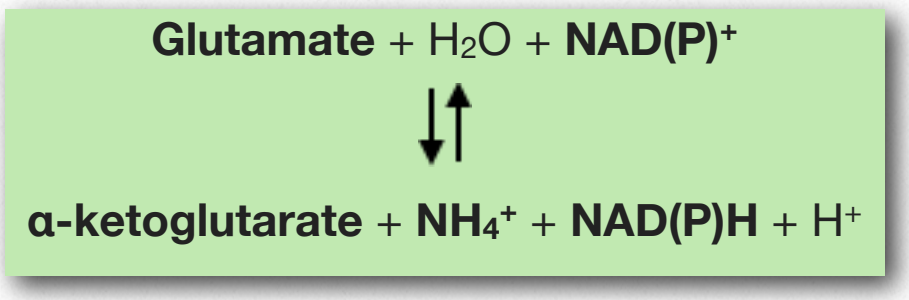
Essential	Non-Essential
Histidine	Alanine
Isoleucine	Arginine
Leucine	Asparagine
Lysine	Aspartic acid
Methionine	Cysteine
Phenylalanine	Glutamic acid
Threonine	Glutamine
Tryptophan	Glycine
Valine	Proline
	Selenocysteine
	Serine
	Tyrosine

Figure 6.135 - Essential and non-essential amino acids

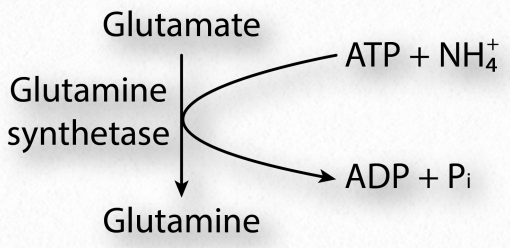
Image by Pehr Jacobson

Glutamate

α-ketoglutarate is readily converted to glutamate in transamination reactions, as noted above. It can also be produced by the enzyme glutamate dehydrogenase, which catalyzes the reaction below (in reverse) to make glutamate.



In the forward direction, the reaction is a source of ammonium ion, which is important both for the urea cycle and for glutamine metabolism. Because it is a byproduct of a citric acid cycle intermediate, glutamate can therefore trace its roots to any of the intermediates of the cycle. Citrate and isocitrate, for example, can be thought of as precursors of glutamate. In addition, glutamate can be made by transamination from α-ketoglutarate in numerous transamination reactions involving other amino acids.



Inhibitors of Glutamine Synthetase		
Amino acids	Nucleotides	Other
Glycine Alanine Serine Histidine Tryptophan	AMP CTP	Carbamoylphosphate Glucosamine-6-phosphate

Figure 6.136 Action and inhibitors of glutamine synthetase

Image by Pehr Jacobson

catalyzed by glutamate synthetase commonly arises from nitrite reduction, amino acid breakdown, or photorespiration. Because it builds ammonia into an amino acid, glutamine synthetase helps reduce the concentration of toxic ammonia - an important consideration in brain tissue. Some inhibitors of glutamine synthetase are, in fact, the products of glutamine metabolism. They include histidine, tryptophan, carbamoyl phosphate, glucosamine-6-phosphate, CTP, and AMP. The glutamine

Glutamine

Synthesis of glutamine proceeds from glutamate *via* catalysis of the enzyme glutamine synthetase, one of the most important regulatory enzymes in all of amino acid metabolism (Figure 6.136).

Regulation of the enzyme is complex, with many allosteric effectors. It can also be controlled by covalent modification by adenylylation of a tyrosine residue in the enzyme (Figure 6.137). In the figure, P_A and P_D are regulatory proteins facilitating conversion of the enzyme.

Ammonia used in the reaction

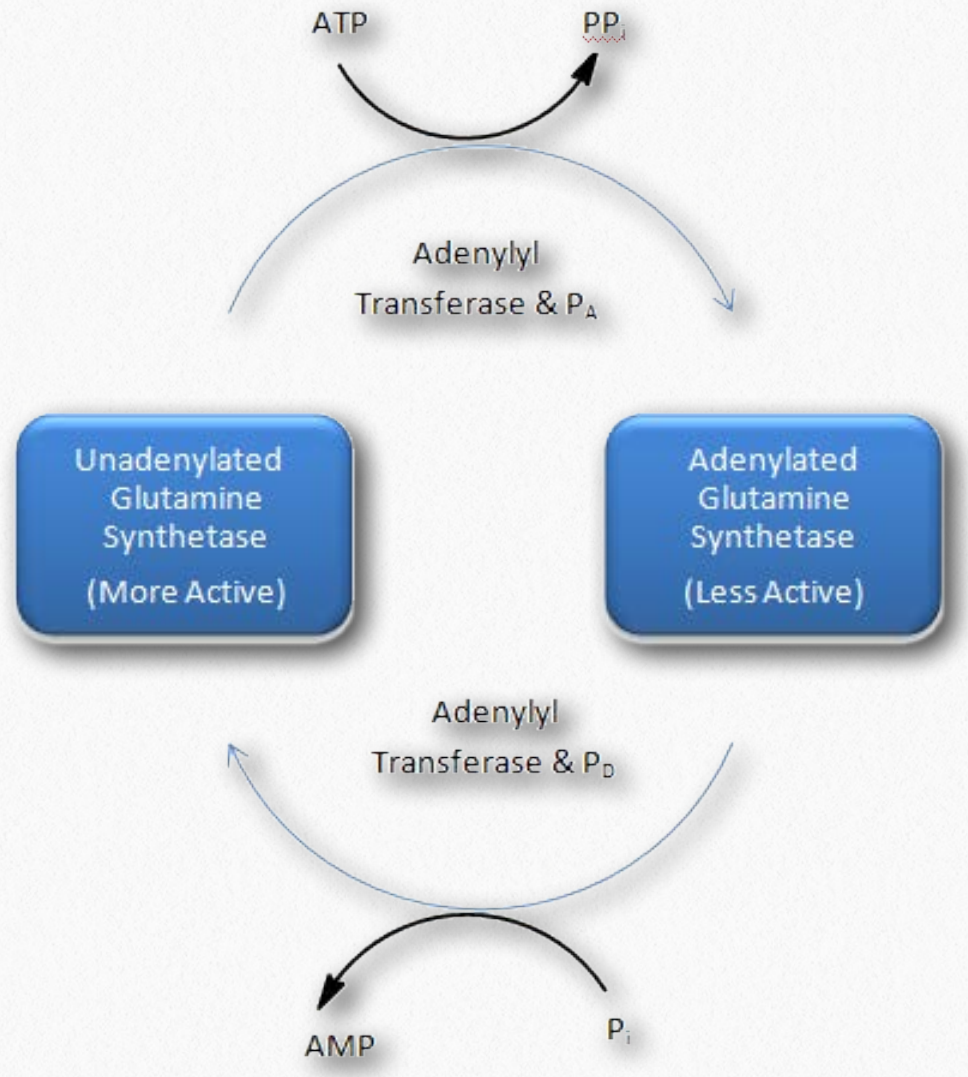


Figure 6.137 - Regulation of glutamine synthetase by adenylylation

mate substrate site is a target for the inhibitors alanine, glycine, and serine. The ATP substrate site is a target for the inhibitors GDP, AMP, and ADP. Complete inhibition of the enzyme is observed when all of the substrate sites of the multi-subunit enzyme are bound by inhibitors. Lower levels of inhibitors results in partial or full activity, depending on the actual amounts.

Proline

Synthesis of proline starts with several reactions acting on glutamate. They are shown below in the green text box.

1. **ATP** + **L-glutamate**
   ⇅ (Glutamate-5-kinase)
   ADP + **L-glutamate 5-phosphate**

2. **L-glutamate 5-phosphate** + **NADPH** + H^+
   ⇅ (Glutamate-5-semialdehyde dehydrogenase)
   L-glutamate 5-semialdehyde + **Pi** + **NADP$^+$**

The L-glutamate-5-semialdehyde, so produced, is a branch point for synthesis of proline or ornithine. In the path to make proline, spontaneous cyclization results in formation of 1-pyrroline-5-carboxylic acid (Figure 6.138).

This, in turn, is reduced to form proline by pyrroline-5-carboxylate reductase.

1-pyrroline-5-carboxylate + **NAD(P)H** + H^+
⇅
L-proline + **NAD(P)$^+$**

Arginine

Arginine is a molecule synthesized in the urea cycle and, thus, all urea cycle molecules can be considered as precursors. Starting with citrulline, synthesis of arginine can proceed as shown on the next page. The urea cycle can be seen HERE.

Figure 6.138 - Spontaneous cyclization of L-glutamate-5-semialdehyde (left) to 1-pyrroline-5-carboxylic acid (right)
Image by Aleia Kim

1. **Citrulline** + **ATP** + **Aspartate**

   ⇅ (**Argininosuccinate synthase**)

   Argininosuccinate + **PP_i** + **AMP**

2. **Argininosuccinate**

   ⇅ (**Argininosuccinase**)

   Arginine + **Fumarate**

An alternate biosynthetic pathway for making arginine from citrulline involves reversing the reaction catalyzed by nitric oxide synthase. It catalyzes an unusual five electron reduction reaction that proceeds in the following manner

Citrulline + **Nitric Oxide** + 3/2 **$NADP^+$**

⇅

L-arginine + 3/2 **NADPH** + H^+ + 2 O_2

Yet another way to synthesize arginine biologically is by reversal of the arginase reaction of the urea cycle

Arginine + Water

⇅

Ornithine + **Urea**

Arginine can also be made starting with glutamate. This 5 step pathway leading to ornithing is illustrated at the top of the next page (enzymes in blue). Ornithine, as noted above can readily be converted to arginine.

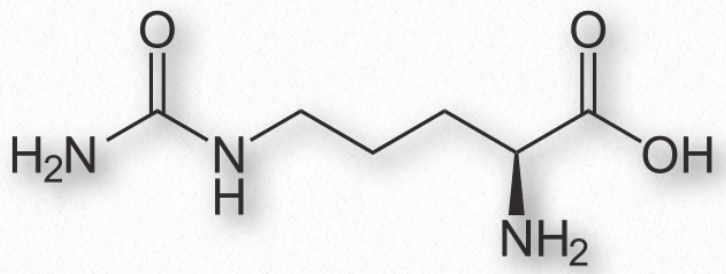


Figure 6.139 - Citrulline

The last means of making arginine is by reversing the methylation of asymmetric dimethylarginine (ADMA - Figure 6.140). ADMA is a metabolic byproduct of protein modification. It interferes with production of nitric oxide and may play a role in cardiovascular disease, diabetes mellitus, erectile dysfunction, and kidney disease.

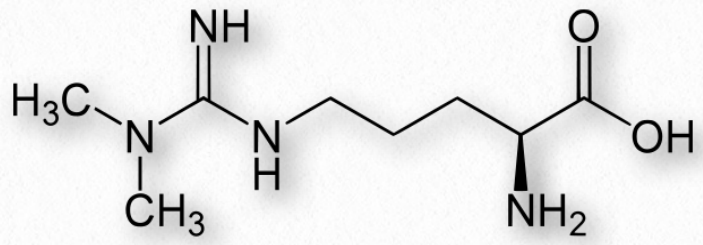


Figure 6.140 - Asymmetric dimethyl arginine (ADMA)

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1. **Glutamate** + **Acetyl-CoA**

   ⇅ (**Acetylglutamate synthetase**)

   N-acetylglutamate + **CoA-SH**

2. **N-acetylglutamate** + **ATP**

   ⇅ (**N-acetylglutamate kinase**)

   N-acetyl-γ-glutamyl phosphate

3. N-acetyl-γ-glutamyl phosphate + **NAD(P)H**

   ⇅ (**N-acetylglutamate dehydrogenase**)

   N-acetylaglutamate-γ-semialdehyde + **NAD(P)$^+$**

4. N-acetylaglutamate-γ-semialdehyde + **Glutamate**

   ⇅ (**Transaminase**)

   N-acetylornithine + **α-ketoglutarate**

5. **N-acetylornithine** + H_2O

   ⇅ (**N-acetylornithinase**)

   Ornithine + **Acetate**

Serine family

Serine is a non-essential amino acid synthesized from several sources. One starting point is the glycolysis intermediate, 3-phosphoglycerate, (3-PG) in a reaction

3-PG + **NAD$^+$**

⇅

3-phosphohydroxypyruvate + **NADH** + H^+

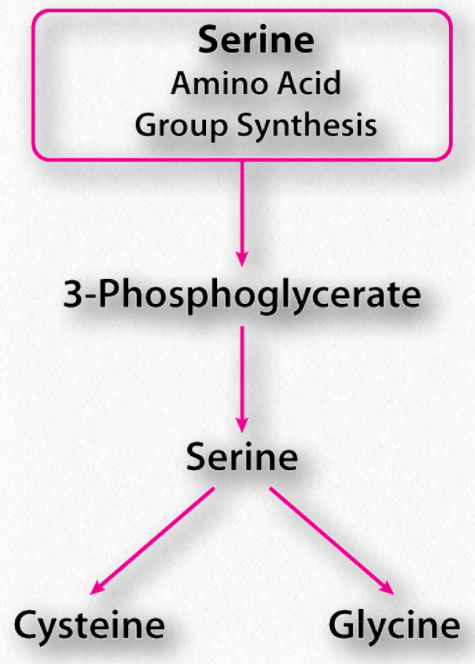

Image by Aleia Kim

catalyzed by 3-PG dehydrogenase.

Transamination by phosphoserine aminotransferase produces O-phosphoserine. The phosphate is then removed by phosphoserine phosphatase, to make serine. These reactions are shown below. Phosphoserine phosphatase is missing in the genetic disease known as Williams-Beuren syndrome.

1. **3-phosphohydroxypyruvate** + **Glutamate**

   ⇅

   O-phosphoserine + **α-ketoglutarate**

2. **O-phosphoserine** + H_2O

   ⇅

   Serine + **P_i**

Serine can also be derived from glycine and *vice versa*. Their metabolic paths are intertwined as will be seen below. Serine is important for metabolism of purines and pyrimidines, and is the precursor for glycine, cysteine, and tryptophan in bacteria, as well as for sphingolipids and folate. Serine in the active site of serine proteases is essential for catalysis. A serine in the active site of acetylcholinesterases is the target of nerve gases and insecticides.

Covalent modification target

Serine in proteins can be the target of glycosylation or phosphorylation. D-serine is the second D-amino acid known to function in humans. It serves as a neuromodulator for NMDA receptors, by serving as a co-agonist, together with glutamate. D-serine is being studied as a schizophrenia treatment in rodents and as a possible biomarker for Alzheimers.

Glycine

As noted, glycine's metabolism is intertwined with that of serine. This is apparent in the reaction catalyzed by serine hydroxymethyltransferase.

Serine + **Tetrahydrofolate**

⇅

Glycine + **N_5,N_{10}-Methylene Tetrahydrofolate** + H_2O

Notably, the previous reaction is also needed for recycling of folate molecules, which are important for single carbon reactions in nucleotide synthesis.

Vertebrates can also synthesize glycine in their livers using the enzyme glycine synthase.

Glycine is a very abundant component of collagen. It is used in the synthesis of purine nucleotides and porphyrins. It is an inhibitory neurotransmitter and is a co-agonist of NMDA receptors with glutamate. Glycine was detected in material from Comet Wild 2.

Cysteine

Cysteine can be synthesized from several sources. One source is the metabolism of the other sulfur-containing amino acid, methionine. This begins with formation of S-Adenosyl-Methionine (SAM), catalyzed by methionine adenosyltransferase.

Methionine + **ATP**

⇅

SAM + **P_i** + **PP_i**

SAM is a methyl donor for methyl transfer reactions and that is the next step in the pathway - donation of a methyl group (catalyzed by transmethylase)

SAM + Acceptor

⇅

SAH + CH_3-Acceptor

SAH (S-Adenosylhomocysteine) is cleaved by S-adenosylhomocysteine hydrolase,

SAH

⇅

Homocysteine + **Adenosine**

Homocysteine can be recycled back to methionine by action of methionine synthase

On the path to making cysteine, homocysteine reacts as follows (catalyzed by cystathionine **β**-synthase).

Homocysteine + **Serine**

⇅

Cystathionine

Last, cystathionase catalyzes release of cysteine

Cystathionine + H_2O

⇅

Cysteine + **β-ketobutyrate** + NH_4^+

β-ketobutyrate can be metabolized to propionyl-CoA and then to succinyl-CoA to be used ultimately in the citric acid cycle.

Another route to making cysteine is a two-step process that begins with serine, catalyzed first by serine-O-acetyltransferase

Serine + **Acetyl-CoA**

⇅

CoA-SH + **O-acetyl-L-serine**

and then by cysteine synthase

O-acetyl-L-serine + **H_2S**

⇅

L-cysteine + **Acetate**

Cysteine can be also released from cystine by cystine reductase

L-cystine + 2 **NADH** + $2H^+$

⇅

2 **Cysteine** + 2 **NAD^+**

Finally, cysteine can be made from cysteic acid by action of cysteine lyase

L-cysteic Acid + **H_2S**

⇅

L-cysteine + **Sulfite**

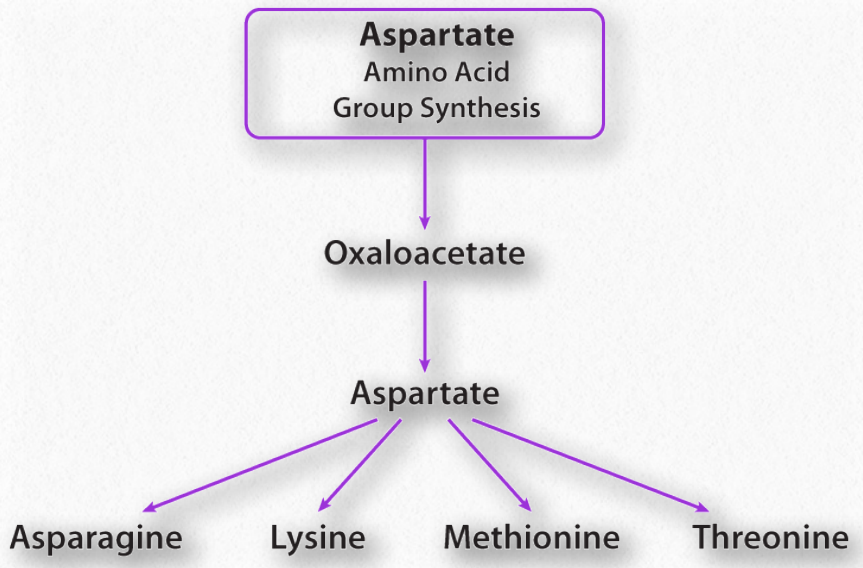

Image by Aleia Kim

Aspartate family

Metabolism of aspartic acid is similar to that of glutamate. Aspartic acid can arise from transamination of a citric acid cycle intermediate (oxaloacetate).

Aspartate can also be generated from asparagine by the enzyme asparaginase.

Asparagine + H_2O

⇅

Aspartate + **NH_4^+**

Further, aspartate can be produced by reversal of a reaction in the urea cycle (see HERE)

Aspartate is also a precursor to four amino acids that are essential in humans. They are methionine, isoleucine, threonine, and lysine. Because oxaloacetate can be produced from aspartate, aspartate is an important intermediate for gluconeogenesis when proteins are the energy source.

YouTube Lectures by Kevin HERE & HERE

Asparagine

Asparagine, too, is an amino acid produced in a simple transamination reaction. In this case, the precursor is aspartate and the amine donor is glutamine (catalyzed by asparagine synthetase)

Aspartate + **Glutamine** + **ATP**

⇅

Asparagine + **Glutamate** + **AMP** + **PP_i**

Methionine

Metabolism of methionine overlaps with metabolism of the other sulfur-containing amino acid, cysteine. Methionine is not made in humans (essential) so the pathway shown in Figure 6.141 is from bacteria.

The process begins with phosphorylation of aspartate. Numbers for each catalytic step in the figure are for the enzymes that follow:

1 - Aspartokinase
2 - Aspartate-semialdehyde dehydrogenase
3 - Homoserine dehydrogenase
4 - Homoserine O-transsuccinylase
5 - Cystathionine-γ-synthase
6 - Cystathionine-β-lyase
7 - Methionine synthase

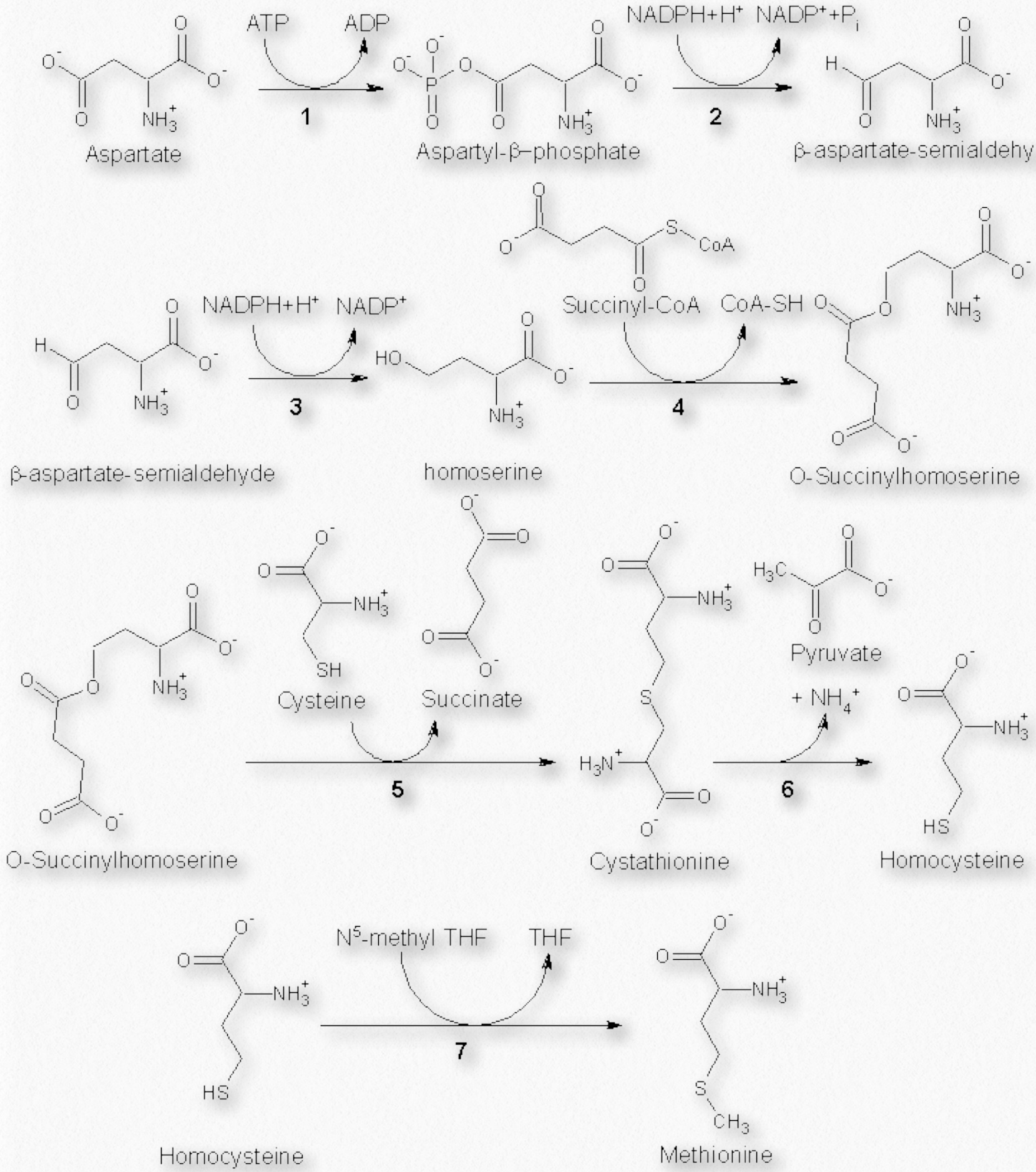

Figure 6.141 - Synthesis of methionine from aspartic acid

Wikipedia

Though humans cannot make methionine by the pathway shown in the figure, they can recycle methionine from homocysteine (a product of S-adenosylmethionine metabolism). This reaction requires the enzyme methionine synthase and Vitamin B_{12} as a co-factor.

An alternative pathway of converting homocysteine to methionine involves a prominent liver enzyme, betaine-homocysteine methyltransferase. This enzyme catalyzes the reaction below.

Glycine Betaine + **Homocysteine**

⇅

Dimethylglycine + **Methionine**

In this reaction, a methyl group is transferred to homocysteine from glycine betaine to make the methionine. Glycine betaine is a trimethylated amine of glycine found in plants. It is a byproduct of choline metabolism.

Bacteria, mitochondria, and chloroplasts use a modified form of methionine, N-formylmethionine (Figure 6.142), as the first amino acid incorporated into their proteins. Formylation of methionine occurs only after methionine has been attached to its tRNA for translation. Addition of the formyl group is catalyzed by the enzyme methionyl-tRNA formyltransferase

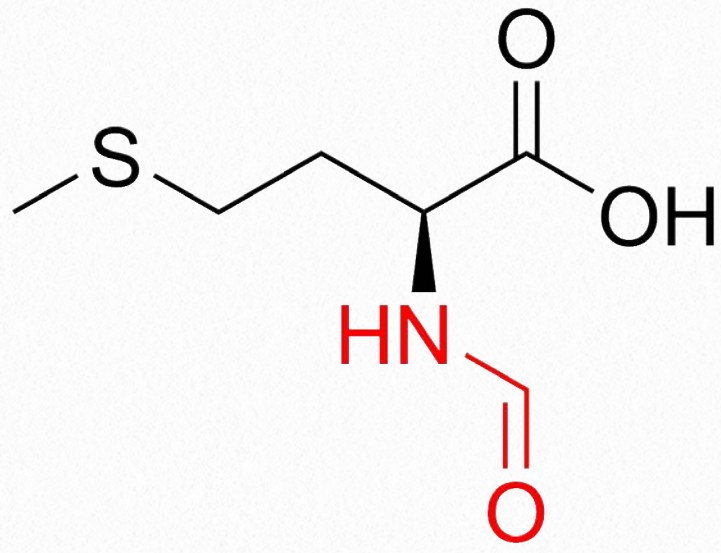

Figure 6.142 - **N-formyl-methionine**

Threonine

Though threonine is chemically similar to serine, the metabolic pathway leading to threonine does not overlap with that of serine. As seen in the figure, aspartate is a starting point for synthesis. Two phosphorylations/dephosphorylations and two reductions with electrons from NADPH result in production of threonine.

Enzymes in Figure 6.143 are as follows:

1 Aspartokinase
2 β-aspartate semialdehyde dehydrogenase
3 Homoserine dehydrogenase
4 Homoserine kinase
5 Threonine synthase

Breakdown of threonine produces acetyl-CoA and glycine. It can also produce α-ketobutyrate, which can be converted to succinyl-CoA for oxidation in the citric acid cycle.

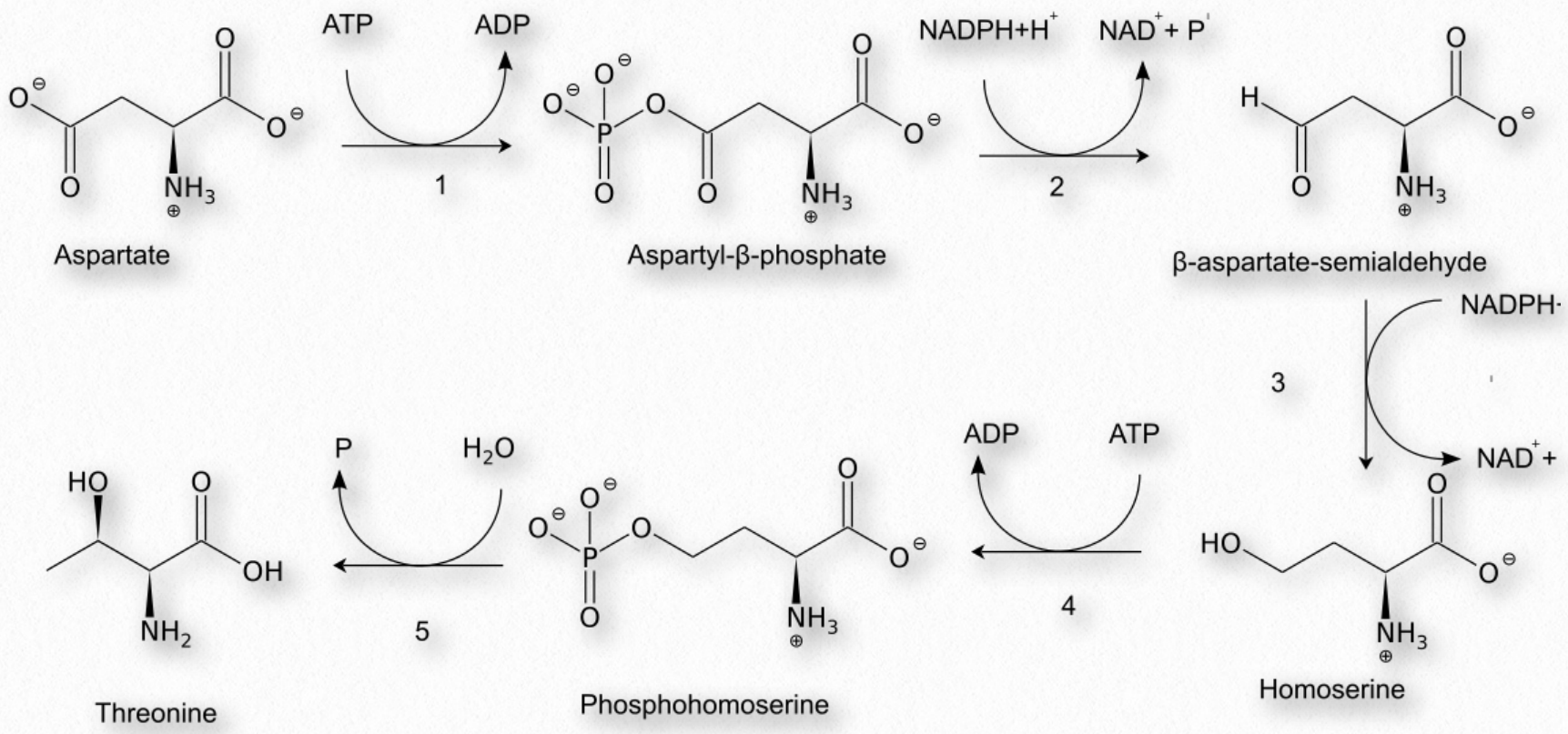

Figure 6.143 - Synthesis of threonine from aspartate

Wikipedia

Lysine

To get from aspartate to lysine, nine reactions and two non-enzymatic steps are involved, as seen in Figure 6.144. Enzymes involved in lysine biosynthesis include (numbers correspond to numbered reactions in Figure 6.144):

1 - Aspartokinase
2 - Aspartate-semialdehyde dehydrogenase
3 - 4-hydroxy-tetrahydrodipicolinate synthase
4 - 4-hydroxy-tetrahydrodipicolinate reductase
5 - 2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase
6 - Succinyl-diaminopimelate transaminase
7 - Succinyl-diaminopimelate desuccinylase
8 - Diaminopimelate epimerase
9 - Diaminopimelate decarboxylase

Low in cereal grains

Lysine is the essential amino acid found in the smallest quantity in cereal grains, but is found abundantly in legumes. Besides its synthesis and breakdown, lysine can be methylated, acetylated, hydroxylated, ubiquitinated, sumoylated, neddylated, biotinylated, pupylated, and carboxylated within proteins containing it. Hydroxylation of lysine is important for strengthening collagen and acetylation/methylation of lysine in histone proteins play roles in control of gene expression and epigenetics. Besides being used to make proteins, lysine is impor-

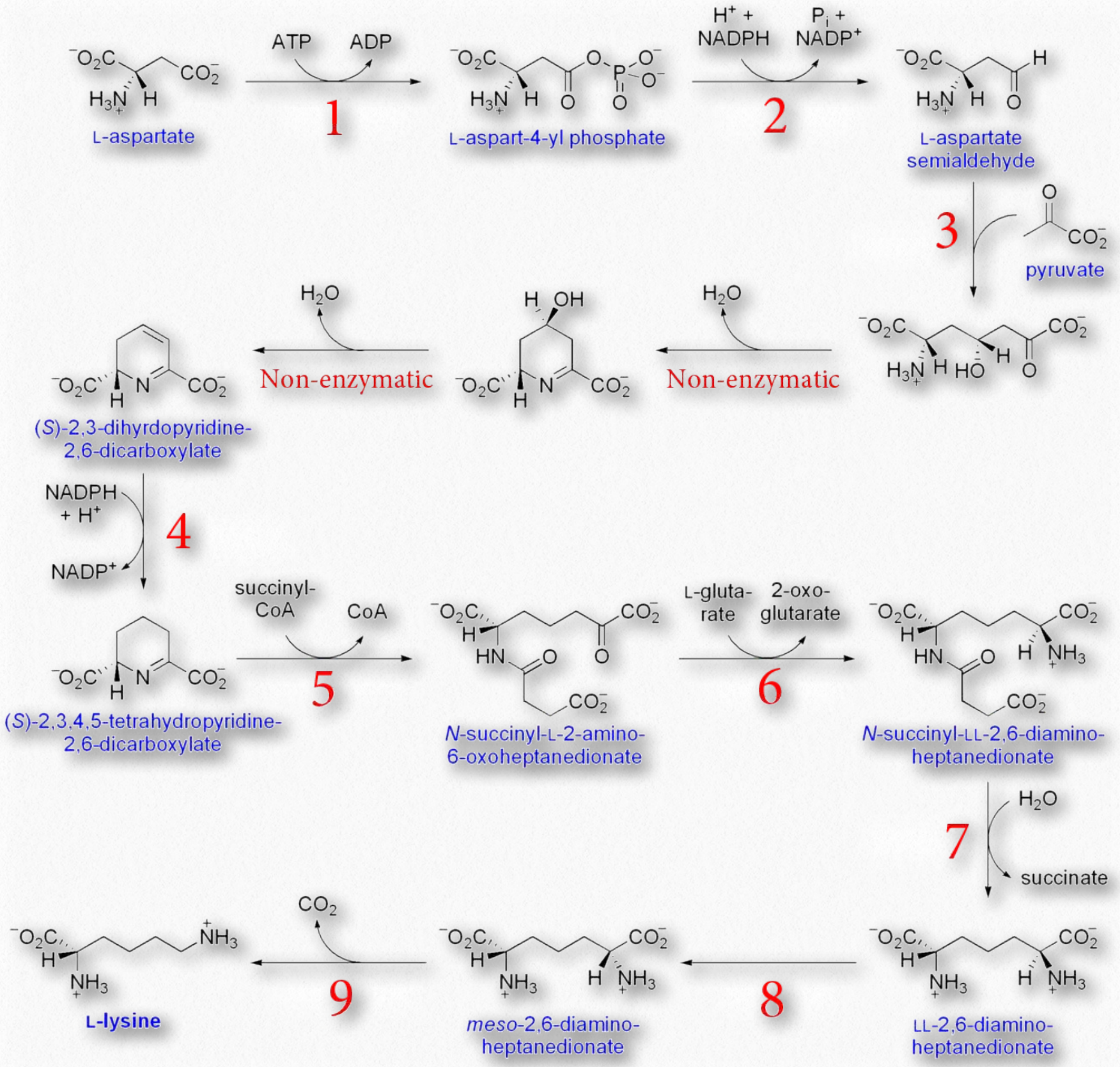

Figure 6.144 - Synthesis of Lysine from Aspartic Acid

tant for calcium absorption, recovery from injuries, and for production of hormones.

Oral lysine has been used as a treatment for herpes infections (cold sores) but its efficacy is not established and it is not clear by what mechanism is would reduce the duration of the infection or reduce the number of outbreaks of viral infection..

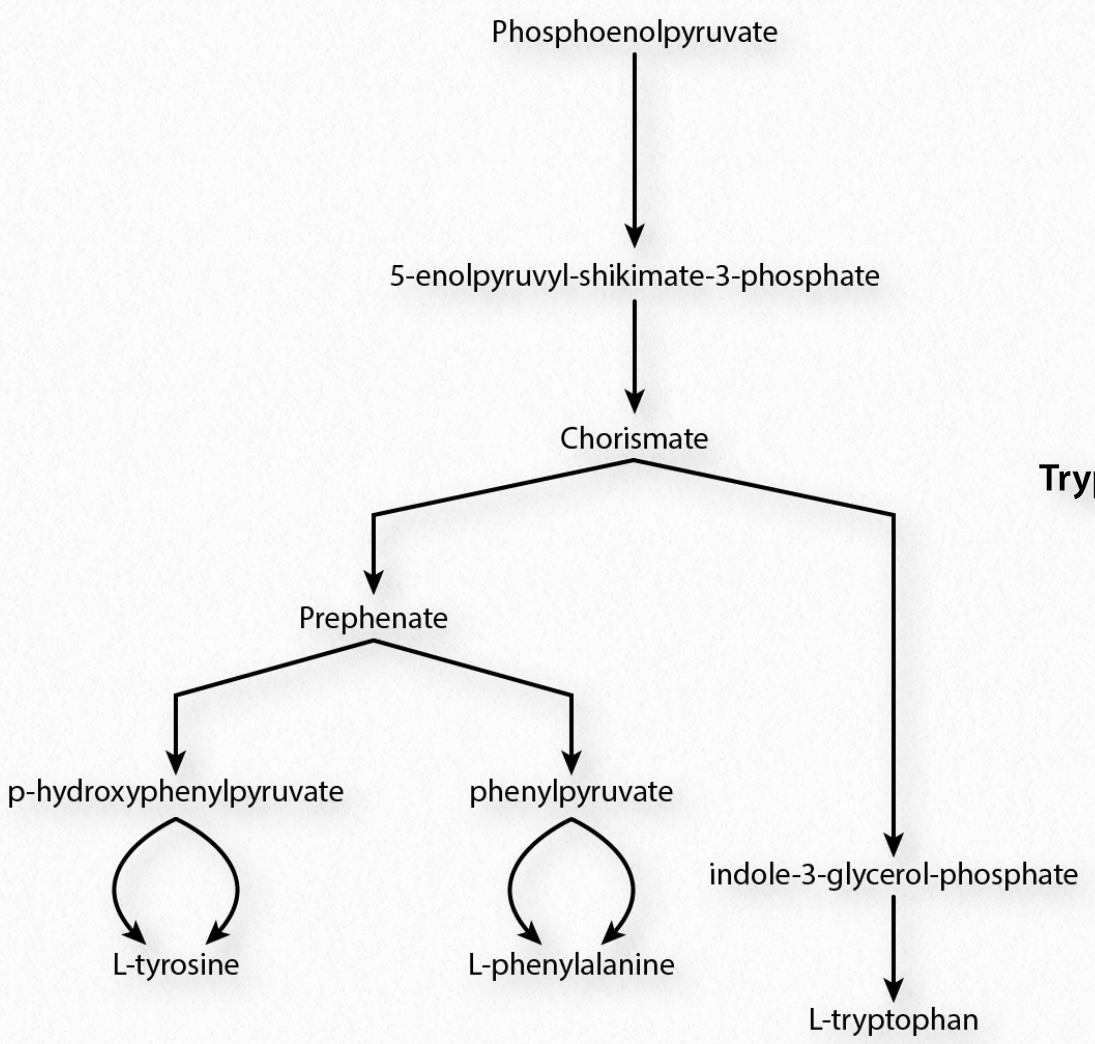

Figure 6.145 - Schematic pathway from PEP to aromatic amino acids

Image by Pehr Jacobson

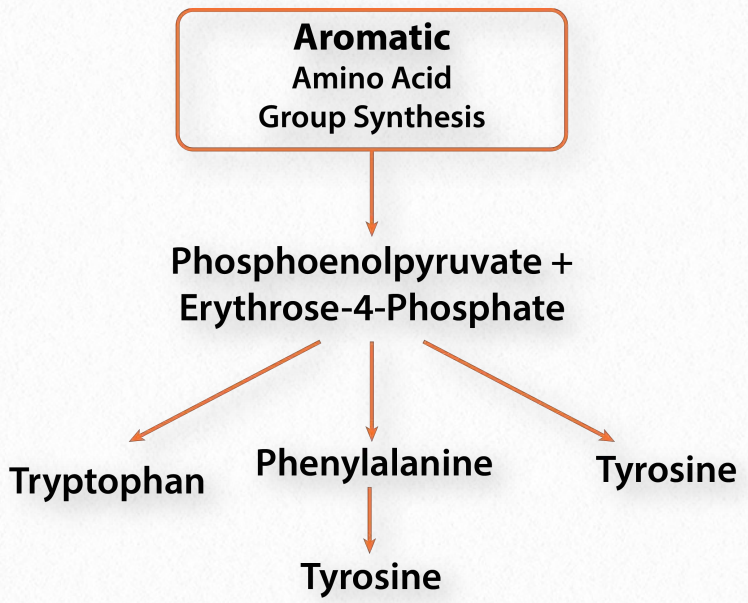

Image by Aleia Kim

Aromatic amino acids

The aromatic amino acids, tryptophan, phenylalanine, and tyrosine can all be made starting with two simple molecules - PEP and erythrose-4-phosphate (Figure 6.145). All three aromatic amino acids are also important sources of hormones, neurotransmitters, and even the skin pigment melanin.

YouTube Lectures by Kevin HERE & HERE

Tryptophan synthesis

The proteogenic amino acid with the largest R-group, tryptophan is an essential amino acid distinguished structurally by its indole group. The amino acid is made in bacteria and plants from shikimic acid or anthranilate and serine is used in its synthesis.

Erythrose-4-phosphate and phosphenolpyruvate (PEP) also serve as building blocks of tryptophan. The pathway of its synthesis is shown in Figures 6.146 to 6.148.

Erythrose-4-phosphate and phosphoenolpyruvate (PEP) are joined and then, after one hydrolysis, one dehydration, one oxidation and one reduction, the product is shikimic acid (Figure 6.147).

Shikimic acid is converted to chorismic acid in three steps, as shown in Figure 6.147. Finally, synthesis of tryptophan from chorismic acid is shown in Figure 6.148.

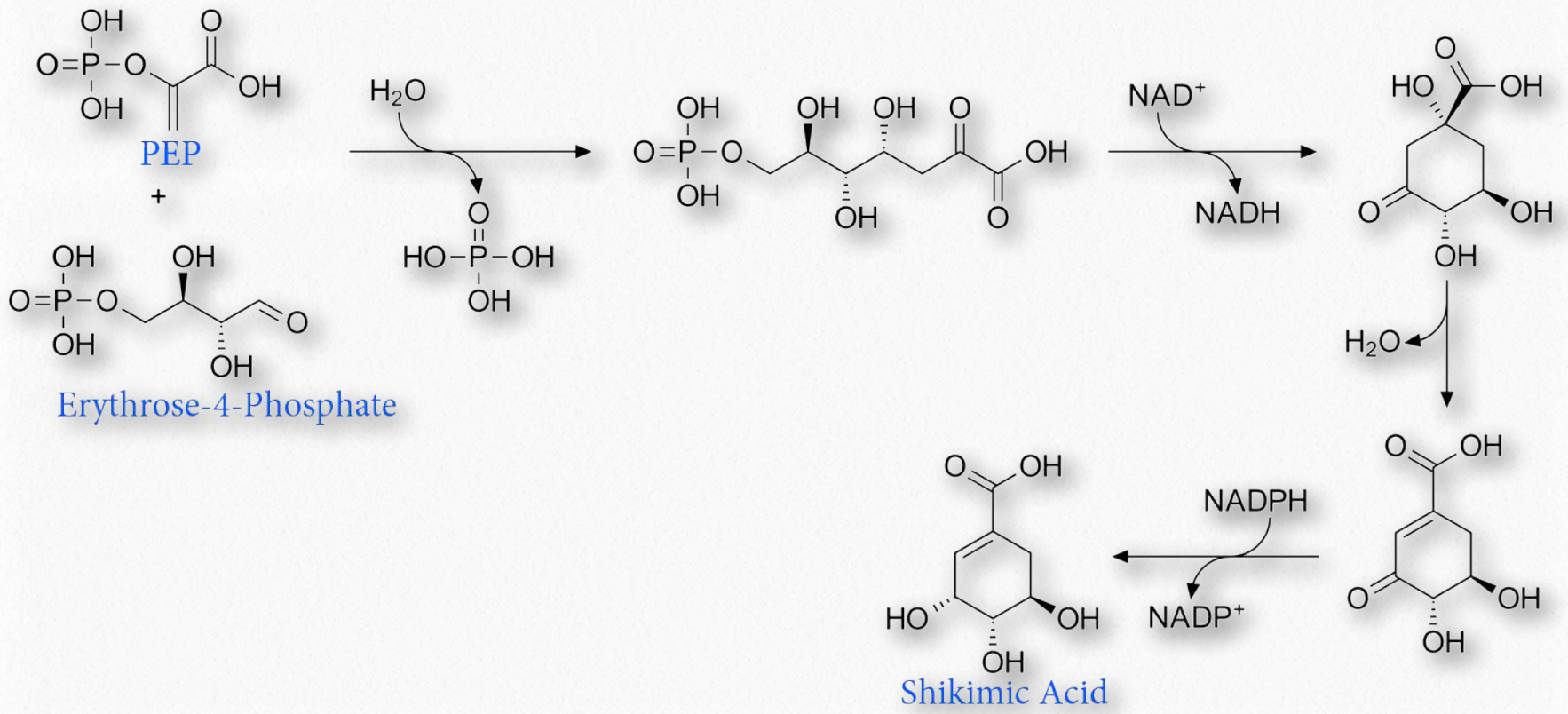

Figure 6.146 - Synthesis of shikimic acid from PEP and erythrose-4-phosphate

Wikipedia

Regulation

Regulation of tryptophan synthesis in bacteria occurs partly *via* a process called attenuation that operates through the trp operon. In this mechanism, low levels of tryptophan slow ribosomal movement (and translation) through the operon. This is particularly important because bacteria can have transcription and translation occurring simultaneously. Slowing translation due to low tryptophan levels allows a tran-

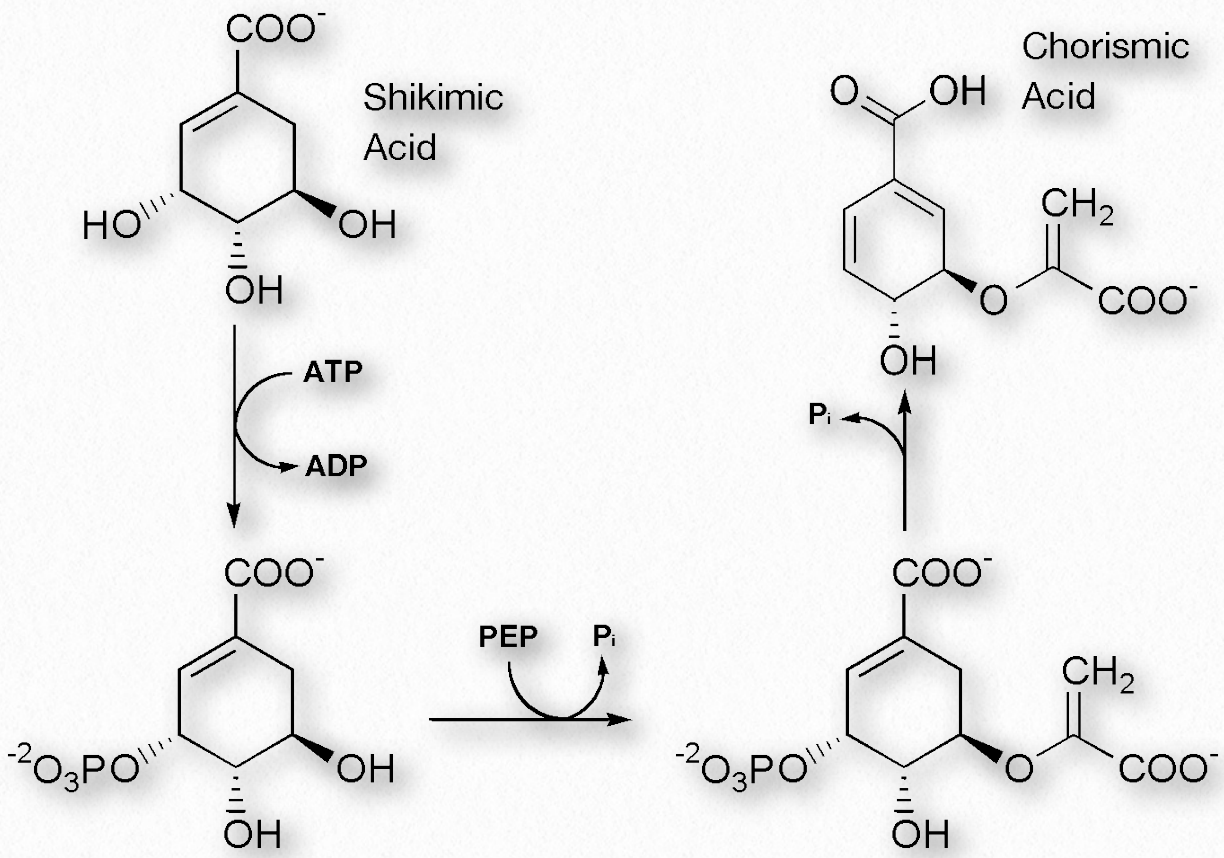

Figure 6.147 - The route to tryptophan - making chorismic acid from shikimic acid

Wikipedia

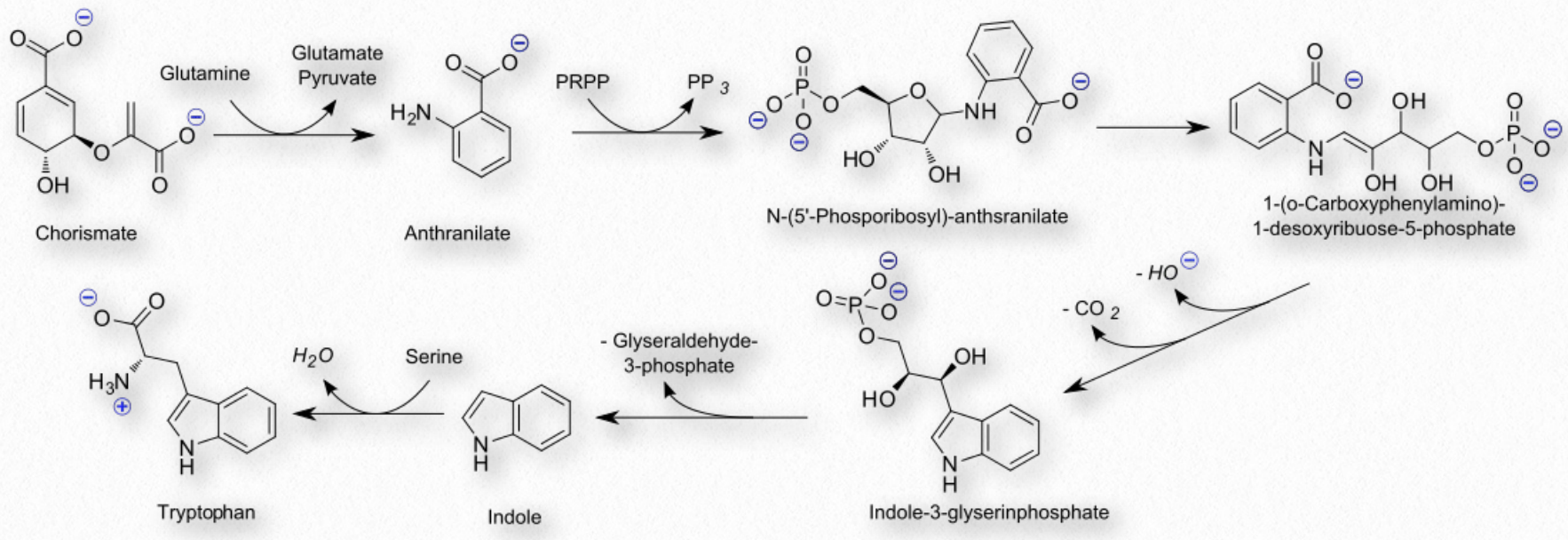

Figure 6.148 - Synthesis of tryptophan from chorismic acid

scription termination mechanism to be inhibited. Since translation only slows when tryptophan is in short supply, premature termination of transcription occurs when tryptophan is abundant (see also HERE).

Besides its importance for making proteins, tryptophan is an important precursor of serotonin (neurotransmitter), melatonin (hormone), niacin (vitamin), and auxin (plant hormone). The two pathways leading from tryptophan to three of these molecules is shown in Figure 6.149.

Melatonin

Melatonin is a compound made from tryptophan that is found in a wide spectrum of biological systems, including plants, animals, fungi, and bacteria. In animals, it acts as a hormone for circadian rhythm synchronization, signaling the onset of darkness each day. It has effects on the timing of sleep, seasonal effects, and can affect blood pressure, among other physiological phenomena. It can cross cell membranes, as well as the blood-brain barrier. Melatonin is a potent anti-oxidant and provides protective functions for nucleic acids. It is used sometimes to help in treatment of sleep disorders. Some reports have indicated that children with autism have abnormal melatonin pathways with low levels of the hormone.

Blue light

Melatonin production is affected by blue light and may be linked to sleep abnormalities for people using computer monitors after dark. To protect against this, some computer programs are available that reduce the screen's blue light output in the evenings. Special eyeglasses that block blue light are also available. Though melatonin is linked to sleep in some animals (including humans), noctur-

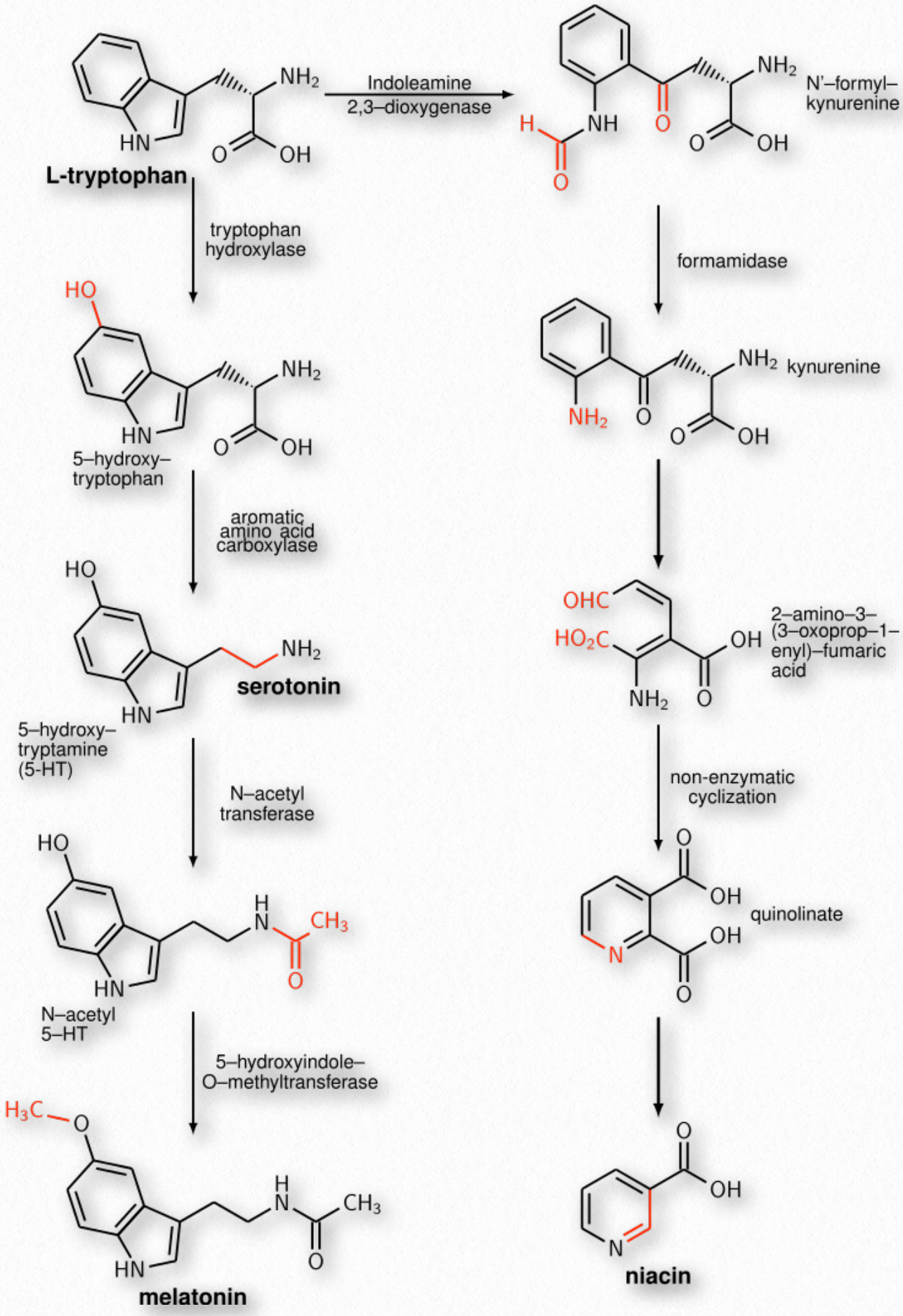

Figure 6.149 - Tryptophan is a precursor of serotonin, melatonin, and niacin

nal animals are activated by increasing melatonin levels. Varying day/night lengths during the year alter melatonin production and provide biological signals of the seasons. These are especially important in the seasonal coloring and breeding habits of some animals. Melatonin is present in cherries, bananas, grapes, rice, cereals, olive oil, wine, and beer.

Serotonin

Serotonin, or 5-hydroxytryptamine, is a monoamine neurotransmitter derived from tryptophan. Blood platelets store serotonin and release it when they bind to a clot, causing vasoconstriction. Serotonin plays a role in cognitive functions and enhances memory and learning. Serotonin is widely thought to be a contributor to feelings of happiness and well-

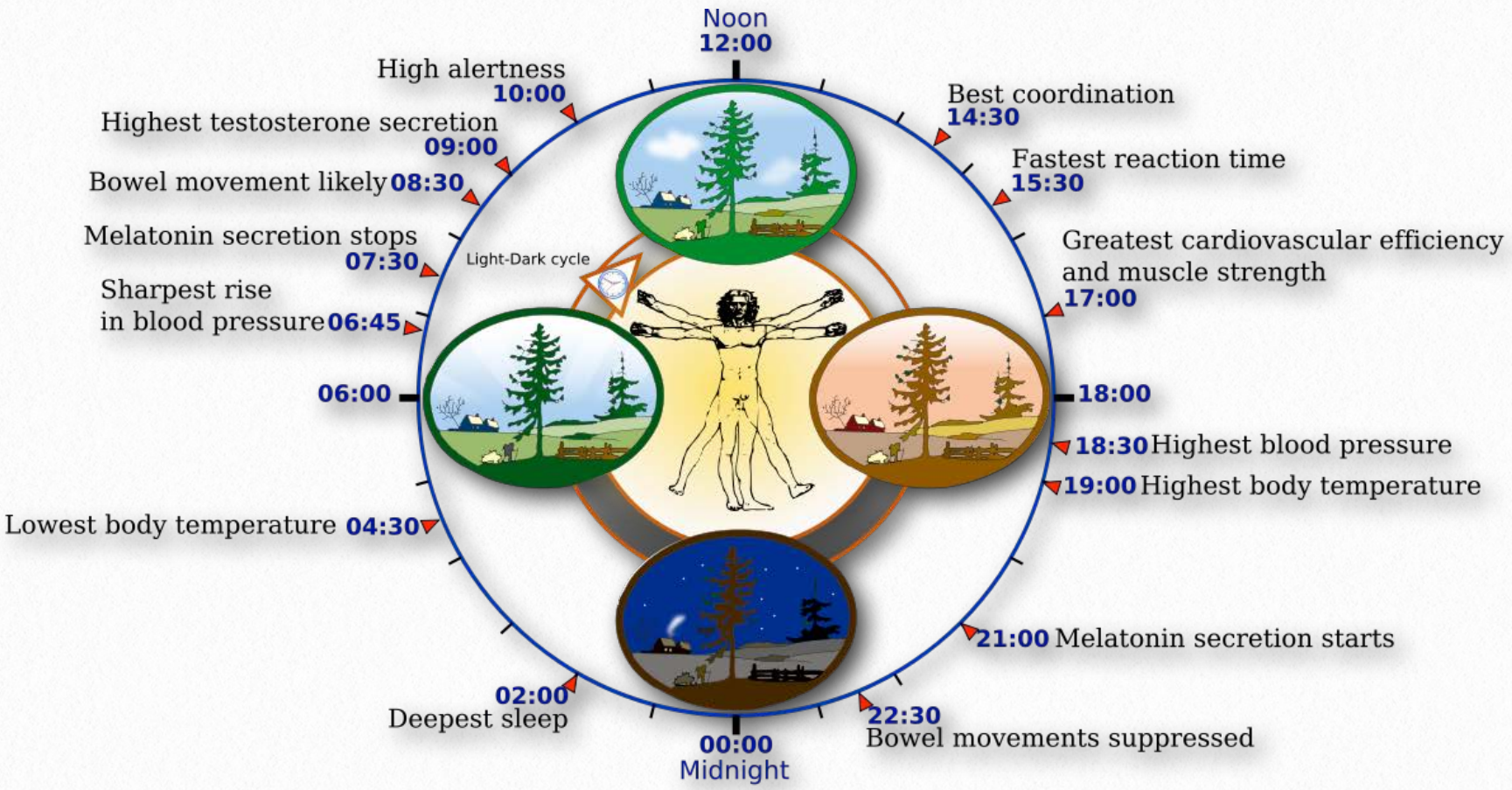

Figure 6.150 - Melatonin and human circadian rhythms

Wikipedia

being. Some common anti-depressant drugs, including Prozac, Paxil and Zoloft, act to modulate action of serotonin at synapses.

Niacin

Niacin is also known as Vitamin B_3 and nicotinic acid. Niacin can be made from tryptophan and people who have the inability to absorb tryptophan in the digestive system exhibit symptoms similar to niacin deficiency.

YouTube Lectures by Kevin HERE & HERE

Extreme deficiency of niacin in the diet leads to the disease known as pellagra, while insufficient amounts of niacin in the diet are linked with nausea, anemia, headaches, and tiredness. A diet that is primarily composed of grains like corn can lead to niacin deficiency, because the niacin in these sources is not readily bioavailable. Treatment of the grain with alkali, as in the traditional Mexican practice of soaking corn in lime, can make the niacin more easily absorbed from food.

Niacin is related to pyridine and the amide form of it is nicotinamide, an important component of NAD^+/NADH and $NADP^+$/NADPH. The last pairs of molecules are essential as electron acceptors/carriers for most cellular oxidation-reduction reactions.

Auxins

Auxins are plant growth hormones derived from tryptophan. The most important of these

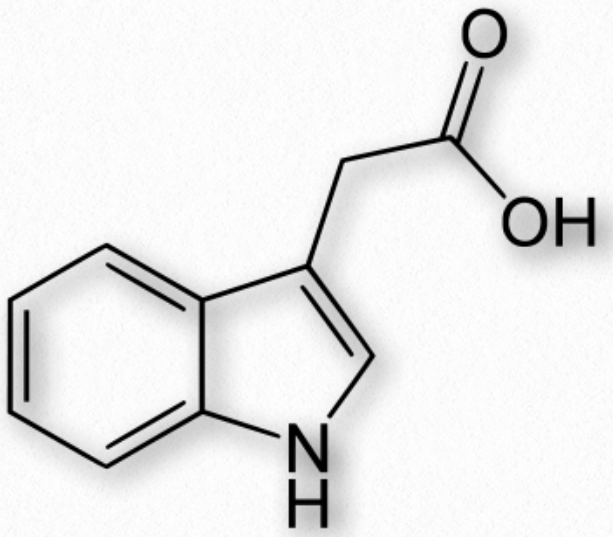

Figure 6.151 - Auxin - indole-3-acetic acid

is indole-3-acetic acid (Figure 6.151). Auxins are involved in almost every aspect of plant growth and development. They activate proteins, such as expansins and various enzymes that modify the structure of cell wall components, to loosen the cell walls of a plant and stimulate elongation of cells. In the presence of cytokinins, auxins stimulate cell division. Auxins are also involved in the maintenance of meristems and in cell patterning and organogenesis. Auxins are crucial for establishing root primordia as well as for elongation of root hairs. Auxins play important roles in organizing the xylem and phloem of plants, and it has long been known that plant callus tissue can be made to differentiate into shoots or roots, depending on the relative concentrations of auxins and cytokinins supplied in the medium.

Figure 6.152 - Wild type *Arabidopsis* (left) and a mutant unable to transmit auxin signals (right)

Wikipedia

Figure 6.153 Crown gall on a rose

Wikipedia

Agrobacterium tumefaciens, a bacterium which infects a wide variety of plants, inserts its own DNA, including genes necessary for the synthesis of plant hormones, into its host's cells. The subsequent overproduction of auxins stimulates the growth of tumors (called crown galls) on the plant (Figure 6.153).

Phenylalanine

Phenylalanine is an essential, hydrophobic amino acid in humans that is a precursor of tyrosine and since tyrosine is a precursor of several important catecholamines, phenylalanine is, thus, a precursor of them as well.

PKU

Phenylalanine is linked to the genetic disease phenylketonuria (PKU) which arises from an inability to metabolize the amino acid in people lacking (or deficient in) the enzyme phenylalanine hydroxylase. If left untreated, the disease can cause brain damage and even death, but if detected early, it can be easily managed by carefully monitoring dietary intake of the amino acid. Because of this, newborns are routinely tested for PKU. Phenylalanine is a component of the artificial sweetener known as aspartame (Nutrasweet - Figure 6.154) and is consequently dangerous for people suffering from this disorder.

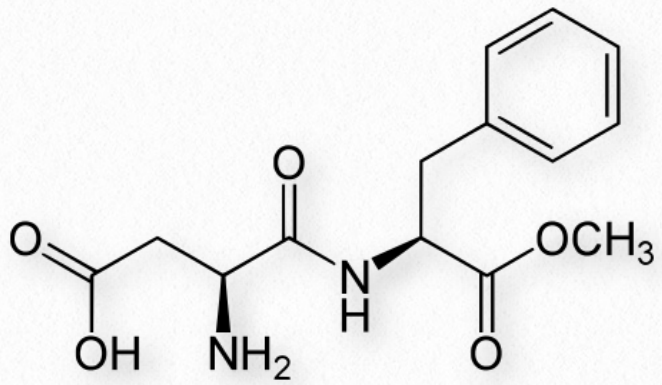

Figure 6.154 - Aspartame - a methyl ester of the aspartic acid-phenylalanine dipeptide

Biosynthesis of phenylalanine in bacteria overlaps with synthesis of tryptophan. The branch occurs at chorismic acid where the enzyme chorismate mutase catalyzes a molecular rearrangement to produce prephenate.

Chorismate ⇅ **Prephenate**

Proton attack on prephenate results in loss of water and carbon dioxide to yield phenylpyruvate.

Prephenate ⇅ **Phenylpyruvate** + H_2O + CO_2

Transamination of phenylpyruvate yields phenylalanine.

Phenylpyruvate + Glutamate ⇅ **Phenylalanine + α-ketoglutarate**

Alternatively, phenylalanine can obtain its amine group in a transamination reaction from alanine.

Phenylpyruvate + Alanine ⇅ **Phenylalanine + Pyruvate**

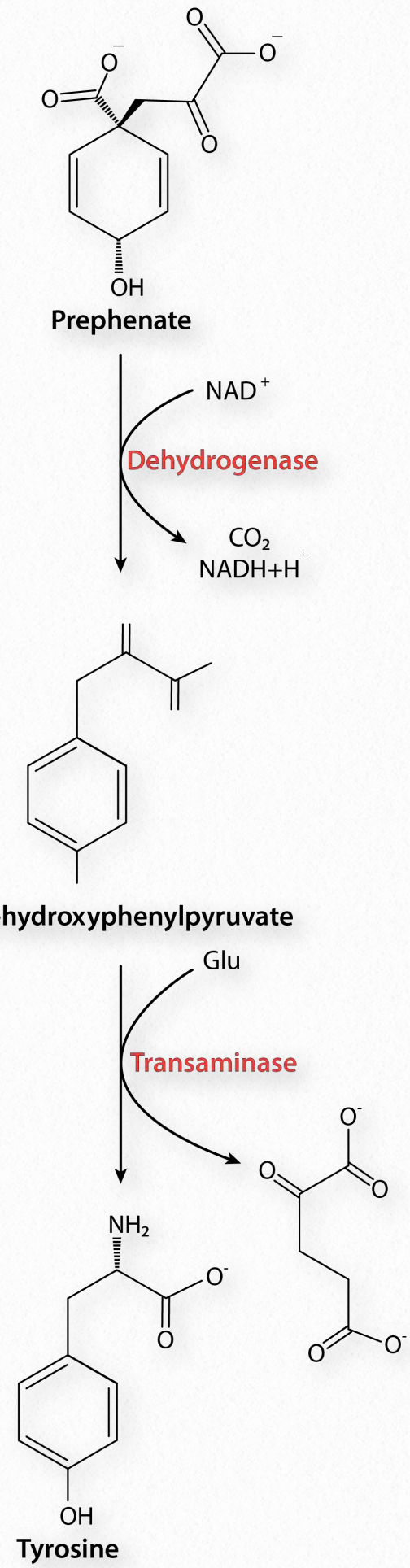

Figure 6.155 - Synthesis of tyrosine from prephenate

Image by Pehr Jacobson

Hydroxylation of phenylalanine by aromatic amino acid hydroxylase (phenylalanine hydroxylase) yields tyrosine.

Tyrosine

Because tyrosine is made from phenylalanine and the latter is an essential amino acid in humans, it is not clear whether to classify tyrosine as essential or non-essential. Some define it as a conditionally essential amino acid. Others simply categorize it as non-essential.

As noted above, tyrosine can arise as a result of hydroxylation of phenylalanine. In addition, plants can synthesize tyrosine by oxidation of prephenate followed by transamination of the resulting 4-hydroxyphenylpyruvate (Figure 6.155).

The hydroxyl group on tyrosine is a target for phosphorylation by protein kinase enzymes involved in signal transduction path-

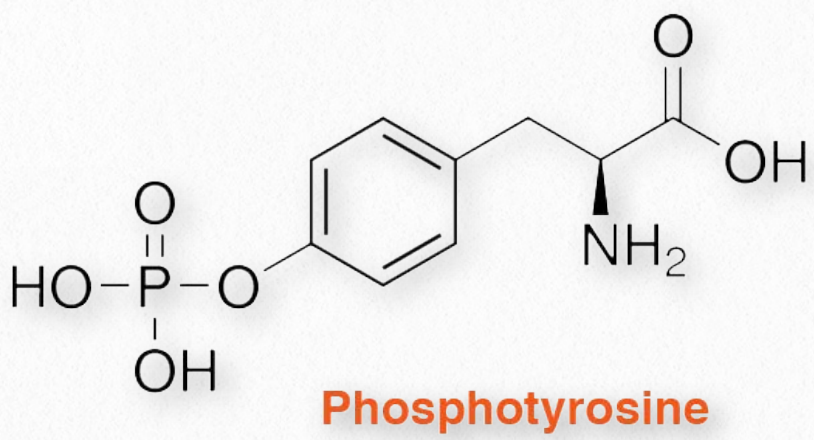

Figure 6.156 - The phosphorylated form of tyrosine

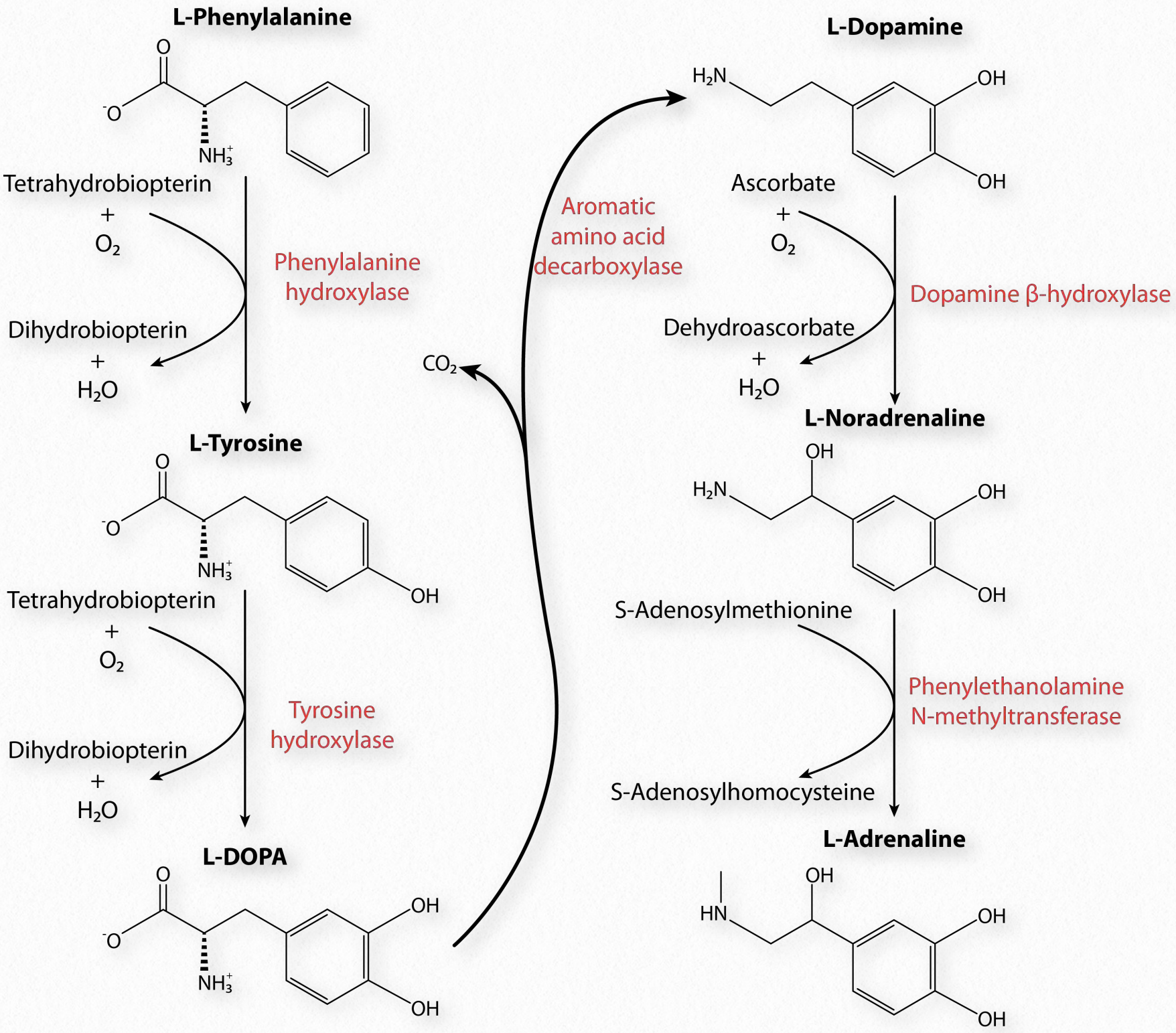

Figure 6.157 - Conversion of phenylalanine and tyrosine to catecholamines

Image by Pehr Jacobson

ways (Figure 6.156). When located in membranes, these enzymes are referred to as receptor tyrosine kinases and they play important roles in controlling cellular behavior/response.

In photosystem II of chloroplasts, tyrosine, at the heart of the system, acts as an electron donor to reduce oxidized chlorophyll. The hydrogen from the hydroxyl group of tyrosine is lost in the process, requiring re-reduction by four core manganese clusters.

Tyrosine is also important in the small subunit of class I ribonucleotide reducta-

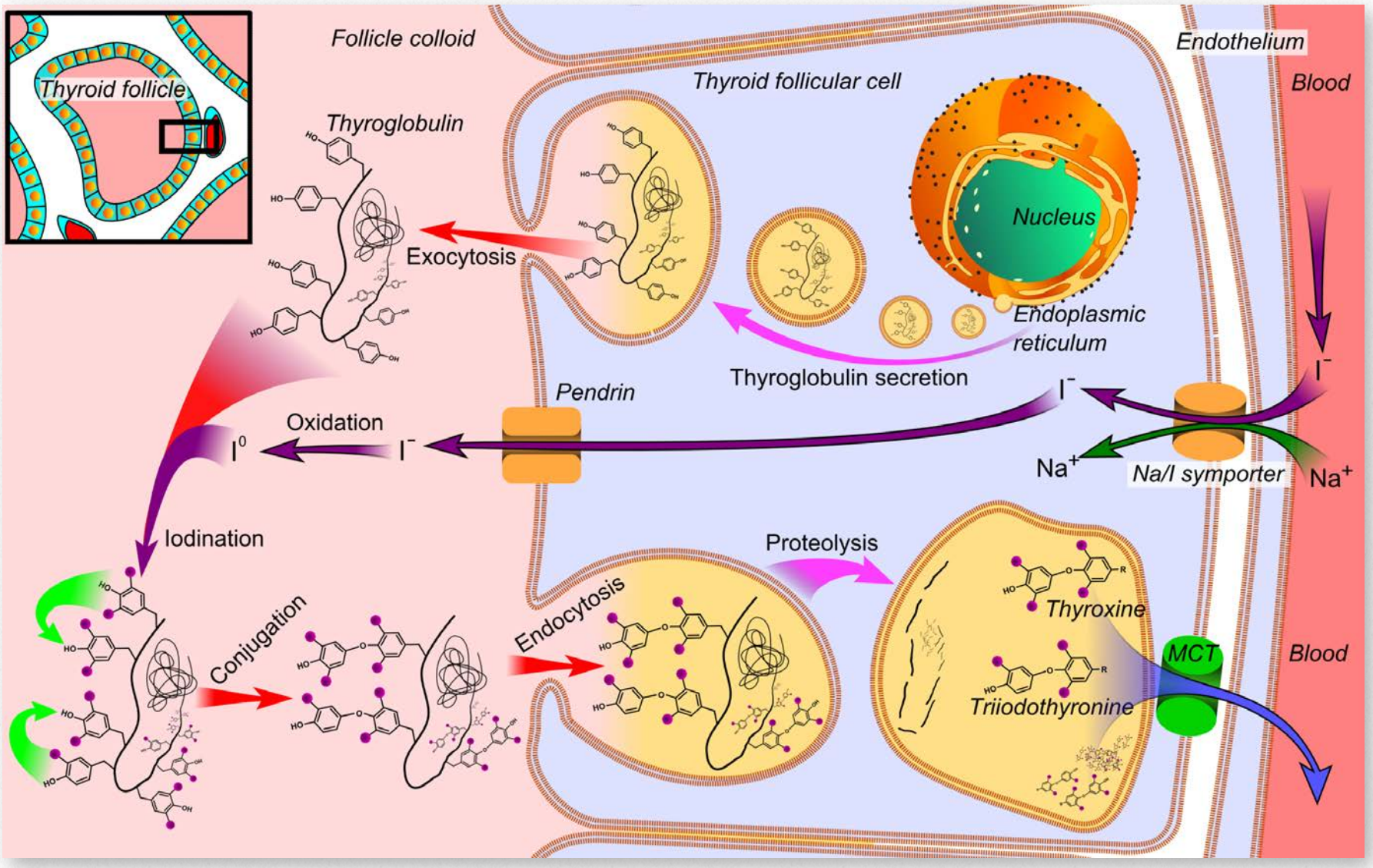

Figure 6.158 - Synthesis of thyroid hormones from tyrosine and movement in the body

Wikipedia

ses where it forms a stable radical in the catalytic action of the enzyme (see HERE).

Tyrosine metabolites

Tyrosine is a precursor of catecholamines, such as L-dopa, dopamine, norepinephrine, and epinephrine (Figure 6.157). The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are also synthesized from tyrosine. As shown in Figure 6.158, this involves a series of iodinations of tyrosines side-chains of a protein known as thyroglobulin. Combinations of iodinated tyrosines give rise to thyroxine and triiodothyronine. These are subsequently cleaved from the protein and released into the bloodstream.

YouTube Lectures by Kevin HERE & HERE

Oxidation and polymerization of tyrosine is involved in synthesis of the family of melanin pigments. Tyrosine is involved in the synthesis of at least two types - eumelanin and pheomelanin (Figure 6.159).

Another molecule derived from tyrosine is the benzoquinone portion of Coenzyme Q (CoQ). This

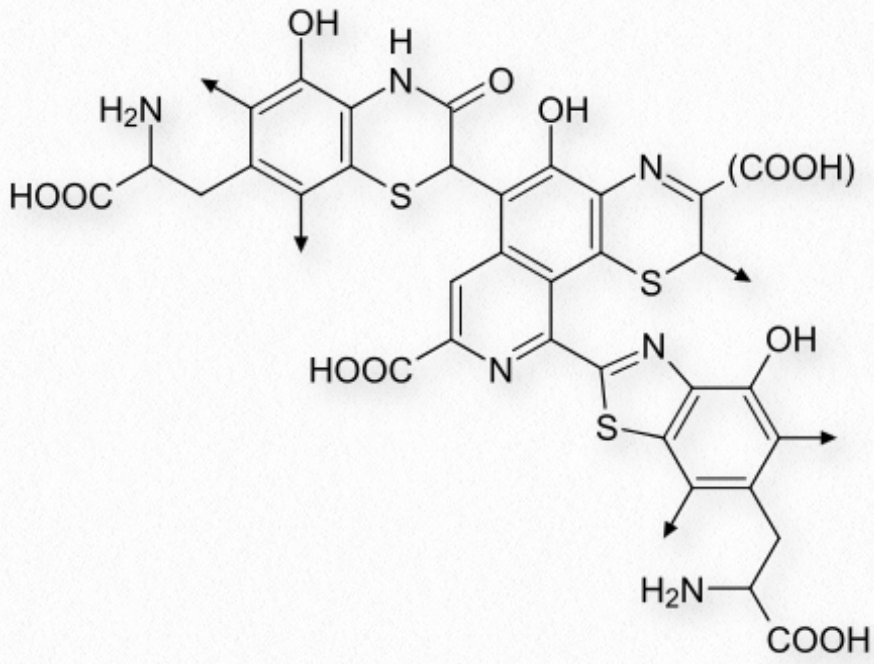

Figure 6.159 - A portion of pheomelanin - Arrows show directions of polymer extension

pathway requires the enzyme HMG-CoA Reductase and since this enzyme is inhibited by cholesterol-lowering statin drugs, CoQ can be limited in people being treated for high cholesterol levels.

Dopamine

Dopamine plays several important roles in the brain and body. A member of the catecholamine and phenethylamine families, its name comes from the fact that it is an amine made by removing a carboxyl group from L-DOPA. Dopamine is synthesized in the brain and kidneys. It is also made in plants, though its function in plants is not clear. Conversion of dopamine to norepinephrine (Figure 6.157) requires vitamin C.

Dopamine is a neurotransmitter, being released by one nerve cell and then traveling across a synapse to signal an adjacent nerve cell. Dopamine plays a major role in the brain's reward-mediated behavior. Rewards, such as food or social interaction, increase dopamine levels in the brain, as do addictive drugs. Other brain dopamine pathways are involved in motor control and in managing the release of various hormones.

Chemical messenger

Outside the nervous system, dopamine is a local chemical messenger. In blood vessels, it inhibits norepinephrine release and causes vasodilation. In the kidneys, it increases sodium excretion and urine output. It reduces gastrointestinal motility and protects intestinal mucosa in the digestive system and in the immune system, it reduces lymphocyte activity. The effect dopamine has on the pancreas is to reduce insulin production. With the exception of the blood vessels, dopamine is synthesized locally and exerts its effects near the cells that release it.

Epinephrine

Epinephrine (also called adrenalin) is a catecholamine chemically related to norepinephrine that is a hormone with medical applications. It is used to treat anaphylaxis, cardiac arrest, croup, and, in some cases, asthma, when other treatments are not working, due to its ability to favor bronchodilation.

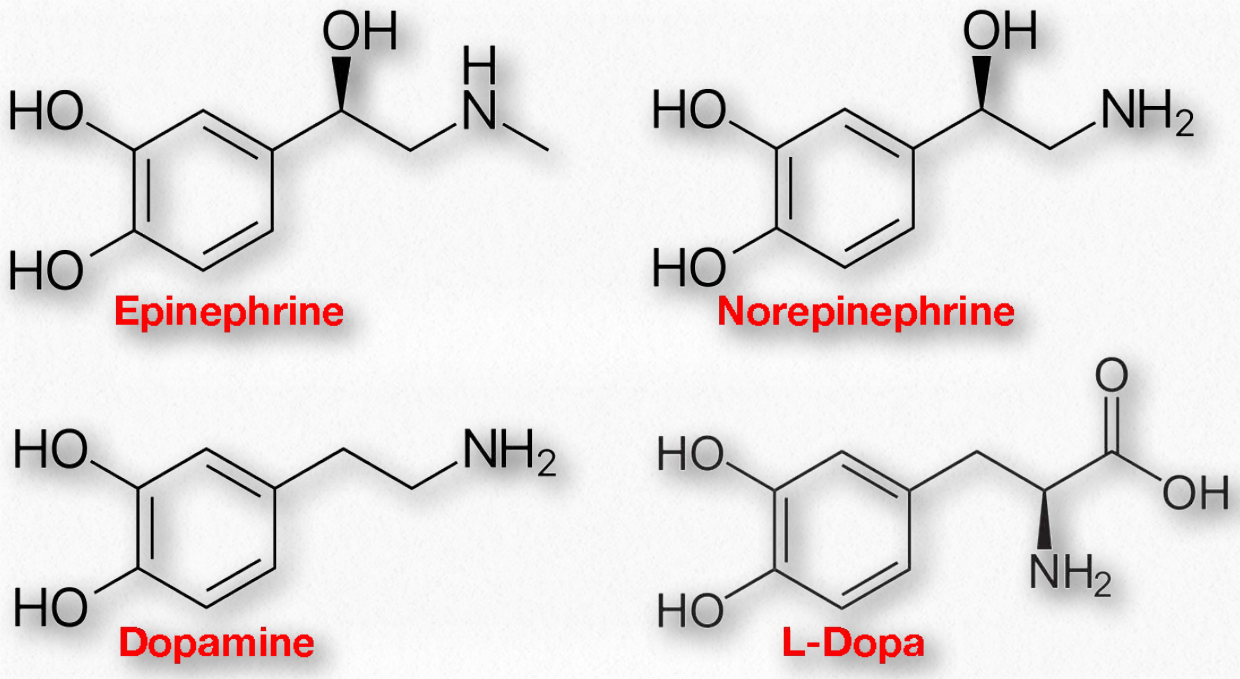

Figure 6.160 - Four catecholamines made from tyrosine

Epinephrine is the drug of choice for treating anaphylaxis. The compound may be given through inhalation, by intravenous injection, or subcutaneous injection and exerts effects through the α- and β-adrenergic receptors. In the body, it is produced and released by adrenal glands and some neurons.

Effects

Physiological effects of epinephrine may include rapid heart beat, increased blood pressure, heart output, pupil dilation, blood sugar concentration and increased sweating. Other physical effects may include shakiness, increased anxiety, and an abnormal heart rhythm.

Norepinephrine

Norepinephrine (also called noradrenalin) is a catecholamine molecule that acts as a hormone and neurotransmitter. It is chemically similar to epinephrine, differing only in the absence of a methyl group on its amine. Norepinephrine is made and released by the central nervous system (*locus coeruleus* of the brain) and the sympathetic nervous system. The compound is released into the blood stream from adrenal glands and affects α- and β-adrenergic receptors.

Norepinephrine is at its lowest levels during sleep and at its highest levels during stress (fight or flight response). The primary function of norepinephrine is to prepare the body for action. It increases alertness, enhances memory functions, and helps to focus attention. Norepinephrine increases heart rate and blood pressure, increases blood glucose and blood flow to skeletal muscle and decreases flow of blood to the gastrointestinal system.

Medical considerations

Norepinephrine may be injected to overcome critically low blood pressure and drugs countering its effects are used to treat heart conditions. α-blockers, for example, are used to battle cardiovascular and psychiatric disor-

ders. β-blockers counter a different set of norepinephrine's effects than α-blockers and are used to treat glaucoma, migraine headaches and other cardiovascular problems.

Pyruvate family

The family of amino acids derived from pyruvate has four members, each with a simple aliphatic side chain no longer than four carbons. The simplest of these is alanine.

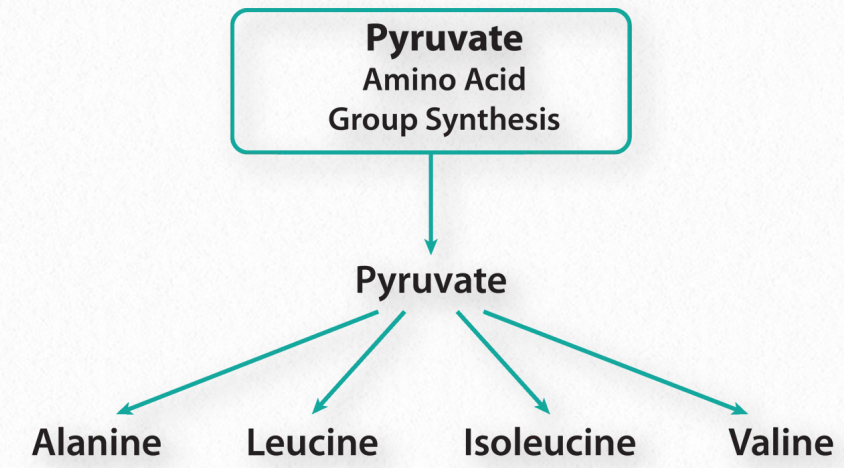

Image by Aleia Kim

Alanine

Alanine is the amino acid that is most easily produced from pyruvate. The simple transamination catalyzed by alanine transaminase produces alanine from pyruvate.

Alternative pathways for synthesis of alanine include catabolism of valine, leucine, and isoleucine.

Glucose-alanine cycle

The glucose-alanine cycle is an important nitrogen cycle related to the Cori cycle that occurs between muscle and liver cells in the body (see HERE). In it, breakdown of glucose in muscles leads to pyruvate. When nitrogen levels are high, pyruvate is transaminated to alanine, which is exported to hepatocytes.

Glutamate + Pyruvate

⇅

Alanine + α-ketoglutarate

In the liver cells, the last transamination of the glucose-alanine cycle occurs. The amine group of alanine is transferred to α-ketoglutarate to produce pyruvate and glutamate. Glucose can then be made by gluconeogenesis from pyruvate. Importantly, breakdown of glutamate yields ammonium ion, which can be made into urea for excretion, thus reducing the body's load of potentially toxic amines. This pathway may be particularly important in the brain.

Another way of removing excess ammonium from a tissue is by attaching it to glutamate to make glutamine. Glutamate is a neurotransmitter, so having an alternative way of removing amines (glucose-alanine cycle) is important, especially in the brain.

YouTube Lectures by Kevin
HERE & HERE

Leucine

Like valine and isoleucine, leucine is an essential amino acid in humans. In adipose tissue and muscle, leucine is used in sterol synthesis. It is the only amino acid to stimulate muscle protein synthesis, and as a dietary supple-

ment in aged rats, it slows muscle degradation. Leucine is an activator of mTOR, a protein which, when inhibited, has been shown to increase life span in *Saccharomyces cerevisiae*, *C. elegans*, and *Drosophila melanogaster*.

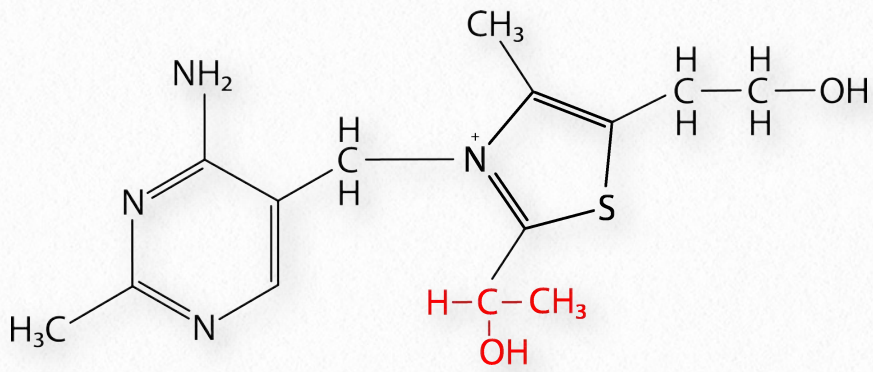

Figure 6.161 - Hydroxyethyl fragment (in red) attached to thiamine pyrophosphate

Image by Pehr Jacobson

Metabolism of leucine, valine, and isoleucine (also called Branched Chain Amino Acids - BCAAs) starts with decarboxylation of pyruvate and attachment of the two-carbon hydroxyethyl fragment to thiamine pyrophosphate (Figure 6.161). Metabolism of isoleucine proceeds with attachment of the hydroxylated two carbon piece (hydroxyethyl-TPP) to α-ketobutyrate and is covered in the section describing that amino acid (see HERE).

Metabolism of valine and leucine proceeds with attachment of the hydroxyethyl piece from TPP to another pyruvate to create α-acetolactate. Rearrangement of α-acetolactate by acetolactate mutase makes 3-hydroxy-3-methyl-2-oxobutanoate.

α-acetolactate

⇅

3-hydroxy-3-methyl-2-oxobutanoate

Reduction with NAD(P)H by acetohydroxy acid isomeroreductase yields α,β-dihydroxyisovalerate.

3-hydroxy-3-methyl-2-oxobutanoate + NADP(P)H

⇅

α,β-dihydroxyisovalerate + NAD(P)$^+$

Loss of water, catalyzed by dihydroxyacid dehydratase produces α-ketoisovalerate.

α,β-dihydroxyisovalerate

⇅

α-ketoisovalerate + H_2O

This molecule is a branch point for synthesis of leucine and valine. Addition of an acetyl group from acetyl-CoA yields α-isopropylmalate (catalyzed by α-isopropylmalate synthase).

α-ketoisovalerate + Acetyl CoA

⇅

α-isopropylmalate + CoA-SH

Rearrangement, catalyzed by isopropylmalate dehydratase, gives rise to **β**-isopropylmalate.

α-isopropylmalate

⇅

β-isopropylmalate.

Oxidation by isopropylmalate dehydrogenase and NAD^+, gives **α**-ketoisocaproate.

β-isopropylmalate + NAD^+

⇅

α-ketoisocaproate + NADH

Transamination of it (catalyzed by leucine aminotransferase and using glutamate) gives the final product of leucine (top of next column).

α-ketoisocaproate + Glutamate

⇅

Leucine + α-ketoglutarate

Valine

An essential amino acid in humans, valine is derived in plants from pyruvate and shares part of its metabolic synthesis pathway with leucine and a small slice of it with isoleucine. Metabolism of all three amino acids starts with decarboxylation of pyruvate and attachment of the two-carbon hydroxyethyl fragment to thiamine pyrophosphate (Figure 6.161), as noted above.

As seen earlier, **α**-ketoisovalerate is the molecule at the point in the metabolic pathway where synthesis of valine branches from that of leucine. In fact, α-ketoisovalerate is only one step away from valine. Transamination of α-ketoisovalerate catalyzed by valine isoleucine aminotransferase gives valine.

α-ketoisovalerate + Glutamate

⇅

Valine + α-ketoglutarate

Isoleucine

Synthesis of isoeleucine (an essential amino acid in humans) begins in plants and microorganisms with pyruvate and **α**-ketobutyrate (a byproduct of threonine metabolism - threonine deaminase - Figure 6.162).

Metabolism of isoleucine proceeds with attachment to α-ketobutyrate of the hydroxyethyl-TPP product of pyruvate decarboxylation to form **α**-aceto-**α**-hydroxybutyrate. The reaction is catalyzed by acetolactate synthase. Rearrangement and reduction by acetohydroxy acid isomeroreductase and NAD(P)H yields **α**,**β**-dihydroxy-**β**-methylvalerate. Shown on next page.

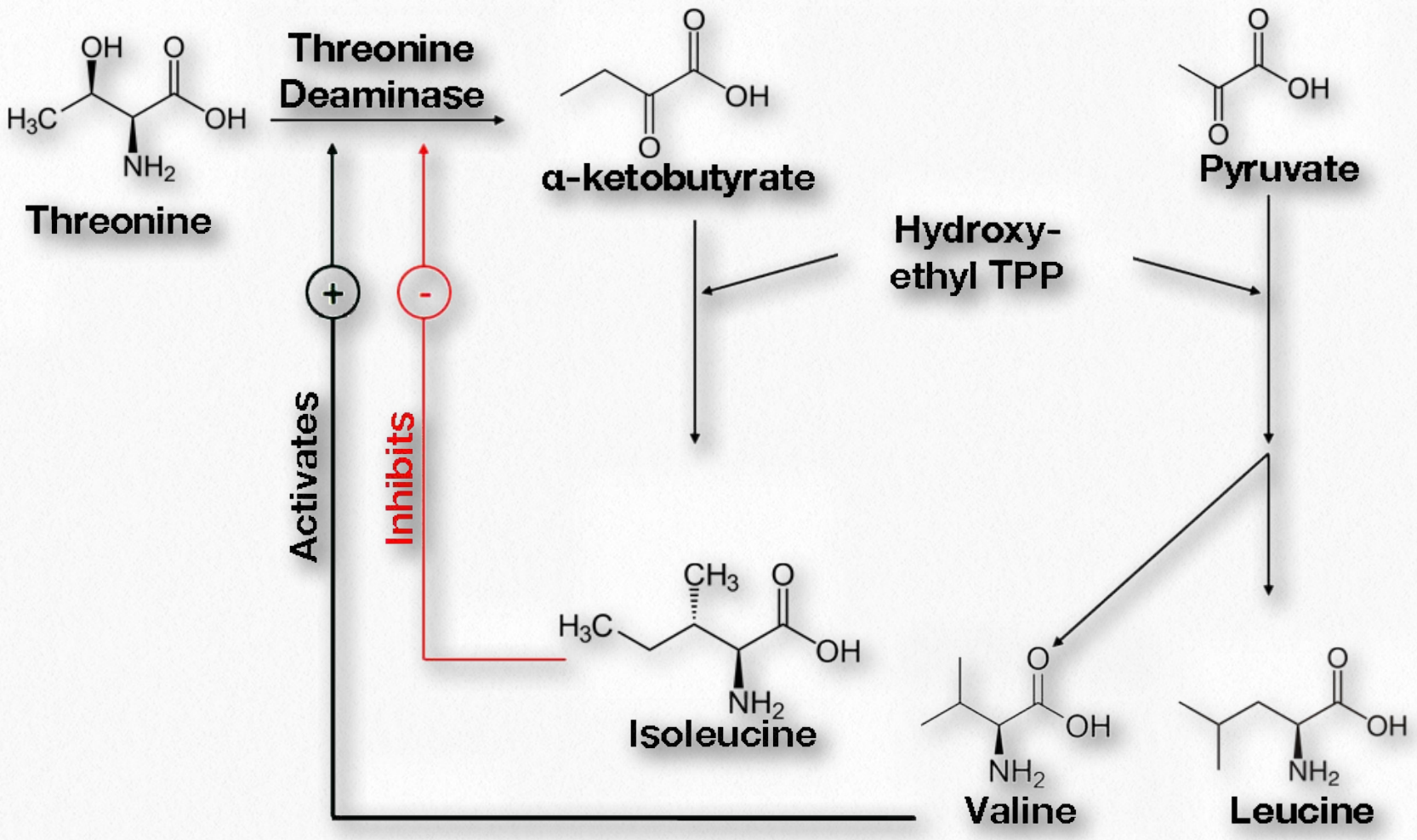

Figure 6.162 - **Threonine deaminase and regulation of BCAA synthesis**

Wikipedia

α-aceto-α-hydroxybutyrate + Pyruvate

⇅

α,β-dihydroxy-β-methylvalerate + CO_2

α-keto-β-methylvalerate + Glutamate

⇅

Isoleucine + α-ketoglutarate

Loss of water (catalyzed by dihydroxy acid dehydratase) gives **α**-keto-**β**-methylvalerate.

α,β-dihydroxy-β-methylvalerate

⇅

α-keto-β-methylvalerate + H_2O

Transamination (using glutamate and valine isoleucine transaminase) yields isoleucine.

Interestingly, several of the enzymes of valine metabolism catalyze reactions in the isoleucine pathway. Though the substrates are slightly different, they are enough like the valine intermediates that they are recognized as substrates.

Isoleucine has a second asymmetric center within it, but only one isomeric form of the four possible ones from the two centers is found biologically.

Regulation of synthesis

Regulation of synthesis of the branched chain amino acids (BCAAs - valine, leucine, and isoleucine) is complex. The key molecule in the regulation is α-ketobutyrate, which is synthesized in cells as a breakdown product of threonine. The enzyme catalyzing its synthesis is threonine deaminase (Figure 6.162), which is allosterically regulated. The enzyme is inhibited by its own product (isoleucine) and activated by valine, a product of a parallel pathway.

Thus, when valine concentration is high, the balances shifts in favor of production of isoleucine and since isoleucine competes with valine and leucine for hydroxyethyl-TPP, synthesis of these two amino acids goes down. When isoleucine concentration increases, threonine deaminase is inhibited, shifting the balance back to production of valine and leucine.

Attenuation

Another control mechanism for regulation of leucine synthesis occurs in bacteria and is known as attenuation. In this method, accumulation of leucine speeds the process of translation of a portion of the mRNA copy of the leucine operon (coding sequences for enzymes necessary to make leucine). This, in turn, causes transcription of the genes of the leucine operon to terminate prematurely, thus stopping production of the enzymes necessary to make leucine.

When leucine levels fall, translation slows, preventing transcription from terminating prematurely and allowing leucine metabolic enzymes to be made. Thus, leucine levels in the cell control the synthesis of enzymes necessary to make it.

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Histidine family

Synthesis of histidine literally occurs in a class by itself - there are no other amino acids in its synthesis family. The amino acid is made in plants (*Arabidopsis*, in this case) by a pathway that begins with ribose-5-phosphate. The overall pathway is show in the green text boxes on the next two pages. Abbreviations used in the boxes are shown below.

Enzyme names

1 = Ribose-phosphate diphosphokinase

2= ATP-phosphoribosyltransferase

3 = Phosphoribosyl-ATP pyrophosphohydrolase

4 = Phosphoribosyl-AMP cyclohydrolase

5 = ProFAR-I (N'-[(5'phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide ribonucleotide isomerase)

6 = Imidazole glycerol-phosphate syn-

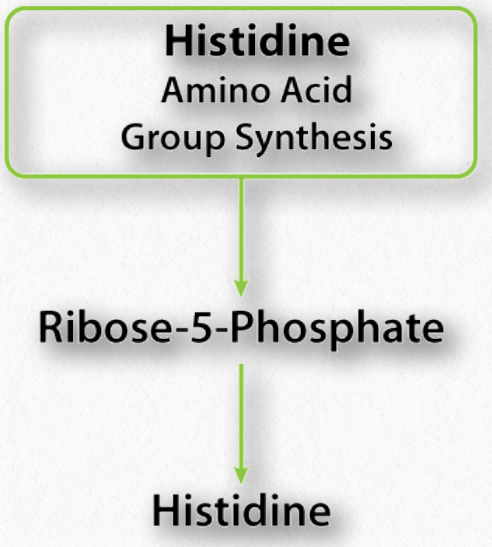


Image by Aleia Kim

thase (IGPS)

7 = Imidazole glycerol-phosphate dehydratase

8 = Histidinol-phosphate aminotransferase

9 = Histidinol-phosphate phosphatase

10 = Histidinol dehydrogenase

Abbreviations used

1 - PRPP = Phosphoribosyl Pyrophosphate

2. PRATP = Phosphoribosyl ATP

3. PRAMP = Phosphoribosyl AMP

4. ProFAR = (N′-[(5′-phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide) ribonucleotide

5. PRFAR = (N′-[(5-phosphoribulosyl)formimino]-5-aminoimidazole-4-carboxamide) ribonucleotide

6. IGP = Imidazole glycerol-phosphate

7. AICAR = 5′-phosphoribosyl-4-carboximide-5-aminoimidazole

8. IAP = Imidazole acetol-phosphate

9. α-KG = α-ketoglutarate

Ribose-5-Phosphate + ATP

(1)

PRPP + AMP

PRPP + ATP

(2)

PRATP

PRATP

(3)

PRAMP + PP_i

PRAMP

(4)

ProFAR

ProFAR

(5)

PRFAR

PRFAR + Glutamine

(6)

IGP + Glutamate + AICAR

IGP

7

IAP

IAP + Glutamate

⇅ (8)

Histidinol-phosphate + α-KG

Histidinol-phosphate

⇅ (9)

Histidinol + P_i

Histidinol + 2 **NAD^+**

⇅ (10)

Histidine + 2 **NADH** + 2 H^+

Histidine is a feedback inhibitor of ATP-phosphoribosyltransferase and thus helps to regulate its own synthesis. Histidine is the only amino acid to contain an imidazole ring. It is ionizable and has a pKa of about 6. As a result, histidine's R-group can gain/lose a proton at pH values close to cellular conditions.

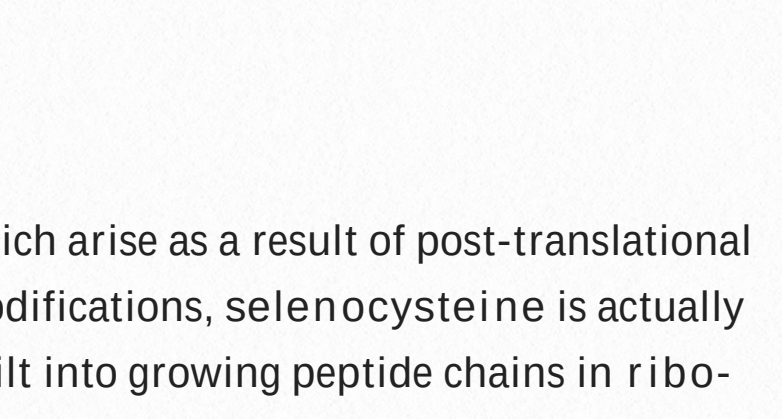
Selenocysteine

A cysteine analog commonly referred to as the 21st amino acid, selenocysteine (Figure 6.163) is an unusual amino acid occasionally found in proteins. Although it is rare, selenocysteine has been found in proteins in bacteria, archaea and eukaryotes.

In contrast to amino acids such as phosphoserine, hydroxyproline, or acetyl-lysine, which arise as a result of post-translational modifications, selenocysteine is actually built into growing peptide chains in ribosomes during the process of translation.

No codon specifies selenocysteine, so to incorporate it into a protein, a tRNA carrying it must bind to a codon that normally specifies STOP (UGA). This alternative reading of the UGA is dependent on formation of a special hairpin loop structure in the mRNA encoding selenoproteins.

Selenium is rather toxic, so cellular and dietary concentrations are typically exceedingly



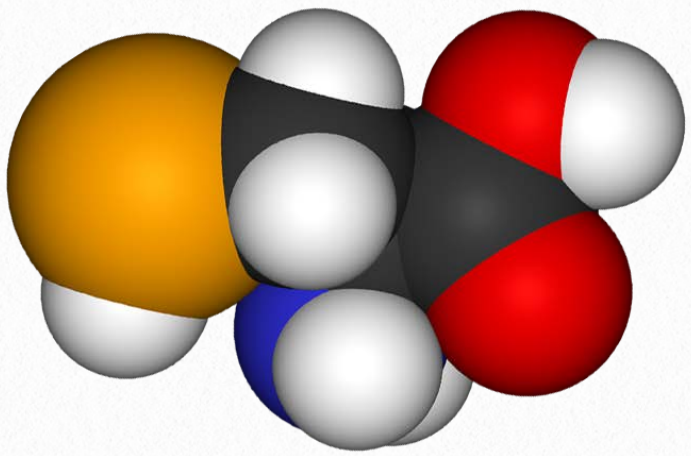


Figure 6.163 - Selenocysteine

low. About 25 human proteins are known to contain the amino acid. These include five glutathione peroxidases, and three thioredoxin reductases. Iodothyronine deiodinase, a key enzyme that converts thyroxine to the active T3 form, also contains selenocysteine in its active site. All of these proteins contain a single selenocysteine.

A eukaryotic protein known as selenoprotein P, found in the blood plasma of animals, contains ten selenocysteine residues and is thought to function as an antioxidant and/or in heavy metal detoxification. Besides selenocysteine, at least two other biological forms of a seleno-amino acid are known. These include 1) selenomethionine (Figure 6.164), a naturally occurring amino acid in Brazil nuts, cereal grains, soybeans, and grassland legumes and 2) methylated forms of selenocysteine, such as Se-methylselenocysteine, are found in *Astragalus*, *Allium*, and *Brassica* species.

Stop codon

The specifics of the process of translation will be described elsewhere in the book, but to get selenocysteine into a protein, the tRNA carrying selenocysteine pairs with a stop codon (UGA) in the mRNA in the ribosome. Thus, instead of stopping translation, selenocysteine can incorporated into a growing protein and translation continues instead of stopping.

Four genes are involved in preparation of selenocysteine for incorporation into proteins. They are known as sel A, sel B, sel C, and sel D. Sel C codes for the special tRNA that carries selenocysteine. The amino acid initially put onto the selenocysteine tRNA is not selenocysteine, but rather serine. Action of sel A and sel D are necessary to convert the serine to a selenocysteine.

An intermediate in the process is selenophosphate, which is the selenium donor. It is derived from H_2Se, the form in which selenium is found in the cell. The tRNA carrying selenocysteine has a slightly different structure than other tRNAs, so it requires assistance in translation. The sel B gene encodes for an EF-Tu-like protein that helps incorporate the selenocysteine into the protein during translation.

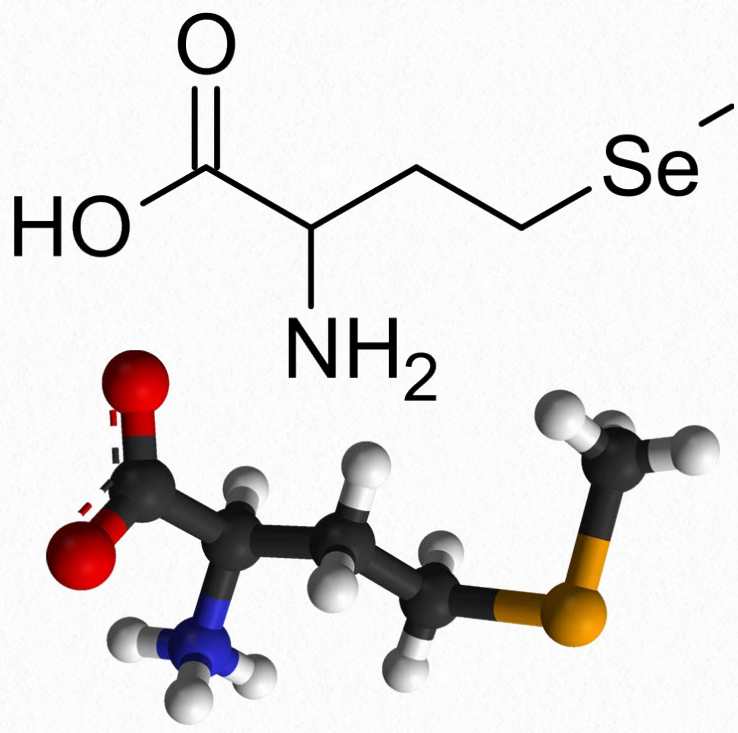


Figure 6.164 - Selenomethionine

Recoding the UGA

Using UGA codons to incorporate selenocysteine into proteins could wreak havoc if done routinely, as UGA, in fact, almost always functions as a stop codon and is only rarely used to code for selenocysteine. Fortunately, there is a mechanism to ensure that the reading of a UGA codon as selenocysteine occurs only when the mRNA encodes a selenoprotein.

Unusual structures in mRNAs

The mRNAs for selenocysteine-containing proteins form unusual mRNA structures around the UGA codon that make the ribosome "miss" it as a stop codon and permit the tRNA with selenocysteine to be incorporated instead.

Pyrrolysine

Like selenocysteine, pyrrolysine is a rare, unusual, genetically encoded amino acid found in some cells. Proteins containing it are enzymes involved in methane metabolism and so far have been found only methanogenic archaeans and one species of bacterium. The amino acid is found in the active site of the enzymes containing it. It is sometimes referred to as the 22nd amino acid.

Synthesis of the amino acid biologically begins with two lysines. One is converted to (3R)-3-Methyl-D-ornithine, which is attached to the second lysine. After elimination of an amine group, cyclization, and dehydration, L-pyrrolysine is produced. Pyrrolysine is attached to an unusual tRNA (pylT gene product) by action of the aminoacyl tRNA synthetase encoded by the pylS gene. This unusual tRNA can pair with the UAG stop codon during translation and allow for incorporation of pyrrolysine into the growing polypeptide chain during translation in a manner similar to incorporation of selenocysteine.

Urea cycle

The urea cycle holds the distinction of being the first metabolic cycle discovered - in 1932, five years before the citric acid cycle. It is an important metabolic pathway for balancing nitrogen in the bodies of animals and it takes place primarily in the liver and kidney.

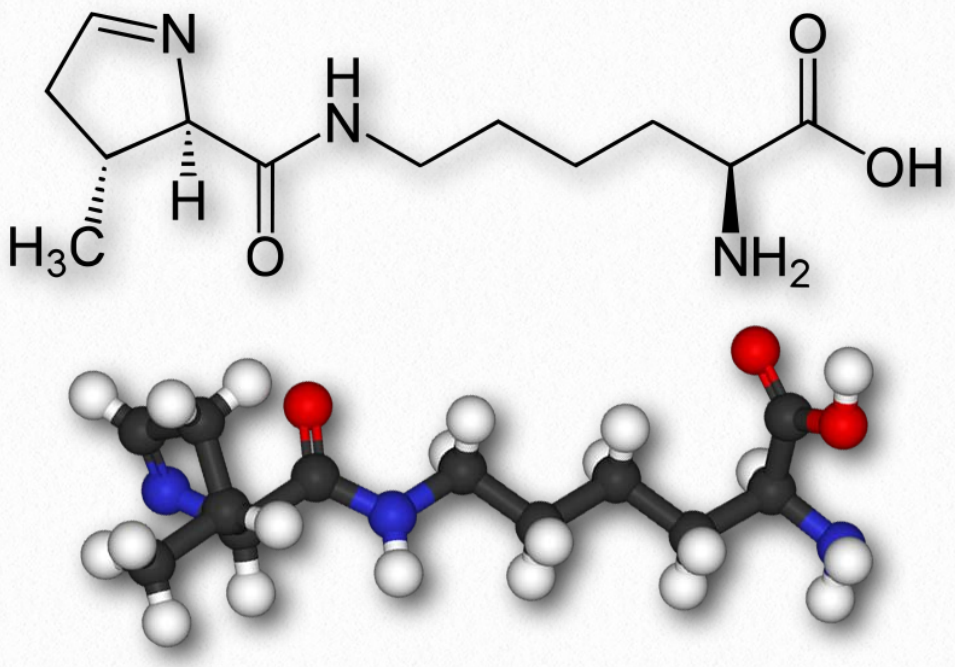


Figure 6.165 - Pyrrolysine

Organisms, like humans, that excrete urea are called ureotelic. Those that excrete uric acid (birds, for example) are called uricotelic and those that excrete ammonia (fish) are ammonotelic. Ammonia, of course, is generated by metabolism of amines and is toxic, so managing levels of it is critical for any organism. Excretion of ammonia by fish is one reason that an aquarium periodically requires cleaning and replacement of water.

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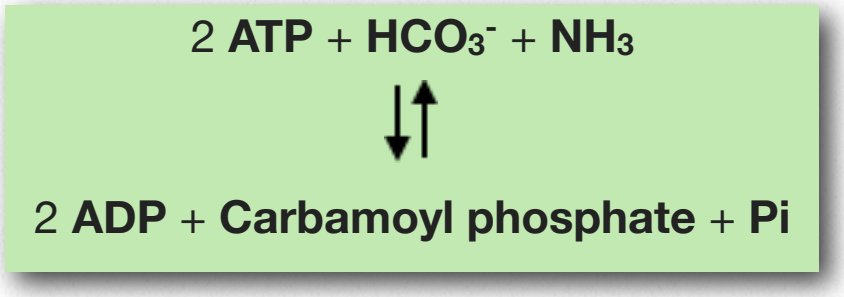
Liver failure can lead to accumulation of nitrogenous waste and exacerbates the problem. As shown in Figure 1.166, the cycle contains five reactions, with each turn of the cycle producing a molecule of urea. Of the five reactions, three occur in the cytoplasm and two take place in the mitochondrion. (The reaction making carbamoyl phosphate, catalyzed by carbamoyl phosphate synthetase is not shown in the figure.)

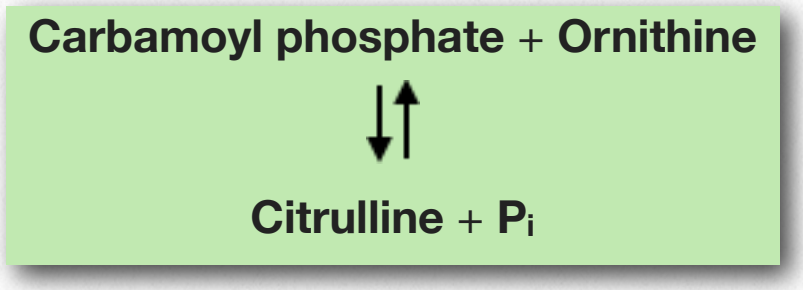
Ornithine synthesis

Though the cycle doesn't really have a starting point, a common place to begin discussion is with the molecule of ornithine. As discussed elsewhere in this book, ornithine intersects the metabolic pathways of arginine and proline.

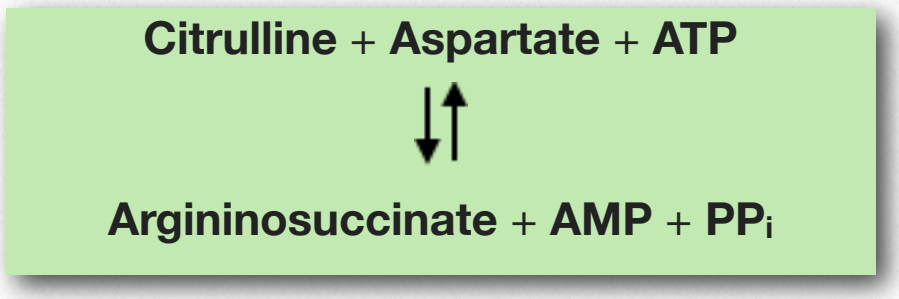
Ornithine is found in the cytoplasm and is transported into the mitochondrion by the ornithine-citrulline antiport of the inner mitochonrial membrane. In the matrix of the mitochondrion, two reactions occur relevant to the cycle. The first is formation of carbamoyl phosphate from bicarbonate, ammonia, and ATP catalyzed by carbamoyl phosphate synthetase I.



Carbamoyl phosphate then combines with ornithine in a reaction catalyzed by ornithine transcarbamoylase to make citrulline.



The citrulline is transported out to the cytoplasm by the ornithine-citrulline antiport mentioned above. In the cytoplasm, citrulline combines with L-aspartate using energy of ATP to make citrullyl-AMP (an intermediate) followed by argininosuccinate. The reaction is catalyzed by argininosuccinate synthase.



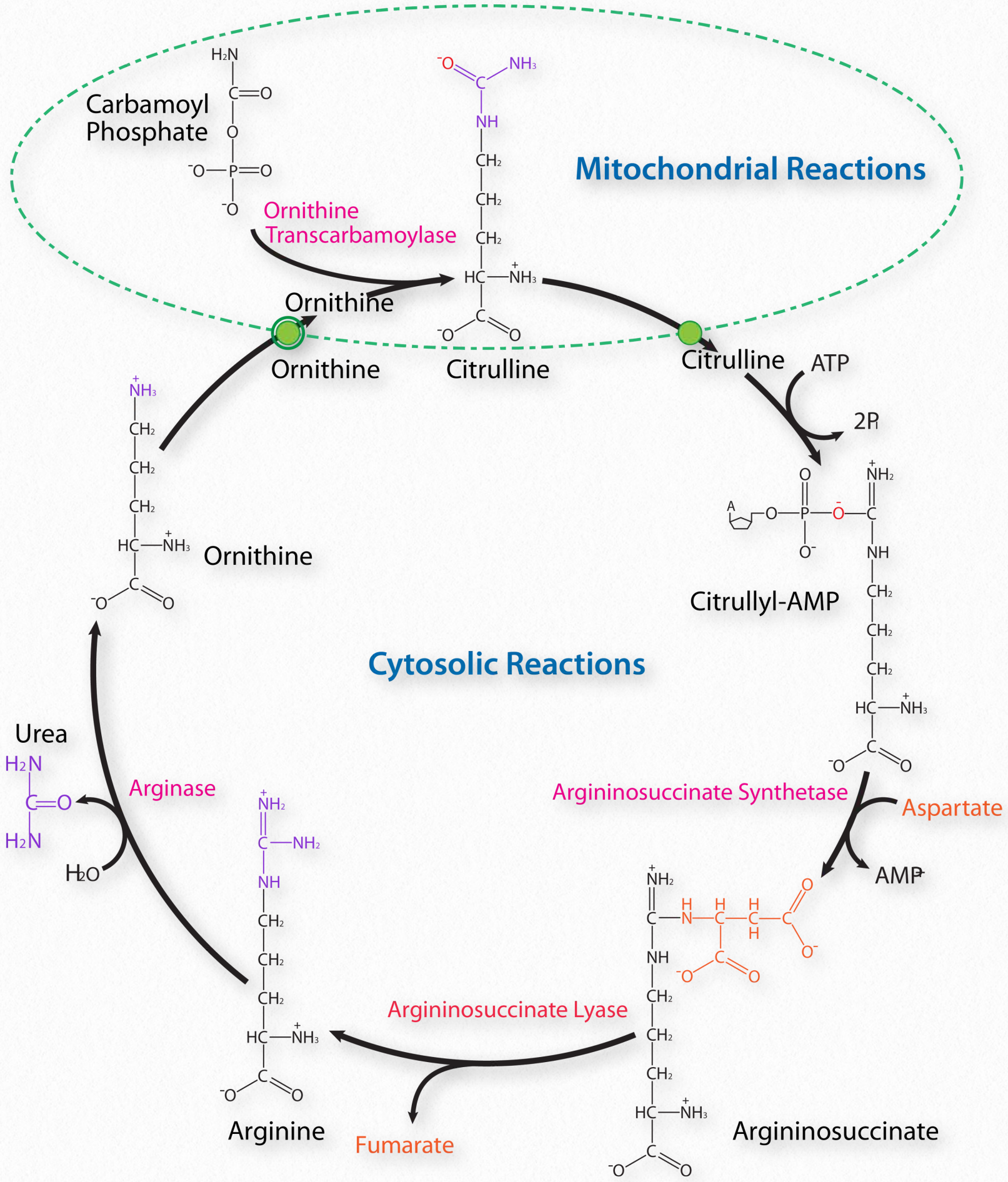


Figure 6.166 - The urea cycle

Image by Aleia Kim

Next, fumarate is split from argininosuccinate by argininosuccinate lyase to form arginine.

Argininosuccinate

⇅

Arginine + **Fumarate**

Water is used by arginase to cleave arginine into urea and ornithine, completing the cycle.

Arginine + H_2O

⇅

Ornithine + **Urea**

Urea is less toxic than ammonia and is released in the urine. Some organisms make uric acid for the same reason.

It is worth noting that aspartic acid, ammonia, and bicarbonate enter the cycle and fumarate and urea are produced by it. Points to take away include 1) ammonia is converted to urea using bicarbonate and the amine from aspartate; 2) aspartate is converted to fumarate which releases more energy than if aspartate were converted to oxaloacetate, since conversion of fumarate to malate to oxaloacetate in the citric acid cycle generates an NADH, but direct conversion of aspartate to oxaloacetate does not; and 3) glutamate and aspartate are acting as shuttles to funnel ammonia into the cycle. Glutamate, as will be seen below, is a scavenger of ammonia.

Urea cycle regulation

The urea cycle is controlled both allosterically and by substrate concentration. The cycle requires N-acetylglutamate (NAG) for allosteric activation of carbamoyl phosphate synthetase I. The enzyme that catalyzes synthesis of NAG, NAG synthetase, is activated by arginine and glutamate. Thus, an indicator of high amine levels, arginine, and an important shuttler of amine groups, glutamate, stimulates the enzyme that activates the cycle.

The reaction catalyzed by NAG synthetase is

Acetyl-CoA + **L-glutamate**

⇅

CoA-SH + **N-acetyl-L-glutamate**

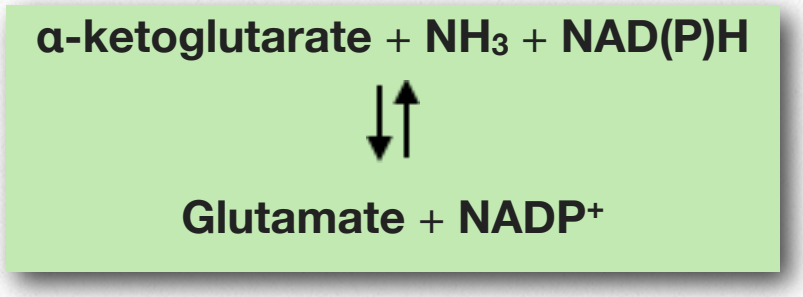
At the substrate level, all of the other enzymes of the urea cycle are controlled by the concentrations of substrates they act upon. Only at high concentrations are the enzymes fully utilized.

Complete deficiency of any urea cycle enzyme is fatal at birth, but mutations resulting in reduced expression of enzymes can have mixed effects. Since the enzymes are usually not limiting for these reactions, increasing substrate can often overcome reduced enzyme

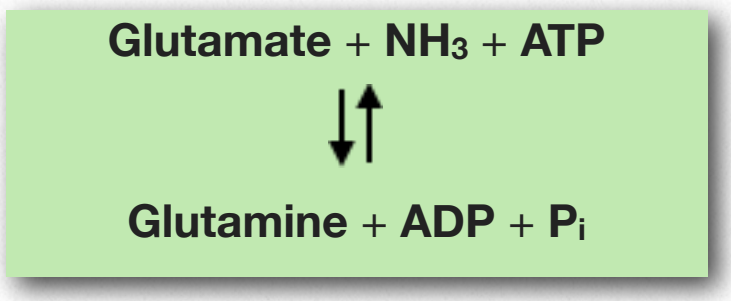
amounts to a point by simply fully activating enzymes present in reduced quantities.

Ammonia accumulation

However, if the deficiencies are sufficient, ammonium can accumulate and this can be quite problematic, especially in the brain, where mental deficiencies or lethargy can result. Reduction of ammonium concentration relies on the glutamate dehydrogenase reaction (named for the reverse reaction).



Additional ammonia can be taken up by glutamate in the glutamine synthetase reaction.



The result of these reactions is that α-ketoglutarate and glutamate concentrations will be reduced and the concentration of glutamine will increase. For the brain, this is a yin/yang situation. Removal of ammonia is good, but reduction of α-ketoglutarate concentration means less energy can be generated by the citric acid cycle. Further, glutamate is, itself, an important neurotransmitter and a precursor of another neurotransmitter - γ-aminobutyric acid (GABA).

Energy generation

From an energy perspective, the urea cycle can be said to break even or generate a small amount of energy, if one includes the energy produced in releasing ammonia from glutamate (one NADH). There are two NADHs produced (including the one for converting fumarate to oxaloacetate), which give 4-6 ATPs, depending on how efficiently the cell performs electron transport and oxidative phosphorylation.

The cycle takes in 3 ATPs and produces 2 ADPs and one AMP. Since AMP is equivalent to 2 ATP, the cycle uses 4 ATP. Thus, the cycle either breaks even in the worst case or generates 2 ATPs in the best case.

Amino acid catabolism

Amino acids are divided according to the pathways involved in their degradation. There are three general categories. Ones that yield intermediates in the glycolysis pathway are called glucogenic and those that yield intermediates of acetyl-CoA or acetoacetate are called ketogenic. Those that involve both are called glucogenic and ketogenic. These are shown in Figures 6.167 and 6.168.

As seen in the two figures, amino acids largely produce breakdown products related to intermediates of the citric acid cycle or glycolysis, but this isn't the complete picture. Some amino acids, like tryptophan,

Glucogenic and Ketogenic Amino Acids

Glucogenic	Ketogenic	Both Glucogenic and Ketogenic
Aspartate	Leucine	Isoleucine
Asparagine	Lysine	Phenylalanine
Alanine		Tryptophan
Glycine		Tyrosine
Serine		
Threonine		
Cysteine		
Glutamate		
Glutamine		
Arginine		
Proline		
Histidine		
Valine		
Methionine		

Figure 6.167 - Results of amino acid catabolism

Image by Aleia Kim

phenylalanine, and tyrosine yield hormones or neurotransmitters on further metabolism (as noted earlier). Others like cysteine and methionine must dispose of their sulfur and all of the amino acids must rid themselves of nitrogen, which can happen *via* the urea cycle, transamination, or both.

Tyrosine catabolism

Breakdown of tyrosine (Figure 6.169) is a five step process that yields acetoacetate and fumarate. Enzymes involved include 1) tyrosine transaminase; 2) p-hydroxylphenylpyruvate dioxygenase; 3) homogentisate dioxygenase; 4) maleylacetoacetate *cis*-*trans*-isomerase; and 5) 4-fumaryl acetoacetate hydrolase.

Breakdown of leucine is a multi-step process ultimately yielding the ketone body acetoacetate and acetyl-CoA. Branched chain amino acids (BCAAs - valine, leucine,

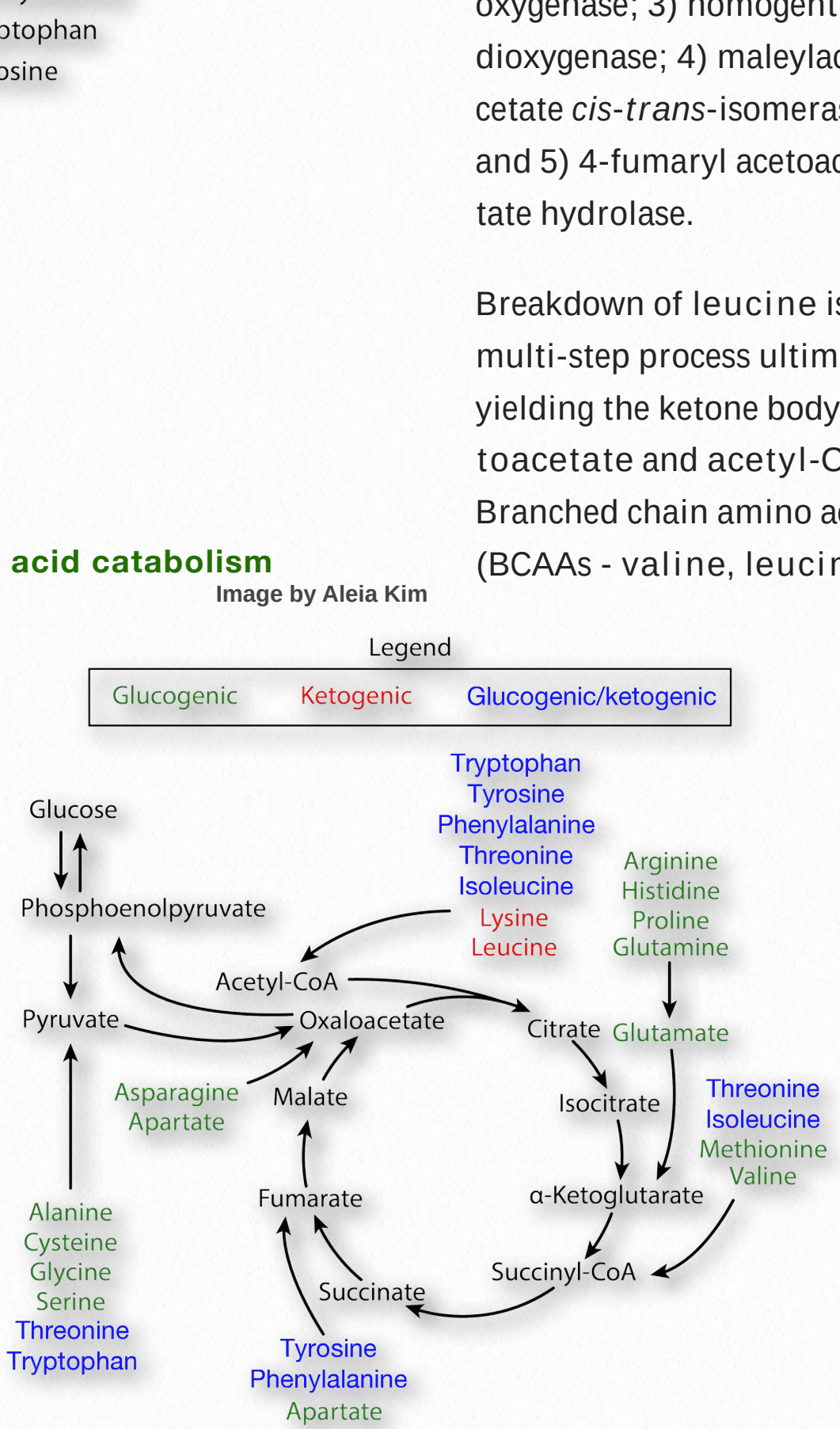


Figure 6.168 - Breakdown pathways for amino acids. Some yield more than one intermediate.

Image by Pehr Jacobson

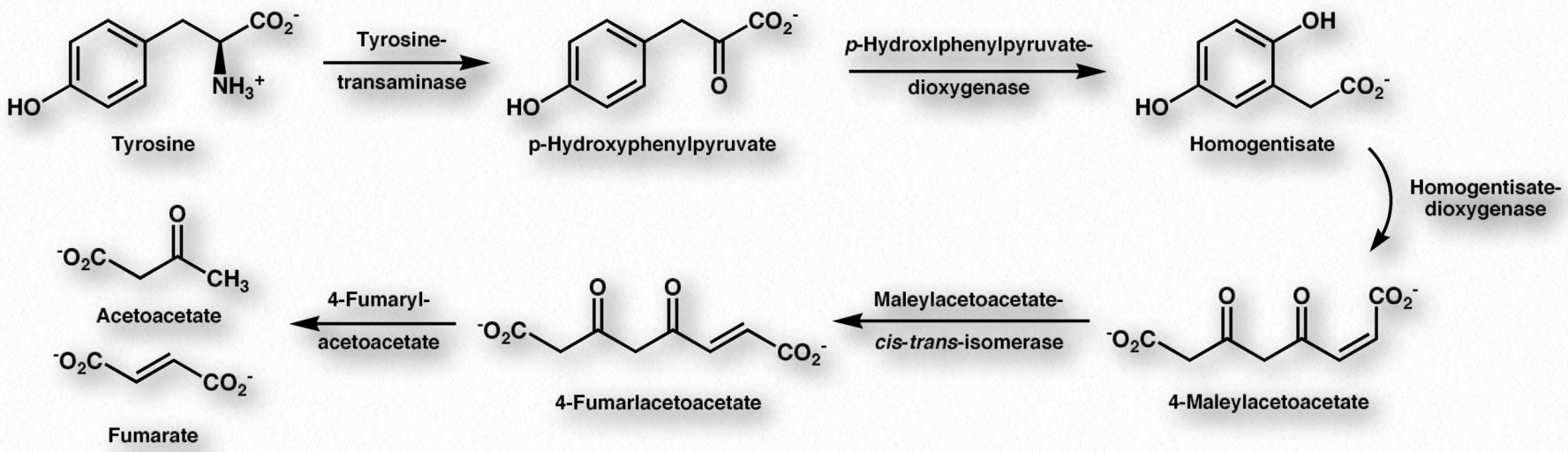


Figure 6.169 - Catabolism of tyrosine to fumarate and acetoacetate.

and isoleucine) rely on Branched Chain AminoTransferase (BCAT) followed by Branched Chain α-ketoacid dehydrogenase (BCKD) for catabolism.

Breakdown of isoleucine yields intermediates that are both ketogenic and glucogenic. These include acetyl-CoA and propionyl-CoA.

Breakdown of valine is a multi-step process ultimately yielding propionyl-CoA.

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Click HERE for Aleia Kim's Web Page

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They Call The Stuff Urea

To the tune of "*They Call The Wind Mariah*"

Metabolic Melodies Website HERE

Get ATPs, bicarbonate,
Ammonia catalyzing
To make carba-mo-yl phosphate
And then start the synthesizing

When joined up with an ornithine
In THE mi-TOE-chon-DREE-a
It turns into a citrulline
When cycling to urea

Urea!
Urea!
They call the stuff urea!

On exit to the cytosol
There's bonding aspartat-ic
The argininosuccinate
Is produced in this schematic

Bid farewell to a fumarate
Amino panacea
Arises when the arginine
Gets lysed to form urea

Urea!
Urea!
You've just made some urea!

The body handles many things
Requiring its attention
Like balancing aminos for
Uremia prevention

So if there's excess nitrogen
It is a good idea
To rid yourself of surplus by
Producing some urea

Urea!
Urea!
Go out and take a pee, yeah!

Urea!
Urea!
Have yourself a pee, yeah!

Recorded by David Simmons
Lyrics by Kevin Ahern

I Studied So Hard Last Night

To the tune of "*I Saw Her Again Last Night*"

Metabolic Melodies Website HERE

I studied so hard last night
But you know that I couldn't
Get all the reactions down right
Oh my brain simply wouldn't

I made lots of tries
To memorize
But it seemed the more I read the book
I never learned

'Twas much too complex in my head
And so truly confusing
Like most of the things Ahern said
Awfully tough but amusing

I got so upset
That I would forget
Oh I had to find another way
Or I'd never learn

Bridge
Metabolic Melodies
The pathways I could sing in time
They all put my mind at ease
Using just the power of rhyme
My grades began to climb

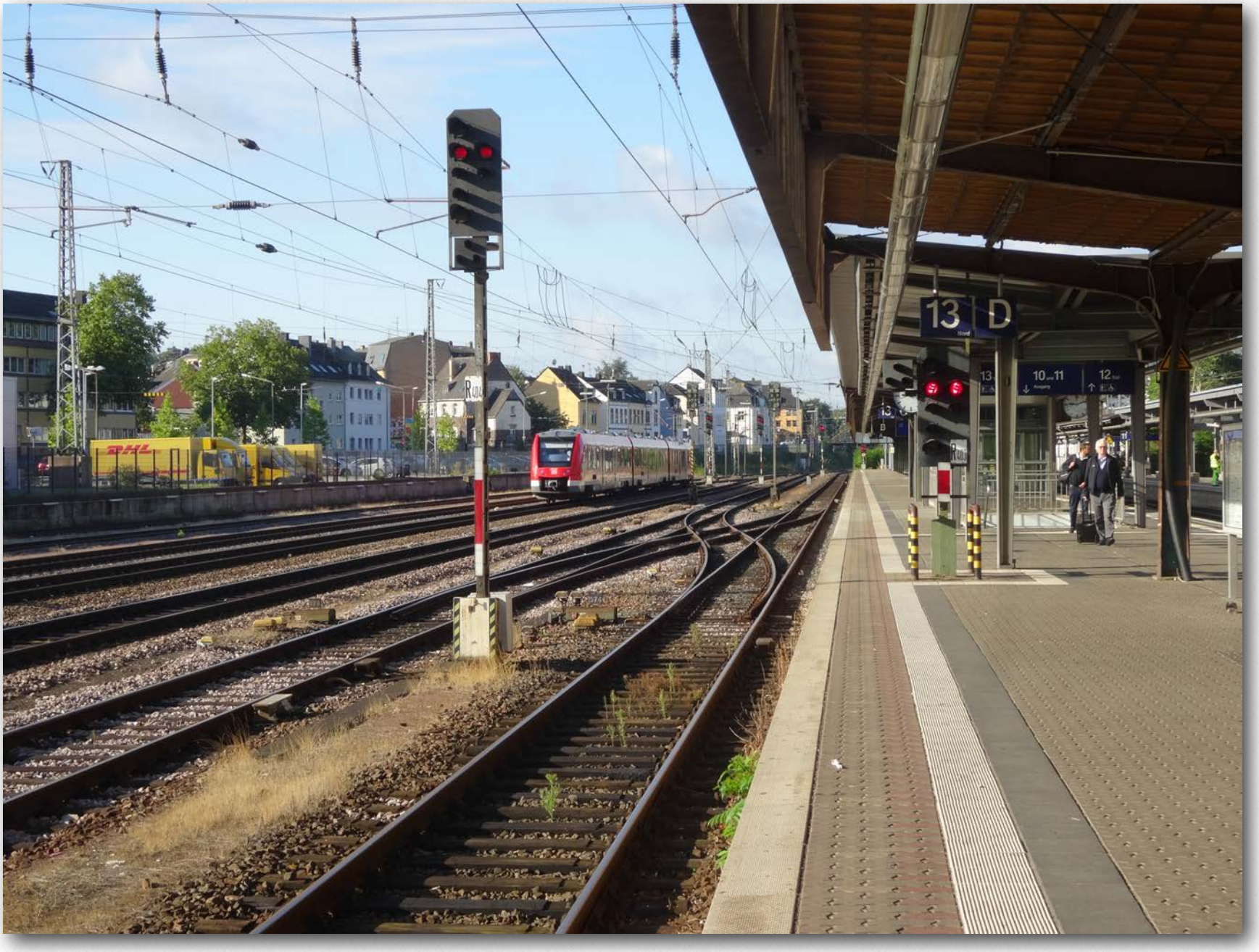
I studied so hard last night
Now I'll never forget it
The Melodies helped get it right
Just the way Kevin said it

I won't get it wrong
If I sing along
And it makes me feel so good to know
I've truly learned

Lyrics by Kevin Ahern

No Recording Yet For This Song

Metabolism: Nucleotides



Diverse functions of nucleotides

Nucleotides are most often thought of as the building blocks of the nucleic acids, DNA and RNA. While this, is, of course, a vital function, nucleotides also play other important roles in cells. Ribonucleoside triphosphates like ATP, CTP, GTP and UTP are necessary, not just for the synthesis of RNA, but as part of activated intermediates like UDP-glucose in biosynthetic pathways. ATP is also the universal “energy currency” of cells, and coupling of energetically unfavorable reactions with the hydrolysis of ATP makes possible the many reactions in our cells that require an input of energy. Adenine nucleotides serve as components of $NAD(P)^+$ and FAD. Nucleotides can also serve as allosteric and metabolic regulators. The synthesis and breakdown pathways for nucleotides and the molecules derived from them are thus, of vital importance to cells. Regulation of nucleotide synthesis, especially for deoxyribonucleotides, is important to ensure that the four nucleotides are made in the

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right proportions, as imbalances in nucleotide concentrations can lead to increases in mutation rates.

Pathways of nucleotide metabolism are organized in two major groups and one minor one. These include, respectively, metabolism of 1) purines; 2) pyrimidines; and 3) deoxyribonucleotides. Each group can be further subdivided into pathways that make nucleotides from simple precursors (*de novo* pathways) and others that use pieces of nucleotides to reassemble full ones (salvage pathways). Notably, *de novo* synthesis pathways for all of the nucleotides begin with synthesis of ribonucleotides. Deoxyribonucleotides are made from the ribonucleotides.

Purine nucleotide metabolism

Synthesis of purine nucleotides by the *de novo* pathway begins with addition of a pyrophosphate to carbon 1 of ribose-5-phosphate, creating phosphoribosylpyrophosphate (PRPP). The reaction is catalyzed by PRPP synthetase. Some number the purine metabolic pathway starting with the next reaction. We have therefore given this reaction the number of zero in Figure 6.172.

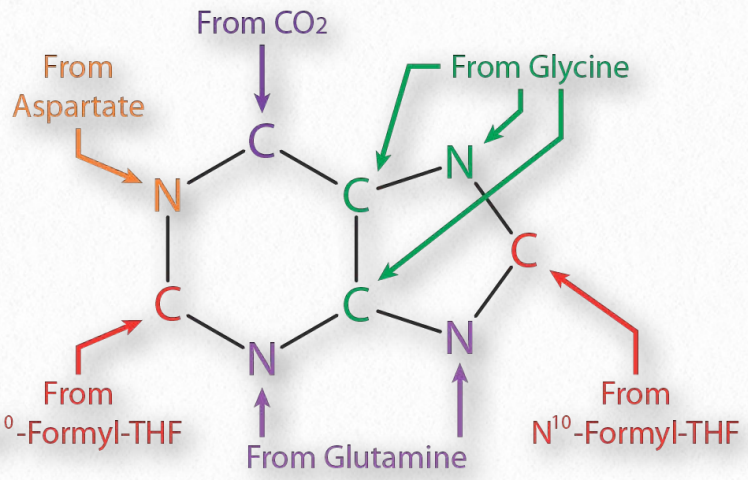


Figure 6.170 - Origin of atoms in purines

Image by Aleia Kim

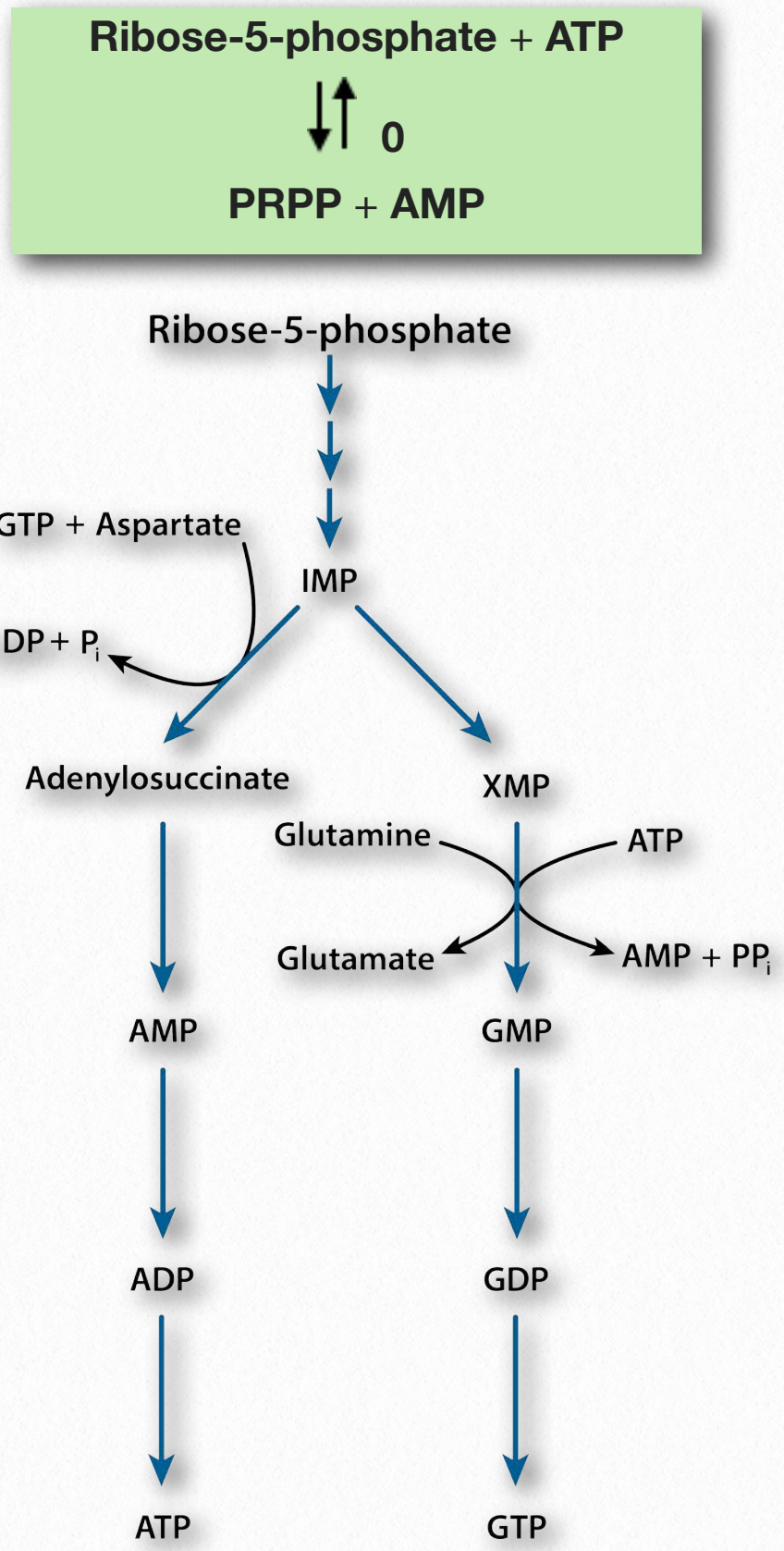


Figure 6.171 - Purine metabolism overview

Image by Pehr Jacobson

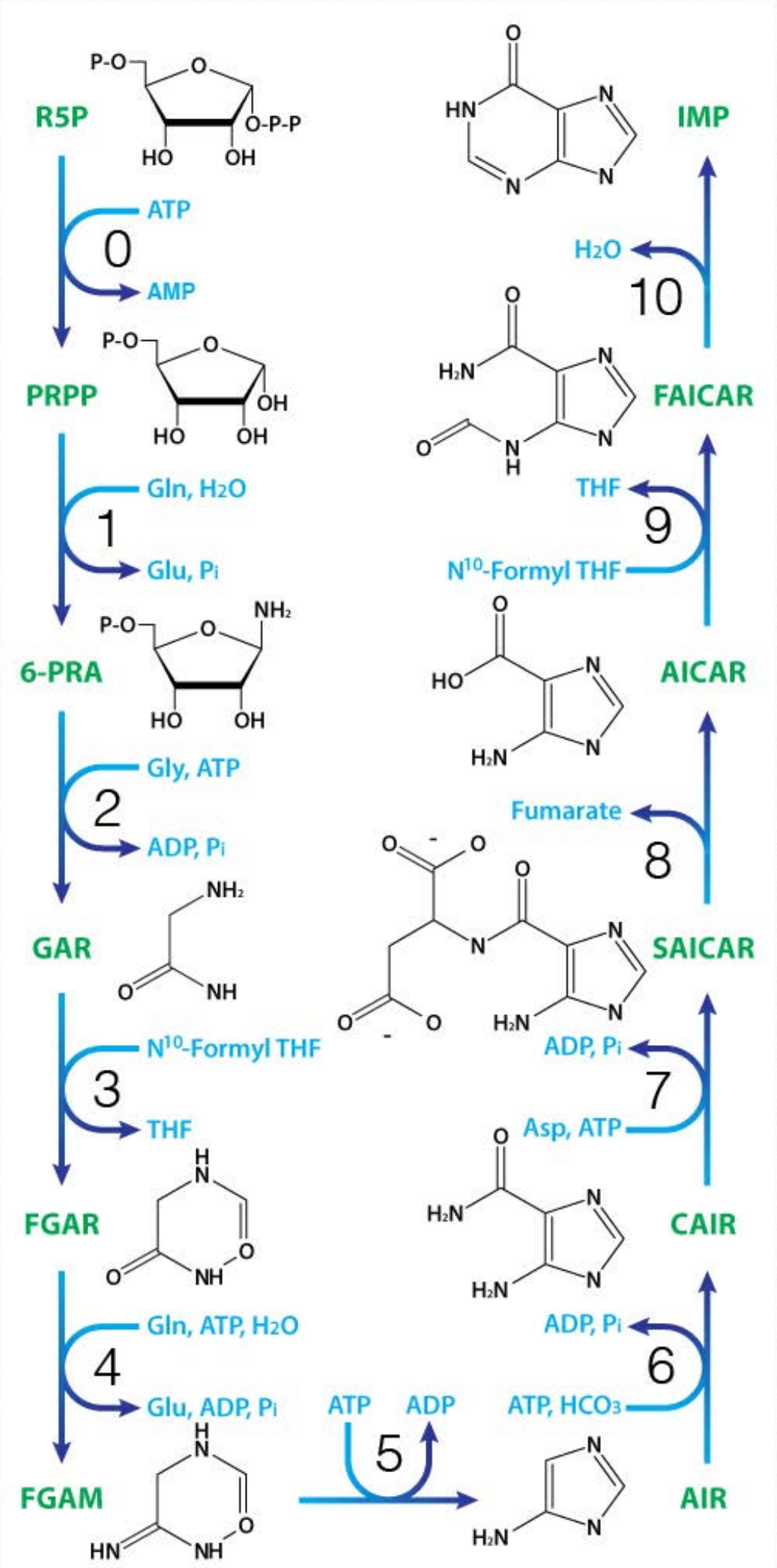


Figure 6.172 - Purine *de novo* synthesis

Image by Aleia Kim

In the next step (reaction 1 in Figure 6.172), the pyrophosphate is replaced by an amine from glutamine in a reaction catalyzed by PRPP amidotransferase (PPAT). The product is 5-phosphoribosylamine (5-PRA).

PRPP + **Glutamine** + H_2O

⇅ 1

5-PRA + **Glutamate** + **PP_i**

PPAT is an important regulatory enzyme for purine biosynthesis. The end products of the pathway, AMP and GMP both inhibit the enzyme and PRPP activates it. Interestingly, full inhibition of the enzyme requires binding of both AMP and GMP.

Binding of only one of the two nucleotides allows the enzyme to remain partially active so that the missing nucleotide can be synthesized. Through this enzyme, the relative amounts of ATP and GTP are controlled.

5-PRA is very unstable chemically (half-life of 38 seconds at

37°C), so it has been proposed that it is shuttled directly from PRPP amidotransferase to GAR synthetase for the next reaction.

In this reaction (#2), glycine is added to the growing structure above the ribose-5-phosphate to create glycineamide ribonucleotide (GAR). This reaction, which requires ATP, is catalyzed, as noted, by the enzyme GAR synthetase.

5-PRA + Glycine + ATP
⇅ 2
GAR + ADP + Pi

In reaction #3, a formyl group is transferred onto the GAR from N^{10}-formyl-tetrahydrofolate (N^{10}-formyl-THF or fTHF) by phosphoribosylglycinamide formyltransferase (GART).

GAR + fTHF
⇅ 3
fGAR + THF

Next, the double bonded oxygen in the ring is replaced with an amine in a reaction catalyzed by phosphoribosylformylglycinamidine synthase (PFAS) that uses glutamine and produces glutamate. The reaction requires energy from ATP (top of next column).

fGAR + L-Glutamine + ATP
⇅ 4
fGAM + L-Glutamate + ADP + P_i

In humans the GAR synthetase, phosphoribosylglycinamide formyltransferase, and the enzyme catalyzing the next reaction (#5), AIR synthetase activities are all on the same protein known as trifunctional purine biosynthetic protein adenosine-3.

fGAM + ATP
⇅ 5
AIR + ADP + P_i + H_2O

In reaction #6, carboxylation of AIR occurs, catalyzed by phosphoribosylaminoimidazole carboxylase (PAIC)

AIR + HCO_3^-
⇅ 6
CAIR + $2H^+$

Aspartic acid is then added to donate its amine group and fumarate will be lost in the reaction that follows this one. The enzyme involved here is phosphoribosyl-

CAIR + L-Aspartate + ATP
⇅ 7
SAICAR + ADP + P_i

aminoimidazole-succinocarboxamide synthase (PAICS)

In the next reaction, the carbon shell of aspartate is released (as fumarate) and the amine is left behind. The reaction is catalyzed by adenylosuccinate lyase (ADSL).

SAICAR

⇅ 8

AICAR + **Fumarate**

Reaction #9 involves another formylation reaction, catalyzed by phosphoribosylaminoimidazolecarboxamide formyltransferase (ATIC-E1).

AICAR + **fTHF**

⇅ 9

FAICAR + **THF**

Next, inosine monophosphate synthase (ATIC-E2) catalyzes release of water to form the first molecule classified as a purine - inosine monophosphate or IMP).

FAICAR

⇅ 10

IMP + H_2O

Though it doesn't appear in DNA, IMP does, in fact, occur in the anticodon of many tRNAs where its ability to pair with numerous bases is valuable in reading the genetic code.

IMP is a branch point between pathways that lead to GMP or AMP. The pathway to GMP proceeds via catalysis by IMP dehydrogenase as follows:

IMP + **NAD^+** + H_2O

⇅

Xanthosine 5'-phosphate + **NADH** + H+

In the last step of GMP synthesis, GMP synthase catalyzes a transamination to form GMP using energy from ATP.

ATP + **Xanthosine 5'-P** + **Glutamine** + H_2O

⇅

AMP + **PP_i** + **GMP** + **Glutamate**

The energy source being ATP makes sense, since the cell is presumably making GMP because it needs guanine nucleotides. If the cell is low on guanine nucleotides, GTP would be in short supply.

Adenine nucleotide synthesis

Synthesis of AMP from IMP follows. First, adenylosuccinate synthetase catalyzes the addition of aspartate to IMP, using energy from GTP.

IMP + Aspartate + GTP

⇅

Adenylosuccinate + GDP + P_i

Then, adenylosuccinate lyase splits fumarate off to yield AMP.

Adenylosuccinate

⇅

AMP + Fumarate

In humans, the bifunctional purine biosynthesis protein known as PURH contains activities of the last two enzymes above.

Abbreviations used above

PRPP = Phosphoribosyl Pyrophosphate
5-PRA = 5-phosphoribosylamine
GAR = glycineamide ribonucleotide
fGAR = Phosphoribosyl-N-formylglycineamide
THF = Tetrahydrofolate
fTHF = N^{10}-formyl-Tetrahydrofolate
fGAM = 5'-Phosphoribosylformylglycinamidine
AIR = 5-Aminoimidazole ribotide
CAIR = 5'-Phosphoribosyl-4-carboxy-5-aminoimidazole
SAICAR = Phosphoribosylamino-imidazolesuccinocarboxamide
AICAR = 5-Aminoimidazole-4-carboxamide ribonucleotide
FAICAR = 5-Formamidoimidazole-4-carboxamide ribotide
IMP = inosine monophosphate

Regulation

It is worth repeating that synthesis of GMP from IMP requires energy from ATP and that synthesis of AMP from IMP requires energy from GTP. In addition, the enzymes converting IMP into intermediates in the AMP and GMP pathways are each feedback inhibited by the respective monophosphate nucleotide. Thus, IMP dehydrogenase is inhibited by GMP (end product of pathway branch) and adenylosuccinate synthetase is inhibited by AMP, the end product of that pathway branch.

Purine nucleotide levels are balanced by the combined regulation of PRPP amidotransferase , IMP dehydrogenase, adenylosuccinate synthetase and the nucleotides AMP and GMP. The importance of the regu-

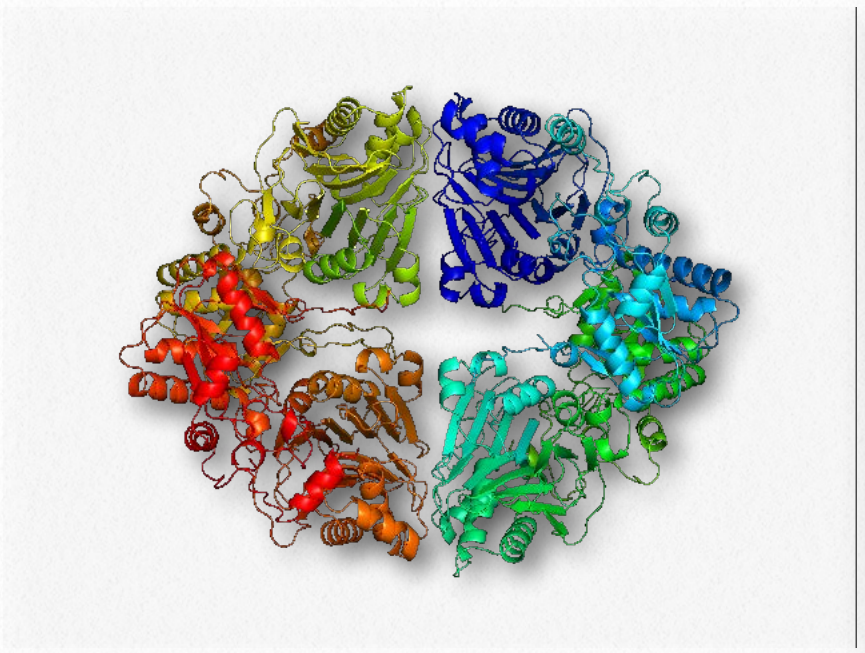


Figure 6.173 - PRPP amidotransferase
Wikipedia

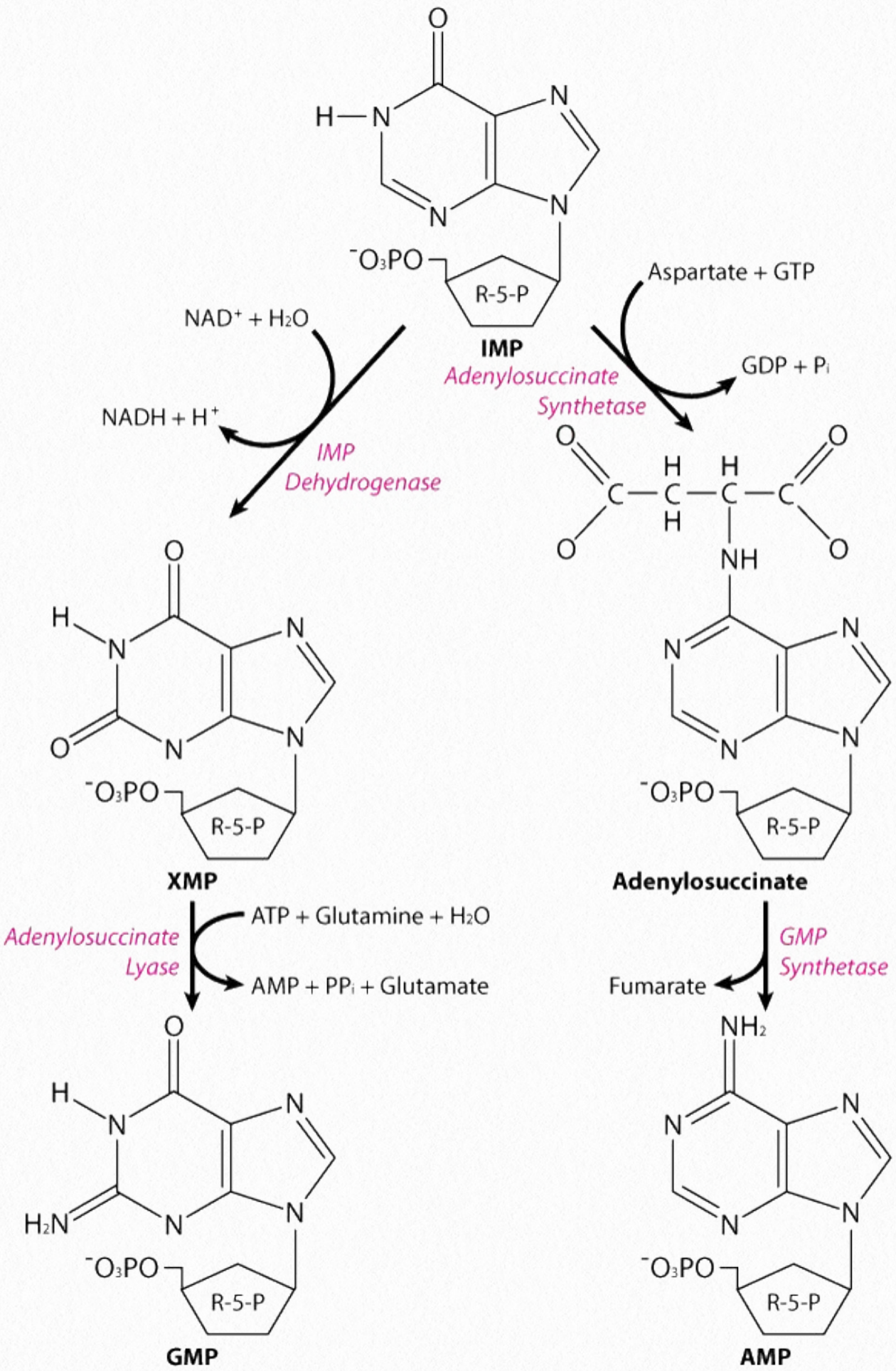


Figure 6.174 - The path from IMP (top) to AMP and GMP

Image by Aleia Kim

latory scheme of purines is illustrated by two examples. First imagine both AMP and GMP are abundant. When this occurs, PRPP amidotransferase will be completely inhibited and no purine synthesis will occur.

Partial activity

High levels of GMP and low levels of AMP would result in PRPP amidotransferase being slightly active, due to the fact GMP will fill one allosteric site, but low AMP levels will mean second allosteric site will likely be unfilled. This lowered (but not completely inhibited) activity of PRPP amidotransferase will allow for limited production of 5-PRA and the rest of the pathway intermediates, so it will remain active.

At the IMP branch, however, the high levels of GMP will inhibit

IMP dehydrogenase, thus shutting off that branch and allowing all of the intermediates to be funneled into making AMP. When the AMP level rises high enough, AMP binds to PRPP amidotransferase and along with GMP, shuts off the enzyme. A reversal will occur if AMP levels are high, but GMP levels are low.

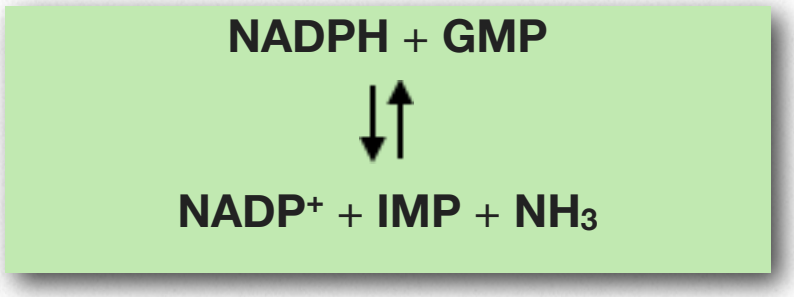
Proper balance

Regulated in this way, AMP and GMP levels can be maintained in a fairly narrow concentration range. Properly balancing nucleotide levels in cells is critical. It is likely for this reason that cells have numerous controls on the amount of each nucleotide made.

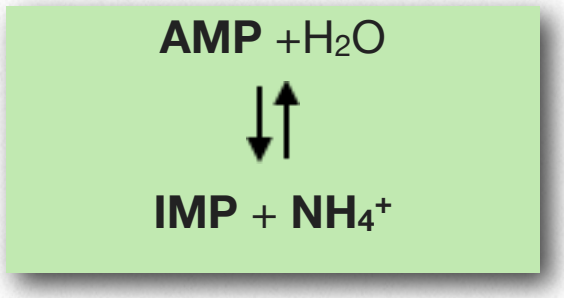
YouTube Lectures by Kevin HERE & HERE

Other mechanisms

Cells have two other ways of balancing GMP and AMP nucleotides. First, the enzyme GMP reductase will convert GMP back to IMP using electrons from NADPH.

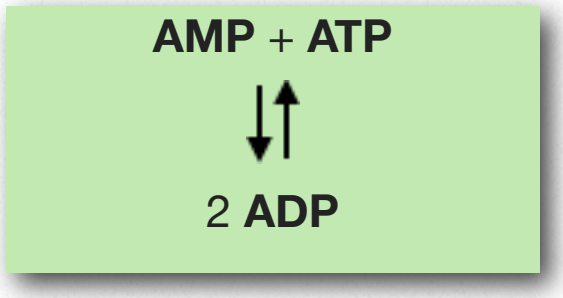


The IMP, in turn, can then be made into AMP if its concentration is low. Second, AMP can be converted back to IMP by the enzyme AMP deaminase. In this case, the IMP can then be made into GMP.



It is important to maintain appropriate proportions of the different nucleotides. Excess or scarcity of any nucleotide of any nucleotide can result in an increased tendency to mutation.

To convert AMP to ATP and GMP to GTP requires action of kinase enzymes. Each monophosphate nucleotide form has its own specific nucleoside monophosphate kinase. For adenine-containing nucleotides (ribose forms and deoxyribose forms), adenylate kinase catalyzes the relevant reaction.



The adenylate kinase reaction is reversible and is used to generate ATP when the cell's ATP concentration is low. When ATP is made from 2 ADPs in this way, AMP levels increase and this is one way the cell senses that it is low on energy.

Guanosine monophosphates also have their own kinase and it catalyzes the reaction at the top of the next page.

GMP + ATP

⇅

GDP + ADP

Other monophosphate kinases for UMP and CMP use ATP in a similar fashion.

In going from the diphosphate form to the triphosphate form, the picture is simple - one enzyme catalyzes the reaction for all diphosphates (ribose and deoxyribose forms). It is known as nucleoside diphosphate kinase or (more commonly) NDK or NDPK and it catalyzes reactions of the form

(d)XTP + (d)YDP

⇅

(d)XDP + (d)YTP

where X and Y refer to any base.

Purine salvage reactions

Not all nucleotides in a cell are made from scratch. The alternatives to *de novo* syntheses are salvage pathways. Salvage reactions to make purine nucleotides start with attachment of ribose to purine bases using phosphoribosylpyrophosphate (PRPP).

The enzyme catalyzing this reaction is known as hypoxanthine/guanine phosphoribosyltransferase (HGPRT - Figure 6.175) and is interesting from an enzymological as well as a medical perspective. First, the enzyme is able to catalyze both of the next two important salvage reactions - converting hypoxanthine to IMP or guanine to GMP.

Hypoxanthine + PRPP

⇅

IMP + PP_i

Guanine + PRPP

⇅

GMP + PP_i

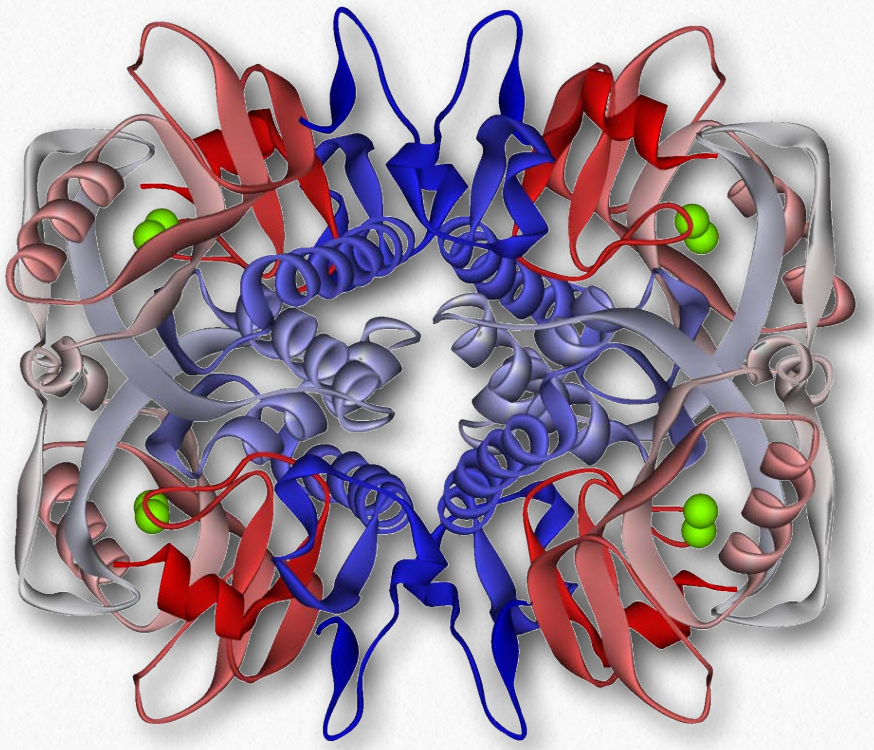
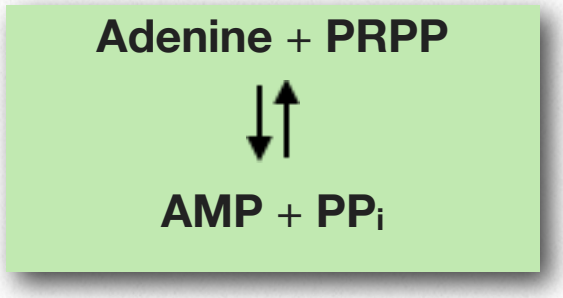


Figure 6.175 - HGPRT

HGPRT is able to bind a variety of substrates at its active site and even appears to bind non-natural substrates, such as acyclovir preferentially over its natural ones.



Medical perspective

From a medical perspective, reduction in levels of HGPRT leads to hyperuricemia, a condition where uric acid concentration increases in the body. Complete lack of HGPRT is linked to Lesch-Nyhan syndrome, a rare, inherited disease in high uric acid concentration throughout the body is associated with severe accompanying neurological disorders.

Reduced production of HGPRT occurs frequently in males and has a smaller consequence (gout) than complete absence. Interestingly, gout has been linked to a decreased likelihood of contracting multiple sclerosis, suggesting uric acid may help prevent or ameliorate the disease.

Expression of HGPRT is stimulated by HIF-1, a transcription factor made in tissues when oxygen is limiting, suggesting a role for HGPRT under these conditions.

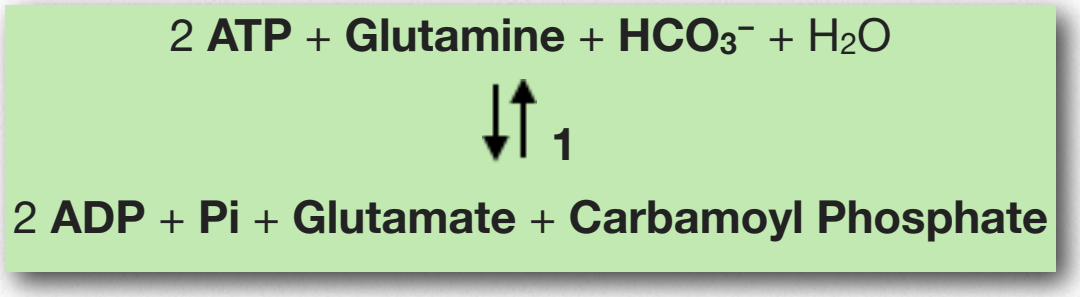
Adenine salvage

The enzyme known as adenine phosphoribosyltransferase (APRT) catalyzes the reaction corresponding to HGPRT for salvaging adenine bases.

Pyrimidine nucleotide metabolism

The *de novo* pathway for synthesizing pyrimidine nucleotides has about the same number of reactions as the purine pathway, but also has a different strategy. Whereas the purines were synthesized attached to the ribose sugar, pyrimidine bases are made apart from the ribose and then attached later.

The first reaction is catalyzed by carbamoyl phosphate synthetase (Figure 6.176).



Two different forms are found in eukaryotic cells. Form I is found in mitochondria and form II is in the cytoplasm.

The reaction catalyzed by carbamoyl phosphate synthetase is the rate limiting step in pyrimidine biosynthesis and corresponds to reaction 1 in Figure 6.178.

Balance

The enzyme is activated by ATP and PRPP and is inhibited by UMP. This helps to balance pyrimidine vs. purine concentrations. High concentrations of a purine (ATP) acti-

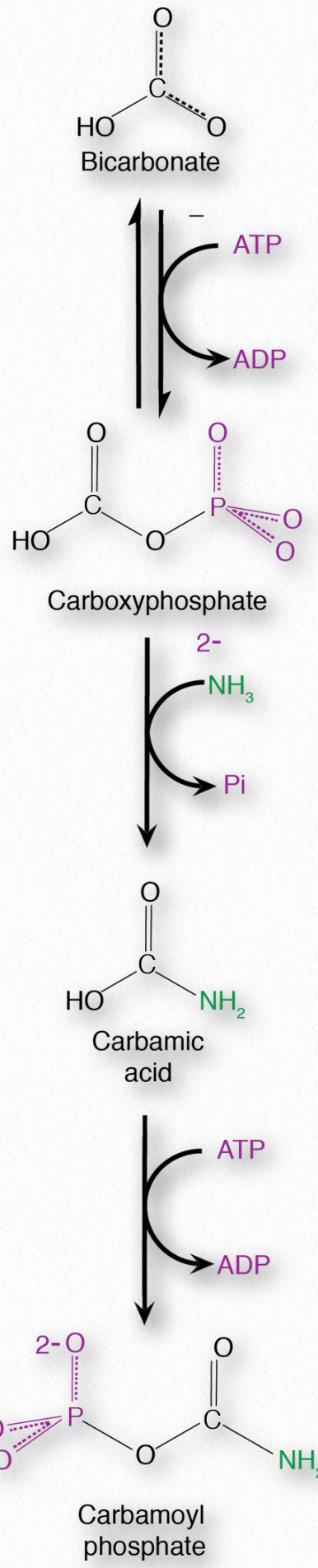


Figure 6.176 - Formation of carbamoyl phosphate in reaction 1

Image by Penelope Irving

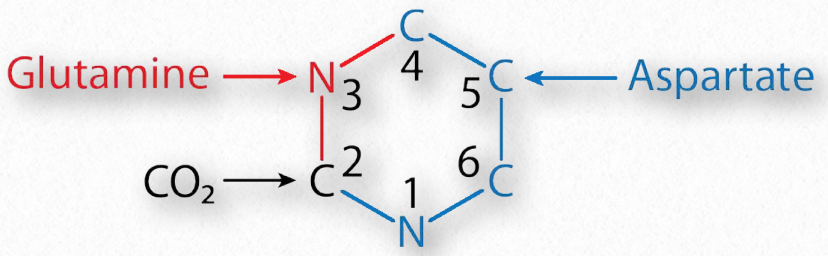


Figure 6.177 - Atom sources in pyrimidines

Image by Pehr Jacobson

vates the synthesis of pyrimidines. PRPP increases in concentration as purine concentration increases, so it too helps to establish that balance. UMP is an end product of pyrimidine metabolism, so the process is self-limiting. The next enzyme in the pathway, aspartate transcarbamoylase (ATCase) also plays a role in the same balance, as we will see. The reaction it catalyzes is shown below and is reaction 2 in Figure 6.178.

Carbamoyl Phosphate + Aspartate ⇅ 2 **Carbamoyl Aspartate + P_i**

ATCase is a classic enzyme exhibiting allosteric regulation and feedback inhibition, having both homotropic and heterotropic effectors (Figure 6.179 and see HERE). With 12 subunits (6 regulatory and 6 catalytic units), the enzyme exists in two states - a low activity T-state and a high activity R-state. Binding of the aspartate substrate to the active site shifts the equilibrium in favor of the R-state.

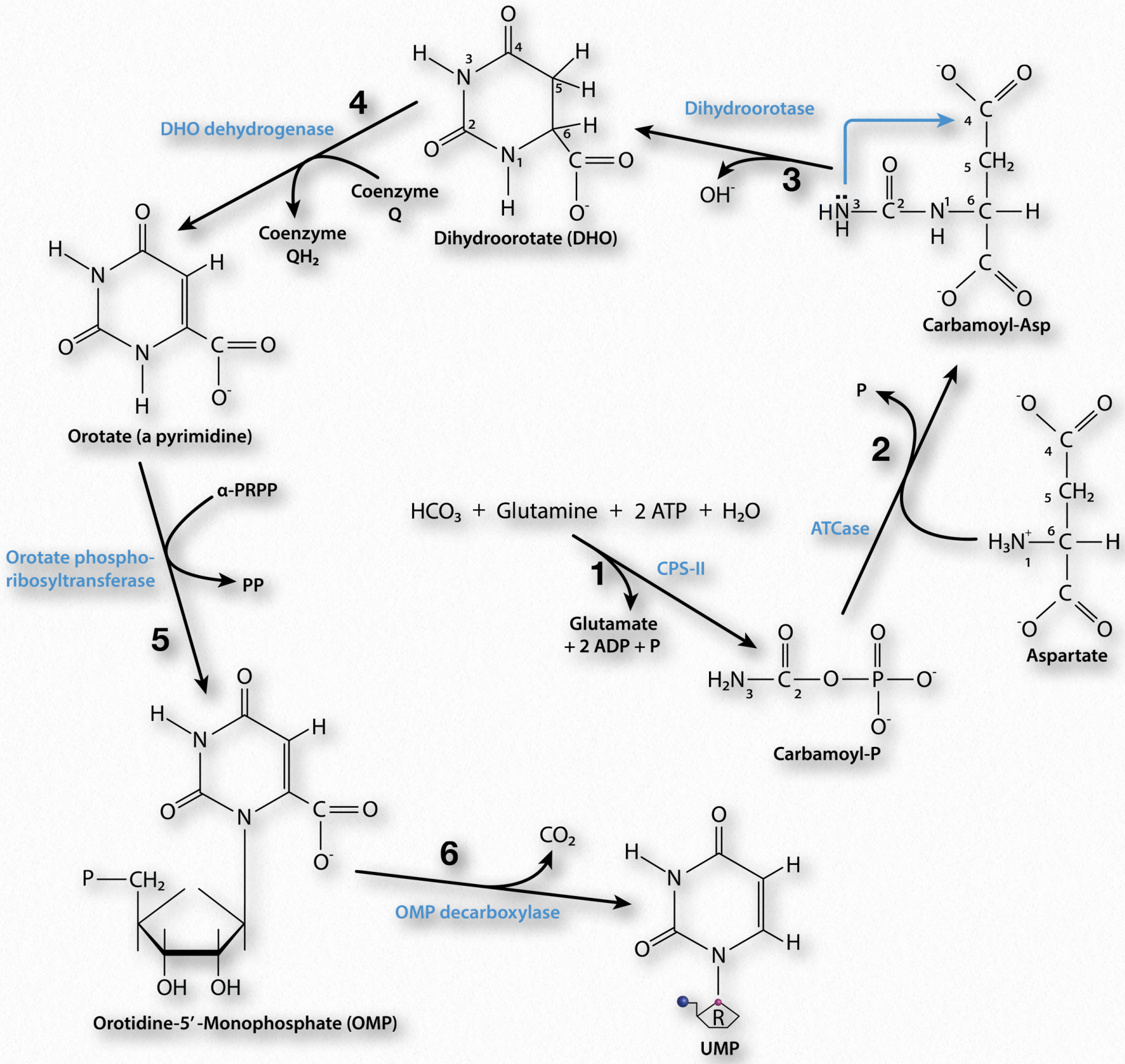


Figure 6.178 - Pyrimidine synthesis by the *de novo* pathway

Image by Pehr Jacobson

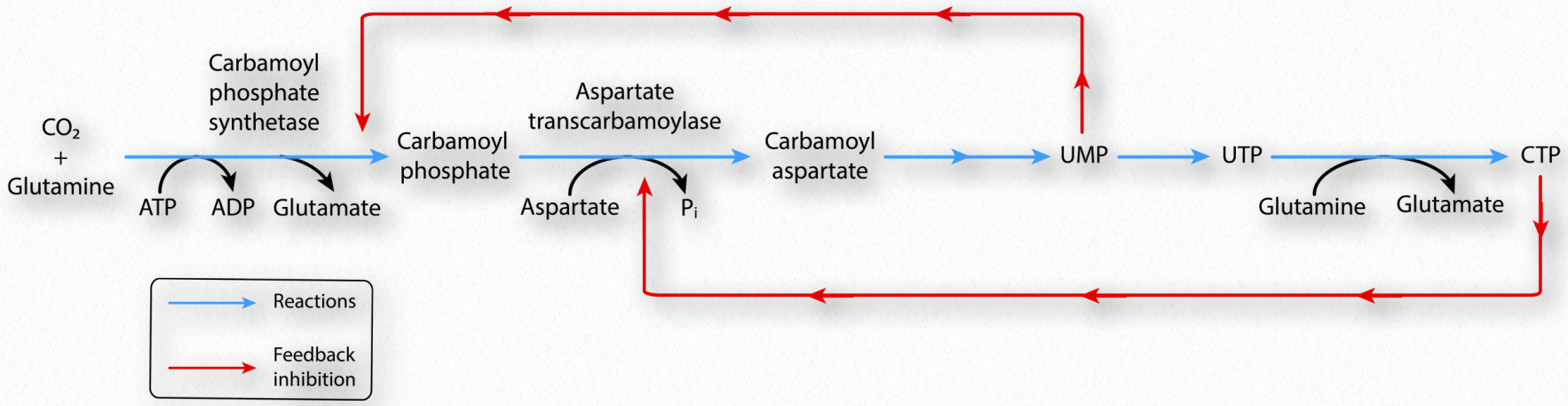


Figure 6.179 - Overview of pyrimidine metabolism feedback regulation

Image by Pehr Jacobson

Aspartate is a homotropic effector of the enzyme, because it acts allosterically on the enzyme and is a substrate for it as well. Similarly, binding of ATP to the regulatory units favors the R-state, whereas binding of CTP to the regulatory units favors the T-state. ATP and CTP are heterotropic effectors of the enzyme because they are not substrates for it, but act allosterically.

YouTube Lectures by Kevin HERE & HERE

Regulation

As was seen with the first enzyme of the pathway, high concentration of purine nucleotides stimulates synthesis of pyrimidines and high concentration of pyrimidines turns off the pathway that synthesizes them.

Dihydroorotase catalyzes reaction 3 and is found in the cytoplasm, as is ATCase.

Carbamoyl Aspartate

⇅ 3

Dihydroorotate + H_2O

Reaction 4 occurs in the mitochondrion, so the product of reaction 3, dihydroorotate, must be transported into the mitochondrion from the cytoplasm. In reaction 4, dihydroorotate is oxidized to orotate. The enzyme catalyzing the reaction is dihydroorotate dehydrogenase.

Dihydroorotate + **NAD^+**

⇅ 4

Orotate + **NADH** + H^+

Reaction #5, catalyzed by orotate phosphoribosyl transferase, involves connection of orotate to ribose to yield a nucleotide - orotidine-5'-monophosphate (OMP).

Orotate + **PRPP**

⇅ 5

OMP + **PP_i**

Last, OMP is converted to uridine-5'-monophosphate (UMP) by action of a fasci-

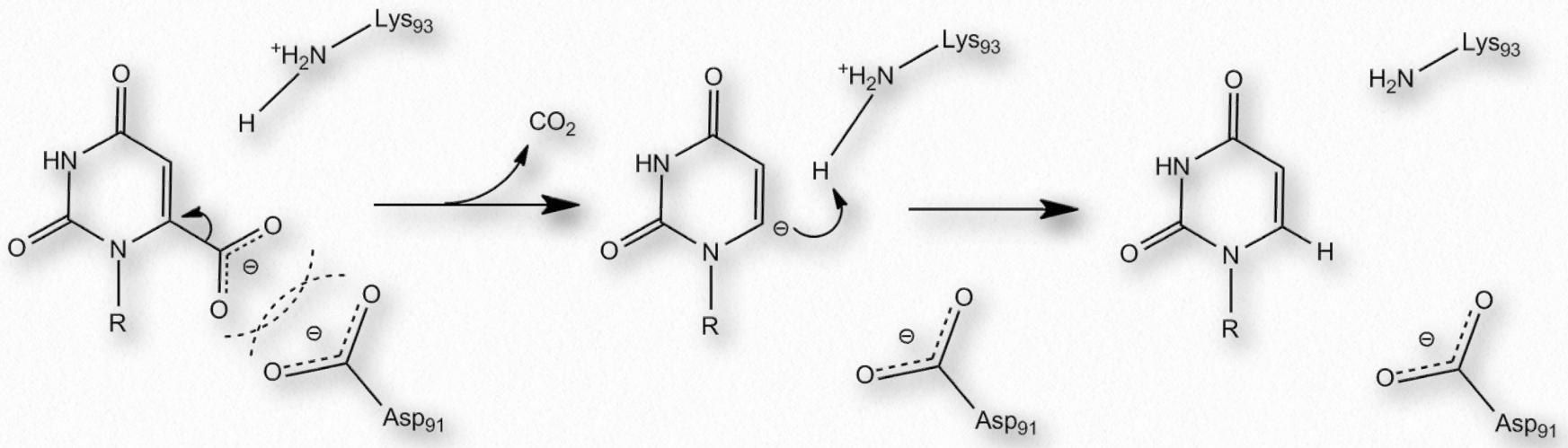


Figure 6.180 - Mechanism of action of OMP decarboxylase

Wikipedia

nating enzyme known as OMP decarboxylase.

OMP

⇅ 6

UMP + CO_2

OMP decarboxylase is frequently cited as an example for the incredible ability of an enzyme to speed a reaction. The decarboxylation of OMP, if allowed to proceed in the absence of an enzyme takes about 78 million years. In the presence of OMP decarboxylase, the reaction takes place in 18 milliseconds, a speed increase of about 10^{17}. Remarkably, the enzyme accomplishes this without any cofactors or coenzymes of any kind.

The mechanism of action of the enzyme is shown in Figure 6.180. In mammals, the activities of OMP decarboxylase and orotate phosphoribosyl transferase are contained on the same protein.

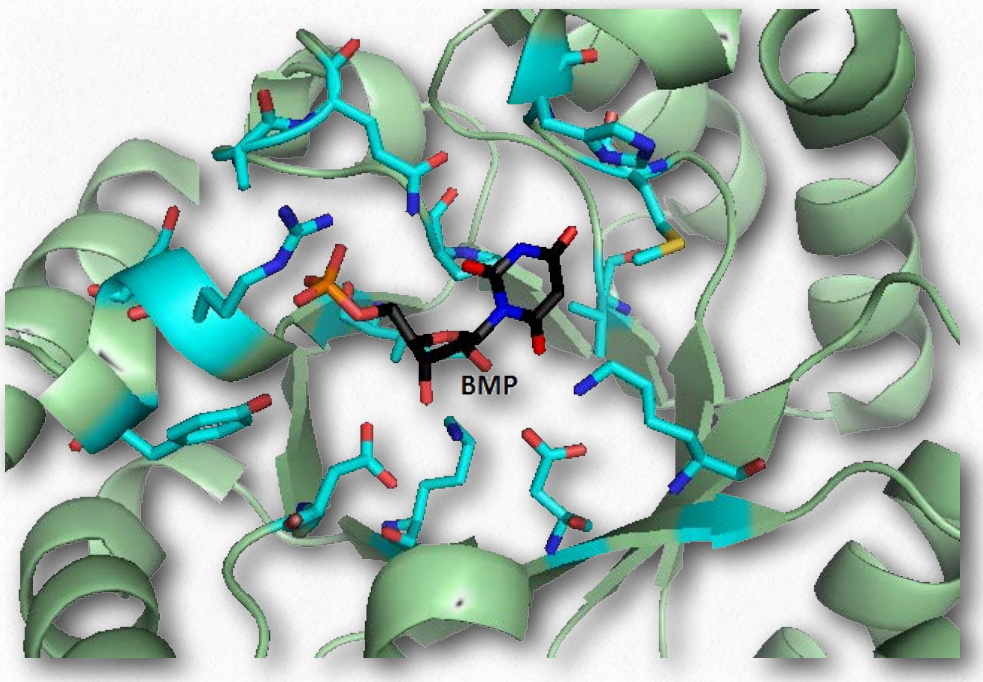


Figure 6.181 - OMP decarboxylase bound to an OMP analog at the active site

Wikipedia

A monophosphate kinase (UMP/CMP kinase) catalyzes conversion of UMP to UDP.

The same enzyme will also phosphorylate CMP to CDP and dCMP to dCDP. Like

UMP + ATP

⇅

UDP + ADP

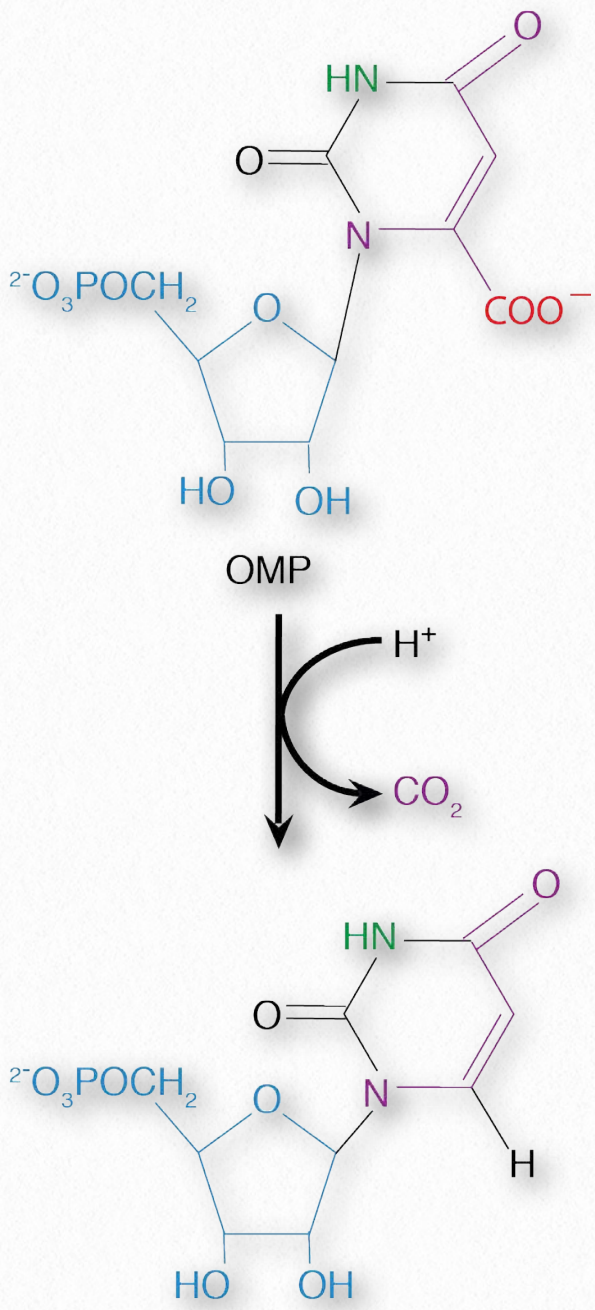


Figure 6.182 - Conversion of OMP to UMP

Image by Penelope Irving

the reaction of adenylate kinase, the reaction above, when run in the reverse direction, can be a source of ATP when the cell is low on energy.

The next step, catalyzed by NDPK, uses energy of any triphosphate nucleotide (XTP) to produce UTP from UDP.

UDP + XTP

⇅

UTP + XDP

CTP Synthase

UTP is the substrate for synthesis of CTP via catalysis by CTP synthase.

UTP + **Glutamine** + **ATP**

⇅

CTP + **Glutamate** + **ADP** + **P_i**

This enzyme is inhibited by its product, ensuring too much CTP is not made and activated by physiological concentrations of ATP, GTP, and glutamine. One human isozyme, CTPS 1, has been shown to be inactivated by phosphorylation by glycogen synthase kinase 3.

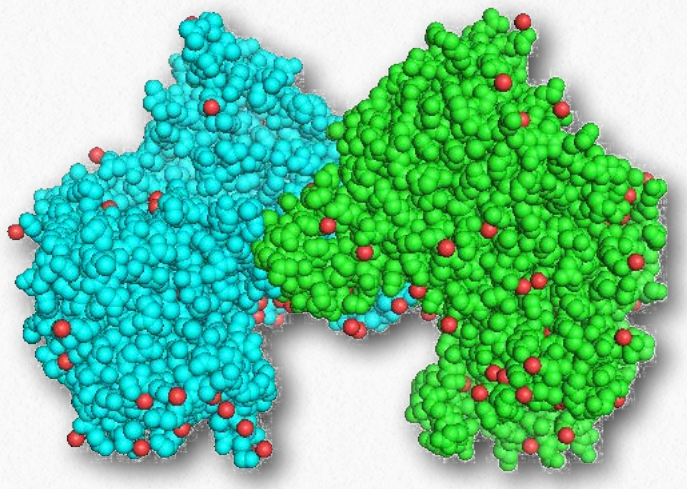


Figure 6.183 - CTP synthase dimer

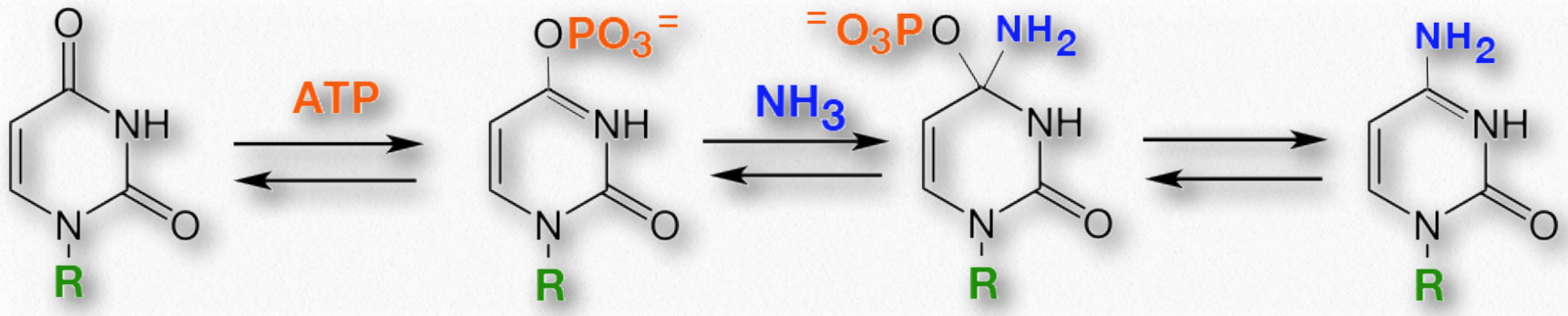


Figure 6.184 - Mechanism of CTP synthase action

CTP synthase has two domains and is a heterodimer (Figure 6.183). It exists as an inactive monomer at low enzyme concentrations or in the absence of UTP and ATP. One domain of the enzyme cleaves the amine group from glutamine and transfers it internally to the UTP. The other domain (synthase domain) binds ATP and initiates the mechanism shown in Figure 6.184 for making CTP.

CTP is the only nucleotide synthesized *de novo* directly as a triphosphate, since it arises directly from UTP. Since deoxyribonucleotides are made from ribonucleoside diphosphates, it means deoxycytidine nucleotides must either be made preferentially from salvage nucleotides or CTP must be dephosphorylated first.

One enzyme that can do this is a membrane-bound enzyme known as apyrase, which sequentially converts CTP to CDP and then CMP.

YouTube Lectures by Kevin HERE & HERE

Pyrimidine salvage reactions

Pyrimidine salvage synthesis allows cells to remake pyrimidine triphosphate nucleotides starting from either the C or U pyrimidine bases, nucleosides, or nucleotides. Figures 1.85 & 6.186 depict salvage pathway reactions. As is apparent in Figure 1.86, there are multiple ways of making the same molecules. For example, uracil can be made into uridine by reaction 11 or by reaction 12.

The figure depicts not only the synthesis of CTP and UTP from basic components, but also shows how these nucleotides can be broken down into smaller pieces.

In many cases, the same enzyme works on cytidine, uridine, and deoxycytidine molecules.

Enzymes of note

There are several enzymes of note in the salvage pathway. Seven enzymes, for example, work on both uracil and cytosine contain-

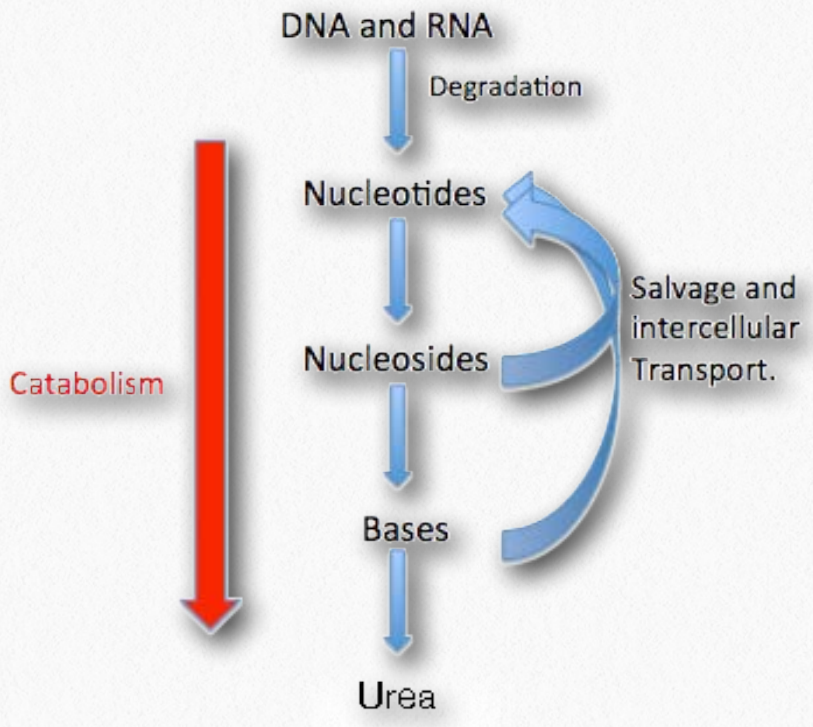


Figure 6.185 - Catabolism and salvage of nucleotides from DNA and RNA

Wikipedia

ing nucleosides/nucleotides. These include NTP phosphatase (reaction 2), NDPK (reaction 3), apyrase (reaction 4), NDP phosphatase (reaction 5), UMP/CMP kinase (reaction 6), pyrimidine-specific 5' nucleotidase (reaction 7), and uridine/ cytidine kinase (reaction 8). The enzymes for reactions 6 and 8 can also use deoxyribonucleosides/ deoxyribonucleotides as substrates.

Cytidine deaminase (reaction #9) converts cytidine to uridine by removing an amine group from the cytosine base and thus is a counter for the UTP to CTP reaction catalyzed by CTP synthetase. Countered reactions allow cells to balance concentrations of nucleosides/nucleotides in either direction if they should get out of balance.

Two other reactions in the figure are worth mentioning. Both UTP and CTP are converted in the breakdown process to UMP and CMP, respectively. Both of these reactions are important for deoxyribonucleotide metabolism. In each case, the monophosphate derivatives are phosphorylated, creating diphosphate derivatives (UDP and CDP) that are substrates for RNR that yield dUDP and dCDP, respectively. dUDP is phosphorylated to dUTP and then pyrophosphate is removed by dUTPase to yield dUMP.

Enzymes of Figure 6.186

1 = **CTP Synthase**
2 = **NTP Phosphatase**
3 = **NDPK**
4 = **Apyrase**
5 = **NDP Phosphatase**
6 = **UMP/CMP Kinase**
7 = **Pyrimidine-specific 5' Nucleotidase**
8 = **Uridine / Cytidine Kinase**
9 = **Cytidine Deaminase**
10 = **Uridine Nucleosidase**
11 = **Uridine Phosphorylase**
12 = **Uracil Phosphoribosyltransferase**

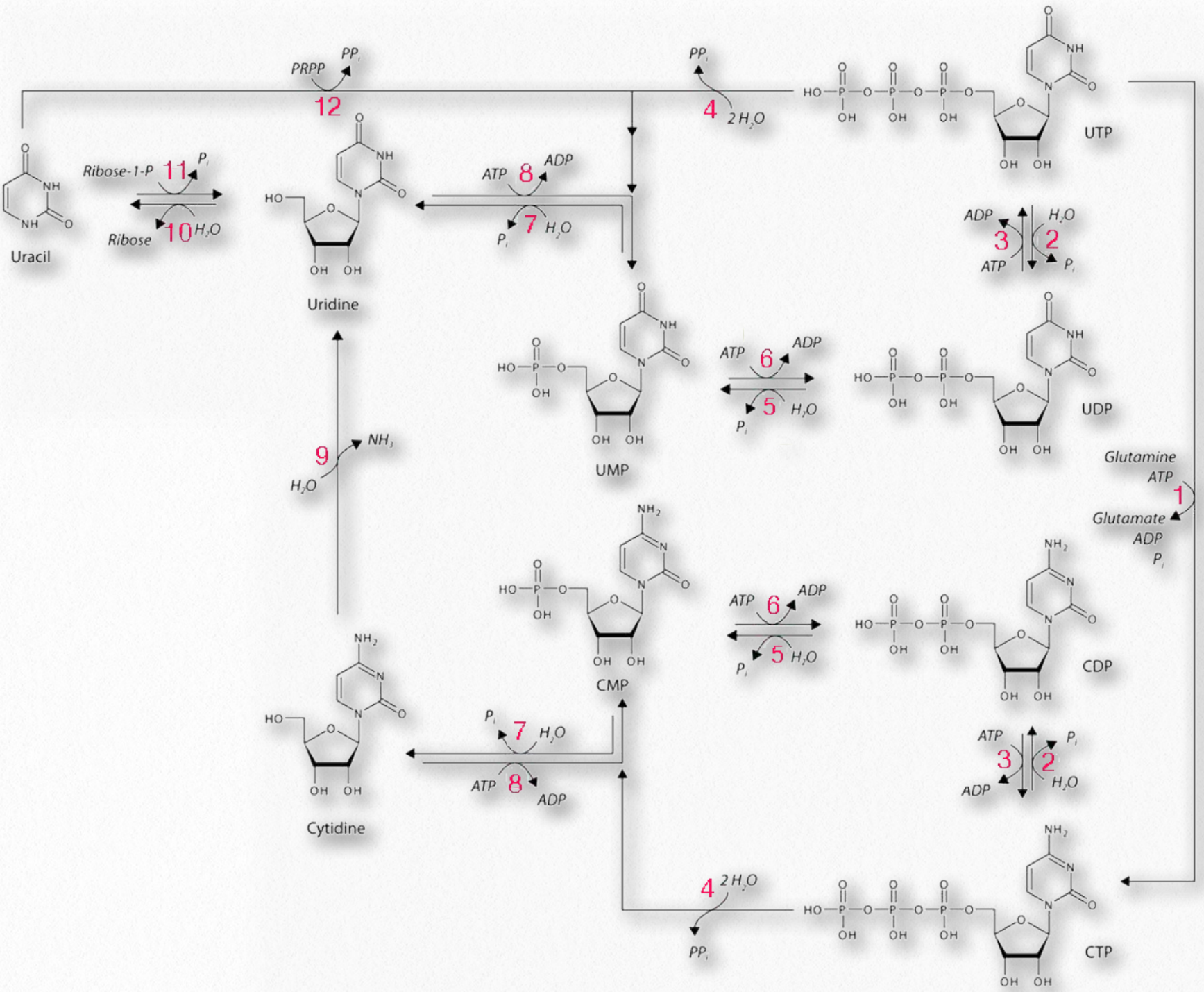


Figure 6.186 - Salvage pathways of pyrimidine nucleotides

dUMP is a substrate for thymidine synthesis (see HERE). dCDP is converted to dCTP by NDPK

Deoxyribonucleotide metabolism

Deoxyribonucleotides, the building blocks of DNA, are made almost exclusively from ribonucleoside diphosphates. A single enzyme called ribonucleotide reductase (RNR) is responsible for the conversion of each of these to a deoxy form (Figure 6.187). The enzyme's substrates are ribonucleoside diphosphates (ADP, GDP, CDP, or UDP) and the products are deoxyribonucleoside diphosphates (dADP, dGDP, dCDP, or dUDP). Thymidine nucleotides are synthesized from dUDP.

RNR has two pairs of two identical subunits - R1 (large subunit) and R2 (small subunit). R1 has two allosteric binding sites and a catalytic site. R2 forms a tyrosine radical necessary for the reaction mechanism of the enzyme.

There are three classes of RNR enzymes and they differ in the nature or means of generating a radical used in the enzyme's catalytic mechanism. Class I RNRs are found in eukaryotes, eubacteria, bacteriophages, and viruses. They all use a ferrous iron center that loses an electron (converting to ferric iron) to generate a free radical on a tyrosine ring. These enzymes only work in aerobic conditions.

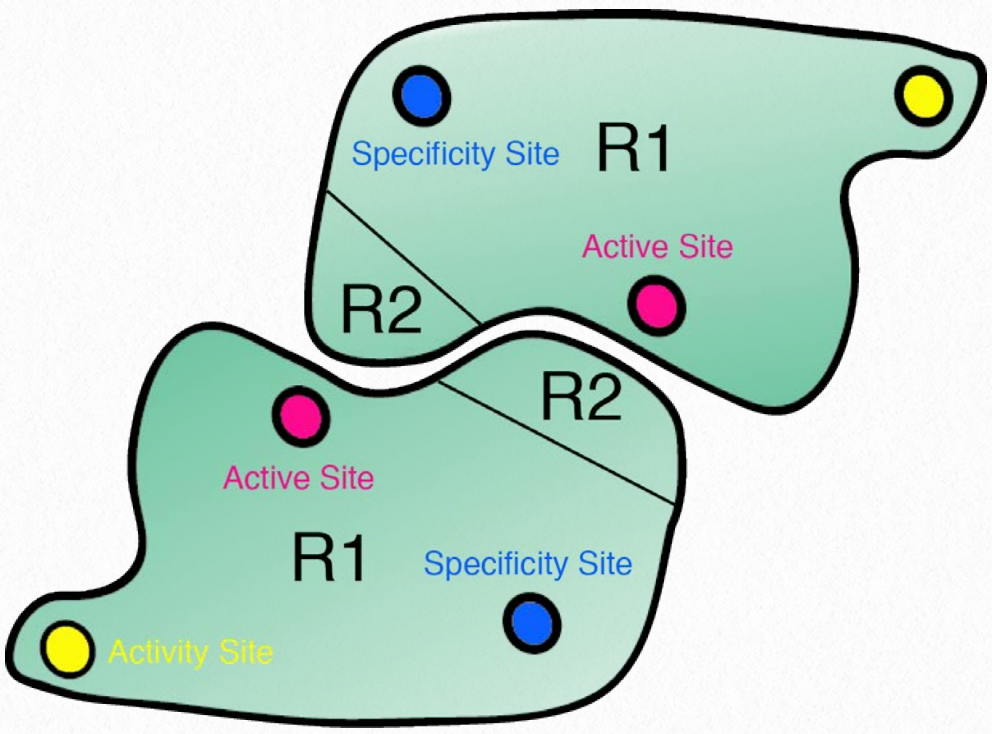


Figure 6.187 Ribonucleotide reductase
Image by Penelope Irving

Class II RNRs use 5'-deoxyadenosyl cobalamin (vitamin B_{12}) to generate a radical and work under aerobic or anaerobic conditions. They are found in eubacteria, archaebacteria, and bacteriophages. Class III RNRs generate a glycine radical using S-adenosyl methionine (SAM) and an iron-sulfur center. They work under anaerobic conditions and are used by archaebacteria, eubacteria, and bacteriophages. Substrates for class I enzymes are ribonucleoside diphosphates. Class II enzymes work on ribonucleoside diphosphates or ribonucleoside triphosphates. Class III enzymes work on ribonucleoside triphosphates.

In class I enzymes, RNR is an iron-dependent dimeric enzyme with each monomeric unit containing a large subunit (known as α or R1) and a small subunit (known as β or R2). The R1 subunit contains regulatory binding sites for allosteric effectors (see below), whereas the R2 subunit houses a tyrosine residue that forms a radical critical to the reaction mechanism of the enzyme. Electrons needed in the reaction are transmitted from NADPH to the enzyme by one of two pathways, reducing a disulfide bond in the enzyme to two sulfhydryls. In the first transfer mechanism, NADPH passes electrons to glutathione, which passes them to glutaredoxin, which then donates them to the RNR enzyme used

in the reaction. In the second mechanism, NADPH passes electrons to FAD, which uses them to reduce thioredoxin, which then passes the electrons to RNR with the same end result as in the first pathway - reduction of a suflhydryl in RNR.

In the reaction mechanism (Figure 6.188), a tyrosine side chain in the R2 unit must be radicalized to start. This electronic change is transmitted through the small R_2 subunit to the active site of the large R1 subunit. Several aromatic amino acid side chains are thought to play a role in that process. Iron atoms in the R2 subunit assist in creation and stabilization of the radical. The tyrosine radical contains an unpaired electron delocalized across its aromatic ring.

Transfer of the electronic instability to the R1 unit results in radicalization of a cysteine (to form a thiyl radical) at the active site. The thiyl radical, thus formed, abstracts a hydrogen atom (proton plus electron) from carbon 3 of ribose on the bound ribonucleoside diphosphate, creating a radical carbon atom. Radicalization of carbon #3 favors release of the hydroxyl group on carbon #2 as water. The extra proton comes from the sulfhydryl of the enzyme's cysteine. In the next step of the process, a proton and two electrons from the same cysteine are transferred to carbon #2 and then carbon #3 takes back the proton originally removed from it to yield a deoxyri-

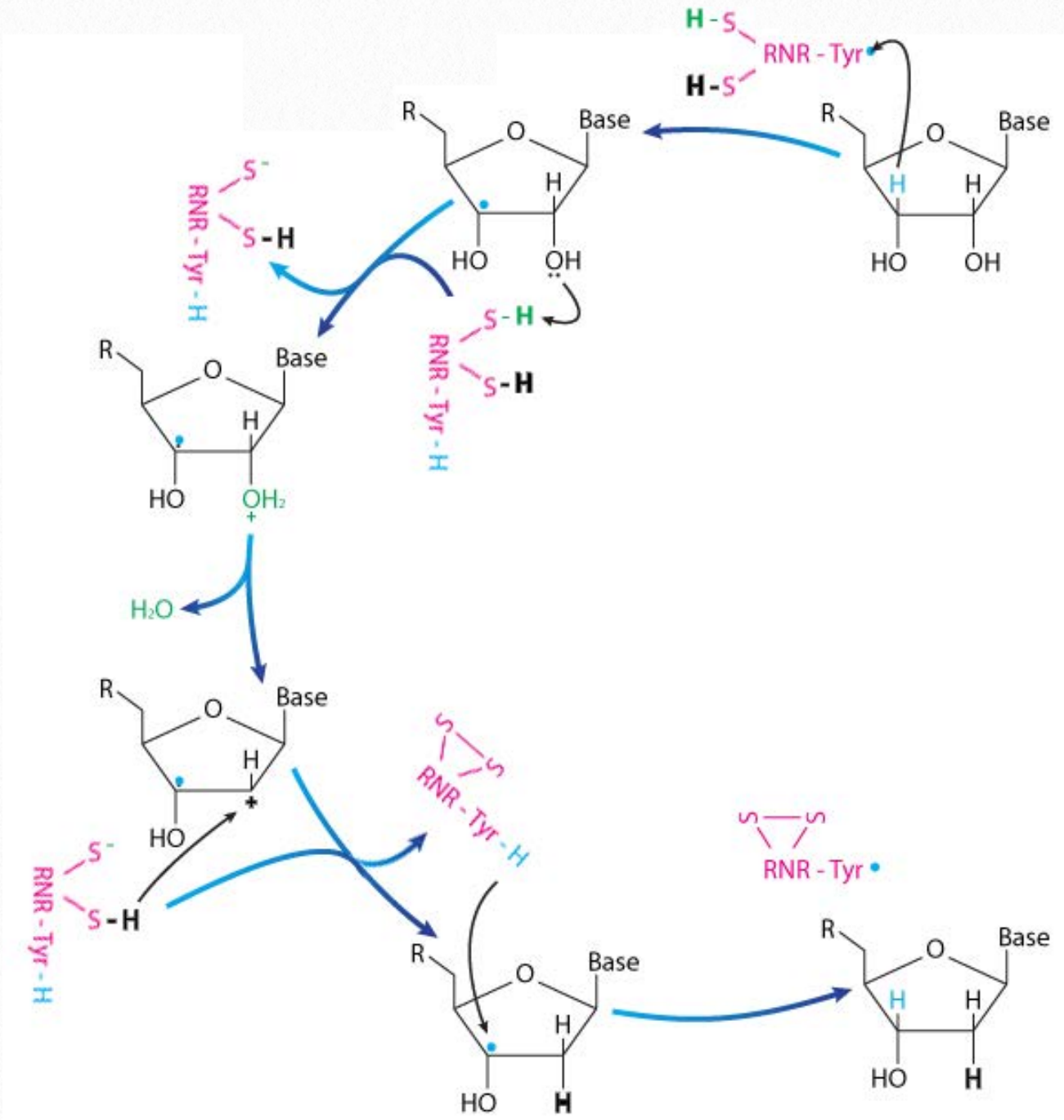


Figure 6.188 Ribonucleotide reductase reaction mechanism
Image by Aleia Kim

bonucleoside diphosphate. The enzyme's thiyl group gains an electron from R2 and the disulfide bond created in the reaction must be reduced by electrons from NADPH again in order to catalyze again.

Regulation

In addition to RNR's unusual reaction mechanism, the enzyme also has a complex system of regulation, with two sets of allosteric binding sites, both found in the R1 subunit. Because a single enzyme, RNR, is responsible for the synthesis of all four deoxyribonucleotides, it is necessary to have mechanisms to ensure that the enzyme produces the correct amount of each dNDP. This is a critical consideration, since imbalances in DNA precursors can lead to mutation.

Consequently, the enzyme must be responsive to the levels of the each deoxyribonucleotide, selectively making more of those that are in short supply, and preventing additional synthesis of those that are abundant. These demands are met by having two separate control mechanisms on the enzyme - one that determines which substrate will be acted on, and another that controls the enzyme's activity.

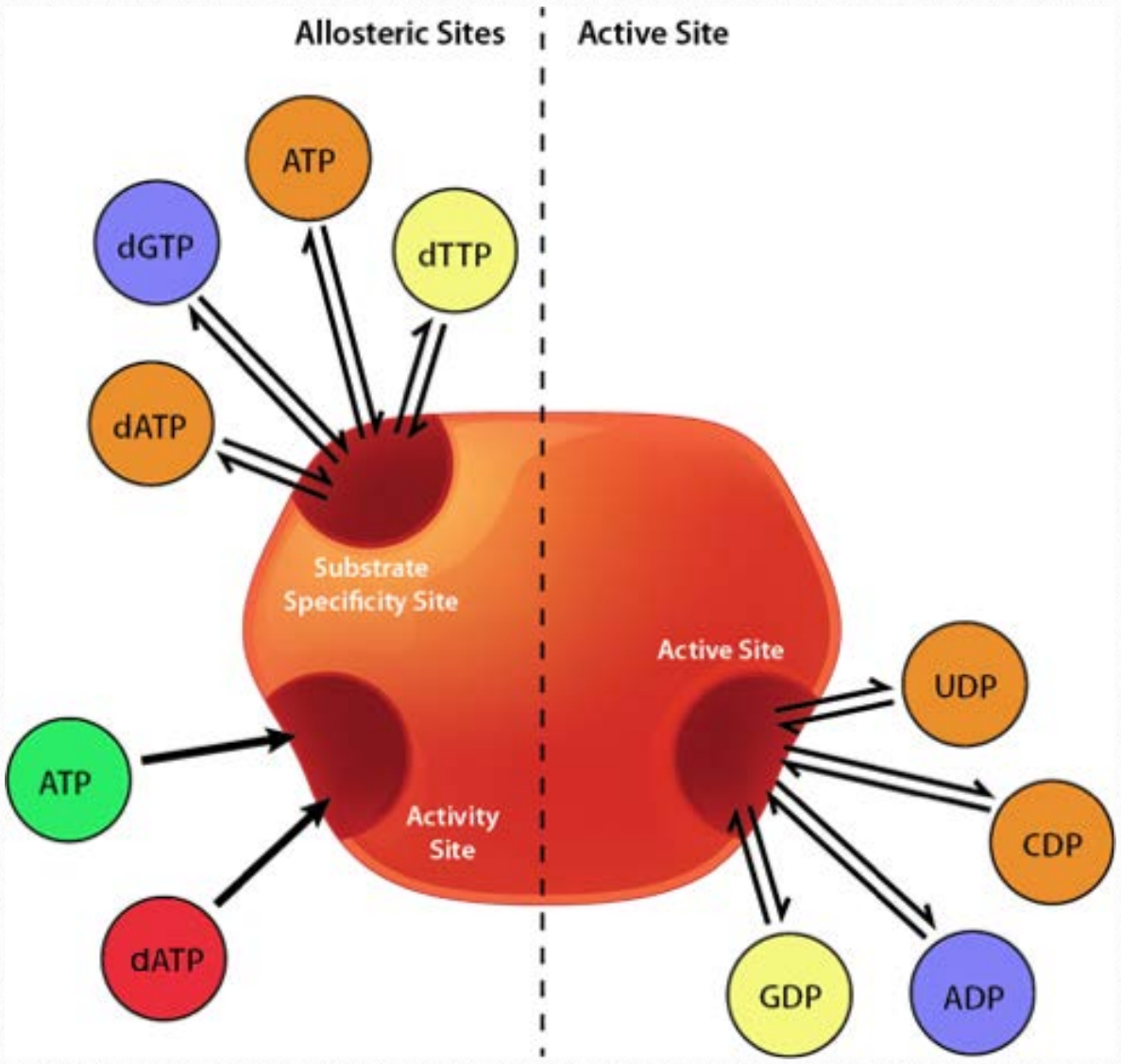


Figure 6.189 Allosteric regulation of RNR activity
Image by Aleia Kim

Two allosteric sites

RNR is allosterically regulated *via* two molecular binding sites - a specificity binding site (binds dNTPs and induces structural changes in the enzyme that determines which substrates preferentially bind at the catalytic site and an activity control site (controls whether or not enzyme is active). The activity control site functions like a simple on/off switch - ATP activates catalysis, dATP inactivates it. (One subset of class I enzymes, however, is not affected by dATP.)

The inactivation of RNR by dATP is an important factor in the disease known as Severe Combined Immunodeficiency Disease (SCID). In SCID, the salvage enzyme adenosine deaminase is deficient, leading to a rise in concentration of dATP in cells of the immune system. dATP shuts down RNR in these cells, thus stopping their proliferation and leaving the affected individual with a very weak or no immune system.

YouTube Lectures by Kevin HERE & HERE

Allosteric effectors

When dTTP is abundant (Figure 6.189), it binds to RNR's specificity site and inhibits binding and reduction of CDP and UDP but stimulates binding and reduction of GDP at the active site of the enzyme. Conversely, binding of ATP or dATP at the specificity site stimulates binding and reduction of CDP and UDP at the active site. Last, binding of dGTP to the specificity site (specificity site B) induces binding and reduction of ADP at the active site.

Students sometimes confuse the active site of RNR with the activity control site (sometimes called the activity site). The active site is where the reaction is catalyzed, and could better be called the catalytic site, whereas the activity site is an allosteric binding site for ATP or dATP that controls whether the enzyme is active. High levels of dATP are an indicator that sufficient dNTPs are available, so the enzyme gets inhibited to stop production of more. Low levels of dATP allow binding of ATP and activation of the enzyme.

In addition to regulation by deoxyribonucleotides and ATP, RNR can be directly inhibited by hydroxyurea.

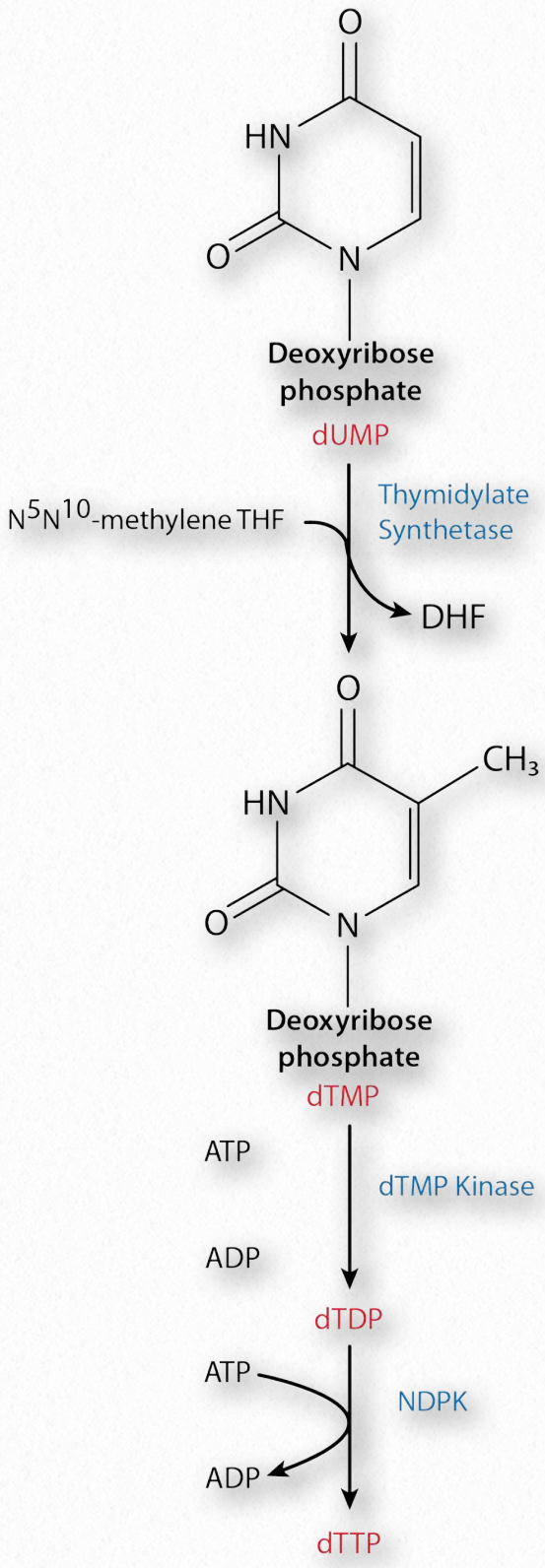


Figure 6.190 - Pathway from dUMP to dTTP

Image by Pehr Jacobson

dTTP synthesis

Synthesis of dTTP by the *de novo* pathway involves a multi-step process from UDP to dTTP. It begins with UDP, which is converted to dUDP by RNR. dUDP is phosphorylated by NDPK to yield dUTP, which is quickly broken down by dUTPase to produce dUMP. The remaining reactions are shown in Figure 6.190.

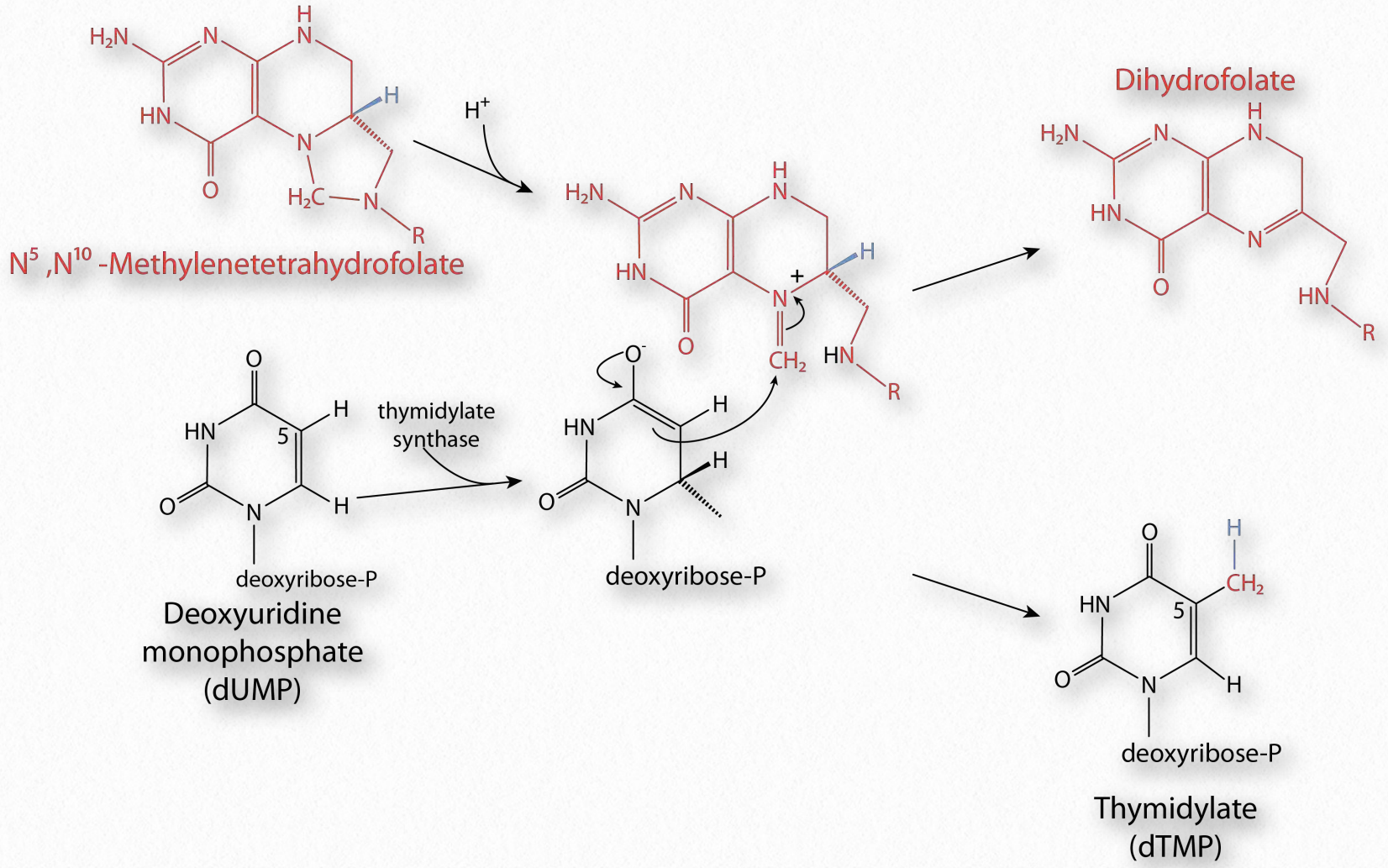


Figure 6.191 - Mechanism of synthesis of dTMP from dUMP

Image by Pehr Jacobson

Important enzymes in the pathway include dUTPase and thymidylate synthetase. dUTPase is important for keeping the concentration of dUTP low so it does not end up in DNA. DNA polymerase can use dUTP just as it does dTTP, and incorporate it into a DNA strand, across from adenine nucleotides.

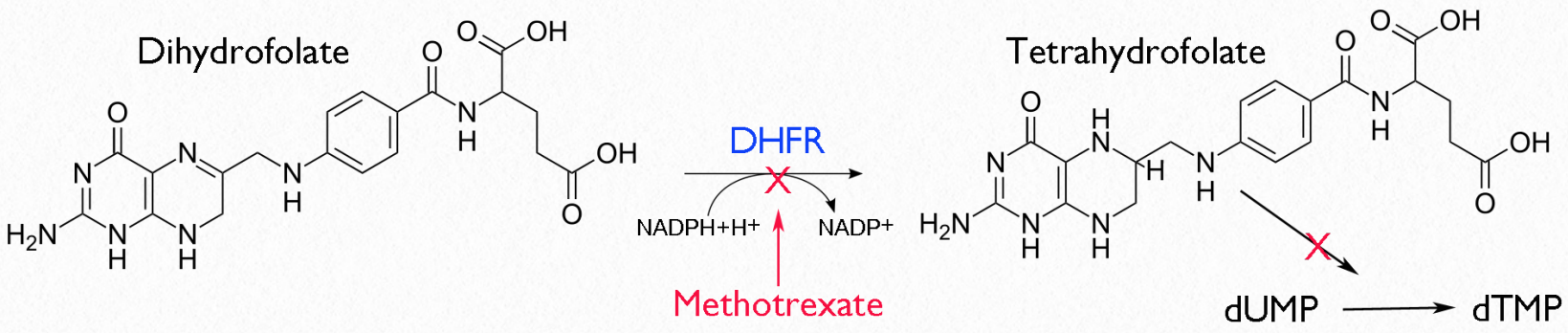


Figure 6.192 Recycling of dihydrofolate to tetrahydrofolate in cells can be inhibited by the drug methotrexate, thus stopping synthesis of thymidine nucleotides

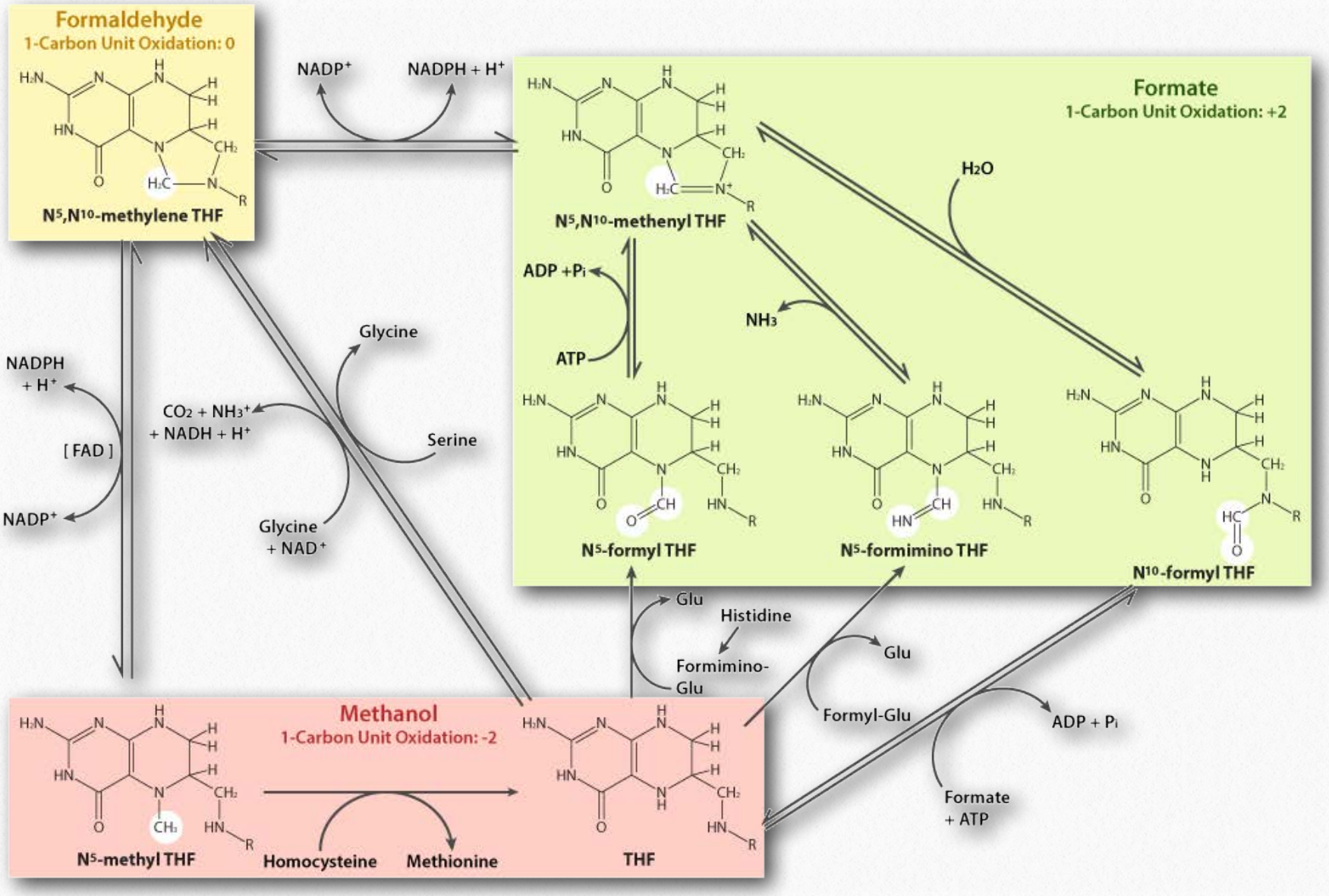


Figure 6.193 - Metabolism of folate molecules

Image by Aleia Kim

Thymidylate synthetase is important because it is a target (directly and indirectly) for anticancer therapies. As shown in Figure 6.191, a methyl group from N^5,N^{10}-methylene-tetrahydrofolate (often called tetrahydrofolate) is donated to dUMP, making dTMP and dihydrofolate (DHF). Folate molecules are in limited quantities in cells and must be recycled, because if they are not, then the reaction to make dTMP cannot occur. Recycling of dihydrofolate to tetrahydrofolate occurs by the reaction shown in Figure 6.192.

The enzyme involved in the conversion of dihydrofolate to tetrahydrofolate, dihydrofolate reductase (DHFR - Figure 6.192), is one target of anticancer drugs because by stopping the regeneration of tetrahydrofolate from dihydrofolate (otherwise a dead end), one can stop production of thymidine nucleotides and, as a result, halt DNA synthesis, thus preventing a cancer cell from dividing. Competitive inhibitors of DHFR include methotrexate (Figure 6.194) or aminopterin. Cells contain numerous folates for performing one carbon metabolism and the path-

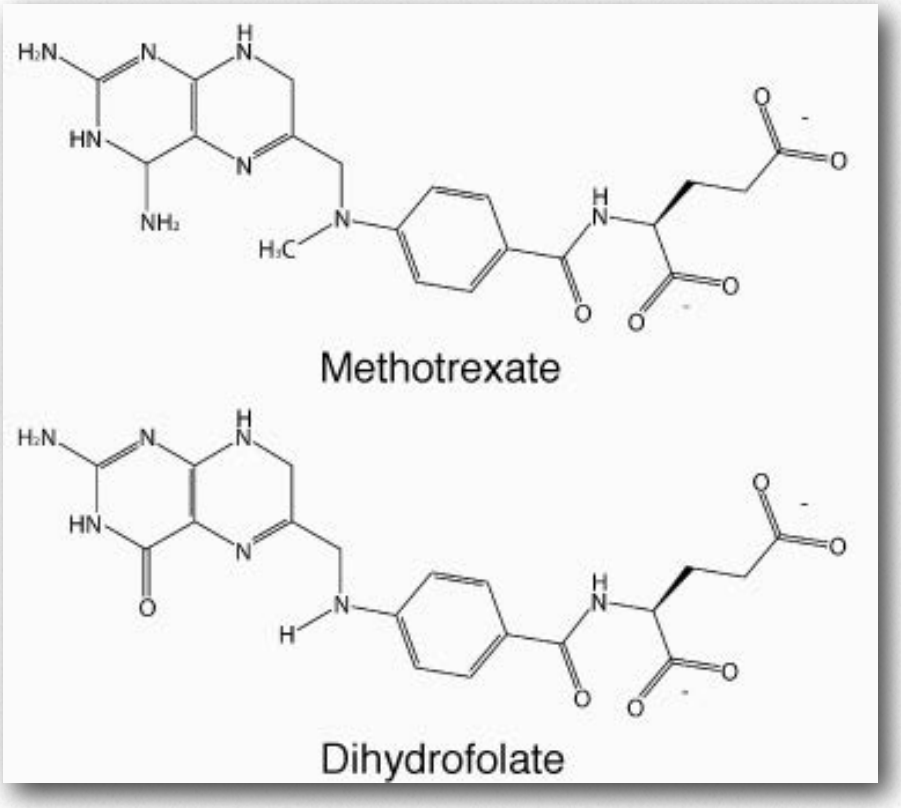


Figure 6.194 Dihydrofolate and competitive inhibitor methotrexate

Image by Ben Carson

ways by which they are all recycled is shown in Figure 6.193.

5-fluorouracil

Yet another important inhibitor of thymidine synthesis is used to treat cancer. This compound, 5-fluorouracil (Figure 6.195 and Movie 6.3) is a suicide inhibitor of thymidylate synthase.

Salvage synthesis

Besides synthesis from simple precursors, nucleotides can also be made from pieces of existing ones. This is particularly relevant, since consumption of food introduces to the

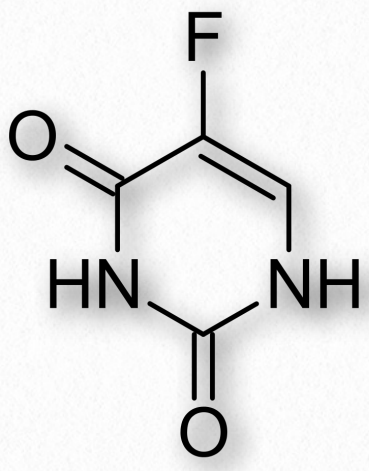
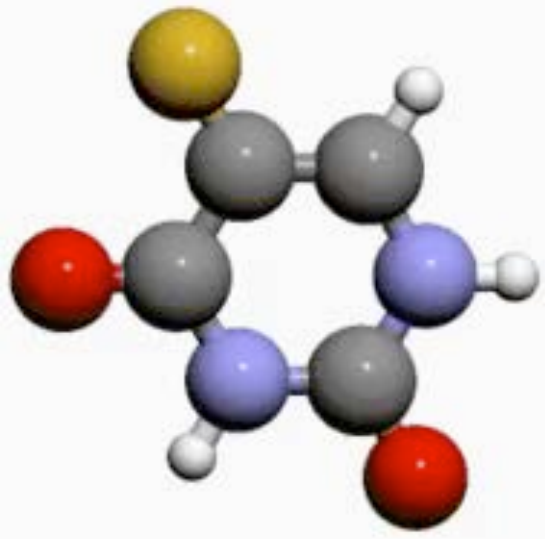


Figure 6.195 - 5-fluorouracil



Movie 6.3 - 5-fluorouracil

Wikipedia

body a large collection of proteins, lipids, and nucleic acids that are all more efficiently recycled than degraded. For proteins, the process is simple. Digestion converts them into constituent building blocks (amino acids) and these are re-assembled into proteins of the consuming organism using the genetic code.

Nucleotides

The multi-component structure of nucleotides, though (base, sugar, phosphate) means subsections of them may be re-utilized. Phosphate is recycled simply by entering the phosphate pool of the cell. It is typically built back into triphosphate forms (ultimately) by oxidative phosphorylation and kinase actions. Salvage of bases is different for purines and pyrimidines and is discussed separately HERE and HERE.

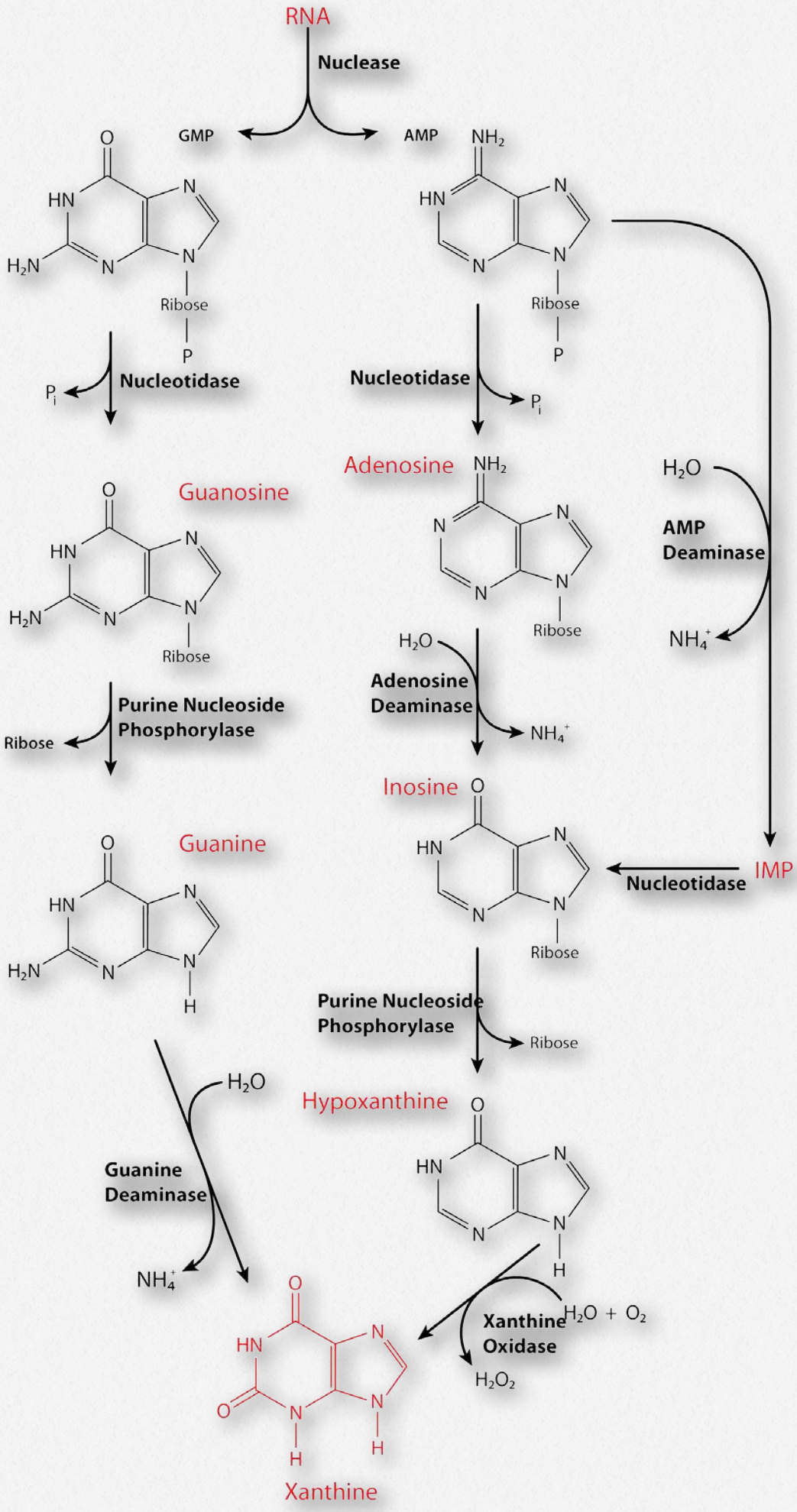


Figure 6.196 - Catabolism of purines - part I

Image by Pehr Jacobson

Nucleotide catabolism

Besides salvage and being built into nucleic acids, nucleotides can also be broken down into simpler component molecules. Some of these molecules, such as uric acid, can have significant impact on organisms (see HERE).

Purine catabolism

Breakdown of purine nucleotides starts with nucleoside monophosphates, which can be produced by breakdown of an RNA, for example, by a nuclease (Figure 6.196).

Metabolism of AMP and GMP converge at xanthine. First, AMP is dephosphorylated by nucleotidase to create adenosine, which is then deaminated by adenosine deaminase to yield inosine. Alternatively, AMP can be deaminated by AMP deaminase to yield IMP.

IMP is also an intermediate in the synthesis pathway for purine anabolism. Dephosphorylation of

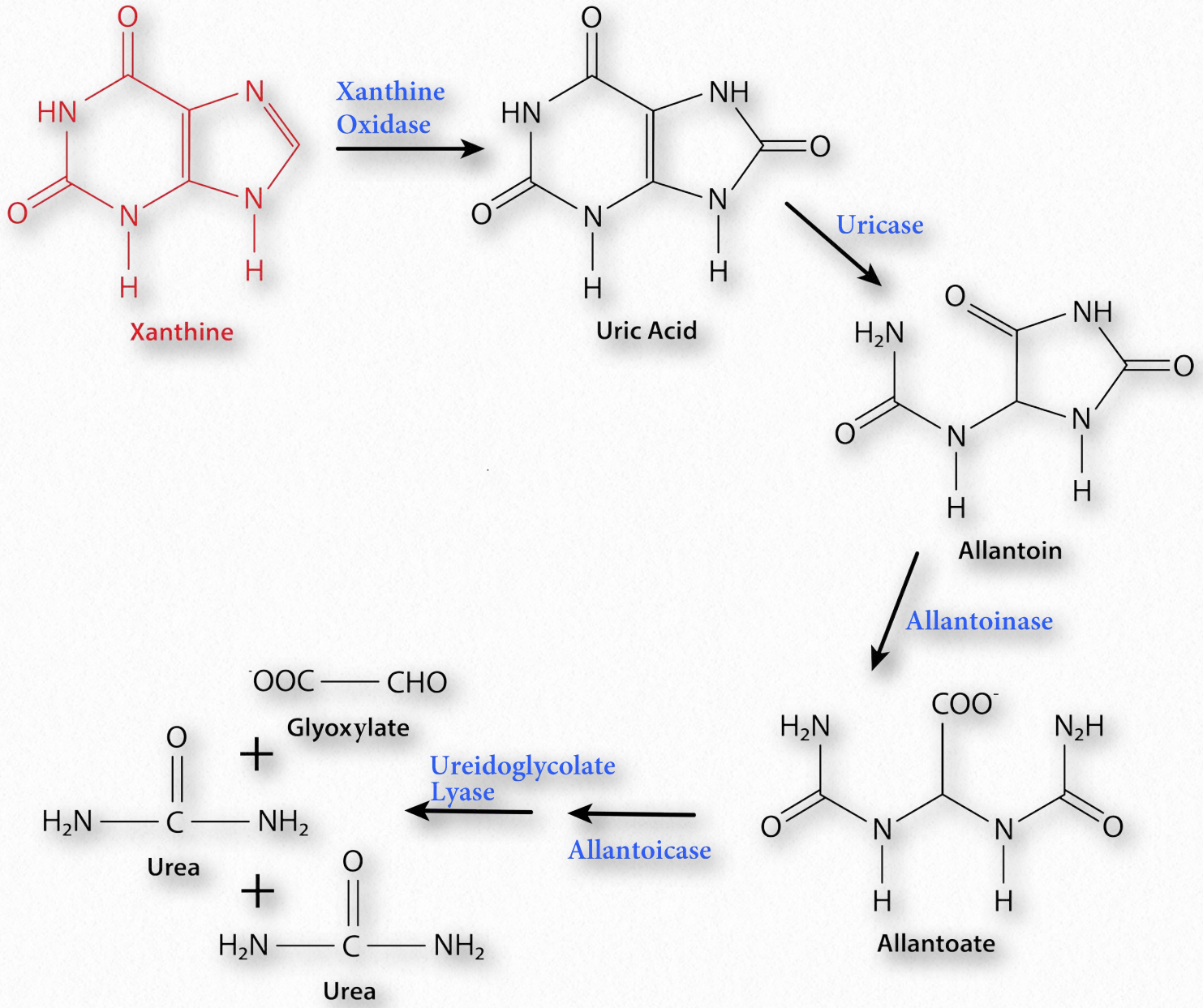


Figure 6.197 - Purine catabolism - part II

Image by Pehr Jacobson

IMP (also by nucleotidase) yields inosine. Inosine has ribose stripped from it by action of purine nucleotide phosphorylase to release hypoxanthine. Hypoxanthine is oxidized to xanthine in a hydrogen peroxide-generating reaction catalyzed by xanthine oxidase.

Hypoxanthine + H_2O + O_2

⇅

Xanthine + **H_2O_2**

Catabolism of GMP proceeds independently, though similarly. First, phosphate is removed by nucleotidase to yield guanosine. Guanosine is stripped of ribose to yield free guanine base, which is deaminated by guanine deaminase (also called guanase) to produce xanthine.

Xanthine oxidase enters the picture a second time in the next reaction catalyzing a second reaction by a similar mechanism to the hypoxanthine oxidation described previously. It is shown on the next page.

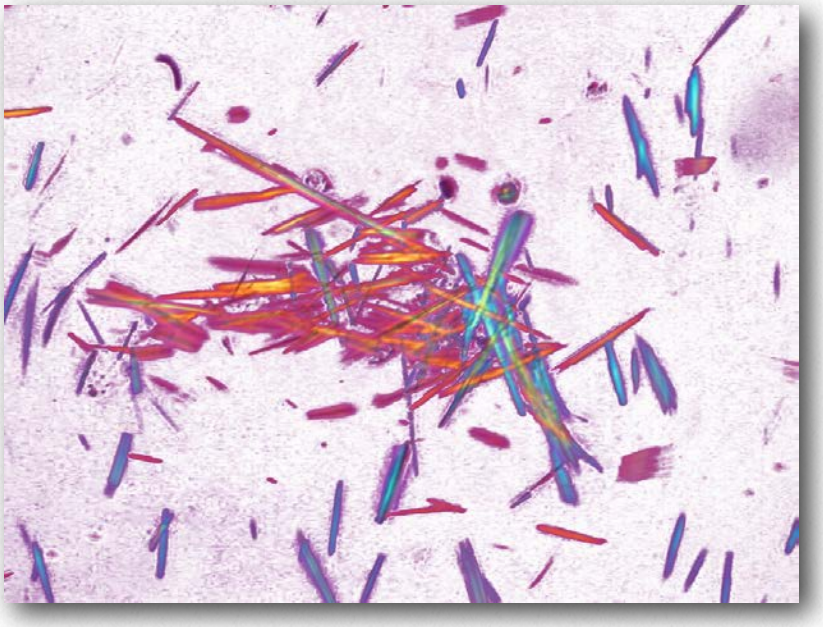


Figure 6.198 - Crystals of uric acid
Wikipedia

Xanthine + H_2O + O_2

⇅

Uric Acid + **H_2O_2**

Uric acid

Uric acid is problematic in some higher organisms (including humans) because it is not very soluble in water. Consequently it precipitates out of solution, forming crystals (Figure 6.198). Those crystals can accumulate in joints and (frequently) in the big toe. Such a condition is known as gout.

Interestingly, there may be a negative correlation between gout and contracting multiple sclerosis. This protective effect may be due to the antioxidant protection afforded by uric acid. Uric acid is the primary excretion form of nitrogen for birds. Dalmation dogs also excrete uric acid instead of urea and may suffer from joint pain as a result of gout-like conditions.

Gout is treated with a hypoxanthine analog known as allopurinol (Figure 6.199). It inhibits action of xanthine oxidase, which favors increase in the concentration of hypoxanthine. The latter is used in salvage synthesis to make additional purines.

Uric acid can be excreted into the urine (in humans) or broken down into allantoin by the uricase enzyme. Since humans lack the enzyme to make allantoin (urea in humans is produced by the urea cycle), its presence in the body means it was produced by non-enzymatic means. This is taken to be an indicator of oxidative stress, since it allantoin is produced non-enzymatically by oxidation of uric acid.

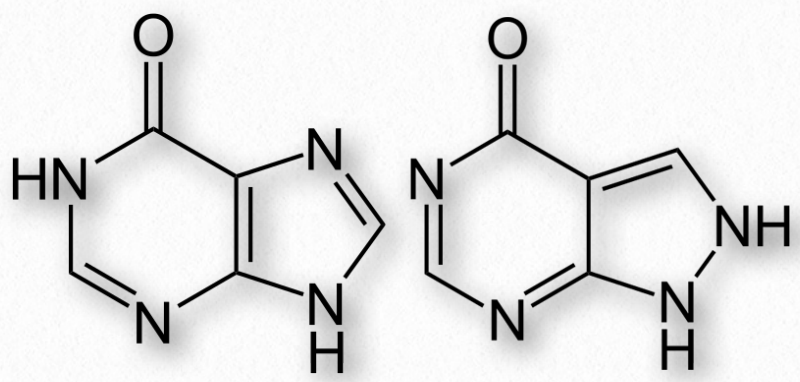


Figure 6.199 - Hypoxanthine (left) and allopurinol (right)
Wikipedia

Pyrimidine catabolism

Catabolism of uridine and thymidine nucleotides is shown above (Figure 6.200). Catabolism of cytidine nucleotides pro-

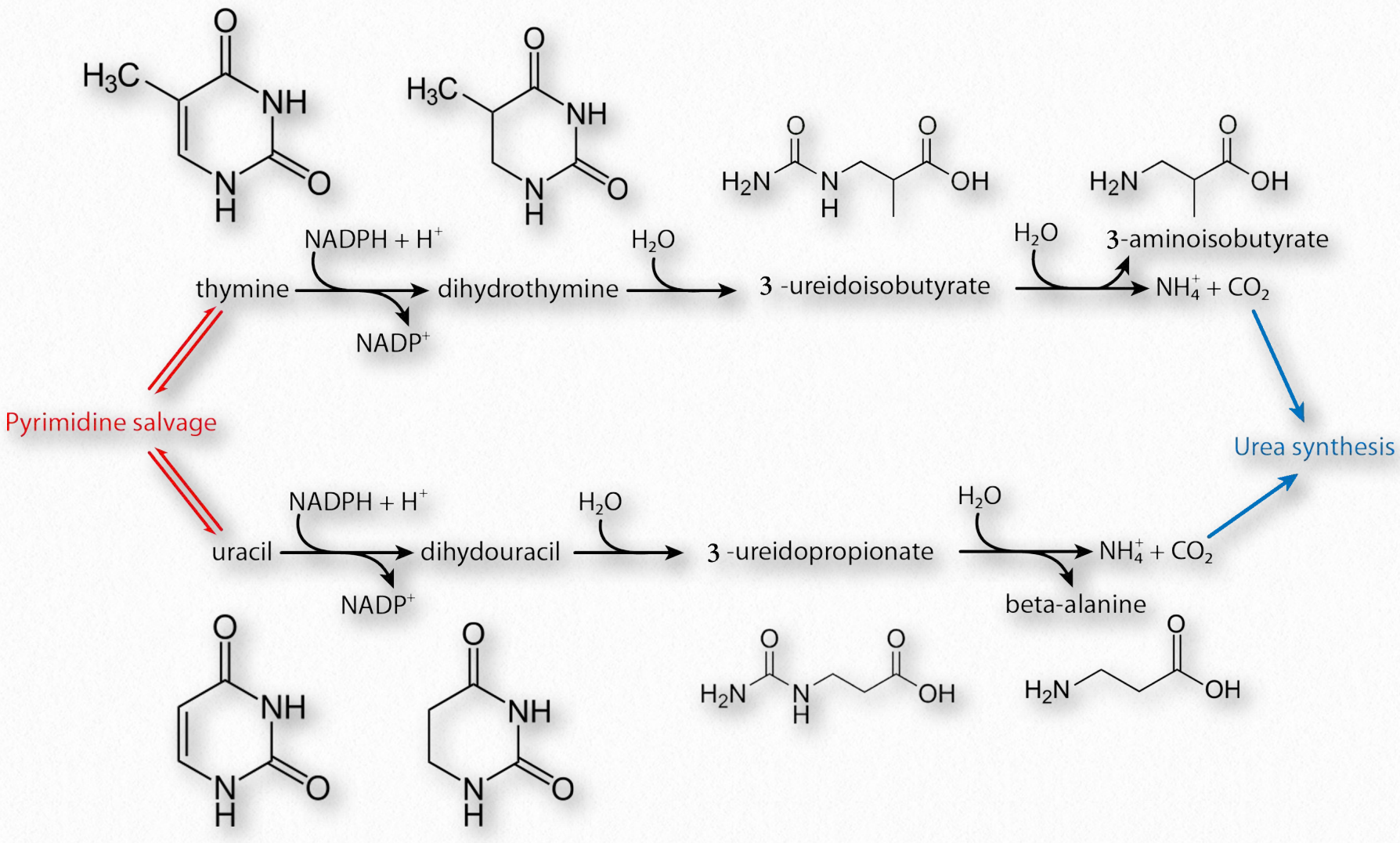


Figure 6.200 - Catabolism of pyrimidine nucleotides

Image by Pehr Jacobson

ceeds through uridine by deamination of cytosine. The free bases, thymine and uracil, are released by the enzyme ribosylpyrimidine nucleosidase In the reductive pathway, uracil and thymine reduction by NADPH gives dihydrothymine and dihydrouracil respectively. Addition of water to these creates 3-ureidoisobutyrate and 3-ureidopropionate respectively. Hydrolysis of both these intermediates yields ammonium ion and carbon dioxide (which are made into urea) plus 3-aminoisobutyrate for the thymine pathway and β-alanine for the product of the uracil pathway. 3-aminoisobutyrate is produced during exercise and activates expression of thermogenic genes in white fat cells.

YouTube Lectures by Kevin HERE & HERE

β-alanine is a rate-limiting precursor of carnosine, a dipeptide of histidine and β-alanine (Figure 6.201). Carnosine functions as an antioxidant that scavenges reactive oxygen species. It also acts as an anti-glycating agent to prevent against attachment of sugar molecules to proteins. These are factors in degenerative diseases and may play a role in aging.

Sugars

Last, but not least, the sugars ribose and deoxyribose can be recycled (ribose) or catabolized (ribose and deoxyribose). In the case of ribose, it can be reattached to bases by phos-

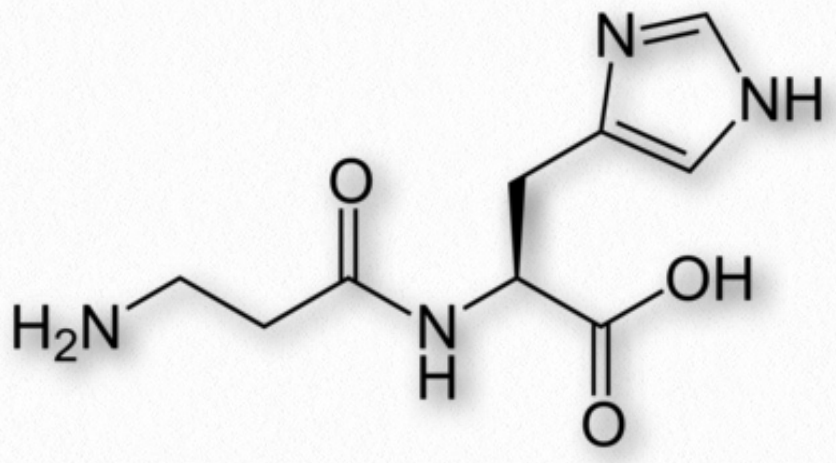


Figure 6.201 - Carnosine

phorylase enzymes, such as uridine phosphorylase, or converted into PRPP for the same purpose, to create nucleosides. Ribose-5-phosphate is an intermediate in the pentose phosphate pathway, allowing it to be converted into other sugars or broken down in glycolysis.

Deoxyribose-5-phosphate can be broken into two pieces by deoxyribose-5-phosphate aldolase. The products of this reaction are glyceraldehyde-3-phosphate and acetaldehyde. The former can be oxidized in glycolysis and the latter can be converted into acetyl-CoA for further metabolism.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

Click HERE for Penelope Irving's Web Page

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Deoxynucleotides

(to the tune of "*Ticket to Ride*")

Metabolic Melodies Website HERE

Tonight I'm feeling quite glad
Because I can say (yeah)
My cells are working like mad
To make DNA

They're making nucleoti-ides
Way down deep and insi-i-ide
Deoxynucleotides
Are on the way

They activate RNR
With an ATP, yeah
Changing a T to an R
Deep inside of me

Deoxynucleoti - ides
That's what the enzyme provi-i-ides
Deoxynucleotides
Are on the way

The enzyme's mechanism's so sly
It is tactical
Using radical
You see
So when it kisses substrate goodbye
It seems magical
In its practical-i-ty

The two prime I will mention
In this exercise, yeah
Its one bit of oxygen
Has got to downsize, yeah

2-prime is de-ox-i-fying
That's what the enzyme is buy-i-ing
2-prime is deoxified
It's gone away

They're gonna go and make DNA
You gotta know that
They're gonna do that in me
They're gonna go and replicate
A polymerase
Is gonna do that for me

Because of structure decrees
In nucleotides, yay
DNA is in b's
But not much in a's

Oh deoxynucleotides
Deoxynucleoti-i-ides
Deoxynucleotides
Give B-forms
That oxygen's gone
That oxygen's gone
That oxygen's gone

Lyrics by Kevin Ahern

No Recording Yet For This Song

Things You Should Remember

To the tune of "*In My Life*"

Metabolic Melodies Website HERE

There are things you should remember
When you're stud-y-ing for this exam
All the pathways since September
And the mol-e-cules comprising them

Though that is an awful lot of information
I hope that you can retain it all
If you do you will avoid a grade deflation
When you study right, you will recall

Now in all your preparation
There is soooome-thing you should regard
How your brain stores information
So transcribe your notes onto a card

I assure you it will up your recollection
Of enzymes and com-plex Haworth rings
It will drive performance to perfection
Simply from the act of writing things

I assure you it will up your recollection
Of enzymes and com-plex Haworth rings
It will drive performance to perfection
Simply from the act of writing things

So go forward now . . . . . and write down things

Recording by David Simmons
Lyrics by Kevin Ahern

7

Information Processing

Man cannot discover new oceans unless he has the courage to lose sight of the shore.

-Andre Gide

"*The blueprints for the construction of one human being requires only a meter of DNA and one tiny cell. ... even Mozart started out this way.*" — L.L. Larison Cudmore

As creatures used to regarding ourselves as exceptional, humans must surely be humbled to realize that the instructions, for making one of our own, reside in a molecule so simple that scientists, for a very long time, did not believe

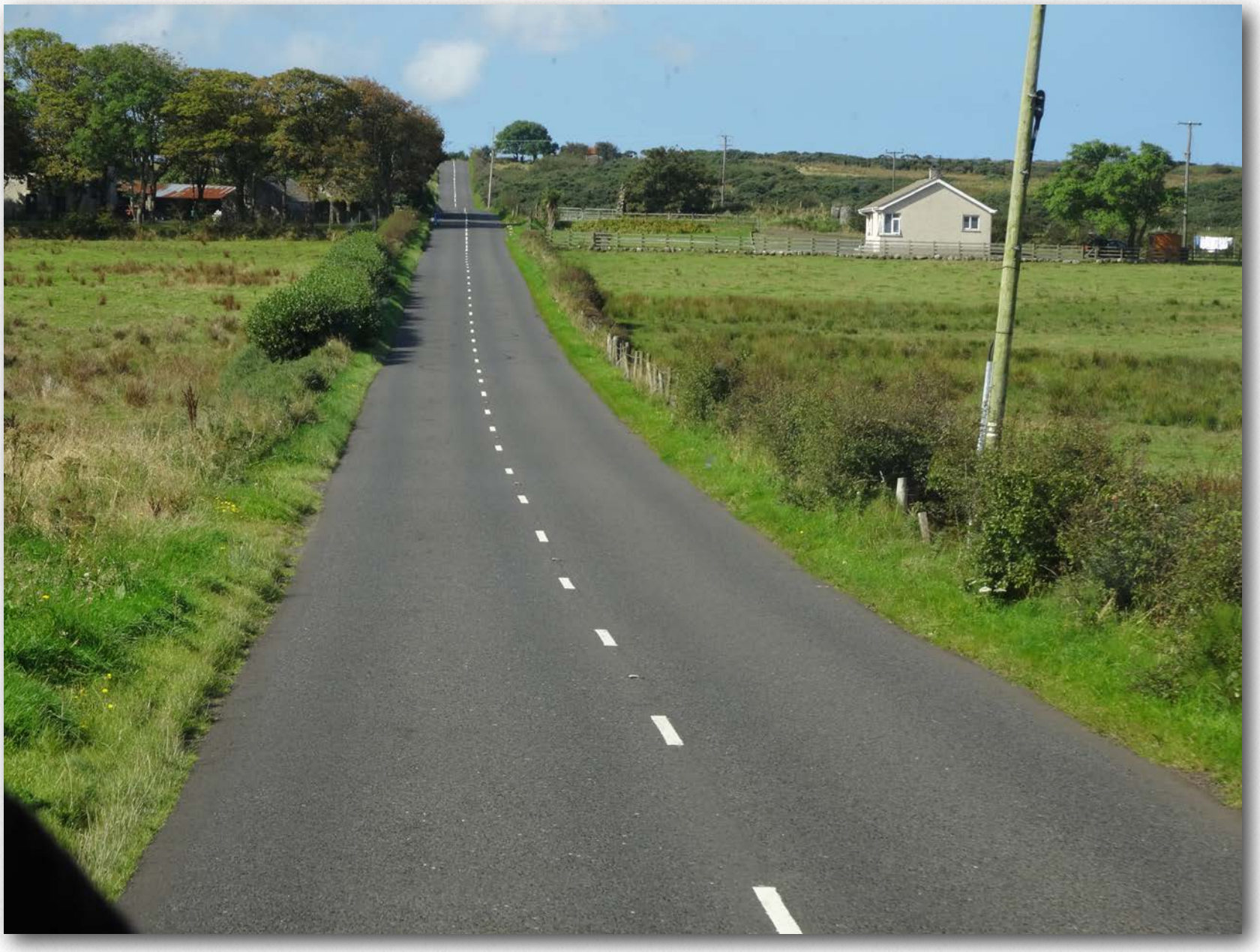
could possibly contain enough information to build even a simple cell. But a large body of evidence, built up over the past century, supports Larison Cudmore's assertion that the information for making you and me (and all the other kinds of living things in the world) is encoded in DNA. Tying in with Mendel's observations about how characteristics are passed on from one generation to the next, the discovery that there was a molecule that carried this information, altered for ever how people thought about heredity.

The elucidation of the structure of DNA provided greater insights into how traits might be encoded in a molecule, and the ways in which the information is used by cells. As we learn more about this topic, scientists have remarked on how the information in our DNA resembles the programs that drive computers. While this analogy is a simplification, there is definitely a sense in which, as Richard Dawkins put it, "the machine code of the genes is uncannily computer-like", with information in our DNA directly determining the properties of the proteins that run our cells. We know, as Ada Yonath described it, that, "DNA is a code of four letters; proteins are made up of amino acids which come in 20 forms. So the ribosome is a very clever machine that reads one language and operates in another. "

If this sounds strange, it is even more intriguing to realize DNA is copied and passed on from cell to cell, from one generation to the next. There is an unbroken line of inheritance from the first cell to every organism alive today. In the words of Lewis Thomas, "All of today's DNA, strung through all the cells of the earth, is simply an extension and elaboration of [the] first molecule."

The nature of this information, how it is copied and passed on, how it is read and interpreted, and how it gives rise to the cellular activities that we can observe, is the subject of this chapter. Another kind of information is also considered, towards the end of the chapter- the molecular information that cells receive from, and send to, each other. Overlaid on the instructions in the genes, this information provides cells with ongoing clues about both their own inner state and the environment around them. The interplay of these two kinds of information is responsible for the form and behavior of all living organisms.

Information Processing: Genes and Genomes



Introduction

For many years, scientists wondered about the nature of the information that directed the activities of cells. What kind of molecules carried the information, and how was the information passed on from one generation to the next? Key experiments, done between the 1920s and the 1950s, established convincingly that this genetic information was carried by DNA. In 1953, with the elucidation of the structure of DNA, it was possible to begin investigating how this information is passed on, and how it is used.

YouTube Lectures by Kevin HERE & HERE

Genomes

We use the word “genome” to describe all of the genetic material of the cell. That is, a genome is the entire sequence of nucleotides in the DNA that is in all of the chromosomes of a cell. When we use the term genome without further qualification, we are generally referring to the chromosomes in the nucleus of a eukaryotic cell. As

you know, eukaryotic cells have organelles like mitochondria and chloroplasts that have their own DNA (Figure 7.1 & 7.2). These are referred to as the mitochondrial or chloroplast genomes to distinguish them from the nuclear genome.

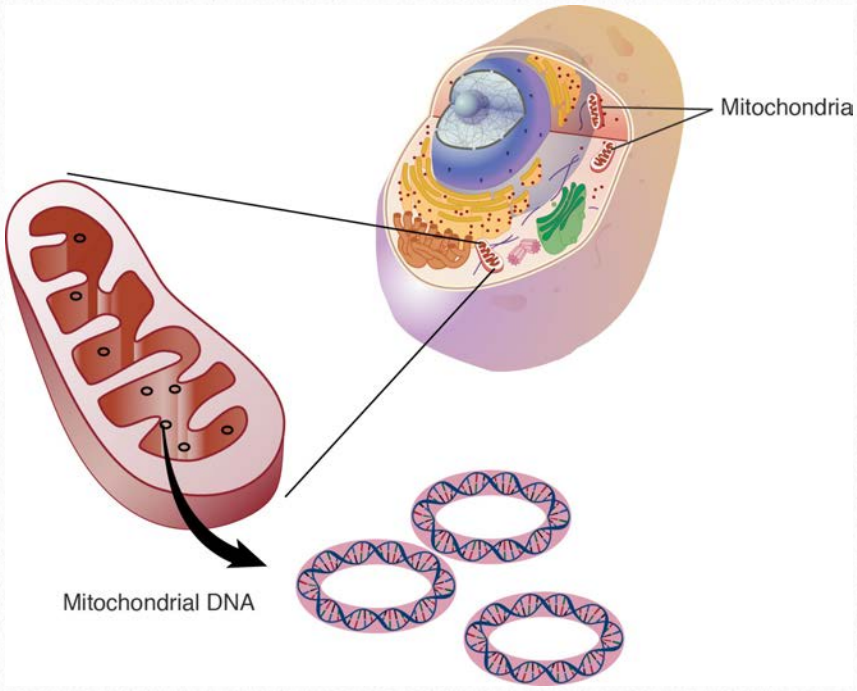


Figure 7.1 - Mitochondria carry their own genome

Starting in the 1980s, scientists began to determine the complete sequence of the genomes of many organisms, in the hope of better understanding how the DNA sequence specifies cellular functions. Today, the complete genome sequences have been determined for thousands of species from all domains of life, and many more are in the process of being worked out by groups of scientists across the world.

Global genome initiative

The Global Genome Initiative, a collaborative effort to sequence at least one species from each of the 9,500 described invertebrate, vertebrate, and plant families is one of many such ventures. The information from these various efforts is collected in enormous online repositories, so that it is freely available to scientists. As the sequence databases compile ever more information, the fields of computational biology and bioinformatics have arisen, to analyze and organize the data in a way that helps biologists understand what the information in DNA means in the cellular context.

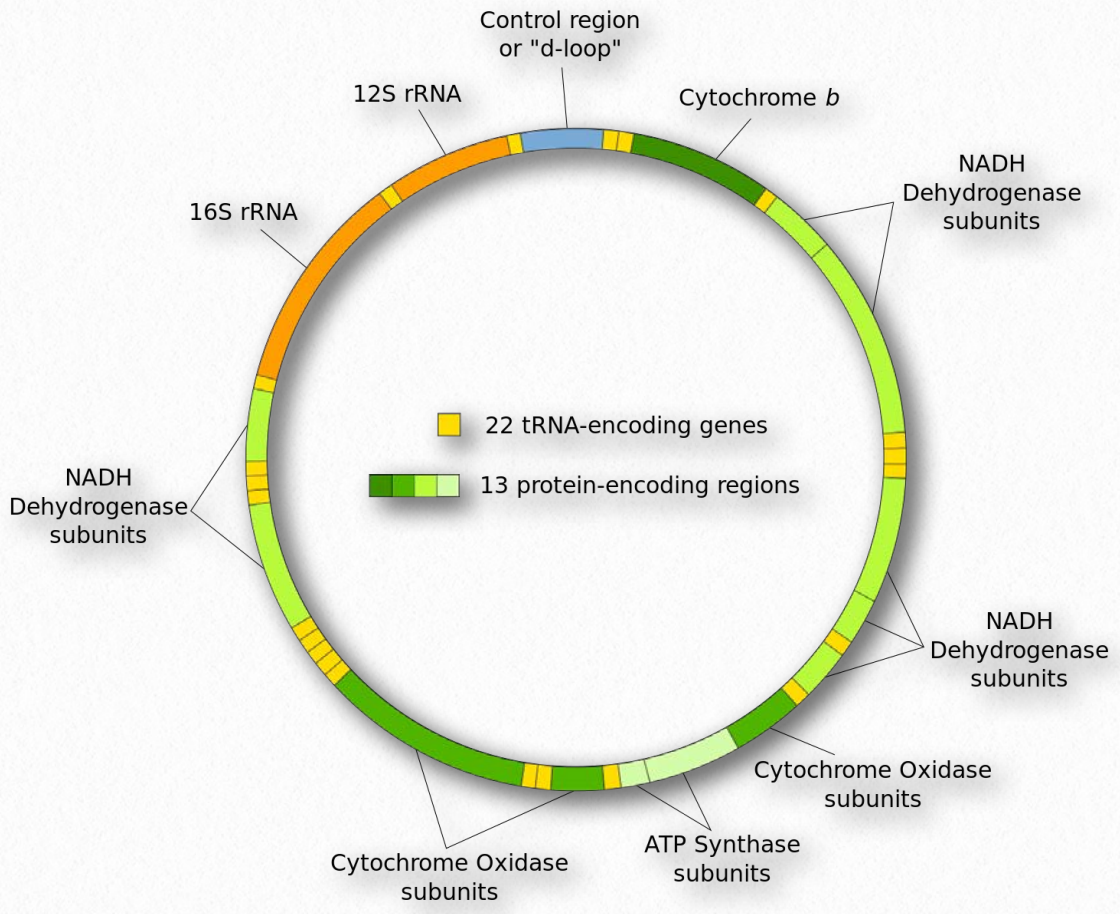


Figure 7.2 - The human mitochondrial genome

Wikipedia

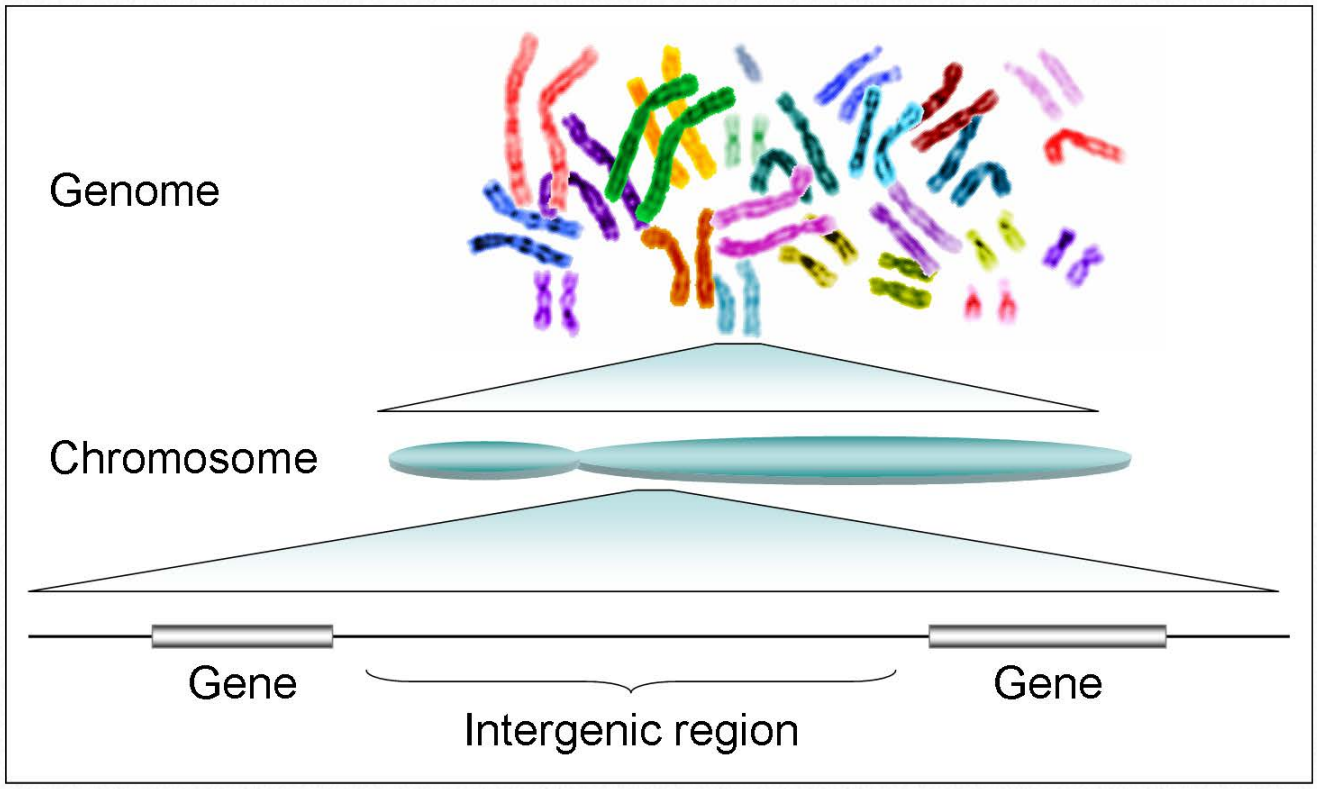


Figure 7.3 - From genomes to genes

Wikipedia

Genes

It has been known for many years that phenotypic traits are controlled by specific regions of the DNA that were termed “genes”. Thus, DNA was envisioned as a long string of nucleotides, in which certain regions, the genes, were separated by non-coding regions that were simply referred to as intergenic sequences (*inter*=between; *genic*=of genes). Early experiments in molecular biology suggested a simple relationship between the DNA sequence of a gene and its product, and led scientists to believe that each gene carried the information for a single protein. Changes, or mutations in the base sequence of a gene would be reflected in

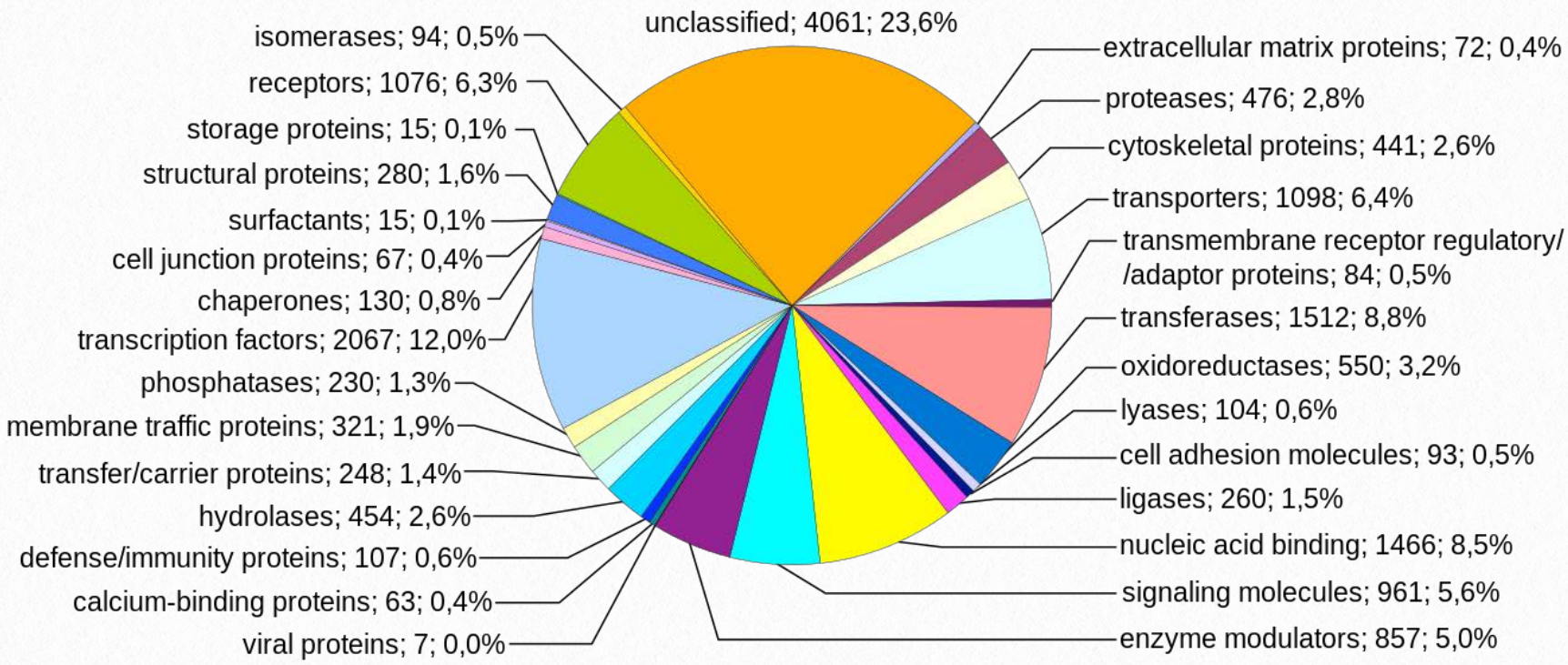


Figure 7.4 - Human genes sorted by class

changes in the gene product, which in turn, would manifest itself in the phenotype or observable trait. This simple picture, while still useful, has been modified by subsequent discoveries that demonstrated that the use of genetic information by cells is somewhat more complicated. Our definition of a gene is also evolving to take new knowledge into consideration.

Matters of size

A common-sense assumption about genomes would be that if genes specify proteins, then the more proteins an organism made, the more genes it would need to have, and thus, the larger its genome would be. Comparison of various genomes shows, surprisingly, that there is not necessarily a direct relationship between the complexity of an organism and the size of its genome (Figure 7.5). To understand how this could be true, it is necessary to recognize that while genes are made up of DNA, all DNA does not consist of genes (for purposes of our discussion, we define a gene as a section of DNA that encodes an RNA or protein product). In the human genome, less than 2% of the total

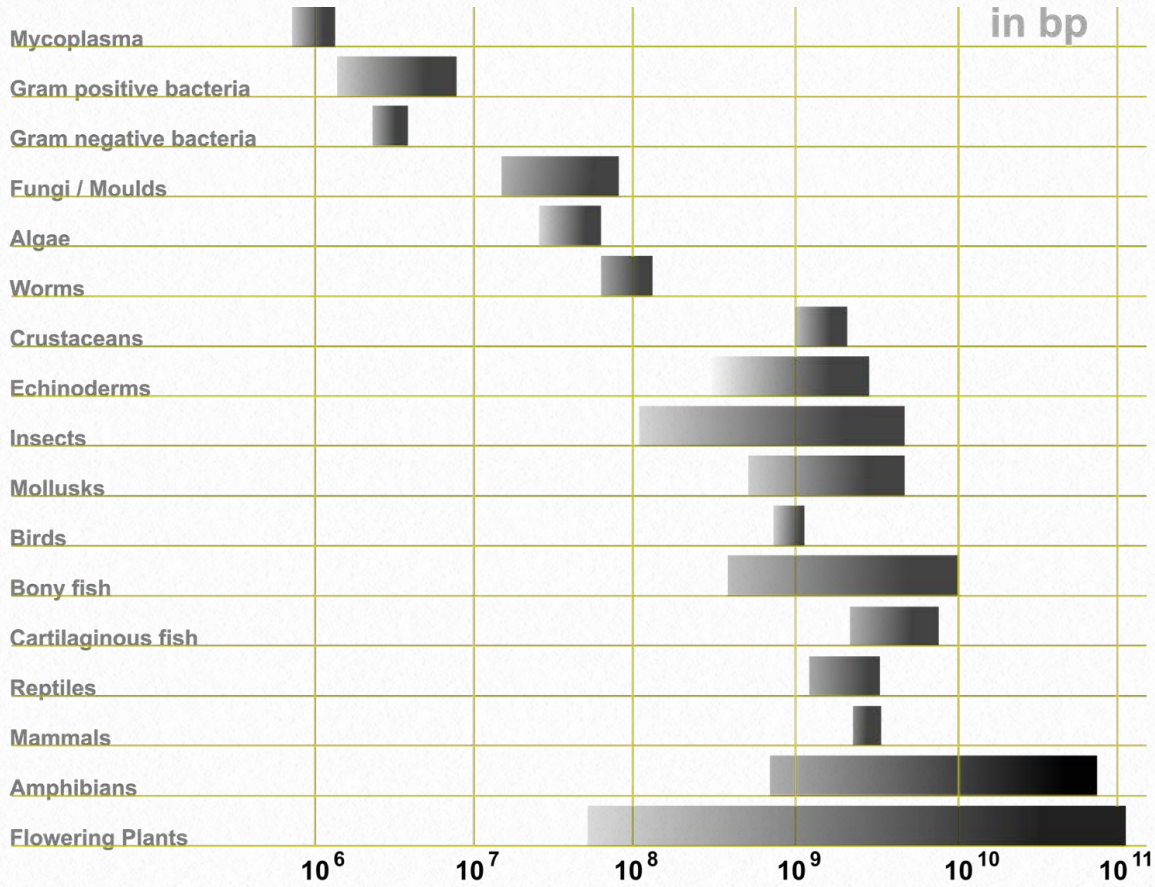


Figure 7.5 - Sizes of various genomes

Wikipedia

DNA seems to be the sort of coding sequence that directs the synthesis of proteins. For many years, non-coding DNA in genomes was believed to be useless, and was described as "junk DNA" although it was perplexing that there seemed to be so much "useless" sequence. Recent discoveries have, however, demonstrated that much of this so-called junk DNA may play important roles in evolution, as well as in regulation of gene expression.

Introns

So, what is all the non-coding DNA doing there? We know that even coding regions in our DNA are interrupted by non-coding sequences called introns. This is true of most eukaryotic genomes. An examination of

genes in eukaryotes shows that non-coding intron sequences can be much longer than the coding sections of the gene, or exons. Most exons are relatively small, and code for fewer than a hundred amino acids, while introns can vary in size from several hundred base-pairs to many kilobase-pairs (thousands of base-pairs) in length. For many genes in humans, there is much more of intron sequence than coding (a.k.a. exon) sequence. Intron sequences account for roughly a quarter of the genome in humans.

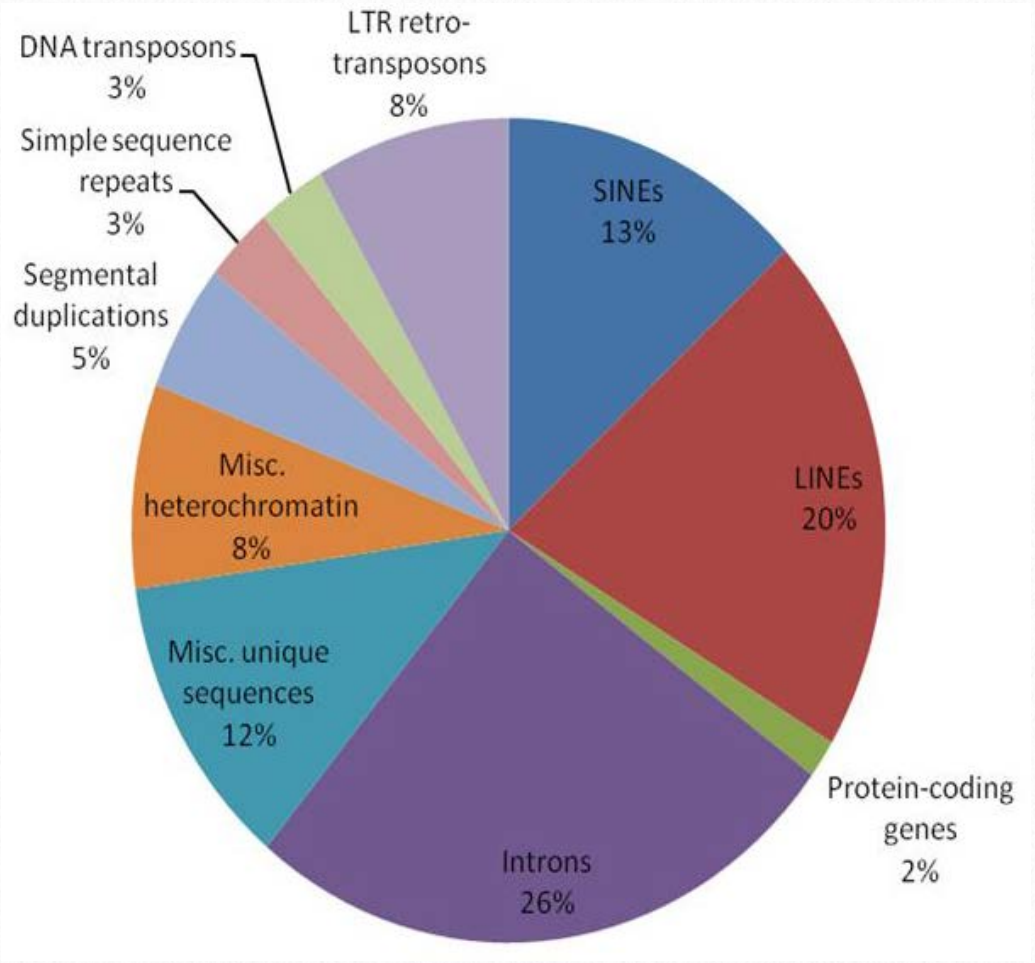


Figure 7.6 - Components of the human genome
Wikipedia

Other non-coding sequences

What other kinds of non-coding sequences are there? One function for some DNA sequences that do not encode RNA or proteins is in specifying when and to what extent a gene is used, or expressed. Such regions of DNA are called regulatory regions and each gene has one or more regulatory sequences that control its expression. However, regulatory sequences do not account for all the rest of the DNA in our genomes, either.

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Transposable sequences

Surprisingly, almost half of the human genome appears to consist of several kinds of repetitive sequences. Many of the repetitive sequences are known to be transposable elements (transposons), sections of DNA that can move around within the genome. Sometimes referred to as "jumping genes" these transposable elements can move from one chromosomal location to another, either through a simple "cut and paste" mechanism that cuts the sequence out of one region of the DNA and inserts it into another location, or through a process called retrotransposition involving an RNA intermediate.

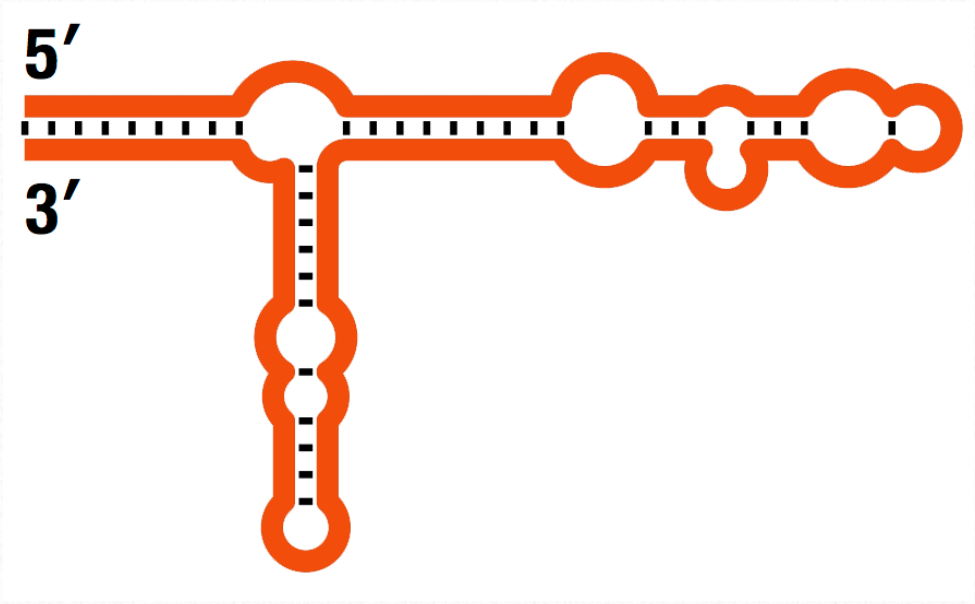

Figure 7.7 - 5S rRNA structure

Wikipedia

LINES & SINES

There are millions of copies of each of two major classes of such transposable elements, the LINEs (Long Interspersed Elements) and SINEs (Short Interspersed Elements) in our genomes.

LINEs and SINEs are both a kind of transposable element called retrotransposons, sequences that are copied into RNA, then reverse transcribed back into DNA before being inserted into new locations. This movement is typically not sequence specific, meaning that the transposons can be inserted randomly in the genome, in many cases within coding regions. As might be expected, this can disrupt the function of the gene. Transposons may also insert within regulatory regions, and change the expression of the genes they control. As a major cause of mutation in genomes, transposons play an important role in evolution.

Finally, recent findings have shown that much of the genome is transcribed into RNAs, even though only about 2% encodes proteins. What are the RNAs that do not encode proteins? Ribosomal RNAs (Figure 7.7) and transfer RNAs, together with the small nuclear RNAs that function in splicing, account for some of these non-translated transcripts, but not all. The remaining RNAs are regulatory RNAs, small molecules that play an important role in regulating gene expression. As we understand more about genomes, it is becoming evident that the so-called “junk” DNA is anything but.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Transposon

To the tune of "*Delta Dawn*"
Metabolic Melodies Website HERE

(*sung in a twangy, country style*)

Trans-po-son
All that movin' hither yon
You're insertin' yourself in the chromosomes
I guess it's why they say
You're the jumpin' DNA
Movin' and affectin' proteomes

You're carryin' a gene that gives assistance
Helpin' tiny bugs to pass resistance
To a drug that otherwise might kill 'em dead
But with it they go on and live instead

McClintock studied you in *Zea maize*
Marveling at your mysterious ways
But the things you did went counter to what's known
Somethin' like a genetic Twilight Zone

Transposon
All the battle lines are gone
Over mechanisms Barbara did surmise
It's good the truth came out
There will never be a doubt
She truly did deserve the Nobel prize

Transposon
All the battle lines are gone
Over mechanisms Barbara did surmise
It's good the truth came out
There will never be a doubt
She truly did deserve the Nobel prize

Lyrics by Kevin Ahern

No Recording Yet For This Song

Information Processing: DNA Replication

Copying instructions

The only way to make new cells is by the division of pre-existing cells. Single-celled organisms undergo division to produce more cells like themselves, while multicellular organisms arise through division of a single cell, generally the fertilized egg. Each time a cell divides, all of its DNA must be copied faithfully so that a copy of this information can be passed on to the daughter cell. This process is called DNA replication. It is the means by which genetic information can be transmitted down generations of cells, and it ensures that every new cell has a complete copy of the genome. In the next section, we will examine the process by which the DNA of a cell is completely and accurately copied.

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The structure of DNA elucidated by Watson and Crick in 1953 immediately suggested a mechanism by which double-stranded DNA could be copied to give two identical copies of the DNA. They proposed that the two strands of the DNA molecule,

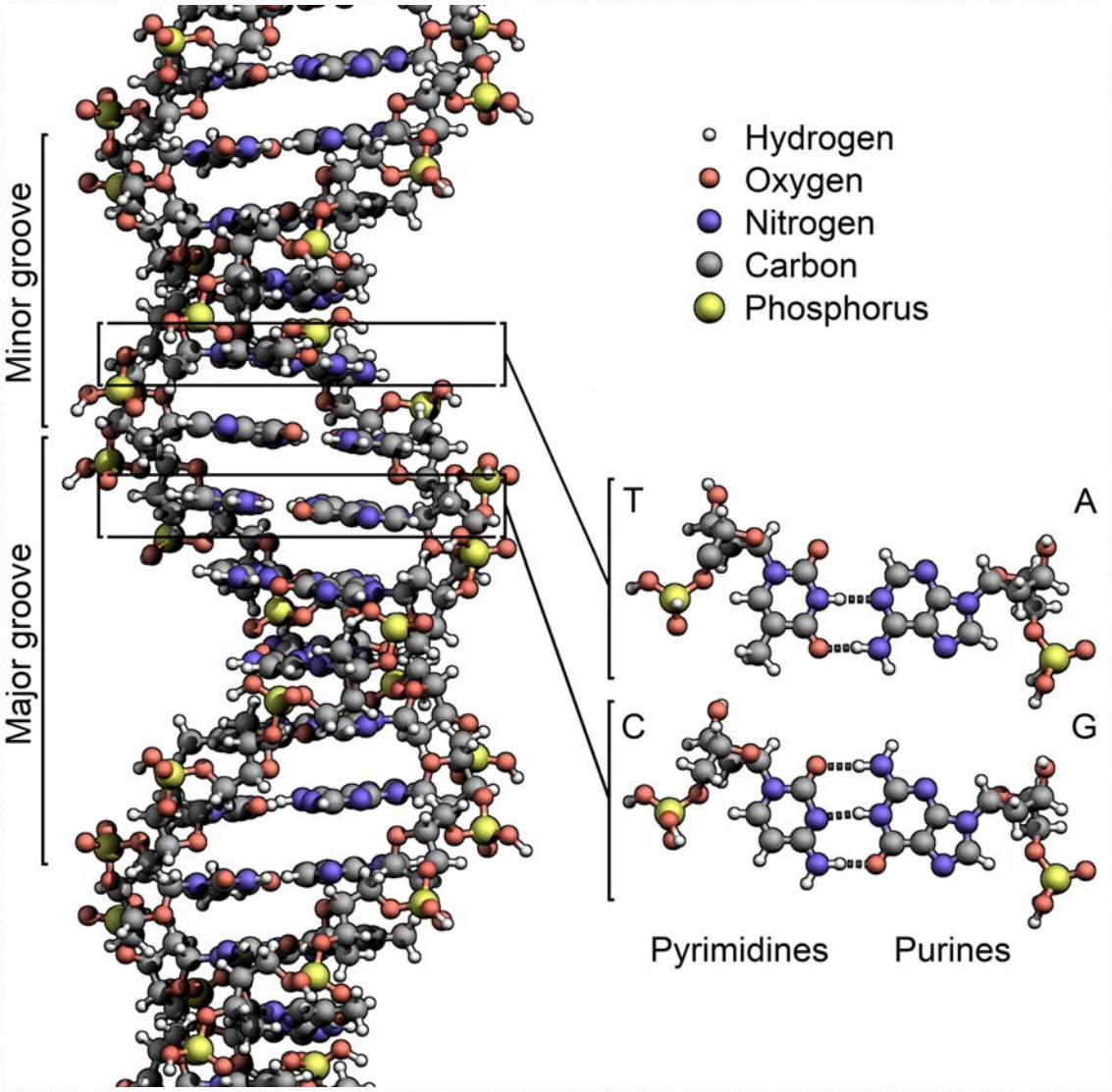

Figure 7.8 - Watson & Crick's DNA structure

Wikipedia

which are held together by hydrogen bonds between the base-paired nucleotides, would separate and each serve as a template on which a complementary strand could be assembled (Figure 7.8). The base-pairing rules would ensure that this process would result in the production of two identical DNA molecules. The beautiful simplicity of this scheme was shown to be correct in subsequent experiments by Meselson and Stahl, that demonstrated that DNA replication was semi-conservative, i.e., that after replication, each of the two resulting DNA molecules was made up of one old strand and one new strand that had been assembled across from it (Figure 7.9).

Building materials

What are the ingredients necessary for building a new DNA molecule? As noted above, the original, or parental DNA molecule serves as the template. New DNA molecules are assembled across from each template by joining together free DNA nucleotides as directed by the base pairing rules, with As across from Ts and Gs across from Cs.

The nucleotides used in DNA synthesis are deoxyribonu-

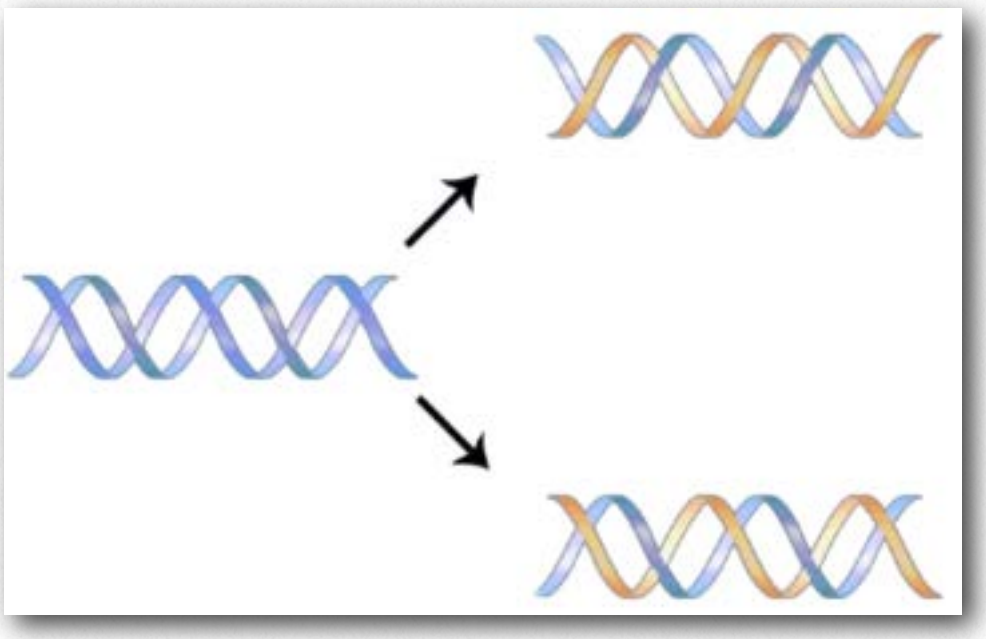

Figure 7.9 - Semi-conservative replication

Image by Martha Baker

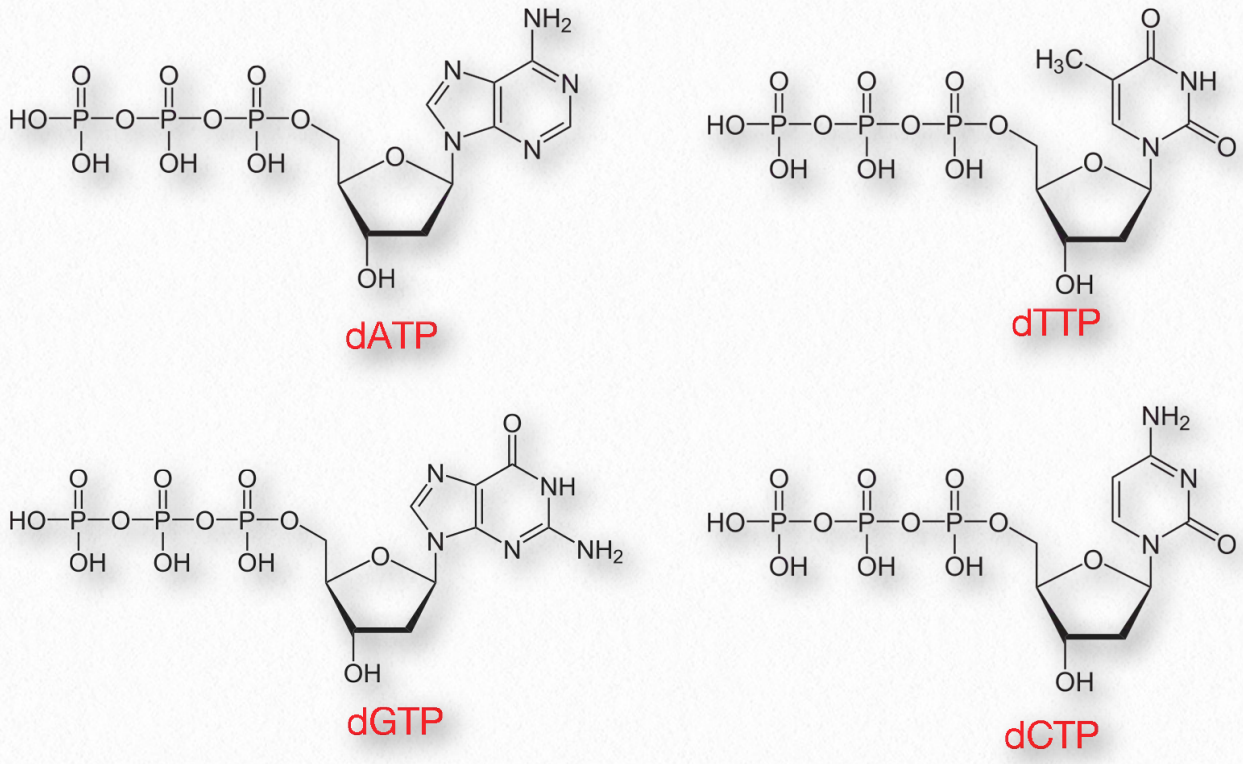

Figure 7.10 - The building blocks of DNA

cleoside triphosphates or dNTPs. As can be inferred from their name, such nucleotides have a deoxyribose sugar and three phosphates, in addition to one of the four DNA bases, A, T, C or G (Figure 7.10).

When dNTPs are added into a growing DNA strand, two of those phosphates will be cleaved off, as described later, leaving the nucleotides in a DNA molecule with only one phosphate per nucleotide. This reaction is catalyzed by enzymes known as DNA polymerases, which create phosphodiester linkages between one nucleotide and the next.

Challenges

Before examining the actual process of DNA replication, it is useful to think about what it takes to accomplish this task successfully. Consider the challenges facing a cell in this process:

- The sheer number of nucleotides to be copied is enormous: e.g., in human cells, on the order of several billions.
- A double-helical parental DNA molecule must be unwound to expose single strands of DNA that can serve as templates for the synthesis of new DNA strands.
- Unwinding must be accomplished without introducing topological distortion into the molecule.
- The unwound single strands of DNA must be kept from coming back together long enough for the new strands to be synthesized.
- DNA polymerases cannot begin synthesis of a new DNA strand *de novo* and require a free 3' OH to which they can add deoxynucleotides.
- DNA polymerases can only extend a strand in the 5' to 3' direction. The 5' to 3' growth of both new strands means that one of the strands is made in pieces.
- The use of RNA primers requires that the RNA nucleotides must be removed and re-

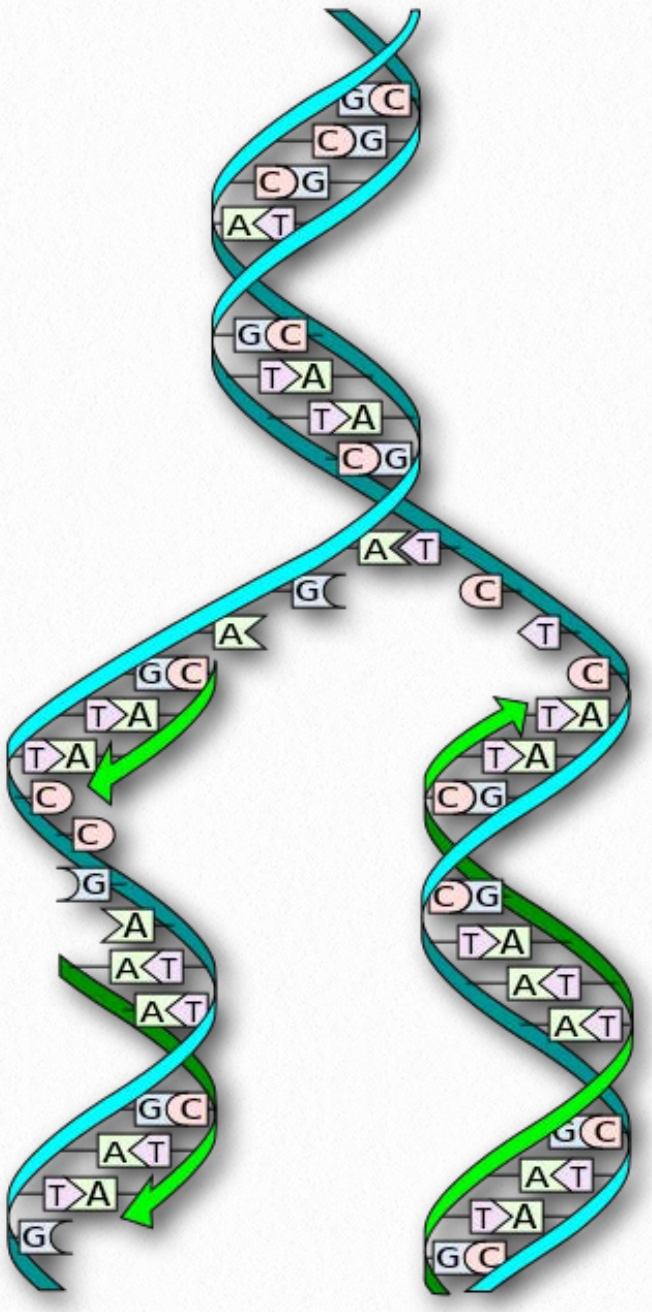

Figure 7.11 - Replication of DNA

Wikipedia

placed with DNA nucleotides and the resulting DNA fragments must be joined.

• The copying of all the parental DNA must be accurate, so that mutations are not introduced into the newly made DNA..

Addressing challenges

With this in mind, we can begin to examine how cells deal with each of these challenges. Our understanding of the process of DNA replication is derived from studies using bacteria, yeast, and other systems. These investigations have revealed that DNA replication is carried out by the action of a large number of proteins that act together as a complex protein machine. Numerous proteins involved in replication have been identified and characterized, including multiple different DNA polymerases in both prokaryotes and eukaryotes. Although the specific proteins involved are different in bacteria and eukaryotes, it is useful to understand the basic considerations that are relevant in all cells. A generalized account of the steps in DNA replication is presented below, focused on the challenges mentioned above.

• The sheer number of nucleotides to be copied is enormous: e.g., in human cells, on the order of several billions.

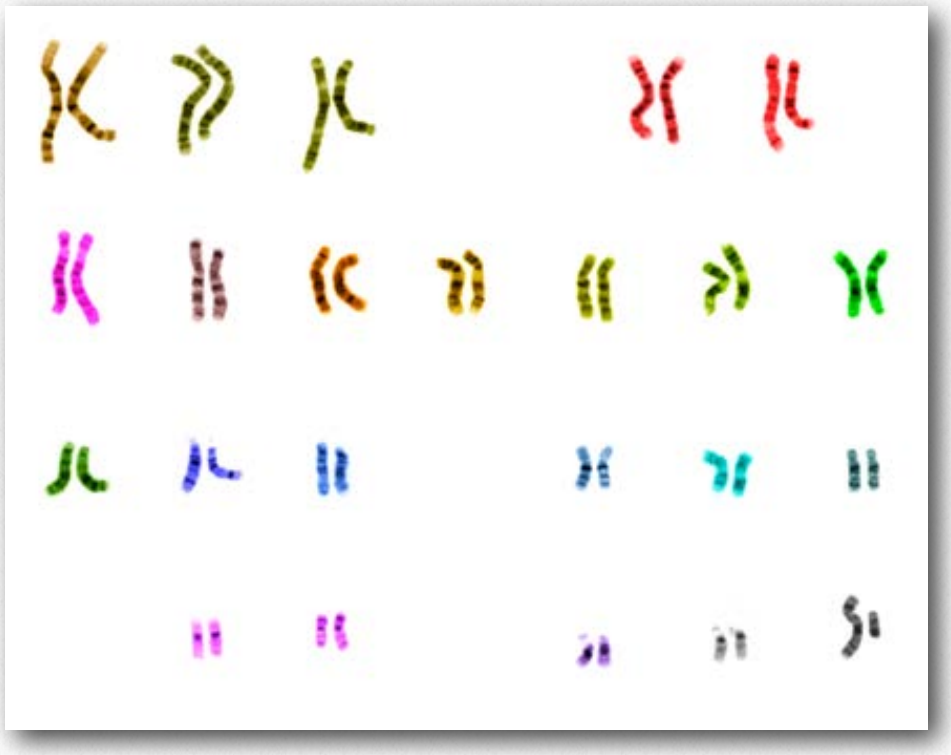

Figure 7.12 - Human chromosomes

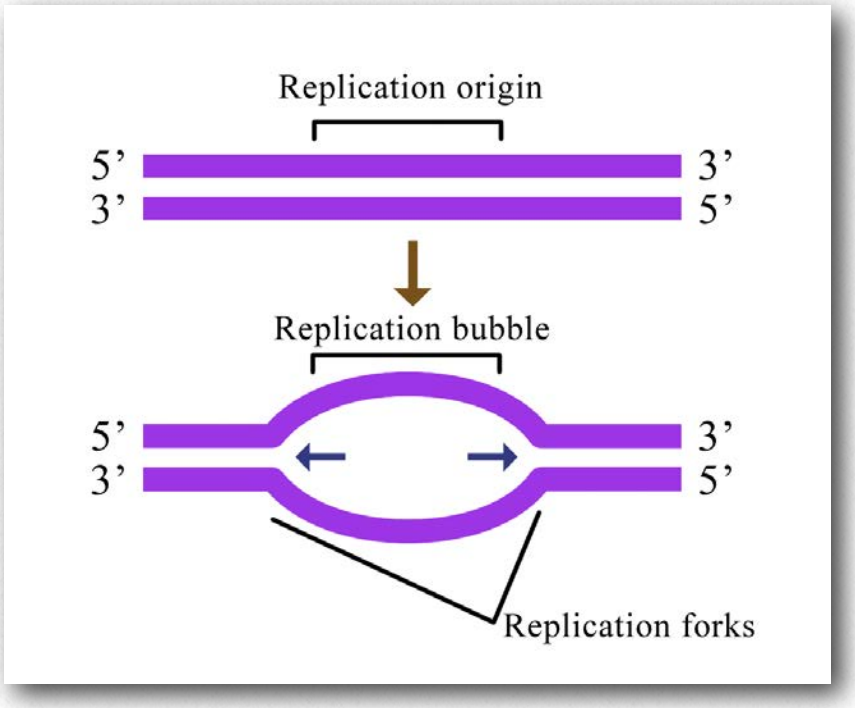

Figure 7.13 - Bidirectional replication from an origin

Martha Baker

Cells, whether bacterial or eukaryotic, have to replicate all of their DNA before they can divide. In cells like our own, the vast amount of DNA is broken up into many chromosomes, each of which is composed of a linear strand of DNA (Figure 7.12). In cells like those of *E. coli*, there is a single circular chromosome.

In either situation, DNA replication is initiated at sites called origins of replication.

These are regions of the DNA molecule that are recognized by special proteins called initiator proteins that bind the DNA. In *E.coli*, origins have small regions of A-T-rich sequences that are "melted" to separate the strands,

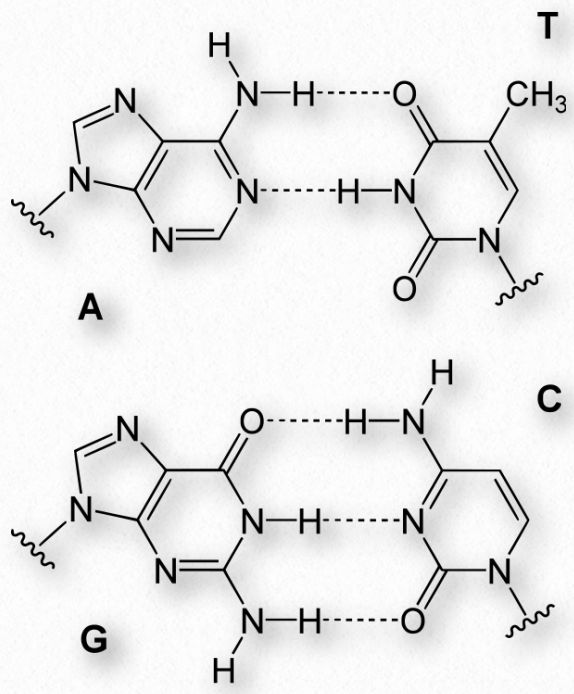

Figure 7.15 - A-T and G-C base pairs

when the initiator proteins bind to the origin or replication. As you may remember, A-T base-pairs, which have two hydrogen bonds between them are more readily disrupted

Prokaryotic DNA Replication	Eukaryotic DNA replication
Occurs inside the cytoplasm	Occurs inside the nucleus
Only one origin of replication per molecule of DNA	Have many origins of replication in each chromosome
Origin of replication is about 100-200 or more nucleotides in length	Each origin of replication is formed of about 150 nucleotides
Replication occurs at one point in each chromosome	Replication occurs at several points simultaneously in each chromosome
Only have one origin of replication	Has multiple origins of replication
Initiation is carried out by protein DnaA and DnaB	Initiation is carried out by the Origin Recognition Complex
Topoisomerase is needed	Topoisomerase is needed
Replication is very rapid	Replication is slow

Figure 7.14 - Prokaryotic vs. eukaryotic DNA replication

Wikipedia

than G-C base-pairs which have three apiece (Figure 7.15).

How many origins of replication are there on a chromosome? In the case of *E. coli*, there is a single origin of replication on its circular chromosome. In eukaryotic cells there may be many thousands of origins of replication, with each chromosome having hundreds (Figure 7.16). DNA replication is, thus, initiated at multiple points along each chromosome in eukaryotes. Electron micrographs of replicating DNA from eukaryotic cells show many replication bubbles on a single chromosome. This makes sense in light of the large amount of DNA that there is to be copied in cells like our own, where beginning at one end of each chromosome and replicating all the way through to the other end from a single origin would simply take too long. This is despite the fact that the DNA polymerases in human cells are capable of building new DNA strands at the very respectable rate of about 50 nucleotides per second!

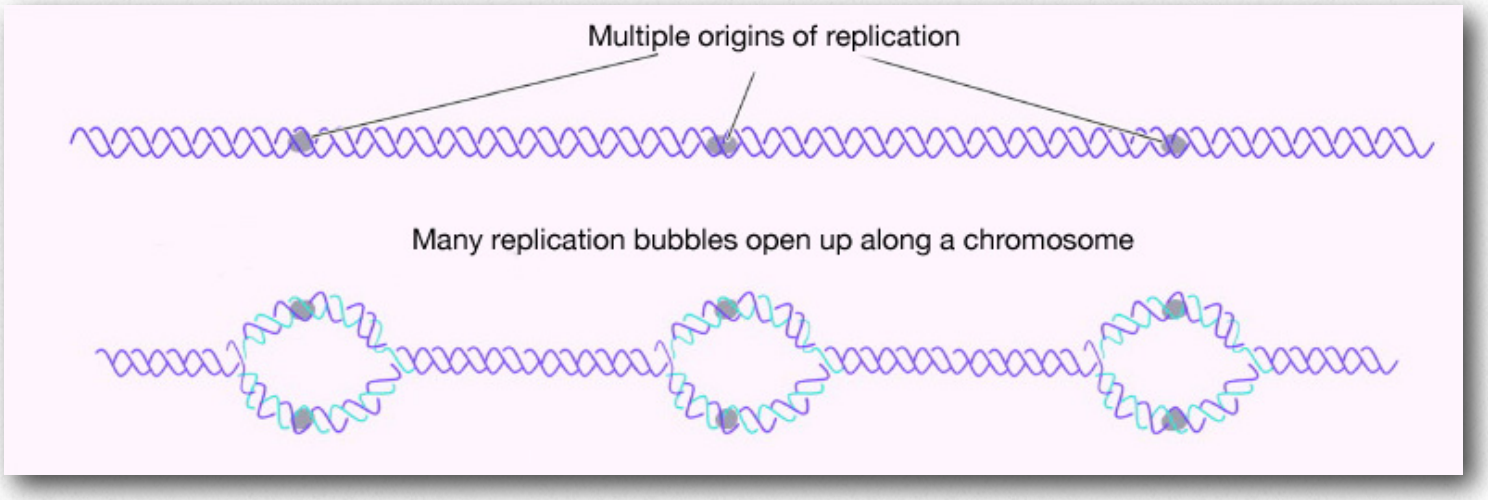

Figure 7.16 - Multiple replication bubble on a eukaryotic chromosome
Image by Martha Baker

YouTube Lectures by Kevin HERE & HERE

- A double-helical parental molecule must be unwound to expose single strands of DNA that can serve as templates for the synthesis of new DNA strands.

Unwinding

Once a small region of the DNA is opened up at each origin of replication, the DNA helix must be unwound to allow replication to proceed. The unwinding of the DNA helix requires the action of an enzyme called helicase.

Helicase uses the energy released when ATP is hydrolyzed, to break the hydrogen bonds between the bases in DNA and separate the two strands (Figure 7.17). Note that a replication bubble is made up of two replication forks that "move" or open up, in opposite directions. At each replication fork, the parental DNA strands must be un-

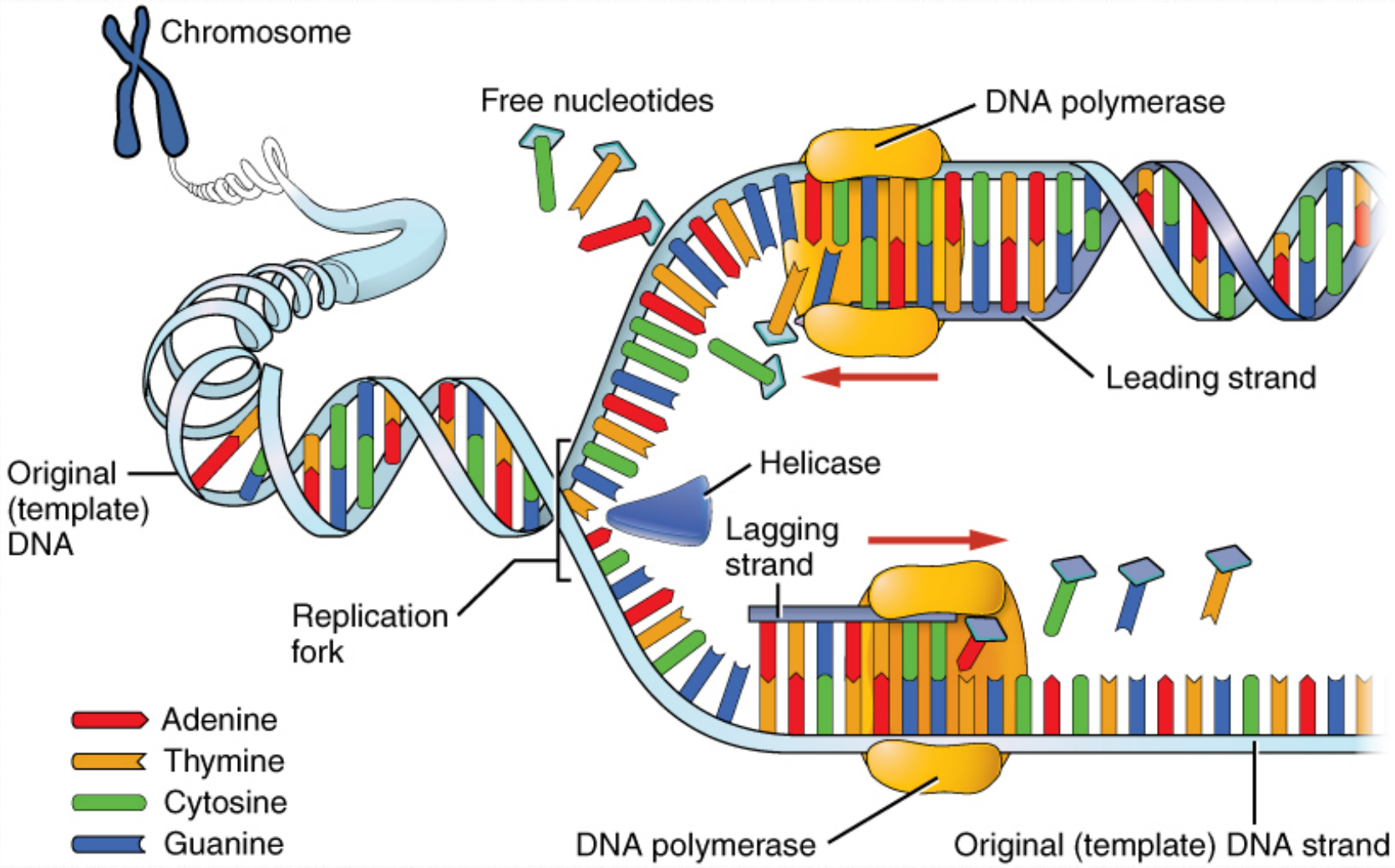

Figure 7.17 - View of a eukaryotic DNA replication fork with helicase shown in blue

Wikipedia

wound to expose new sections of single-stranded template.

- This unwinding must be accomplished without introducing topological distortion into the molecule.

What is the effect of unwinding one region of the double helix? Local unwinding of the double helix causes over-winding (increased positive supercoiling) ahead of the unwound region.

The DNA ahead of the replication fork has to rotate, or it will get twisted on itself and halt replication. This is a major problem, not only for circular bacterial chromosomes, but also for linear eukaryotic chromosomes, which, in principle, could rotate to relieve the stress caused by the increased supercoiling.

Topoisomerases

The reason this is problematic is that it is not possible to rotate the entire length of a chromosome, with its millions of base-pairs, as the DNA at the replication fork is unwound. How, then, is this problem solved? Enzymes called topoisomerases can relieve the topological stress caused by local “unwinding” of

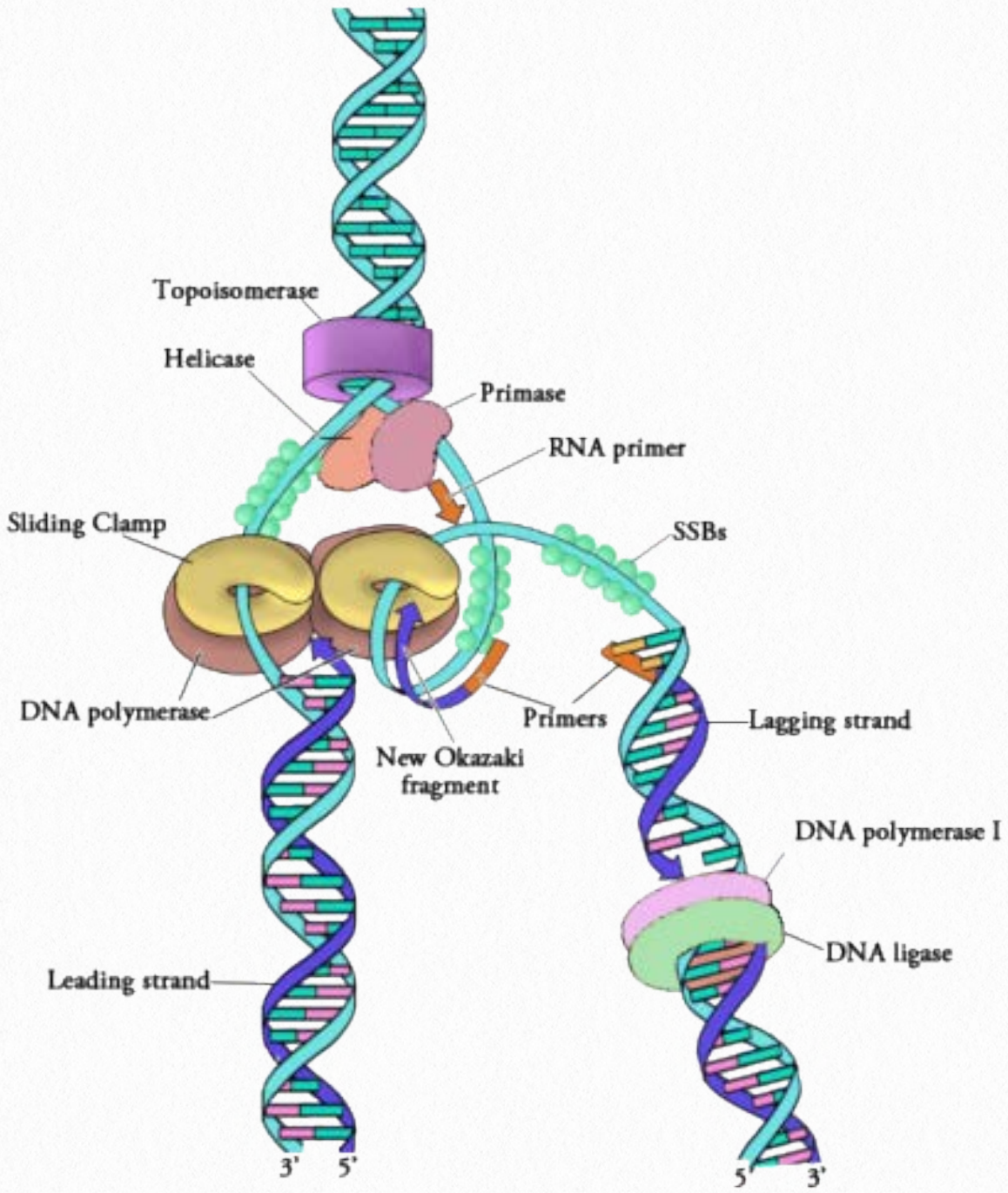

Figure 7.18 - Proteins at a prokaryotic DNA replication fork
Image by Martha Baker

the extra winds of the double helix. They do this by cutting one or both strands of the DNA and allowing the strands to swivel around each other to release the tension before rejoining the ends. In *E. coli*, the topoisomerase that performs this function is called gyrase.

•The separated single strands of DNA must be kept from coming back together so the new strands to be synthesized.

Single-strand DNA binding protein

Once the two strands of the parental DNA molecule are separated, they must be prevented from going back together to form double-stranded DNA. To ensure that unwound regions of the parental DNA remain single-stranded and available for copying, the separated strands of the parental DNA are bound by many molecules of a protein called single-strand DNA binding protein (SSB - Figure 7.18).

•DNA polymerases cannot begin synthesis of a new DNA strand *de novo* and require a free 3' OH to which they can add DNA nucleotides.

Although single-stranded parental DNA is now available for copying, DNA polymerases cannot begin synthesis of a complementary strand *de novo*. This simply means that DNA

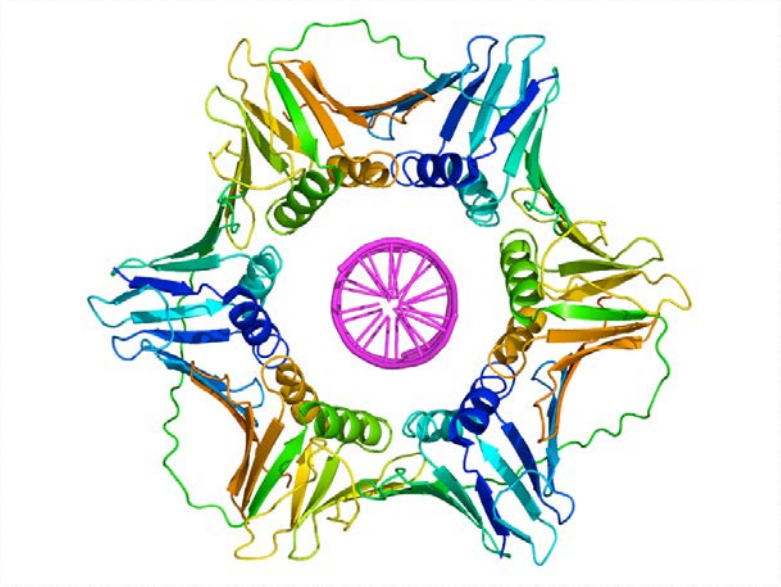

Figure 7.19 - Top view of the sliding clamp (outside) surrounding DNA strand (inside)

polymerases can only add new nucleotides on to the 3' end of a pre-existing chain, and cannot start a chain of nucleotides on their own. Because of this limitation, some enzyme other than a DNA polymerase must first make a small region of nucleic acid, complementary to the parental strand, that can provide a free 3' OH to which DNA polymerase can add a deoxyribonucleotide. This task is accomplished by an enzyme called a primase, which assembles a short stretch of RNA base-paired to the parental DNA template. This provides a short base-paired region, called the RNA primer, with a free 3'OH group to which DNA polymerase can add the first new DNA nucleotide (Figure 7.12).

Sliding clamp

Once a primer provides a free 3'OH for extension, other proteins get into the act. These proteins are involved in loading the DNA polymerase onto the primed template and keeping it associated with the DNA. The first of these is the clamp loader. As its name suggests, the clamp loader helps to load a protein complex called the sliding clamp onto the DNA at the replication fork (Figure 7.19 and 7.20). The sliding clamp, a multi-subunit ring-shaped protein, is then joined by the DNA Polymerase. The function of the sliding clamp is to keep the polymerase associated

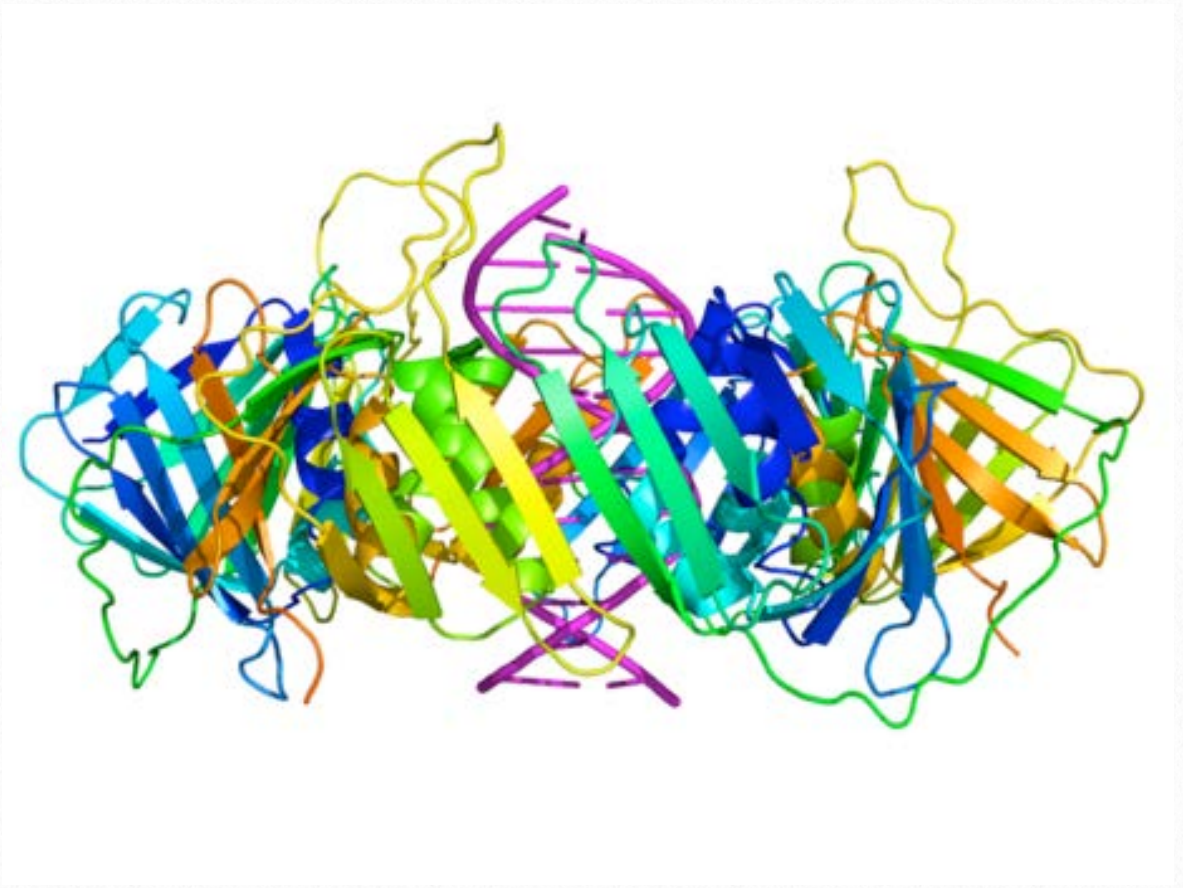

Figure 7.20 - Side view of the sliding clamp surrounding a DNA strand (in purple)

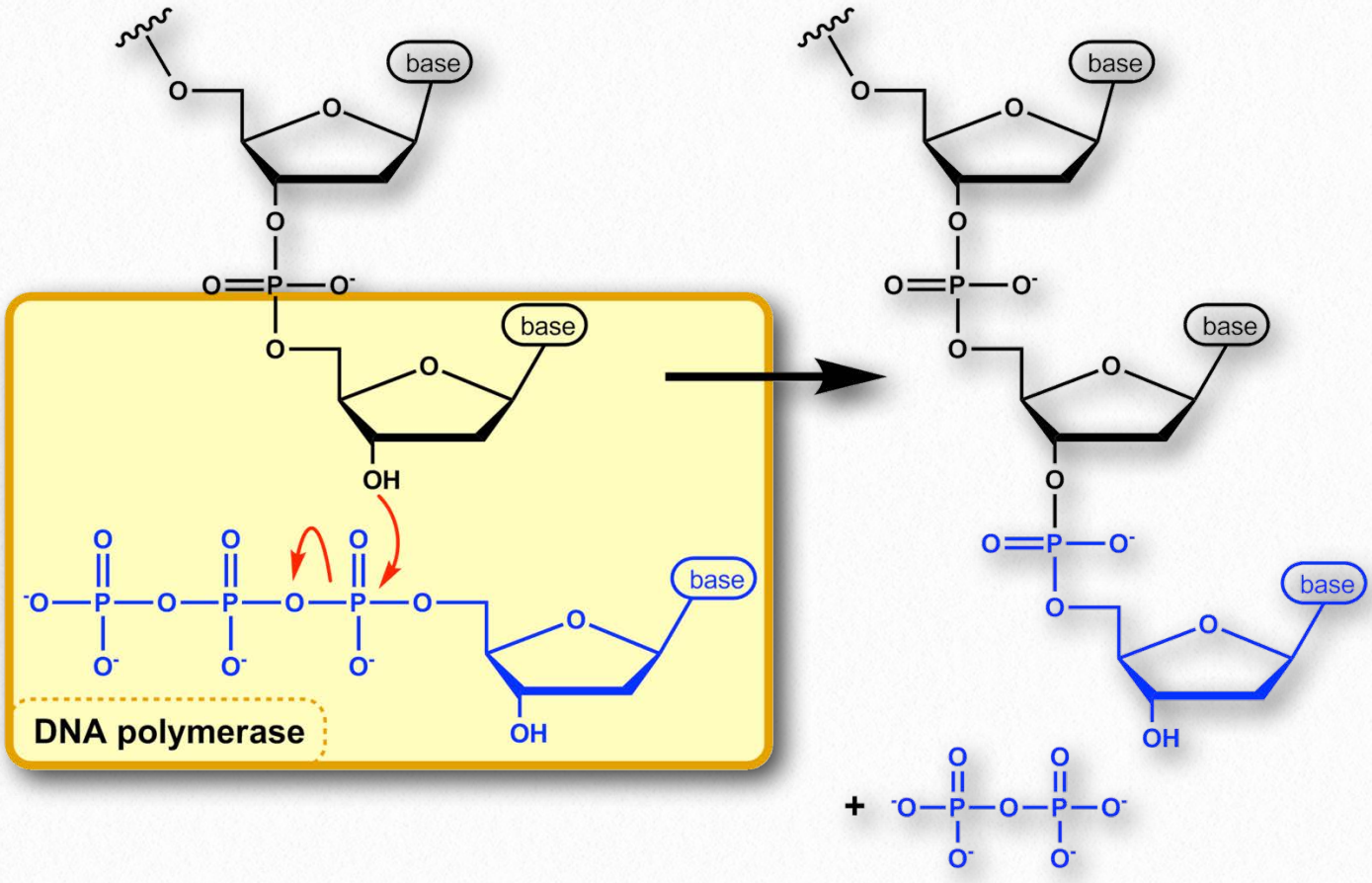

Figure 7.21 - Mechanism of DNA chain growth

Wikipedia

with the replication fork - in fact, it has been described as a seat-belt for the DNA polymerase. The sliding clamp ensures that the DNA polymerase is able to synthesize long stretches of new DNA before it dissociates from the template. The property of staying associated with the template for a long time before dissociating is known as the processivity of the enzyme. In the presence of the sliding clamp, DNA polymerases are much more processive, making replication faster and more efficient.

YouTube Lectures by Kevin HERE & HERE

Extending the primer

The DNA polymerase is now poised to start synthesis of the new DNA strand (in *E. coli*, the primary replicative polymerase is called DNA polymerase III). As you already know, the synthesis of new DNA is accomplished by the addition of new nucleotides complementary to those on the parental strand. DNA polymerase catalyzes the reaction by which an incoming deoxyribonucleotide, complementary to the template, is added onto the 3' end of the previous nucleotide, starting with the 3'OH on the end of the RNA primer. The importance of the 3'OH group lies in the nature of the reaction that builds a chain of nucleotides.

The reaction catalyzed by the DNA polymerase occurs through the nucleophilic attack by the 3'OH group at the end of a nucleic acid strand on the α phosphate of the incoming dNTP (Figure 7.21). The immediate hydrolysis of the pyrophosphate that is cleaved off the incoming dNTP drives the reaction forward. The sequential addition of new

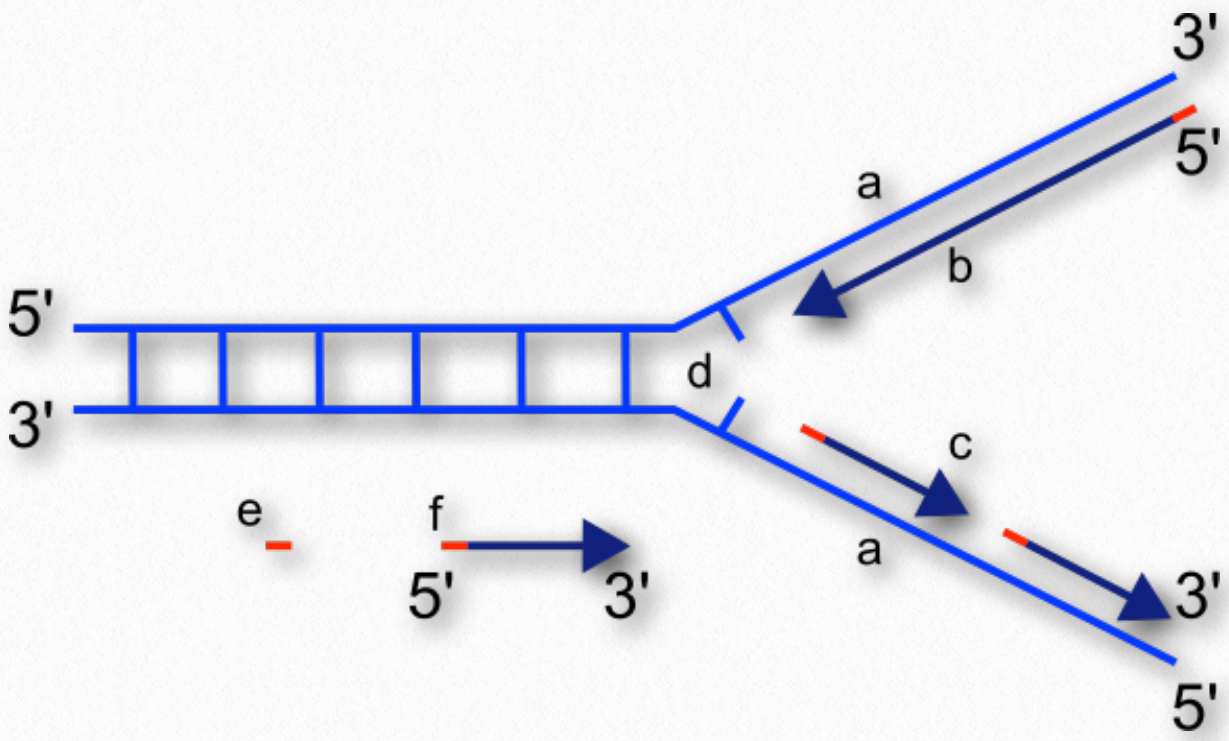

Figure 7.22 - Bidirectional DNA replication with template strand (a), leading strand (b), Okazaki fragments (c), replication fork (d), RNA primer (e), and DNA extended RNA primers (f)

Wikipedia

nucleotides at the 3' end of the growing chain of DNA accounts for the fact that the strand grows in a 5'to 3' direction.

The 5' phosphate on each incoming nucleotide is joined by the DNA polymerase to the 3' OH on the end of the growing nucleic acid chain, to make a phosphodiester bond. Each added nucleotide provides a new 3'OH, allowing the chain to be extended for as long as the DNA polymerase continues to synthesize the new strand. As we already noted, the new DNA strands are synthesized by the addition of DNA nucleotides to the end of an RNA primer. The new DNA molecule thus has a short piece of RNA at the beginning.

•DNA polymerases can only extend a strand in the 5' to 3' direction. The 5' to 3' growth of both new strands means that one of the strands is made in pieces.

Leading strand

We know that DNA polymerases can only build a new DNA strand in the 5' to 3' direction. We also know that the two parental strands of DNA are anti-parallel. This means that at each replication fork, one new strand, called the leading strand can be synthesized continuously in the 5' to 3' direction because it is being made in the same direction that the replication fork is opening up.

Lagging strand

The synthesis of the other new strand, called the lagging strand, also proceeds in the 5' to 3' direction. But because the template strands are running in opposite directions, the lagging strand is being extended in the direction opposite to the opening of the replication fork (Figure 7.22). As the replication fork opens up, the region behind the original start point for the lagging strand will need to be copied. This means another RNA primer must be laid down and extended. This process repeats

itself as the replication fork opens up, with multiple RNA primers laid down and extended, producing many short pieces that are later joined. These short nucleic acid pieces, each composed of a small stretch of RNA primer and about 1000-2000 DNA nucleotides, are called Okazaki fragments, for Reiji Okazaki, the scientist who first demonstrated their existence.

• The use of RNA primers requires that the RNA nucleotides must be removed and replaced with DNA nucleotides.

Primer removal

We have seen that each newly synthesized piece of DNA starts out with an RNA primer, effectively making a new nucleic acid strand that is part RNA and part DNA. The newly made DNA strand cannot be allowed to have pieces of RNA attached. So, the RNA nucleotides must be removed and the gaps filled in with DNA nucleotides (Figure 7.23). This is done by DNA polymerase I in *E. coli*. This enzyme begins adding DNA nucleotides at the end of each Okazaki fragment. However, the end of one Okazaki fragment is adjacent to the RNA primer at the beginning of the next Okazaki fragment. DNA polymerase I has an exonuclease activity acting in the 5' to 3' direction that removes the RNA nucleotides ahead of it, while the polymerase activity replaces the RNA nucleotides with dNTPs. Once all the RNA nucleotides have been re-

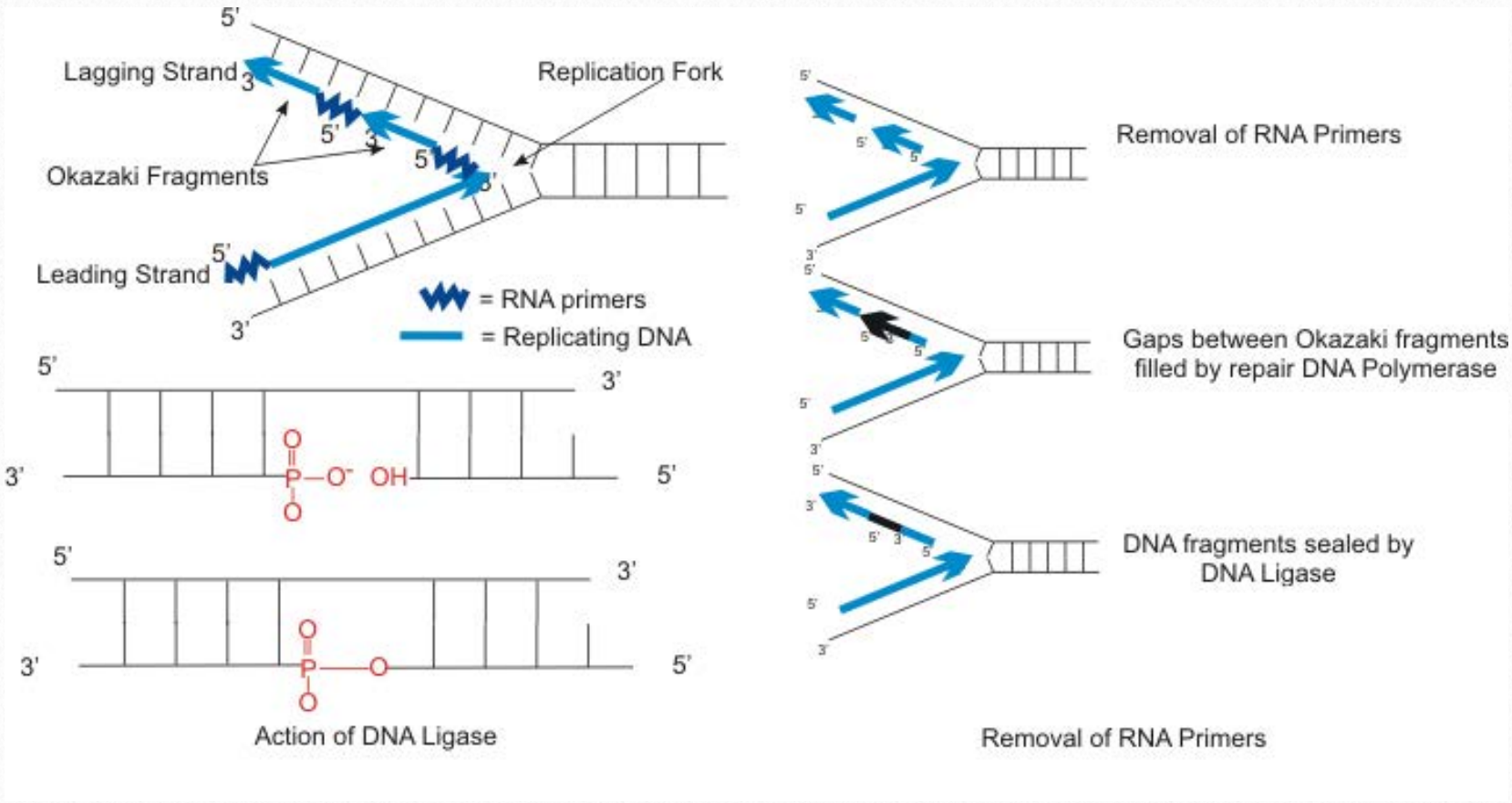

Figure 7.23 - Removal of RNA primers and joining of Okazaki fragments

Wikipedia

moved, the lagging strand is made up of stretches of DNA. The DNA pieces are then joined together by the enzyme DNA ligase.

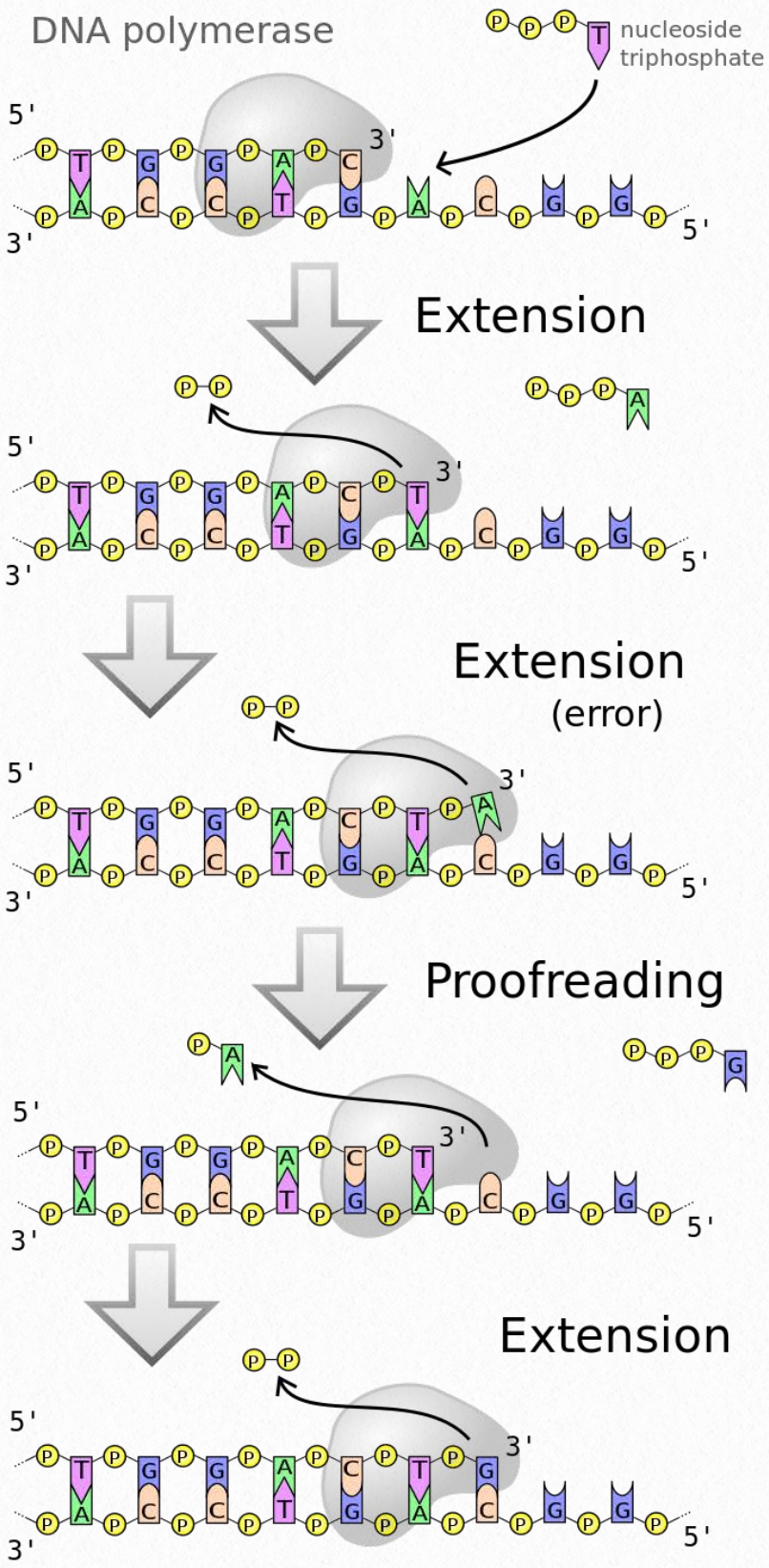

Figure 7.24 - Error corrected by DNA polymerases

The steps outlined above essentially complete the process of DNA replication. But one issue still remains.

- Ensuring accuracy in the copying of so much information

Accuracy

How accurate is the copying of information by DNA polymerase? As you are aware, changes in DNA sequence (mutations) can change the amino acid sequence of the encoded proteins and that this is often, though not always, deleterious to the functioning of the organism. When billions of bases in DNA are copied during replication, how do cells ensure that the newly synthesized DNA is a faithful copy of the original information?

DNA polymerases, as we have noted earlier work fast (averaging 50 bases a second in human cells and up to 200 times faster in *E. coli*). Yet, both human and bacterial cells seem to replicate their DNA quite accurately. This is because replicative DNA polymerases have a proofreading function that enables the polymerase to detect when the wrong base has been inserted across from a template strand, back up and remove the mistakenly inserted base, before continuing with synthesis (Figure 7.24).

Multiple activities

This is possible because most DNA po-

lymerases are dual-function enzymes. They can extend a DNA chain by virtue of their 5' to 3' polymerase activity. Some polymerases like DNA polymerase I can also remove RNA primers in the 5’ to 3’ direction, though that is not a common activity of polymerases. Many polymerases, however have an ability to backtrack and remove the last inserted base because they possess a 3' to 5' exonuclease activity.

The exonuclease activity of a DNA polymerase allows it to excise a wrongly inserted base, after which the polymerase activity inserts the correct base and proceeds with extending the strand.

In other words, the DNA polymerase is monitoring its own accuracy (also termed its *fidelity*) as it makes new DNA, correcting mistakes immediately before moving on to add the next base. This mechanism, which operates during DNA replication, corrects many errors as they occur, reducing by about a 100-fold the mistakes made when DNA is copied.

DNA polymerases

As noted earlier, both prokaryotic and eukaryotic cells have multiple DNA polymerases. In *E.coli*, for example, DNA polymerase III is the major replicative polymerase (a.k.a. replicase) while DNA polymerase I is responsible for DNA repair as well as removal of RNA primers and their replacement with DNA nucleotides during replication. DNA polymerase II plays a role in restarting replication after DNA damage stalls replication, while DNA polymerases IV and V are both required in trans-lesion, or bypass, synthesis, which allows replication past sites of DNA damage.

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Eukaryotic polymerases

In eukaryotes, there are over fifteen different DNA polymerases. The primary replicative polymerases in the nucleus are ∂ and ε. DNA polymerase α is also important for replication because it has primase and repair activities. Replication is initiated in eukaryotic cells by DNA polymerase α, which binds to the initiation complex at the origin

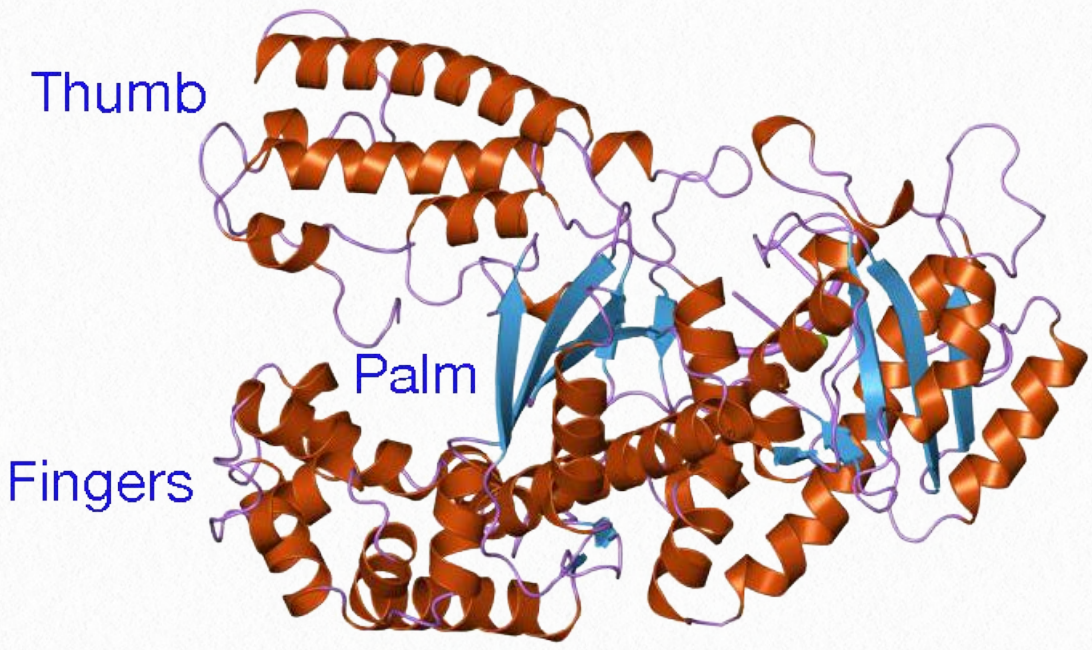
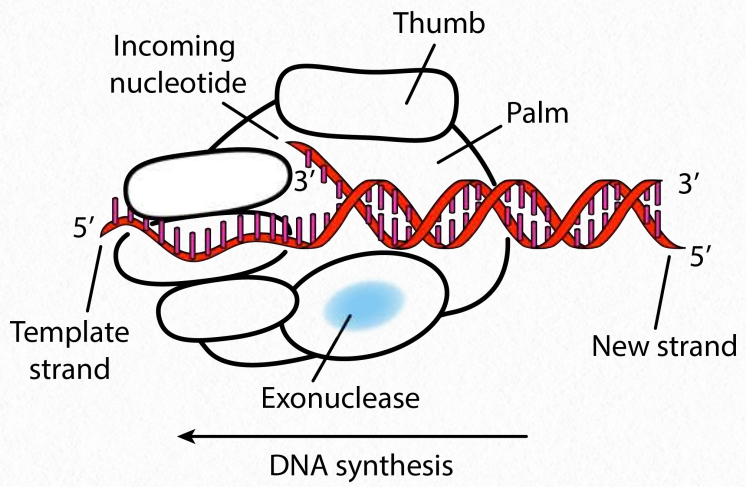


Figure 7.25 DNA polymerase I with hand structure

and lays down an RNA primer, followed by about 25 nucleotides of DNA. It is then replaced by another polymerase, in a step called the pol switch. DNA polymerase ∂ or ε then continues synthesizing DNA, depending on the strand. The role of polymerase ε appears to be synthesis of the leading strand due to its high processivity and accuracy, whereas polymerase ∂ extends Okazaki fragments on the lagging strands. Proteins analogous to the clamp loader and sliding clamp are also present. The protein RFC plays the role of clamp loader, while another protein, PCNA acts like the sliding clamp. Several other DNA polymerases like β, γ and μ function in repairing gaps. Yet others are involved in trans-lesion synthesis following DNA damage and are associated with hypermutation.

Despite their diversity, DNA polymerases share some common structural features. X-ray crystallographic studies have shown that these enzymes have a structure that has been compared to a human right hand (Figures 7.25 & 7.26). The «palm» of the hand forms a cleft in which the DNA lies. The cleft is also the where the polymerase catalytic activity resides. This is where the incoming nucleotide is added on to the growing chain. «The fingers» position the DNA in the active site, while the «thumb» holds the DNA as it exits the polymerase. A separate domain contains the exonuclease (proofreading) activity of the enzyme.



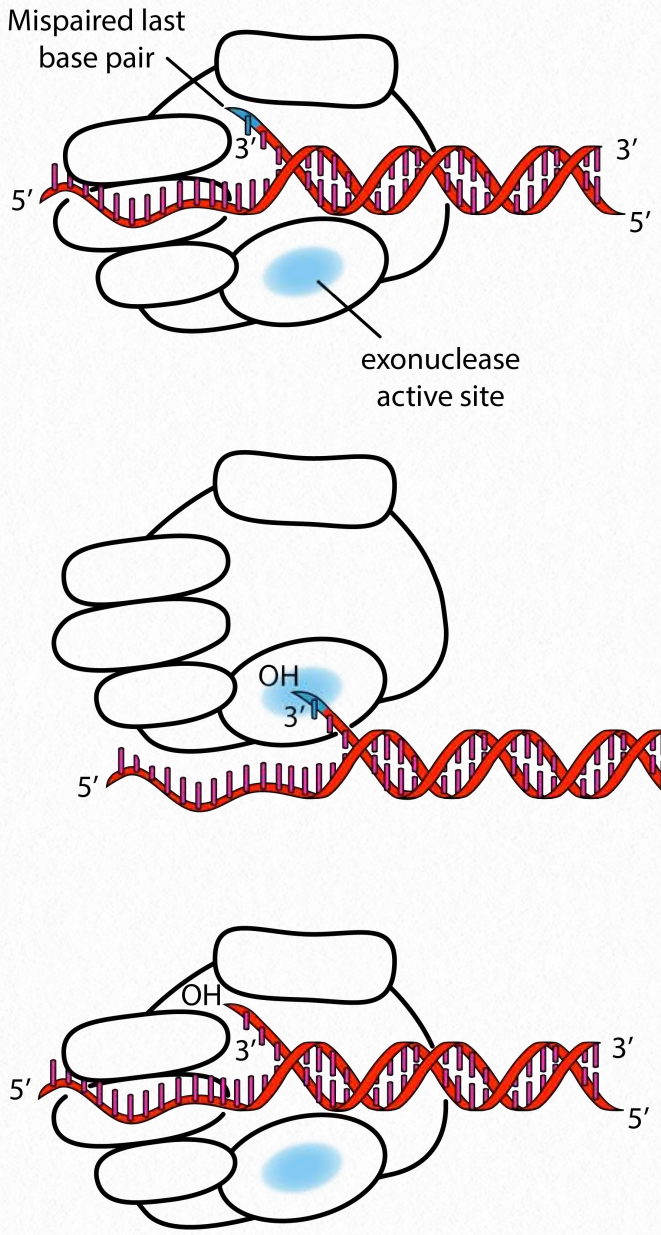


Figure 7.26 - Proofreading by DNA polymerase

Image by Pehr Jacobson

The enzyme alternates between its polymerizing activity and its proofreading activity.

Name	Name	M.W.	Other Activity	Function
α	alpha	165,000	Primase	Repair
β	beta	39,000	Lyase	Base excision repair
δ	delta	100,000	3' exonuclease	Replication, DNA repair
ε	epsilon	225,000	3' exonuclease	Replication, DNA repair
γ	gamma	140,000	3' exonuclease	Mitochondrial replication
η	eta	78,000		Bypass of thymine dimers
I	iota	80,000	Lyase	Repair?
K	kappa	76,000		Nucleotide excision repair
λ	lambda	66,000	Lyase	Repair/recombination
μ	mu	55,000		Repair/recombination
ν	nu	100,000		Repair?
θ	theta	290,000	Helicase	Repair? Hypermutation?
ζ	zeta	353,000		Repair/hypermutation

Figure 7.27 - **Mammalian DNA polymerases**

When a mismatched base pair is in the polymerase catalytic site, the 3'end of the growing strand is moved from the polymerase site to the exonuclease active site (Figure 7.26). The mispair at the end is removed by the exonuclease, followed by repositioning of the 3' end in the polymerase active site to continue synthesis.

Termination of replication

In circular bacterial chromosomes, there are specific sequences known as terminator or Ter sites. These are multiple short sequences that serve as termination sites, allowing the replication forks traveling clockwise and anticlockwise across the circular chromosome to meet at one of the sites.

The binding of a protein, Tus, at a Ter site prevents further movement of the replication fork and ends replication. The parental and newly made circular DNA are, at this point topologically interlinked and must be separated with the help of topoisomerase.

The end-replication problem

There is no fixed site for termination in linear eukaryotic chromosomes. As the replication forks reach the ends of the chromosome, the leading strand can be synthesized all the way to the end of the template strand. On the lagging strand, the need for an RNA primer to start synthesis creates a challenge. When the RNA primer at the extreme end of the lagging strand is removed, there is a small stretch of the template strand

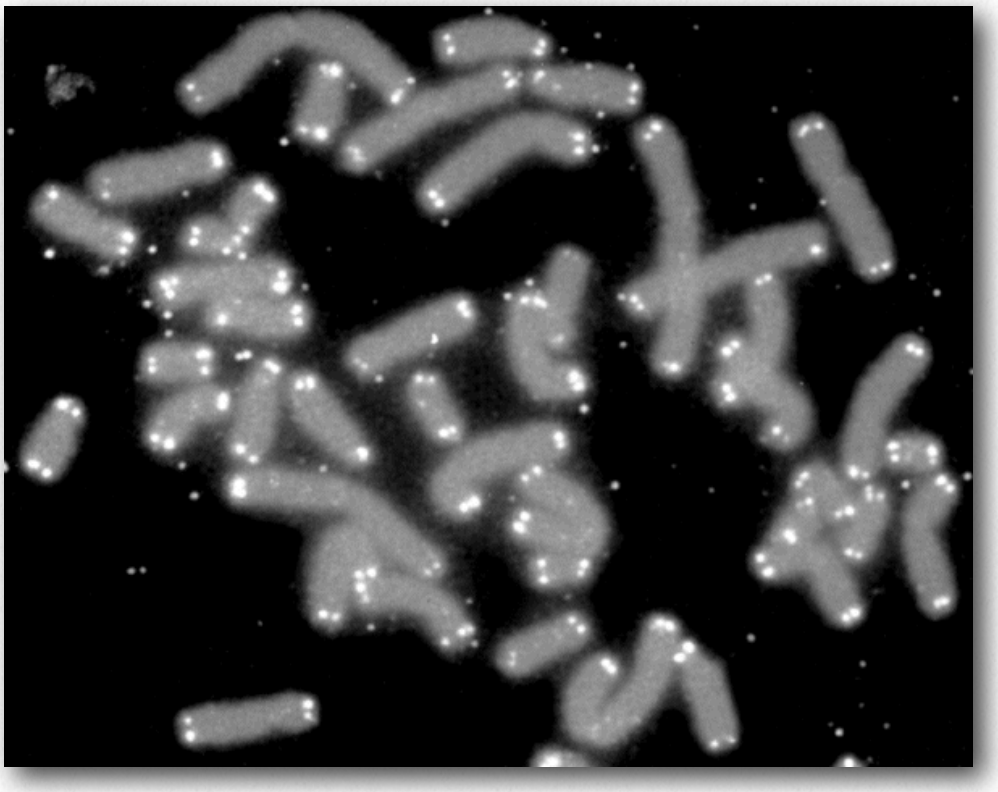


Figure 7.28 - Chromosomes with telomeres marked in white

that cannot be copied. As a result, in each round of replication a short sequence at the ends of the chromosome will be lost. Over time, with many cycles of replication, chromosomes would become noticeably shorter. This shortening of chromosomes has been observed *in vitro*, in cultured mammalian somatic cells. It is also seen in intact organisms, with increasing age.

Telomeres

What effect does the loss of sequence from the ends of the chromosomes have on cells? We know that the ends of chromosomes are characterized by structures called telomeres (Figure 7.28). Telomeres are made up of many copies of short repeated sequences (in humans, the repeat is TTAGGG) and special proteins that specifically bind to these sequences. This structure of telomeres is useful in distinguishing the ends of chromosomes from double-strand breaks in DNA, thus preventing the DNA repair mechanisms in cells from joining chromosomes end to end.

The other advantage of the repeated sequences, which do not encode proteins, is that losing some of the repeats does not lead to loss of important coding information. Thus, the repeats act as a sort of buffer zone, where the loss of sequence does not doom the cell. However, the shortening of chromosomes cannot continue indefinitely. After a certain number of replication cycles, cells are known to stop dividing and enter a state known as replicative senescence. This suggests that the shortening of the telomeres serves as a sort of clock, with the extent of shrinkage of the chromosomes serving as a measure of aging. Eventually cells that enter senescence will die.

Problems with sequence loss

Even if our cells are able to function with shorter chromosomes during our lifetimes, this leaves us with another problem. If our chromosomes grow shorter with age, then presumably our children, who inherit our chromosomes will be born with shorter chromosomes than we started with. They, in turn, would have their chromosomes shrink as they

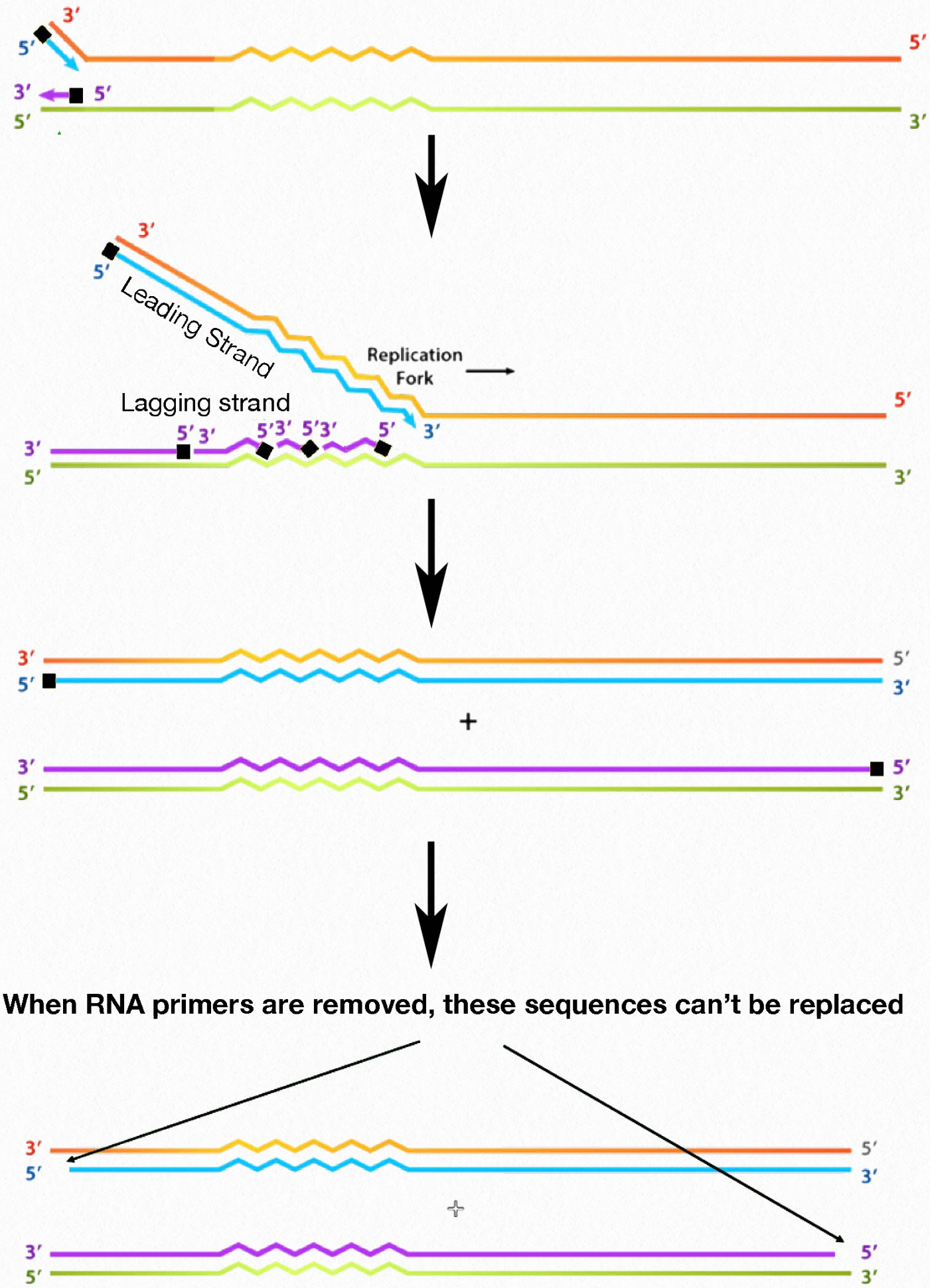


Figure 7.29 - Replication of a linear chromosome results in loss of sequences at the very ends with each round of replication

grew older, and their children would have even shorter chromosomes. Over the course of multiple generations, this would lead to the point where further chromosome shrinkage would result in cells that would enter senescence very early in life and die soon after. This obviously does not happen. Generation after generation of children are born with full-length chromosomes, so there is a mechanism that must ensure that at least in the reproductive cells, chromosomes do not get shorter.

To understand this mechanism, it is necessary to first examine the end of a newly made DNA molecule (Figure 7.29). While the leading strand, which grows in the same direction as the movement of the replication fork, can copy its template all the way to the end, the lagging strand encounters a problem. RNA primers are, as we noted, needed to start each of the Okazaki fragments of the lagging strand. The primers must be removed later, and the RNA nucleotides replaced with DNA nucleotides. When the RNA primer across from the end of the parental strand is removed, the RNA nucleotides cannot be replaced by DNA nucleotides because the DNA polymerase has no primer to start from. A short region of the template cannot, therefore be copied.

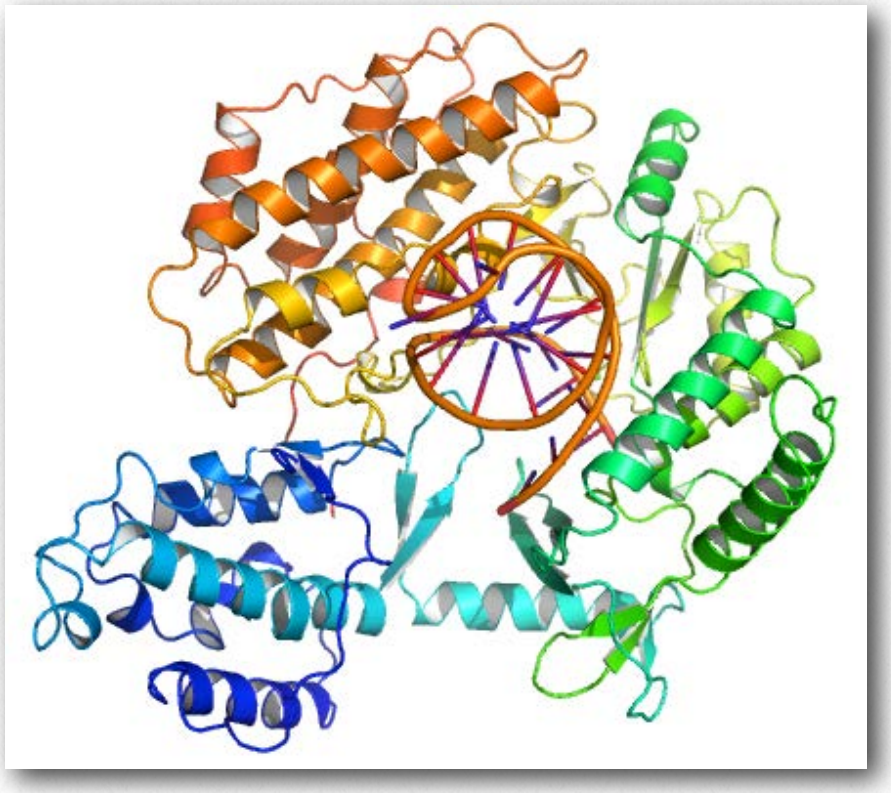


Figure 7.30 - Telomerase holding its RNA template (in center)

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YouTube Lectures by Kevin HERE & HERE

Telomerase

How can this problem be solved? It can be seen from Figure 7.29 that the end of the original template strand has a short 3' overhang resulting from the removal of the RNA primer across from it. In order to fill in this region, another primer would be needed, situated past the end of the template strand. But in order to build such a primer, it would be necessary for the template overhang to be longer. If it were possible to make the template strand longer, then another primer could be placed across from its end and the end of the strand could be copied. Such an extension of the template strand is exactly what happens in our reproductive cells. The parental template strand is extended by the enzyme telomerase, which adds telomere repeats and lengthens the template. We will see shortly how it accomplishes that feat.

RNA template

Telomerase is an unusual enzyme, in that it is made up of two components, an RNA and a reverse transcriptase. A reverse transcriptase is an RNA-dependent DNA polymerase, an enzyme that copies an RNA template to make DNA. The RNA component of the human telomerase, called hTERC, has a sequence that is complementary to the telomere repeat, TAGGG. As seen in Figure 7.31, this RNA can base-pair with the last telomere repeat on the parental DNA strand, while a portion of the RNA remains unpaired.

Template for extension

The function of the unpaired region of the RNA is to serve as a template that can be used to extend the overhanging 3' end of the original DNA molecule. The protein component of telomerase has reverse transcriptase activity and can copy the RNA sequence into DNA. In human telomerase, the protein component is known as hTERT (telomerase reverse transcriptase). As seen in Figure 7.31 and 7.32, the reverse transcriptase extends the original 3' overhang using the RNA component as its template. The telomerase can then dissociate, and repeat the process multiple times to add many repeats of the telomere sequence.

Once the overhang has been extended by the addition of at least several telomere repeats, there is now room for the synthesis of an RNA primer complementary to the newly extended overhang (pointing back towards the rest of the chromosome). This primer can then be extended to complete synthesis of the lagging strand all the way to the end of the original parental DNA strand. Thus, the addition of telomere repeats on the parental DNA strands keeps the newly made DNA strands from becoming shorter with each cycle of replication. The fact that this happens in germ cells (reproductive cells) explains why each generation does not have shorter chro-

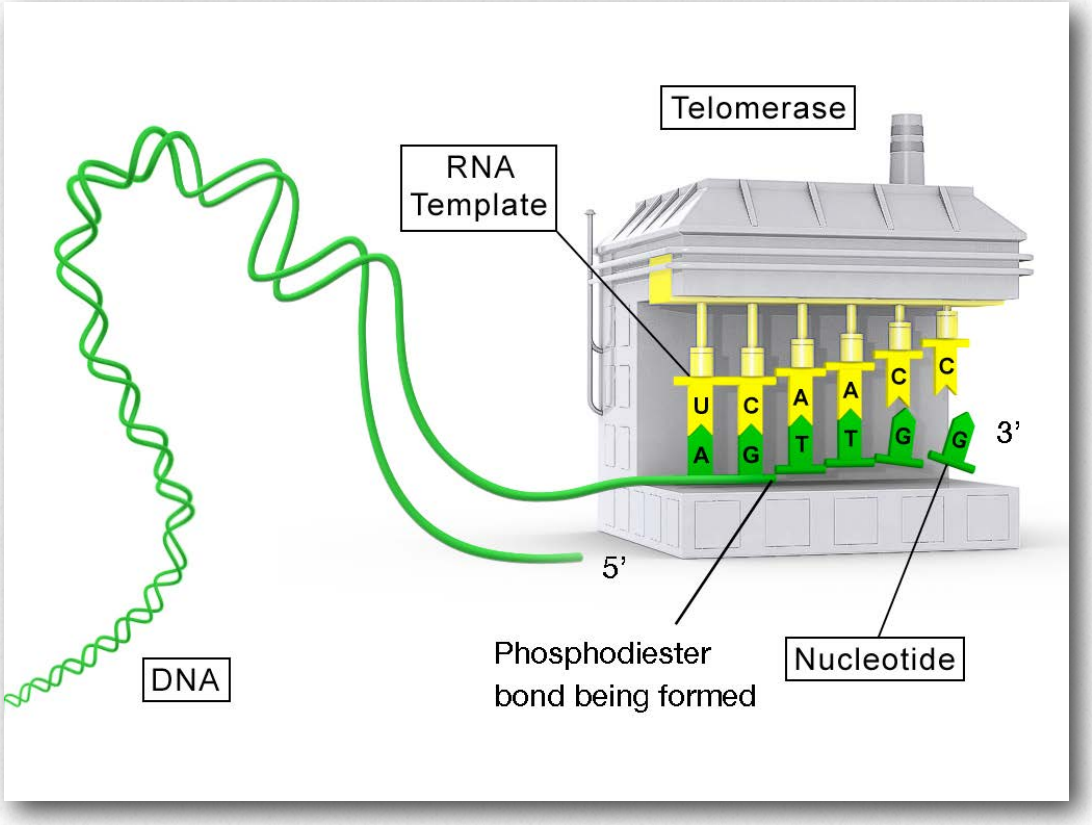

Figure 7.31 - Telomerase extends the template strand using its own RNA as template

Wikipedia

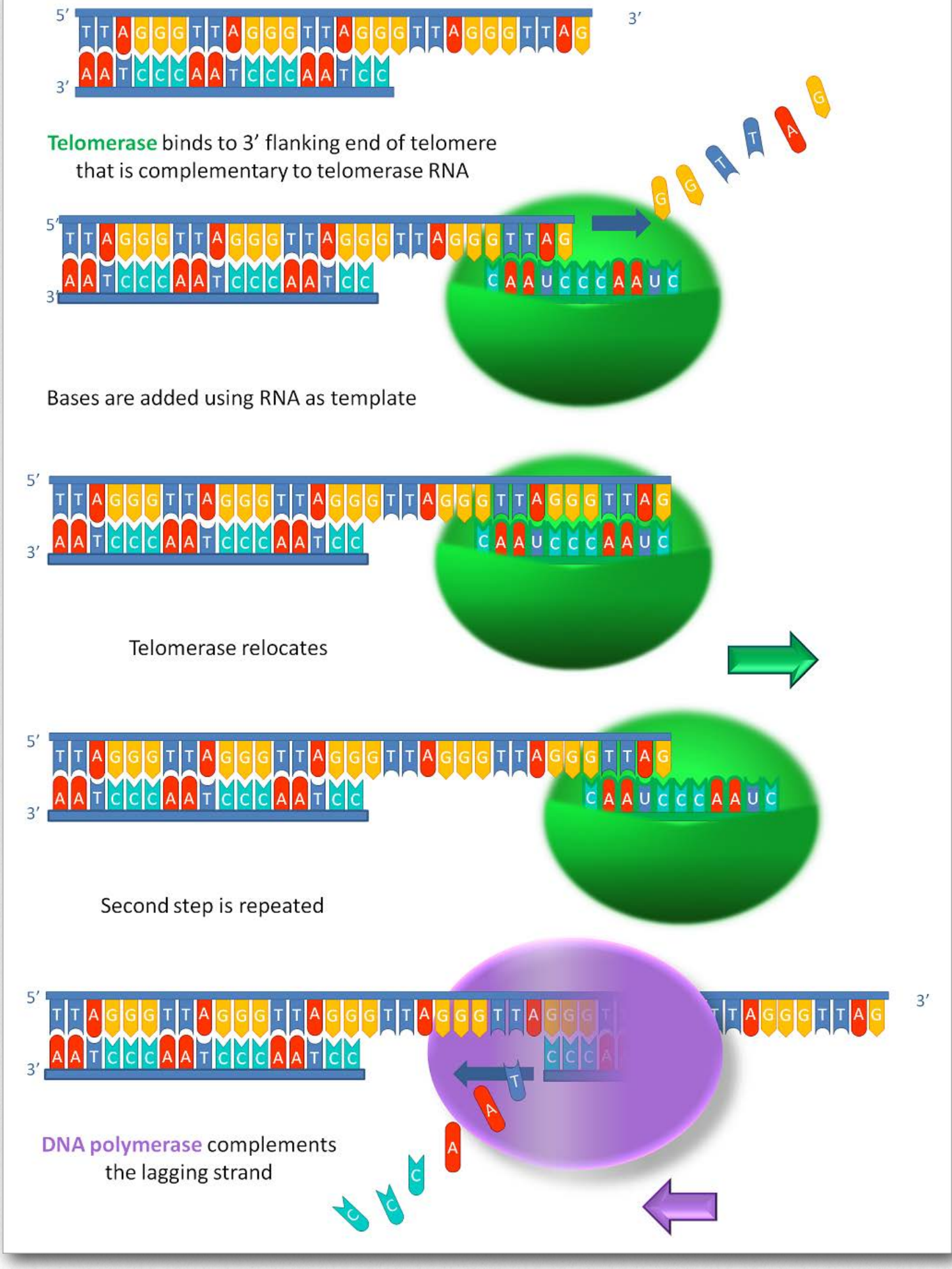

Figure 7.32 - Growing telomeres with telomerase and DNA polymerase. First, the 3' end of the template is extended by telomerase, then DNA polymerase completes synthesis of the lagging strand

Wikipedia

mosomes than the parental generation.

The proofreading function of DNA polymerases monitors the accuracy of DNA replication while the enzyme telomerase keeps chromosomes that will be passed on to offspring from shortening. Between them, these two activities ensure that the genetic information is copied accurately, and that succeeding generations receive a full complement of the genetic information

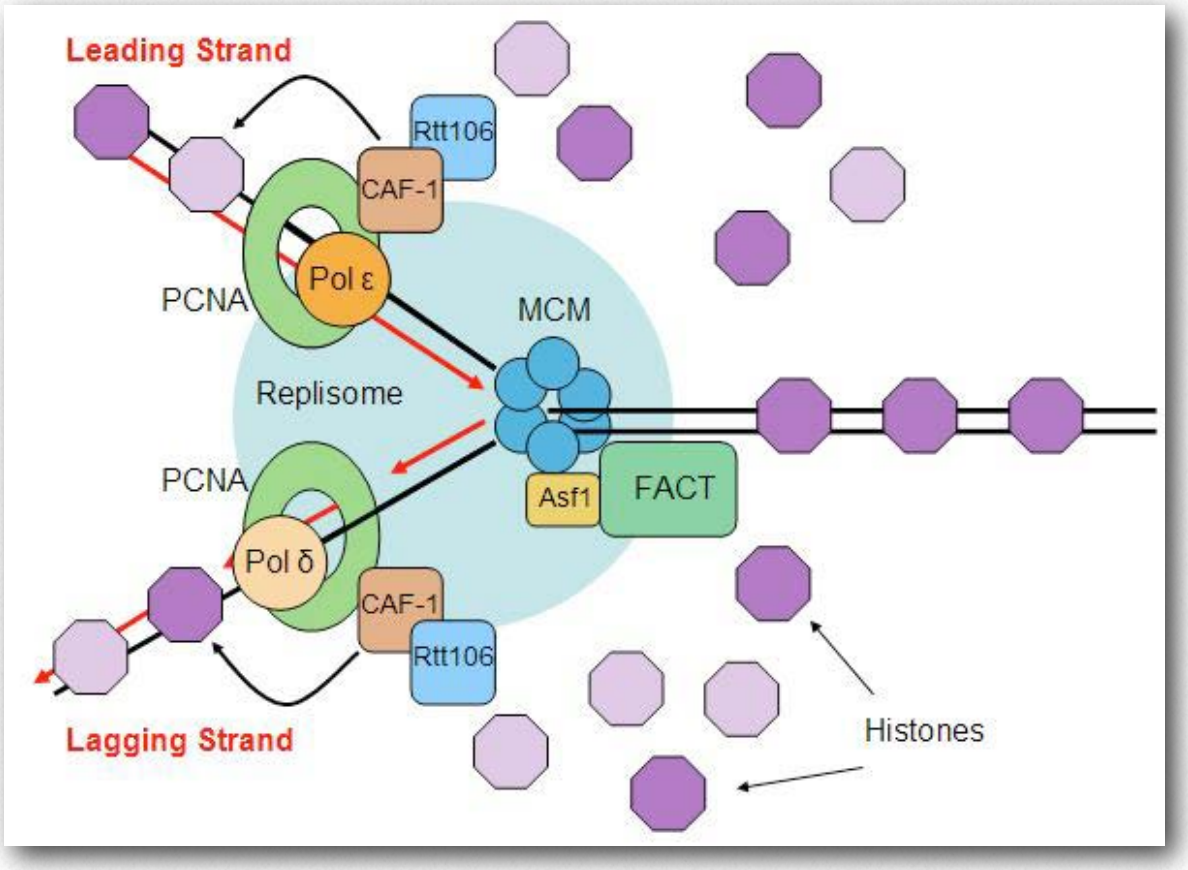

Figure 7.33 - Disruption of nucleosomes during DNA replication

Wikipedia

Disassembly and reassembly of nucleosomes

The events of replication have an additional twist in eukaryotes. Recall that DNA is found in eukaryotic cells as chromatin, a complex of the DNA with proteins. At its least condensed, chromatin looks like a string of beads, consisting of the DNA wrapped around histone cores to make nucleosomes. The nucleosome structure must be disrupted to make DNA available for replication and restored after replication is completed (Figure 7.33).

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Ahead of the replication fork, chromatin structure is disassembled by ATP-dependent chromatin remodeling complexes, allowing access to the DNA template. Once the new strands of DNA have been synthesized, both the original nucleosomes and new nucleosomes must be reassembled behind the replication fork. Since replication gives rise to two DNA molecules where there was one, twice the amount of histones is needed to package the DNA. Preparation for DNA replication, therefore, involves the synthesis of large amounts of histones to supply the need. Interestingly, it appears that newly synthesized DNA is packaged into nucleosomes using the original histones

that were displaced to allow the replication fork to pass, as well as newly synthesized histones.

We also know that post-translational modifications like acetylation, methylation or phosphorylation of the histones can regulate the degree to which a given region of the genome is accessible for use. One question that remains the subject of intense research is how these modifications are accurately passed on to the new nucleosomes.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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I Wanna Hold Your Strands

To the tune of "*I Wanna Hold Your Hand*"
Metabolic Melodies Website HERE

Oh yeah, I'll tell you something
It helps to understand
Pol III de-crees
To meet the cell's demands
It has to hold the straaaaaands
It's gotta hold the strands

The key, Pol III
Acts most processively
'Cuz see, Pol III
Has beta clamping ha-a-a-a-ands
It uses beta's ba-a-a-a-a-a-ands (note this is 'bands,' not 'hands')
To hold onto the strands

As it starts rep-li-CAT-ING a d---N-A (emphasis as noted)
The un-win-DING requires a lone
Helicase
Helicase
Helica-a-a-a-a-a-a-ase!

Pri-mase starts the primer
That Pol I can erase
Pol III takes the primer
And starts the DNAs
It starts the DNA-a-a-a-as
By using RNA

And when a fragment Okazaki - displays
There must be joining
That requires
A ligase
A ligase
A liga-a-a-a-ase

Thanks to all the factors
And all of their ligands
The cell has what matters
To replicate the strands
It replicates the strands
It replicates the strands
It replicates the stra-a-a-a-a-a-a-a-ands

Lyrics by Kevin Ahern

No Recording Yet For This Song

Complementary Bases

To the tune of "*California Dreamin'*"
Metabolic Melodies Website HERE

Mendel took the lead (Mendel took the lead)
Working with his peas (working with his peas)
And then Miescher found the seed (Miescher found the seed)
Studying disease (studying disease)
By the nineteen forties (by the nineteen forties)
'Twas clear it causes traits (clear it causes traits)
Complementary knowledge (complementary knowledge)
Led us to DNA

Chargaff's bases had
Only set ratios
Well then Watson-Crick took that (Watson-Crick took that)
Info and proposed (info and proposed)
Bases each must have a partner (each must have a partner)
G and C, T and A (G, C, T and A)
Complementary bases (Complementary bases)
Make up our DNA

Now we know the truth (Now we know the truth)
Of the form called B (of the form called B)
Thanks to Franklin's work (thanks to Franklin's work)
And skullduggery (and skullduggery)
Though she hadn't told them (though she hadn't told them)
They got it anyway (got it anyway)
Complementary data (gave us our D-N)
Complementary data (gave us our D-N)
Complementary data
Gave us our DNA

Lyrics by Kevin Ahern

No Recording Yet For This Song

Information Processing: DNA Repair

Safeguarding the genome

In the last section we considered the ways in which cells deal with the challenges associated with replicating their DNA, a vital process for all cells. It is evident that if DNA is the master copy of instructions for an organism, then it is important not to make mistakes when copying the DNA to pass on to new cells. Although proofreading by DNA polymerases greatly increases the accuracy of replication, there are additional mechanisms in cells to further ensure that newly replicated DNA is a faithful copy of the original, and also to repair damage to DNA during the normal life of a cell.

YouTube Lectures by Kevin HERE & HERE

DNA damage

All DNA suffers damage over time, from exposure to ultraviolet and other radiation, as well as from various chemicals in the environment (Figures 7.34 & 7.35). Even chemical reactions naturally occurring within cells can give rise to compounds that can damage DNA. As you already know, even minor changes in

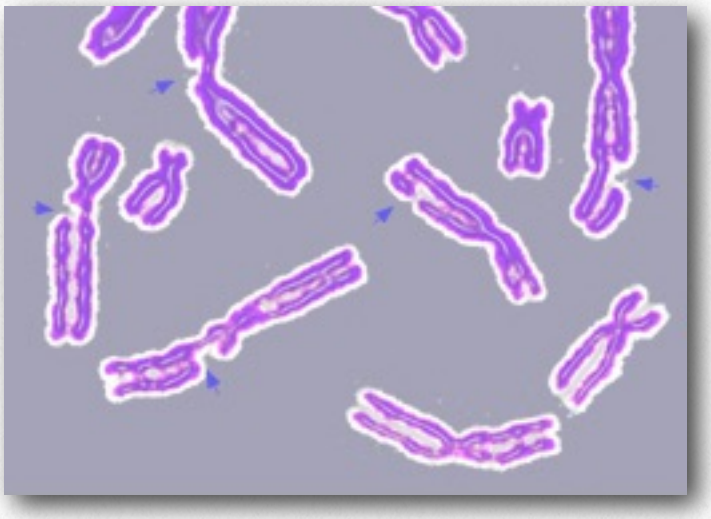

Figure 7.34 - Chromosome breaks

Wikipedia

DNA sequence, such as point mutations can sometimes have far-reaching consequences. Likewise, unrepaired damage caused by radiation, environmental chemicals or even normal cellular chemistry can interfere with the accurate transmission of information in DNA. Maintaining the integrity of the cell's "blueprint" is of vital importance and this is reflected in the numerous mechanisms that exist to repair mistakes and damage in DNA.

Post-replicative mismatch repair

We earlier discussed proofreading by DNA polymerases during replication. While proofreading significantly reduces the error rate, not all mistakes are fixed on the fly by DNA polymerases.

What mechanisms exist to correct the replication errors that are missed by the proofreading function of DNA polymerases? Errors that slip by proofreading during replication can be corrected by a mechanism called mismatch repair. While the error rate of DNA replication is about one in 10^7 nucleotides in the absence of mismatch repair, this is further reduced a hundred-fold to one in 10^9 nucleotides when mismatch repair is functional.

What are the tasks that a mismatch repair system faces?

It must:

- Scan newly made DNA to see if there are any mispaired bases (e.g., a G paired to a T)
- Identify and remove the region of the mismatch.
- Correctly fill in the gap created by the excision of the mismatch region.

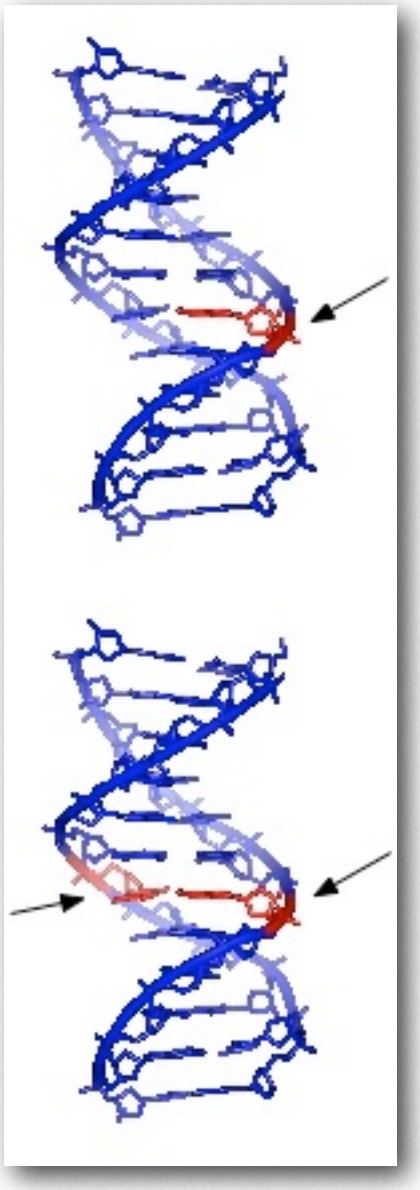

Figure 7.35 - Single- (top) and double-strand (bottom) damaged DNA

Wikipedia

Distinguishing strands

Importantly, the mismatch repair system must have a means to distinguish the newly made DNA strand from the template strand, if replication errors are to be fixed correctly. In other words, when the mismatch repair system encounters an A-G mispair, for example, it must know whether the A should

be removed and replaced with a C or if the G should be removed and replaced with a T.

But how does the mismatch repair system distinguish between the original and the new strands of DNA? In bacteria, the existence of a system that methylates the DNA at GATC sequences is the solution to this problem. *E.coli* has an enzyme, DNA adenine methylase (Dam) that adds methyl groups on the to adenines in GATC sequences in DNA (Figure 7.36). Newly replicated DNA has not yet undergone methylation and thus, can be distinguished from the template strand, which is methylated.

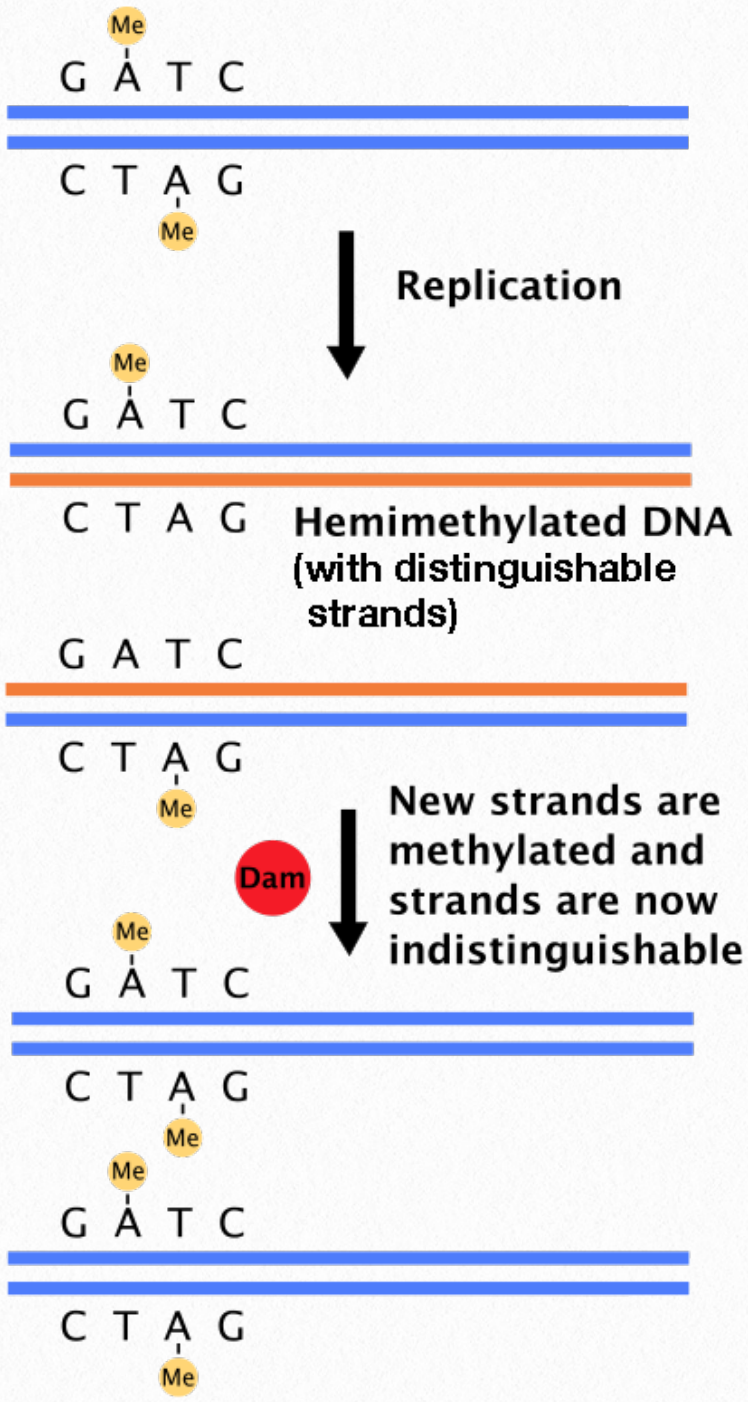

Figure 7.36- Dam methylase adds methyl groups at GATC sequences

The mismatch repair proteins selectively replace the strand lacking methylation, thus ensuring that it is mistakes in the newly made strand that are removed and replaced. Because methylation is the criterion that enables the mismatch repair system to choose the strand that is repaired, the bacterial mismatch repair system is described as being *methyl-directed*.

Mismatch repair genes

Mismatch repair has been well studied in bacteria, and the proteins involved have been identified. In *E.coli*, mismatch repair proteins are encoded by a group of genes collectively known as the mut genes. Important components of the mismatch repair machinery are the proteins MutS, MutL and MutH (Figure 7.37).

MutS acts to recognize the mismatch, while MutL and MutH are recruited to the mismatch site by the binding of MutS. MutH is an endonuclease that cuts the newly synthesized and, as yet, unmethylated DNA strand at a GATC. This activates a DNA helicase and an exonuclease that help unwind and remove the region containing the mismatch.

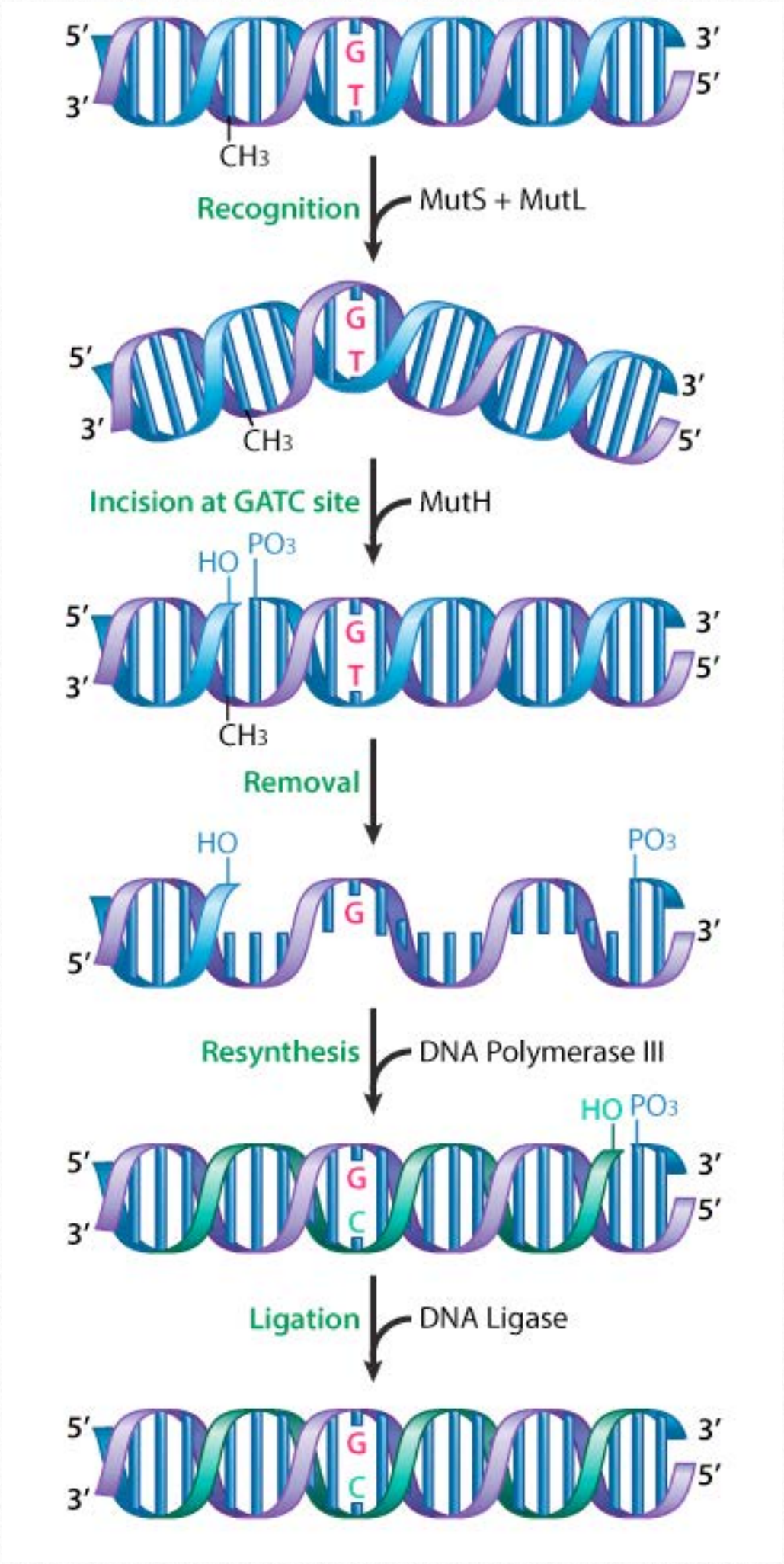

Figure 7.37 - Mismatch repair in *E. coli*

Image by Aleia Kim

DNA polymerase III fills in the gap, using the opposite strand as the template, and ligase joins the ends, to restore a continuous strand.

Eukaryotes also have a mismatch repair system that repairs not only single base mismatches but also insertions and deletions. Homologs to the *E. coli* MutS and MutL have been identified in other organisms, including humans: hMSH1 and hMSH2 (human MutS homolog 1 and 2) are homologous to MutS, while hMLH 1 is homologous to MutL. These, together with additional proteins, carry out mismatch repair in eukaryotic cells.

DNA methylation is not used by eukaryotic cells as a way to distinguish the new strand from the template, and it is not yet completely understood how the mismatch repair system in eukaryotes "knows" which strand to repair. There is evidence that the newly made DNA may be recognized by the fact that it is nicked, or discontinuous. This suggests that discontinuity resulting from Okazaki fragments that have not yet been joined together may permit the new strand to be distinguished from the old, continuous template strand.

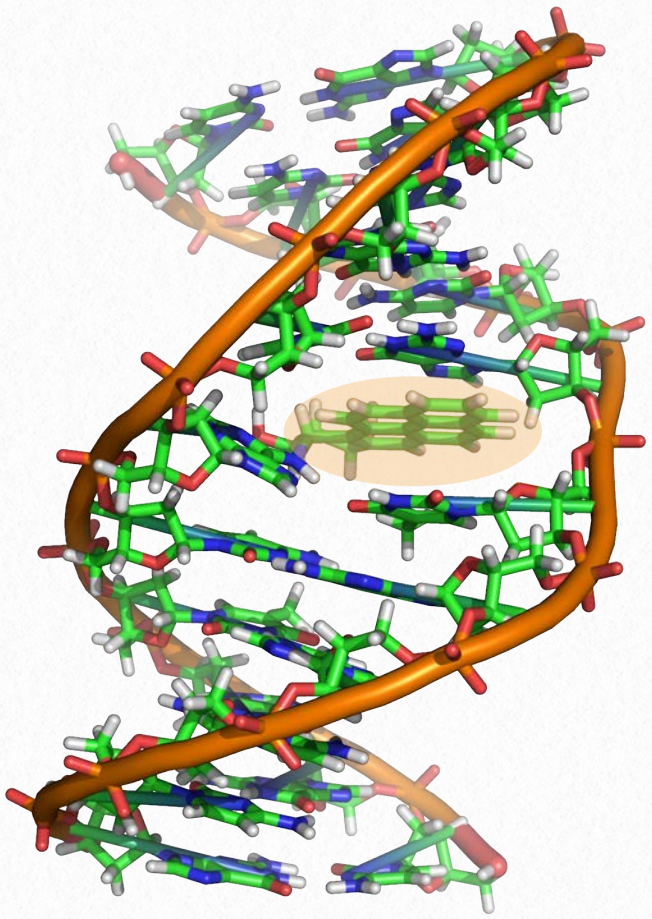

Figure 7.38 - DNA adducted to benz-o-pyrene (highlighted in orange)

Repairing damage to DNA

In the preceding section we looked at mistakes made when DNA is copied, where the wrong base is inserted during synthesis of the new strand. But even DNA that is not being replicated can get damaged or mutated. These sorts of damage are not associated with DNA replication, rather they can occur at any time.

What causes damage to DNA?

Some major causes of DNA damage are:

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a. Radiation (e.g., UV rays in sunlight and in tanning booths, or ionizing radiation)

b. Exposure to damaging chemicals, such as nitrosamines or polycyclic aromatic hydrocarbons, in the environment (see Figure 7.38)

c. Chemical reactions within the cell (such as the deamination of cytosine to give uracil, or the methylation of guanine to produce methylguanine).

This means the DNA in your cells is vulnerable to damage simply from normal sorts of actions, such as walking outdoors, being in traffic, or from the chemical transformations occurring in every cell as part of its everyday activities. (Naturally, the damage is much worse in situations where exposure to radiation or damaging chemicals is greater, such as when people use tanning beds, or smoke, regularly.)

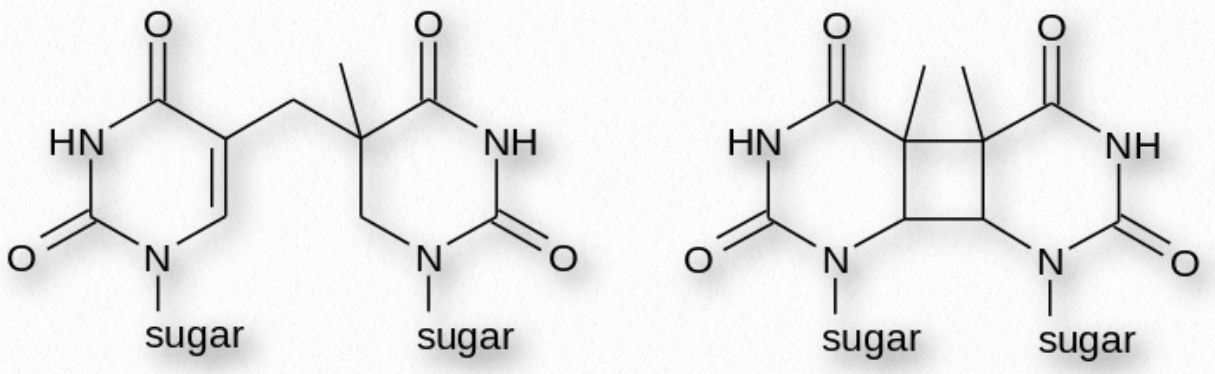

Figure 7.39 - Possible chemical structures of a pyrimidine dimer - 6-4PP (left) and CPD (right)

Wikipedia

Types of damage

What kinds of damage do these agents cause? Radiation can cause different kinds of damage to DNA.

Sometimes, as with much of the damage done by UV rays, two adjacent pyrimidine bases in the DNA will be cross-linked to form cyclobutane pyrimidine dimers or CPDs (see Figure 7.39). Note that these are two neighboring pyrimidine bases on the same strand of DNA. UV exposure can also lead to the formation of another type of lesion, known as a (6-4) photoproduct or 6-4PP (Figure 7.39). Ionizing radiation can cause breaks in the DNA backbone, in one or both strands.

Molecules like benzopyrene, found in automobile exhaust, can attach themselves to bases, forming bulky DNA adducts in which large chemical groups are linked to bases in the DNA. Damage like pyrimidine dimers, 6-4PPs or chemical adducts can physically distort the DNA helix, causing DNA and RNA polymerase to stall when they attempt to copy those regions of DNA (Figure 7.40).

Chemical reactions occurring within cells can cause cytosines in DNA to be deaminated to uracil. Other sorts of damage in this category include the formation of oxidized bases like 8-oxo-guanine or alkylated bases like O^6-methylguanine. These do not actually change the physical structure of the DNA helix, but they can cause problems because uracil and 8-oxo-guanine pair with different bases than the original cytosine or guanine, leading to mutations on the next round of replication. O^6-methylguanine similarly can form base pairs with thymine instead of cytosine.

Removing damage

Cells have several ways to remove the sorts of damage described above. The first of these is described as direct reversal. Many organisms (though, unfortunately for us, not humans) can repair UV damage like CPDs and 6-4PPs

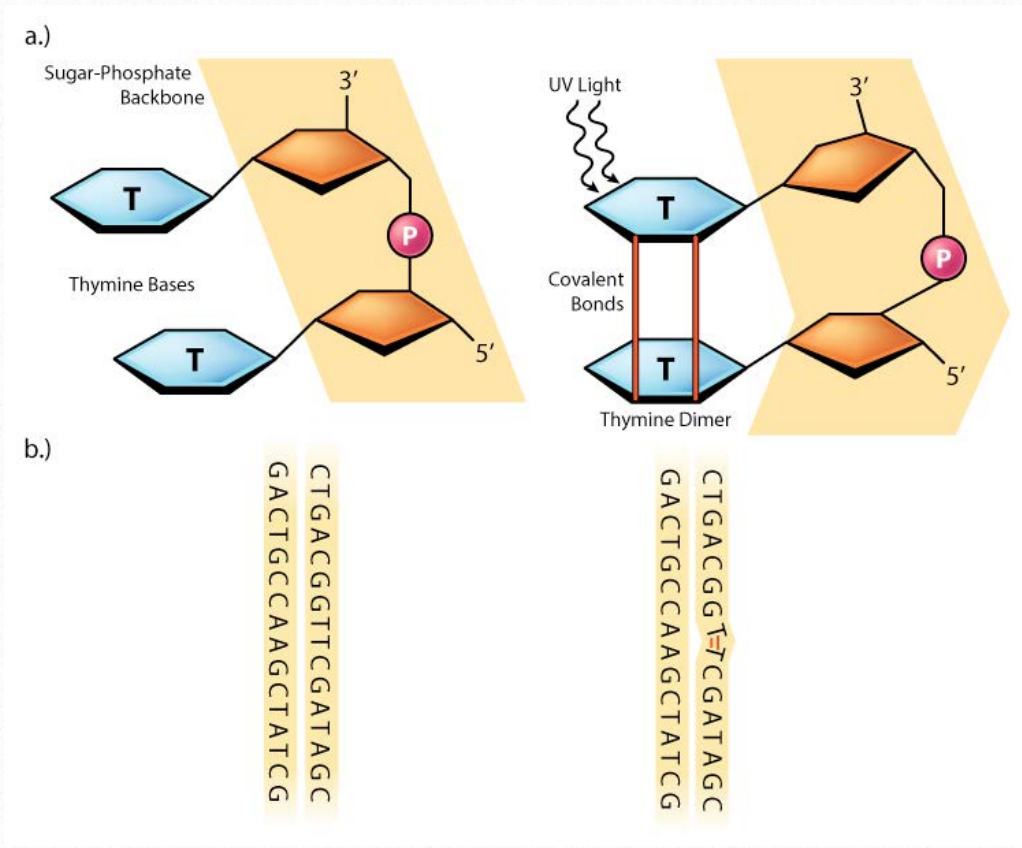

Figure 7.40- Thymine dimers distort the DNA helix

Aleia Kim

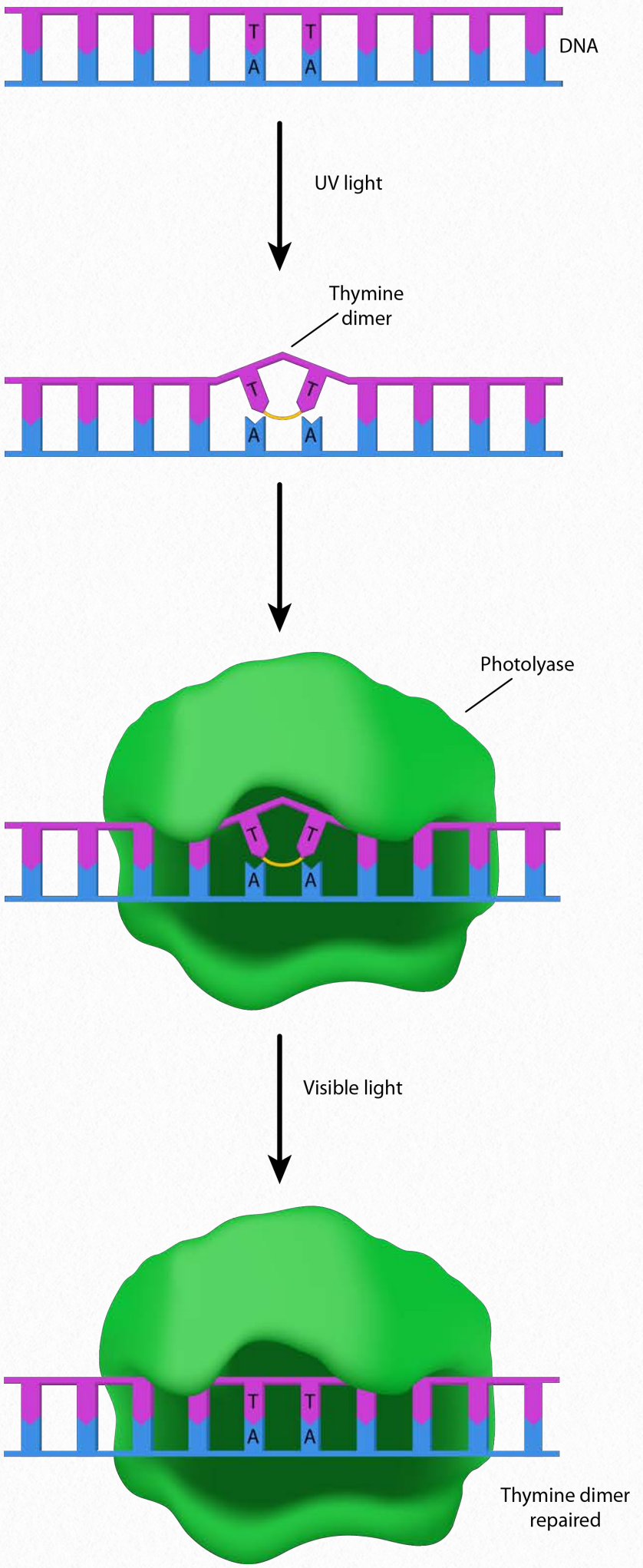

Figure 7.41- Direct repair of thymine dimers by photolyase

Pehr Jacobsen

because they possess enzymes called photolyases (photo=light; lyase=breakdown enzyme - Figure 7.41). Photolyases work through a process called photoreactivation, and use blue light energy to catalyze a photochemical reaction that breaks the aberrant bonds in the damaged DNA and returns the DNA to its original state.

Suicide enzyme

O^6-methylguanine in DNA can also be removed by direct reversal, with the help of the enzyme O^6-methylguanine methyltransferase. This is a very unusual enzyme that removes the methyl group from the guanine and transfers it onto a cysteine residue in the enzyme. The addition of the methyl group to the cysteine renders the enzyme non-functional.

As you know, most enzymes are catalysts that remain unchanged over the course of the reaction, permitting a single enzyme molecule to repeatedly catalyze a reaction. Because the O^6-methylguanine methyltransferase does not fit this description, it is sometimes not regarded as a true enzyme. It has also been called a suicide enzyme, because the enzyme “dies” as a result of its own activity.

Excision repair

Excision repair is another common strategy. Excision repair is a general term for the cutting out and re-synthesizing of the damaged region of a DNA. There are several different

kinds of excision repair, but they all involve excising the portion of the DNA that is damaged, followed by repair synthesis using the other strand as template, and finally, ligation to restore continuity to the repaired strand. Cells possess several different kinds of excision repair, each geared to specific kinds of DNA damage. Between them, these repair systems deal with the wide variety of insults to the genome.

Nucleotide excision repair

Nucleotide excision repair (NER) fixes damage such as the formation of chemical adducts, as well as UV damage. Both chemical adducts and the formation of CPDs or 6,4 photoproducts can cause significant distortion of the DNA helix. NER proteins act to cut the damaged strand on either side of the lesion. A short portion of the DNA strand containing the damage is then removed and a DNA polymerase fills in the gap with the appropriate nucleotides. Nucleotide excision repair has been extensively studied in bacteria.

In *E. coli*, recognition and excision of the damage is carried out by a group of proteins encoded by the uvrABC and uvrD genes. The protein products of the uvrA, uvrB and uvrC genes function together as the so-called UvrABC excinuclease. The damage is initially recognized and bound by a complex of the UvrA and UvrB proteins. Once the complex is bound, the UvrA dissociates, leaving the UvrB attached to the

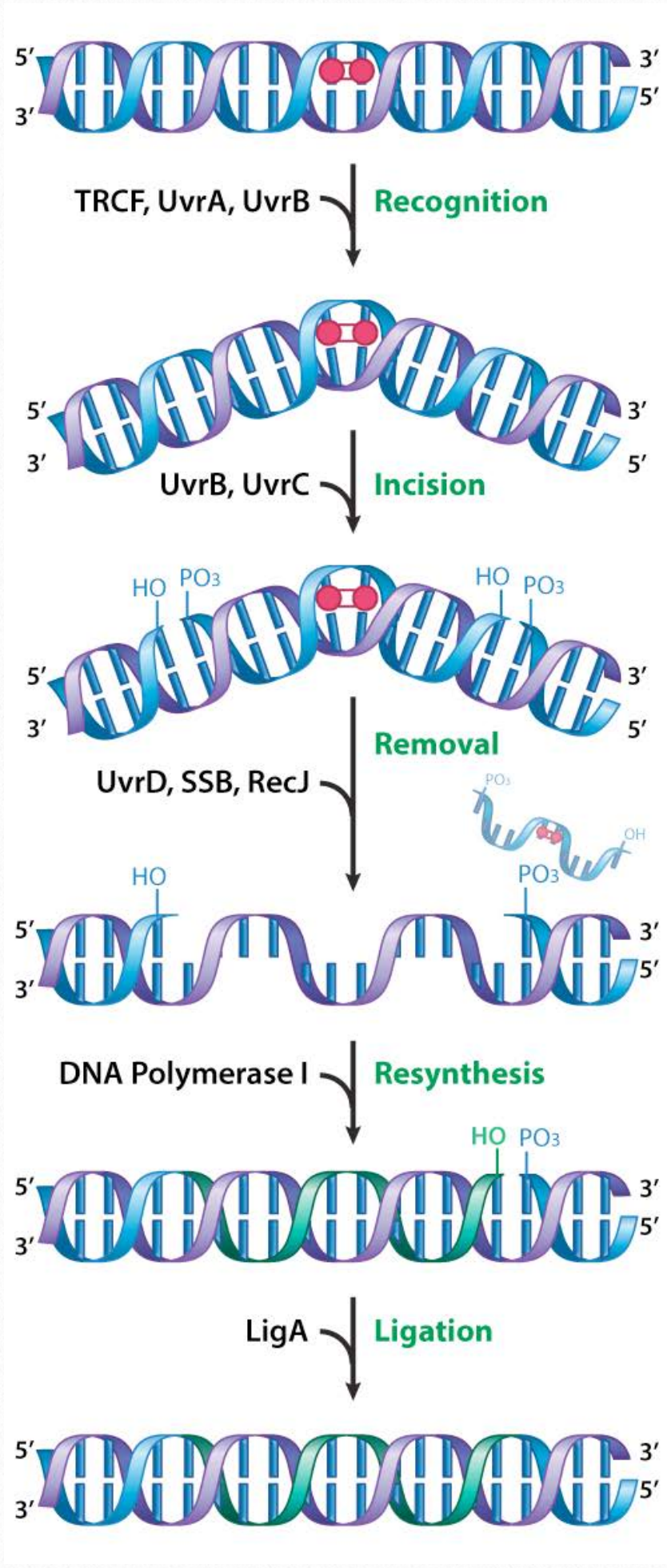

Figure 7.42 - Nucleotide excision repair
Aleia Kim

DNA, where it is then joined by the UvrC protein.

Strand nicking

It is the complex consisting of UvrB and C that acts to cut the phosphodiester backbone on either side of the damage, creating nicks in the strand about 12-13 nucleotides apart. A helicase encoded by uvrD then unwinds the region containing the damage, displacing it from the double helix together with UvrBC. The gap in the DNA is filled in by DNA polymerase, which copies the undamaged strand, and the nick is sealed with the help of DNA ligase.

Nucleotide excision repair is also an important pathway in eukaryotes. It is particularly important in the removal of UV damage in humans, given that we lack photolyases. A number of proteins have been identified that function in ways similar to the Uvr proteins.

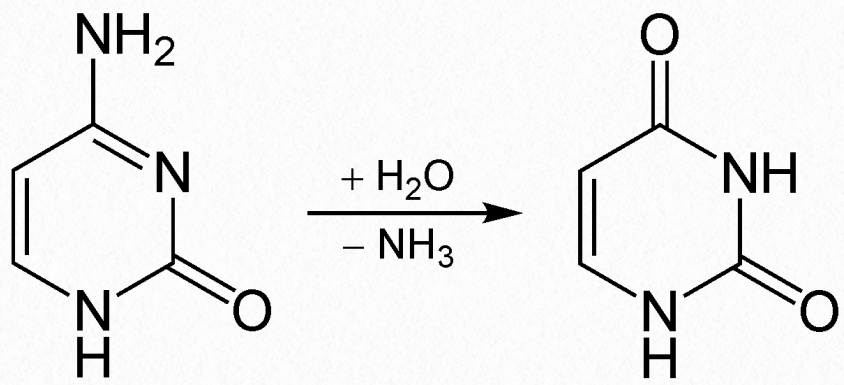

Figure 7.43 - Spontaneous hydrolysis of cytosine to form uracil

The importance of these proteins is evident from the fact that mutations in the genes that encode them can lead to a number of genetic diseases, like Xeroderma pigmentosum, or XP. People with XP are extremely sensitive to UV exposure, because the damage caused by it cannot be repaired, leaving them at a much higher risk of developing skin cancer.

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Two repair modes

Nucleotide excision repair operates in two modes, one known as global genomic repair and the other as transcription-coupled repair. While the function of both is to remove helix-destabilizing damage like cyclobutane pyrimidine dimers or chemical adducts, the way in which the lesions are detected differs.

In global genomic repair, damage is identified by surveillance of the entire genome for helix distorting lesions. In the case of transcription-coupled repair, the stalling of the RNA polymerase at a site of DNA damage is the indicator that activates this mode of nucleotide excision repair.

Base excision repair

Base excision repair (BER) is a repair mechanism that deals with situations like the deamination of cytosine to uracil (Figure 7.43) or the methylation of a purine base. These changes do not typically distort

the structure of the DNA helix, unlike chemical adducts or UV damage.

In base excision repair a single damaged base is first removed from the DNA, followed by removal of a region of the DNA surrounding the missing base. The gap is then repaired.

Uracil-DNA glycosylase

The removal of uracil from DNA is accomplished by the enzyme uracil-DNA glycosylase that can recognize uracil in DNA and break the glycosidic bond between the uracil and the sugar in the nucleotide (Figure 7.44). The removal of the base leaves a gap called an apyrimidinic site (AP site) because, in this case, uracil, a pyrimidine was removed. It is important to remember that at this point the backbone of the DNA is still intact, and the removal of a single base simply creates a gap like a tooth that has been knocked out.

The formation of the AP site triggers the activity of an enzyme known as an AP endonuclease that cuts the DNA backbone 5' to the AP site. In the remaining steps, a DNA polymerase binds to the nick, then using its exonuclease and polymerase activities, replaces the sequence in this region. Depending on the situation, a single nucleotide may be replaced (short patch BER) or a stretch of several nucleotides may be removed and replaced (long patch BER). Finally, as always, DNA ligase acts to seal the nick in the DNA.

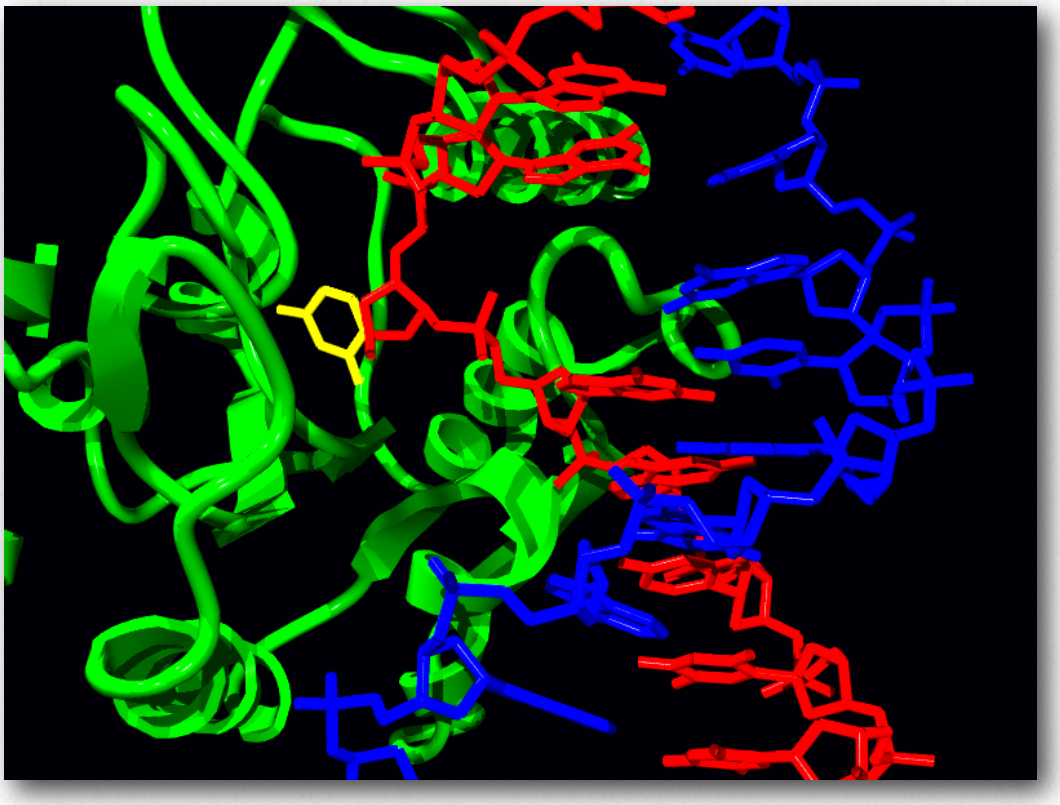

Figure 7.44 - Base excision repair by uracil-DNA glycosylase. The yellow uracil base has been "flipped" out of the DNA helix for excision

Repair of double-strand breaks

While all the repair mechanisms discussed so far fixed damage on one strand of DNA using the other, undamaged strand as a template, these mechanisms cannot repair damage to both strands. What happens if both strands are damaged? Ionizing radiation, exposure to certain chemicals, or reactive oxygen species generated in the cell can lead to double-strand breaks (DSBs) in DNA.

DSBs are a potentially lethal form of damage that, in addition to blocking replication and transcription,

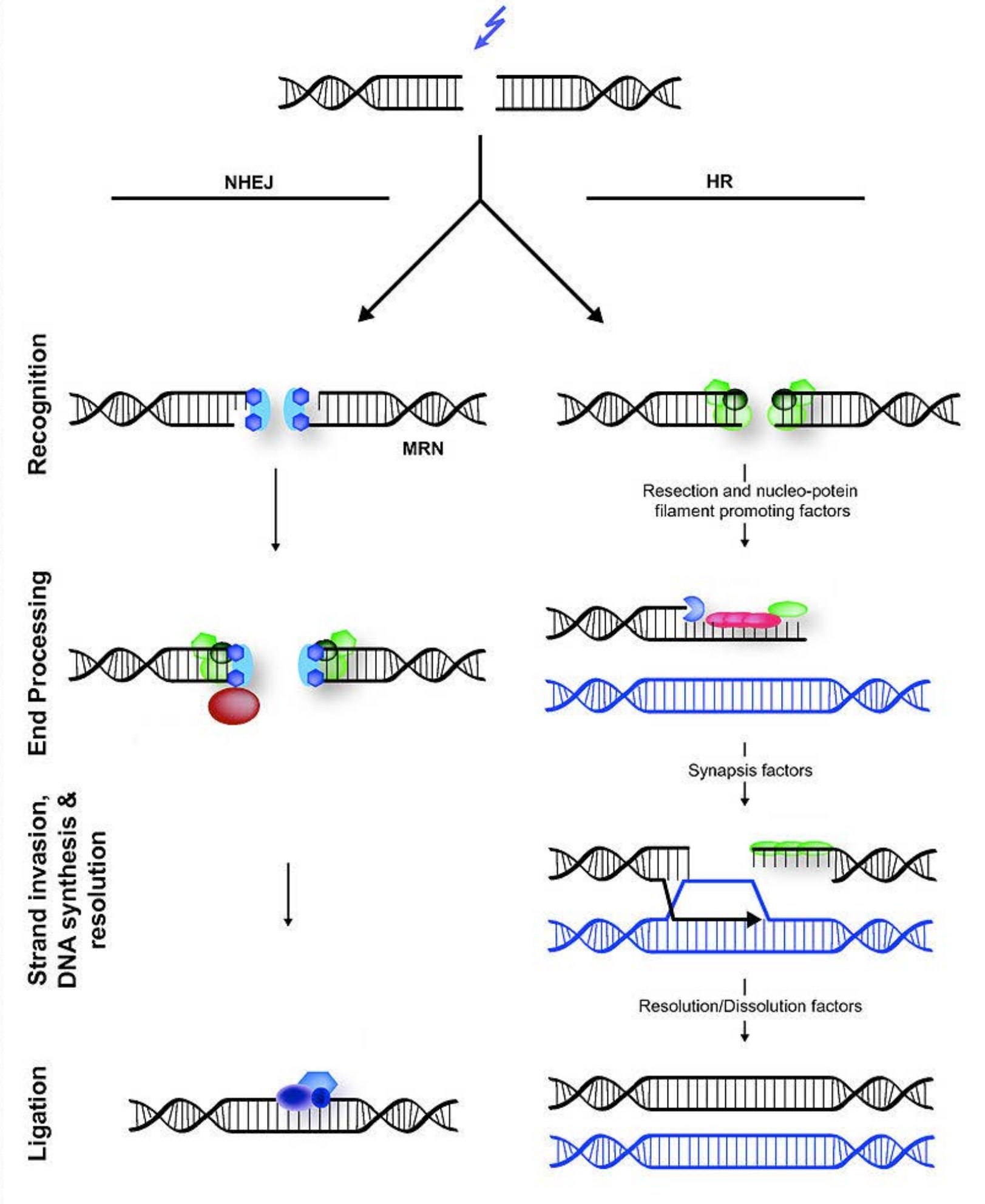

Figure 7.45 - Non-homologous end joining (left) versus homologous recombination (right)

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can also lead to chromosomal translocations, where part of one chromosome gets attached to a piece of another chromosome.

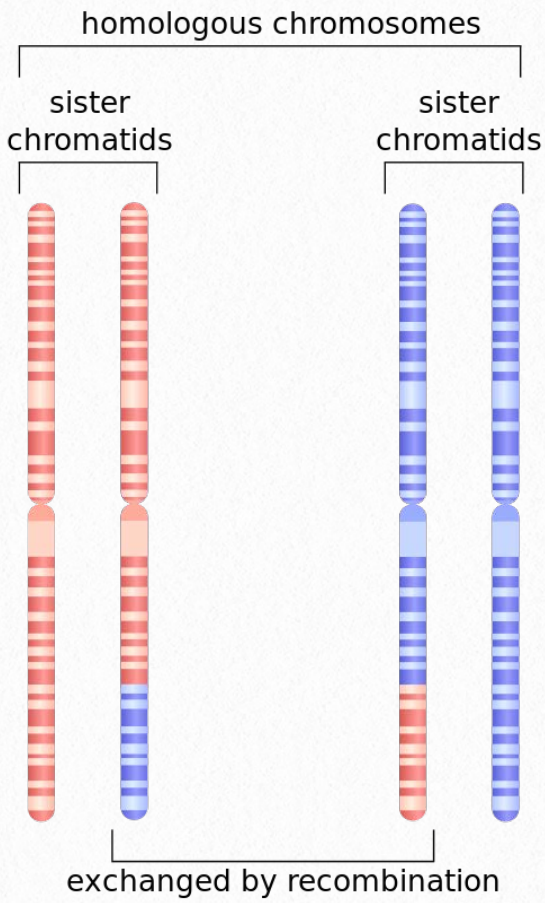

Figure 7.46 - Result of homologous recombination

Wikipedia

Two different cellular mechanisms exist that help repair DSBs (Figure 7.45), homologous recombination (HR) and non-homologous end joining (NHEJ).

Homologous recombination repair commonly occurs in the late S and G_2 phases of the cell, when each chromosome has been replicated and information from a sister chromatid can be used as a template to achieve error-free repair. Note that in contrast to excision repair, where the damaged strand was removed and the undamaged sister strand

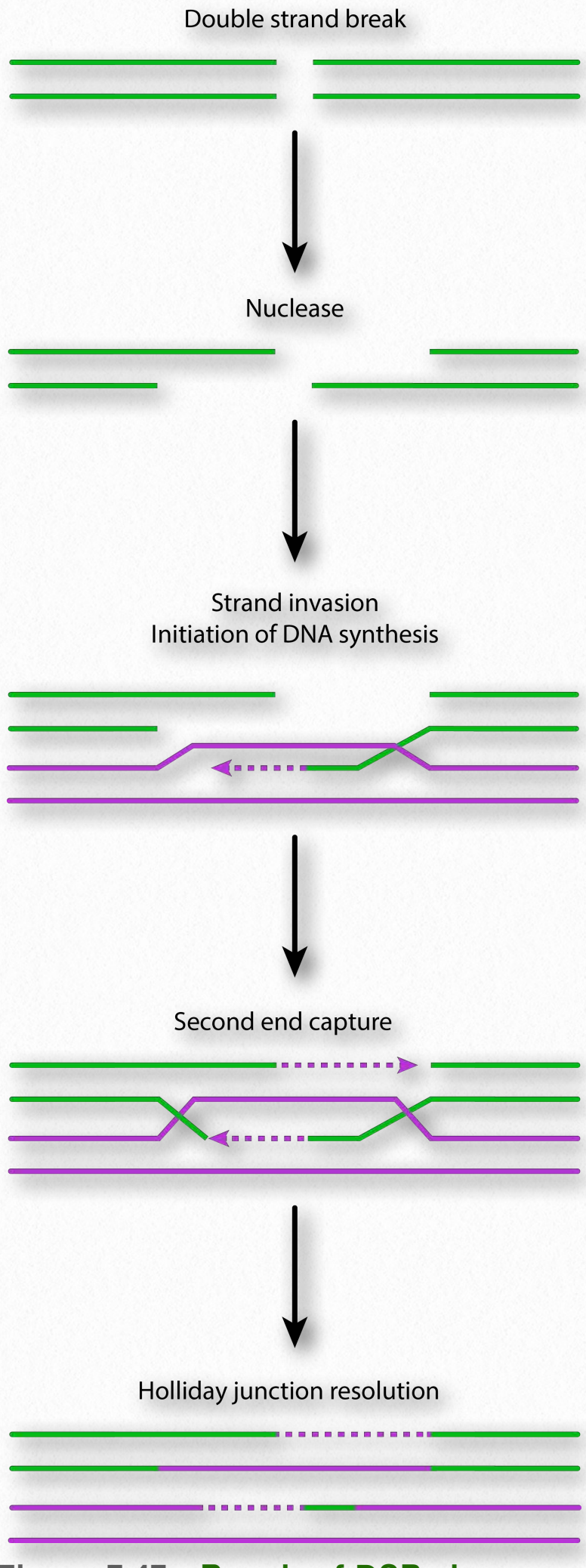

Figure 7.47 - Repair of DSBs by homologous recombination

Image by Pehr Jacobson

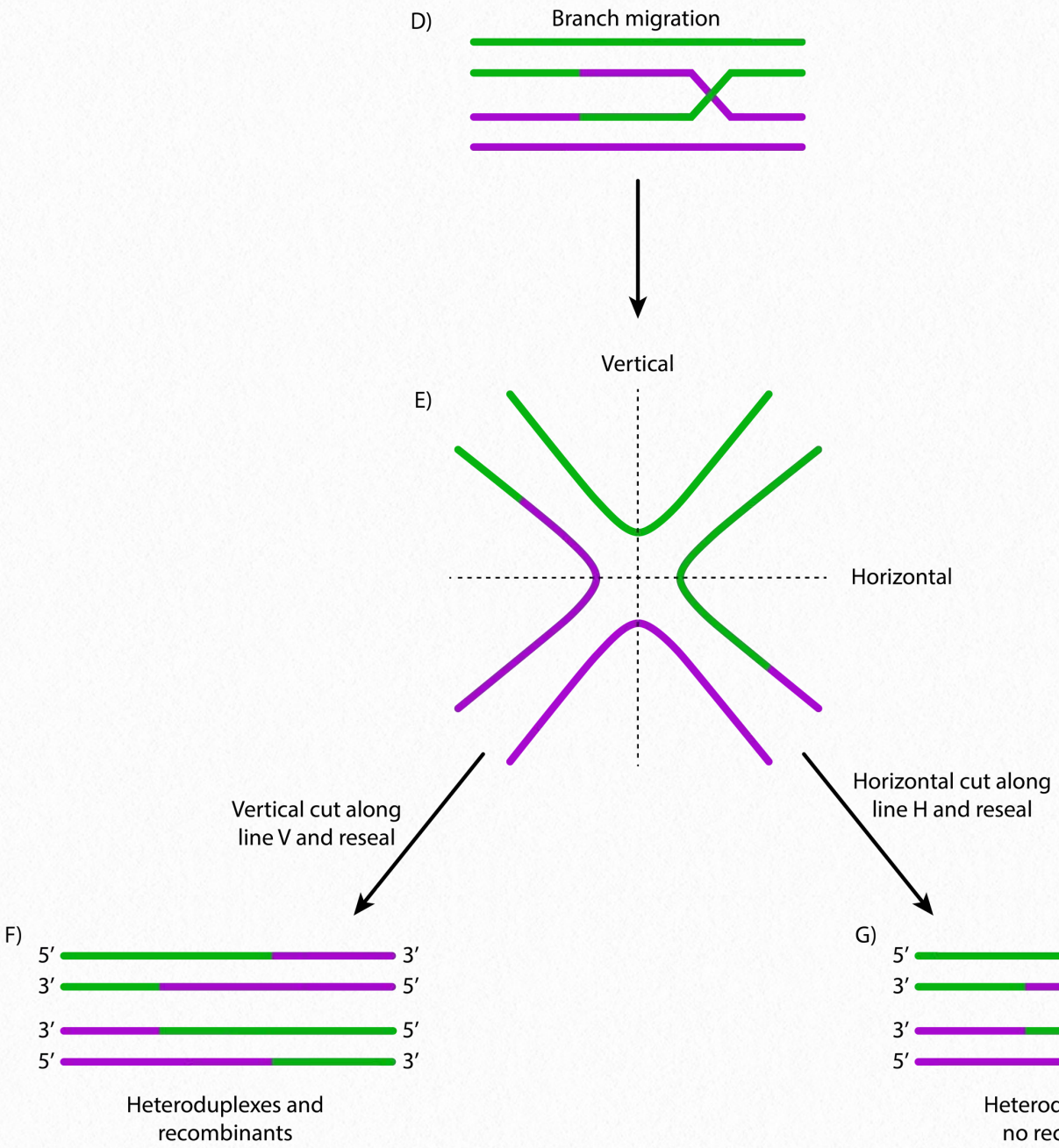

Figure 7.48 - Resolution of Holliday Junctions

Image by Pehr Jacobsen

served as the template for filling in the damaged region, HR must use the information from another DNA molecule, because both strands of the DNA are damaged in DSBs.

Nuclease action

Detection of the double-strand break triggers nuclease activity that chews back one strand on each end of the break. This results in the production of single-stranded 3' overhangs on each end. These single-stranded ends are bound by several proteins, creating a nucleoprotein filament that can then "search" for homologous (matching) sequences on a sister chromatid.

When such sequences are found, the nucleoprotein filament invades the undamaged sister chromatid, forming a crossover. This creates heteroduplexes made up of DNA strands from different chromatids. Strand invasion (Figure 7.47) is followed by branch migra-

tion, during which the Holliday junction moves along the DNA, extending the heteroduplex away from the original site of the crossover (Figure 7.48). In *E. coli*, branch migration depends on the activity of two proteins, RuvA and RuvB. The resulting recombination intermediate can be resolved, with the help of RuvC to give complete, error-free strands.

Non-homologous end joining

In contrast to homologous recombination, Non-homologous end joining (NHEJ) is error-prone. It does not use or require a homologous template to copy, and works by simply chewing back the broken ends of DSBs and ligating them together. Not surprisingly, NHEJ introduces deletions in the DNA as a result.

Translesion DNA synthesis

As we have seen, cells have a variety of mechanisms to help safeguard the integrity of the information in DNA. One measure of last resort is translesion DNA synthesis, also known as bypass synthesis. Translesion synthesis occurs when a DNA polymerase encounters DNA damage on the template strand, but instead of stalling or skipping past the damage, replication switches to an error-prone mode, ignoring the template and incorporating random nucleotides into the new strand. In *E.coli*, translesion synthesis is dependent on the activities of proteins encoded by the umuC and umuD genes. Under the appropriate conditions (see SOS response, below) UmuC and UmuD are activated to begin bypass synthesis. Being error-prone, translesion synthesis gives rise to many mutations.

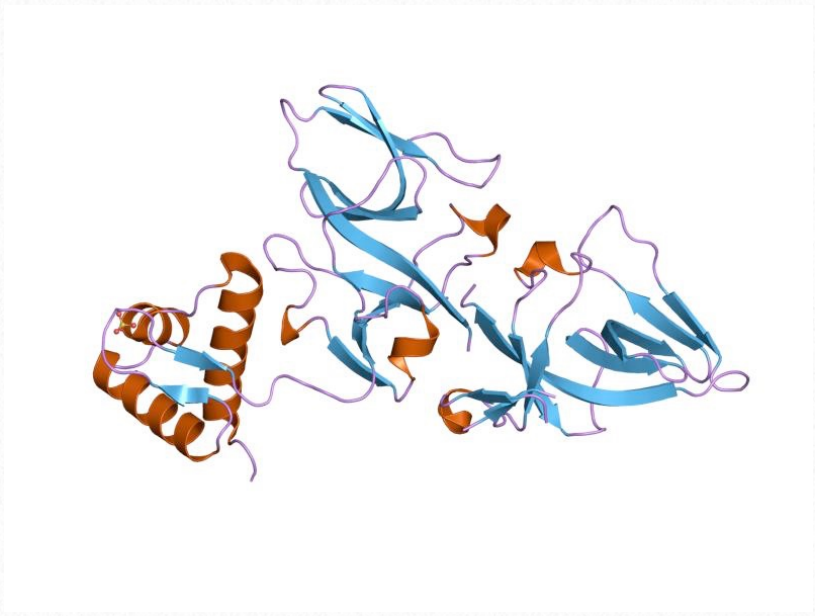

Figure 7.49 -Lex A repressor, N-terminal domain

The SOS response

Named for standard SOS distress signals, the term "SOS repair" refers to a cellular response to UV damage. When bacterial cells suffer extensive damage to their DNA as a result of UV exposure, they turn on the coordinated expression of a large number of genes that are necessary for DNA repair. These include the uvr genes needed for nucleotide excision repair and recA, which is involved in homologous recombination. In addition to these mechanisms, which can carry out error-free repair, the SOS response can also induce the expression of translesion polymerases encoded by the dinA, dinB and umuCD genes.

How are all these genes induced in a coordi-

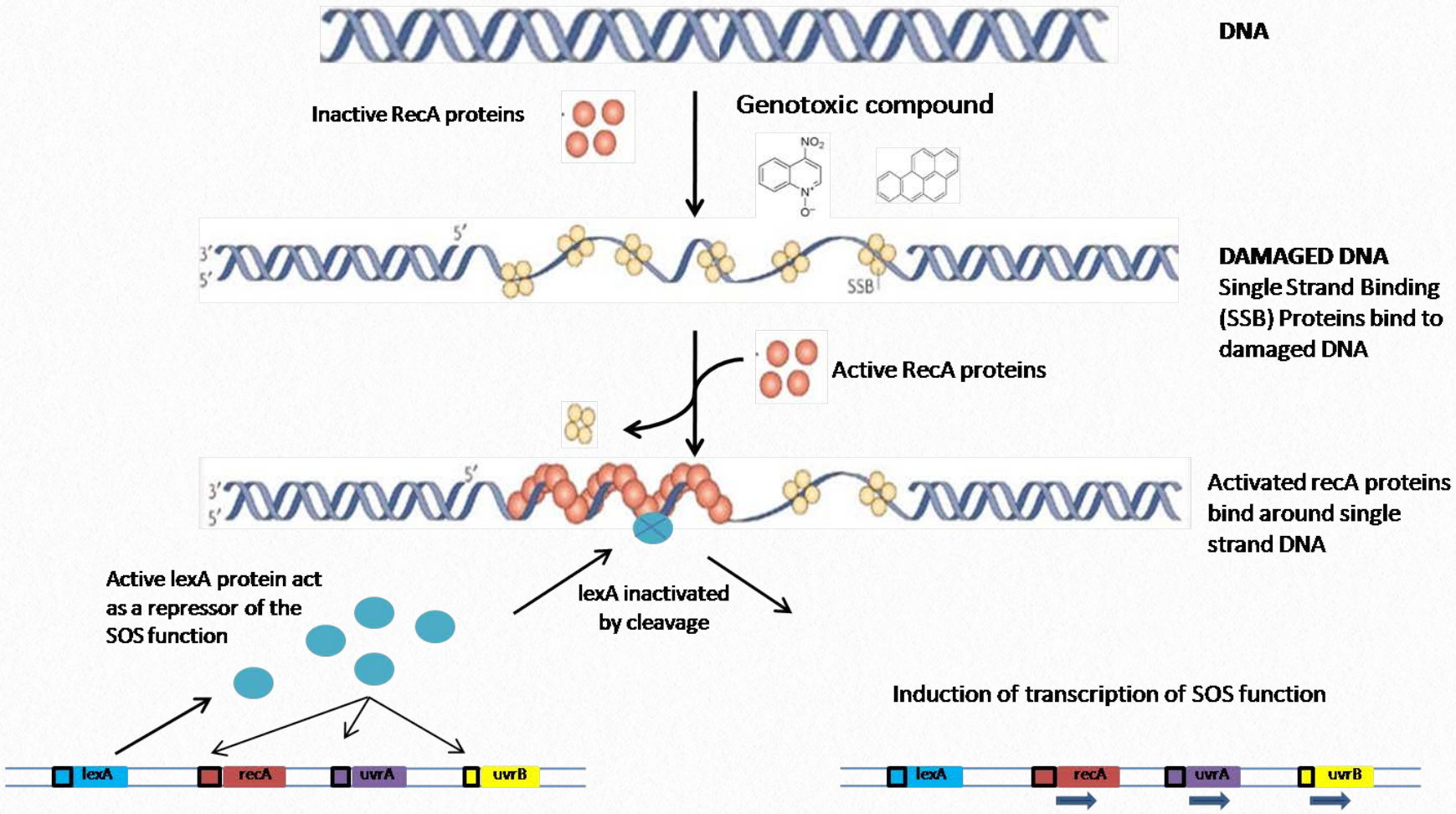

Figure 7.50 - Activation of SOS genes by lexA in *E. coli*

nated way following UV damage? All of the genes induced in the SOS response are regulated by two components. The first is the presence of a short DNA sequence upstream of their coding region, called the SOS box. The second is a protein, the LexA repressor (Figure 7.49), that binds to the SOS box and prevents transcription of the downstream genes. Expression of the genes requires the removal of LexA from its binding site. How is this achieved?

When exposure to radiation results in DNA breaks, the presence of single-stranded regions triggers the activation and binding of RecA proteins to the single-stranded region, creating a nucleoprotein filament. The interaction of the RecA with the LexA repressor leads to autocleavage of the repressor, allowing the downstream gene(s) to be expressed (Figure 7.50).

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The genes controlled by the LexA repressor, as mentioned earlier, encode proteins that are necessary for accurate DNA repair as well as error-prone translesion synthesis. The various genes involved in DNA repair are induced in a specific order. In the initial stages, the repair genes that are derepressed are for nucleotide excision repair, followed by homologous recombination, both error-free mechanisms for repair. If the damage is too

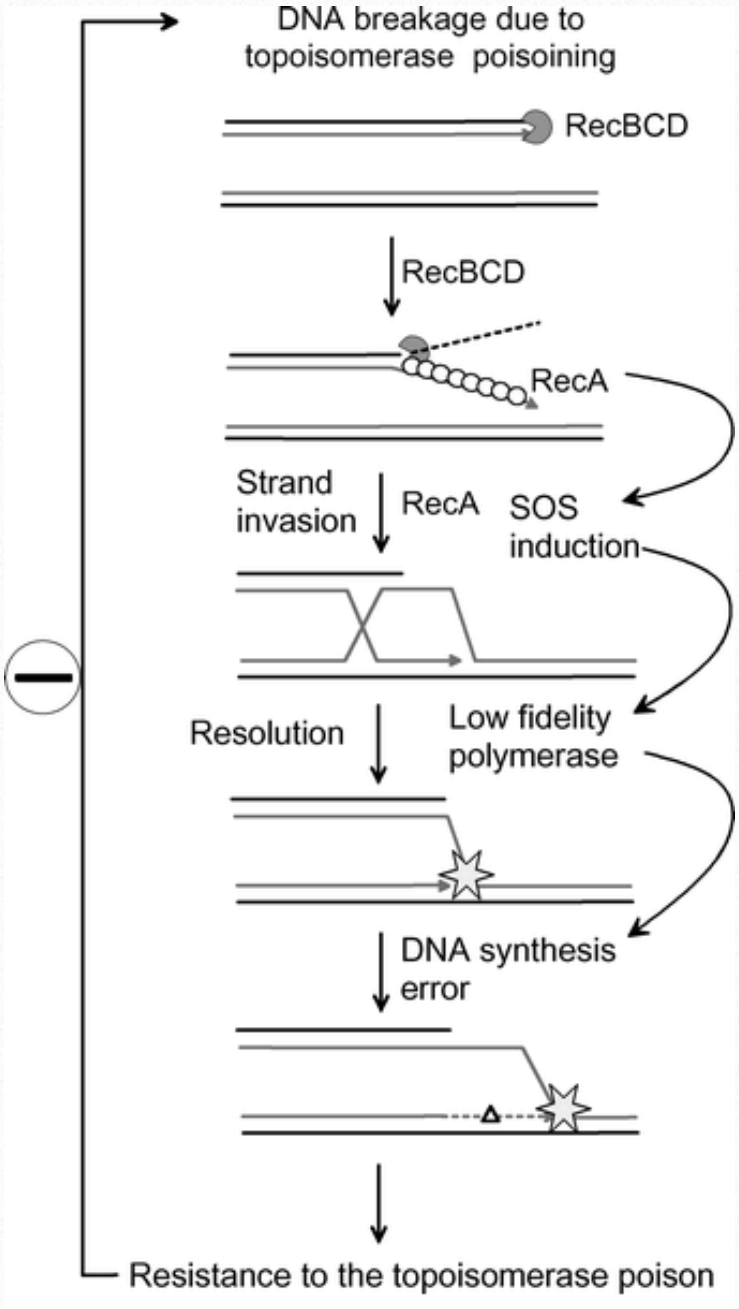

Figure 7.51 - A proposed mechanism of evolved bacterial antibiotic resistance

Wikipedia

extensive to be repaired by these systems, error-prone repair mechanisms may be brought into play as a last resort.

SOS response and antibiotic resistance

The increased mutation rate in the SOS response may play a role in the acquisition of antibiotic resistance in bacteria (Figure 7.51).

An example is the development of resistance to topoisomerase poisons like the fluoroquinolone family of drugs. Fluoroquinolones inhibit the ability of topoisomerases to religate the ends of their substrates after nicking them to allow overwound DNA to relax. This results in accumulation of strand breaks that can trigger the SOS response. As a consequence of error-prone DNA synthesis by low fidelity polymerases during the SOS response, there is a large increase in the number of mutations. While some mutations may be lethal to the bacteria, others can contribute to the rapid development of drug resistance in the population.

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Mismatch Site

To the tune of "*Silent Night*"

Metabolic Melodies Website HERE

Mismatch site. Bases might
Mutate here. Code re-write
Evolution is moving along
Happ'ning as I am singing this song
Viruses changing you see - ee
Flu bugs evolving in me

Screening tonight. Blue from white
Beta-gal. Get it right
Plasmid insertions that I create
Help me study the mutation rate
DNA changes I see
Show evolution to me

Lyrics by Kevin Ahern

No Recording Yet For This Song

Information Processing: Transcription

In the preceding sections, we have discussed the replication of the cell's DNA and the mechanisms by which the integrity of the genetic information is carefully maintained. What do cells do with this information? How does the sequence in DNA control what happens in a cell? If DNA is a giant instruction book containing all of the cell's "knowledge" that is copied and passed down from generation to generation, what are the instructions for? And how do cells use these instructions to make what they need?

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Information flow

You have learned in introductory biology courses that genes, which are instructions for making proteins, are made of DNA. You also know that information in genes is copied into temporary instructions called messenger RNAs that direct the synthesis of specific proteins. This description of flow of information from DNA to RNA to protein is often called the central dogma of molecular biology and is a good starting point for

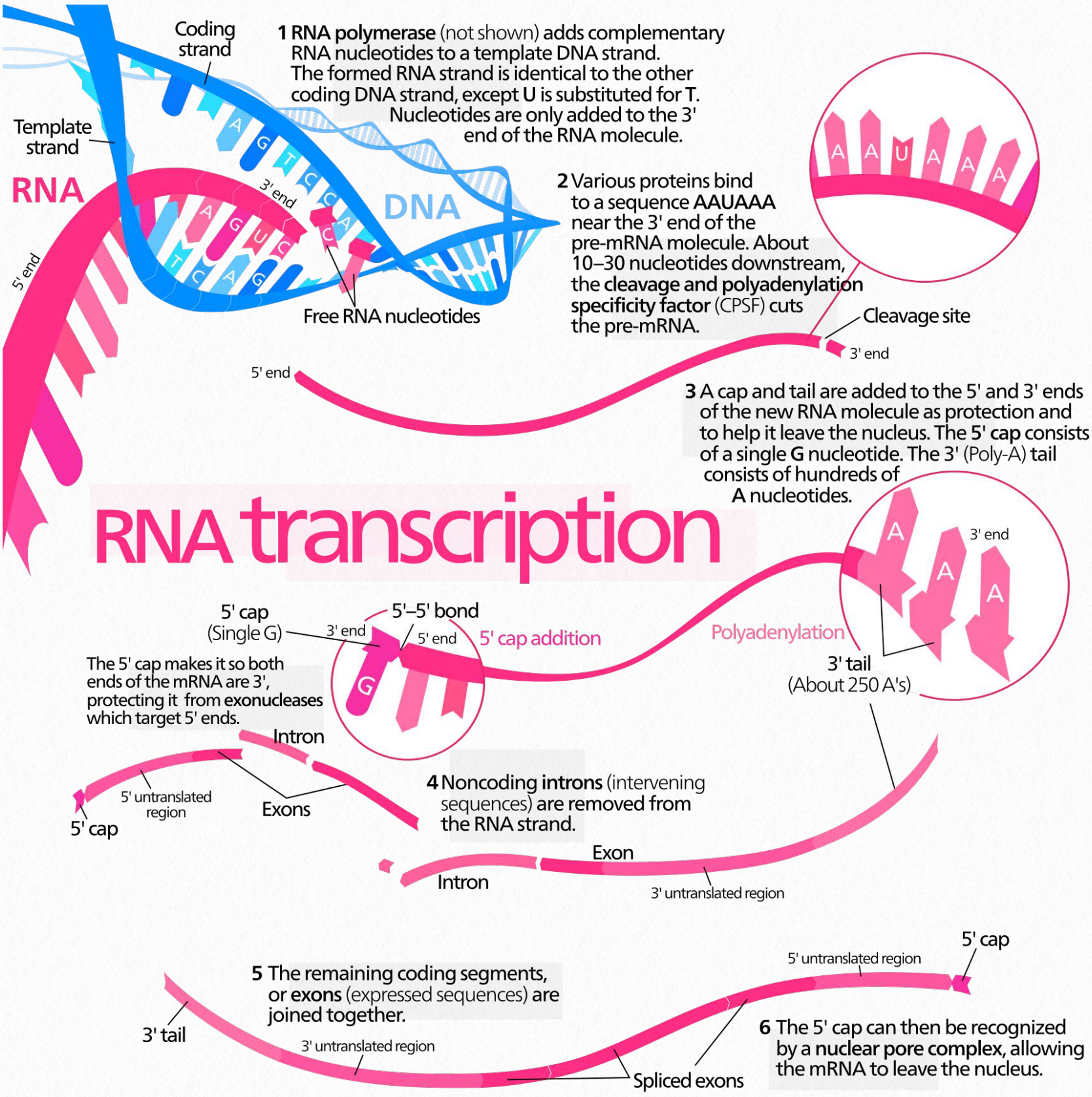

Figure 7.52 - Overview of eukaryotic transcription

Wikipedia

an examination of how cells use the information in DNA.

Consider that all of the cells in a multicellular organism have arisen by division from a single fertilized egg and therefore, all have the same DNA. Division of that original fertilized egg produces, in the case of humans, over a trillion cells, by the time a baby is produced from that egg (that's a lot of DNA replica-

tion!). Yet, we also know that a baby is not a giant ball of a trillion identical cells, but has the many different kinds of cells that make up tissues like skin and muscle and bone and nerves. How did cells that have identical DNA turn out so different?

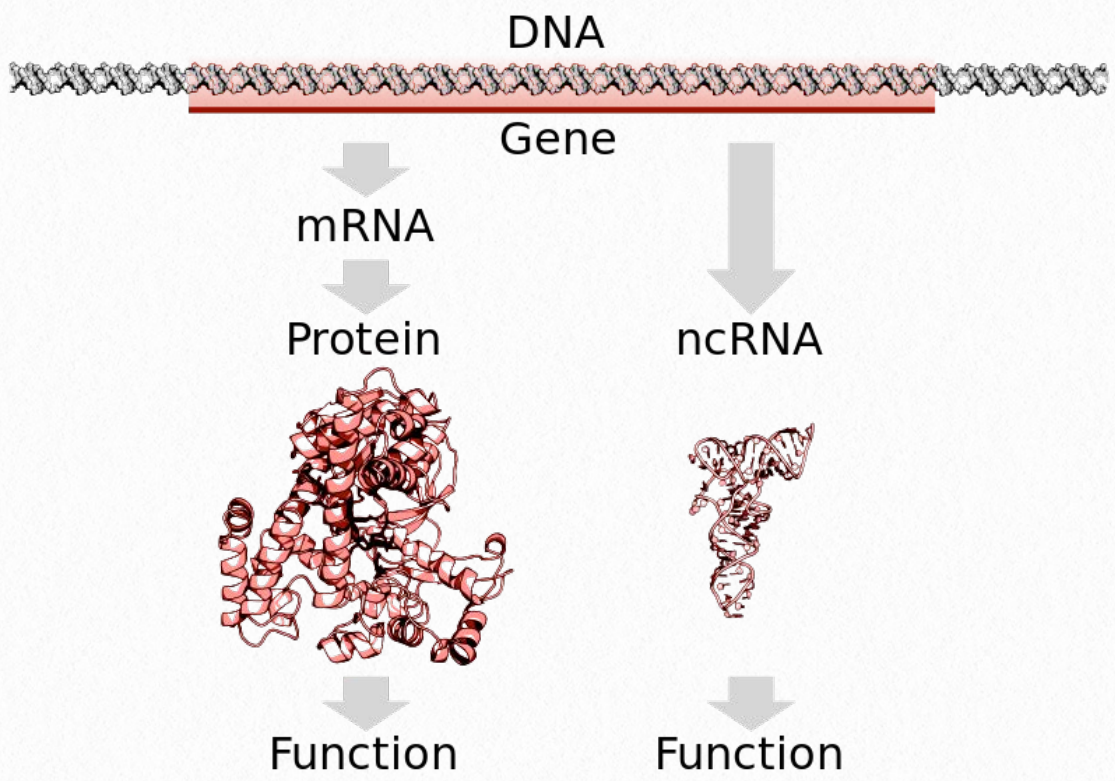

Figure 7.53 - Transcripts may code for protein or may be functional as RNAs

Wikipedia

The answer lies in gene expression, which is the process by which the information in DNA is used. Although all the cells in a baby have the same DNA, each different cell type uses a different subset of the genes in that DNA to direct the synthesis of a distinctive set of RNAs and proteins. The first step in gene expression is transcription, which we will examine next (Figure 7.52).

Transcription

Transcription is the process of copying information from DNA sequences into RNA sequences. This process is also known as DNA-dependent RNA synthesis. When a sequence of DNA is transcribed, only one of the two DNA strands is copied into RNA. We will consider what determines which strand of DNA is copied into RNA, later on.

But, apart from copying one, rather than both strands of DNA, how is transcription different from replication of DNA? DNA replication serves to copy all the genetic material of the cell and occurs before a cell divides, so that a full copy of the cell's genetic information can be passed on to the daughter cell. Transcription, by contrast, copies short stretches of the coding regions of DNA to make RNA. Different genes may be copied into RNA at different times in the cell's life cycle. RNAs are, essentially, temporary copies of the information in DNA and different sets of instructions are copied for use at different times and in different cell types.

Cells make several different kinds of RNA:

- mRNAs that code for proteins
- rRNAS that form part of ribosomes

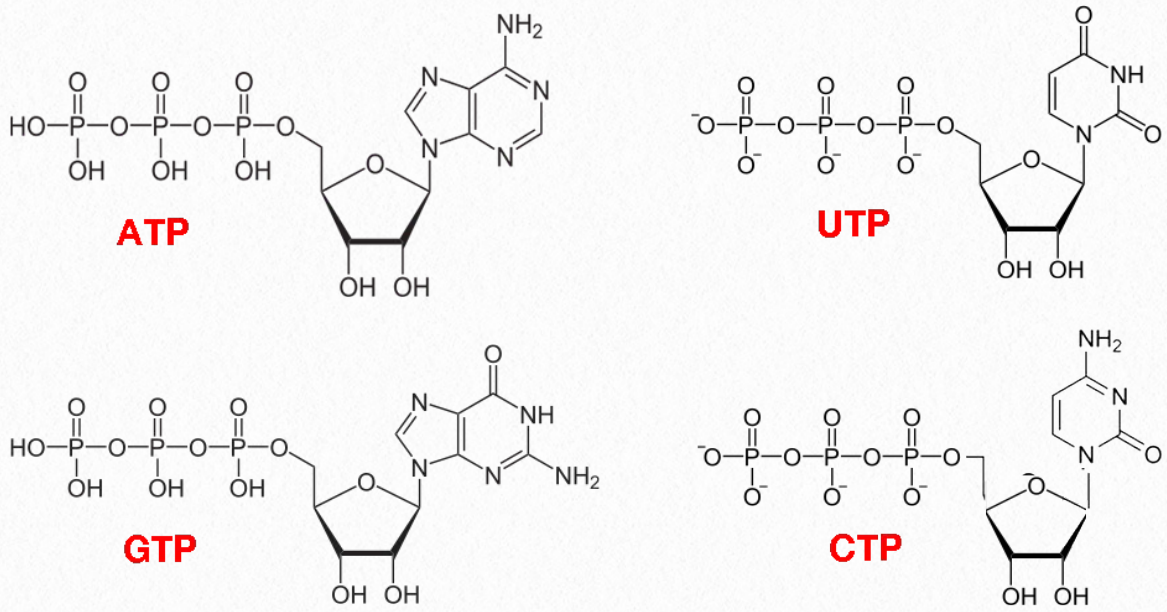

Figure 7.54 - The four ribonucleotides for making RNA

- tRNAs that serve as adaptors between mRNA and amino acids during translation

- Small RNAs that regulate gene expression, including miRNAs and siRNAs

- Other small RNAs that have a variety of functions, including the small nuclear RNAs that are part of the splicing machinery.

- Long noncoding RNAs (lnc RNAs - Figure 7.53)

Building an RNA strand is very similar to building a DNA strand. This is not surprising, knowing that DNA and RNA are very similar molecules. Transcription is catalyzed by the enzyme RNA Polymerase. "RNA polymerase" is a general term for an enzyme that makes RNA. There are several different kinds of RNA polymerases in eukaryotic cells, while in prokaryotes, a single type of RNA polymerase is responsible for all transcription.

RNA synthesis

Like DNA polymerases, RNA polymerases synthesize new strands only in the 5' to 3' direction, but because they are making RNA, they use ribonucleotides (i.e., RNA nucleotides - Figure 7.54) rather than deoxyribonucleotides. Ribonucleotides are joined in exactly the same way as deoxyribonucleotides, i.e., the 3'OH of the last nucleotide on the growing chain is joined to the 5' phosphate on

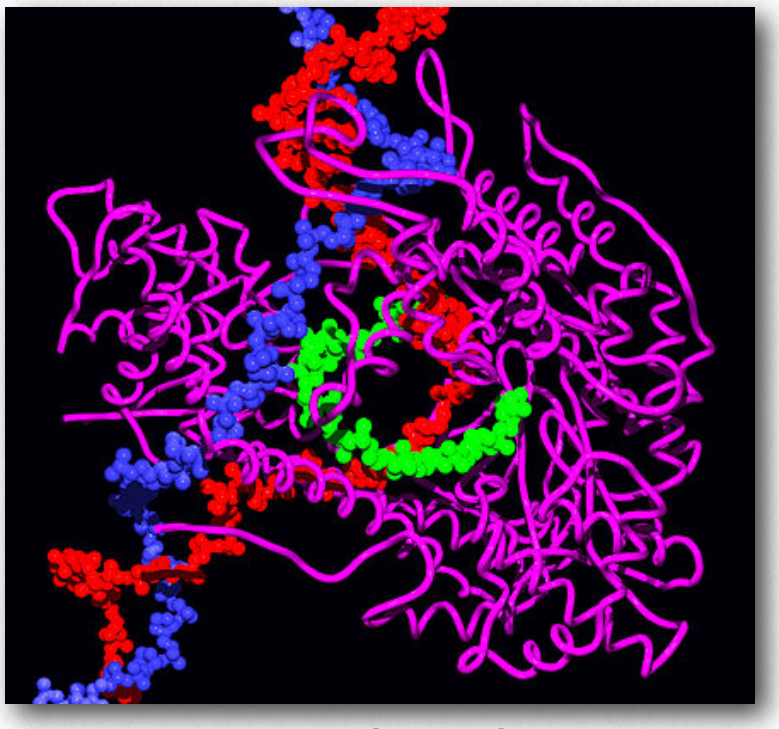

Figure 7.55 - RNA (green) being synthesized from DNA template (blue strand) by T7 RNA polymerase (purple). The non-template DNA strand is in red.

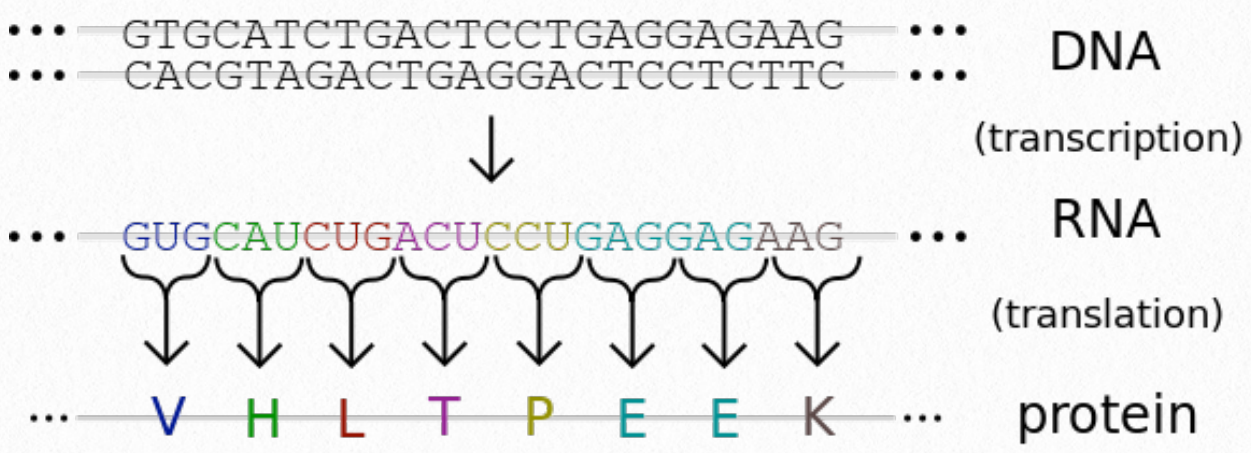

Figure 7.56 - Central dogma - DNA to RNA to protein Wikipedia

the incoming nucleotide to make a phosphodiester bond.

One important difference between DNA polymerases and RNA polymerases is that the latter do not require a primer to start making RNA. Once RNA polymerases are in the right place to start copying DNA, they just begin making RNA by joining together RNA nucleotides complementary to the DNA template.

Starting points

This, of course, brings us to an obvious question- how do RNA polymerases "know" where to start copying on the DNA?

Unlike the situation in replication, where every nucleotide of the parental DNA must eventually be copied, transcription, as we have already noted, only copies selected portions of the DNA into RNA at any given time. Consider the challenge here: in a human cell, there are approximately 6 billion base-pairs of DNA. Much of this is non-coding DNA, meaning that it will not need to be transcribed. The small percentage of the genome that is made up of coding sequences still amounts to between 20,000 and 30,000 genes in each cell. Of these genes, only a small number will need to be expressed at any given time.What indicates to an RNA polymerase where to start copying DNA to make a transcript?

Promoters

It turns out that patterns in the DNA sequence indicate where RNA polymerase should start and end transcription. These sequences are recognized by the RNA polymerase or by proteins that help RNA polymerase determine where it should bind the DNA to start transcription. A DNA sequence at which the RNA polymerase binds to start transcription is called a promoter. The DNA sequence that indicates the endpoint of transcription, where the RNA polymerase should stop adding nucleotides and dissociate from the template is known as a terminator sequence. The promoter and terminator, thus, bracket the region of the DNA that is to be transcribed.

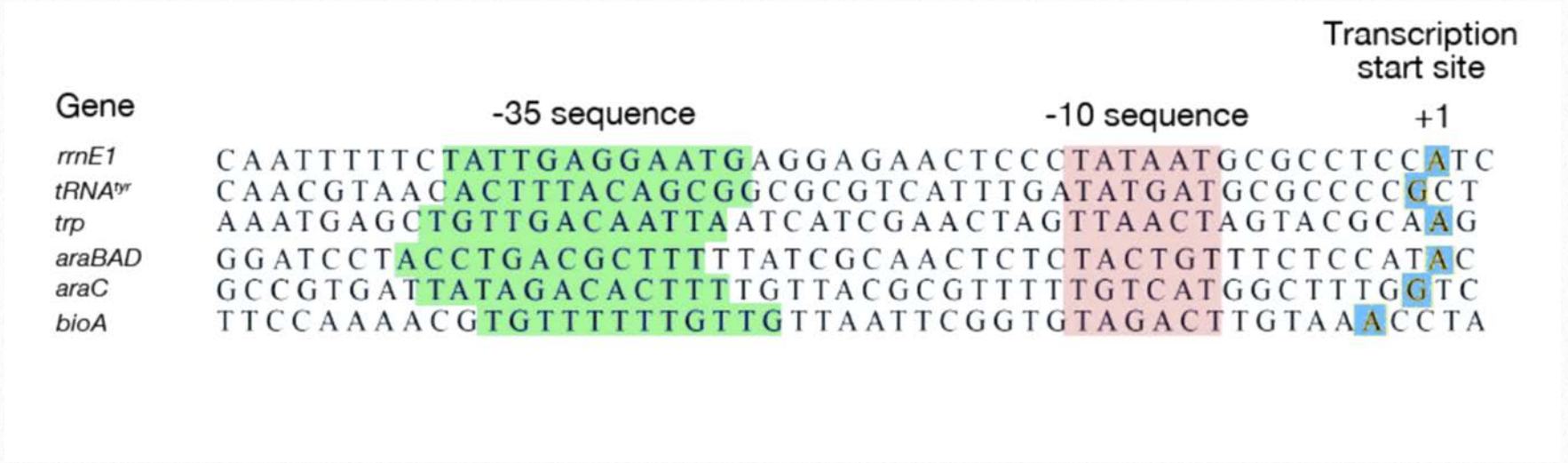

Figure 7.57 - Sequences upstream of transcription start site in several prokaryotic genes

Image by Martha Baker

A promoter is described as being situated upstream of the gene that it controls (Figure 7.57). What this means is that on the DNA strand that the gene is on, the promoter sequence is "before" the gene, or to put it differently, it is on the side of the gene opposite to the direction of transcription. Also notice that the promoter is said to "control" the gene it is associated with. This is because expression of the gene is dependent on the binding of RNA polymerase to the promoter sequence to begin transcription. If the RNA polymerase and its helper proteins do not bind at the promoter, the gene cannot be transcribed and it will therefore, not be expressed.

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What is special about a promoter sequence? In an effort to answer this question, scientists examined many genes and their surrounding sequences (Figure 7.57). Because the same RNA polymerase has to bind to many different promoters, it would be predicted that promoters would have some similarities in their sequences. As expected, common sequence patterns were seen to be present in many promoters.

We will first take a look at prokaryotic promoters.

When prokaryotic genes were examined, the following features commonly emerged:

- A transcription start site (this the base in the DNA across from which the first RNA nucleotide is paired), which, by convention, is denoted as +1.
- A -10 sequence: this is a 6 bp region centered about 10 bp upstream of the start site. The consensus sequence at this position is TATAAT. In other words, if you count back from the transcription start site, the se-

quence found at roughly -10 in the majority of promoters studied is TATAAT.

- A -35 sequence: this is a 6 bp sequence at about 35 basepairs upstream from the start of transcription. The consensus sequence at this position is TTGACA.

-10 Sequence

T	A	T	A	A	T
77%	76%	60%	61%	56%	82%

-35 Sequence

T	T	G	A	C	A
69%	70%	61%	56%	54%	54%

It is important to understand that each nucleotide in a consensus sequence is simply the one that appeared at that position in the majority of promoters examined, and does not mean that the entire consensus sequence is found in all promoters. In fact, few promoters have -10 and -35 sequences that exactly match the consensus. The box at the left shows the -10 and -35 sequences by percentage of occurrence of each base in the promoter.

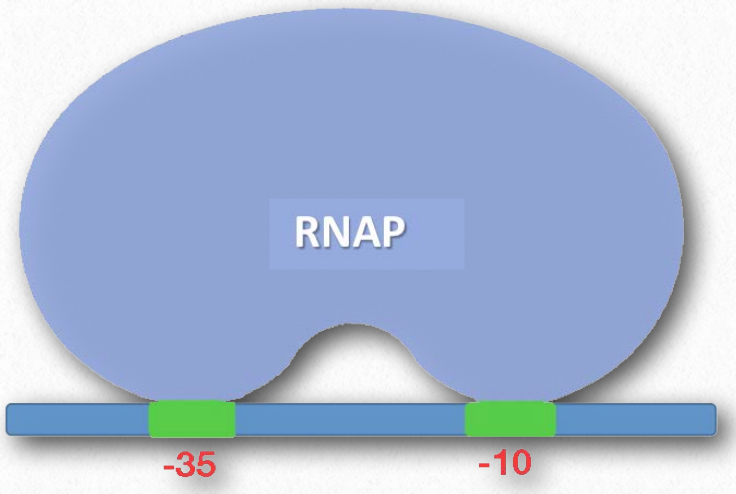

Figure 7.58 - RNA polymerase promoter binding

Wikipedia

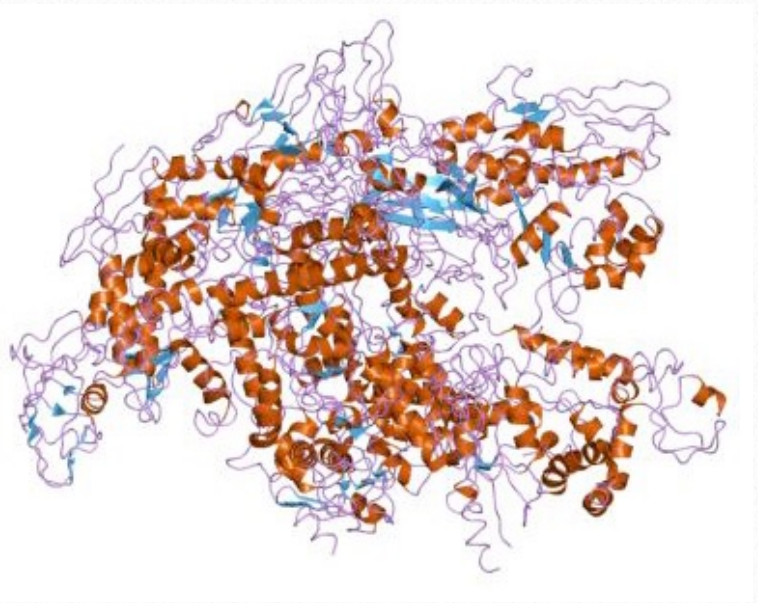

Figure 7.59 - A bacterial RNA polymerase (α2ββ'and ω)

What is the significance of these sequences? It turns out that the sequences at -10 and -35 are necessary for recognition of the promoter region by RNA polymerase (Figure 7.58). The sequences at -10 and -35 may vary a little in individual promoters, as mentioned above, but the extent to which they are different is limited. It is only when the RNA polymerase has stably bound at the promoter that transcription can begin. The process by which the promoter is recognized and bound stably has been well studied for the RNA polymerase of *E. coli*.

Core polymerase and holoenzyme

The *E. coli* RNA polymerase is made up of a core enzyme of five subunits (α2ββ'and ω) and an additional subunit called the σ

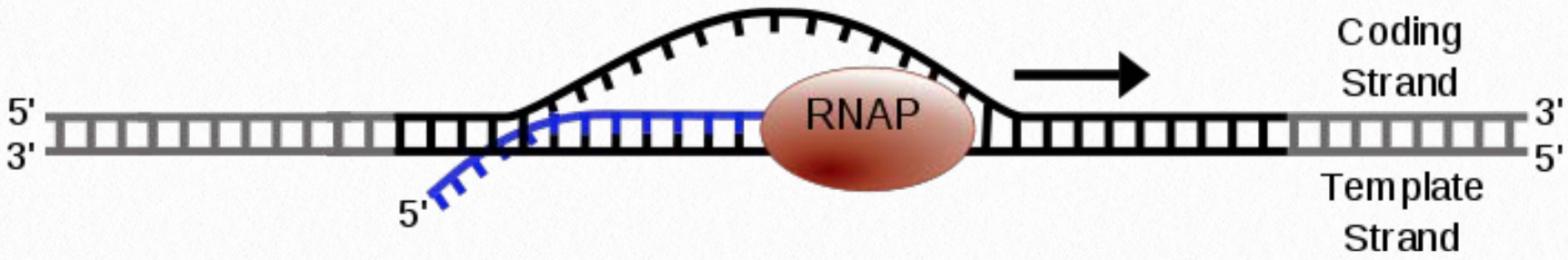

Figure 7.60 - Synthesis of RNA in the transcription bubble

(sigma) subunit. Together, the σ subunit and core polymerase make up what is termed the RNA polymerase holoenzyme. The core polymerase is the part of the RNA polymerase that is responsible for the actual synthesis of the RNA, while the σ subunit is necessary for binding of the enzyme at promoters to initiate transcription.

Loose association

The core polymerase and σ subunit are not always associated with each other. For the most part, the core polymerase is loosely associated with DNA, although it does not discriminate between promoters and other sequences in DNA, and the DNA strands are not opened up to allow transcription in this state. The role of the σ subunit is to reduce the affinity of the core polymerase for non-specific DNA sequences and to help the enzyme specifically bind to promoter sequences.

Holoenzyme binding

It is when the σ subunit associates with the core polymerase that the holoenzyme is able to bind specifically to promoter sequences. The initial binding of the holoenzyme at the promoter results in what is called a "closed" complex, meaning that the DNA template is still double-stranded and has not opened up to allow transcription. This closed complex is then converted to an "open" complex by the separation of the DNA strands to create a transcription bubble about 12-14 base-pairs long (Figure 7.60). The conversion of the closed complex to the open complex also requires the presence of the σ subunit.

Open complex & initiation

Once the open complex has formed, the DNA template can begin to be copied, and the core polymerase adds nucleotides complementary to one strand of the DNA. At this stage, known as initiation, the polymerase adds several nucleotides while still bound to the promoter, and without moving along the DNA template. Initially, short pieces of RNA a few nucleotides long may be made and released, without the polymerase leaving the promoter. Eventually, the enzyme makes the transition to the next stage, elongation, when

an RNA of 8-9 bases is made and the enzyme moves beyond the promoter region.

Elongation

Once elongation commences and the RNA polymerase is moving down the DNA template, the σ subunit is no longer necessary and may dissociate from the core enzyme. The core polymerase can move along the template, unwinding the DNA ahead of it to maintain a transcription bubble of 12-15 base-pairs and synthesizing RNA complementary to one of the strands of the DNA. As already mentioned, an RNA chain, complementary to the DNA template, is built by the RNA polymerase by the joining of the 5' phosphate of an incoming ribonucleotide to the 3'OH on the last nucleotide of the growing RNA strand. Behind the RNA polymerase, the DNA template is rewound, displacing the newly made RNA from its template strand.

Termination

As mentioned earlier, a sequence of nucleotides called the terminator is the signal to the RNA polymerase to stop transcription and dissociate from the template. Some terminator sequences, known as intrinsic terminators, allow termination by RNA polymerase without the help of any additional factors, while others, called rho-dependent terminators, require the assistance of a protein factor called rho (ρ).

How does the sequence of the terminator cause the RNA polymerase to stop adding nucleotides and release the transcript?

To understand this, it is useful to know that the terminator sequence precedes the last nucleotide of the transcript. In other words, the terminator is part of the end of the sequence that is transcribed (Figure 7.61).

Intrinsic terminators

In intrinsic terminators, this sequence in the RNA has self-complementary regions that can base-pair with each other to form a hairpin structure that contains a GC-rich run in the “stem” of the hairpin. This hairpin is fol-

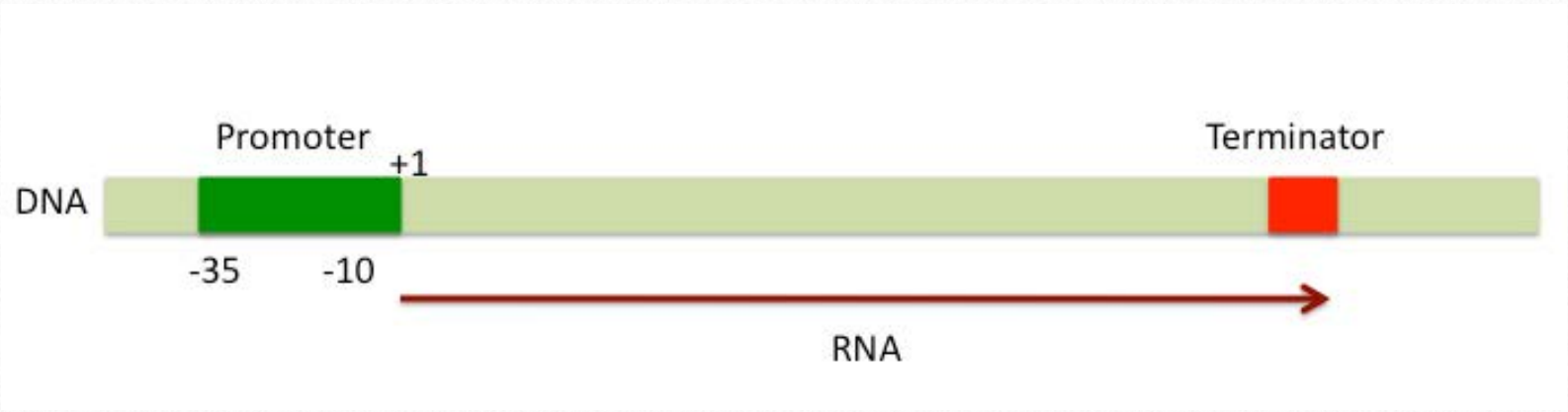

Figure 7.61 - Promoter and Terminator sequences determine where transcription starts and ends.

lowed by a single-stranded region that is rich in U's (Figure 7.62). The secondary structure formed by the folding of the end of the RNA into the hairpin causes the RNA polymerase to pause. Meanwhile, the run of U's at the end of the hairpin permits the RNA-DNA hybrid in this region to come apart, because the base-pairing between A's in the DNA template and the U's in the RNA is relatively weak. This allows the transcript to be released from the DNA template and from the RNA polymerase.

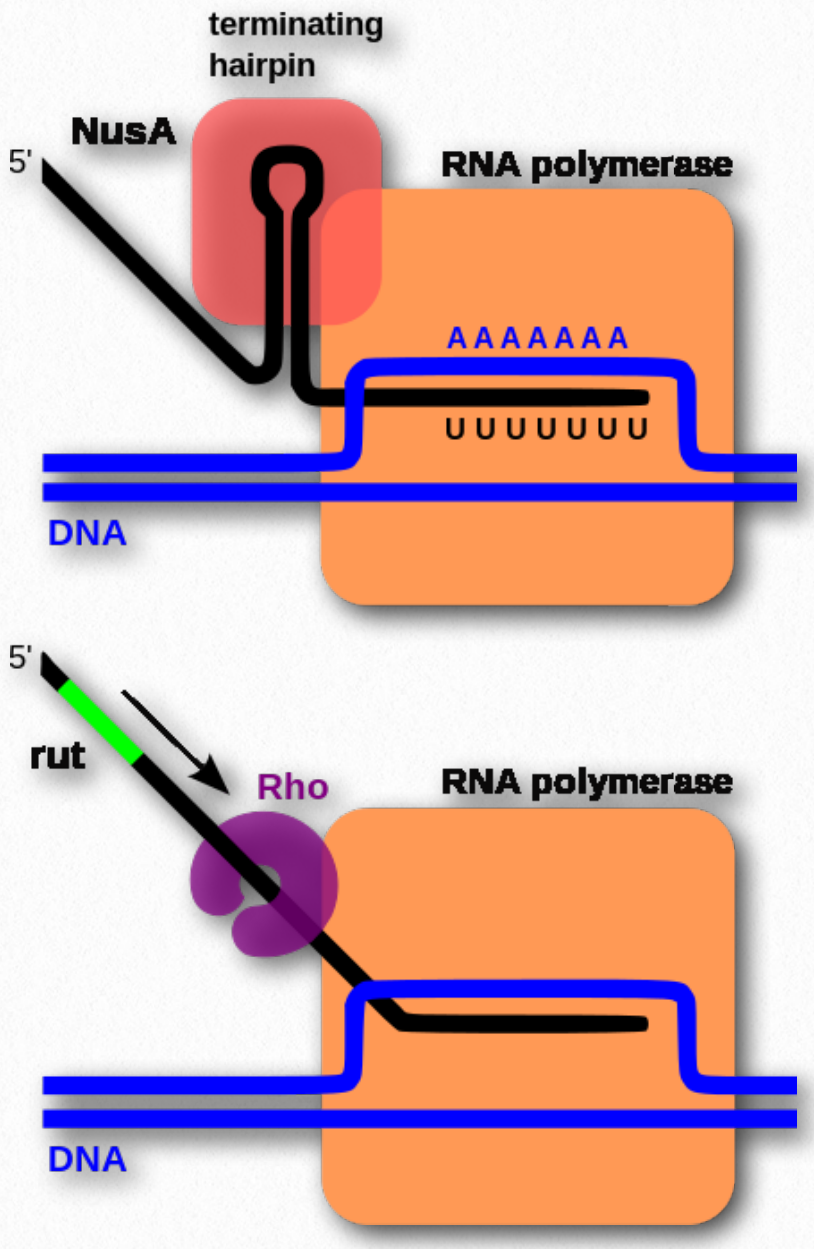

Figure 7.62 Transcription termination by intrinsic (top) and rho-dependent (bottom) mechanisms

Wikipedia

Rho-dependent termination

In the case of rho-dependent termination, an additional protein factor, rho, is necessary. Rho is a helicase that can separate the transcript from the template it is paired with. As in intrinsic termination, rho-dependent termination requires the formation of a hairpin structure in the RNA that causes pausing of the RNA polymerase. Meanwhile, rho binds to a region of the transcript called the rho utilization site (rut) and moves along the RNA till it reaches the paused RNA polymerase. It then acts on the RNA-DNA hybrid, releasing the transcript from the template.

Coupled transcription and translation

In prokaryotes, which lack a nucleus, the DNA is not separated from the rest of the cell in a separate compartment, so the mRNA is immediately available to the translation machinery, as the transcript is coming off the template DNA. Indeed, in prokaryotic cells, translation of the mRNA can begin before the entire gene has been transcribed. Ribosomes can assemble at the 5' end of the transcript, as it is displaced from the template, while the 3' end of the gene is still being copied. The lag time between transcrip-

tion and translation is thus, very short in prokaryotes.

Transcription in eukaryotes

Although the process of RNA synthesis is the same in eukaryotes as in prokaryotes, there are some additional considerations in eukaryotes. One is that in eukaryotes, the DNA template exists as chromatin, where the DNA is tightly associated with histones and other proteins. The "packaging" of the DNA must therefore be opened up to allow the RNA polymerase access to the template in the region to be transcribed (Figure 7.63). The restructuring of chromatin to allow access to regions of DNA is thus an important factor in determining which genes are expressed.

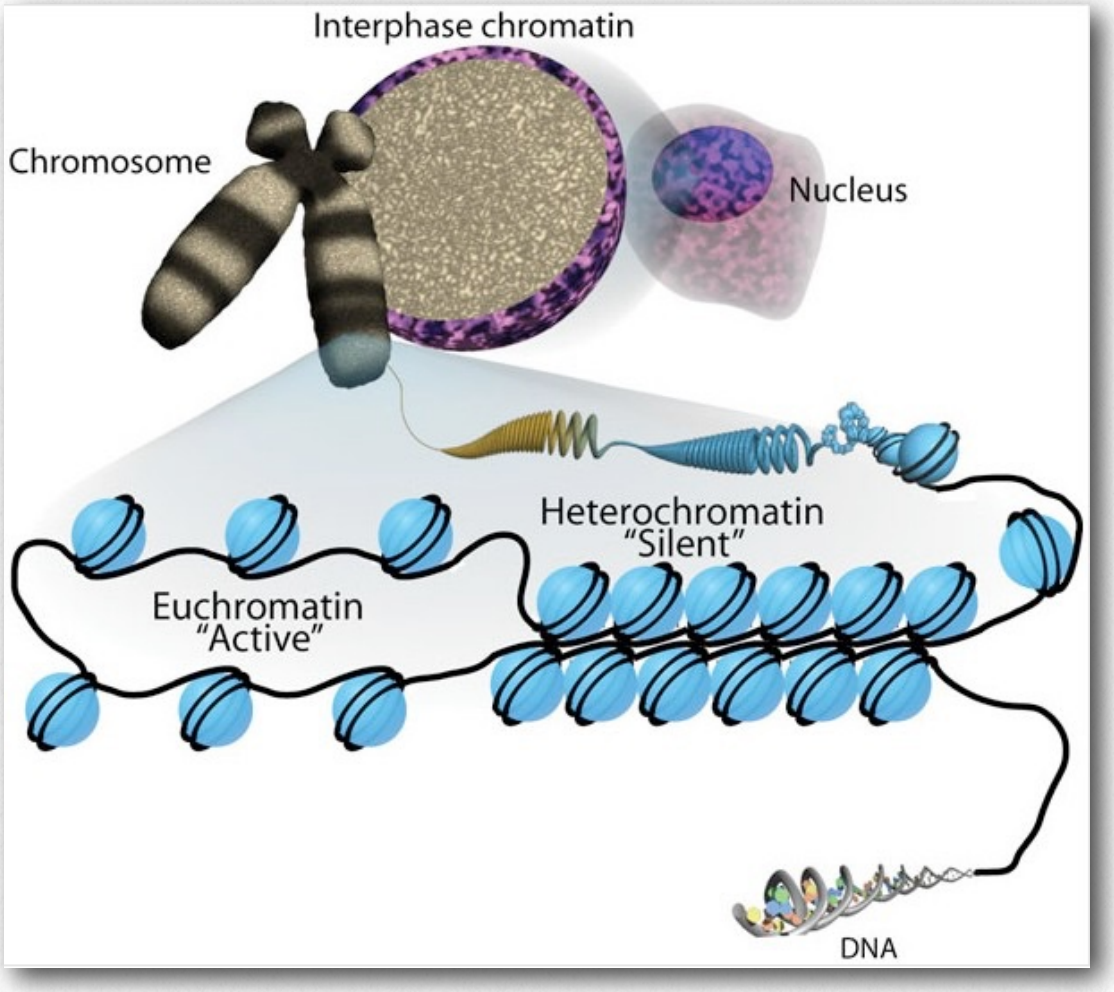

Figure 7.63 - Eukaryotic DNA is complexed with proteins in chromatin

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Multiple RNA polymerases

A second difference is that eukaryotes have multiple RNA polymerases, not just one as in bacterial cells. The different eukaryotic polymerases transcribe different classes of genes. For example, RNA polymerase I transcribes the ribosomal RNA genes, while RNA polymerase III copies tRNA genes. The RNA polymerase we will focus on most is RNA polymerase II, which transcribes protein-coding genes to make mRNAs.

All three eukaryotic RNA polymerases need additional proteins to help them get transcription started. In prokaryotes, RNA polymerase by itself can initiate transcription (the σ subunit is a subunit of the RNA polymerase, not an entirely separate protein). The additional proteins needed by eukaryotic RNA polymerases are referred to as transcription factors. We will see below that there are various categories of transcription factors.

Transcription and translation are de-coupled

Finally, in eukaryotic cells, transcription is separated in space and time from translation. Transcription happens in the nucleus, and the RNAs produced are processed further before they are sent into the cytoplasm. Protein synthesis (translation) happens in the cytoplasm. As noted earlier, in prokaryotic cells, mRNAs can be translated as they are coming off the DNA template, and because there is no nuclear envelope, transcription and protein synthesis occur in a single cellular compartment. A representative eukaryotic gene, depicted in Figure 7.64 shows that transcription starts some 25 bp downstream of the TATA box, and creates a transcript that begins with a 5' untranslated region (5'UTR) followed by the coding region which may include multiple introns and ending in a 3' untranslated region or 3'UTR (Figure 7.64). As detailed below, the initial transcript is further processed before it is used.

Eukaryotic promoters

Like genes in prokaryotes, eukaryotic genes also have promoters that determine where transcription will begin. As with prokaryotes, there are specific sequences in the promoter regions that are recognized and bound by proteins involved in the initiation of transcription. We will focus primarily on the genes encoding proteins that are transcribed by RNA polymerase II. Such promoters commonly have a TATA box, a sequence similar to the -10 sequence in prokaryotic promoters. The TATA box is a sequence about 25-35 basepairs upstream of the start of transcription (+1). (Some eukaryotic promoters lack TATA boxes, and have, instead, other recognition sequences, known as DPE, or downstream promoter elements.) Interestingly, the TATA box is not directly recognized and bound by RNA polymerase II. Instead, this sequence is bound by other proteins that, together with the RNA polymerase, form the transcription initiation complex.

Eukaryotic promoters also have, in addition, several other short stretches of sequences, that affect transcription, within about 100 to 200 base-pairs upstream of the transcription start site. These sequences, which are sometimes called upstream elements or

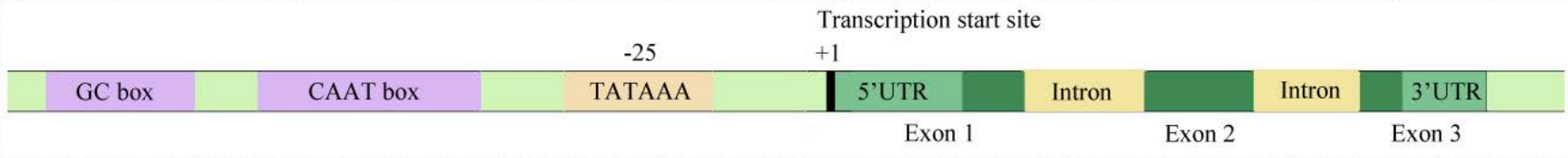

Figure 7.64 - Region surrounding the transcriptional start site in eukaryotic DNA

promoter-proximal upstream elements, are bound by activator proteins that interact with the transcription complex that forms at the TATA box. Examples of such upstream elements are the CAAT box and the GC box (Figure 7.64).

Making transcripts in eukaryotes

We noted earlier that all eukaryotic RNA polymerases need additional proteins to bind promoters and start transcription. The proteins that help eukaryotic RNA polymerases find promoter sites and initiate RNA synthesis are termed general transcription factors. We will focus on the transcription factors that assist RNA polymerase II, the enzyme that transcribes protein-coding genes. These transcription factors are named TFIIA, TFIIB and so on (TF= transcription factor, II=RNA polymerase II, and the letters distinguish individual transcription factors).

Transcription by RNA polymerase II requires the general transcription factors and the RNA polymerase to form a complex, at the TATA box, called the basal transcription complex or transcription initiation complex (Figure 7.65).

This is the minimum requirement for any gene to be transcribed. The first step in the formation of this complex is the binding of the TATA box by a transcription factor, TFIID. TFIID is made up of several proteins, one of which is called the TATA Binding Protein or TBP. Binding of the TBP causes the DNA to bend at this spot and take on a structure that is suitable for the binding of additional transcription factors and RNA polymerase.

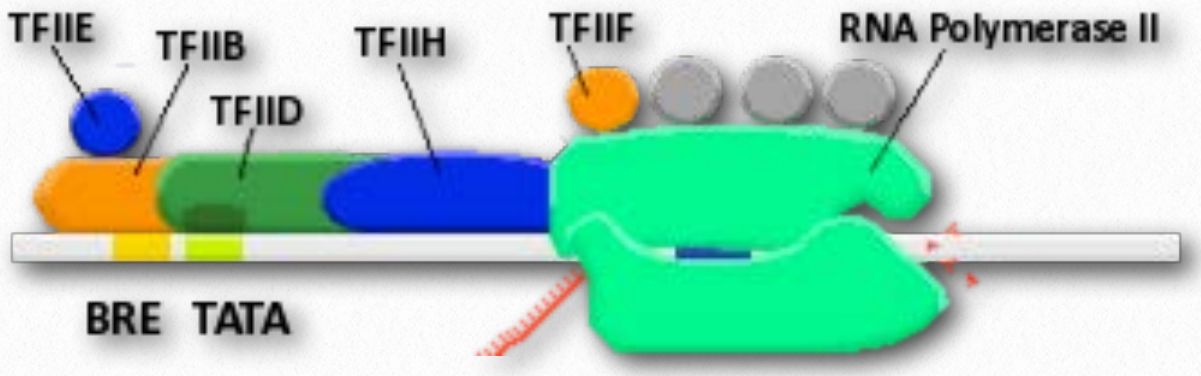

Figure 7.65 - Transcription pre-initiation complex in eukaryotes

Wikipedia

Interestingly, the binding of the TBP is a necessary step in forming a transcription initiation complex even when the promoter lacks a TATA box. The order of binding of additional proteins after binding of the TBP, as determined through *in vitro* experiments, appears to be TFIIB, followed by TFIIF and RNA polymerase II, then TFIIE. The final step in the assembly of the basal transcription complex is the binding of a general transcription factor called TFIIH. Some evidence suggests that following the binding of the TBP to DNA, the rest of the proteins in the initiation complex may assemble as a very large

The Student's Guide to a Perfect Transcript

Pol II's so smart, now let me see
It makes a transcript, one, two, three,
From a billion base pairs can it find
The one promoter it must bind?

I need some help, I hear it plead,
This DNA I cannot read
I cannot see where I must start
'Til TFIIs have done their part.

When TATA's bound by TBP
That sends a signal out, you see
Once DNA has made a bend
More TFIIs will soon attend.

When B arrives, it clears a place
For RNA polymerase
And F and E soon join the fun
TFIIH, the final one.

The last one is a special case
It moonlights as a helicase
And sends Pol II upon its way
To make a brand new RNA.

How does it do that, you may ask
A phosphate does the crucial task
Added on to CTD,
That's how the H sets Pol II free.

And Pol II goes its merry way
There soon will be some RNA
Then introns must be all excised
As RNA is capped and spliced.

Then PolyA polymerase
Will add a couple hundred As
For my own transcript, I can say
That all I want is one more A

Verse by Indira Rajagopal

complex that then binds directly to the DNA. In any case, the presence of all of these general transcription factors and RNA Polymerase II bound at the promoter is necessary for the initiation of transcription.

As in prokaryotic transcription, once the RNA polymerase binds, it can begin to assemble a short stretch of RNA. This must be followed by promoter clearance, in order to move down the template and elongate the transcript. This requires the action of TFIIH. TFIIH is a multifunctional protein that has helicase activity (i.e., it is capable of opening up a DNA double helix) as well as kinase activity. The kinase activity of TFIIH adds phosphates onto the C-terminal domain (CTD) of the RNA polymerase II. This

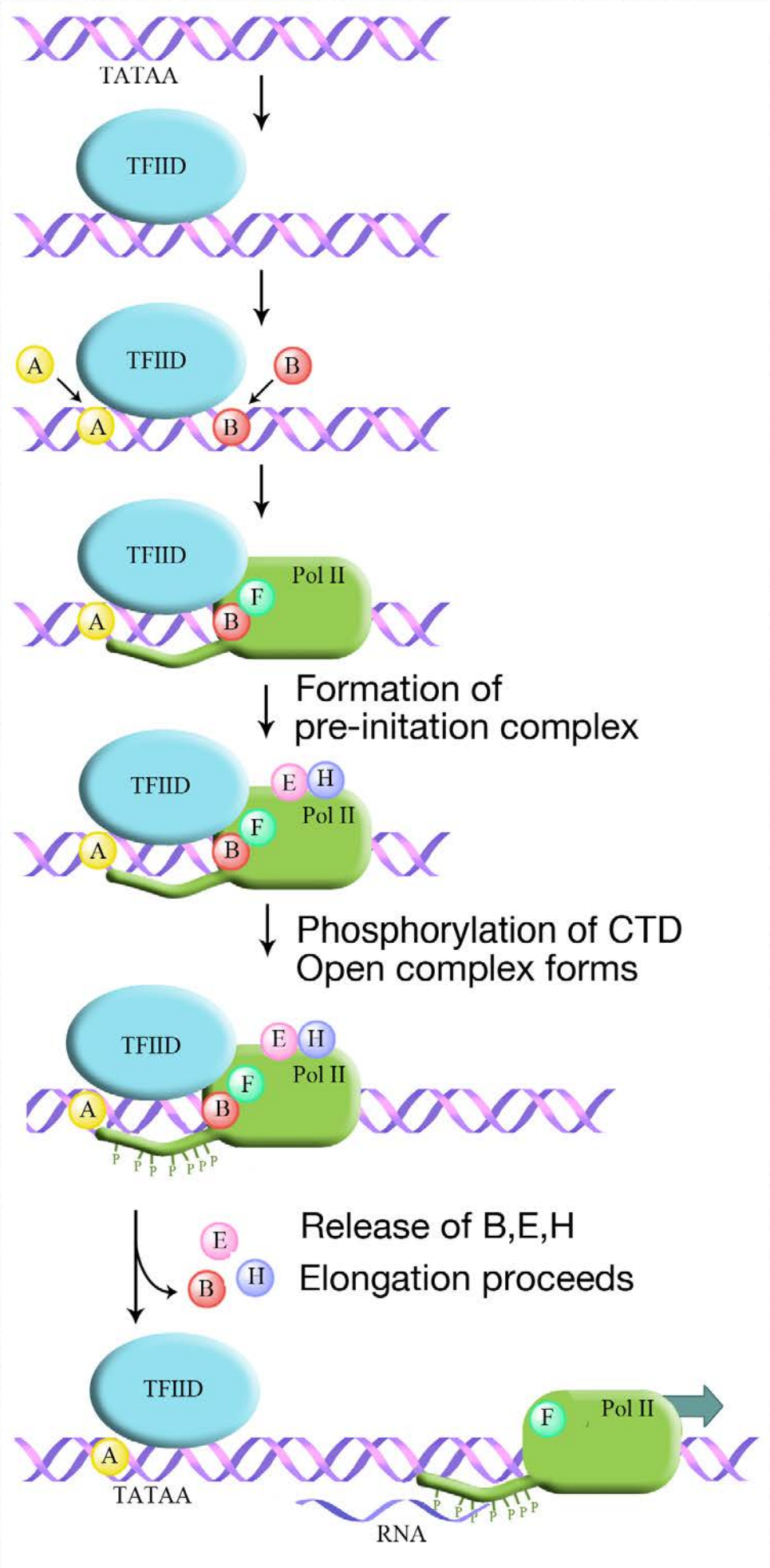

Figure 7.66 - Assembly of the basal transcription complex and transcription initiation

phosphorylation appears to be the signal that releases the RNA polymerase from the basal transcription complex and allows it to move forward on the template, building the new RNA as it goes (Figure 7.66).

Termination of transcription is not as well understood as it is in prokaryotes. Termination does not occur at a fixed distance from the 3' end of mature RNAs. Rather, it seems to occur hand in hand with the processing of the 3' end of the primary transcript. The polyadenylation signal in the 3' untranslated region of the transcript appears to play a role in RNA polymerase pausing, and subsequent release of the completed primary transcript. Recognition of the polyadenylation signal triggers the binding of proteins involved in 3'end processing and termination.

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Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Central Dogma Zen

To the tune of "*Those Were the Days, My Friend*"
Metabolic Melodies Website HERE

Once upon a time a cell decided
The time was ripe for it to split in two
Had to copy cellular instructions
For the daughter cell would need them too.

Bring in a helicase
Unzip the DNAs
To ease the stress a gyrase joins the fray
Strands must be held apart
SSBs do their part
And primase builds a primer RNA.

Sliding clamp comes in behind clamp loader
dNTPs floating all around
In the wings a replicase is waiting
For the chance to start another round.

Polymerase, my friend
Starts at the 3' end
It puts a T across from every A
A G across from C
Perfect simplicity
The leading strand is made in just this way.

The lagging strand is made in little pieces
Okazaki fragments, you recall
Pol I fills the gaps that lie between them
Ligase comes in next and joins them all.

Blueprints can't have mistakes
That's why polymerase
Corrects its work
With exonuclease
Proofreading one by one
Till all its work is done
Hurray for D-N-A polymerase!

An organism's cellular construction
With blueprints for the things they have to do
Requires converting DNA instructions
To ribopolymers, oh yes it's true

Because they've been bestowed
With a genetic code
The RNAs provide the cell with means
To link amino A's
In most directed ways
Inside the protein-making cell machines

If "*coli*" cells don't have galactosidase
And lactose should appear inside its food
The lac repressor leaves the operator
'Cause otherwise metabolism's screwed

Polymerase unwinds
The DNAs it binds
Adjacent to the start site where it docks
Unravels A's and T's
With such amazing ease
At the promoter's little TATA box

The process moves along without much trouble
While making RNA inside the cell
It all occurs inside transcription bubbles
Where bases get linked anti-parallel

mRNA then roams
To find some ribosomes
Subunits large and small bind near the end
The A-U-G's in place
Inside the P site space
Initiation you can comprehend

The mechanism shifts to elongation
Proceeding by three bases at a stretch
A GTP's required for translocation
Advancing 5 to 3 the whole complex

The process moves anon
Until a stop codon
Arrives and causes movement to suspend
Translation has to cease
A peptide gets released
And we have reached the central dogma's end

Recording by Tim Karplus
Lyrics by Indira Rajagopal and Kevin Ahern

Transcription

To the tune of "*Frosty the Snowman*"
Metabolic Melodies Website HERE

Phos-pho-di-esters
Are the bonds of RNA
That support a ribopolymer
Made of G,C,U and A

The RNA polymerase
Binds to a TATA box
And copies from the template strand
All the along the way it walks

IN-i-ti-a-tion
Of transcription thus proceeds
From the closed to open complexing
In the DNA it reads

The sigma factor gets released
Its work is over fast
Polymerase can then advance
After this step has been passed

In elongation
The polymerizing spree
Moves along the way in fits and starts
Synthesizing five to three

The RNA is floppy and
It dangles from one end
Oh that's a most important thing
For you to comprehend

Then termination
Fin-ish-ES the RNAs
Thanks to protein rho or hairpin forms
That release polymerase

So this describes transcription's steps
In three part harmonies
Here's hoping with this melody
You can learn it all with ease
fade

Recorded by David Simmons
Lyrics by Kevin Ahern

Chromatin

To the tune of "*Sunshine on My Shoulders*"

Metabolic Melodies Website HERE

Charges of the lysines bind to phosphates
Minus charges cling to plusses tight
Chromatin assembly is essential
Eukaryotic cells must get it right

Cells are tiny micro-scaled enclosures
With nuclei tucked deep in their insides
That's the place amazingly enough that
Seven feet of DNA resides

H2a and H2b have lysines
That's how they get charges don't forget
Paired with H's three and four they make up
A chromatin core's octameric set

These get organized in higher orders
Changing with the cycles of the cell
Denser packing going through mitosis
At other times the structures simply swell

So because of all the hyperpacking
Nuclei can hold entire genomes
Thank the histones spooling DNA for
Physically downsizing chromosomes

Recording by David Simmons
Lyrics by Kevin Ahern

Information Processing: RNA Processing

So far, we have looked at the mechanism by which the information in genes (DNA) is transcribed into RNA. The newly made RNA, also known as the primary transcript is further processed before it is functional. Both prokaryotes and eukaryotes process their ribosomal and transfer RNAs.

mRNA processing

The major difference in RNA processing, however, between prokaryotes and eukaryotes, is in the processing of messenger RNAs. We will focus on the processing of mRNAs in this section. You will recall that in bacterial cells, the mRNA is translated directly as it comes off the DNA template. In eukaryotic cells, RNA synthesis, which occurs in the nucleus, is separated from the protein synthesis machinery, which is in the cytoplasm. The initial product of transcription of an mRNA is sometimes referred to as the pre-mRNA. After it has been processed and is ready to be exported from the nucleus, it is called the mature

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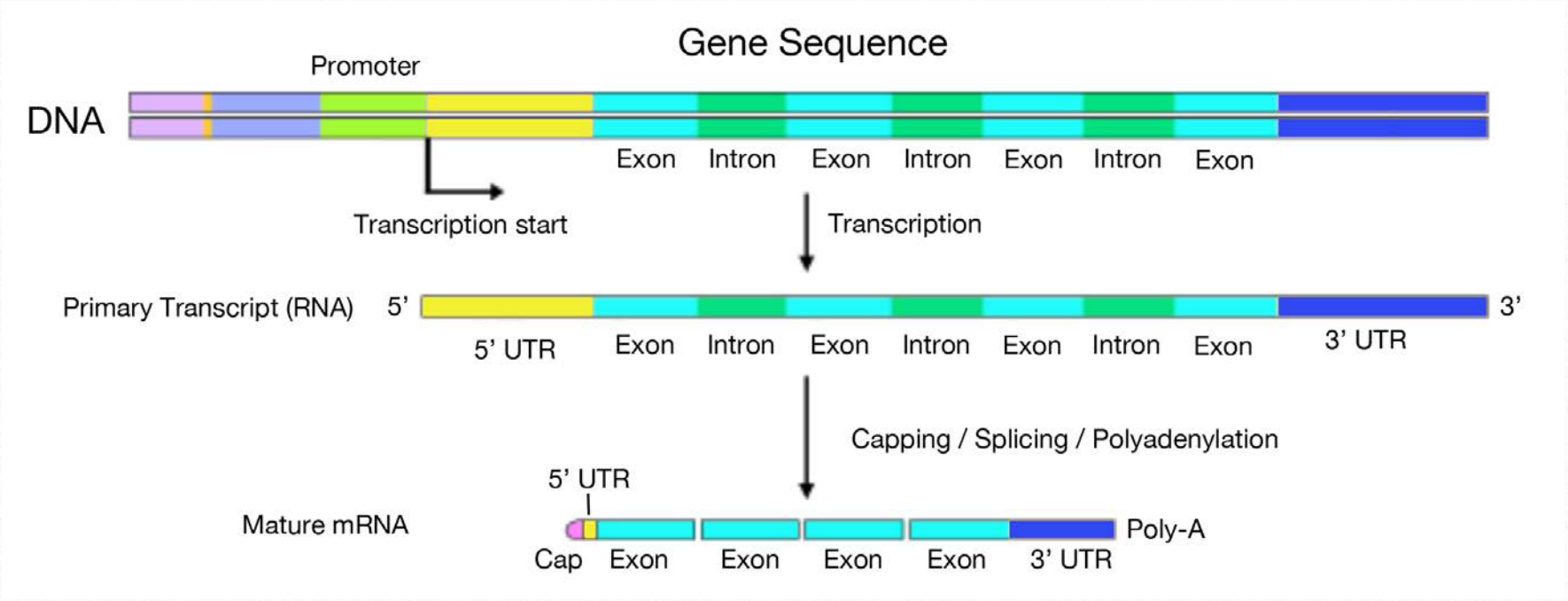

Figure 7.67 - Steps in processing of pre-mRNA

mRNA. The three main processing steps for mRNAs are (Figure 7.67):

- Capping at the 5' end
- Splicing to remove introns
- Addition of a polyA tail at the 3' end.

Although this description suggests that these processing steps occur post-transcriptionally, after the entire gene has been transcribed, there is evidence that processing occurs co-transcriptionally. That is, the steps of processing are occurring as the mRNA is being made. Proteins involved in mRNA processing have been shown to be associated with the phosphorylated C-terminal domain (CTD) of RNA polymerase II.

Capping

As might be expected, the addition of an mRNA cap at the 5' end is the first step in mRNA processing, since the 5'end of the RNA is the first to be made. Capping occurs once the first 20-30 nucleotides of the RNA

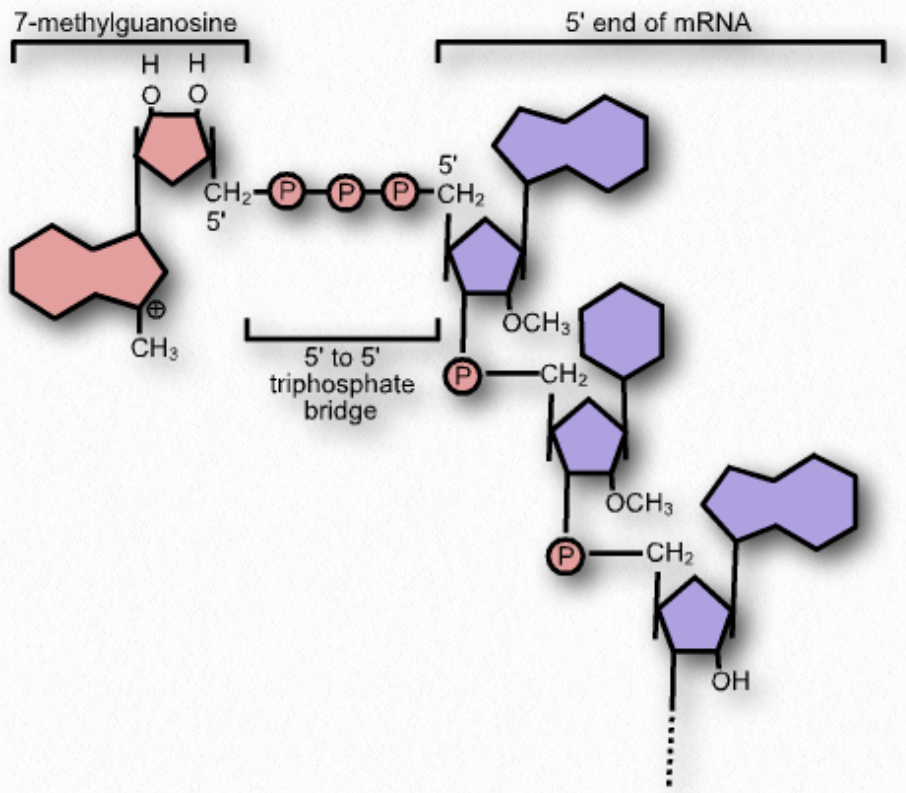

Figure 7.68 - 5' capping of eukaryotic mRNAs
Wikipedia

have been synthesized. The addition of the cap involves removal of a phosphate from the first nucleotide in the RNA to generate a diphosphate. This is then joined to a guanosine monophosphate which is subsequently methylated at N^7 of the guanine to form the 7mG cap structure (Figure 7.68). This cap is recognized and bound by a complex of proteins that remain associated with the cap till the mRNA has been transported into the cytoplasm. The cap protects the 5' end of the mRNA from degradation by nucleases and also helps to position the mRNA correctly on the ribosomes during protein synthesis.

mRNA is sent out of the nucleus to be used to direct protein synthesis.

Intron removal

Introns are removed from the pre-mRNA by the activity of a complex called the spliceosome. The spliceosome is made up of proteins and small RNAs that are associated to form protein-RNA enzymes called small nuclear ribonucleoproteins or snRNPs (pronounced snurps).

Splice junctions

The splicing machinery must be able to recognize splice junctions (i.e., where each exon ends and its associated intron begins) in order to correctly cut out the introns and join the exons to make the mature, spliced mRNA. What signals indicate exon-intron boundaries? The junctions between exons and introns are indicated by specific base sequences. The consensus sequence at the 5' exon-intron junction (also called the 5' splice site) is AG-

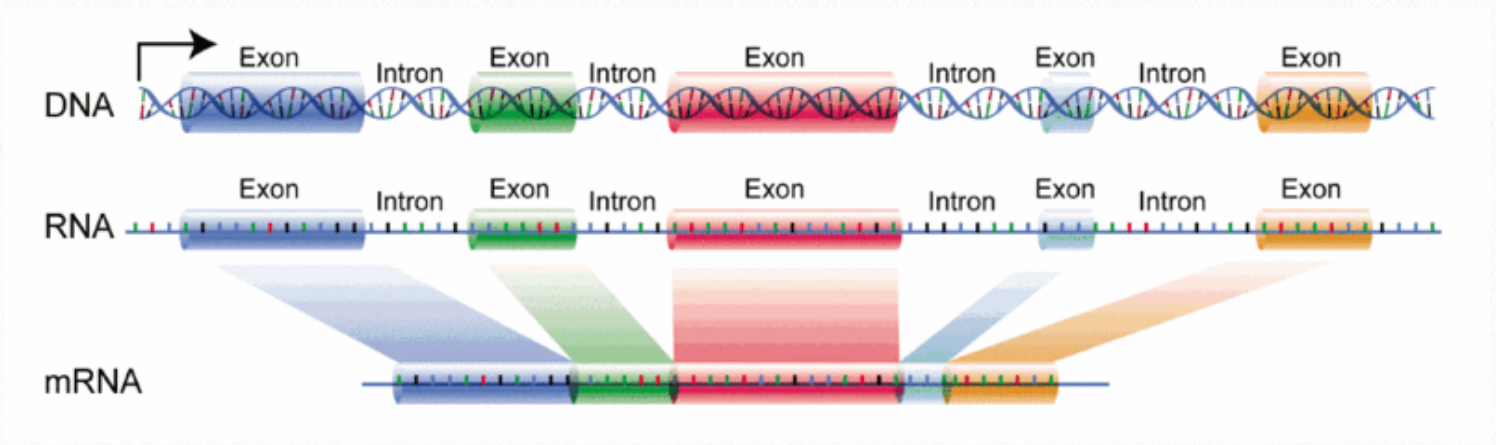

Figure 7.69 - Removal of introns from the primary transcript

Splicing

Eukaryotic genes have introns, noncoding regions that interrupt the gene. The mRNA copied from genes containing introns will also therefore have noncoding regions that interrupt the information in the gene. These noncoding regions must be removed (Figure 7.69) before the

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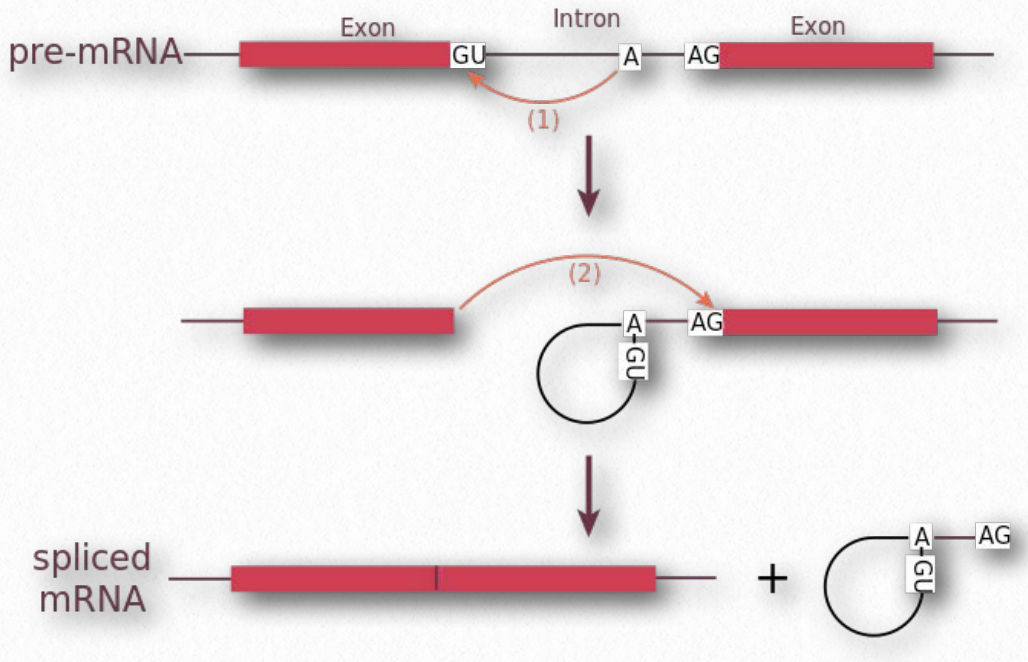

Figure 7.70 - Splicing of introns

Wikipedia

GURAGU. In this sequence, the intron starts with the second G (R stands for any purine). The 3' splice junction has the consensus sequence YAGRNNN, where YAG is within the intron, and RNNN is part of the exon (Y stands for any pyrimidine, and N for any nucleotide).

There is also a third important sequence within the intron, about a hundred nucleotides from the 3' splice site, called a branch point or branch site, that is important for splicing. This site is defined by the presence of an A followed by a string of pyrimidines. The importance of this site will be seen when we consider the steps of splicing.

Splicing mechanism

There are two main steps in splicing. The first step is the nucleophilic attack by the 2'OH of the branch point A on the 5' splice site (the junction of the 5' exon and the intron). As a result of a *trans*-esterification reaction, the 5' exon is released, and a lariat-shaped molecule composed of the 3' exon and the intron sequence is generated (Figure 7.70). In the second step, the 3' OH of the 5' exon attacks the 3' splice site, and the two exons are joined together, and the lariat-shaped intron is released.

Spliceosome

As mentioned earlier, splicing is carried out by a complex consisting of small RNAs and proteins. The five small RNAs crucial to this complex, U1, U2, U4, U5 and U6 are found associated with proteins, as snRNPs. These and many other proteins work together to facilitate splicing. Although many details remain to be worked out, it appears that components of the splicing machinery associate with the CTD of the RNA polymerase and that this association is important for efficient splicing. The assembly of the spliceosome requires the stepwise interaction of the various snRNPs and other splicing factors (Figure

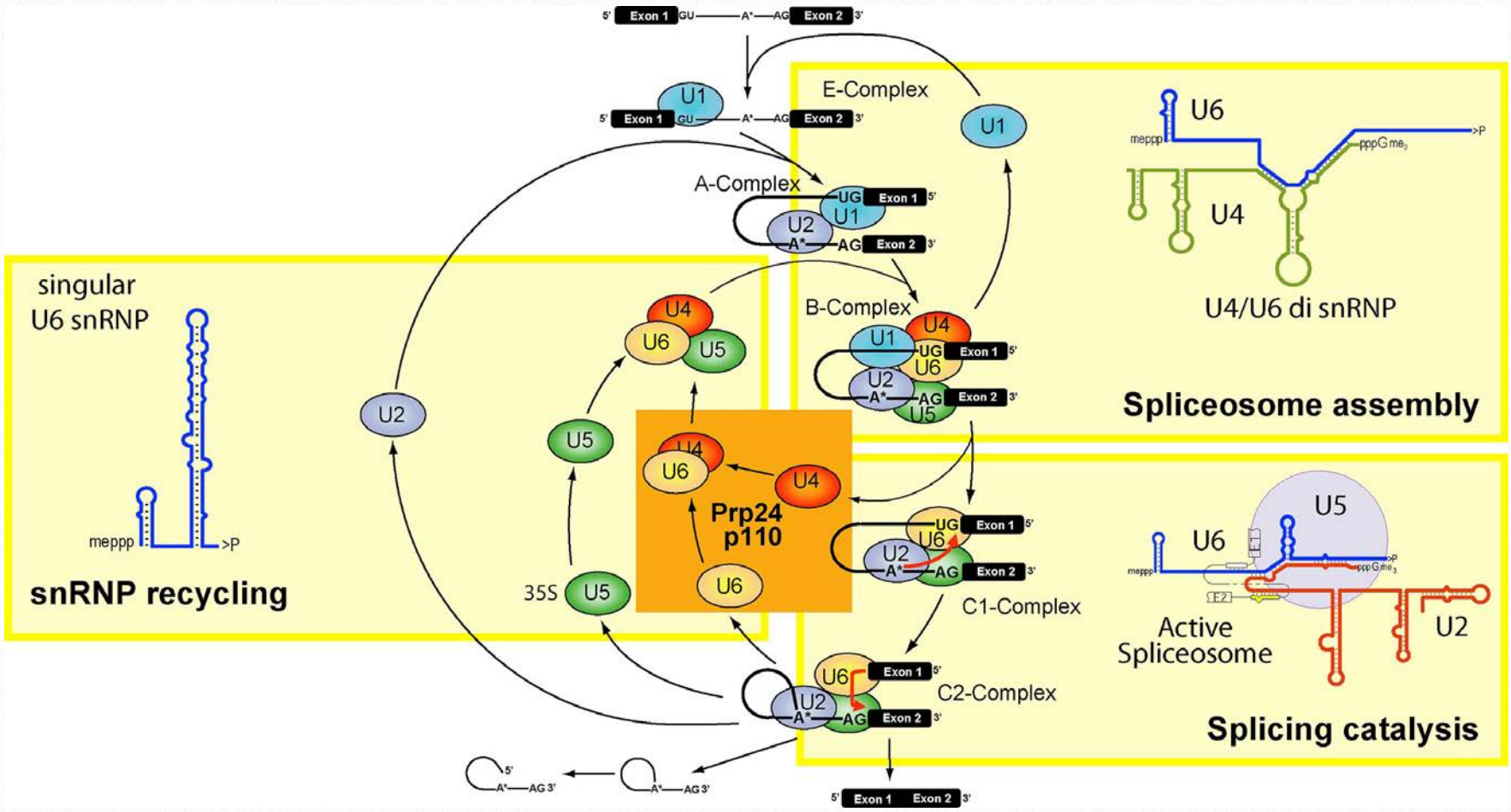

Figure 7.71 - Assembly of the spliceosome complex

Wikipedia

7.71). The initial step in this process is the interaction of the U1 snRNP with the 5' splice site. Additional proteins such as U2AF (AF = associated factor) are also loaded onto the pre-mRNA near the branch site. This is followed by the binding of the U2 snRNA to the branch site.

Next, a complex of the U4/U6 and U5 snRNPs is recruited to the spliceosome to generate a pre-catalytic complex. This complex undergoes rearrangements that alter RNA-RNA and protein-RNA interactions, resulting in displacement of the U4 and U1 snRNPs and the formation of the catalytically active spliceosome. This complex then carries out the two splicing steps described earlier.

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Alternative splicing

On average, human genes have about 9 exons each. However, the mature mRNAs from a gene containing nine exons may not include all of them. This is because the exons in a pre-mRNA can be spliced together in different combinations to generate different mature mRNAs. This is called alternative splicing, and allows the production of many different proteins using relatively few genes, since a single RNA with many exons can, by combining different exons dur-

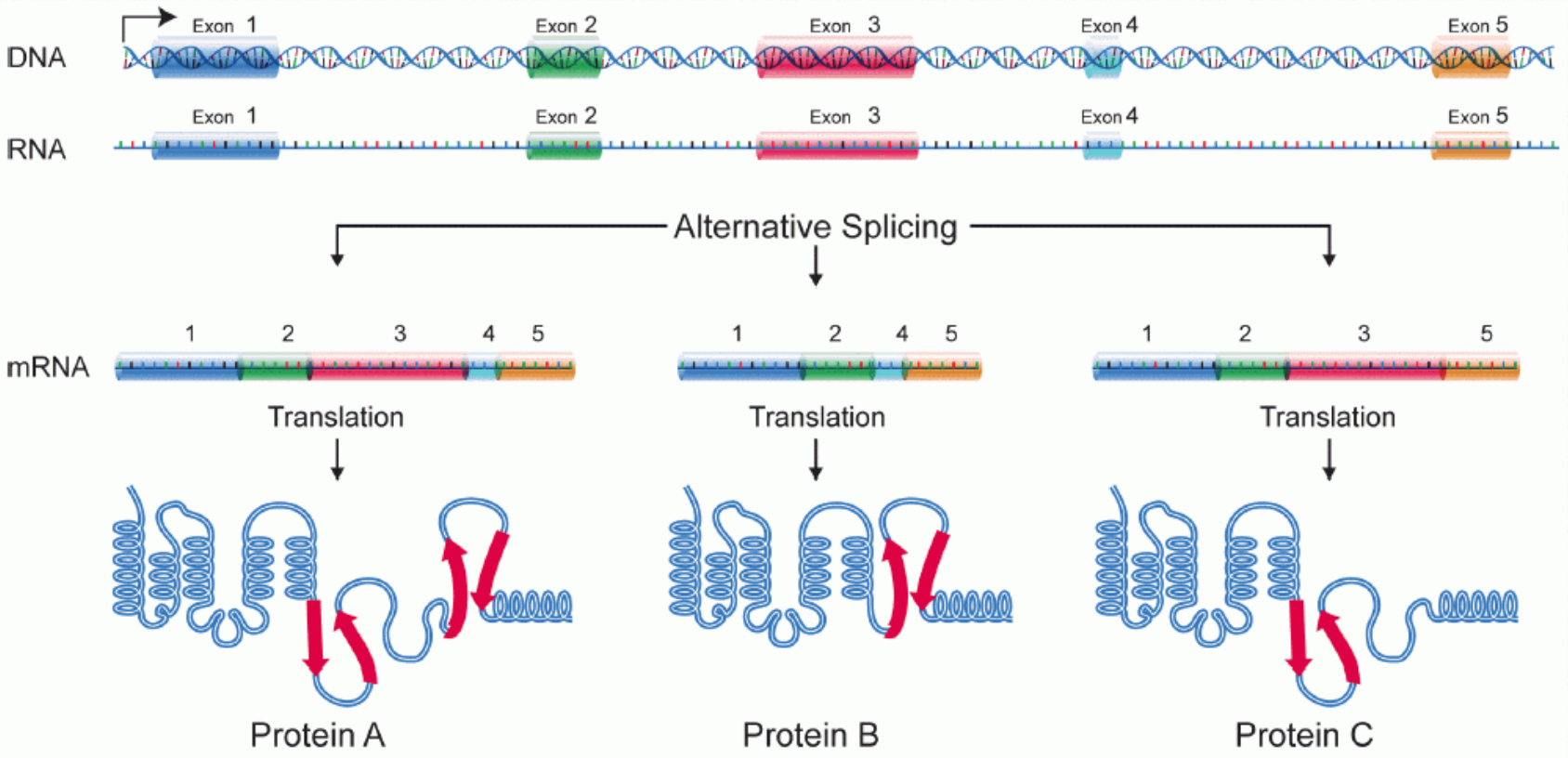

Figure 7.72 - Alternative splicing leads to different forms of a protein from the same gene sequence

ing splicing, create many different protein coding messages. Because of alternative splicing, each gene in our DNA gives rise, on average, to three different proteins. Alternative splicing allows the information in a single gene to be used to specify different proteins in different cell types or at different developmental stages (Figure 7.72).

Polyadenylation

The 3' end of a processed eukaryotic mRNA typically has a "poly(A) tail" consisting of about 200 adenine-containing nucleotides. These residues are added by a template-independent enzyme, poly(A)polymerase, following cleavage of

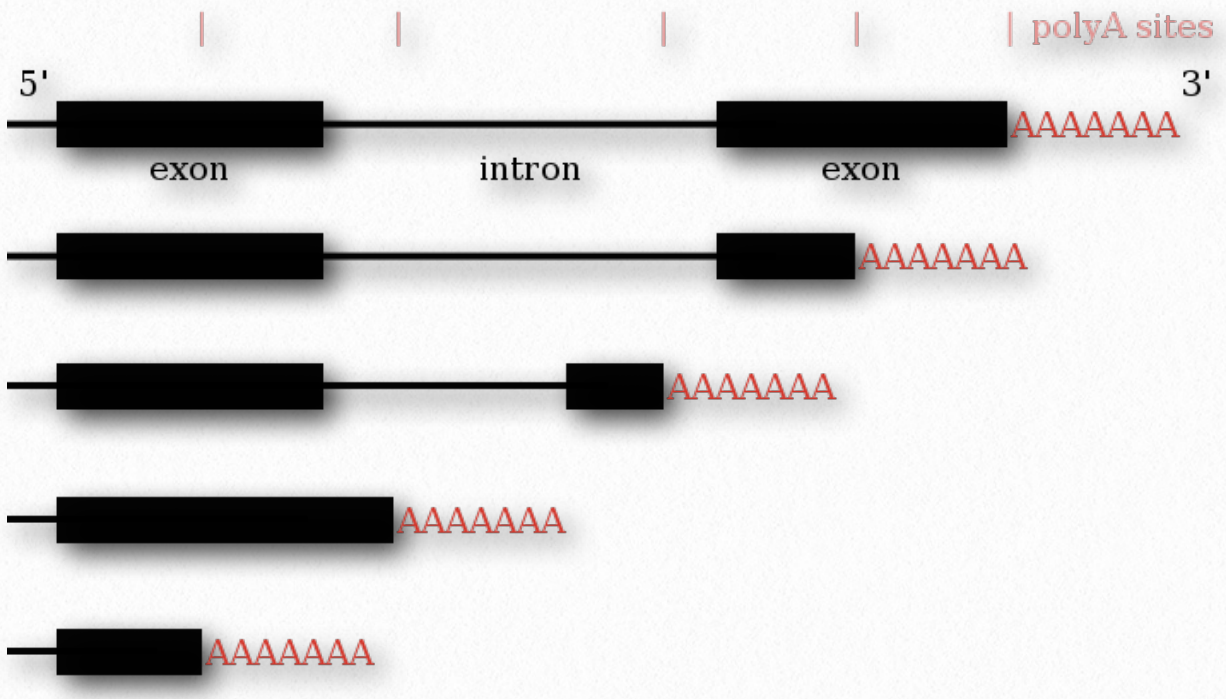

Figure 7.73 - Alternative poly-adenylation sites for a gene

the RNA at a site near the 3' end of the new transcript. Components of the polyadenylation machinery have been shown to be associated with the CTD of the RNA polymerase, showing that all three steps of pre-mRNA processing are tightly linked to transcription. There is evidence that the polyA tail plays a role in efficient translation of the mRNA, as well as in the stability of the mRNA. Like alternative splice sites, genes can have alternative polyA sites as well (Figure 7.73).

The cap and the polyA tail on an mRNA are also indications that the mRNA is complete (i.e., not defective). Once protein-coding messages have been processed by capping, splicing and addition of a poly A tail, they are transported out of the nucleus to be translated in the cytoplasm. Mature mRNAs are sent into the cytoplasm bound to export proteins that interact with the nuclear pore complexes in the nuclear envelope (Figure 7.74). Once the mature mRNA has been translocated to the cytoplasm, it is ready to be translated.

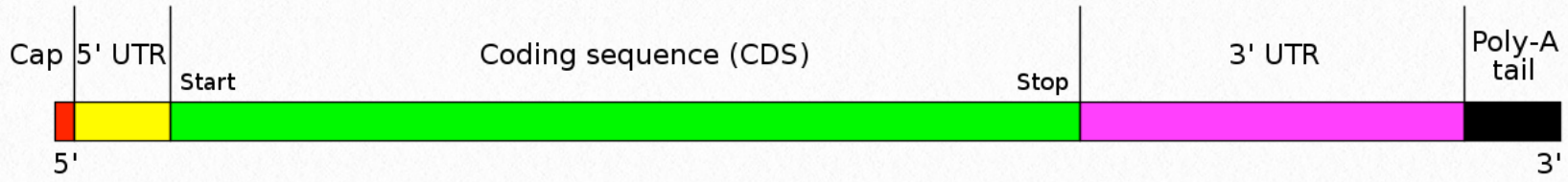

Figure 7.74 - Structure of a mature eukaryotic mRNA

RNA editing

In addition to undergoing the three processing steps outlined above, many RNAs undergo further modification called RNA editing. Editing has been observed in not only mRNAs but also in transfer RNAs and ribosomal RNAs. As the name suggests, RNA editing is a process during which the sequence of the transcript is altered post-transcriptionally. A well-studied example of RNA editing is the alteration of the sequence of the mRNA for apolipoprotein B (see also HERE). The editing results in the deamination of a cytosine in the transcript to form a uracil, at a specific location in the mRNA. This change converts the codon at this position, CAA, which encodes a glutamine, into UAA, a stop codon. The consequence of this is that a shorter version of the protein is made, when the edited transcript is translated. It is interesting that the editing of this transcript occurs

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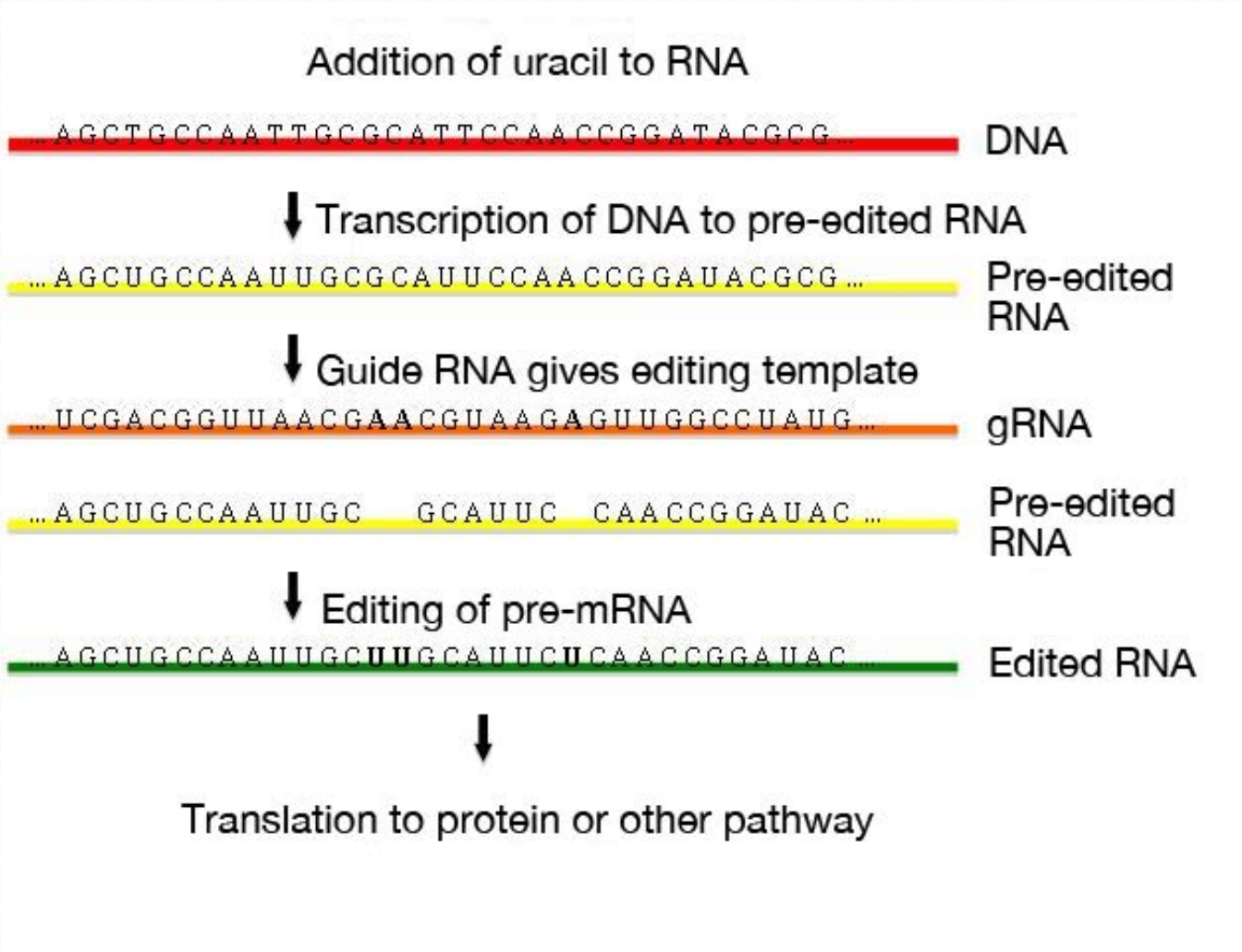

Figure 7.75 - Template guided - one mechanism of RNA editing

in intestinal cells but not in liver cells. Thus, the protein product of the apolipoprotein B gene is longer in the liver than it is in the intestine.

Insertion/deletion

Another kind of RNA editing involves the insertion or deletion of one or more nucleotides. One example of this sort of editing is seen in the mitochondrial RNAs of trypanosomes. Small guide RNAs indicate the sites at which nucleotides are inserted or deleted to produce the mRNA that is eventually translated (Figure 7.75).

The effect of either of these kinds of editing on the mRNA is that the encoded protein product is different, providing another point at which the product of expression of a gene can be controlled.

tRNA synthesis & processing

tRNAs are synthesized by RNA polymerase III, which makes precursor molecules called pre-tRNA that then undergo proc-

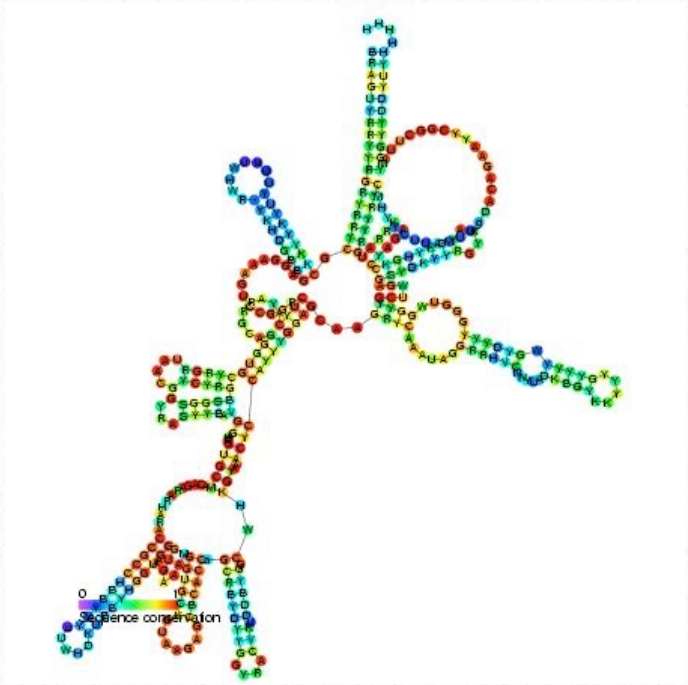

Figure 7.76 - Structure of the RNA component of ribonuclease P

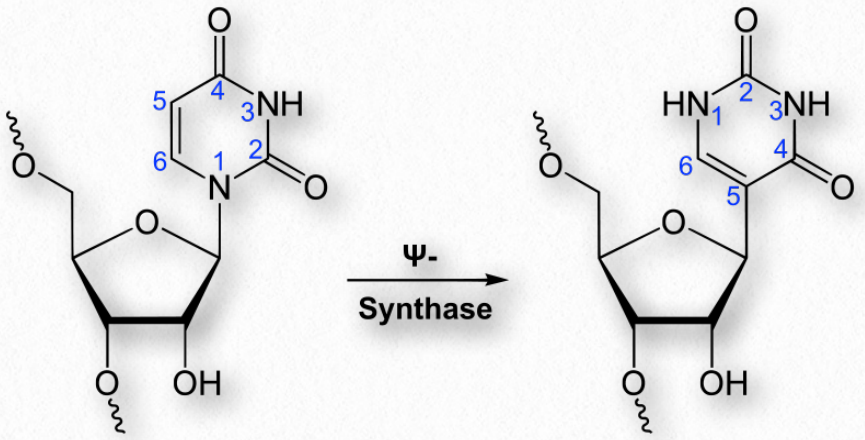

Figure 7.77 - Synthesis of pseudouridine from uridine

Wikipedia

essing to generate mature tRNAs. The initial transcripts contain additional RNA sequences at both the 5' and 3' ends. Some pre-tRNAs also contain introns. These additional sequences are removed from the transcript during processing.

The 5' leader sequence of the pre-tRNA (the additional nucleotides at the 5'-end) is removed by an unusual endonuclease called ribonuclease P (RNase P - Figure 7.76). RNase is a ribonucleoprotein complex composed of a catalytic RNA and numerous proteins. The 3' trailer sequence (extra nucleotides at the 3' end of the pre-tRNA) is later removed by different nucleases. All tRNAs must have a 3' CCA sequence that is necessary for the charging of the tRNAs with amino acids. In bacteria, this CCA sequence is encoded in the tRNA gene, but in eukaryotes, the CCA sequence is added post-transcriptionally by an enzyme called tRNA nucleotidyl transferase (tRNT).

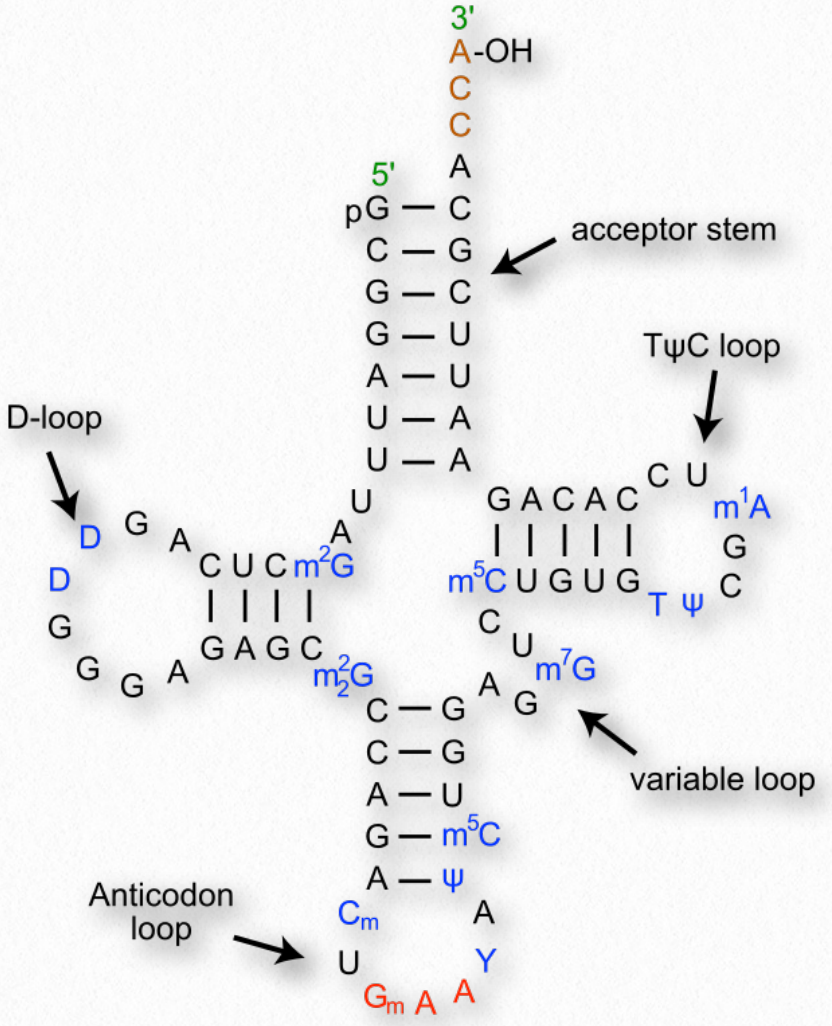

Figure 7.78 - Sequence of a mature tRNA

Wikipedia

Introns

As mentioned earlier, some tRNA precursors contain an intron located in the anticodon arm. In eukaryotes, this intron is typically found immediately 3' to the anticodon. The introns is spliced out with the help of a tRNA splicing endonuclease and a ligase.

Base modifications

Mature tRNAs contain a high proportion of bases other than the usual adenine (A), guanine (G), cytidine (C) and uracil (U). These unusual bases are produced by modifying the bases in the tRNA to form variants,

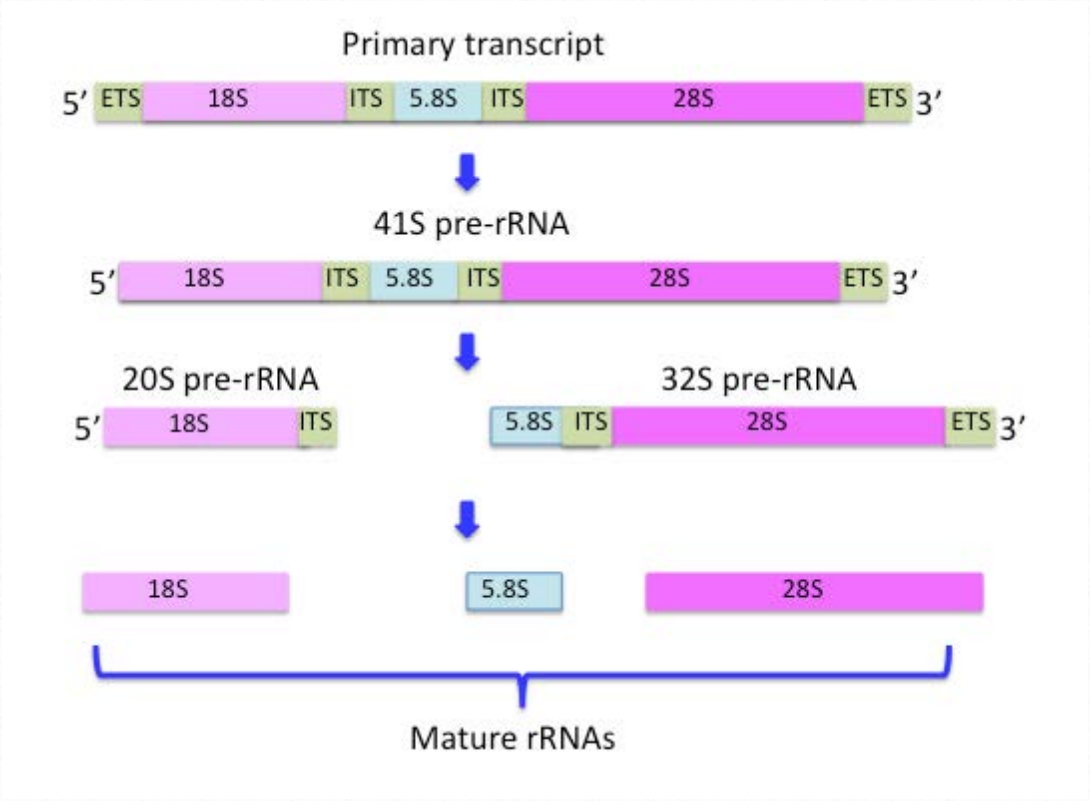

Figure 7.79 - Processing of ribosomal RNA

such as pseudouridine (Figure 7.77) or dihyrouridine. Modifications to the bases are introduced into the tRNA at the final processing step by a variety of specialized enzymes. Different tRNAs have different subsets of modifications at specific locations, often the first base of the anti-codon (the wobble position).

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rRNA synthesis and processing

Cells contain many copies of rRNA genes (between 100 and 2000 copies are seen in mammalian cells). These genes are organized in transcription units separated by non-transcribed spacers. Each transcription unit contains sequences coding for 18S, 5.8S and 28S rRNA, and is transcribed by RNA polymerase I into a single long transcript (47S). The 5S rRNA is separately transcribed.

The sizes of ribosomal RNAs are, by convention, indicated by their sedimentation coefficients, which is a measure of their rate of sedimentation during centrifugation. Sedimentation is expressed in Svedberg units (hence the S at the end of the number) with larger numbers indicating greater mass.

The initial transcript contains 5' and 3' external transcribed spacers (ETS) as well as internal transcribed sequences (ITS). The primary transcript is first trimmed at both ends by nucleases to give a 45S pre-rRNA. Further processing of the pre-rRNA through cleavages guided by RNA-protein complexes containing snoRNAs (small nucleolar RNAs), gives rise to the mature 18S, 5.8S and 28S rRNAs (Figure 7.79). Ribosomal RNAs are also modified both on the ribose sugars and on the bases. Interestingly, methylation of ribose sugars is the major modification in rRNA. The modified base pseudouridine is also common in rRNA. Other modifications include base methylation, and acetylation. These modifications are thought to be important in modulating ribosome function.

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The Codon Song

To the tune of "*When I'm Sixty Four*"

Metabolic Melodies Website HERE

Building of proteins, you oughta know
Needs amino A's
Peptide bond catalysis in ribosomes
Triplet bases, three letter codes

Mixing and matching nucleotides
Who is keeping score?
Here is the low down
If you count codons
You'll get sixty four

Got - to - line - up - right
16-S R-N-A and
Shine Dalgarno site

You can make peptides, every size
With the proper code
Start codons positioned
In the P site place
Initiator t-RNAs

UGA stops and AUGs go
Who could ask for more?
You know the low down
Count up the codons
There are sixty four

Recording by Tim Karplus
Lyrics by Kevin Ahern

Information Processing: Translation

Translation is the process by which information in mRNAs is used to direct the synthesis of proteins. As you have learned in introductory biology, in eukaryotic cells, this process is carried out in the cytoplasm of the cell, by large RNA-protein machines called ribosomes. Ribosomes contain ribosomal RNA (rRNA) and proteins. The proteins and rRNA are organized into two subunits, a large and a small. Ribosomes function by binding to mRNAs and holding them in a way that allows the amino acids encoded by the RNA to be joined sequentially to form a polypeptide. Transfer RNAs are the carriers of the appropriate amino acids to the ribosome.

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The genetic code

We speak of genes (i.e., DNA) coding for proteins and the central dogma, which states that DNA makes RNA makes protein. What does this actually mean? A code can be thought of as a system for storing or communicating information. A familiar ex-

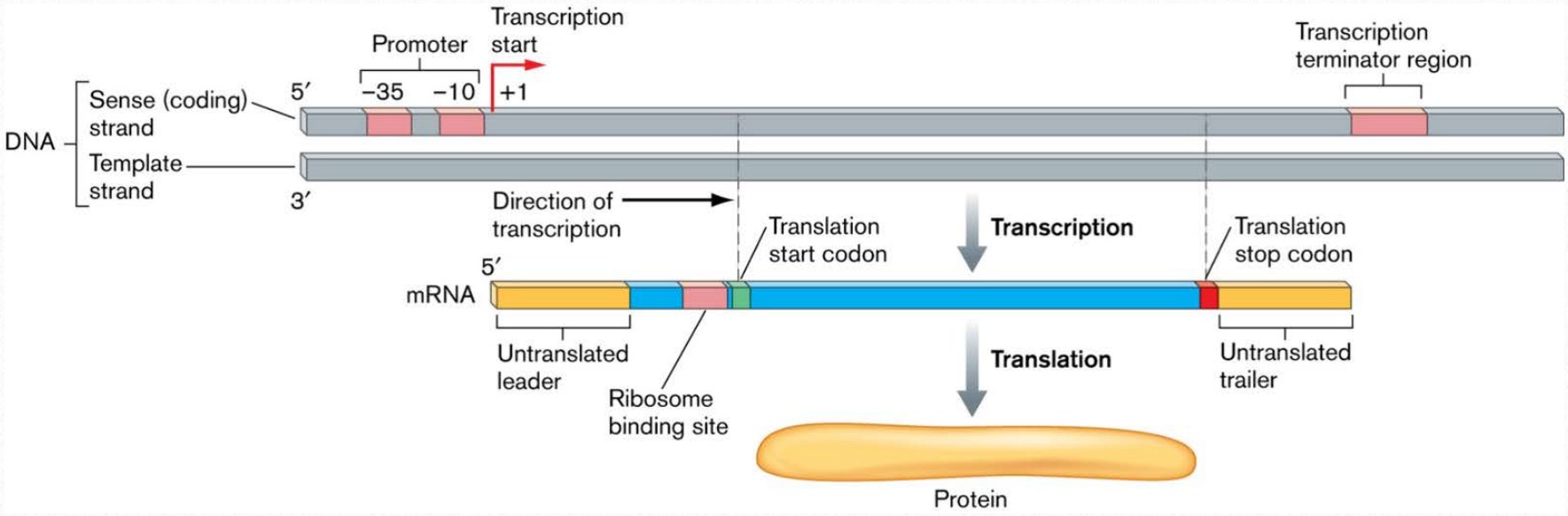


Figure 7.80 - The central dogma in a bacterial cell

Wikipedia

ample is the use of letters to represent the names of airports (e.g., PDX for Portland, Oregon and ORD for Chicago's O'Hare). When a tag on your luggage shows PDX as the destina-

nonpolar | polar | basic | acidic | (stop codon)

Standard genetic code

1st base	2nd base								3rd base
	U		C		A		G		
U	UUU	(Phe/F) Phenylalanine	UCU	(Ser/S) Serine	UAU	(Tyr/Y) Tyrosine	UGU	(Cys/C) Cysteine	U
	UUC		UCC		UAC		UGC		C
	UUA	(Leu/L) Leucine	UCA		UAA	Stop (*Ochre*)	UGA	Stop (*Opal*)	A
	UUG		UCG		UAG	Stop (*Amber*)	UGG	(Trp/W) Tryptophan	G
C	CUU		CCU	(Pro/P) Proline	CAU	(His/H) Histidine	CGU	(Arg/R) Arginine	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	(Gln/Q) Glutamine	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	(Ile/I) Isoleucine	ACU	(Thr/T) Threonine	AAU	(Asn/N) Asparagine	AGU	(Ser/S) Serine	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	(Lys/K) Lysine	AGA	(Arg/R) Arginine	A
	AUG[A]	(Met/M) Methionine	ACG		AAG		AGG		G
G	GUU	(Val/V) Valine	GCU	(Ala/A) Alanine	GAU	(Asp/D) Aspartic acid	GGU	(Gly/G) Glycine	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	(Glu/E) Glutamic acid	GGA		A
	GUG		GCG		GAG		GGG		G

Figure 7.81 - The standard genetic code

Wikipedia

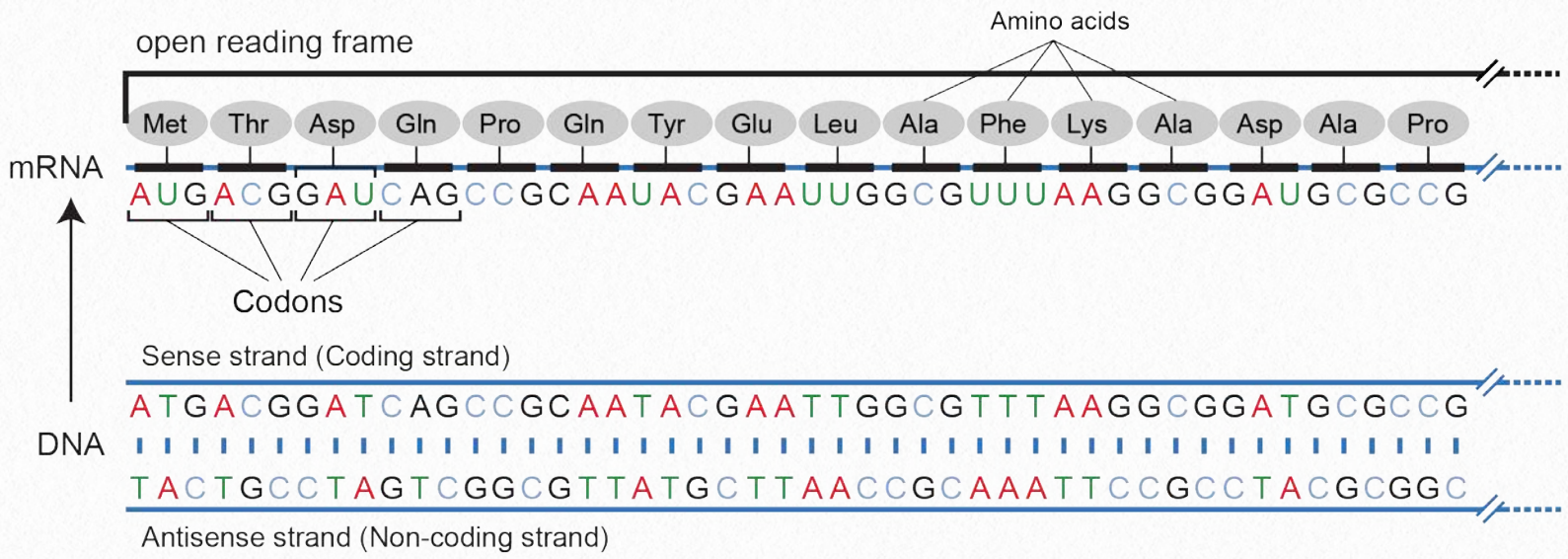


Figure 7.82 - Coding in DNA, transcribed to RNA, translated to protein

tion, it conveys information that your bag should be sent to Portland, Oregon. To function well, such a set-up must have unique identifiers for each airport and people who can decode the identifiers correctly. That is, PDX must stand only for Portland, Oregon and no other airport. Also, luggage handlers must be able to correctly recognize what PDX stands for, so that your luggage doesn't land in Phoenix, instead.

How does this relate to genes and the proteins they encode?

Genes are first transcribed into mRNA, as we have already discussed. The sequence of an mRNA, copied from a gene, directly specifies the sequence of amino acids in the protein it encodes. Each amino acid in the protein is specified by a sequence of 3 bases called a codon in the mRNA (Figure 7.81). For example, the amino acid tryptophan is encoded by the sequence UGG on an mRNA. All of the twenty amino acids used to build proteins have, likewise, 3-base sequences that encode them.

Degeneracy

Given that there are 4 bases in RNA, the number of different 3-base combinations that are possible is 4^3, or 64. There are, however, only 20 amino acids that are used in building proteins in cells. This discrepancy in the number of possible codons and the actual number of amino acids they specify is explained by the fact that the same amino acid may be specified by more than one codon. In fact, with the exception of the amino acids methionine and tryptophan, all the other amino acids are encoded by multiple codons. Codons for the same amino acid are often related, with the first two bases the same and the third being variable. An example would be the codons for alanine: GCU, GCA, GCC and GCG all stand for alanine. This sort of re-

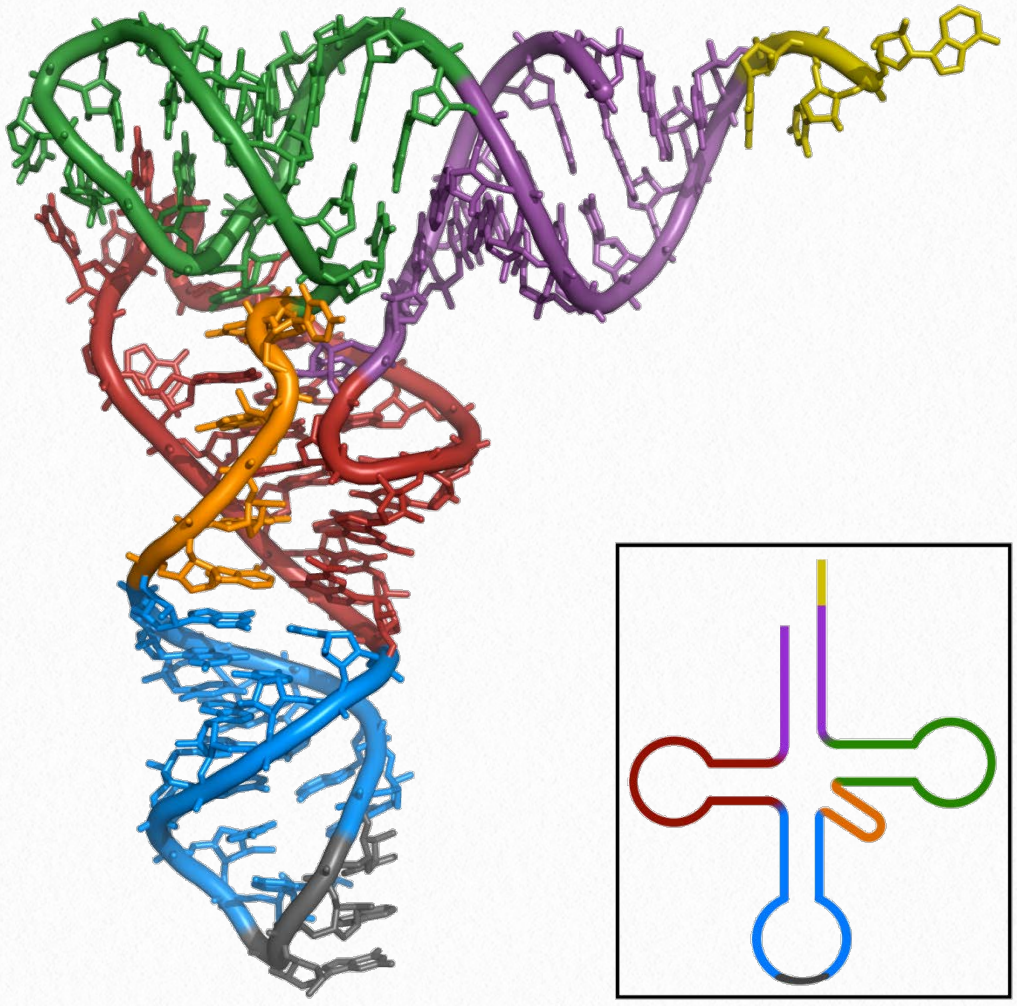


Figure 7.83 - tRNA - 3D projection (left) and 2D projection (inset)
Wikipedia

dundancy in the genetic code is termed degeneracy.

Stop and start codons

Three of the 64 codons are what are known as termination or stop codons, and as their name suggests, indicate the end of a protein coding sequence. The codon for methionine, AUG, is used as the initiation or start codon for the majority of proteins. This ingenious system is used to direct the assembly of a protein in the same way that you might string together colored beads in a particular order using instructions that used symbols like UGG for a red bead, followed by UUU for a green bead, CAC for yellow, and so on, till you came to UGA, indicating that you should stop stringing beads.

Translating the code

While the ribosomes are literally the factories that join amino acids together using the instructions in mRNAs, another class of RNA molecules, the transfer RNAs (tRNAs) are also needed for translation (Figure 7.83 and Interactive 7.1). Transfer RNAs are small RNA molecules, about 75-90 nucleotides long, that function to 'interpret' the instructions in the mRNA during protein synthesis. Transfer RNAs are extensively modified post-transcriptionally and contain a large number of unusual bases. The sequences of tRNAs have several self complementary regions, where the single-stranded tRNA folds on itself and base-pairs to form what is sometimes described as a clover leaf structure.

This structure is crucial to the function of the tRNA, providing both the sites for attachment of the appropriate amino acid and for recognition of codons in the mRNA. In terms of the bead analogy above, someone or something has to be able to bring a red bead in when the instructions indicate UGG, and a green bead when the instructions say UUU. This, then, is the function of the tRNAs. They must be able to bring the amino acid corre-

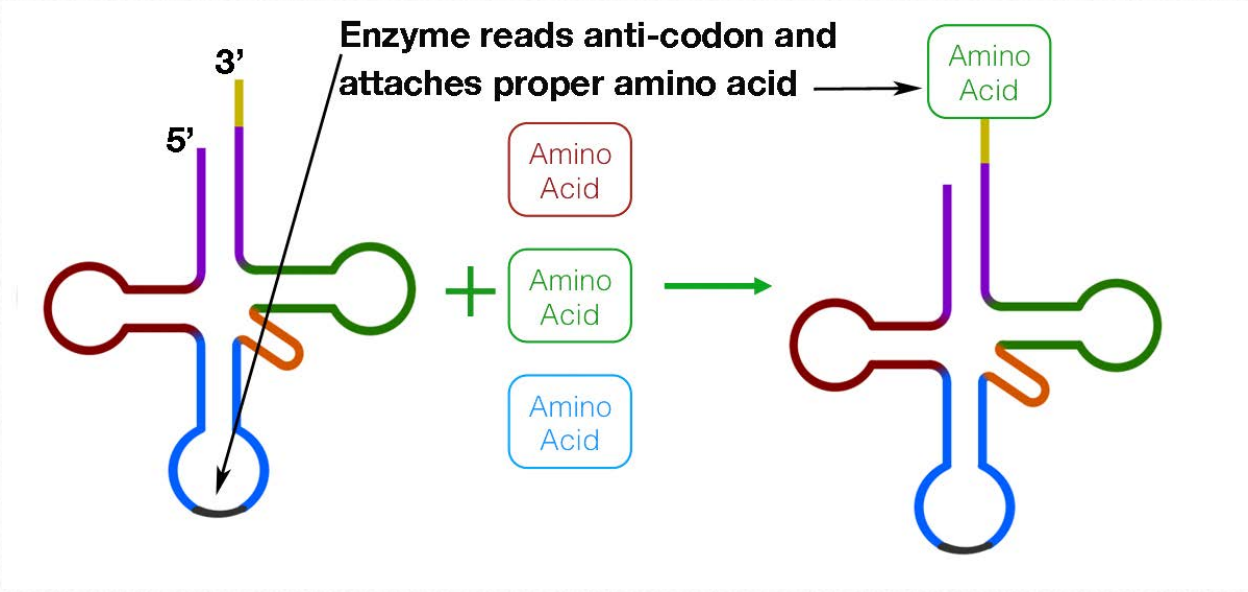


Figure 7.84 - Charging of a tRNA by aminoacyl tRNA synthetase

Wikipedia

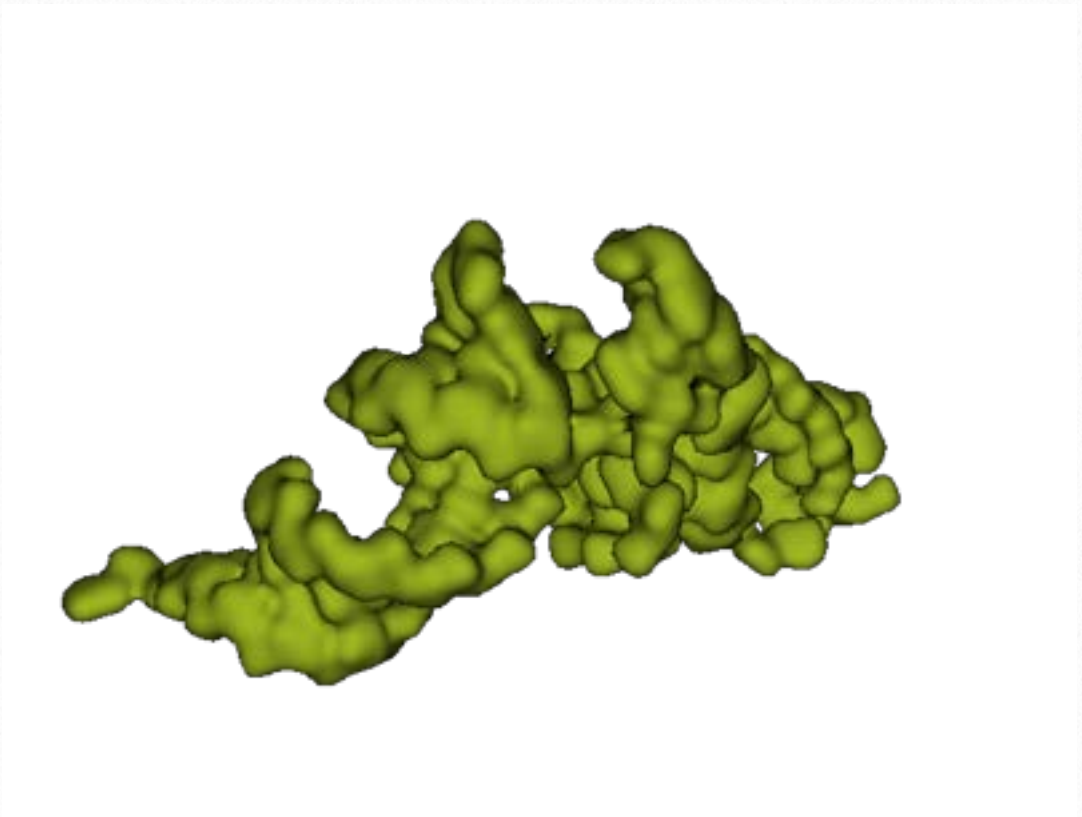
sponding to the instructions to the ribosome.

t-RNA specificity

A given transfer RNA is specific for a particular amino acid. It is linked covalently at its 3' end to the appropriate amino acid by an enzyme called aminoacyl tRNA synthetase. For example, there is a transfer RNA that is specific to the amino acid tryptophan, and a corresponding aminoacyl tRNA synthetase, called a tryptophanyl tRNA synthetase, that can attach the tryptophan specifically to this tRNA. Likewise, there is an aminoacyl tRNA synthetase specific for each amino acid. A tRNA with an amino acid attached to it is said to be *charged* (Figure 7.84). A pool of charged tRNAs is necessary to carry out protein synthesis. How do these tRNAs, carrying specific amino acids assist the ribosome in stringing together the correct amino acids, as specified by the sequence of the mRNA?

Codon recognition

As we already know, the amino acid sequence of the protein is determined by the order of the codons in the mRNA. We also have charged tRNAs carrying the various amino acids present. How are the amino acids attached to each other in the order indicated by the base se-



Interactive 7.1 - Phenylalanyl-tRNA

PDB

quence of the mRNA? This requires recognition of the codons on the mRNA by the appropriate charged tRNAs. The amino acid tryptophan, as we noted, is specified by the codon UGG in the mRNA. This codon must be recognized by a tRNA charged with tryptophan. Every tRNA has a a sequence of 3 bases, the anticodon, that is complementary to the codon for the amino acid it is carrying. When the tRNA encounters the codon for its amino acid on the messenger RNA, the anticodon will base-pair with the codon. For the tryptophan tRNA this is what it would look like:

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Sequence of tryptophan codon in mRNA:

5’ UGG 3’

Anticodon sequence in tryptophan tRNA:

5’ CCA 3’

Note that the sequences are both written, by convention, in the 5’ to 3’ direction. To base pair, though, they must be oriented in opposite directions (anti-parallel). The codon-anticodon basepair in the antiparallel orientation then would be:

5’ UGG 3’
3’ ACC 5’

The base-pairing of the anticodon on a charged tRNA with the codon on the mRNA is what brings the correct amino acids in to the ribosome to be added on to the growing protein chain (Figure 7.85).

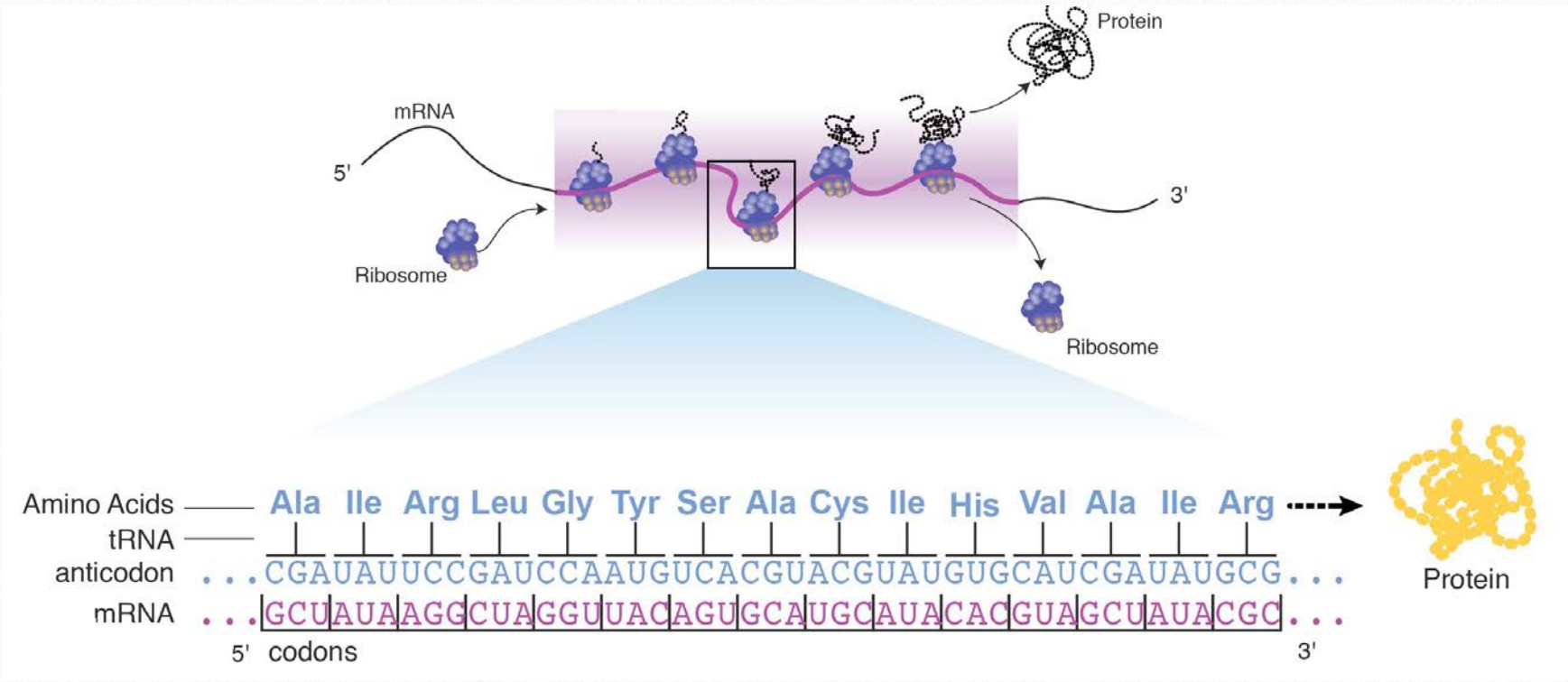

Figure 7.85 - Codons in mRNA pair with anticodons on tRNA to bring the appropriate amino acid to the ribosome for polypeptide assembly

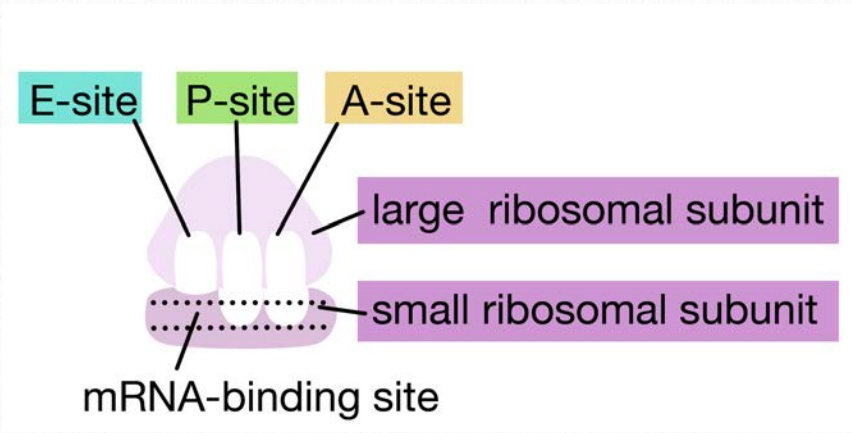

Figure 7.86 - The A, P, and E sites in a ribosome

Image by Martha Baker

Making a polypeptide

With an idea of the various components necessary for translation and how they work, we can now take a look at the process of protein synthesis. The main steps in the process are similar in prokaryotes and eukaryotes. As we already noted, ribosomes bind to mRNAs and facilitate the interaction between the codons in the mRNA and the anticodons on charged tRNAs.

Ribosomes have two sites (P-site and A-site) for binding and positioning charged tRNAs so each can form base pairs between their anticodon and a codon from the mRNA. The start codon (AUG) is positioned to base pair with the tRNA in the P-site (peptidyl site). Next, the charged tRNA complementary to the codon adjacent to the start codon binds and occupies the A-site (aminoacyl site) in the ribosome (Figure 7.86).

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At this point, the ribosome joins the amino acids carried on each tRNA by making a peptide bond. The bond between the amino acid and the tRNA in the P-site is broken and the dipeptide is joined to the tRNA on the A-site.

The initiator tRNA without its amino acid is then released, moving into a site known as the Exit or E-site, while the second tRNA carrying the dipeptide (and the codon it is base paired to) moves into the P-site. The A-site now is ready with a new codon for the next incoming charged tRNA.

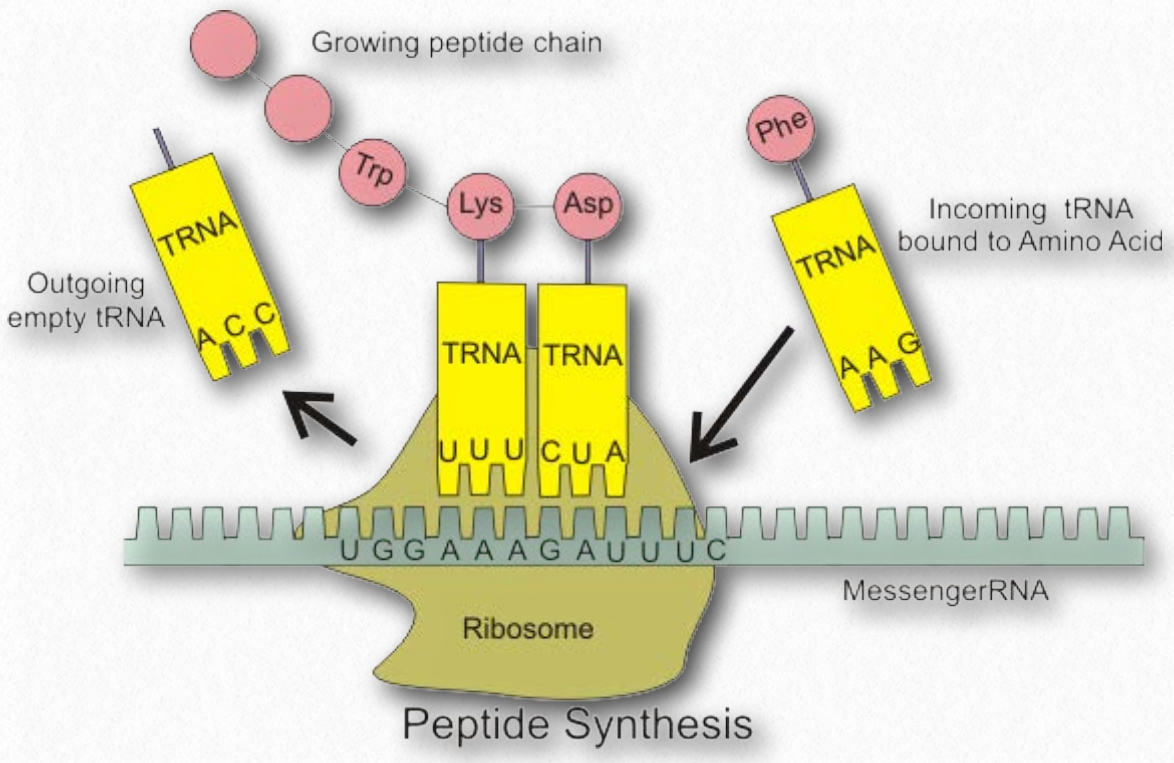


Figure 7.87 - Overview of elongation

Wikipedia

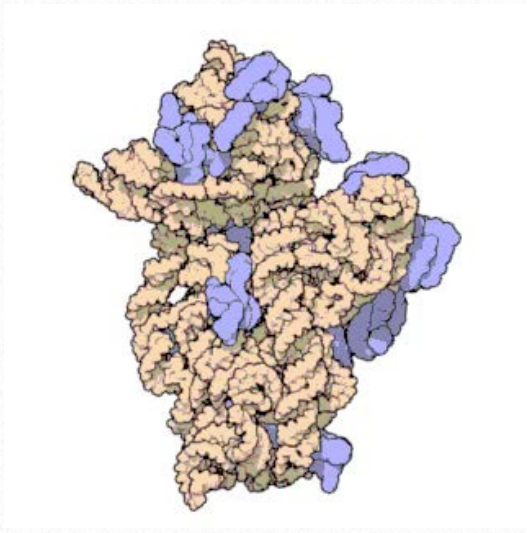
This process is repeated, with the ribosome moving on the mRNA one codon at a time, until the stop codon reaches the A-site. At this point, a release factor binds at the A-site, and helps to free the completed polypeptide from the ribosome. The ribosome then dissociates into the small and large subunits, once more.

rRNA Name	Prokaryotes	Eukaryotes	Function
5S	Large Subunit	Large Subunit	tRNA binding?
5.8S		Large Subunit	Translocation?
16S	Small Subunit		mRNA alignment
18S		Large Subunit	mRNA alignment
23S	Large Subunit		Peptide bond formation
28S		Large Subunit	Peptide bond formation

Table 7.1 - Location and function of rRNAs.

Three steps

Having considered the steps of translation in broader terms, we can now look at them in greater detail. We will consider the three steps of translation (bel0w) individually.



Movie 7.1 - 30S ribosomal subunit

Wikipedia

- Initiation (binding of the ribosomal subunits to the transcript and initiator tRNA)
- Elongation (repeated addition of amino acids to the growing polypeptide, based on the sequence of the mRNA - Figure 7.87)
- Termination (release of the completed polypeptide and dissociation of the ribosome into its subunits).

We already know that processed mRNAs are sent from the nucleus to the cytoplasm in eukaryotic cells, while in prokaryotic cells, transcription and translation occur in a single cellular compartment. The small and large subunits of ribosomes, each composed of characteristic rRNAs and proteins, are found in the cytoplasm and assemble on mRNAs to form complete ribosomes that carry out translation. Both prokaryotic

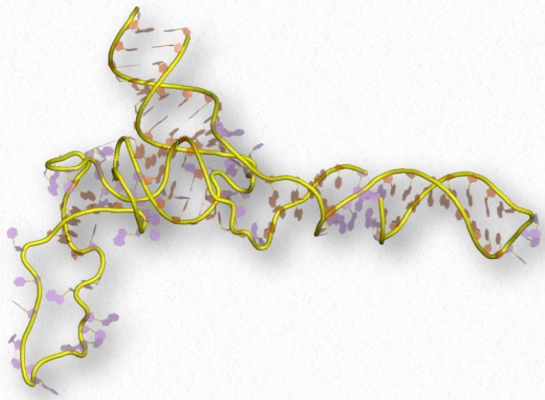


Figure 7.88 - Structure of 5S rRNA

and eukaryotic ribosomal subunits are made up of one or more major rRNAs together with a large number of ribosomal proteins. The small subunits of prokaryotic cells are called the 30S ribosomal subunits, while their counterparts in eukaryotes are the 40S subunits. The large ribosomal subunits in prokaryotes are the 50S subunits, while those in eukaryotic cells are 60S. These differences reflect the larger mass of eukaryotic ribosomes. The rRNA components of ribosomes are important for the recognition of the 5' end of the mRNA, and also play a catalytic role in the formation of peptide bonds.

Initiation

Messenger RNAs have non-coding sequences both at their 5' and 3' ends, with the actual protein-coding region sandwiched in between these untranslated regions (called the 5' UTR and 3' UTR, respectively). The ribosome must be able to recognize the 5' end of the mRNA and bind to it, then determine where the start codon is located. It is important to note that both in prokaryotes and eukaryotes, ribosomes assemble at the 5' end of the transcript by the stepwise binding of the small and large subunits. The small subunit first binds to the mRNA at specific sequences in the 5' UTR. The large subunit then binds to the complex of the mRNA and small subunit, to form the complete ribosome.

Initiator tRNA

Initiation also requires the binding of the first tRNA to the ribosome. As we have noted earlier, the initiation, or start codon is usually AUG, which codes for the amino acid methionine. Thus, the initiator tRNA is one that carries methionine and is designated as $tRNA^{met}$ or methionyl $tRNA^{met}$. In bacteria, the methionine on the initiator tRNA is modified by the addition of a formyl group, and is designated $tRNA^{fmet}$. The initiator tRNA carrying methionine to the AUG is different from the tRNAs that carry methionine

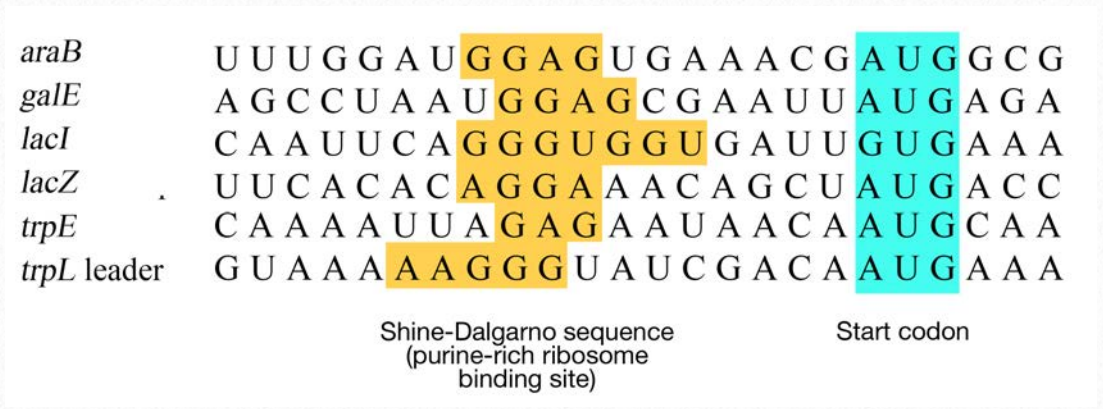
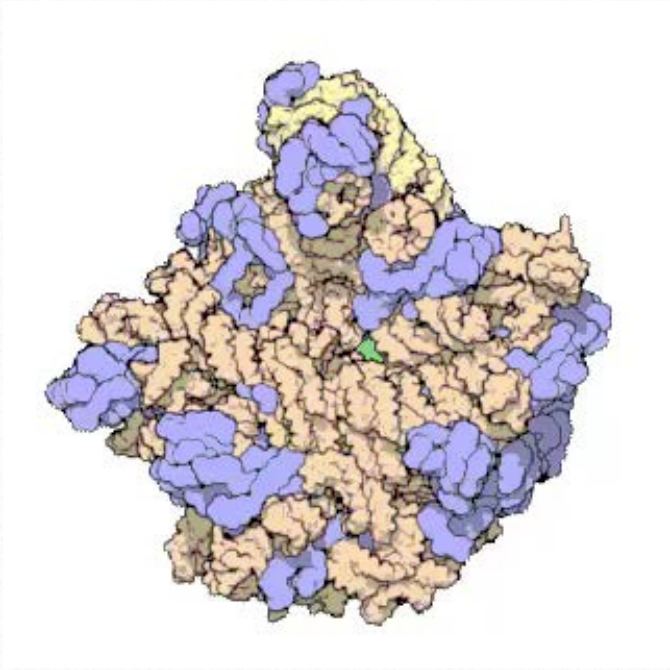


Figure 7.89 - Conserved sequences adjacent to start codons for various bacterial genes

Image by Martha Baker



Movie 7.2 - Large ribosomal subunit
Wikipedia

intended for other positions in proteins. As such, the initiator tRNA is sometimes referred to as $tRNA^{imet}$.

Prokaryotic initiation

In prokaryotes, the 5' end of the mRNA is the only free end available, as transcription is tightly coupled to translation and the entire mRNA is not transcribed before translation begins. Nevertheless, the ribosome must be correctly positioned at the 5' end of the messenger RNA in order to initiate translation. How does the ribosome "know" exactly where to bind in the 5'UTR of the mRNA?

Shine-Dalgarno sequence

Examination of the sequences upstream of the start codon in prokaryotic mRNAs reveals that there is a short purine-rich sequence ahead of the start codon that is crucial to recognition and binding by the small ribosomal subunit (Figure 7.89). This sequence, called the Shine-Dalgarno sequence, is complementary to a stretch of pyrimidines at the 3' end of the 16S rRNA component of the small ribosomal subunit (Figure 7.90). Base-pairing between these complementary sequences positions the small ribosomal subunit at the right spot on the mRNA, with the AUG start codon at the P-site.

Initiation factors

The binding of the small ribosomal subunit to the mRNA requires the assistance of three protein factors called Initiation Factors 1, 2 and 3 (IF1, IF2, IF3). These proteins, which are associated with the small ribosomal subunit, are necessary for its bind-

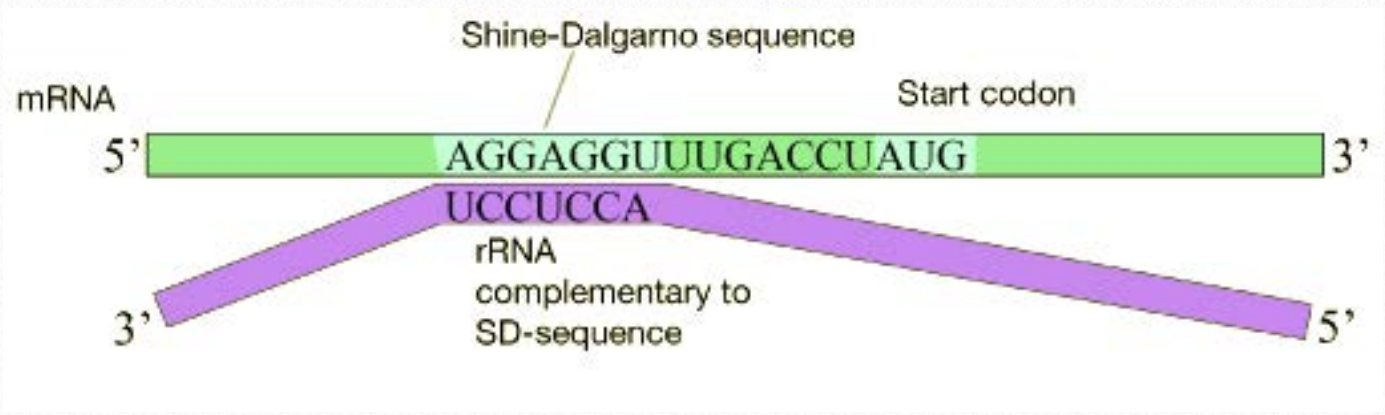


Figure 7.90 - Base pairing between the Shine-Dalgarno sequence in the mRNA and the 16S rRNA

Image by Martha Baker

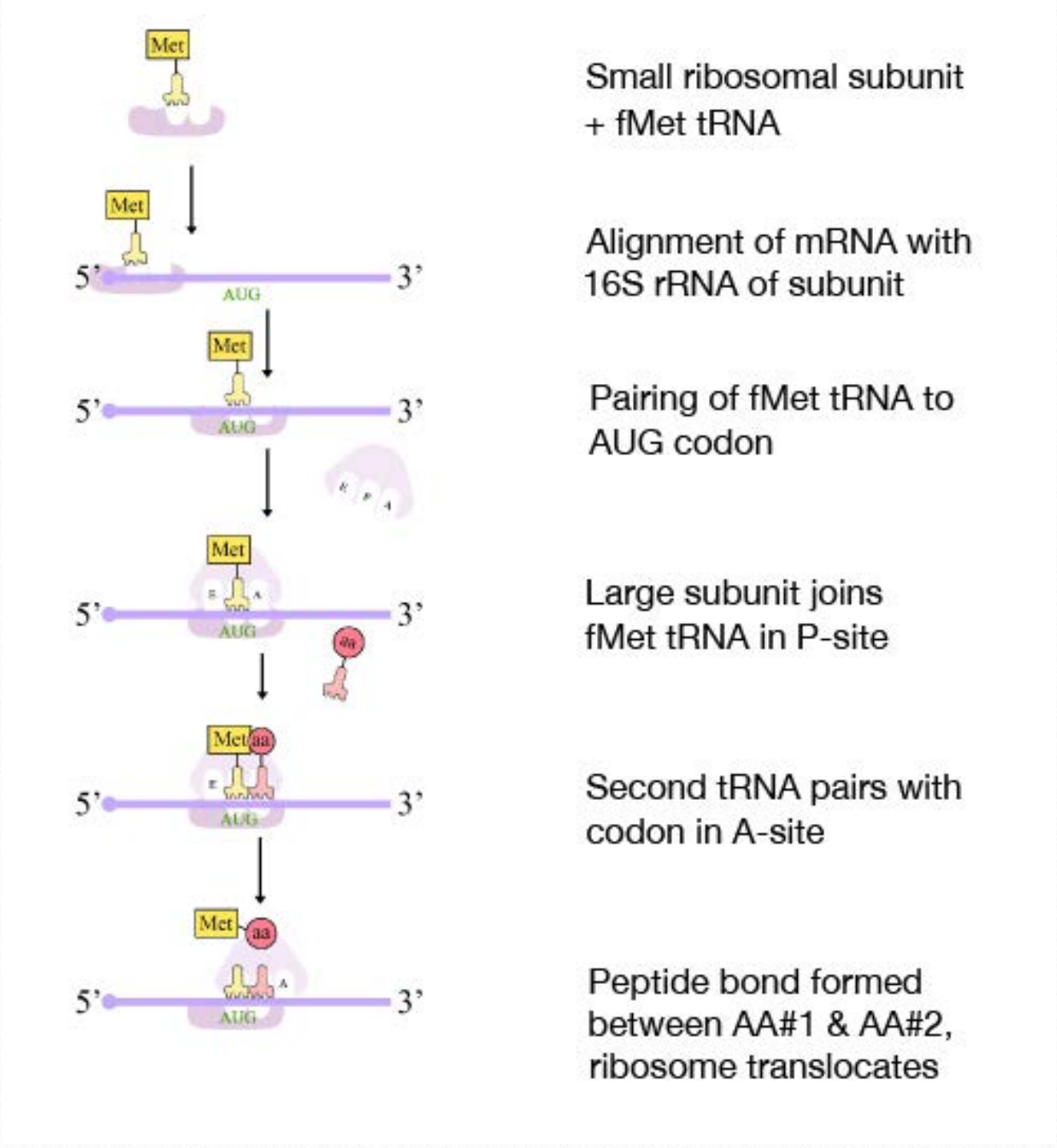


Figure 7.91 - Initiation - assembly of the ribosomal translation complex

Image by Martha Baker

ing to mRNA, but dissociate from it when the 50S ribosomal subunit binds. Of these proteins, IF3 is important for the binding of the small subunit to the mRNA, while IF2 is involved in bringing the initiator tRNA to the partial P-site of the small ribosomal subunit. IF1 occupies the A-site, preventing the binding of the initiator tRNA at that site.

Once the small ribosomal subunit is bound to the mRNA and the initiator tRNA is positioned at the P-site, the large ribosomal subunit is recruited and the initiation complex is formed. Binding of the 50S ribosomal subunit is accompanied by the dissociation of all three initiation factors. The removal of IF1 from the A-site on the ribosome frees up the site for the binding of the charged tRNA corresponding to the second codon (Figure 7.91).

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Eukaryotic initiation

In eukaryotes, initiation follows a similar pattern, although the order of events and the specific initiation factors are different.

Eukaryotes have a large number of

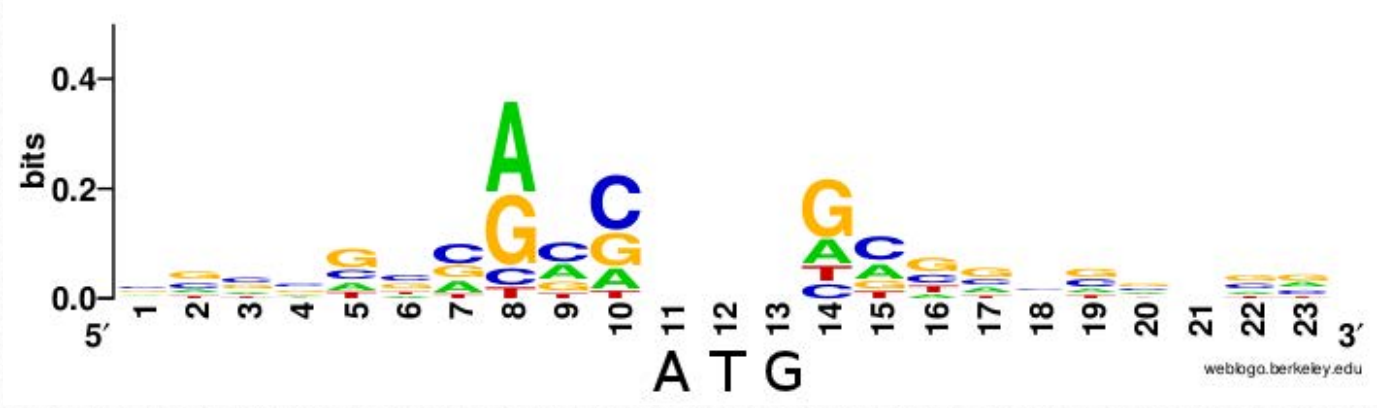

Figure 7.92 - Kozak sequence plot showing relative abundance of bases surrounding the AUG (ATG) start codon of human genes

Kozak sequences

Specific sequences surrounding the AUG, called Kozak sequences for the scientist who defined them, have been shown to be necessary for the binding of the 40S subunit, with the bases at -4 and +1 relative to the AUG being especially important.

IFs that are known as eIFs (eukaryotic initiation factors). These initiation factors are involved in the binding of the initiator tRNA to the small subunit, as well as in association of the small subunit with mRNA and subsequent attachment of the large subunit.

Ribosome assembly

The assembly of the translation machinery in eukaryotes begins with the binding of the initiator tRNA to the 40S (small) subunit. This step requires the assistance of eIF2 and eIF3. Next the small subunit with the initiator tRNA binds to the 7-methyl G cap on the 5'end of the mRNA. The 40S subunit then moves along the mRNA, scanning for a a start codon. Binding of the ribosomal subunit to the mRNA is dependent not just on finding an AUG, but on the sequences surrounding the codon.

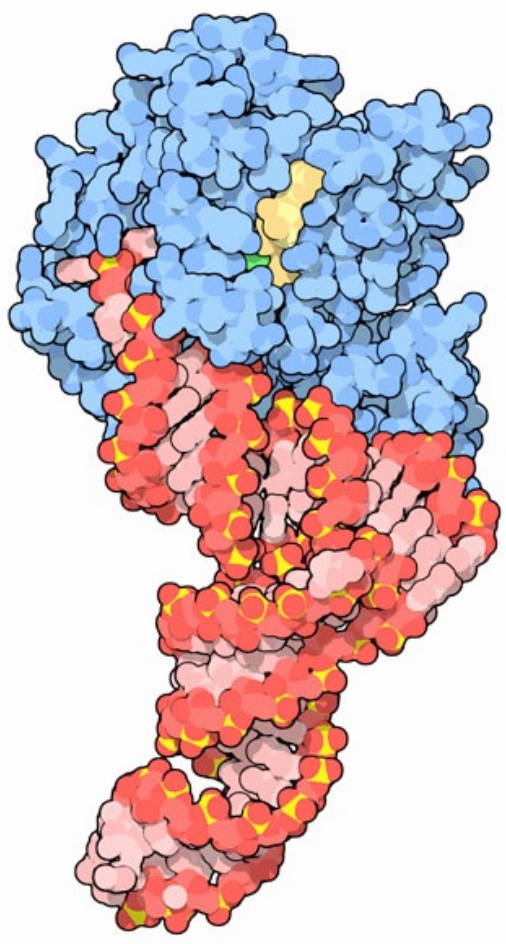

Figure 7.93 - EF-Tu (blue) bound to tRNA (red) and GTP (yellow)

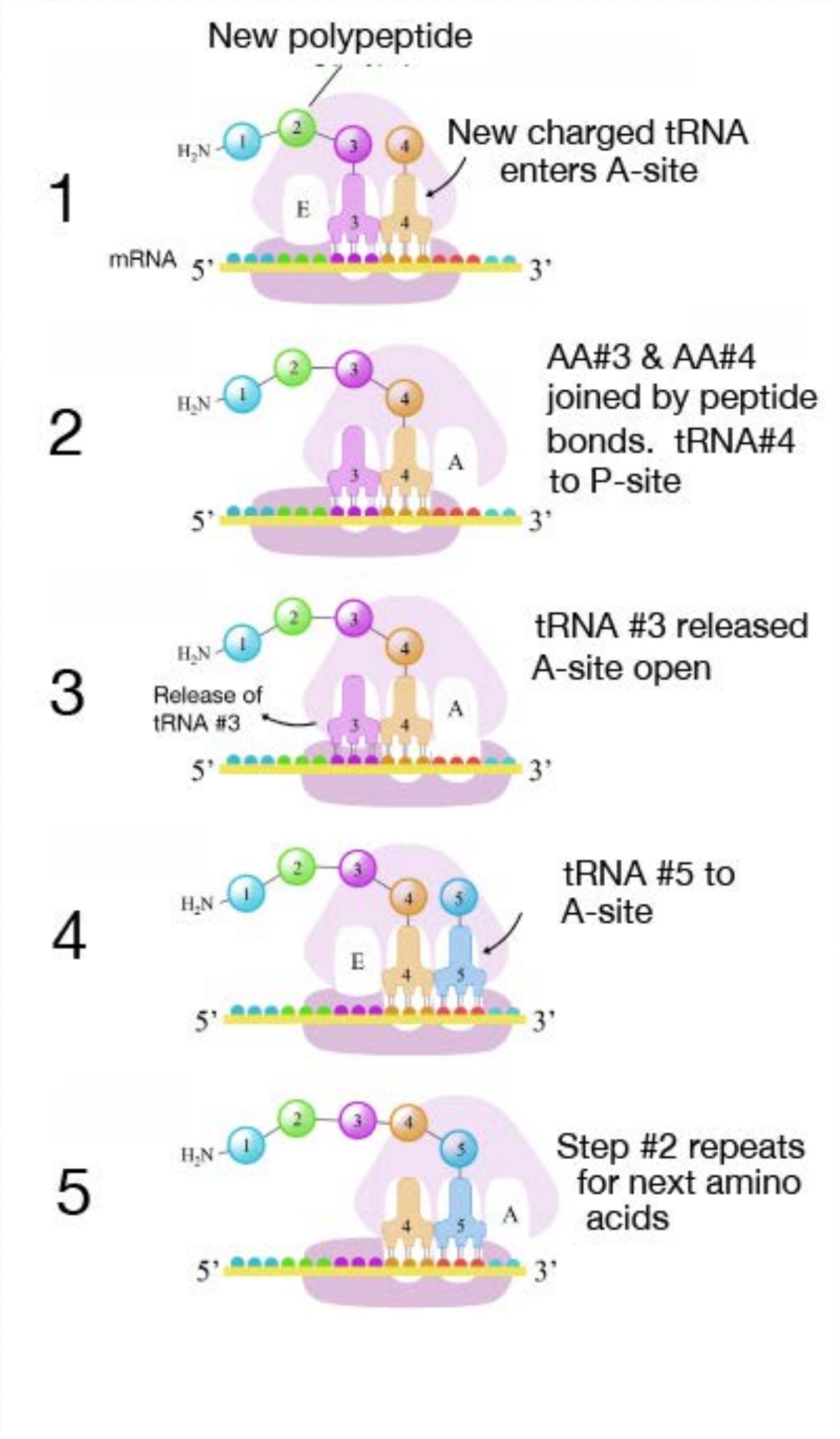

Figure 7.94 - The process of elongation

Image by Martha Baker

tant (Figure 7.92). Once the small subunit is properly positioned, the large ribosomal subunit (60S) binds, forming the initiation complex.

Elongation

After the ribosome is assembled with the initiator tRNA positioned at the AUG in the P-site, the addition of further amino acids can begin. In both prokaryotes and eukaryotes, the elongation of the polypeptide chain requires the assistance of elongation factors. In bacteria, the binding of the second charged tRNA at the A-site requires the elongation factor EF-Tu complexed with GTP (Figure 7.93). When the charged tRNA has been loaded at the A-site, EF-Tu hydrolyzes the GTP to GDP and dissociates from the ribosome. The free EF-Tu can then work with another charged tRNA to help position it at the A-site (Figure 7.94), after exchanging its GDP for a new GTP.

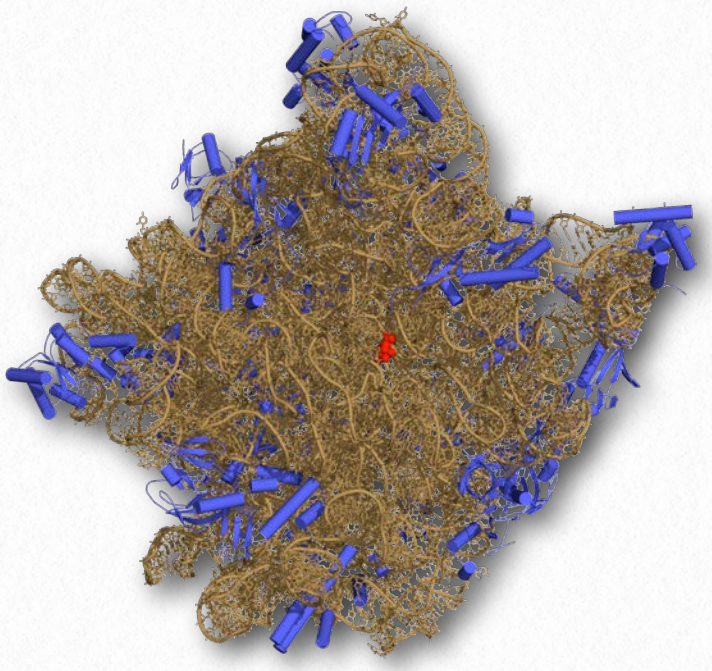

Figure 7.95 - 50S ribosomal subunit. RNA in brown. Protein in blue. Peptidyl transferase site in red.
Wikipedia

The corresponding step in eukaryotic cells is dependent on the elongation factor eEF1α.GTP. Once both P-site and A-site are occupied, the methionine carried by the tRNA in the P-site is joined to the amino acid carried by tRNA in the A-site, forming a peptide bond.

The reaction that joins the amino acids occurs in the ribosomal peptidyl transferase center, which is part of the large ribosomal subunit (Figure 7.95).

Ribozyme

Interestingly, there is strong evidence that this reaction is catalyzed by rRNA components of the large subunit, making the formation of peptide bonds an example of the activity of RNA enzymes, or ribozymes. The result of the peptidyl transferase activity is that the tRNA in the A-site now has two amino acids attached to it, while the tRNA at the P-site has none. This "empty" or deacylated tRNA is moved to the E-site on the ribosome, from which it can exit. The tRNA in the A-site, then moves to occupy the vacated P-site, leaving the A-site open for the next incoming charged tRNA. Yet another elongation factor, EF-G complexed with GTP, is required for the translocation of the ribosome along the mRNA in bacteria, while in eukaryotes, this role is played by eEF2.GTP. Repeated cycles of these steps result in the elongation of the polypeptide by one amino acid per cycle, until a termination, or stop codon is in the A-site.

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Termination

When a stop codon is in the A-site, proteins called release factors (RFs) are needed to recognize the stop codon and cleave and release the newly made polypeptide. In bacteria, RF1 is a release factor that can recognize the stop codon UAG, while RF2 recognizes UGA. Both RF1 and RF2 can recognize UAA. A third release factor, RF3, works with RF1 and RF2 to hydrolyze the linkage between the polypeptide and the final tRNA, to release the newly synthesized protein. This is followed by the dissociation of the ribosomal subunits from the mRNA, ending the process of translation.

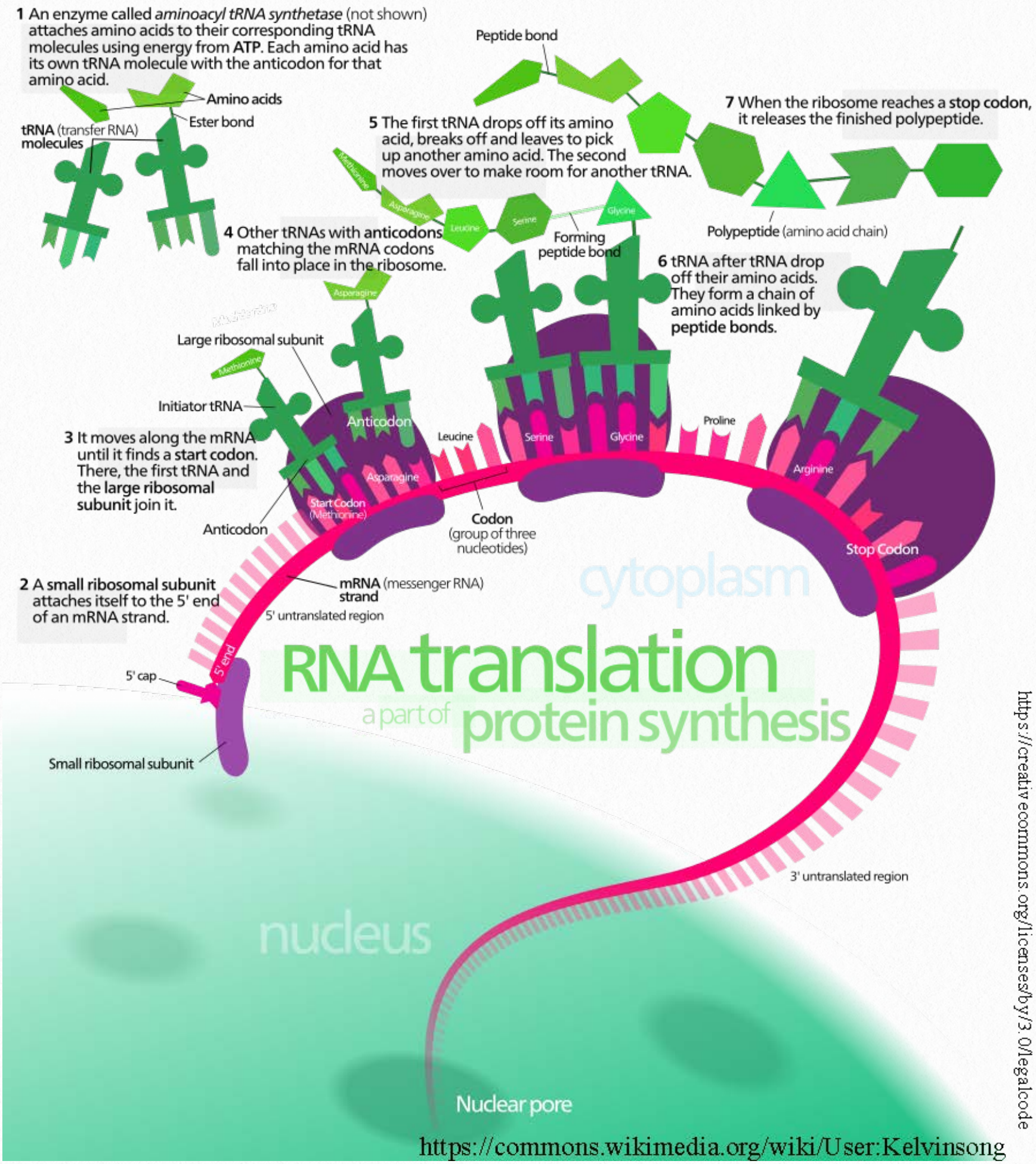


Figure 7.96 - The process of translation

Wikipedia

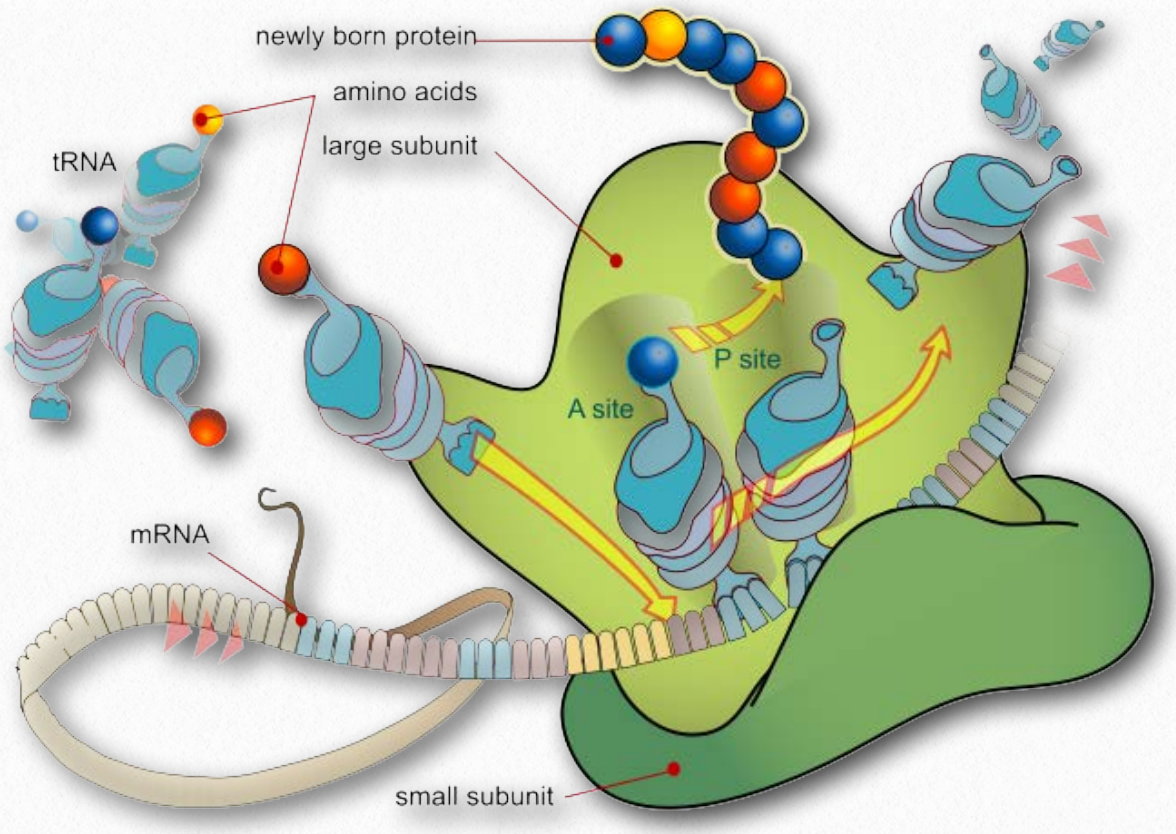


Figure 7.97 - Another perspective of translation. The 3' end of the mRNA is on the left and the ribosome is moving from right to left

But the vast majority of proteins in eukaryotic cells are made by ribosomes, free or membrane-bound, in the cytoplasm of the cell (the exceptions are a handful of proteins made within mitochondria and chloroplasts).

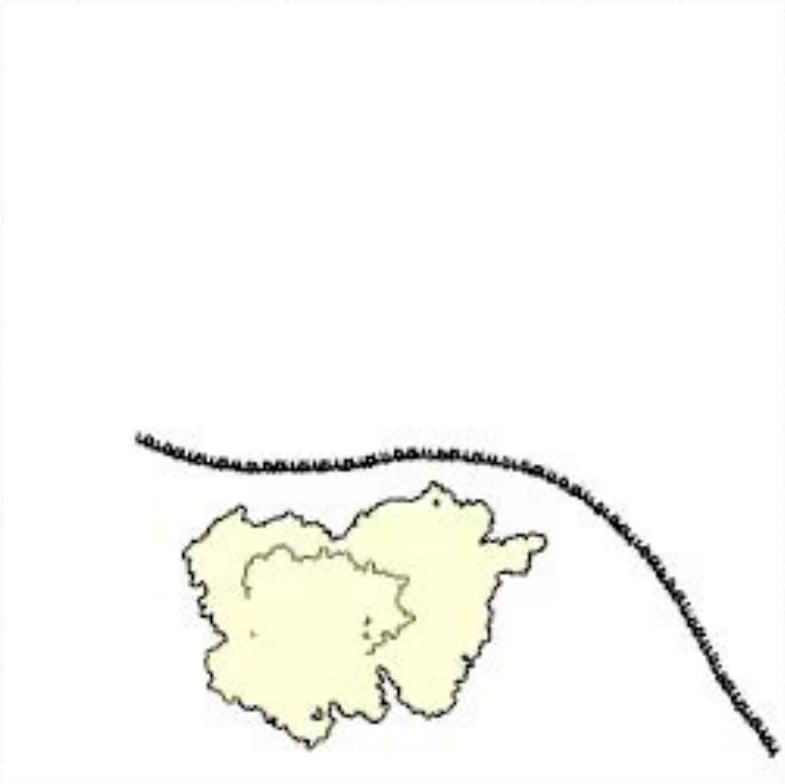
Delivery

Each of the thousands of proteins made in the cytoplasm must, therefore, be delivered to the appropriate cellular compartment in which it functions.

Polypeptide processing

What happens to the newly synthesized polypeptide after it is released from the ribosome? As you know, functional proteins are not simply strings of amino acids. The polypeptide must fold properly in order to perform its function in the cell. It may also undergo a variety of modifications such as the addition of phosphate groups, sugars, lipids, etc. Some proteins are produced as inactive precursors that must be cleaved by proteases to be functional.

An additional challenge in eukaryotic cells is the presence of internal, membrane-bounded compartments. Each compartment contains different proteins with different functions.



Movie 7.3 Translation of a protein secreted into the endoplasmic reticulum. Small subunit in yellow. Large subunit in green. tRNAs in blue.

Wikipedia

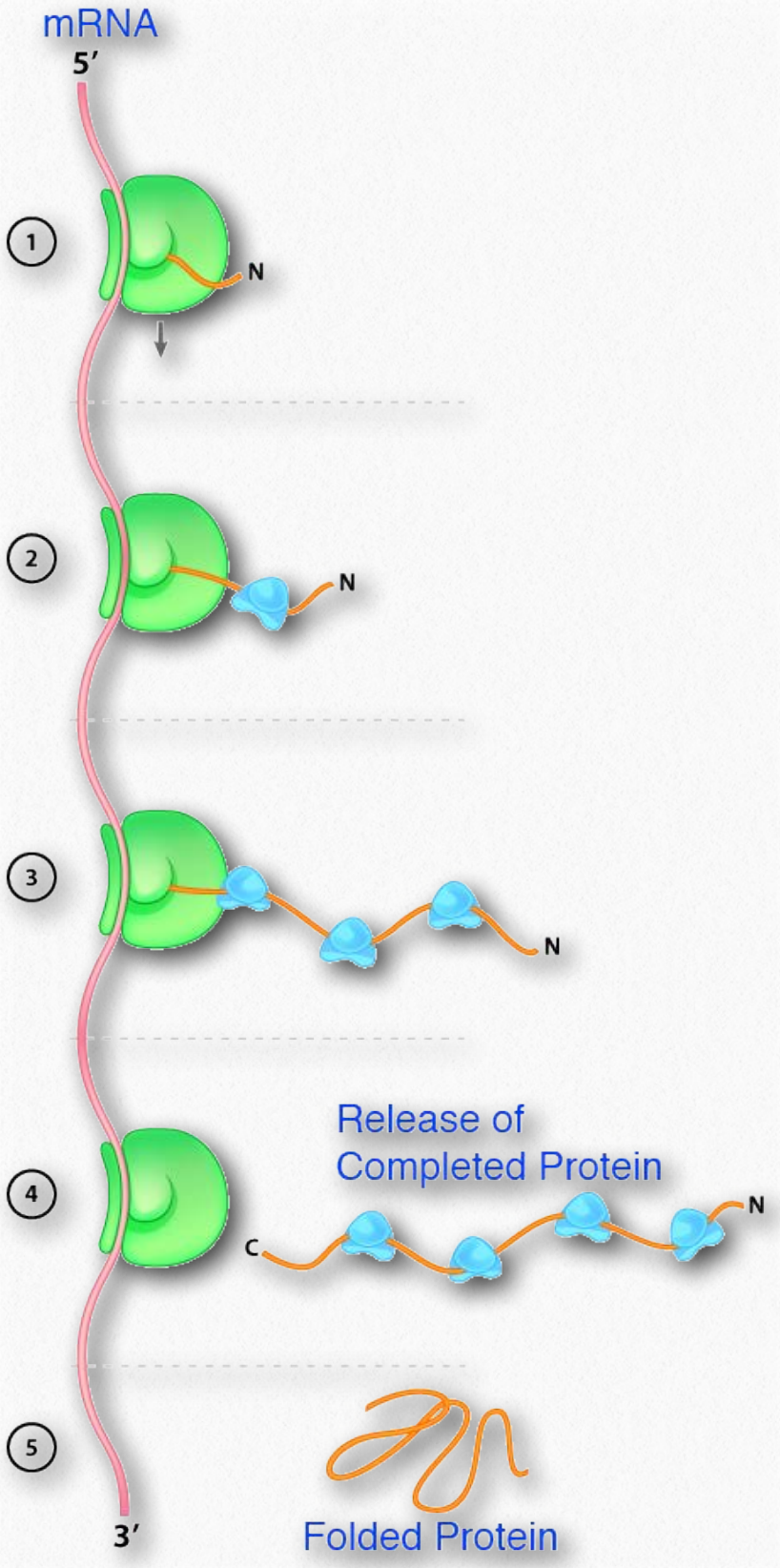


Figure 7.98 - Action of chaperone to facilitate proper folding of a protein (orange)

Image by Aleia Kim

Some proteins are delivered to their destinations in an unfolded state, and are folded within the compartment in which they function. Others are fully folded and may be post-translationally modified before they are sent to their cellular (or extracellular) destinations.

Some proteins are delivered as they are being synthesized (co-translationally - see Movie 7.3) while others are sorted to their compartments post-translationally. But, with the exception of cytosolic proteins, all proteins must cross membrane barriers, through membrane channels or other "gates", or by transport within membrane vesicles that fuse with the membrane of the target organelle to deliver their contents.

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Folding and post-translational modifications

Proper folding of a protein into its 3-dimensional conformation is necessary for it to function effectively. As described in an earlier chapter (HERE), the folding of a protein is largely influenced by hydrophobic interactions that result in folding of the protein in such a way as to position hydrophobic residues in the interior, or core, of the protein, away from the aqueous environment of the cell.

Proper folding may also involve the interaction of regions of the polypeptide that are distant from each other, so that portions of the N-terminal region of the polypeptide may be in close proximity to parts of the C-terminus of the final folded mole-

cule.

As a polypeptide emerges from the ribosome, however, the N-terminal region of the polypeptide may begin to fold on itself, with adjacent parts of the chain interacting in inappropriate ways, before the entire protein has been made. This can result in misfolding of the protein and consequent malfunction. To prevent misfolding, cells have protein chaperones, whose function is to bind to and shield regions of polypeptides as they emerge from the ribosome, and keep them from improperly interacting with one another or with other proteins in the vicinity, until they can fold into their correct final shape (Figure 7.98). In addition, there are classes of chaperones that are able sequester proteins in such a way as to permit unfolding and refolding of misfolded polypeptides. These proteins ensure that the vast majority of proteins in cells are folded into their correct, functional 3-dimensional shapes.

Protein sorting

The process by which proteins are identified as belonging to a particular compartment and then correctly delivered to that destination is known as protein sorting. How does a cell know where a particular protein should be sent?

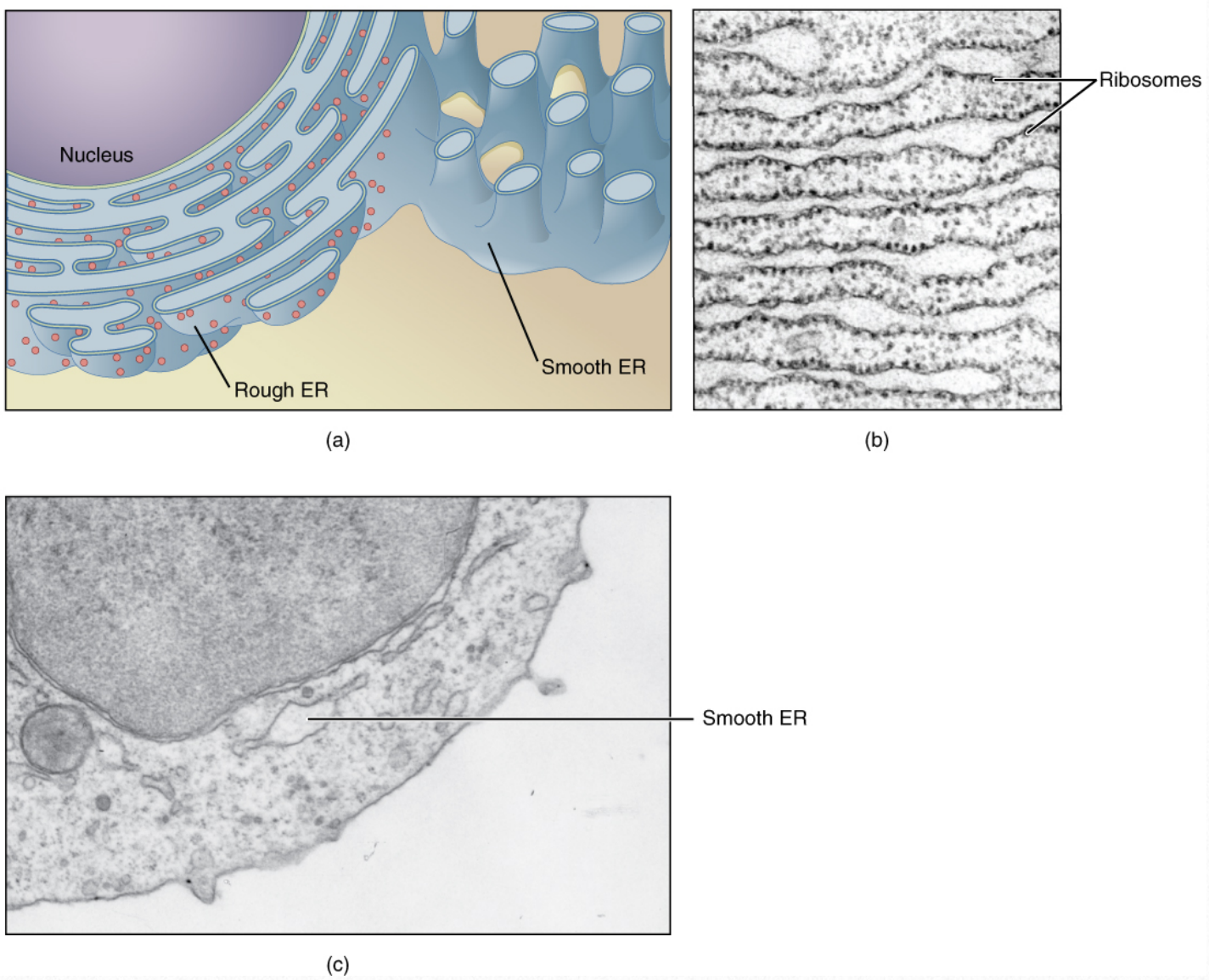

Figure 7.99 - Rough (ribosome bound) and smooth endoplasmic reticulum

Wikipedia

Proteins have "address labels" or sorting signals that indicate which cellular compartment they are destined for. Characteristic sorting signals are found on proteins that are sent to the nucleus, the ER (Figure 7.99), the mitochondria, etc.

Signal sequences

What do these sorting signals look like? Most sorting signals (also called signal sequences) are short stretches of amino acid sequence (that is, they are part of the amino acid sequence of the protein). Different cellular compartments have different "address labels".

Signal sequences may be found at the N-terminal or C-terminal region of proteins, or they may be within the amino acid sequence of the proteins. The location of the signal sequence for any given protein is fixed, however. Signal sequences for proteins to be delivered to the endoplasmic reticulum (ER) are found at the N-terminus of the protein. Mitochondrial and chloroplast proteins encoded by nuclear genes also have N-terminal signal sequences. Signal sequences for nuclear proteins, by contrast, are internal to the polypeptide, and may consist of one or more stretches of amino acids that will be displayed on the surface of these proteins once they are folded.

Figure 7.100 - N-terminal signal sequence (green) emerging from the ribosome.

Free and membrane-bound ribosomes

Proteins are synthesized by ribosomes in the cytoplasm or by those that associate with membranes temporarily (membrane-bound ribosomes). The free ribosomes make proteins that are destined for the nucleus, as well as those going to chloroplasts, mitochondria and peroxisomes. Nuclear proteins are delivered in their folded state, while chloroplast and mitochondrial proteins are threaded through translocation channels in the membranes of these organelles, to be folded at their destination.

Proteins that are destined for the ER, the Golgi apparatus, lysosomes as well as those that are to be secreted from the cell are first delivered to the ER by ribosomes that associate with the membrane of the rough ER and synthesize the protein directly into the ER. Proteins delivered by this manner into the lumen of the ER undergo folding and modification in the ER. All proteins delivered to the ER, regardless of their final destination, have an N-

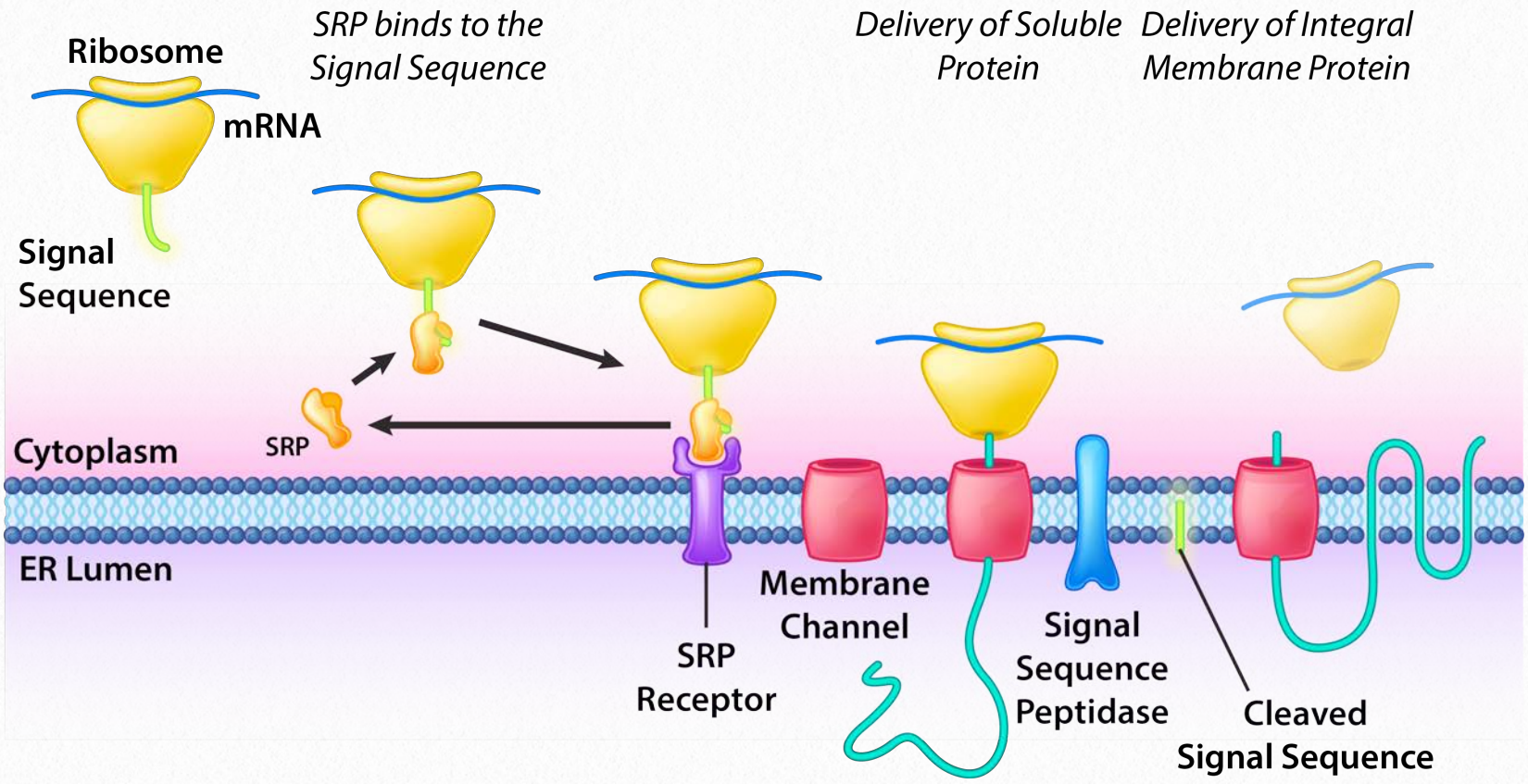

Figure 7.101 - Translation of a protein into the endoplasmic reticulum

Image by Aleia Kim

terminal ER signal sequence of 15-30 amino acids.

Protein delivery into the endoplasmic reticulum

The N-terminal part of a protein is the first part of a nascent polypeptide that emerges from the ribosome (Figure 7.100). The sequence of amino acids in this region, if it is an ER signal, will be recognized and bound by a ribonucleoprotein complex called the Signal Recognition Particle (SRP). Binding of the SRP to the N-terminal signal sequence causes translation to pause. The SRP, in turn, is bound by an SRP receptor in the ER membrane (Movie 7.3 & Figure 7.101), effectively anchoring the ribosome to the membrane.

The location of SRP receptors near membrane channels in the ER positions the ribosome over a translocation channel. Once the ribosome is docked over the channel, the SRP releases the signal sequence, which is threaded through the channel, with its hydrophobic residues interacting with the hydrophobic interior of the membrane. Translation resumes at this point and the rest of the protein is delivered into the lumen of the ER as it is made. The ribosome remains associated with the ER membrane till translation is completed, at which point it dissociates. The signal sequence, which is no longer needed once the protein has been delivered, is cleaved off by a membrane associated signal peptidase, releasing the completed protein into the ER lumen.

While soluble proteins are delivered into the ER, integral membrane proteins do not pass all the way through, but, instead, are anchored in the membrane of the ER by hydrophobic stop transfer sequences.

Folding and modification

Proteins in the lumen of the ER are folded with the help of numerous chaperones resident in the endoplasmic reticulum. The environment within the ER lumen is also more oxidizing than the cytosol, and permits the formation of disulfide bonds to stabilize the folded proteins. Protein disulfide isomerase, an enzyme active in the ER lumen both helps to make disulfide bonds and removes bonds that were incorrectly made during the folding process. In addition, proteins in the ER undergo modifications such as glycosylation and addition of glycolipids. Multimeric proteins are also assembled from their subunits in the ER.

Proteins that have been correctly folded and modified are transported from the ER, in membrane vesicles, to their final destinations. Improperly folded proteins are recognized by a surveillance mechanism in the ER and are sent back to the cytoplasm to be degraded in proteasomes.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

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Translation

To the tune of "*Maria*" (from "West Side Story")

Metabolic Melodies Website HERE

Translation
The most intricate thing I ever saw

From five prime to three prime, translation, translation
The final step that we know about the central dog-ma

Amino, carboxyl, translation, translation. . . .
Translation, translation, translation . .
Translation!

I just learned the steps of translation
And all the things they say
About tRNA
Are true

Translation!
To form peptide bonds in translation
The ribosomal cleft
Must bind to an E-F
tee-you!

Translation!
A-U-G binds the f-met's cargo
16S lines up Shine and Dalgarno
Translation
I'll never stop needing translation
The most intricate thing I ever saw
Translationnnnnnnnnnnnnnnn

Recording by Tim Karplus
Lyrics by Kevin Ahern

Good Protein Synthesis

To the tune of "*Good King Wenceslaus*"

Metabolic Melodies Website HERE

Amino acids cannot join
By themselves together
They require ribosomes
To create the tether

All the protein chains get made
'Cording to instruction
Carried by m-R-N-A
In peptide bond construction

Small subunit starts it all
With initiation
Pairing up two RNAs
At the docking station

Shine Dalgarno's complement
In the 16 esses
Lines the A-U-G up so
Synthesis commences

Elongation happens in
Ribosomic insides
Where rRNA creates
Bonds for polypeptides

These depart the ribosome
Passing right straight through it
In the tiny channels there
Of the large subunit

Finally when the sequence of
One of the stop codons
Parks itself in the A site
Synthesis can't go on

P-site RNA lets go
Of what it was holding
So the polypeptide can
Get on with its folding

Recording by David Simmons
Lyrics by Kevin Ahern

Information Processing: Gene Expression

Regulating gene expression

The processes of transcription and translation described so far tell us what steps are involved in the copying of information from a gene (DNA) into RNA and the synthesis of a protein directed by the sequence of the transcript (Figure 7.102). These steps are required for gene expression, the process by which information in DNA directs the production of the proteins needed by the cell.

But what determines whether a gene is expressed at a given time? Cells do not, as we know, express all of their genes all of the time. Some genes are expressed in particular cell types but not others, while others may be expressed at specific stages of development. Cells must also be able alter their patterns of gene expression in response to internal and external cues, controlling the production of proteins as needed, to meet their changing needs. Regulating gene expression is, therefore, crucial. Given that there are multiple steps involved in gene ex-

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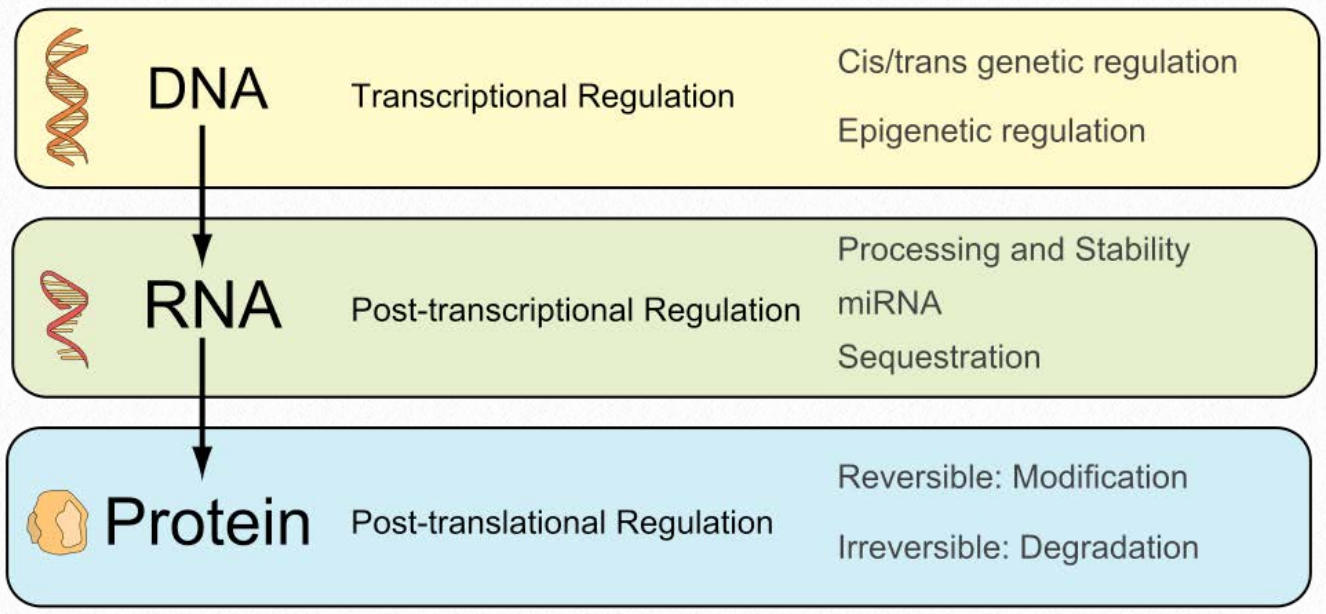

Figure 7.102 - Multiple levels of control of gene expression

Wikipedia

pression, there are several different points at which the process could be regulated. Not surprisingly, many regulatory mechanisms are known, each acting at a different stage in the path from DNA to protein.

Regulation of transcription

The first step in gene expression is transcription, so regulation of transcription is an obvious way to affect whether a gene is expressed and to what extent.

What are the molecular switches that turn transcription on or off? Although there are additional factors that affect transcription, such as the accessibility of a gene to the transcriptional machinery, the basic mechanism by which transcription is regulated depends on highly specific interactions between transcription regulating proteins and regulatory sequences on DNA.

What are these regulatory sequences and what proteins bind them? In addition to the promoter sequences required for transcription initiation, genes have additional *cis* regulatory sequences (sequences of DNA on the same DNA molecule as the gene) that control when a gene is transcribed. Regulatory sequences are bound tightly and specifically by transcriptional regulators, proteins that can recognize DNA sequences and bind to them. The binding of such proteins to the DNA can regulate transcription by preventing or increasing transcription from a particular promoter.

Transcriptional regulation in prokaryotes

Let us first consider some examples from prokaryotes. In bacteria, genes are often clustered in groups, such that genes that need to be expressed at the same time are next to each other and all of them are controlled as a single unit by the same promoter. Groups of genes that are coordinately regulated by a single promoter are referred to as operons. The entire set of genes in an operon can be controlled through the action of DNA binding proteins

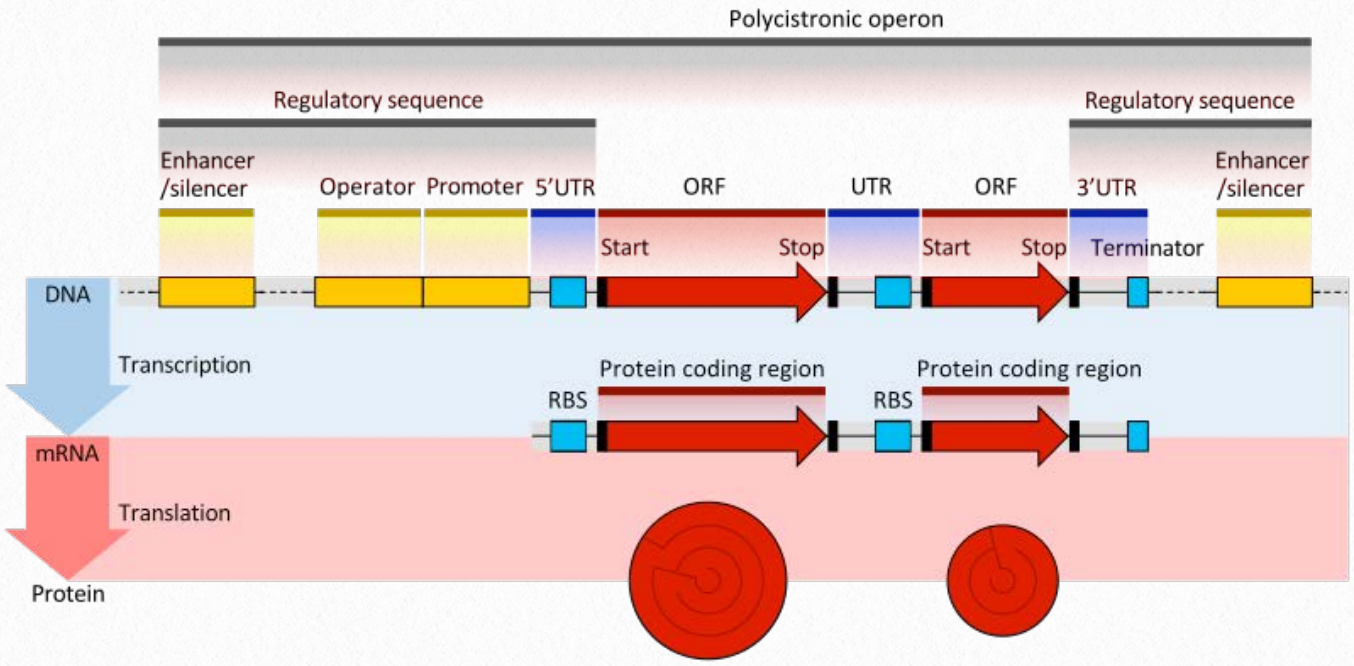

Figure 7.103 - Prokaryotic genes organized in an operon

Wikipedia

that act as either repressors (preventing transcription of the genes) or activators (increasing transcription of the genes). The binding of these proteins to their DNA targets is allosterically controlled by the binding of specific small molecules that signal the state of the cell.

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Induction of the *lac* operon

The *lac* operon is one such group of coordinately regulated genes that encode proteins needed for the uptake and breakdown of the sugar lactose. *E.coli* cells preferentially use glucose for their energy needs, but if glucose is unavailable, and lactose is present, the bacteria will take up lactose and break it down for energy. Since the proteins for taking up and breaking down lactose are only needed when glucose is absent and lactose is available, the bacterial cells need a way to express the genes of the *lac* operon only under those conditions. The default state of the *lac* operon is OFF.

Removing a repressor

Transcription of the *lac* cluster of genes is primarily controlled by a repressor protein that binds to a region of the

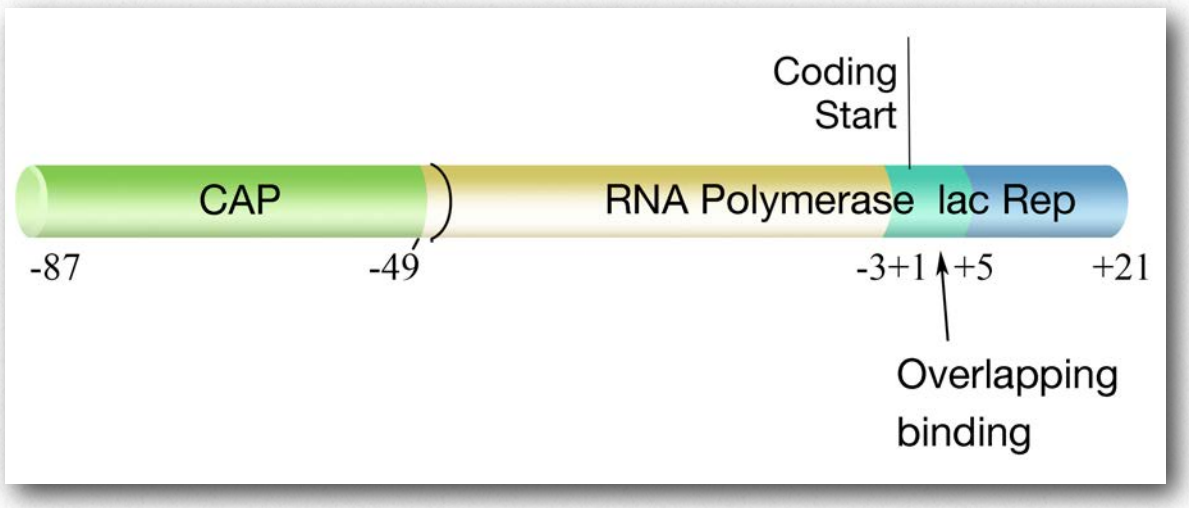

Figure 7.104 - Protein binding sites in the lac regulatory region

Image by Martha Baker

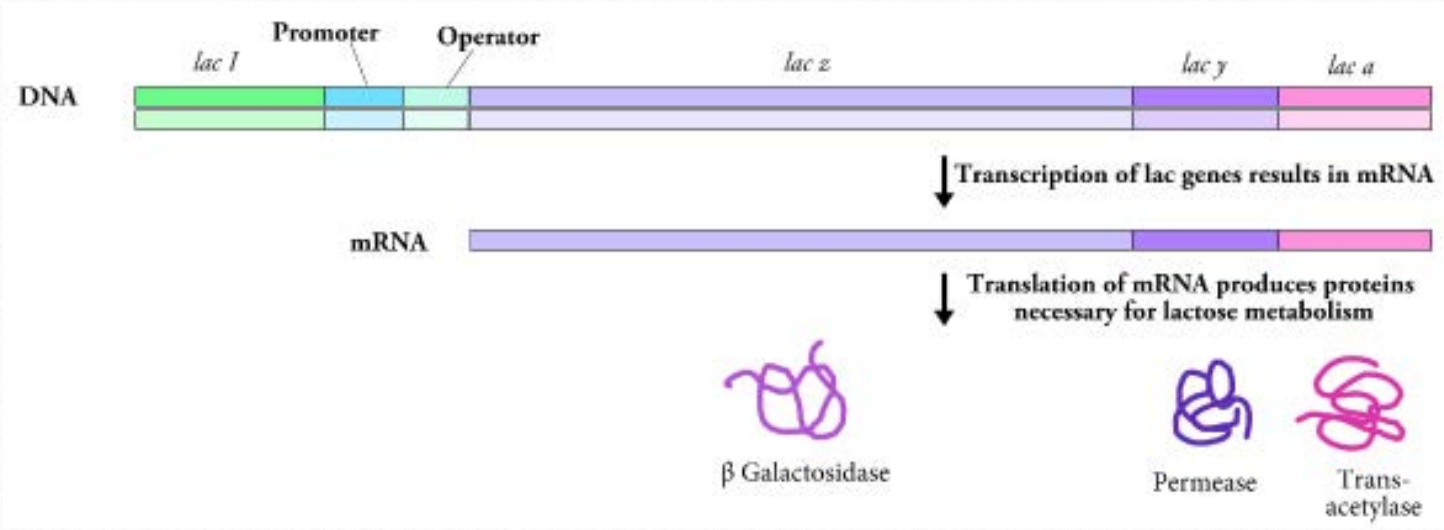

Figure 7.105 - Lac operon structure and products

Image by Martha Baker

DNA just downstream of the -10 sequence of the *lac* promoter (Figure 7.104). Recall that the promoter is where the RNA polymerase must bind to begin transcription. The location on the DNA where the lac repressor is bound is called the operator (Figure 7.105). When the repressor is bound at this position, it physically blocks the RNA polymerase from transcribing the genes, just as a vehicle blocking your driveway would prevent you from pulling out. Obviously, if you want to leave, the vehicle that is blocking your path must be removed. Likewise, in order for transcription to occur, the repressor must be removed from the operator to clear the path for RNA polymerase (Figure 7.106).

How is the repressor removed? When the sugar lactose is present, a small amount of it is taken up by the cells and converted to an isomeric form, allolactose (Figure 7.107). Allolactose binds to the repressor, changing its conformation so that it no longer binds to the operator. When the repressor is no longer bound to the operator, the "roadblock" in front of the RNA polymerase is re-

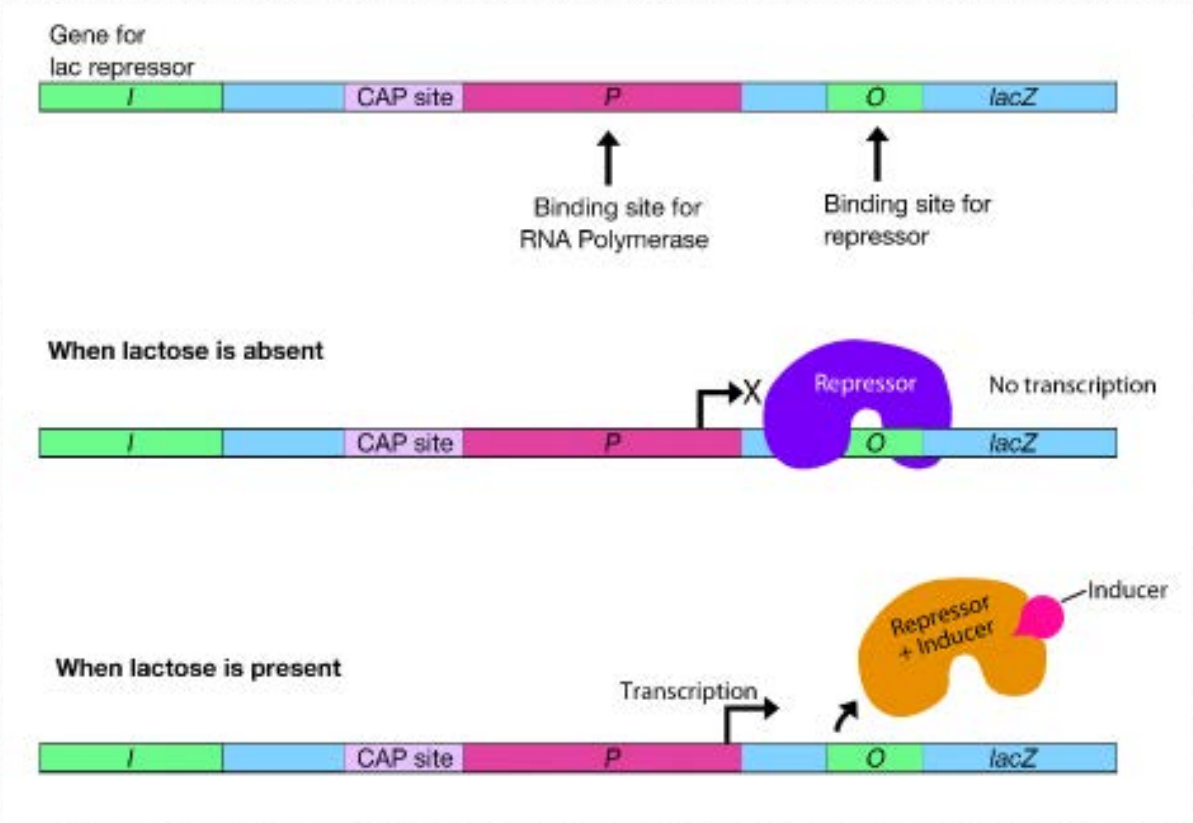

Figure 7.106 - Lac operon in the absence (middle) and presence (bottom) of inducer

Image by Martha Baker

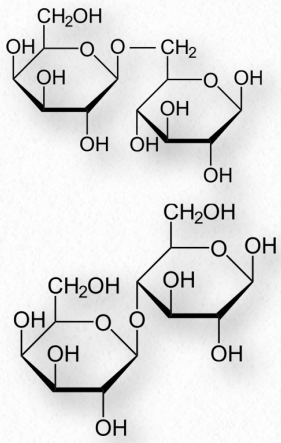

Figure 7.107 - Allolactose (top) and lactose (bottom)

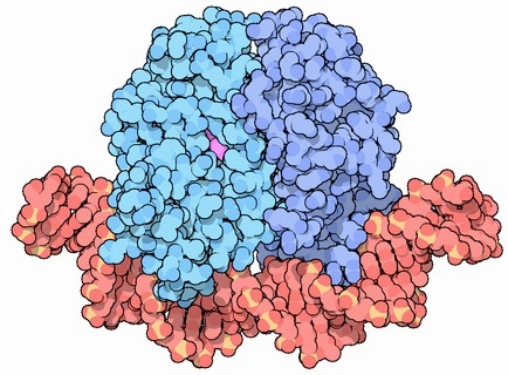

Figure 7.108 - CAP (blue) bound to the DNA adjacent to the lac promoter (orange). cAMP shown in pink.

Wikipedia

moved, permitting the transcription of the genes of the *lac* operon

What makes this an especially effective control system is that the genes of the *lac* operon encode proteins that enable the break down of lactose. Turning on these genes requires lactose to be present. Once the lactose has been broken down, the lac repressor binds to the operator once more and the *lac* genes are no longer expressed. This allows the genes to be expressed only when they are needed.

Recruiting RNA polymerase

But how do glucose levels affect the expression of the *lac* genes? We noted earlier that if glucose was present, lactose would not be used. A second level of control is exerted by a protein called Catabolite Activator Protein (CAP - Figure 7.108)). CAP (also sometimes called CBP or cAMP binding protein) binds to a site adjacent to the promoter and is necessary to recruit RNA polymerase to bind the *lac* promoter.

cAMP binding

CAP binds to its site only when glucose levels are low. Low glucose levels are linked to the activation of an enzyme, adenylate cyclase, that makes the molecule cyclic AMP

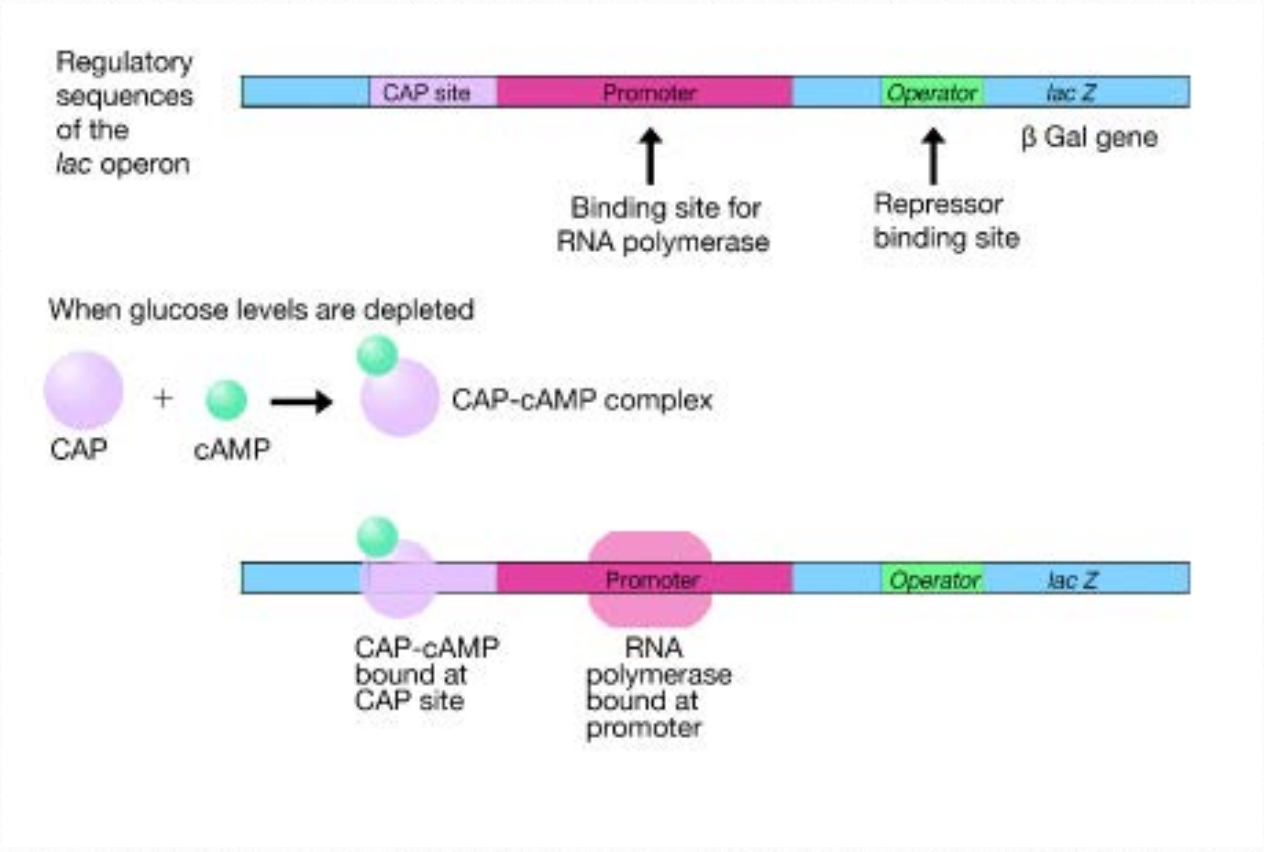

Figure 7.109 - Lac operon in the presence (top) and absence (bottom) of glucose

Image by Martha Baker

(cAMP). The binding of cAMP to the CAP causes a conformational change in CAP that allows it to bind to the CAP-binding site. When CAP is bound at this site, it is able to recruit RNA polymerase to bind at the promoter, and begin transcription.

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The combination of CAP binding and the lac repressor dissociating from the operator when lactose levels are high ensures transcription of the lac operon just when it is most needed. The binding of CAP may be thought of as a green light for the RNA polymerase, while the removal of lac repressor is like the lifting of a barricade in front of it. When both conditions are met, the RNA polymerase transcribes the downstream genes.

Control of the *trp* operon by repression

The *lac* operon we have just described is a set of genes that are expressed only under the specific conditions of glucose depletion and lactose availability. Other genes may be expressed *unless* a particular condition is met. For these genes, the default state is ON.

An example of this is the *trp* operon, which encodes enzymes necessary for the synthesis of the amino acid tryptophan. These genes are constitutively expressed (always on), except when tryptophan is available from the cell's surroundings, making its synthesis unnecessary. Under conditions where tryptophan is abundant in the environment, the trp genes can be turned off. This is achieved by a repressor protein that will bind to the operator only in the presence of tryptophan (Figure 7.110). Binding of tryptophan to the repressor causes binding of the repressor to the operator. Be-

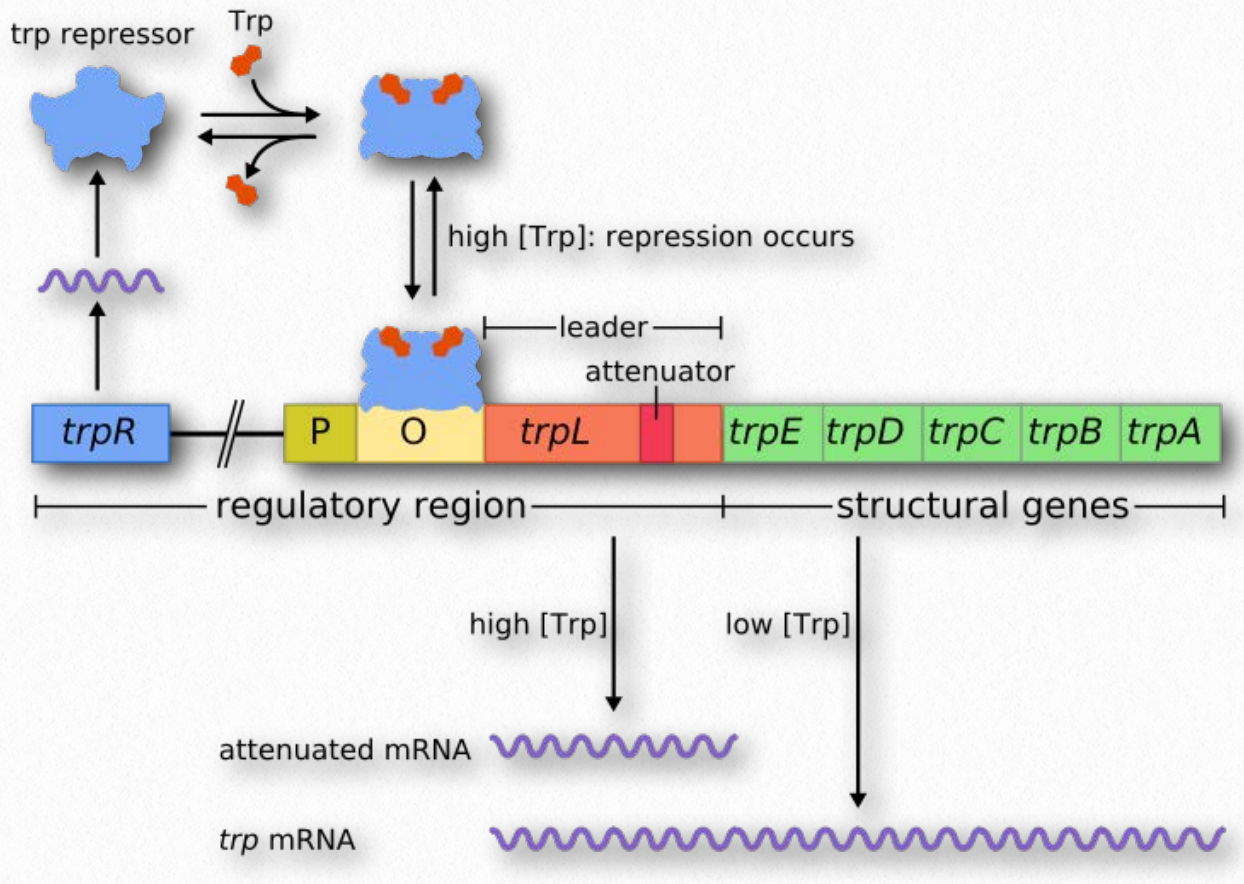

Figure 7.110 - Structure and regulation of the trp operon
Wikipedia

Attenuation

Another mechanism that regulates the expression of the trp operon is attenuation. Attenuation is a process by which the expression of an operon is controlled by termination of transcription before the first gene of the operon (Figure 7.111).

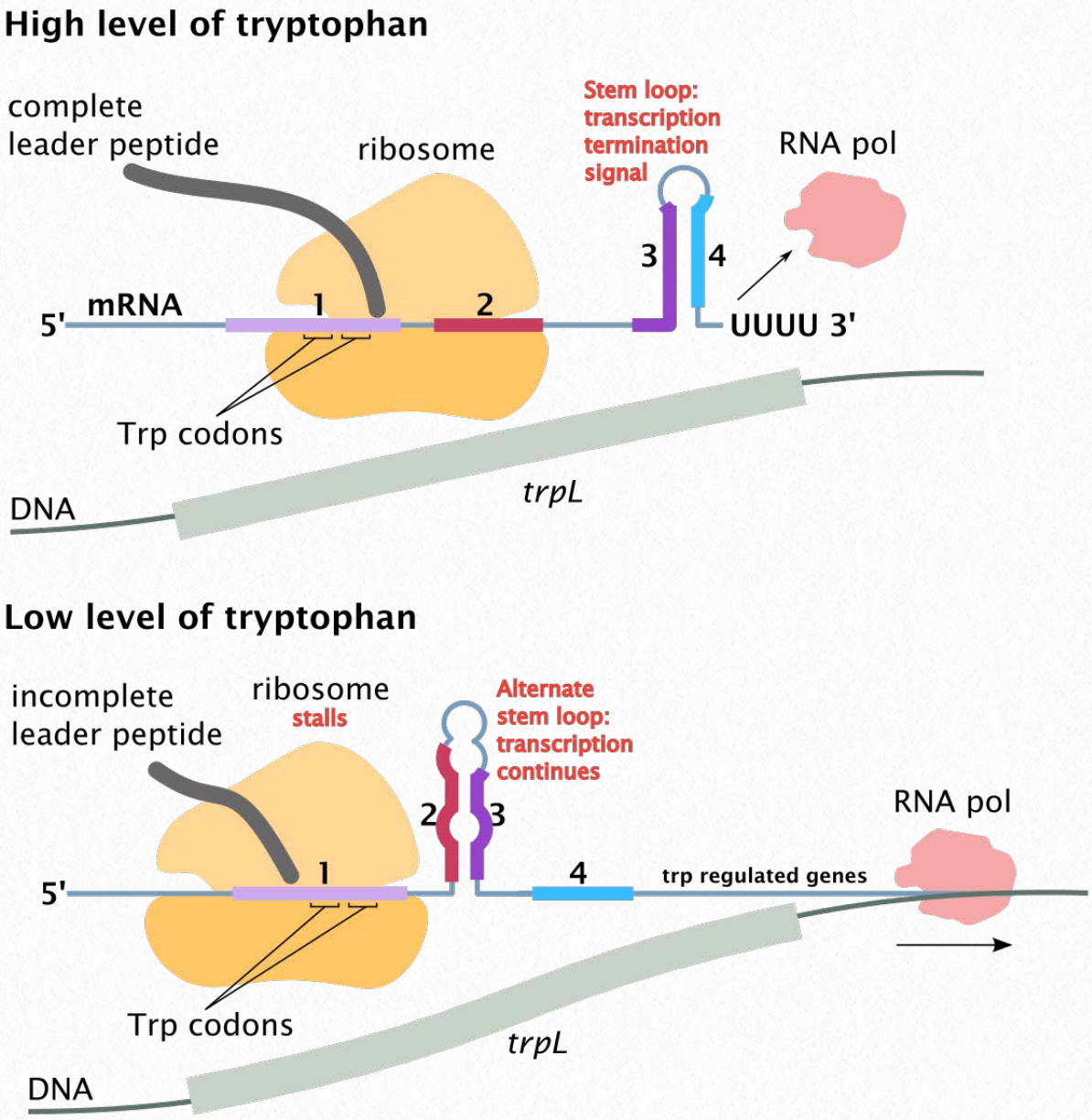

Figure 7.111 - Attenuation in regulation of the trp operon

Wikipedia

In the *trp* operon, this functions as follows: Transcription begins some distance upstream of the first gene in the operon, producing what is termed a 5' leader sequence. This leader sequence contains an intrinsic terminator that can form a hairpin structure that stops transcription when high levels of tryptophan are available to the cells. It can also form a different structure that permits continued tran-

cause it acts together with the repressor to turn off the trp genes, tryptophan is called a co-repressor.

XX AUG AAA GCA AUU UUC GUA CUG AAA GGU UGG UGG CGC ACU UCC UGA -XX
MET LYS ALA ILE PHE VAL LEU LYS GLY TRP TRP ARG THR SER STOP

Figure 7.112 - Sequence of the leader region of the *trp* operon

scription of the genes in the operon when tryptophan levels are low. How does the level of tryptophan influence which of these two structures are formed?

Recall that the 5' end of the RNA is the first part of the transcript to be made and that in bacteria translation is linked to transcription, so the 5' end of the RNA begins to be translated before the entire transcript is made. It turns out that the 5' leader sequence of the *trp* operon mRNA encodes a short peptide that contains two tryptophan codons. If there is plenty of tryptophan available, the leader sequence will be easily translated. Under these conditions, the leader sequence is able to form the termination hairpin, preventing the transcription of the downstream *trp* genes.

If, however, levels of tryptophan are low, then the ribosome stalls as it attempts to translate the leader sequence. Under these conditions, the leader sequence adopts a different conformation that permits continued transcription of the genes of the *trp* operon.

Riboswitches

Similar in concept to the attenuation of the *trp* operon described above, but not dependent on translation, is a control mechanism called a riboswitch (Figure 7.113). Riboswitches are typically found in the 5'UTR of messenger RNAs (i.e., they are part of the sequence of the RNA). These sequences can control transcription of the downstream genes based on the conformation they adopt. One conformation allows continued transcription, while the other terminates it. So, what determines which conformation they adopt?

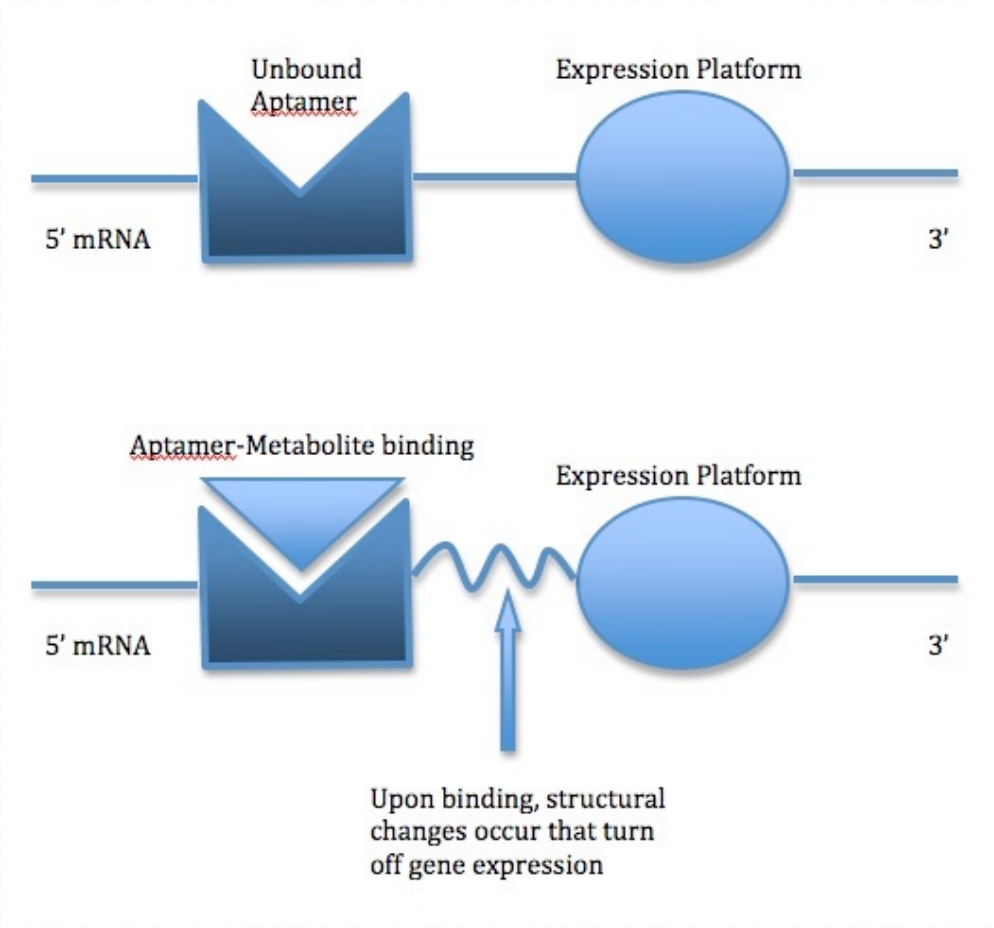

Figure 7.113 - Riboswitch features

Features

Riboswitches have two characteristic features that are important for their function. One is a region of the sequence called an aptamer, which folds into a three-dimensional shape that can bind a small effector molecule. The other is an adjacent region of the

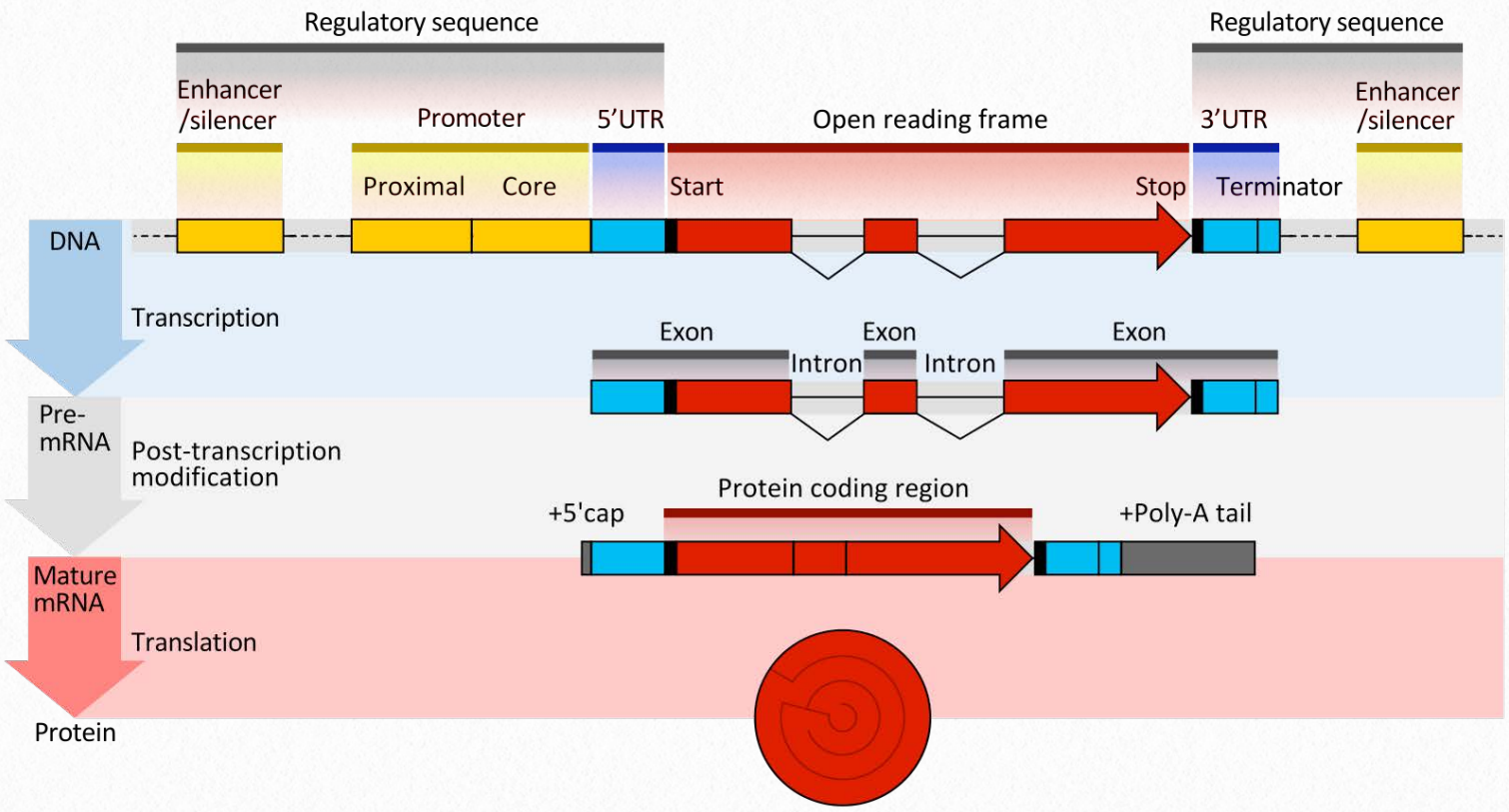

Figure 7.114 - Regulatory sequences for a eukaryotic gene

Wikipedia

RNA, called the expression platform, that can fold into different conformations depending on whether or not the aptamer is bound to the effector.

An example of a riboswitch found in bacteria is the guanine riboswitch, which controls the expression of genes required for purine biosynthesis. The aptamer region of this riboswitch binds to the effector, guanine, when levels of the base are high. The binding of the guanine triggers a change in the folding of the downstream expression platform, causing it to adopt a conformation that terminates transcription of the genes needed for the synthesis of guanine. In the absence of guanine, the expression platform assumes a different conformation that allows transcription of the purine biosynthesis genes. Thus, levels of guanine can be sensed and the genes needed for its synthesis can be expressed as needed.

Regulation of transcription in eukaryotes

Transcription in eukaryotes is also regulated by the binding of proteins to specific DNA sequences, but with some differences from the simple schemes outlined above.

For most eukaryotic genes, general transcription factors and RNA polymerase (i.e., the transcription initiation complex) are necessary but not sufficient for high levels of transcription. Promoter-proximal DNA sequences like the CAAT box and GC

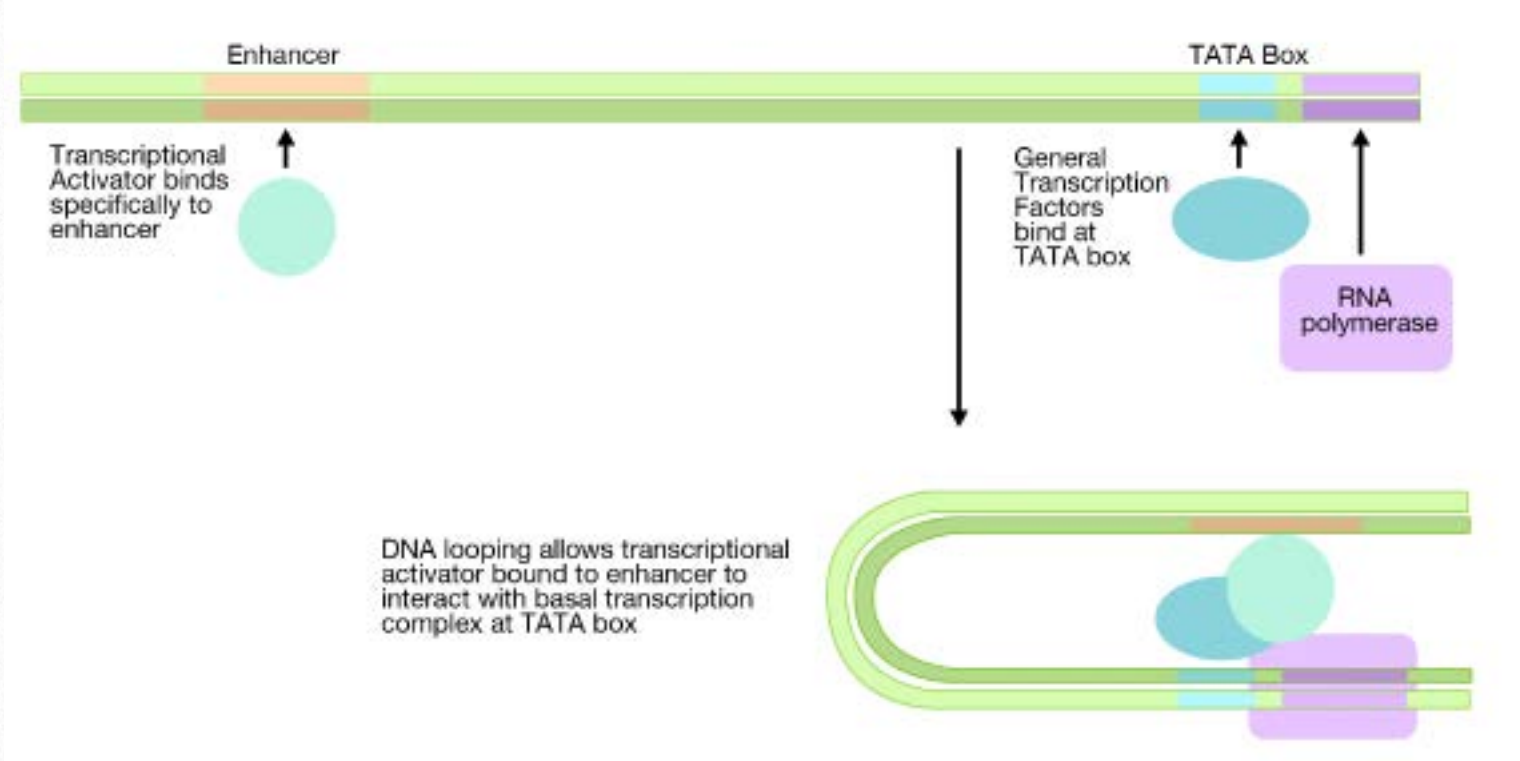

Figure 7.115 - DNA looping allows contact between activator bound at a distant enhancer and the basal transcription complex

Image by Martha Baker

box bind proteins that interact with the transcription initiation complex, influencing its formation (Figure 7.114).

Distant regulatory sequences

Additional regulatory sequences called enhancers and the proteins that bind to them are needed to achieve high levels of transcription. Enhancers are short DNA sequences that regulate the transcription of genes, but may be located at a distance from the gene they control (although they are on the same DNA molecule as the gene). Often enhancers are many kilobases away on the DNA, either upstream or downstream of the gene. As the name suggests, enhancers can enhance (increase) transcription of a particular gene. How can a DNA sequence far from the gene being transcribed affect the level of transcription?

Transcriptional activators

Enhancers work by binding proteins (transcriptional activators) that can, in turn, interact with the proteins bound at the promoter. The enhancer region of the DNA, with its associated transcriptional activator(s) can come in contact with the transcription initiation complex that is bound at a distant site by looping of the DNA (Figure 7.115). This allows the protein bound at the enhancer to make contact with the proteins in the basal transcription complex. The interaction of the activator with the transcription initiation complex may be direct, or it may be through a “middle-man”, a protein complex called mediator.

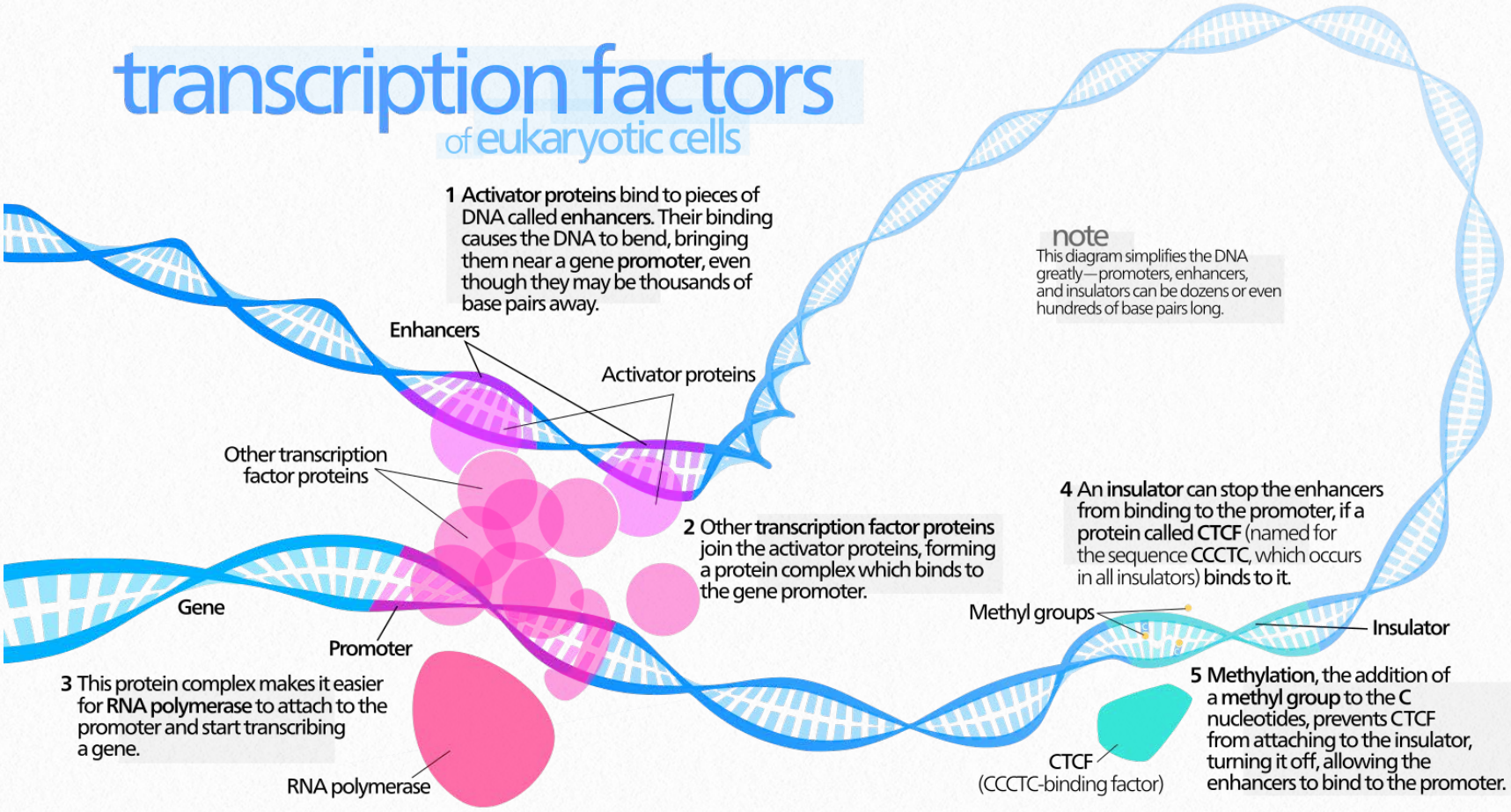

Figure 7.116 - Transcription factors in regulation of eukaryotic transcription

Wikipedia

One effect of this interaction is to assist in recruiting proteins necessary for transcription, like the general transcription factors and RNA polymerase to the promoter, increasing the frequency and efficiency of formation of the transcription initiation complex. There is also evidence that at some promoters, following assembly of the transcription initiation complex, the RNA polymerase remains stalled at the promoter. In such cases, the interaction with the transcription initiation complex of an activator bound to an enhancer could play a role in facilitating the transition of the RNA polymerase to the elongation phase of transcription.

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Chromatin remodeling proteins

Another mechanism by which activators bound at the enhancer can affect transcription is by recruiting to the promoter proteins that can modify the structure of that region of the chromosome. In eukaryotes, DNA is packaged with proteins to form chromatin. When the DNA is tightly associated with these proteins, it is difficult to access for transcription. So proteins that can make the DNA more accessible to the transcription machinery can also play a role in the extent to which transcription occurs.

Silencers

In addition to enhancers, there are also negative regulatory se-

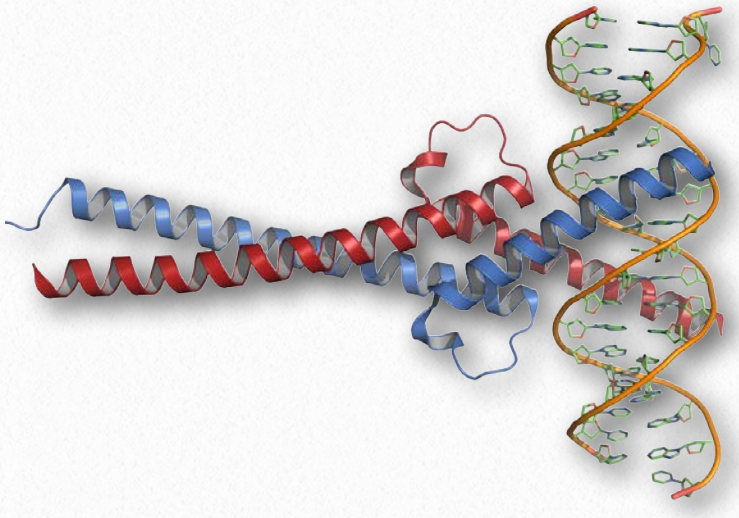

Figure 7.117 - Binding of c-myc protein to its target DNA sequence

Wikipedia

quences called silencers. Such regulatory sequences bind to transcriptional repressor proteins. Like the transcriptional activators, these repressors work by interacting with the transcription initiation complex. In the case of repressors, the effect they have on the transcription initiation complex is to reduce transcription.

DNA binding proteins

Transcriptional activators and repressors are modular proteins- they have a part that binds DNA and a part that activates or represses transcription by interacting with the transcription initiation complex (Figure 7.118). The DNA binding domain is the part of the protein that confers specificity for determining which gene(s) will be activated or repressed. The activation domain is the part of the protein that stimulates or represses transcription. The DNA binding domains of transcriptional activators form characteristic structures that recognize their target DNA sequences by making contacts with bases, usually in the major groove of the DNA helix. It is possible to engineer hybrid transcription factors that combine the DNA binding domain of one activator with the activation domain of another. Such proteins retain the specificity dictated by the DNA binding domain. Truncated transcription factors can also be generated that have their DNA binding domain but lack the activation domain. Such transcription factors can be useful tools in studying transcriptional regulation because their DNA binding domains can compete with the endogenous

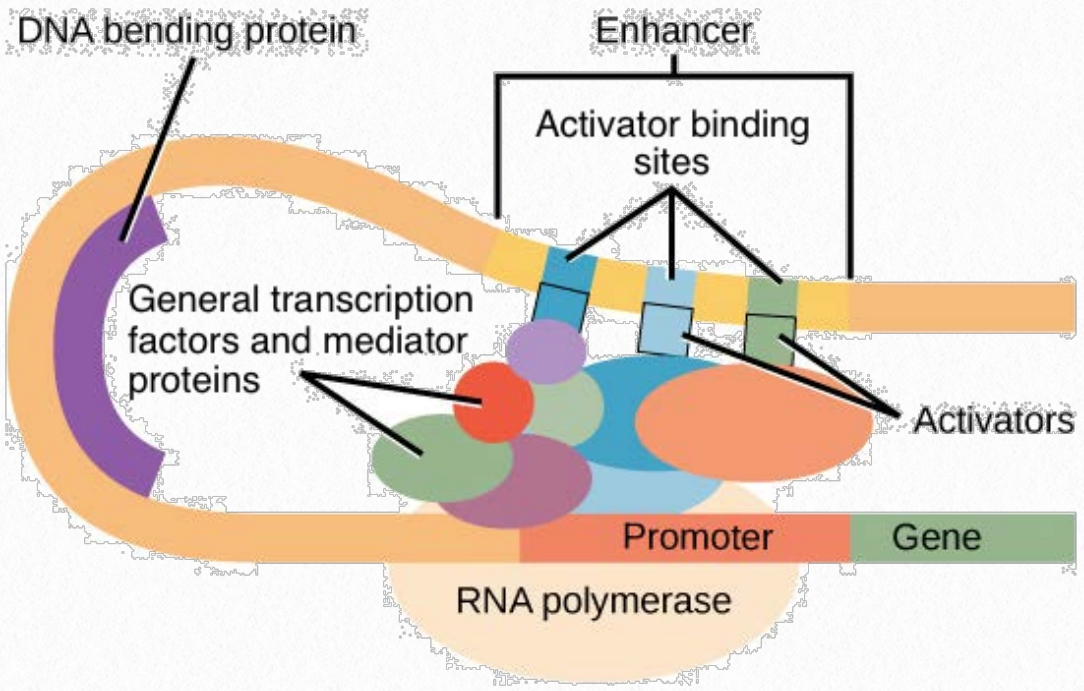

Figure 7.118 Activators bound at multiple sites can regulate transcription from a given promoter

OpenStax

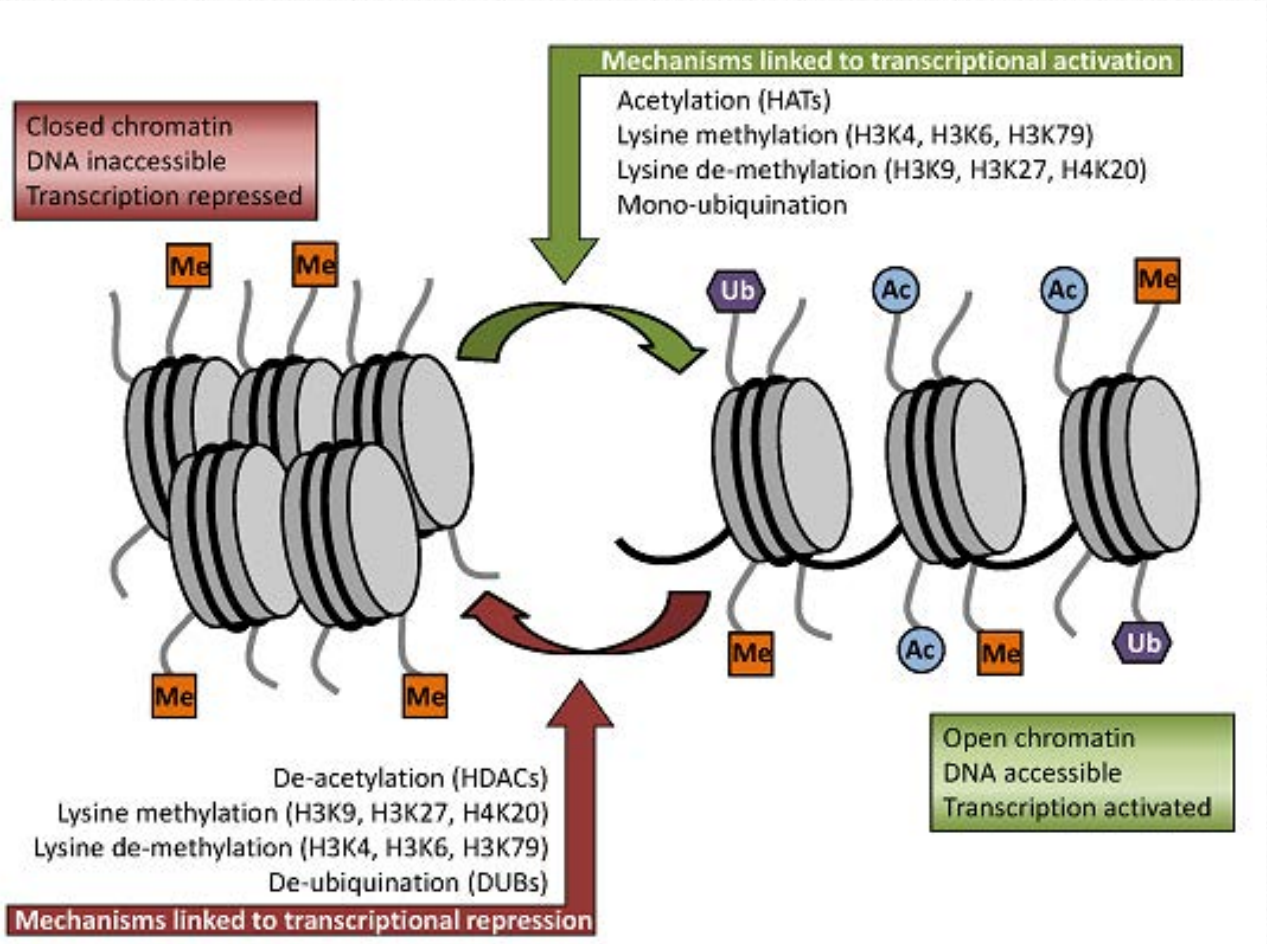

Figure 7.119 - Transcriptional activation (right) and deactivation (left) by histone modification

Wikipedia

transcription factors for regulatory binding sites without increasing transcription from the target promoters.

Multiple factors

The description above may suggest that each gene in eukaryotes is controlled by the binding of a single transcriptional activator or repressor to a particular enhancer or silencer site. However, it turns out that the transcription of any given gene may be simultaneously regulated by a combination of proteins, both activators and repressors, bound at multiple regulatory sites on the DNA, all of which interact with the transcription initiation complex. The combinatorial nature of such regulation provides great versatility, with different combinations of regulatory elements and proteins working together in response to a wide variety of conditions and signals.

The mechanisms described so far have focused on the sequence elements in DNA that regulate transcription through the activator and repressor proteins bound to them. Following transcription, alternative splicing (see HERE) and editing of the transcripts can also modify the proteins that are produced by the cell. We will now examine some of the other ways in which gene expression is modulated in cells.

First, we will consider some so-called epigenetic mechanisms that affect gene expression. The term epigenetics derives from epi (above, or on top of) and genetic (of genes) and refers to the fact that these mechanisms act in addition to, or overlaid on, the information in the gene sequences. Two such epigenetic mechanisms are the covalent modifications of his-

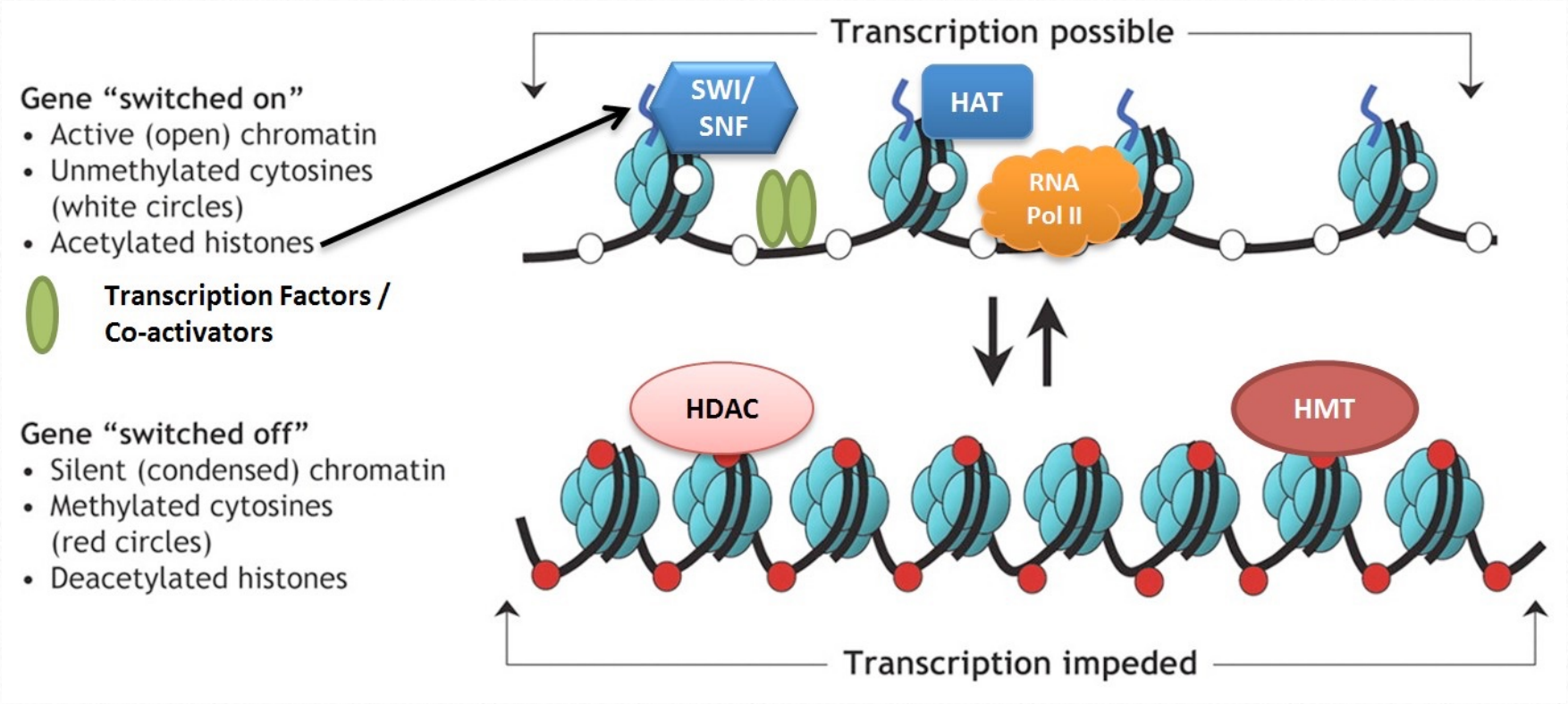

Figure 7.120 - Chromatin configuration affects transcription

Wikipedia

tones in chromatin and the methylation of DNA sequences.

Histone modification

As noted earlier, transcription in eukaryotes is complicated by the fact that the DNA is packaged with histones to make chromatin. This means that for a gene to be transcribed, the relevant regions of the chromatin must be opened up to allow access to the RNA polymerase and transcription factors. This provides another potential point of control of gene expression. Chromatin remodeling factors, mentioned earlier, assist in reorganizing the nucleosome structure at regions that need to be made accessible.

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But what determines that a given region of the chromatin will be acted upon by the remodeling complexes? Transcriptional activator proteins bound at enhancers, sometimes work by recruiting histone modifying enzymes to the promoter region. An example of such a modifying enzyme is histone acetyl transferase (HAT) that works to acetylate specific amino acid residues in the tails of the histones forming the nucleosome core (Figures 7.119 & 7.120). Acetylation of histones is thought to be responsible for loosening the interaction between histones and the DNA in nucleosomes and helps to make the DNA more readily accessible for transcription. The opposite effect may be achieved if the enzymes recruited are histone deacetylases

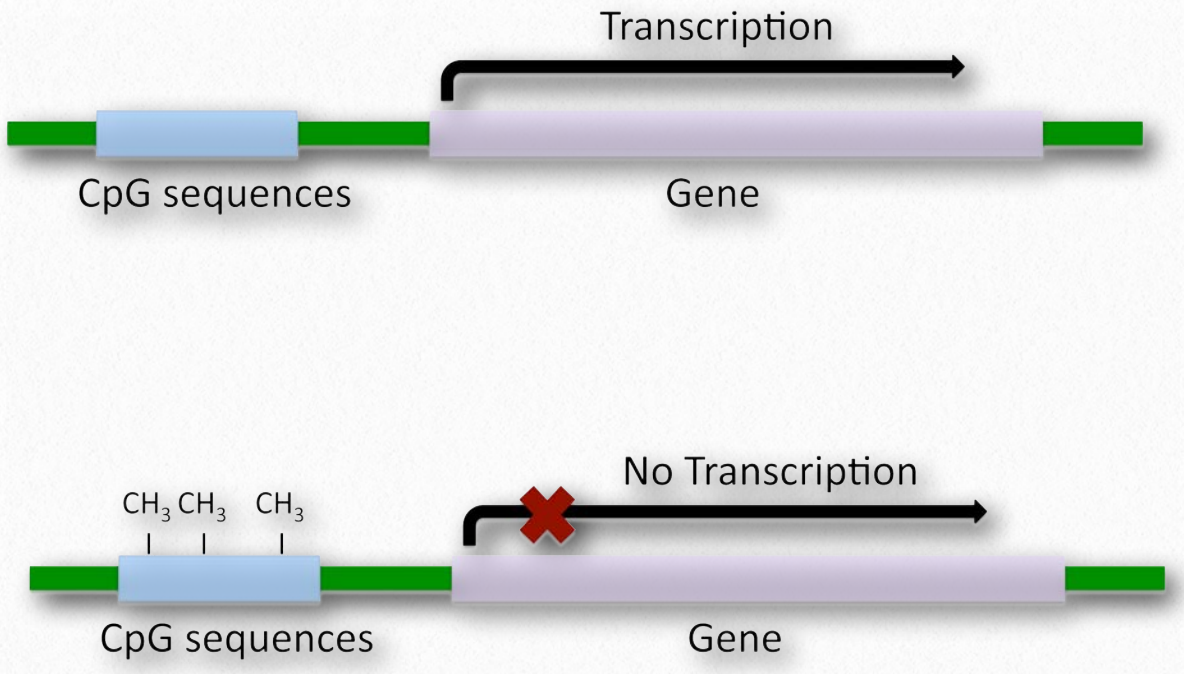

Figure 7.121 - Inactivation of transcription by CpG methylation

Image by Indira Rajagopal

(HDAC) which remove acetyl groups from the tails of the histones in the nucleosome, and lead to tighter packing of the chromatin.

Writers, readers and erasers

In addition to the histone acetyl transferases and the deacetylases, other enzymes may add or remove methyl groups, phosphate groups, and other chemical moieties to specific amino acid side chains on the histone tails. The patterns of these covalent modifications, sometimes called the histone code, are established by the so-called "writers", or enzymes, such as histone methyltransferases, that add the chemical groups on to the histone tails. Yet other enzymes, like the histone demethylases, may act as "erasers," removing the chemical groups added by the "writers." The histone code is interpreted by "readers," proteins that bind to specific combinations of the modifications and assist in either silencing the expression of genes in the vicinity or making the region more transcriptionally active.

YouTube Lectures by Kevin HERE & HERE

DNA methylation

Gene expression can also be regulated by methylation of the other component of chromatin - DNA. Enzymes called DNA methyltransferases (DNMTs) catalyze the covalent addition of a methyl group to C_5 of cytosines in DNA. Patterns of cytosine methylation vary in different organisms, with methylation concentrated in some parts of the genome in some groups and scattered throughout the genome in others. In vertebrates, the cytosines that are methylated are generally next to a guanine (the CG dinucleotide is commonly abbreviated as CpG). Methylation of DNA seems to correlate with gene silencing while demethylation is associated with increased transcription (Figure 7.121).

How does methylation of the DNA at CpG sites regulate gene expression? Although the extent of DNA methylation near promoters

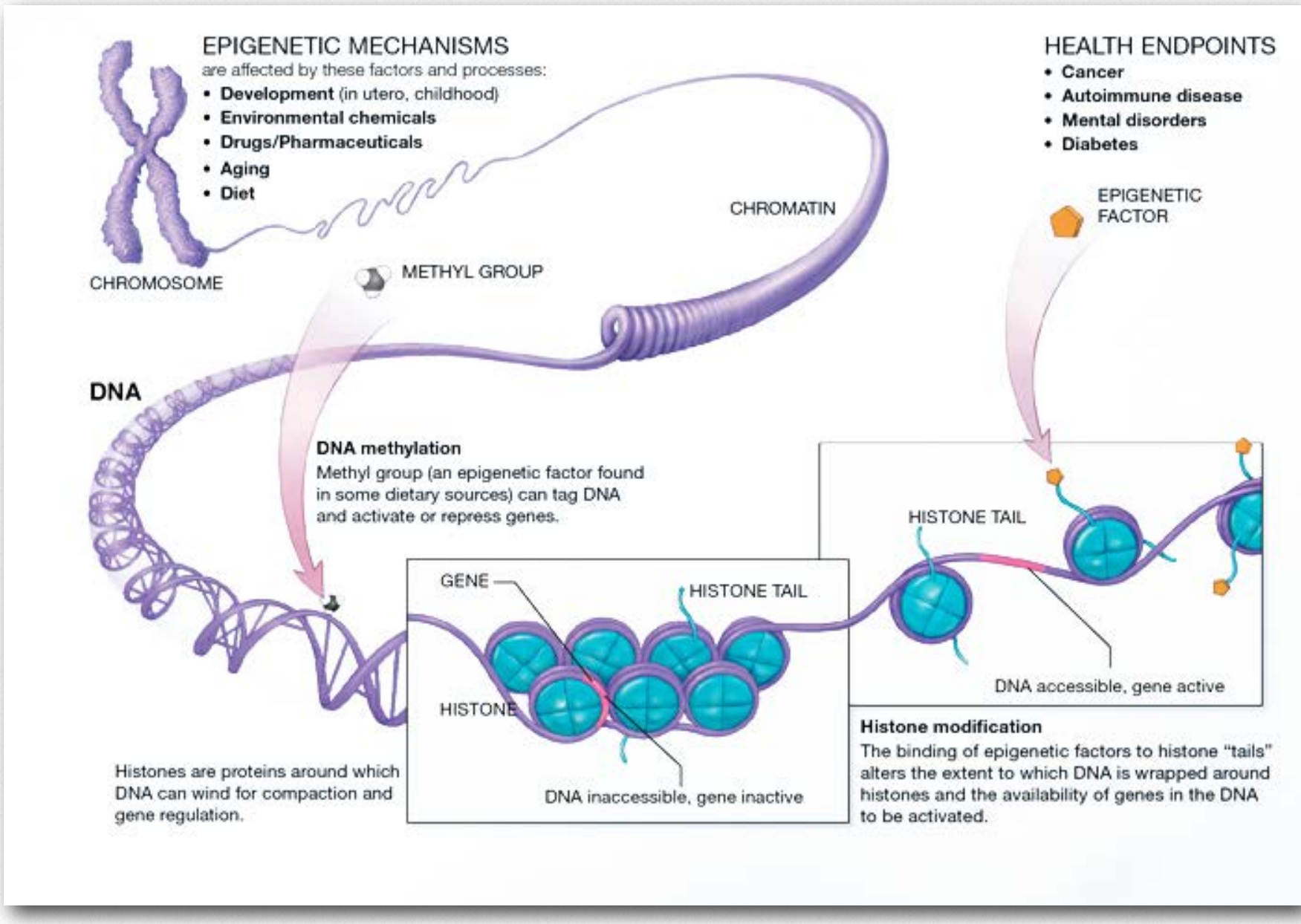

Figure 7.122 - Epigenetic changes through histone and DNA modification

has been observed to correlate with gene silencing, it is not clear how exactly methylation brings about this effect. It has been suggested that methylation could block the binding of proteins necessary for transcription. Methylation at enhancer sites might also prevent the binding of transcriptional activators to them.

Another interesting observation is that certain proteins that bind to methylated CpG sites also seem to interact with histone deacetylases. As noted above, histones deacetylases remove acetyl groups from histones, and promote tighter packing of chromatin and transcriptional silencing. Thus, methylation on DNA likely works in combination with histone modification to affect gene expression.

Regulatory RNAs

One of the most unexpected discoveries in the past few decades has been the role that RNAs play in regulating gene expression. The classic view that RNA either encoded proteins (mRNA) or assisted in their synthesis (rRNA

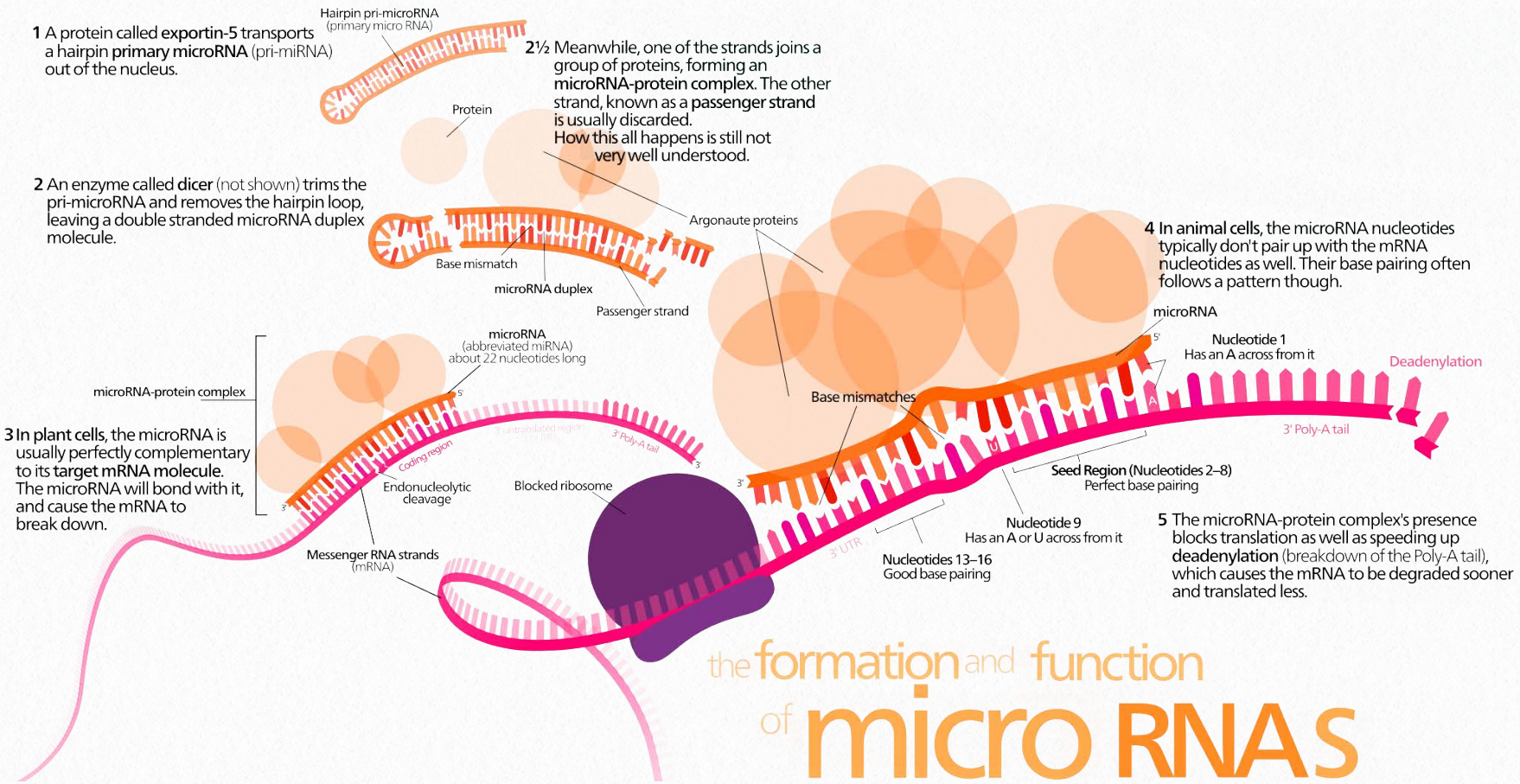

Figure 7.123 - miRNAs function in the regulation of gene expression

Wikipedia

and tRNA) is now known to be a vast underestimate of the various ways in which RNAs function in gene expression. It is now clear that regulatory RNAs have widespread and significant effects on gene expression, a realization that has revolutionized our understanding of gene regulation.

RNAs (siRNAs) are small, non-coding RNAs that act at the post-transcriptional level to regulate gene expression (Figure 7.123 & 7.124). These RNAs appear to silence genes by base-pairing with target mRNAs and marking them for degradation, or by

What are some of the ways in which regulatory RNAs function to modulate the expression of genes?

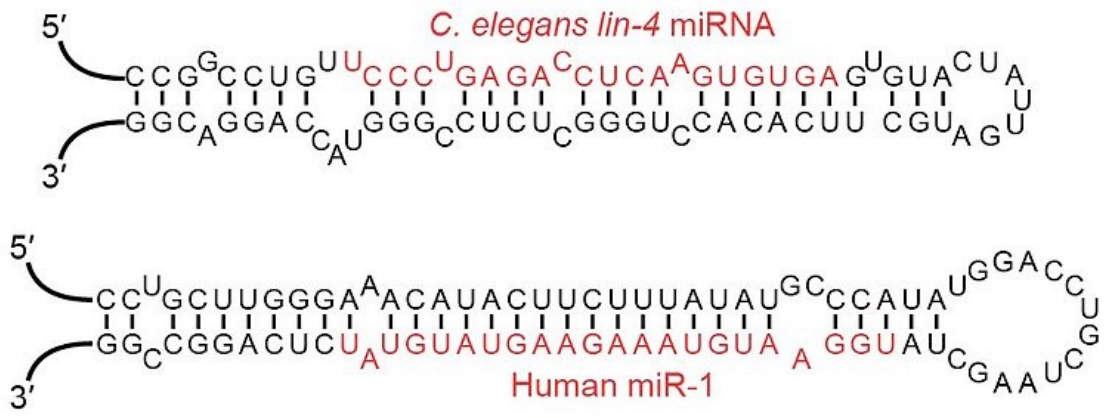

Figure 7.124 Pre-miRNA hairpin structures with the mature guide miRNAs shown in red

Wikipedia

Small regulatory RNAs

MicroRNAs (miRNAs) and Short Interfering

blocking their translation. The functional forms of both miRNAs and siRNAs are from 20-30 nucleotides long and are derived by processing from longer primary transcripts. Mature miRNAs and siRNAs work in association with a class of proteins called Argonaute proteins to form a gene silencing complex.

MicroRNAs are transcribed from specific genes by RNA polymerase II. The primary transcript, known as a pri-miRNA folds on itself to form double-stranded hairpin structures that are cleaved by an RNase in the nucleus called Drosha. The products of Drosha cleavage, double-stranded RNAs of roughly 60-70 nucleotides known as pre-miRNAs, are exported to the cytoplasm, where they are further processed into the small 20-30 nucleotide lengths of mature double-stranded miRNAs by an enzyme known as Dicer. The RNA duplexes of miRNAs are not perfectly matched, and have loops and mismatches (Figure 7.124).

siRNAs also derive from double-stranded RNAs, but these may arise from either endogenous or exogenous sources (such as viruses). These double-stranded RNAs are processed in the cytoplasm by the same enzyme, Dicer, that generates the mature miRNAs, to produce the small, 20-30 nucleotide double-stranded RNAs.

In contrast to miRNAs, the mature siRNAs are perfectly base-paired along their lengths.

RISC assembly

Both miRNAs and siRNAs then are assembled with Argonaute proteins to form a silencing complex called RISC (RNA-induced silencing complex). Recall that both miRNAs

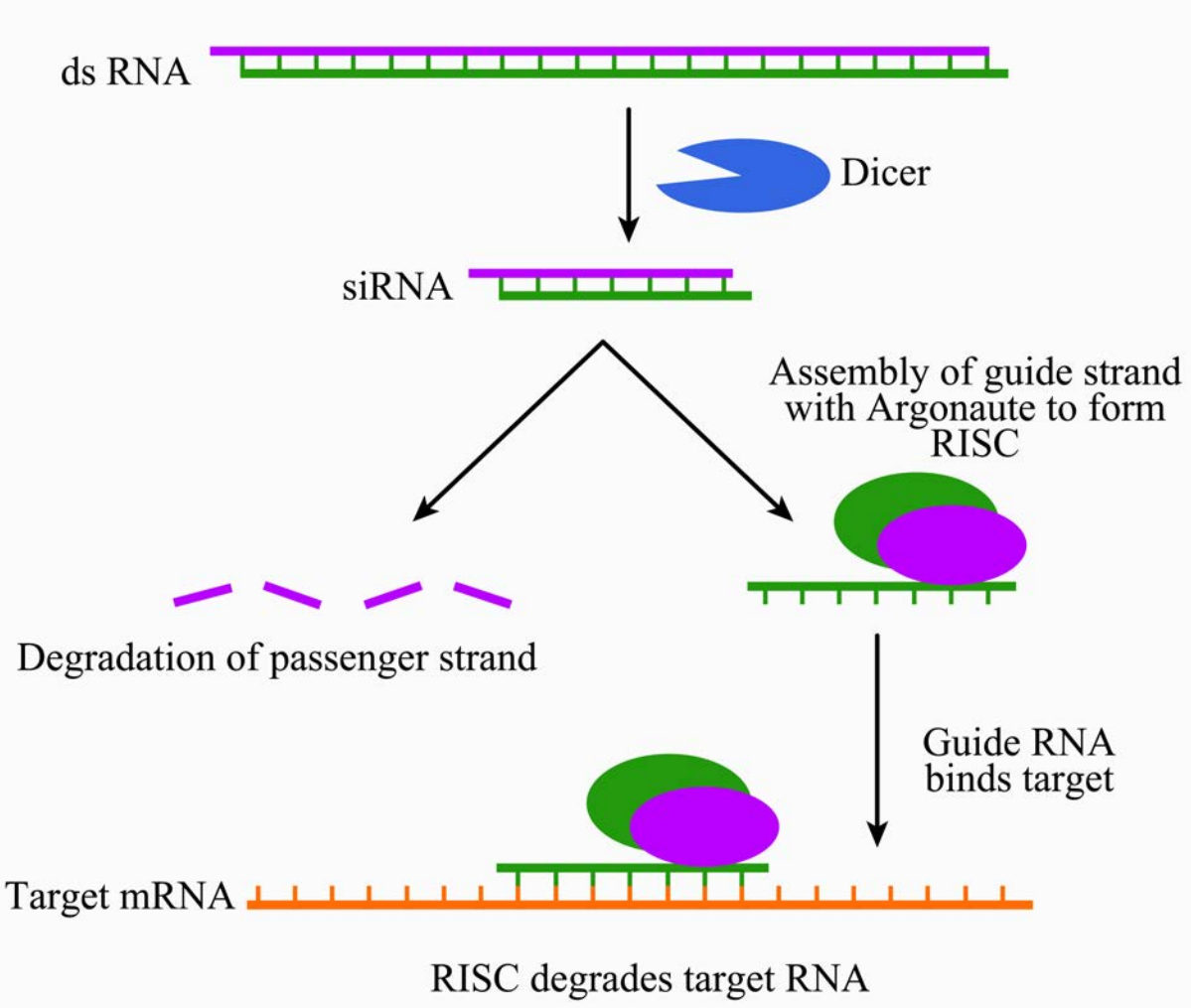

Figure 7.125 - Gene silencing by siRNA

Image by Pehr Jacobson

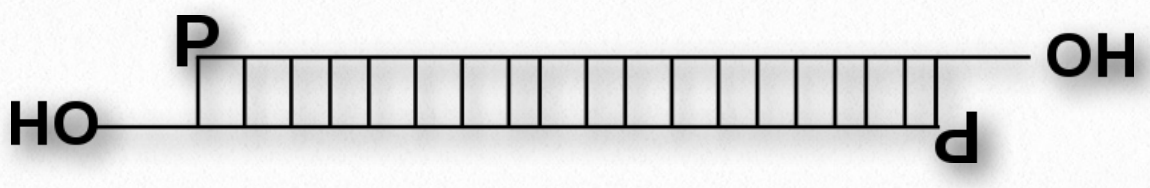

Figure 7.126 - Processed siRNA duplex with perfect base-pairing, 5' phosphates and two bases overhanging at each 3' end

and siRNAs are, at this point double-stranded. One strand of the RNA is referred to as the guide RNA, while the other is called the passenger RNA.

During the process of loading the RNA onto the Argonaute protein, the guide strand of the RNA remains associated with the protein, while the passenger strand is removed. The guide RNA associated with the Argonaute protein is the functional gene silencing complex (Figure 7.125).

Sequence specific base-pairing of the guide RNA with an mRNA leads to either the degradation of the mRNA by the Argonaute protein (in the case of the siRNAs) or in suppression of translation of the mRNA (for miRNAs). The extent to which these processes play a role in regulating gene expression is impressive. The expression of at least a third of all human genes has already been shown to be modulated by miRNAs, demonstrating clearly that these RNAs play a major role in gene regulation.

Long noncoding RNAs

Long noncoding RNAs (lncRNAs) are RNAs of greater than 200 nucleotides that do not code for proteins. Some of these RNAs are derived from intron sequences, while others, transcribed from intergenic regions form a subset of lncRNAs called lincRNAs (long intergenic noncoding RNAs). Yet other lncRNAs are produced as antisense transcripts of coding genes. An astounding 30,000 transcripts in humans are thought to be lncRNAs, but little is known of their function. From the few lncRNAs that have been intensively studied, it is evident that they do not all function in the same way. However, they appear to affect gene expression in a variety of ways including modification of chromatin structure, regulation of splicing, or serving as structural scaffolds for the assembly of nucleoprotein complexes. Additional mechanisms will doubtless be uncovered as these fascinating RNAs are investigated in years to come.

Regulation of translation

The synthesis of proteins is dependent on the availability of the mRNAs encoding them. If an mRNA is blocked at its 5' end, it cannot be translated. The rate of degradation of an mRNA will influence how long it is around to direct the synthesis of the protein it codes for. Gene expression can also, there-

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fore, be regulated by mechanisms that alter the rate of mRNA degradation. Regulation of translation is used to control the production of many proteins. Two examples, ferritin and the transferrin receptor, are important for iron storage and transport in cells. Ferritin is an iron-binding protein that sequesters iron atoms in cells to keep them from reacting. When iron levels are high, there is a need for more ferritin than when iron levels are low. How are ferritin levels regulated? The 5'UTR of the ferritin mRNA contains a 28-nucleotide sequence called the Iron Response Element, or IRE (Figure 7.127). When iron levels are low, the IRE is bound by a protein. The presence of the IRE-binding protein at the 5'UTR blocks translation of the ferritin mRNA. However, if iron levels are high, the iron binds to the IRE-binding protein, which undergoes a conformational change and dissociates from the IRE. This frees up the 5' end of the ferritin mRNA for ribosome assembly and translation, producing more ferritin.

The other protein involved in iron transport, the transferrin receptor, is required for uptake of iron into cells, when intracellular iron levels are low. In the case of the transferrin receptor, it is when iron levels are low that more of it is needed. When iron levels are high, there is no need to make more transferrin receptor. The mRNA encoding the transferrin receptor also has IRE sequences, but in this case, the IRE is situated in the 3'UTR of the transcript (Figure 7.128). The IRE is, as in the case of ferritin, bound by the IRE-binding protein. When iron levels in the cell are high, the iron binds the IRE-binding protein, which dissociates from the IRE. This leaves the 3'UTR susceptible to attack by RNases, leading to degradation of the transferrin receptor

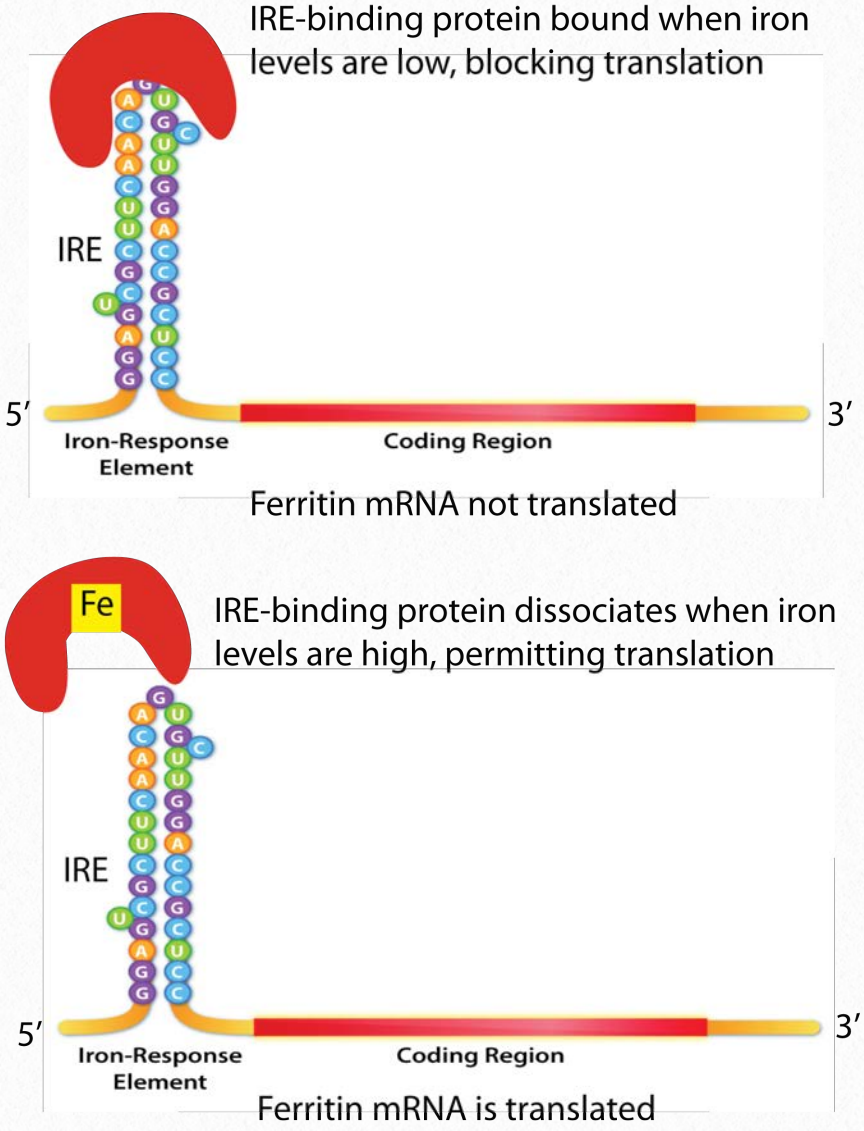
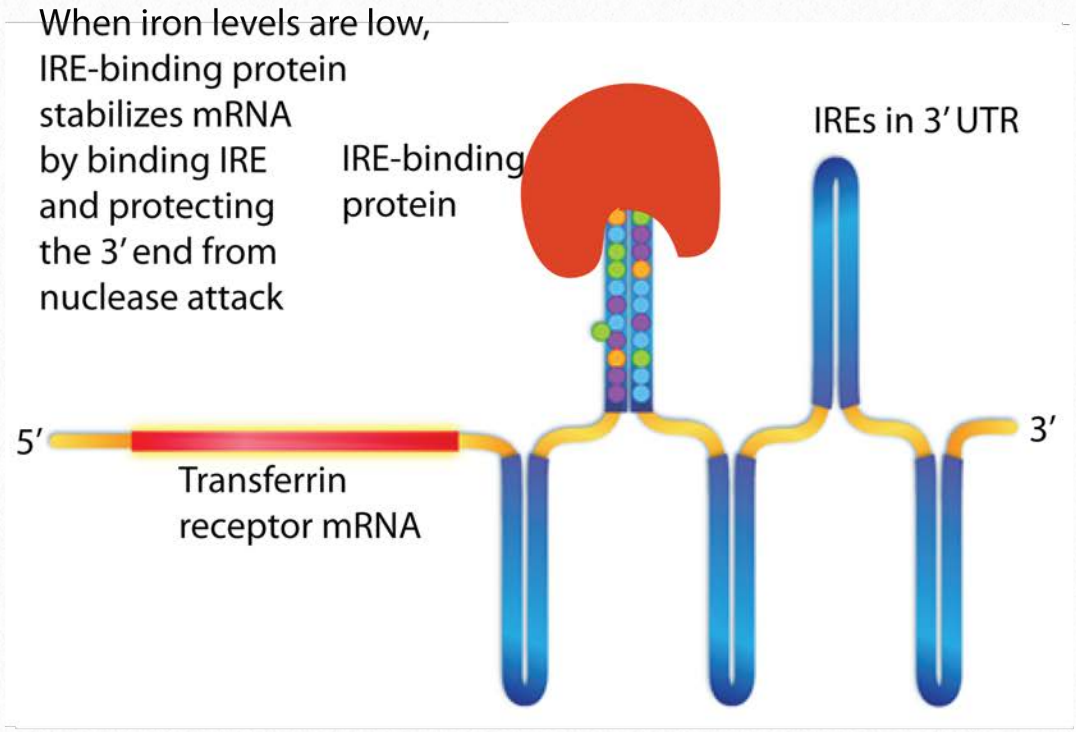
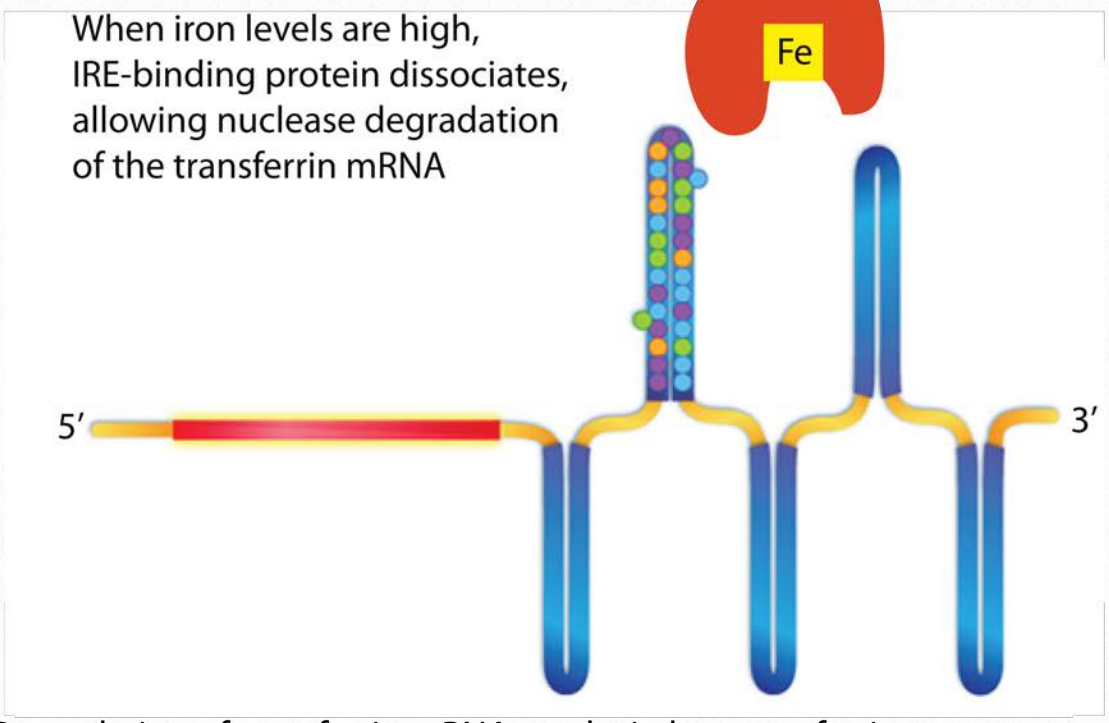


Figure 7.127 -Regulation of ferritin mRNA translation

Image by Aleia Kim



Stabilized transferrin mRNA is translated to make more transferrin receptor



Degradation of transferrin mRNA results in less transferrin receptor made

Figure 7.128 -Regulation of transferrin receptor mRNA translation

Image by Aleia Kim

mRNA. At times when iron levels are low, the IRE-binding protein remains bound to the 3' UTR of the mRNA, stabilizing it and permitting more transferrin receptor to be made by translation.

Gene expression is controlled at many steps

As can be seen from the examples in this section, regulation of gene expression in eukaryotic cells is a function of multiple mechanisms that act at different stages in the flow of information from DNA to protein, responding to the internal state of the cell as well as external conditions and signals.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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God Bless These Complexes

To the tune of "*God Bless America*"

Metabolic Melodies Website HERE

All information in
Cells' DNA
Just increases
With pieces
Mixed and matched in the mRNAs

Linking exons
All together
Using snurps in
Complex-ES

God bless the spliceosomes
And trans-crip-tomes
(*slow and loud*) God bless the spliceosomes
And my ge-nome

Your blueprint info is
In DNA
Since you need it
Proofread it
Or you'll mutate the mRNA

You can translate
All the codons
With the cells' gen-
et-ic code

God bless the ribosomes
They translate code
(*slow and loud*) God bless the ribosomes
And proteomes

Recording by David Simmons
Lyrics by Kevin Ahern

The Book of Life

To the tune of "*The Look of Love*"

Metabolic Melodies Website HERE

The book of life - the stuff of dreams
Is everywhere, it seems

The book of life, is biochemistry and
Its words fill every day
Just what it says is written in the DNA

I just want to get to know it
How the info's coded
What are all the secrets?
Ribosomes can read it
Goodness knows it's needed

And so its alphabet's
In codon forms
For ribosome bookworms

They read it right
A protein's function to its sequence corresponds
It's not just randomly created peptide bonds

What a marvel of creation, how they do translation
Of m-R-N-A chains,
Using bits of glycine
Proline and some lysine
Translate the code

Instrumental

I just marvel at the knowledge
That I got in college
To learn all the secrets
Double helix spaces
Complementary bases

Pyrimidines
Paired to purines
The book of life

Recording by Carol Adriane Smith
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Information Processing: Signaling

Cellular communication

Up to this point we have considered how cells carry out biochemical reactions and how they regulate the expression of the genes in response to their internal and external environments. It is intuitively obvious that even unicellular organisms must be able to sense features of their environment, such as the presence of nutrients, if they are to survive. In addition to being able to receive and respond to information from the environment, multicellular organisms must also find ways by which their cells can communicate among themselves.

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Coordination

Since different cells take on specialized functions in a multicellular organism, they must be able to coordinate activities. Cells grow, divide, or differentiate in response to specific signals. They may change shape or migrate to another location. At the physiological level, cells in a multicellular organism, must respond to everything from a meal

Signal Category	Examples
Indoleamine	Serotonin, melatonin
Catecholamine	Epinephrine, norepinephrine
Peptide hormone	Insulin, glucagon, EGF
Steroid hormone	Cortisol, estrogen, testoterone
Eicosanoids	Leukotrienes, prostaglandins, endocannabinoids

Figure 7.129 - Some examples of signal molecules

just eaten to injury, threat, or the availability of a mate. They must know when to divide, when to undergo apoptosis (programmed cell death), when to store food, and when to break it down. A variety of mechanisms have arisen to ensure that cell-cell communication is not only possible, but astonishingly swift, accurate and reliable.

How are signals sent between cells? Like pretty much everything that happens in cells, signaling is dependent on molecular recognition. The basic principle of cell-cell signaling is simple. A particular kind of molecule, sent by a signaling cell, is recognized and bound by a receptor protein in (or on the surface of) the target cell. The signal molecules are chemically varied- they may be proteins, short peptides, lipids, nucleotides or catecholamines, to name a few.

Signal properties

The chemical properties of the signal determine whether its receptors are on the cell surface or intracellular. If the signal is small and hydrophobic it can cross the cell membrane and bind a receptor inside the cell. If, on the other hand, the signal is charged, or very large, it would not be able to diffuse through the plasma membrane. Such signals need receptors on the cell surface, typically transmembrane proteins that have an extracellular portion that binds the signal and an intracellular part that passes on the message within the cell (Figure 7.130).

Receptors are specific for each type of signal, so each cell has many different kinds of receptors that can recognize and bind the many signals it receives. Because different

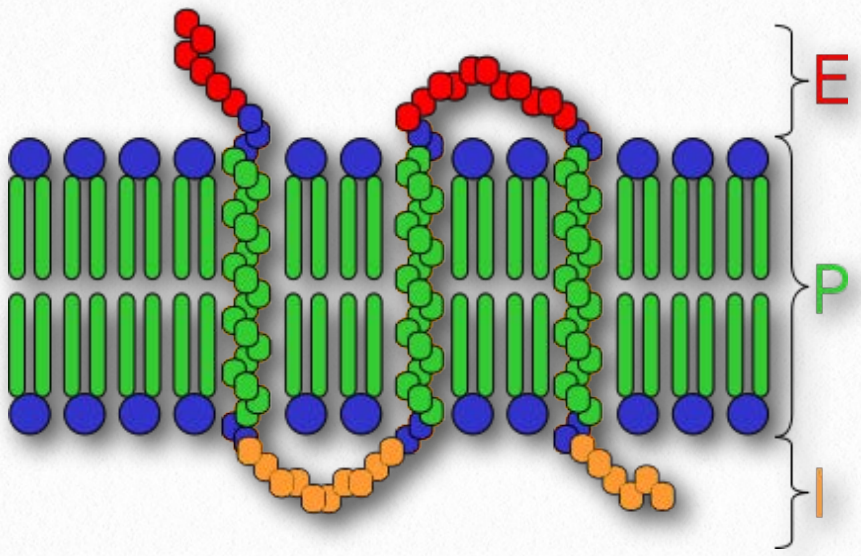

Figure 7.130 - Schematic representation of a transmembrane receptor protein. E = extracellular; P = plasma membrane; I = intracellular

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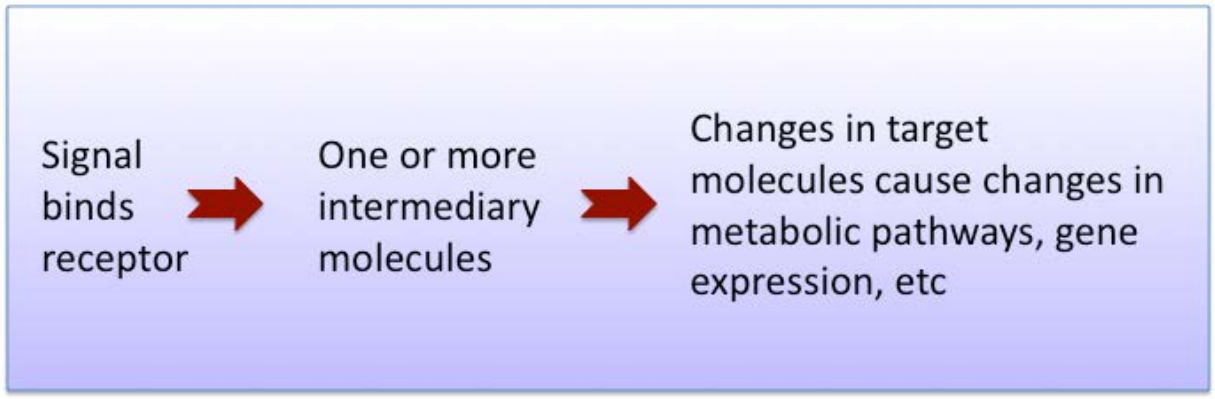

Figure 7.131 -General features of signal transduction pathways

cells have different sets of receptors, they respond to different signals or combinations of signals. The binding of a signal molecule to a receptor sets off a chain of events in the target cell. These events could cause change in various ways, including, but not limited to, alterations in metabolic pathways or gene expression in the target cell.

How the binding of a signal to a receptor brings about change in cells is the topic of this section. We will examine a few of the major receptor types and the consequences of signal binding to these receptors. Although the specific molecular components of the various signal transduction pathways differ, they all have some features in common (Figure 7.131):

• The binding of a signal to its receptor is usually followed by the generation of a new signal(s) within the cell.

The process by which the original signal is converted to a different form and passed on within the cell to bring about change is called signal transduction.

• Most signaling pathways have multiple signal transduction steps by which the signal is relayed through a series of molecular messengers that can amplify and distribute the message to various parts of the cell.

• The last of these messengers usually interacts with a target protein(s) and changes its activity, often by phosphorylation.

• When a signal sets a particular pathway in motion, it is acting like an ON switch. This means that once the desired result has been

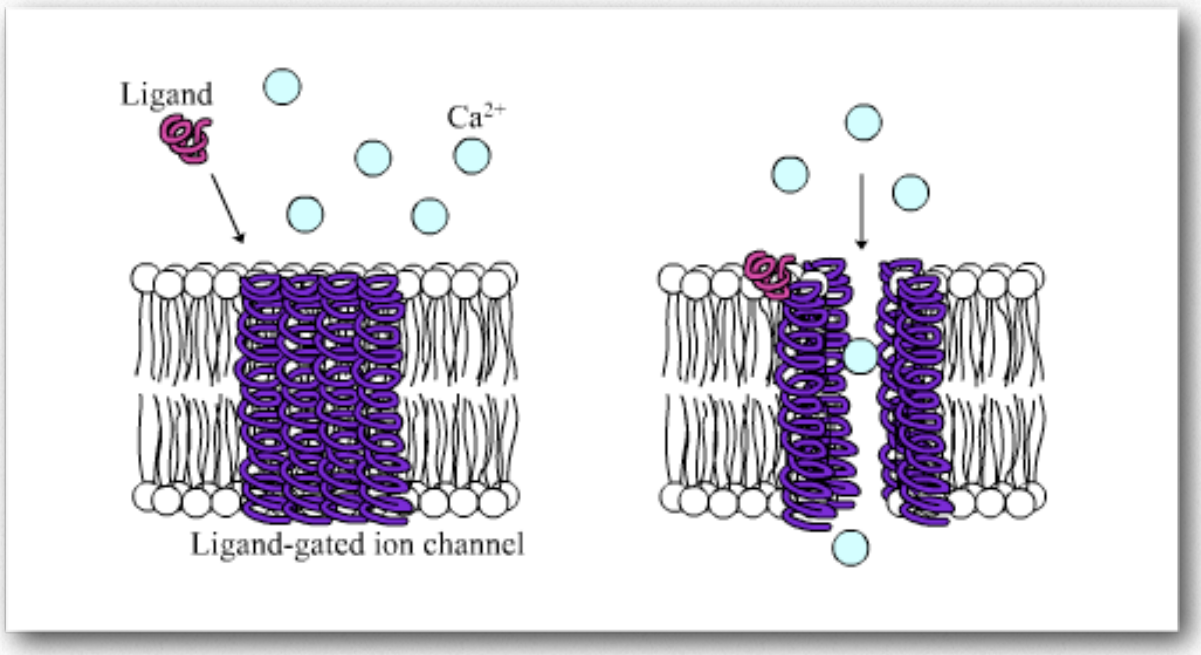

Figure 7.132 - Ligand-gated ion channel receptor opening in response to a signal (ligand)

Wikipedia

obtained, the cell must have a mechanism that acts as an OFF switch.

Understanding this underlying similarity is helpful, because learning the details of the different pathways becomes merely a matter of identifying which molecular component performs a particular function in each individual case. We will consider several different signal transduction pathways, each mediated by a different kind of receptor.

Ligand-gated ion channel receptors

The simplest and fastest of signal pathways is seen in the case of signals whose receptors are gated ion channels (Figure 7.132). Gated ion channels are made up of multiple transmembrane proteins that create a pore, or channel, in the cell membrane. Depending upon its type, each ion channel is specific to the passage of a particular ionic species. The term "gated" refers to the fact that the ion channel is controlled by a "gate" which must be opened to allow the ions through. The gates are opened by the binding of an incoming signal (ligand) to the receptor, allowing the almost instantaneous passage of millions of ions from one side of the membrane to the other. Changes in the interior environment

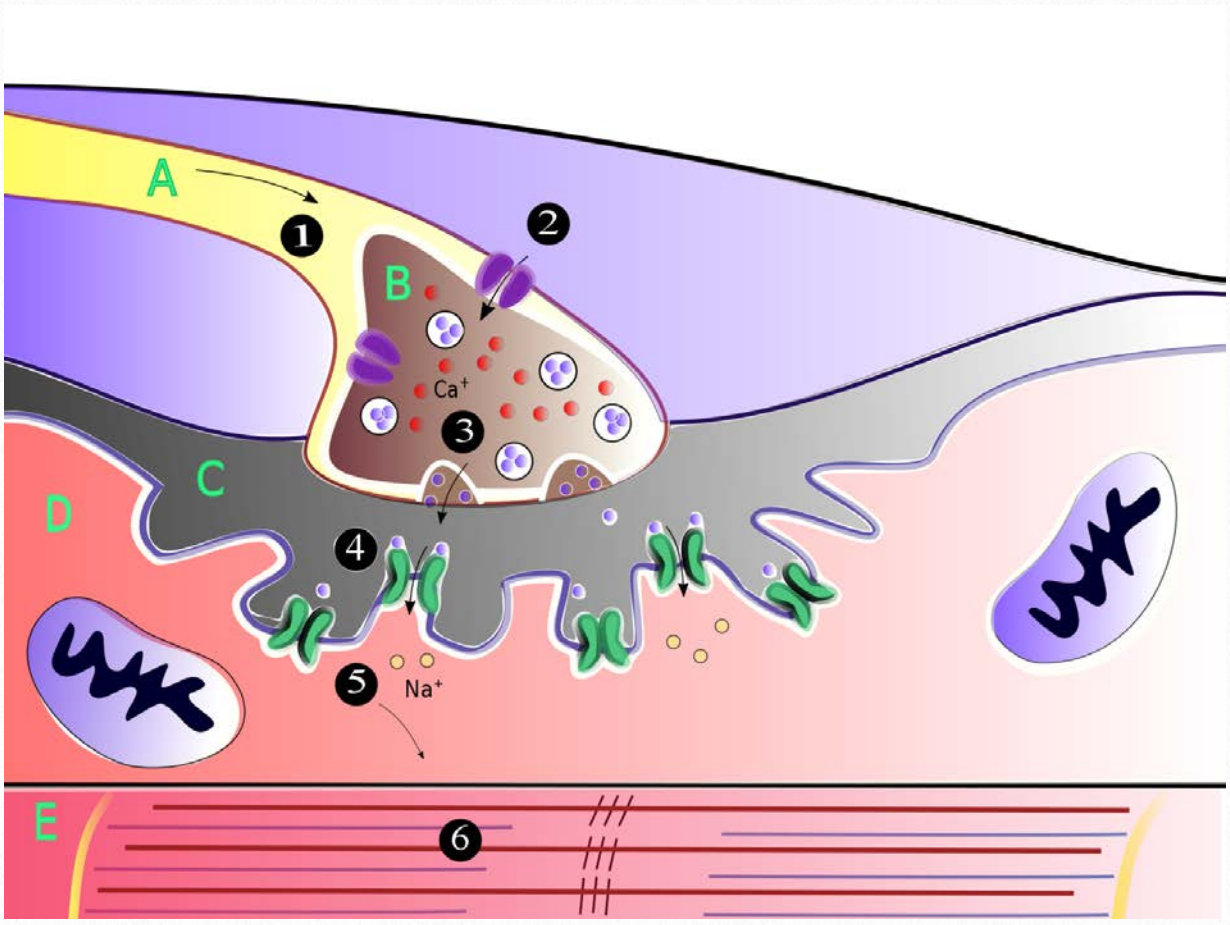

Figure 7.133 - Neuromuscular signaling - A = motor neuron axon; B = axon terminal; C = synaptic cleft; D = muscle cell; E = myofibril . Steps in the process - 1) action potential reaches the axon terminal; 2) voltage-dependent calcium gates open; (3) neurotransmitter vesicles fuse with the presynaptic membrane and acetylcholine (ACh) released into the synaptic cleft; (4) ACh binds to postsynaptic receptors on the sarcolemma; (5) ACh binding causes ion channels to open and allows sodium ions to flow across the membrane into the muscle cell; 6) flow of sodium ions across the membrane into the muscle cell generates action potential which travels to the myofibril and results in muscle contraction.

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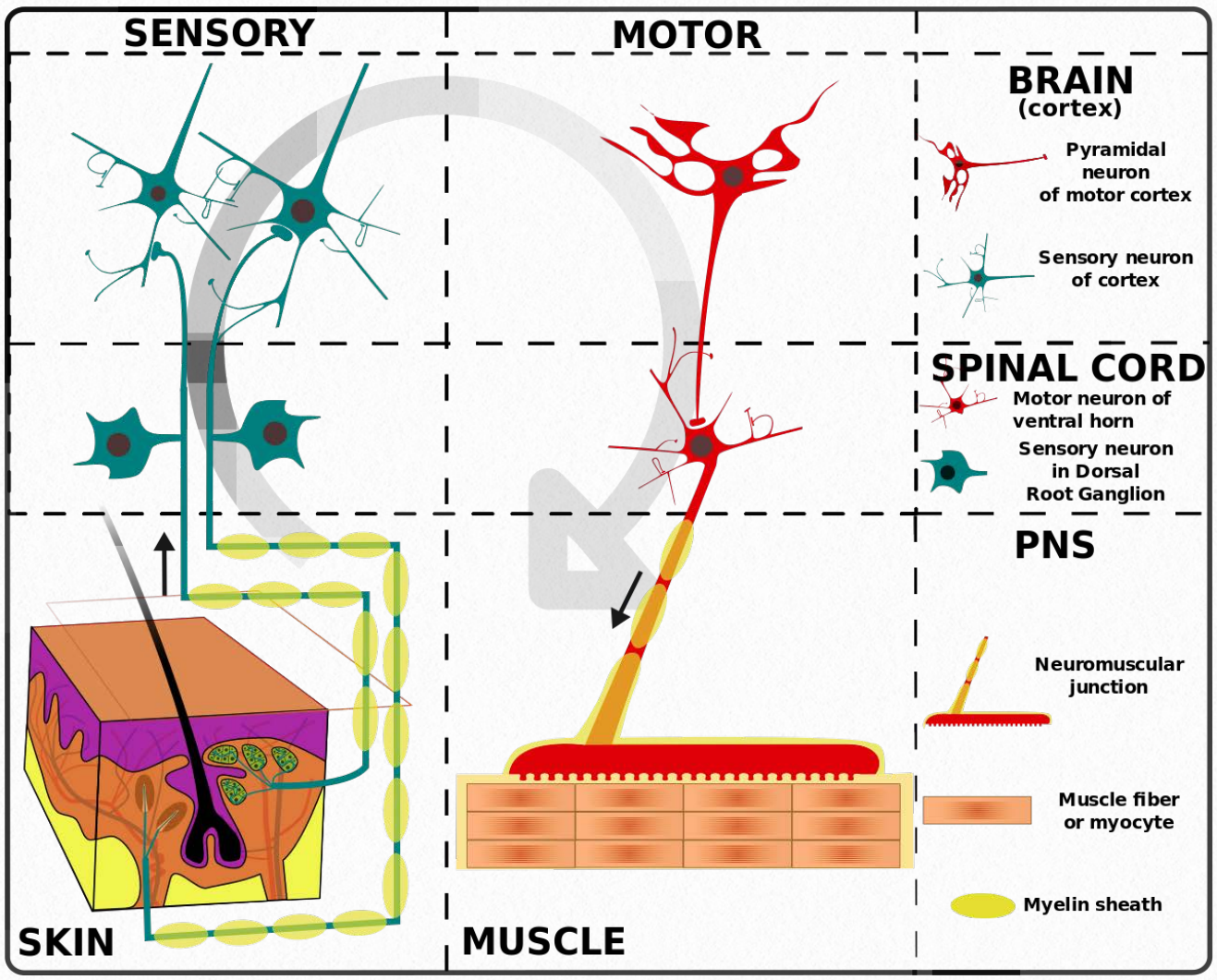

Figure 7.134 - Nerve systems

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of the cell are thus brought about in microseconds and in a single step.

Swift response

This type of swift response is seen, for example, in neuromuscular junctions, where muscle cells respond to a message from the neighboring nerve cell (Figure 7.133). The nerve cell releases a neurotransmitter signal into the synaptic cleft, which is the space between the nerve cell and the muscle cell it is "talking to". An example of such a neurotransmitter signal is acetylcholine. When the acetylcholine molecules are released into the synaptic cleft, they diffuse rapidly till they reach their receptors on the membrane of the muscle cell. The binding of the acetylcholine to its receptor, an ion channel on the membrane of the muscle cell, causes the gate in the ion channel to open. The resulting ion flow through the channel can immediately change the membrane potential of the cell. This, in turn, can trigger other changes in the cell.

The speed with which changes are brought about in neurotransmitter signaling is evident when you think about how quickly you remove your hand from a hot surface. Sensory neurons carry information to the brain from your hand on the hot surface and motor neurons signal to your muscles to move the hand, in less time than it took you to read this sentence!

Nuclear hormone receptors

The receptors for signals like steroid hormones are part of a large group of proteins known as the nuclear hormone receptor superfamily. These receptors recognize and bind not only steroid hormones, but also reti-

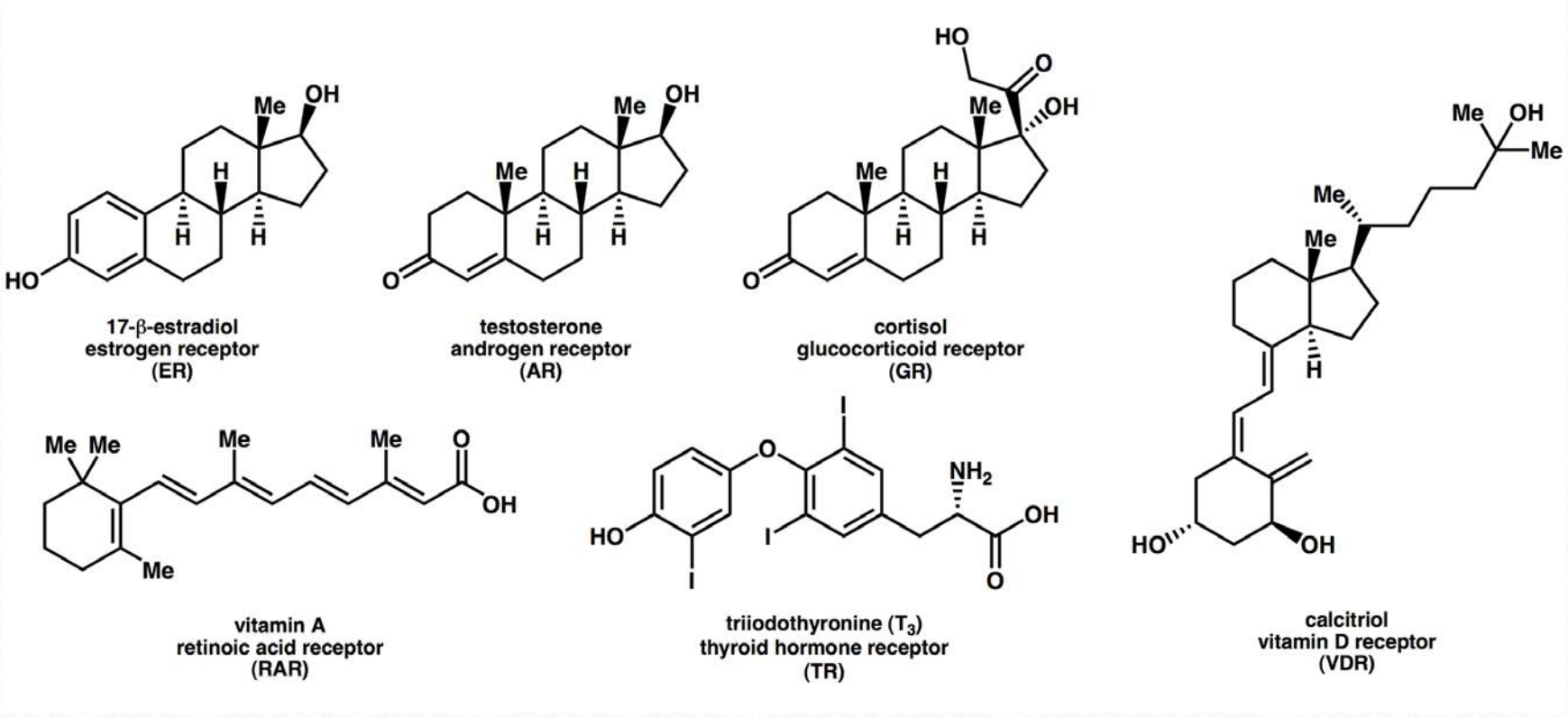

Figure 7.135 - Steroid hormones structures, with the names of their receptors

Wikipedia

noic acid, thyroid hormone, vitamin D and other signals. The subset of the nuclear hormone receptors that bind steroid hormones are intracellular proteins. Steroid hormones (Figure 7.135), as you are aware, are related to cholesterol, and as hydrophobic molecules, they are able to cross the cell membrane by themselves. This is unusual, as most signals coming to cells are incapable of crossing the plasma membrane, and thus, must have cell surface receptors.

Once within the cell, steroid hormones bind to their receptors, which may reside in the cytoplasm or in the nucleus. Steroid hormone receptors are proteins with a double life: they are actually dormant transcription regulators that are inactive till a steroid hormone binds and causes a conformational change in them. When this happens, the receptors, with the hormone bound, bind to regulatory sequences in the DNA and modulate gene expression. Because steroid hormone receptors act by modulating gene expression, the responses to steroid hormones are relatively slow. (There are also some effects of steroid hormones that do not involve transcriptional regulation, but the majority work through changing gene expression.) Like other transcriptional activators, steroid receptors have a DNA-binding domain (DBD) and an activation domain. They also have a ligand-binding domain (LBD) that binds the hormone.

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Glucocorticoid receptor

Examples of such signaling path-

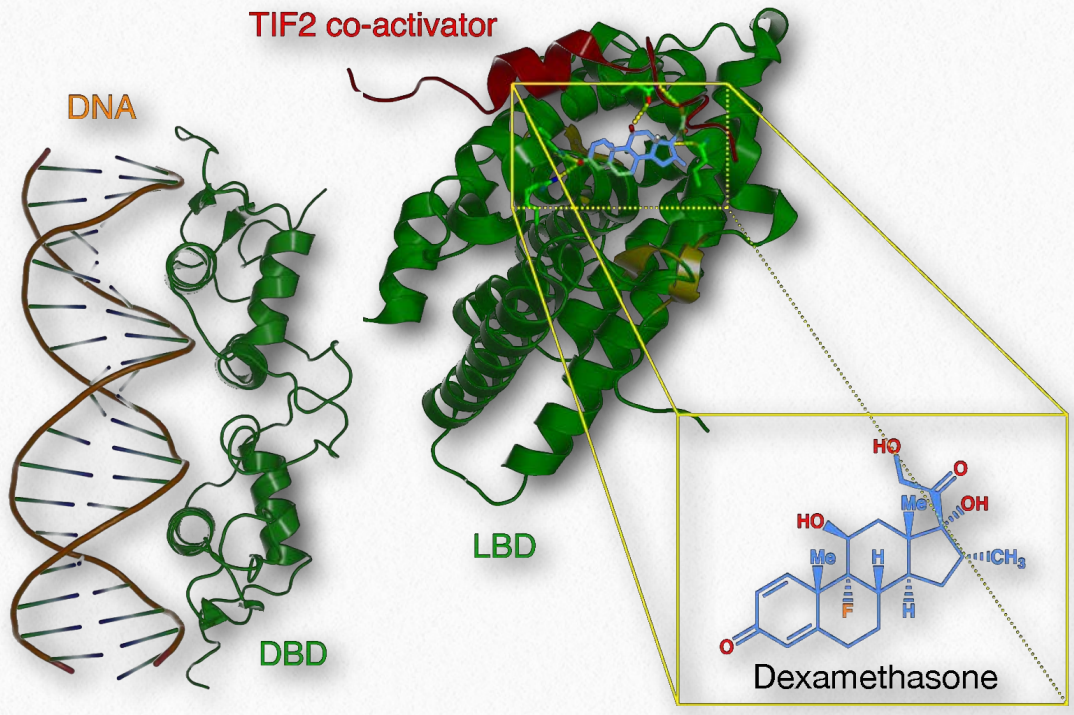

Figure 7.136 - Glucocorticoid receptor with its three domains - DNA binding (left), activator domain (top), and ligand binding domain (boxed).

Wikipedia

ways are those mediated by the glucocorticoid receptor (Figures 7.136 & 7.137). Glucocorticoids, sometimes described as stress hormones, are made and secreted by the adrenal cortex. Physiologically, they serve to maintain homeostasis in the face of stress and exhibit strong anti-inflammatory and immunosuppressive properties. Because of these effects, synthetic glucocorticoids are used in the treatment of a number of diseases from asthma and rheuma-

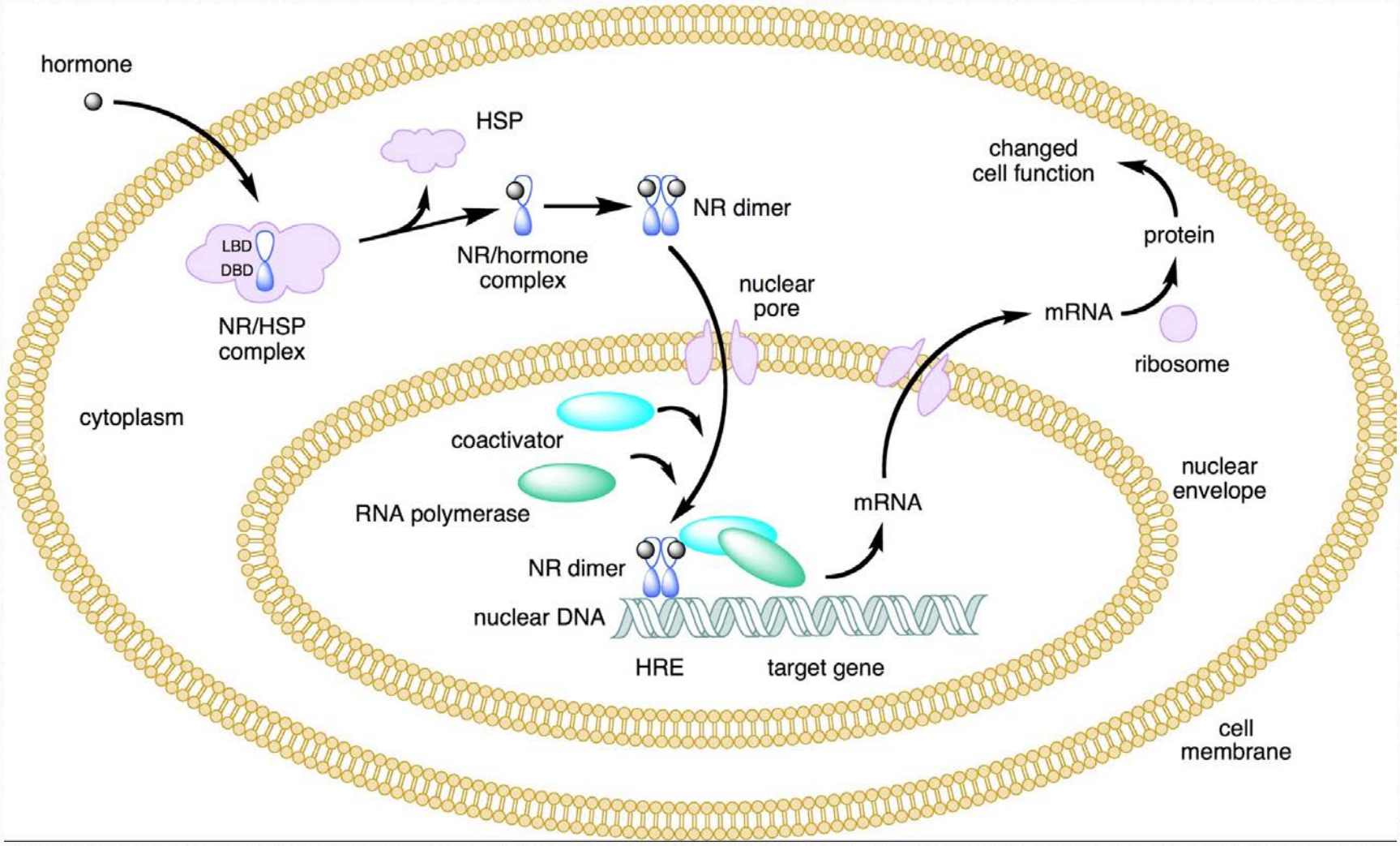

Figure 7.137 - Glucocorticoid signaling pathway

Wikipedia

toid arthritis to multiple sclerosis. All of these effects are mediated through the signaling pathway which starts with the binding of a glucocorticoid hormone to its receptor. Recall that steroids can cross the plasma membrane, so glucocorticoids can diffuse into the cell and bind their receptors which are in the cytoplasm.

In the absence of the signal, glucocorticoid receptors are found bound to a protein chaperone, Hsp90 (Figure 7.137). This keeps the receptors from being transported to the nucleus. When a glucocorticoid molecule binds the receptor, the receptor undergoes a conformational change and dissociates from the Hsp90. The receptor, then, with the hormone bound, translocates into the nucleus. In the nucleus, it can increase the transcription of target genes by binding to specific regulatory sequences (labeled HRE for hormone-response elements). The binding of the hormone-receptor complex to the regulatory elements of hormone-responsive genes modulates their expression. Many of these genes encode anti-inflammatory proteins, and their increased production accounts for the physiological effect of corticosteroid therapies.

The steroid receptor pathways are relatively simple and have only a couple of steps (Figure 7.138). Most other signaling pathways involve multiple steps in which the original signal is passed on and amplified through

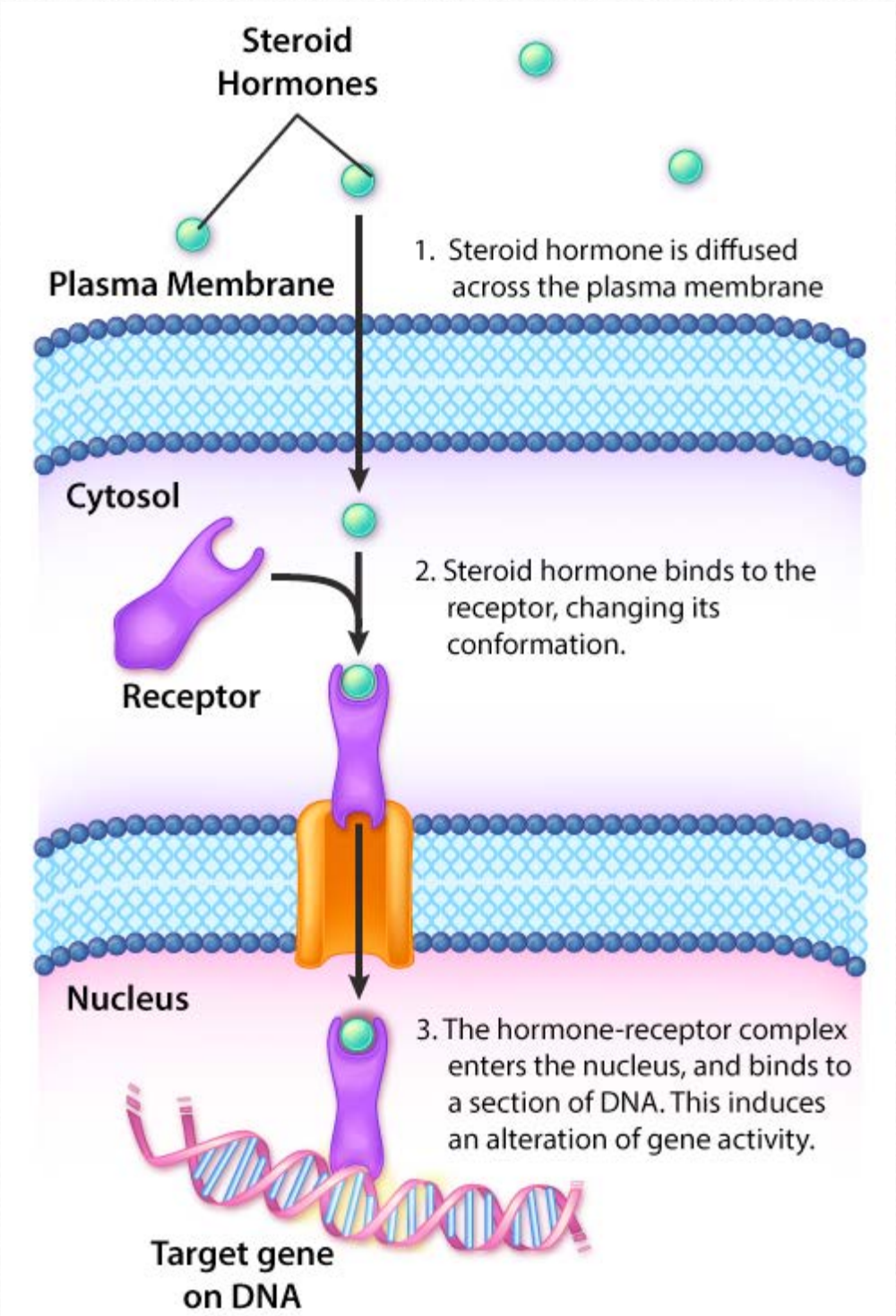

Figure 7.138 - Steroid hormone signaling

Image by Aleia Kim

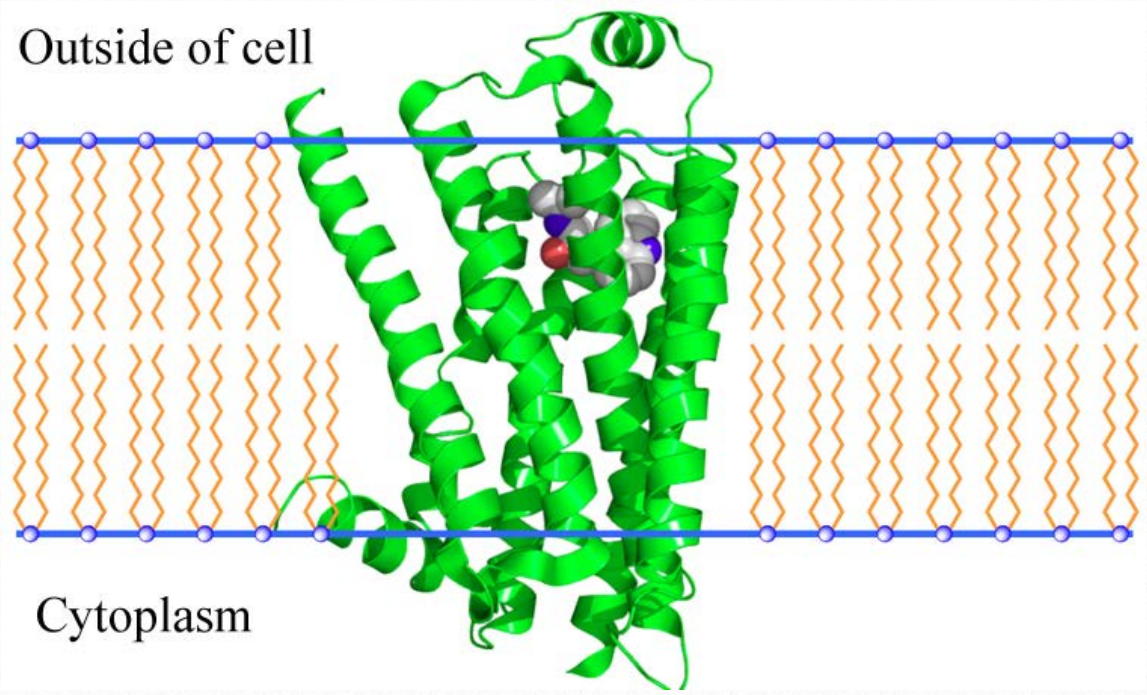

Figure 7.139 - Structure of a G-protein linked receptor
Wikipedia

a number of intermediate steps, before the cell responds to the signal.

Cell surface receptors

We will now take a look at two signaling pathways, each mediated by a major class of cell surface receptor- the G-protein coupled receptors (GPCRs) and the receptor tyrosine kinases (RTKs). While the specific details of the signaling pathways that follow the binding of signals to each of these receptor types are different, it is easier to learn them when you can see what the pathways have in common, namely, interaction of the signal with a receptor, followed by relaying and amplification of the signal through a variable number of intermediate molecules, with the last of these molecules interacting with a target or target proteins and modifying their activity in the cell.

G-protein coupled receptors

G-protein coupled receptors (GPCRs) are involved in responses of cells to many different kinds of signals, from epinephrine, to odors, to light. In fact, a variety of physiological phenomena including vision, taste, smell, and the fight-or-flight response are mediated by GPCRs. What are G-protein coupled receptors?

G-protein coupled receptors are cell surface receptors that pass on the signals that they receive with the help of guanine nucleotide binding proteins (a.k.a. G-proteins). Before thinking any further about the signaling pathways downstream of GPCRs, it is necessary to know a few important facts about these receptors and the G-proteins that assist them.

GPCR structure

Though there are hundreds of different G-protein coupled receptors, they all have the same basic structure (Figure 7.139):

They all consist of a single polypeptide chain that threads back and forth seven times through the lipid bilayer of the plasma membrane. For this reason, they are sometimes called seven-pass transmembrane

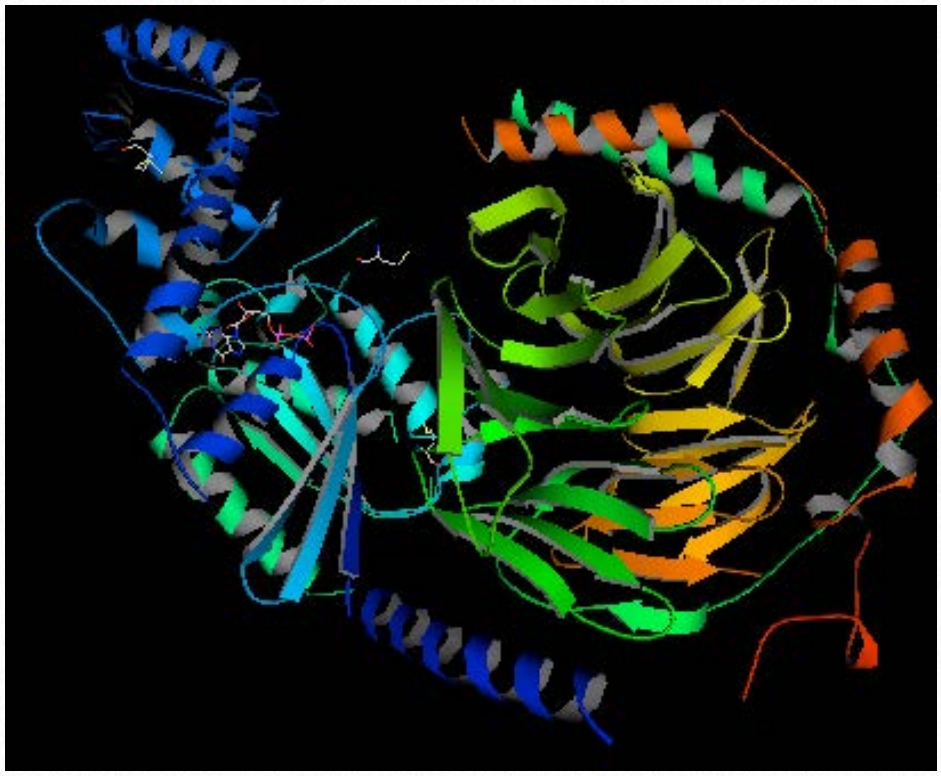

Figure 7.140- A heterotrimeric G-protein: α subunit in blue, βγ subunits red and green

(7TM) receptors. One end of the polypeptide forms the extracellular domain that binds the signal while the other end is in the cytosol of the cell.

When a ligand (signal) binds the extracellular domain of a GPCR, the receptor undergoes a conformational change, on its cytoplasmic side, that allows it to interact with a G-protein that will then pass the signal on to other intermediates in the signaling pathway.

G-proteins

What is a G-protein? As noted above, a G-protein is a guanine nucleotide-binding protein that can interact with a G-protein linked receptor. G-proteins are associated with the cytosolic side of the plasma membrane, where they are ideally situated to interact with the tail of the GPCR, when a signal binds to the GPCR. There are many different G-proteins, all of which share a characteristic structure- they are composed of three subunits called α, β and γ (Figure 7.140). Because of this, they are sometimes called heterotrimeric G proteins (hetero=different, trimeric= having three parts).

Ligand binding

The guanine nucleotide binding site is on the α subunit of the G-protein. This site can bind GDP or GTP. The α subunit also has a GTPase activity, i.e., it is capable of hydrolyzing a GTP molecule bound to it into GDP.

In the unstimulated state of the cell, that is, in the absence of a signal bound to the GPCR, the G-proteins are found in the trimeric form (α-β-γ bound together) and the α subunit has a GDP molecule bound to it. In this form, the α subunit is inactive. With this background on the structure and general properties of the GPCRs and the G-proteins, we can now look at what happens when a signal arrives at the cell surface and binds to a GPCR (Figure 7.141).

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The signaling pathway

The binding of a signal molecule by the extracellular part of the G-protein linked recep-

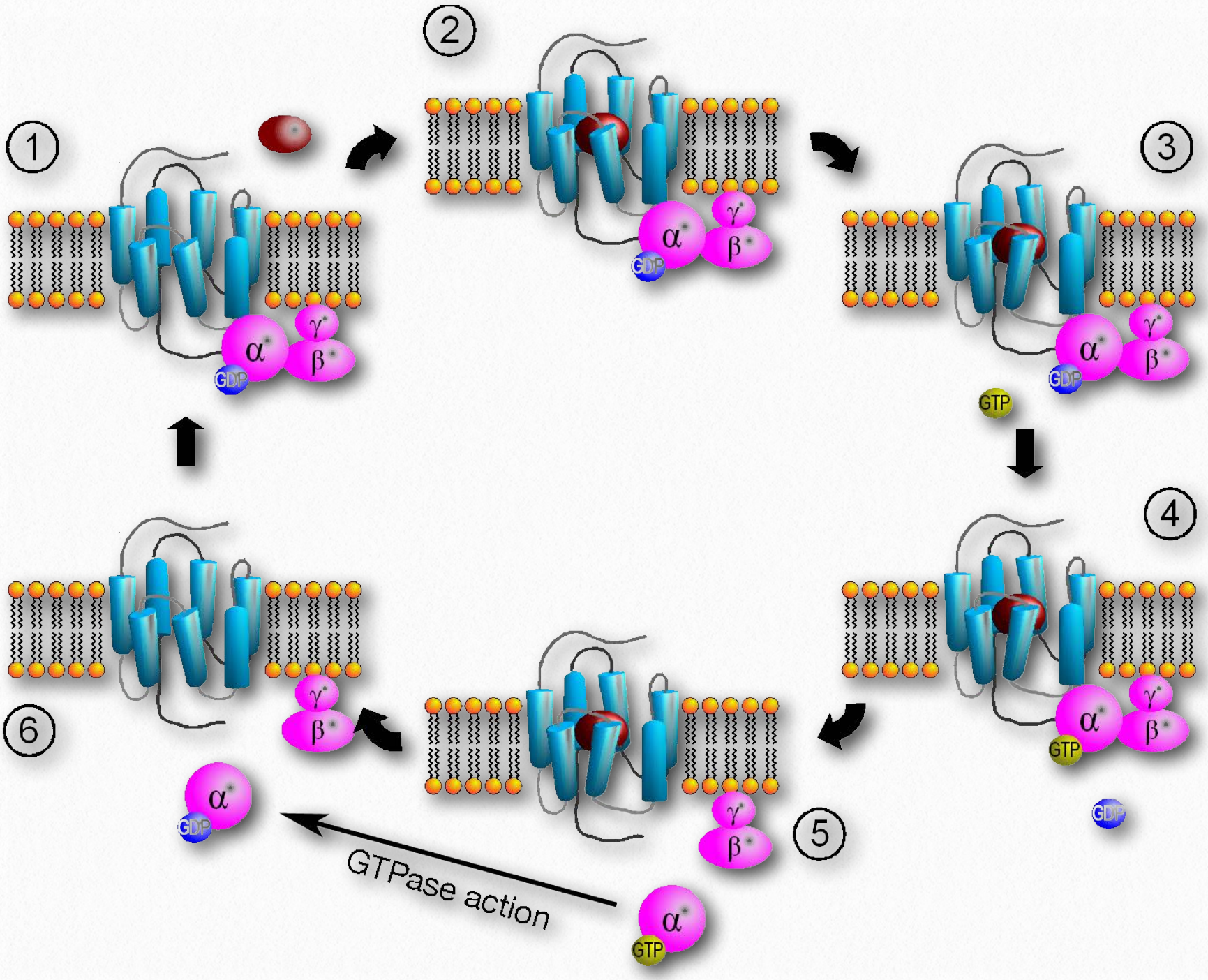

Figure 7.141 - Cycle of G-protein activation - 1) binding of ligand; 2) change of receptor structure; 3) stimulation of α-subunit; 4) binding of GTP, release of GDP; 5) separation of α-subunit from β-γ; 6) hydrolysis of GTP by α-subunit and return to inactive state.

Wikipedia

tor causes the cytosolic tail of the receptor to interact with, and alter the conformation of, a G-protein associated with the inner face of the plasma membrane.

This has two consequences. First, the α subunit of the G-protein loses its GDP and binds a GTP, instead. Second, the G-protein breaks up into the GTP-bound α part and the β-γ part.

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The binding of GTP to the α subunit and its dissociation from the β-γ subunits activate the α subunit. The activated α subunit can diffuse freely along the cytosolic face

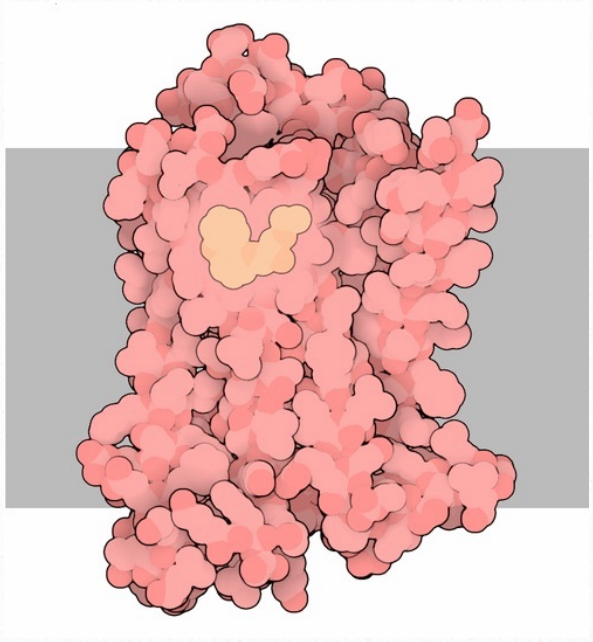

Figure 7.142 - β_2-adrenergic receptor embedded in membrane (gray)

Wikipedia

of the plasma membrane and act upon its targets. (The β-γ unit is also capable of activating its own targets.)

What happens when G-proteins interact with their target proteins? That depends on what the target is. G-proteins interact with different kinds of target proteins, of which we will examine two major categories:

Ion channels

We have earlier seen that some gated ion channels can be opened or closed by the direct binding of neurotransmitters to a receptor that is an ion-channel protein. In other cases, ion channels are regulated by the binding of G-proteins. That is, instead of the signal directly binding to the ion channel, it binds to a GPCR, which activates a G-protein that then may cause opening of the ion channel, either directly, by binding to the channel, or indirectly, through activating other proteins that can bind to the channel. The change in the distribution of ions across the plasma membrane causes a change in the membrane potential.

Enzyme activation

The interaction of G-proteins with their target enzymes can regulate the activity of the enzyme, either increasing or decreasing its activity. The change in activity of the target enzyme, in turn, results in downstream changes in other proteins in the cell, and alters the metabolic state of the cell. This is best understood by examining the well-studied response of cells to epinephrine, mediated through the β-adrenergic receptor, a type of G-protein coupled receptor.

Epinephrine (Figure 7.142), also known as adrenaline, is a catecholamine that plays an important role in the body's 'fight or flight' response. In response to stressful stimuli, epinephrine is secreted into the blood, to be carried to target organs whose cells will respond

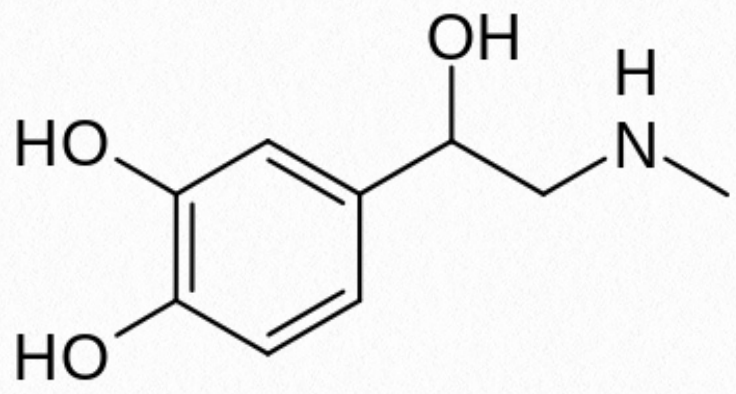

Figure 7.143 - Epinephrine

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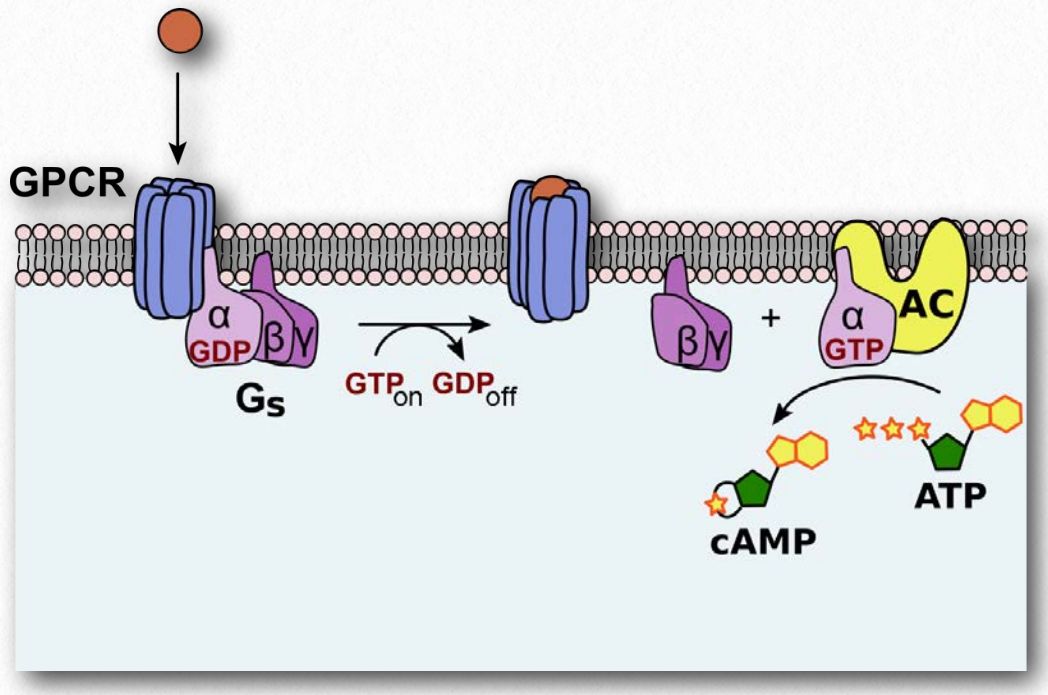

Figure 7.144 - G-protein coupled receptor. Signal starts with ligand binding (orange circle). G_s = G-protein; AC = adenylate cyclase.

Wikipedia

to this signal. If you were walking down a dark alley in an iffy neighborhood, and you heard footsteps behind you, your brain would respond to potential danger by sending signals that ultimately cause the adrenal cortex to secrete epinephrine into the blood stream. The epinephrine circulating in your system has many effects, including increasing your heart rate, but among its prime targets are your muscle cells. The reason for this is that your muscle cells store energy in the form of glycogen, a polymer of glucose. If you need to run or fight off an assailant, your cells will need energy in the form of glucose.

But how does epinephrine get your cells to break down the glycogen into glucose? Binding of epinephrine to the β-adrenergic receptor on the surface of the cells causes the receptor to activate a G-protein associated with its cytoplasmic tail. As described above, this leads to the α subunit exchanging its GDP for GTP and dissociating from the β-γ subunits. The activated α subunit then interacts with the enzyme adenylate cyclase (also known as adenylyl cyclase) stimulating it to produce cyclic AMP (cAMP) from ATP. Cyclic AMP is often described as a "second messenger", in that it serves to spread the

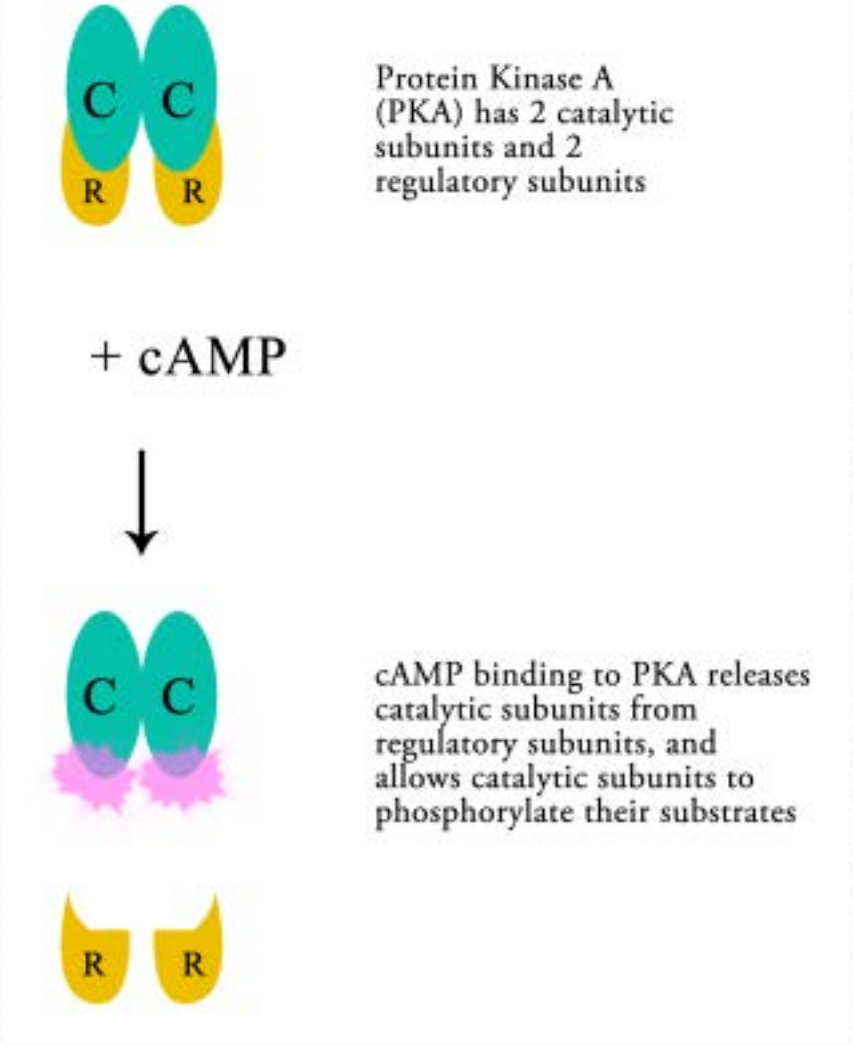

Figure 7.145 - Activation of Protein Kinase A by cAMP

Image by Martha Baker

signal received by the cell. How does cAMP accomplish this?

cAMP molecules bind to, and activate an enzyme, protein kinase A (PKA - Figure 7.145). PKA is composed of two catalytic and two regulatory subunits that are bound tightly together. Upon binding of cAMP, the catalytic subunits are released from the regulatory subunits, allowing the enzyme to carry out its function, namely phosphorylating other proteins. Thus, cAMP can regulate the activity of PKA, which in turn, by phosphorylating other proteins can change their activity. In this case, the relevant protein that is activated is an enzyme, phosphorylase kinase. This enzyme can then phosphorylate and activate glycogen phosphorylase, the enzyme ultimately responsible for breaking glycogen down into glucose-1-phosphate - readily converted to glucose. The activation of glycogen phosphorylase supplies the cells with the glucose they need, allowing you to fight or flee, as you might see fit. Simultaneously, PKA also phosphorylates another enzyme, glycogen synthase. In the case of glycogen synthase, phosphorylation inactivates it, and prevents free glucose from being used up for glycogen synthesis, ensuring that your cells are amply supplied with glucose (Figure 7.146).

Common pattern

Although the steps described above seem complicated, they follow the simple pattern outlined at the beginning of this section:

• Binding of signal to receptor

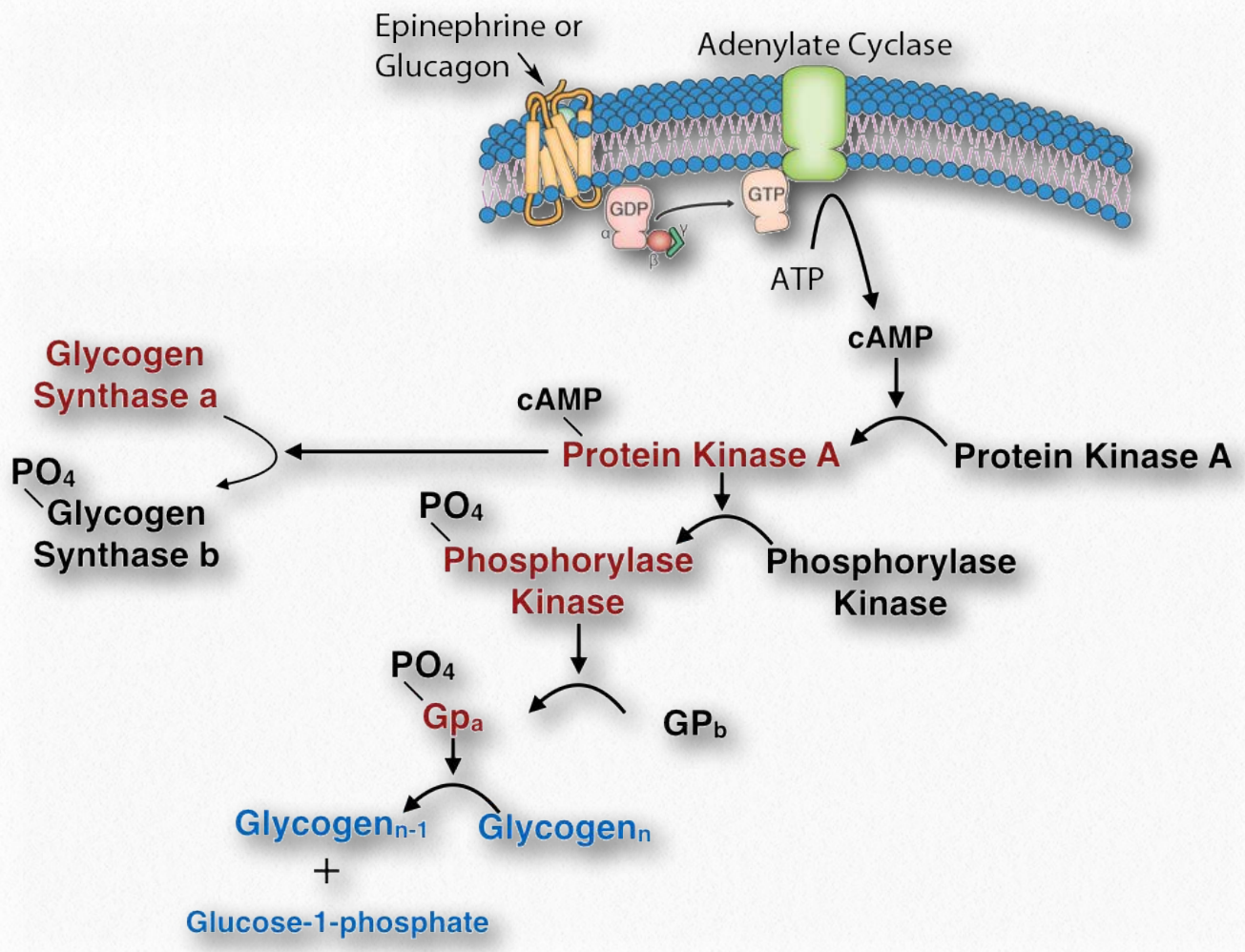

Figure 7.146 - Simultaneous activation of glycogen breakdown and inhibition of glycogen synthesis by epinephrine's binding of b-adrenergic receptor. Red enzyme names = activated forms; black enzyme names = inactivated forms; GPb = glycogen phosphorylase b; GPa = glycogen phosphorylase a.

Image by Penelope Irving

• Several steps where the signal is passed on through intermediate molecules (G-proteins, adenylate cyclase, cAMP, and finally, PKA)
• Phosphorylation of target proteins by the kinase, leading to changes in the cell. The specific changes depend on the proteins that are phosphorylated by the PKA.

Why so many steps? If you need to activate glycogen phosphorylase to break down glucose in a hurry, why not have a system in which binding of a signal to the receptor directly activated the target enzyme?

The answer to this puzzle is simple: there is amplification of the signal at every step of the pathway. A single signal molecule binding to a receptor sets in motion a cascade of reactions, with the signal getting larger at each step, so that binding of one epinephrine molecule to its receptor results in the activation of a million glycogen phosphorylase enzyme molecules!

Turning signals off

If the signal binding to the receptor serves as a switch that sets these events in motion, there must be mechanisms to turn the pathway off. The first is at the level of the receptor itself. A kinase called G-protein receptor kinase (GRK) phosphorylates the cytoplasmic tail of the receptor. The phosphorylated tail is then bound by a protein called arrestin, preventing further interaction with a G-protein.

The next point of control is at the G-protein. Recall that the α subunit of the G-protein is in its free and activated state when it has GTP bound, and that it associates with the β-γ subunits and has a GDP bound when it is inactive. We also

β-Adrenergic Signaling On Switches

1. Binding of Signal Molecule to Receptor
2. Passage of Signal Through Several Molecules (G-proteins, Adenylate Cyclase, cAMP, PKA)
3. Phosphorylation of Target Proteins

β-Adrenergic Signaling Off Switches

1. GRK Phosphorylates Receptor Tail
   Receptor Tail Bound by Arrestin
2. α Subunit G-protein Cleaves GTP to GDP
   β-γ subunits Reassociate with α Subunit
3. cAMP Hydrolyzed by Phosphodiesterase
   PKA Becomes Inactive
4. Dephosphorylation of Phosphorylated Proteins by Phosphoprotein Phosphatase

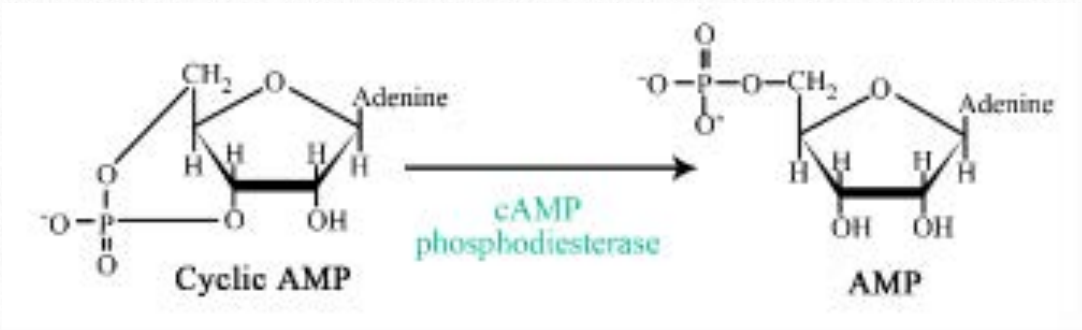

Figure 7.147 - Cyclic AMP is broken down by phosphodiesterase

know that the α subunit has an activity that enables it to hydrolyze GTP to GDP. This GTP-hydrolyzing activity makes it possible for the α subunit, once it has completed its task, to return to its GDP bound state, re-associate with the β-γ part and become inactive again.

A third "off switch" is further down the signaling pathway, and controls the level of cAMP. We just noted that cAMP levels increase when adenylate cyclase is activated. When its job is done, cAMP is broken down by an enzyme called phosphodiesterase (Figure 7.147). When cAMP levels drop, PKA returns to its inactive state, putting a halt to the changes brought about by the activation of adenylate cyclase by an activated G-protein.

Yet another way that the effects of this pathway can be turned off is at the level of the phosphorylated target proteins. These proteins, which are activated by phosphorylation, can be returned to their inactive state by the removal of the phosphates by phosphatases.

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Receptor tyrosine kinases

Another major class of cell surface receptors are the receptor tyrosine kinases or RTKs. Like the GPCRs, receptor tyrosine kinases bind a signal, then pass the message on through a series of intracellular molecules, the last of which acts on target proteins to change the state of the cell.

As the name suggests, a receptor tyrosine kinase is a cell surface receptor that also has a tyrosine kinase activity. The signal binding domain of the receptor tyrosine kinase is on the cell surface, while the tyrosine kinase enzymatic activity resides in the cytoplasmic part of the protein (Figure 7.148). A transmembrane α helix connects these two regions of the receptor.

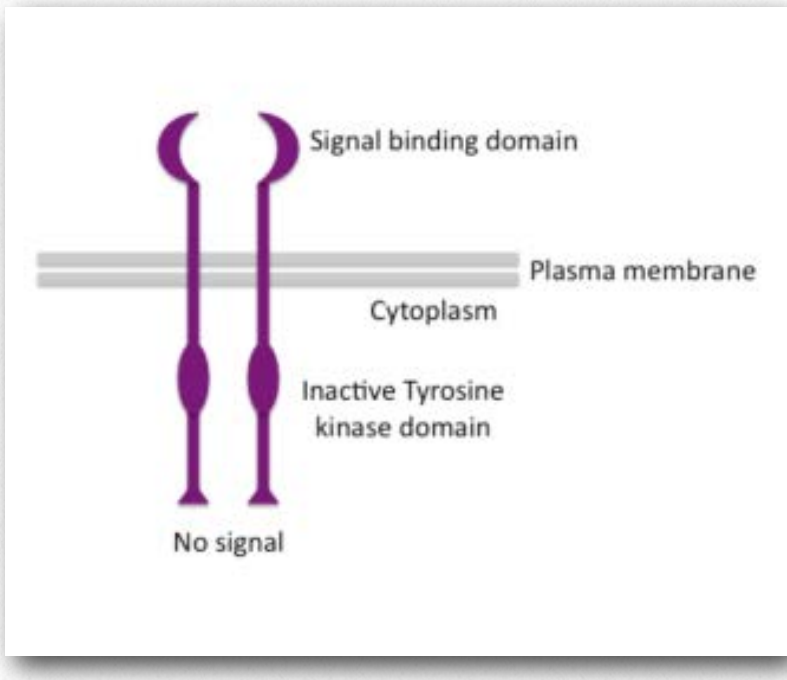

Figure 7.148 - Structure of a receptor tyrosine kinase

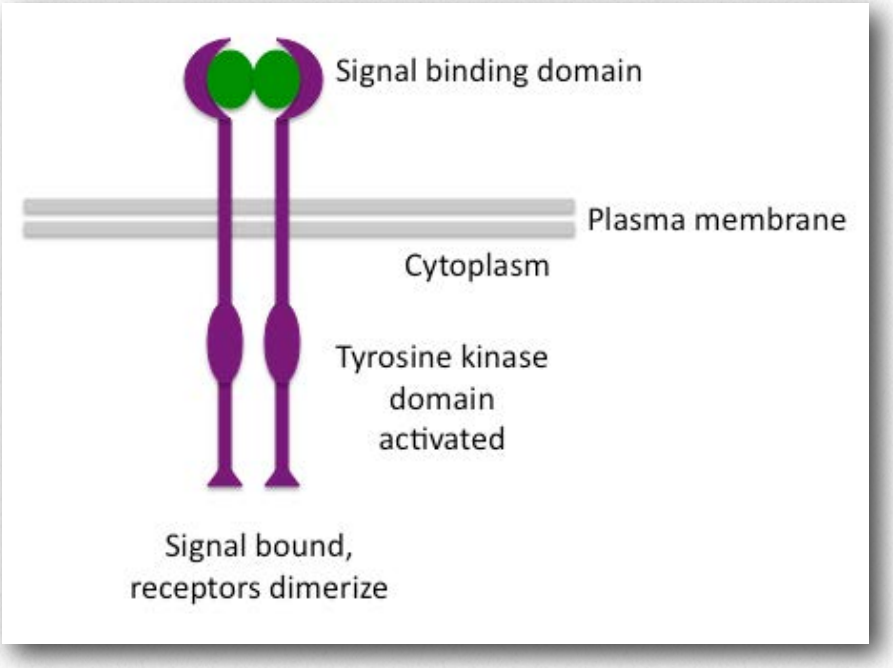

Figure 7.149 - Signal binding results in receptor dimerization and activation of tyrosine kinase activity

What happens when signal molecules bind to receptor tyrosine kinases? Binding of signal molecules to the extracellular domains of receptor tyrosine kinase proteins causes two receptor molecules to dimerize (come together and associate - Figure 7.149). This brings the cytoplasmic tails of the receptors close to each other and causes the tyrosine kinase activity of these tails to be turned on. The activated tails then phosphorylate each other on several tyrosine residues (Figure 7.150). This is called autophosphorylation.

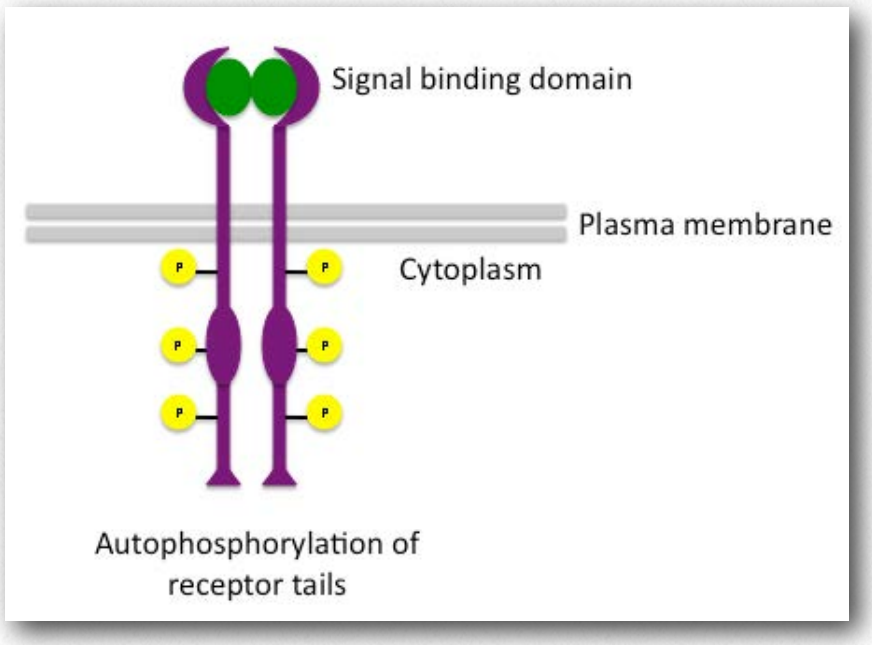

Figure 7.150 - Activated tyrosine kinases phosphorylate tyrosines on the receptor tails.

The phosphorylation of tyrosines on the receptor tails triggers the assembly of an intracellular signaling complex on the tails. The newly phosphorylated tyrosines serve as binding sites for a variety of signaling proteins that then pass the message on to yet other proteins to bring about changes in the cell. Receptor tyrosine kinases mediate responses to a large number of signals, including peptide hormones like insulin and growth factors like epidermal growth factor (EGF). We will examine how insulin

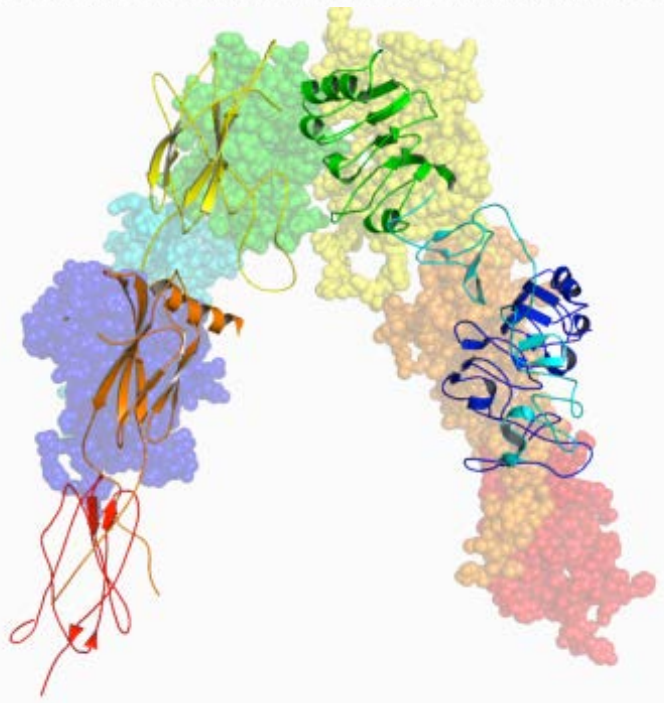

Figure 7.151 -The insulin receptor, a receptor tyrosine kinase

Wikipedia

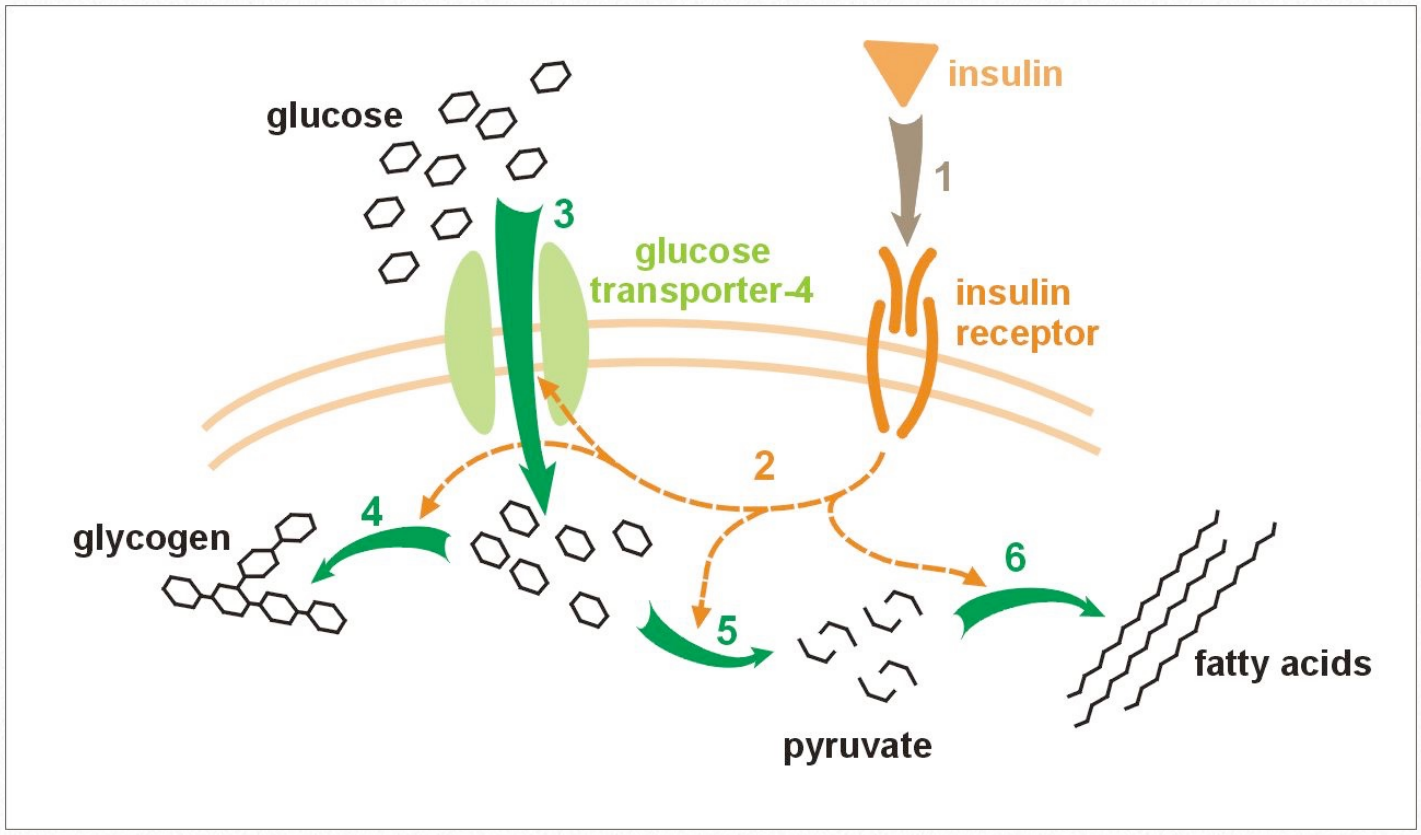

Figure 7.152 - Effects of insulin binding to its receptor tyrosine kinase: 1) insulin binding; 2) activation of protein activation cascades. These include: 3) translocation of Glut-4 transporter to plasma membrane and influx of glucose; 4) glycogen synthesis; 5) glycolysis; and 6) fatty acid synthesis.

Wikipedia

and EGF act on cells by binding to receptor tyrosine kinases.

Insulin receptor

Insulin plays a central role in the uptake of glucose from the bloodstream. It increases glucose uptake by stimulating the movement of glucose receptor GLUT4 to the plasma membrane of cells.

How does insulin increase GLUT4 concentrations in the cell membrane? The binding of insulin to the insulin receptor (IR - Figure 7.151), results in dimerization of the receptor monomers and subsequent autophosphorylation of the cytosolic kinase domains. The activated tyrosine kinase domains also phosphorylate intracellular proteins called Insulin Receptor Substrates or IRS proteins. These proteins interact with, and activate another kinase called the PI_3-kinase. PI_3-kinase then catalyzes the formation of the lipid molecule PIP_3, which serves to activate yet another kinase, PDK1, which in turn, activates the Akt group of kinases. It is this group of enzymes that appears to increase the translocation of the GLUT4 to the plasma membrane (Figure 7.152), as cells that lack functional Akts exhibit poor glucose uptake and insulin resistance.

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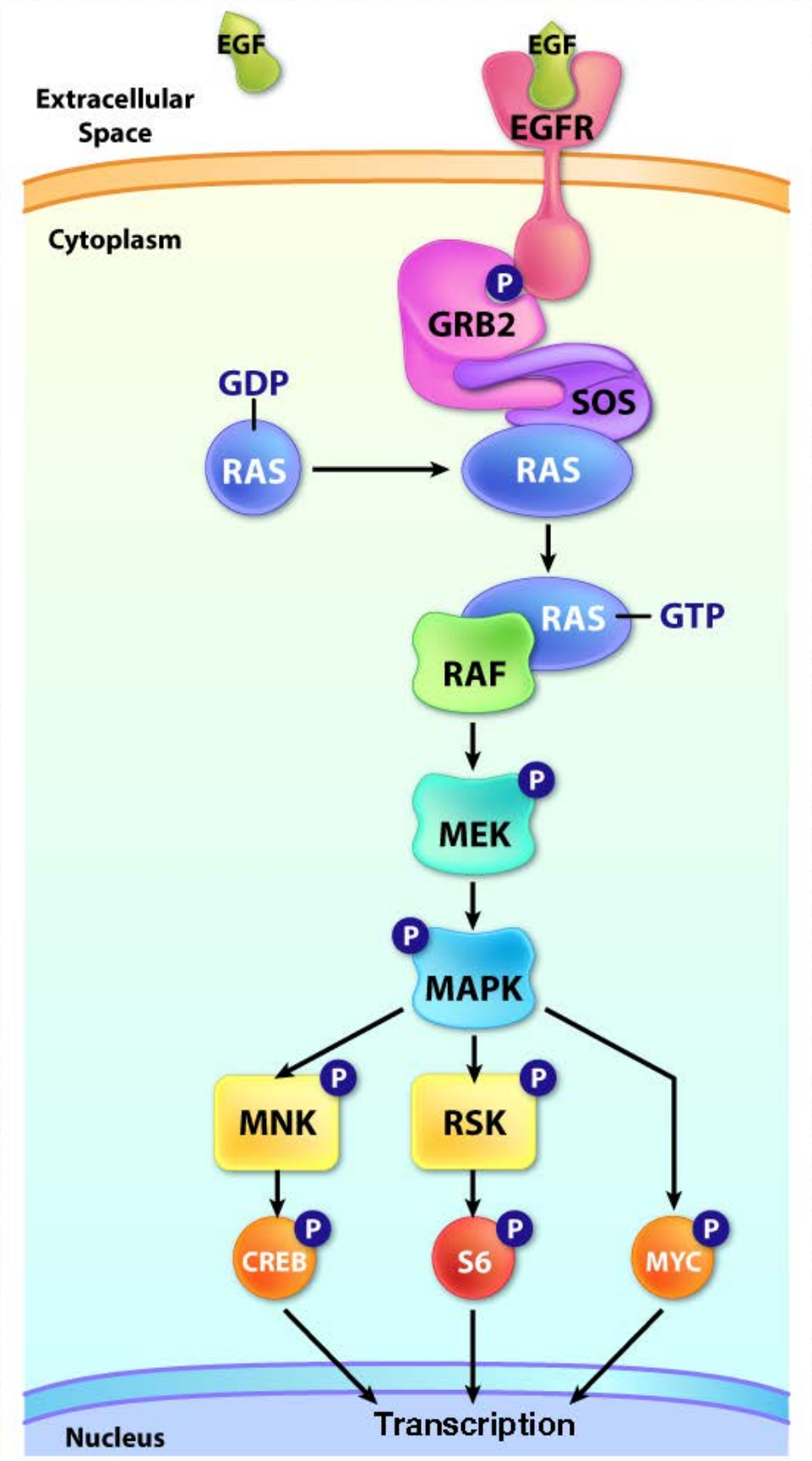

Figure 7.153 - EGFR signaling beginning at top with binding of EGF, dimerization of receptor, transmission of signal through proteins, activation of kinases, phosphorylation of transcription factors and effects on transcription

Image by Aleia Kim

EGFR pathway

Epidermal growth factor, EGF, is an important signaling molecule involved in growth, proliferation and differentiation in mammalian cells. EGF acts through the EGF receptor, EGFR, a receptor tyrosine kinase (Figure 7.153). Because of its role in stimulating cell proliferation and because overexpression of EGFR is associated with some kinds of cancers, EGFR is the target for many anti-cancer therapies. We can trace the signal transduction pathway from the binding of EGF to its receptor to the stimulation of cell division.

EGF binding to the EGFR is followed by receptor dimerization and stimulation of the tyrosine kinase activity of the cytosolic domains of the EGFR. Autophosphorylation of the receptor tails is followed by the assembly of a signaling

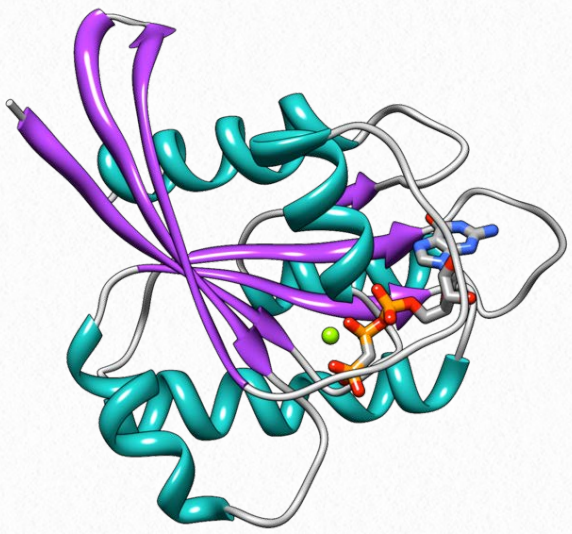

Figure 7.154 - Ras with GTP bound

Wikipedia

complex nucleated by the binding of proteins that recognize phosphotyrosine residues. An important protein that is subsequently activated by the signaling complexes on the receptor tyrosine kinases is called Ras (Figure 7.154). The Ras protein is a monomeric guanine nucleotide binding protein that is associated with the cytosolic face of the plasma membrane (in fact, it is a lot like the α subunit of trimeric G-proteins). Just like the α subunit of a G-protein, Ras is active when GTP is bound to it and inactive when GDP is bound to it. Also, like the α subunit, Ras can hydrolyze the GTP to GDP.

Ras activation

Activation of Ras accompanies the exchange of the GDP bound to the inactive Ras for a GTP. Activated Ras triggers a phosphorylation cascade of three protein kinases, which relay and distribute the signal. These protein kinases are members of a group called the MAP kinases (Mitogen Activated Protein Kinases). The final kinase in this cascade phosphorylates various target proteins, including enzymes and transcriptional activators that regulate gene expression.

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RTK Signal Transduction

1. Receptor binding of signal
2. Receptor dimerization
3. Autophosphorylation of cystosolic tails
4. Passing of message to proteins via signaling complex
5. Stimulation of kinase cascade
6. Terminal kinase acts on target proteins

The phosphorylation of various enzymes can alter their activities, and set off new chemical reactions in the cell, while the phosphorylation of transcriptional activators can change which genes are expressed. The combined effect of changes in gene expression and protein activity alter the cell's physiological state and promote cell division.

Once again, in following the path of signal transduction mediated by RTKs, it is possible to discern the same basic pattern of events: a signal is bound by the extracellular domains of receptor tyrosine kinases, resulting in receptor dimerization and autophosphorylation of the cytosolic tails, thus conveying the message to the interior of the cell.

The message is then passed on *via* a signaling complex to proteins that stimulate a series of kinases. The terminal kinase in the cascade acts on target proteins and brings about in changes in protein activities.

What is the OFF switch for RTKs? It turns out that RTKs with the signal bound can be endocytosed into the cell and broken down. That is, the region of the plasma membrane that the RTK is on can be internally pinched off into a vesicle containing the ligand-bound receptor which is then targeted for degradation.

Ras, which is activated by GTP binding, can also be deactivated by hydrolysis of the GTP to GDP. The importance of this mechanism for shutting down the pathway is evident in cells that have a mutant *ras* gene encoding a Ras protein with defective GTPase activity. Unable to shut off Ras, the cells continue to receive a signal to proliferate. The National Cancer Institute estimates that more than

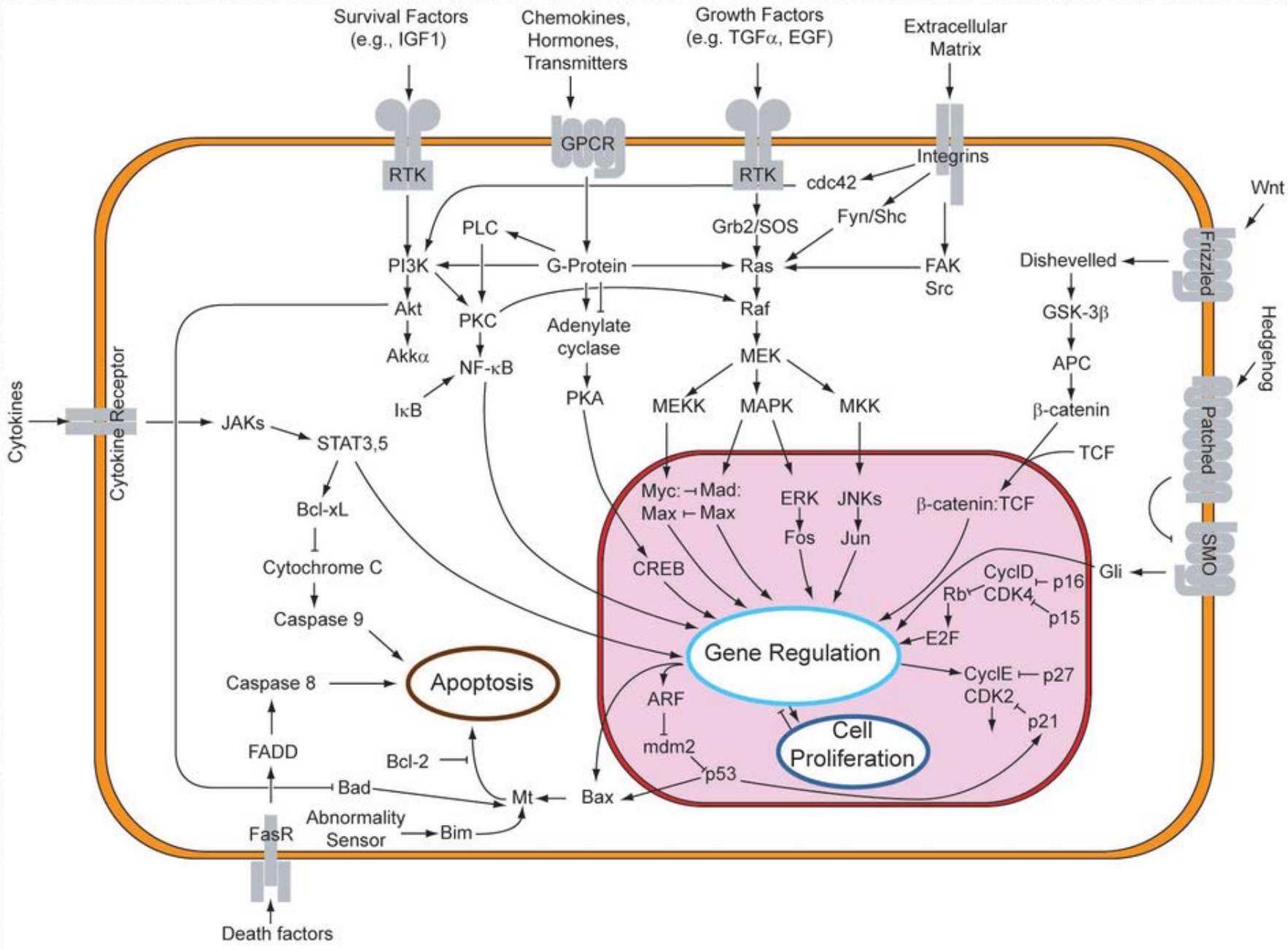

Figure 7.155 - Overview of some cellular signaling pathways

Wikipedia

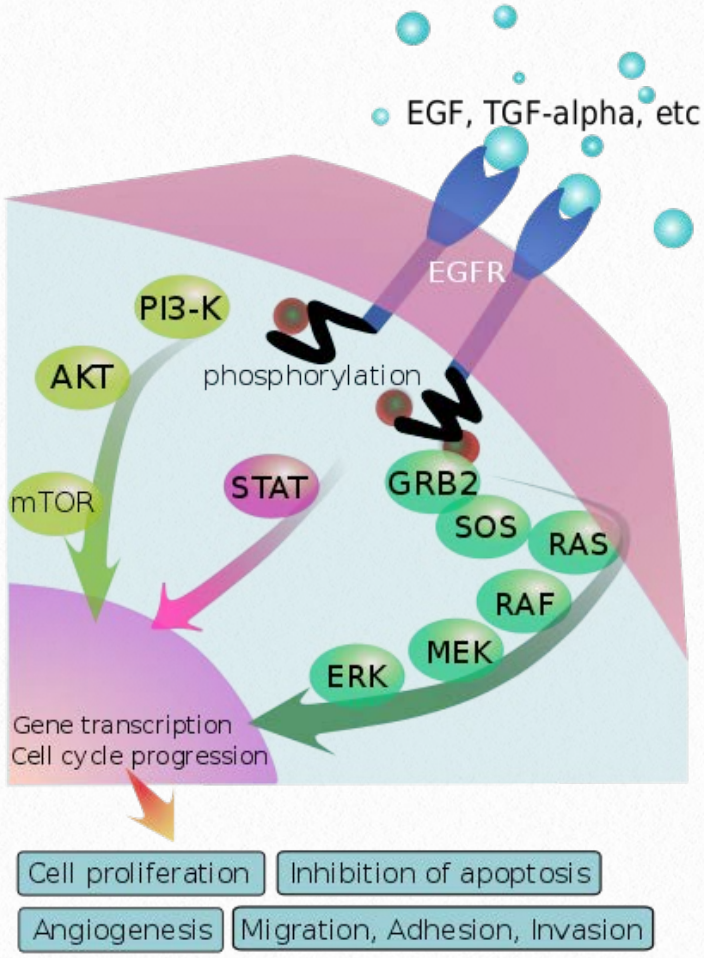

Figure 7.156 -Normal EGF Receptor signaling pathway
Wikipedia

30% of human cancers are driven by mutations in *ras* genes.

The descriptions above provide a very simple sketch of some of the major classes of receptors and deal primarily with the mechanistic details of the steps by which signals received by various types of receptors bring about changes in cells. A major take-home lesson is the essential similarity of the different pathways. Another point to keep in mind is that while we have looked at each individual pathway in isolation, a cell, at any given time receives multiple signals that set off a variety of different responses at once (Figure 7.155).

The pathways described above show a considerable degree of "cross-talk" and the response to any given signal is affected by the other signals that the cell receives simultaneously. The multitude of different receptors, signals, and the combinations thereof are the means by which cells are able to respond to an enormous variety of different circumstances.

RTKs, cancer and cancer therapies

As described above, binding of EGF to its receptor triggers a signaling pathway that results in the activation of a series of Mitogen Activated Protein Kinases (MAP kinases). These kinases are so-called because they are activated by a mitogen, a molecule, like EGF and other growth factors, that stimulates mitosis or cell division. The final kinase in the MAP kinase cascade phosphorylates a number of target proteins, many of them transcription factors, that when activated, increase the expression of genes associated with cell proliferation.

Given that the EGF-receptor pathway normally functions to stimulate cell division, it is not surprising that malfunctions in the pathway could lead to uncontrolled cell proliferation, or cancer. Next, we will take a brief look at some examples of such defects.

HER2

The human EGF receptor (HER) family has four members, HER1, HER2, HER3 and HER4. These are all receptor tyrosine ki-

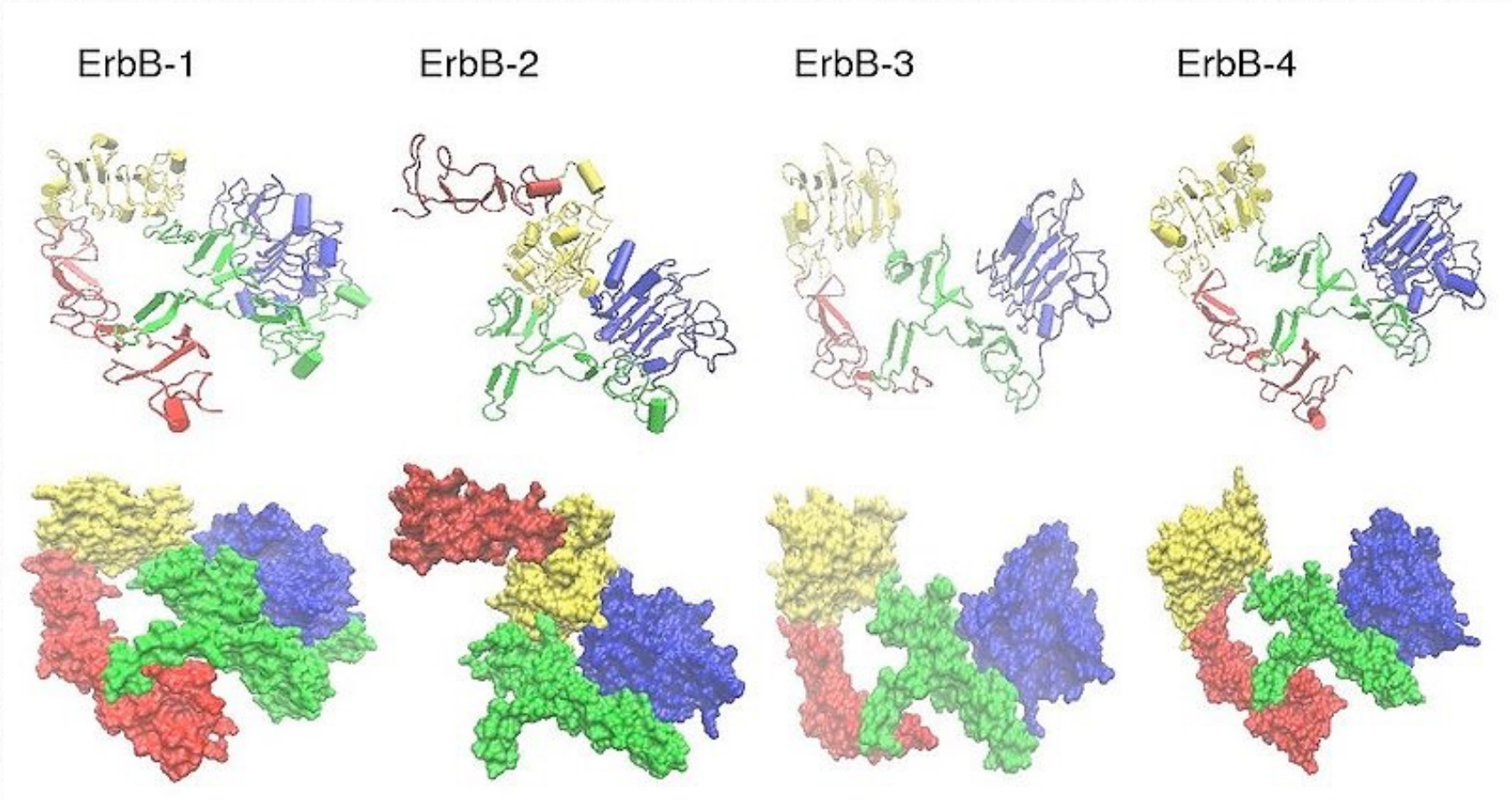

Figure 7.157 - The extracellular domains of the four members of the HER (ErbB) family

nases, cell surface receptors that bind EGF (Figure 7.157) and stimulate cell proliferation.

A crucial step in the signal transduction pathway is the dimerization of the receptors following binding of the signal, EGF, to the receptor. While HER1, HER3 and HER4 must bind the signal to dimerize, the structure of the HER2 receptor can, apparently, allow the receptor monomers to dimerize independently of EGF binding.

This means that the downstream events of the signaling pathway can be triggered even in the absence of a growth signal. In normal cells, only a few HER2 receptors are expressed at the cell surface, so this property of HER2 plays a relatively minor role in stimulating cell division. However, in about a quarter

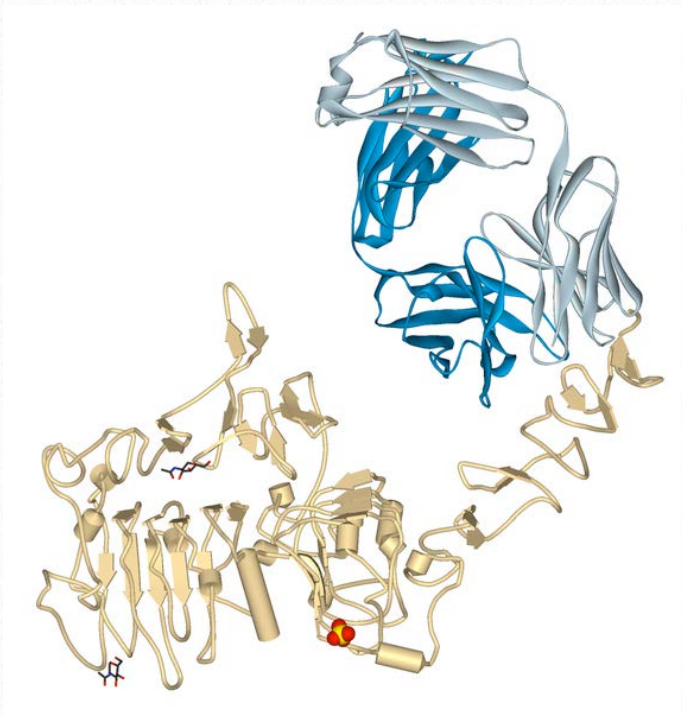

Figure 7.158 - Herceptin (blue) bound to the extracellular domain of HER2 (yellow)

Wikipedia

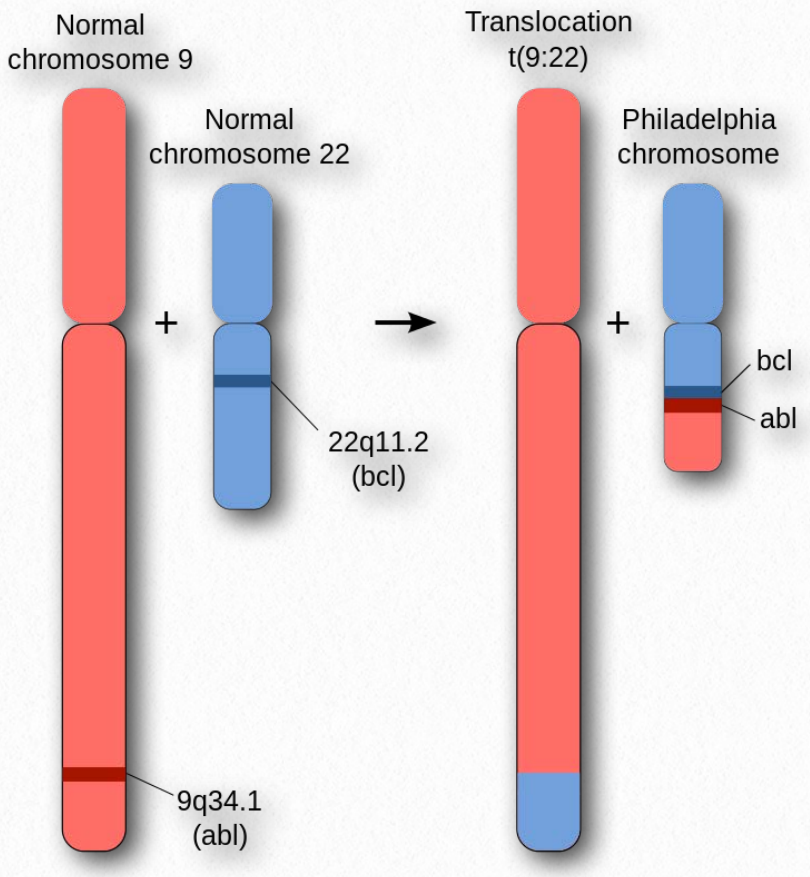

Figure 7.159 - Normal chromosomes (left) and altered chromosomes giving rise to the bcr-abl fusion (right)

Wikipedia

of breast cancer patients, HER2 receptors are overexpressed, leading to increased dimerization and subsequent uncontrolled cell proliferation.

Breast cancers that are HER2-positive can be more aggressive with a greater tendency to metastasize (spread) so therapy that blocks HER2 signaling is key in successful treatment of such cancers. Herceptin, a monoclonal antibody against the HER2 receptor, has been shown to be an effective treatment against Her2-positive breast cancers. Herceptin works by binding specifically to the extracellular domain of the HER2 receptor (Figure 7.158). This prevents dimerization of the receptor and thus blocks downstream signaling. Additionally, the binding of the Herceptin antibody to the receptor signals the immune system to destroy the HER2-positive cells.

Bcr-abl

Another example of a cancer caused by defects in an RTK signaling pathway is chronic myeloid leukemia (CML). Patients with CML have an abnormal receptor tyrosine kinase that is the product of a hybrid gene called bcr-abl, formed by the breakage and rejoining of chromosomes 9 and 22. This abnormal tyrosine kinase is constitutively dimerized, even when no signal is bound. As a result, it continuously signals cells to divide, leading to the massive proliferation of a type of blood cells called granulocytes.

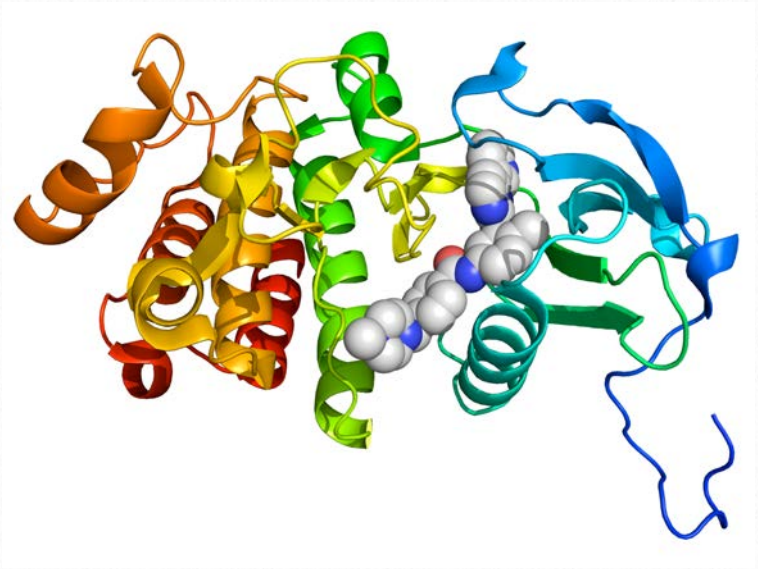

Figure 7.160 - Gleevec bound to the tyrosine kinase portion of abl

Wikipedia

As with HER2, the problem in CML is a receptor tyrosine kinase that dimerizes in the absence of a growth signal. The approach in this case was to target the next step in the signaling pathway. As you know, dimerization of RTKs activates the tyrosine kinase domain of the receptor, which results in the autophosphorylation of the cytoplasmic domains of both monomers. The phosphorylated tyrosines serve to recruit a number of other signaling proteins that pass the signal on within the cell.

In the case of the bcr-abl RTK, the drug Gleevec (imatinib) was designed to bind near the ATP-binding site of the tyrosine kinase domain. This "locks" the site in a conformation that inhibits the enzymatic activity of the tyrosine kinase and thus blocks downstream signaling. With no "grow" signal passed on, cells stop proliferating.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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The Tao of Hormones

To the tune of "*The Sound of Silence*"

Metabolic Melodies Website HERE

Biochemistry my friend
It's time to study you again
Mechanisms that I need to know
Are the things that really stress me so
"Get these pathways planted firmly in your head,"
Ahern said
Let's start with ep-inephrine

Membrane proteins are well known
Changed on binding this hormone
Rearranging selves without protest
Stimulating a G alpha S
To go open up and displace its GDP
With GTP
Because of ep-inephrine

Active G then moves a ways
Stimulating ad cyclase
So a bunch of cyclic AMP
Binds to kinase and then sets it free
All the active sites of the kinases await
Triphosphate
Because of ep-inephrine

Muscles are affected then
Breaking down their glycogen
So they get a wad of energy
In the form of lots of G-1-P
And the synthases that could make a glucose chain
All refrain
Because of ep-inephrine

Now I've reached the pathway end
Going from adrenalin
Here's a trick I learned to get it right
Linking memory to flight or fright
So the mechanism that's the source of anxious fears
Reappears
When I make ep-inephrine

Recording by Tim Karplus
Lyrics by Kevin Ahern

Glucagon is Coming Around

To the tune of "*Santa Claus is Coming to Town*"

Metabolic Melodies Website HERE

You've gotta admire
What molecules do
Their cellular fire
Is ready on cue
Glucagon is coming around

If hormone should bind
Receptor outside
G proteins find
G nucleotides
Glucagon is coming around

They activate cyclases
That make cAMPs
Which bind to Protein Kinase A
And pull the R's from C's

The glycogen shrinks
In liver quite fast
The glucose into
Your bloodstream is passed
Thanks to this you have energy

And muscles uptake
The glucose in turn
Obtaining a substrate
All of them burn
Thanks to this you have energy

The pool of phosphatidyl
Inositides in you
Can send two separate signals
When they get split in two

The muscles contract
When calcium's free
Lowering levels
Of Creatine-P
Now you're gonna need energy

Those little calcium ions
I hope you've learned them well
Are just like Martha Stewart
All locked up in a cell

This story's complete
I know it's a load
My hope is your head
Ain't gonna explode
You will need it in finals week

Recording by Tim Karplus
Lyrics by Kevin Ahern

8

Toolbox

"In theory, there is no difference between theory and practice. But in practice, there is."

Yogi Berra

"The workman who would perfect his craft must first sharpen his tools"- Confucius.

The pace of discovery in biochemistry is astounding. It is hard to believe that the first demonstration that an enzyme was a protein was made only in 1926. The speed with which the field has grown is in no small part due to the development of the tools and techniques with which to study life at the molecular level.

Basic Techniques

Introduction

The environment of a cell is very complex, making it difficult to study individual reactions, enzymes, or pathways in situ. The traditional approach used by biochemists for the study of these things is to isolate molecules, enzymes, DNAs, RNAs, and other items of interest so they can be analyzed independently of the millions of other processes occurring simultaneously. Today, these approaches are used side by side with newer methods that allow us to understand events inside cells on a larger scale- for example, determining all the genes that are being expressed at a given time in specific cells. In this section we take a brief look at some commonly used methods used to study biological molecules and their interactions.

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Breaking cells open

To separate compounds from cellular environments, one must first break open (lyse) the cells. Cells are broken open, in buffered solu-

tions, to obtain a *lysate*. There are several ways of accomplishing this.

Osmotic shock and enzymes

One way to lyse cells is by lowering the ionic strength of the medium the cells are in. This can cause cells to swell and burst. Mild surfactants may be used to disrupt membranes. Most bacteria, yeast, and plant tissues are resistant to osmotic shocks, because of the presence of cell walls, and stronger disruption techniques are usually required. Enzymes may be useful in helping to degrade the cell walls. Lysozyme, for example, is very useful for breaking down bacterial walls. Other enzymes commonly employed include cellulase (plants), proteases, mannases, and others.

Figure 8.1 - A sonicator in use

Wikipedia

Mechanical disruption

Mechanical agitation may be employed in the form of beads that are shaken with a mixture of cells. In this method, cells are bombarded with tiny, glass beads that break the cells open. Sonication (20-50 kHz sound waves) provides an alternative type of agitation that can be effective. The method is noisy, however, and generates heat that can be problematic for heat-sensitive compounds.

Pressure disruption

Another means of disrupting cells involves using a “cell bomb”. In this method, cells are placed under very high pressure (up to 25,000 psi) and then the pressure is rapidly released. The rapid pressure change causes dissolved gases in cells to be released as bubbles which, in turn, break open cells.

Cryopulverization

Cryopulverization is often employed

for samples having a tough extracellular matrix, such as connective tissue, seed, and cartilage. In this technique, tissues are frozen using liquid nitrogen and then impact pulverization (typically, grinding, using a mortar and pestle or a powerful electric grinder) is performed. The powder so obtained is then suspended in the appropriate buffer.

Figure 8.2 - A high-speed centrifuge can be used to obtain different cell fractions from a crude lysate

Wikipedia

Whatever method is employed to create a lysate, crude fractions obtained from it must be further processed *via* fractionation.

Fractionation

Fractionation of samples, as the name suggests, is a process of separating out the components or fractions of the lysate. Fractionation typically begins with centrifugation of the lysate. Using low-speed centrifugation, one can remove cell debris, leaving a supernatant containing the contents of the cell. By using successively higher centrifugation speeds (and resulting g forces) it is possible to separate out different cellular components, like nuclei, mitochondria, etc., from the cytoplasm. These may then be separately lysed to release molecules that are specific to the particular cellular compartment. The soluble fraction of any lysate can, then, be further separated into its constituents using various methods.

Column chromatography

One powerful method used for this purpose is chromatography. We will consider several chromatographic approaches. Chromatography is used to separate out the components of a mixture based on differences in their size, charge or other characteristics. During chromatography, the mobile phase (buffer or other solvent) moves through the stationary phase (usually a solid matrix) carrying the components of the mixture. Separation of the components is achieved, because the different components move at different rates, for reasons that vary, depending on the type of chromatography used. We will consider several different kinds of chromatography to illustrate this process.

1. Ion exchange chromatography
2. Gel exclusion chromatography
3. Affinity chromatography
4. HPLC

These variations on chromatography are performed with the stationary phase held within so-called columns (Figure 8.3). These are

Figure 8.3 -- An ion exchange column apparatus

Wikipedia

tubes containing the stationary phase (also called the “support” or solid phase).

Supports are composed of tiny beads suspended in buffer (Figure 8.4) and are designed to exploit the chemistry or size differences of the components of the samples and thus provide a means of separation. Columns are “packed” or filled with the support, and a buffer or solvent carries the mixture of compounds to be separated through the support. Molecules in the sample interact differentially with the support and, consequently, travel through it at different speeds, thus enabling separation.

Figure 8.4 - Ion exchange beads

Wikipedia

Ion exchange chromatography

In ion exchange chromatography, the support consists of tiny beads to which are attached chemicals possessing a charge. Before use, the beads are equilibrated in a solution containing an appropriate counter-ion to the charged molecule on the bead. Figure 8.5 shows the repeating unit of polystyrolsulfonate, a compound used as a cation exchange resin. As you can see, this molecule is negatively charged, and thus the beads would be equilibrated in a buffer containing a positively charged ion, say sodium. In the suspension, the negatively charged polystyrolsulfonate is unable to leave the beads, due to its covalent attachment, but the counter-ions (sodium) can be “exchanged” for molecules of the same charge.

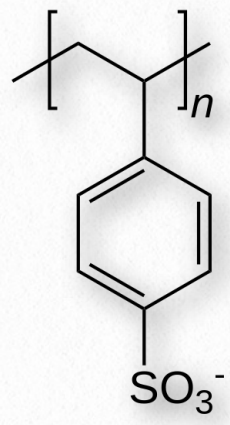

Figure 8.5 - Polystyrolsulfonate, a cation exchange resin

Wikipedia

Exchanges

Thus, a cation exchange column will have positively charged counter-ions and nega-

tively charged molecules covalently attached to the beads. Positively charged compounds from a cell lysate passed through the column will exchange with the counter-ions and "stick" to the negatively charged compounds covalently attached to the beads. Molecules in the sample that are neutral in charge or negatively charged will pass quickly through the column. At this point, only positively charged molecules from the original sample would be bound to the column. These may then be washed off, or eluted, by using buffers containing high concentrations of salt. Under these conditions, the interaction between the positively charged molecules and the polystyrosulfonate would be disrupted, allowing the molecules that were bound to the column to be recovered.

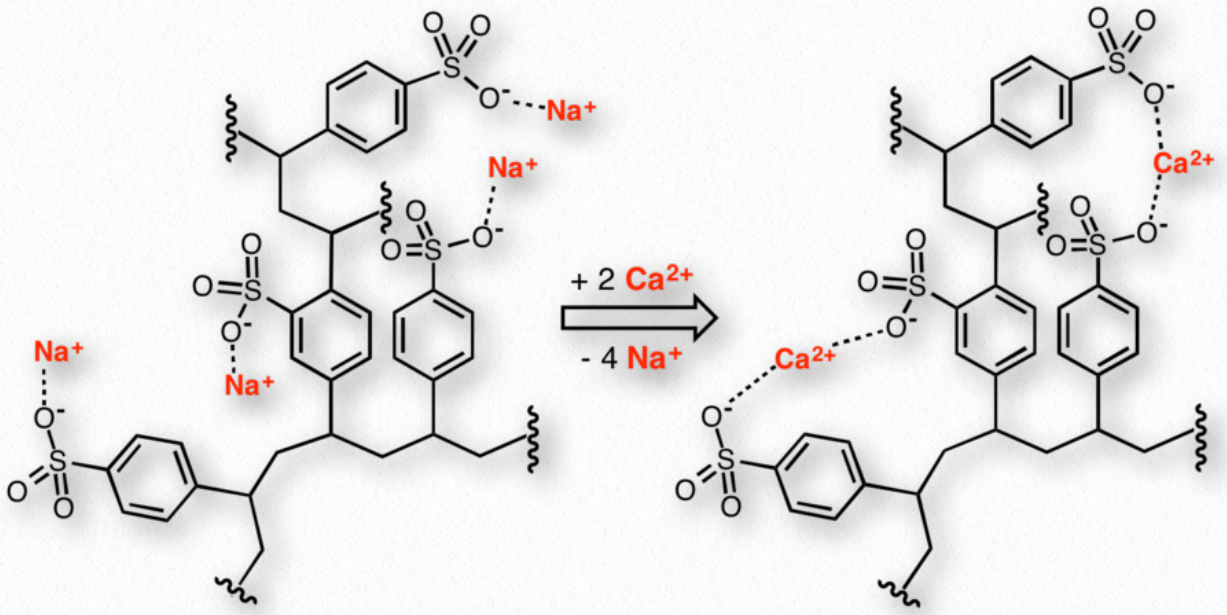

Figure 8.6 - Removal of calcium ions by an ion exchanger
Wikipedia

YouTube Lectures by Kevin HERE & HERE

Anion exchange

On the other hand, in anion exchange chromatography, the chemicals attached to the beads are positively charged and the counterions are negatively charged (chloride, for example). Negatively charged molecules in the cell lysate will "stick" and other molecules will pass through quickly. To remove the molecules "stuck" to a column, one simply needs to add a high concentration of counter-ions to release them.

Uses

Ion exchange resins are useful for separating charged from uncharged, or oppositely charged, biomolecules in solution. The resins have a variety of other applications, including water purification and softening. Figure 8.6 shows use of a polystyrolsulfonate polymer in removing calcium for water softening.

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Size exclusion chromatography

Size exclusion chromatography (also called molecular exclusion chromatography, gel exclusion chromatography, or gel filtration chromatography) is a low resolution separa-

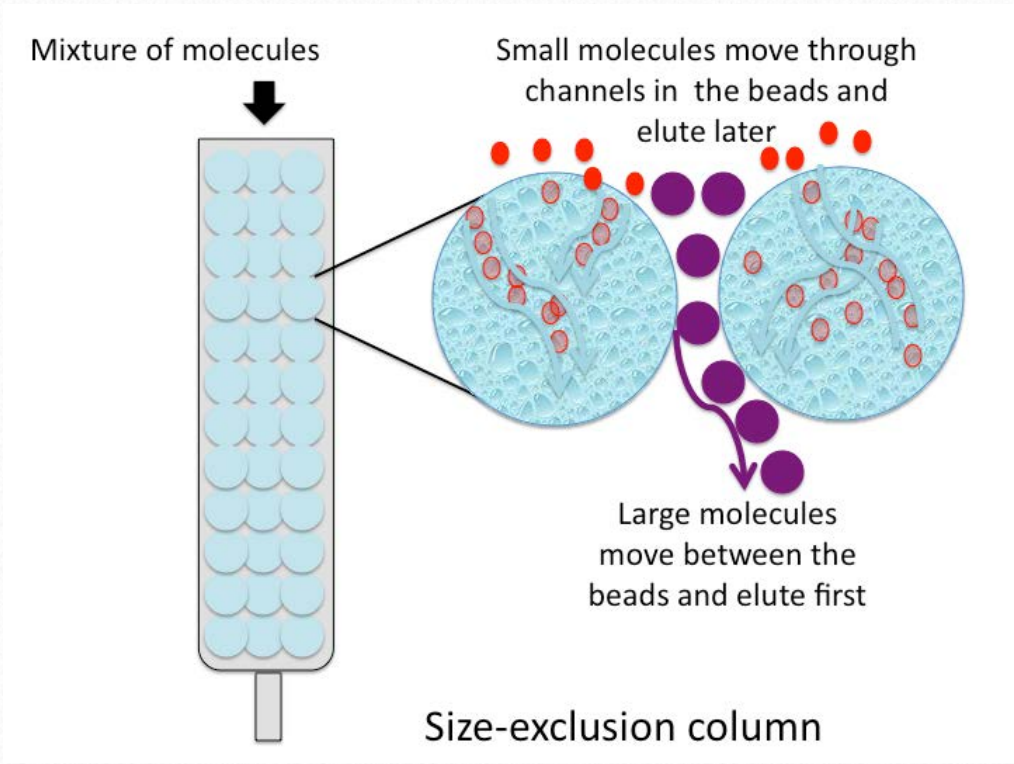

Figure 8.7 - Separation of molecules by size in a size-exclusion (aka gel filtration) column

tion method that employs beads with tiny "tunnels" in them that each have a precise opening. The size of the opening is referred to as an "exclusion limit," which means that molecules above a certain molecular weight will not be able to pass through the tunnels. Molecules with physical sizes larger than the exclusion limit do not enter the tunnels and pass through the column relatively quickly, in the spaces outside the beads. Smaller molecules, which can enter the tunnels, do so, and thus, have a longer path that they take in passing through the column and elute last (Figure 8.7).

Figure 8.8 shows a profile of a group of proteins separated by size exclusion chromatography using beads with an exclusion limit of about 30,000 Daltons. Proteins 30,000 in molecular weight or larger elute in the void volume (left) while smaller proteins elute later (middle and right).

Affinity chromatography

Affinity chromatography is a very powerful and selective technique that ex-

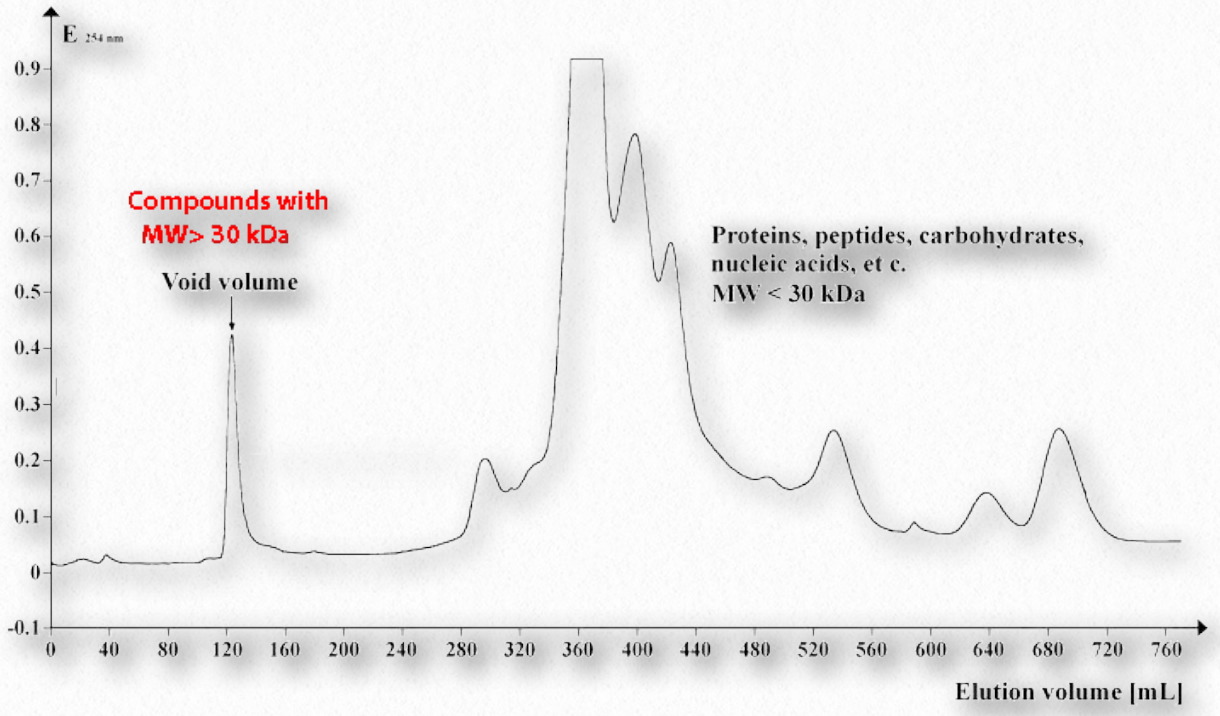

Figure 8.8 - Result of a size exclusion separation

Wikipedia

ploits the binding affinities of sample molecules (typically proteins) for molecules covalently linked to the support beads. In contrast to ion-exchange chromatography, where all molecules of a given charge would bind to the column, affinity chromatography exploits the specific binding of a protein or proteins to a ligand that is immobilized on the beads in the column.

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For example, if one wanted to separate all of the proteins in a cell lysate that bind to ATP from proteins that do not bind ATP, one could use a column that has ATP attached to the support beads and pass the sample through the column. All proteins that bind ATP will "stick" to the column, whereas those that do not bind ATP will pass quickly through it. The bound proteins may then be released from the column by adding a solution of ATP that will displace the bound proteins by competing, for the proteins, with the ATP attached to the column matrix.

Histidine tagging

Histidine tagging (His-tagging) is a special kind of affinity chromatography and is a

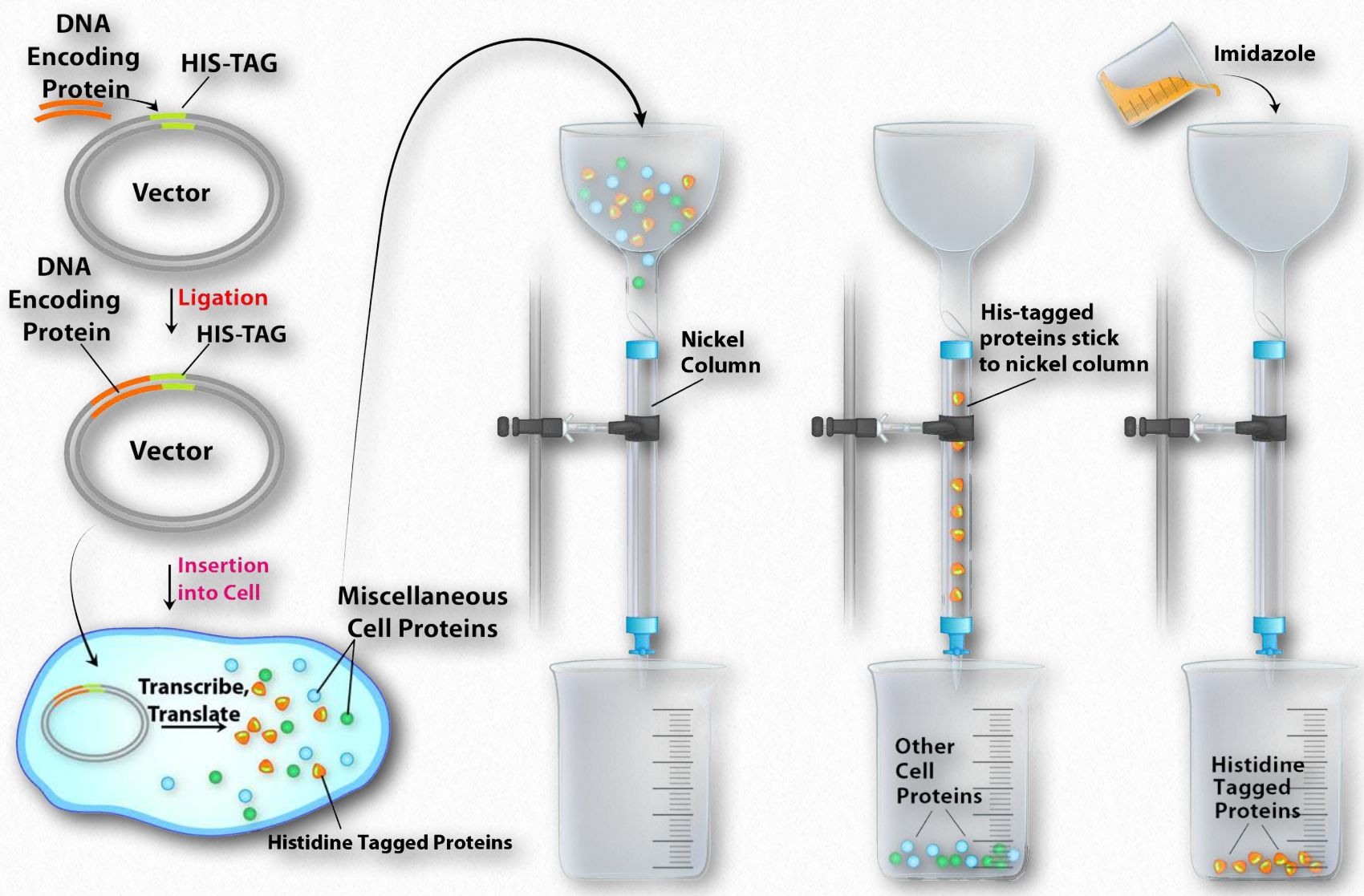

Figure 8.9 - Affinity chromatographic purification of a protein by histidine tagging

Image by Aleia Kim

powerful tool for isolating a recombinant protein from a cell lysate. His-tagging relies on altering the DNA coding region for a protein to add a series of at least six histidine residues to the amino or carboxyl terminal of the encoded protein. This "His-Tag" is useful in purifying the tagged protein because histidine side chains can bind to nickel or cobalt ions. Separation of His-tagged proteins from a cell lysate is relatively easy (Figure 8.9).

Figure 8.10 - HPLC: Pumps on left/Column in center/Detector on the right

Wikipedia

Passing the crude cell lysate through a column with nickel or cobalt attached to beads allows the His-tagged proteins to "stick," while the remaining cell proteins all pass quickly through. The His-tagged proteins are then eluted by addition of imidazole to the column. Imidazole, which resembles the side chain of histidine, competes with the His-tagged proteins and displaces them from the column. Although non-tagged proteins in the lysate may also contain histidine as part of their sequence, they will not bind to the column as strongly as the His-tagged protein and will, thus, be displaced at lower imidazole concentrations than needed to elute the His-tagged protein. Surprisingly, many His-tagged proteins appear to function normally despite the added histidines, but if needed, the histidine tags may be cleaved from the purified protein by treatment with a protease that excises the added histidines, allowing the recovery of the desired protein with its native sequence.

HPLC

High performance liquid chromatography (HPLC) is a powerful tool for separating a variety of molecules based on their differential polarities (Figure 8.10). A more efficient form of column chromatography, it employs columns with tightly packed supports and very tiny beads such that flow of solvents/buffers through the columns requires high pressures. The supports used may be polar (normal phase separation) or non-polar (reverse phase separation). In normal phase separations, non-polar molecules elute first followed by the more polar compounds. This order is switched in reverse phase chromatography. Of the two, reverse phase is much more commonly em-

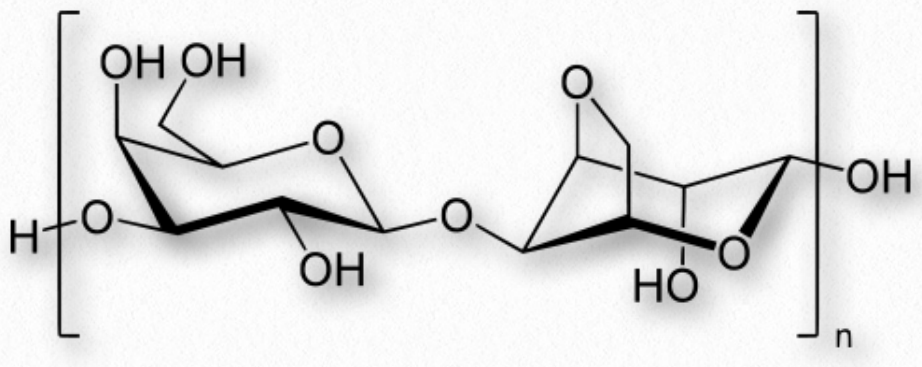

Figure 8.11 - Structure of the agarose polysaccharide

Wikipedia

ployed due to more reproducible chromatographic profiles (separations) that it typically produces.

Gel electrophoresis

Electrophoresis uses an electric field applied across a gel matrix to separate large molecules such as DNA, RNA, and proteins by charge and size. Samples are loaded into the wells of a gel matrix that can separate molecules by size and an electrical field is applied across the gel. This field causes negatively charged molecules to move towards the positive electrode. The gel matrix, itself, acts as a sieve, through which the smallest molecules pass rapidly, while longer molecules are slower-moving. For DNA and RNA, sorting molecules by size in this way is trivial, because of the uniform negative charge on the phosphate backbone. For proteins, which vary in their charges, a clever trick must be employed to make them mimic nucleic acids - see polyacrylamide gel electrophoresis (PAGE) below. Different kinds of gels have different pore sizes. Like sieves with finer or coarser meshes, some gels do a better job of separating smaller molecules while others work better for larger ones.

Gel electrophoresis may be used as a preparative technique (that is, when purifying proteins or nucleic acids), but most often it is used as an analytical tool.

Agarose gel electrophoresis

Agarose gel electrophoresis is a technique used to separate nucleic acids primarily by size. Agarose is a polysaccharide obtained

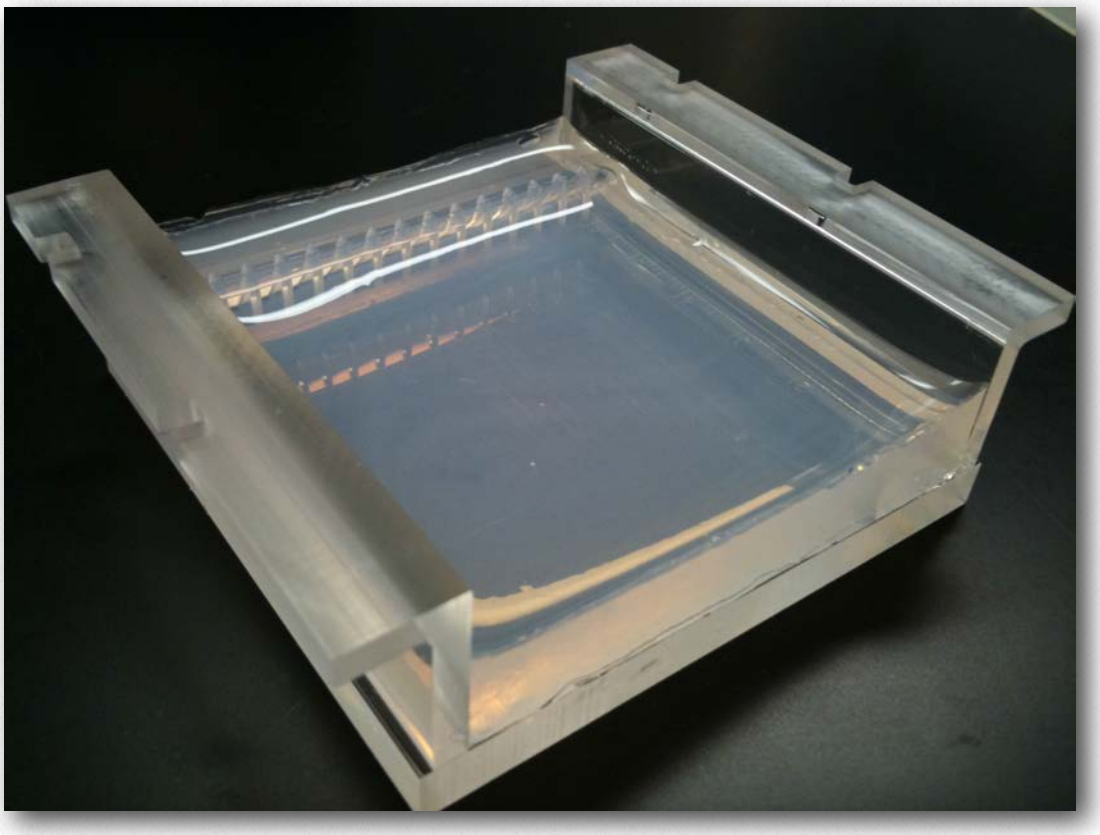

Figure 8.12 - Agarose gel electrophoresis separation of DNA - orange bands are DNA fragments

Wikipedia

from seaweeds (Figure 8.11). It can be dissolved in boiling buffer and poured into a tray, where it sets up as it cools (Figure 8.12) to form a slab. Agarose gels are poured with a comb in place to make wells into which DNA or RNA samples are placed after the gel has solidified. The gel is immersed in a buffer and a current is applied across the slab. Double-stranded DNA has a uniform negative charge that is independent of the sequence composition of the molecule. Therefore, if DNA fragments are placed in an electric field they will migrate from the cathode (-) towards the anode (+). The rate of migration is directly dependent on the ability of each DNA molecule to worm or wiggle its way through the sieving gel. The agarose matrix provides openings for macromolecules to move through. The largest macromolecules have the most difficult time navigating through the gel, whereas the smallest macromolecules slip through it the fastest.

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Because electrophoresis uses an electric current as a force to drive the molecules through the matrix, the molecules being separated must be charged. Since the size to charge ratio for DNA and RNA is constant for all sizes of these nucleic acids, the molecules simply sort on the basis of their size - the smallest move fastest and the largest move slowest.

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All fragments of a given size will migrate the same distance on the gel, forming the so-called “bands” on the gel. Visualization of the DNA fragments in the gel is made possible by addition of a dye, such as ethidium bromide, which intercalates between the bases and fluoresces when viewed under ultraviolet light (Figure 8.13) By running reference DNAs of known sizes alongside the samples, it is possible to determine the sizes of the DNA fragments in the sample. It is useful to note that, by convention, DNA fragments are not described by their molecular

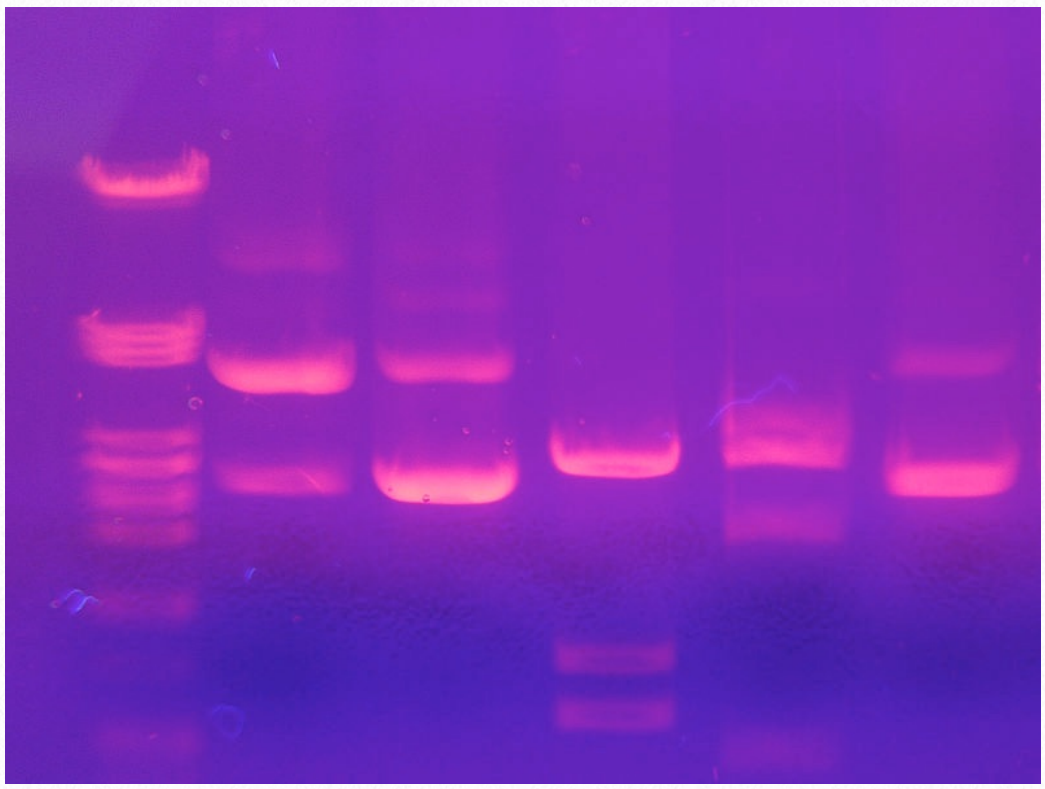

Figure 8.13 - DNA bands visualized with ethidium bromide staining

Wikipedia

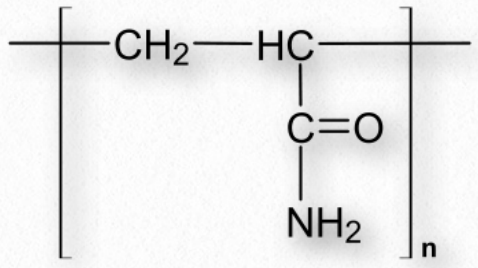

Figure 8.14 - Acrylamide monomer

Wikipedia

weights (unlike proteins), but by their length in base-pairs(bp) or kilobases (kb).

Polyacrylamide gel electrophoresis (PAGE)

Like DNA and RNA, proteins are large macromolecules, but unlike nucleic acids, proteins are not necessarily negatively charged. The charge on each protein depends on its unique amino acid sequence. Thus, the proteins in a mixture will not necessarily all move towards the anode.

Additionally, whereas double-stranded DNA is rod-shaped, most proteins are globular (folded). Further, proteins are considerably smaller than nucleic acids, so the openings of the matrix of the agarose gel are simply too large to effectively provide separation. Consequently, unaltered (native) proteins are not very good prospects for electrophoresis on agarose gels. To separate proteins by mass using electrophoresis, one must make several modifications.

Gel matrix

First, a matrix made by polymerizing and cross-linking acrylamide units is employed. A monomeric acrylamide (Figure 8.14) is polymerized and the polymers are cross-linked using N,N'-Methylene-bisacrylamide (Figure 8.15) to create a mesh-like structure. One can adjust the size of the openings of the matrix/mesh readily by changing the percentage of acrylamide in the reaction. Higher percentages of acrylamide give smaller openings and are more effective for separating smaller molecules, whereas lower percentages of acrylamide are used when resolving mixtures of larger molecules. (Note: polyacrylamide gels are also used to separate small nucleic acid fragments, with some acrylamide gels capable of separating pieces of DNA that differ in length by just one nucleotide.)

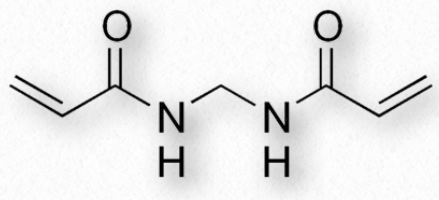

Figure 8.15 - N,N'-Methylenebisacrylamide - acrylamide crosslinking reagent

Wikipedia

Charge alteration by SDS

A second consideration is that proteins must be physically altered to "present" themselves to the matrix like the negatively charged rods of DNA. This is accomplished by treating the proteins with the anionic detergent, SDS (sodium dodecyl sulfate).

SDS denatures the proteins so they assume a rod-like shape and the SDS molecules coat the proteins such that the exterior surface is

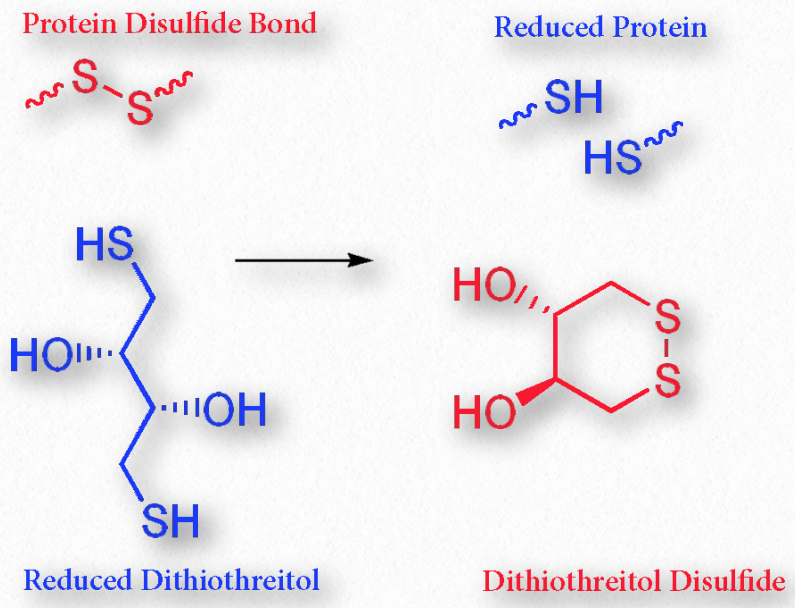

Figure 8.16 - Reduction of disulfide bonds by dithiothreitol

Wikipedia

loaded with negative charges, masking the original charges on the proteins and making the charge on the proteins more proportional to their mass, like the backbone of DNA.

Since proteins typically have disulfide bonds that prevent them from completely unfolding in detergent, samples are boiled with mercaptoethanol to break the disulfide bonds and ensure the proteins are as rod-like as possible in the SDS. Reagents like mercaptoethanol (and also dithiothreitol) are sulfhydryl-containing reagents that become oxidized as they reduce disulfide bonds in other molecules (see Figure 8.16)

Stacking gel

A third consideration is that a "stacking gel" may be employed at the top of a polyacrylamide gel to provide a way of compressing the samples into a tight band before they enter the main polyacrylamide gel (called the resolving gel).

Just like DNA fragments in agarose gel electrophoresis get sorted on the basis of size (largest move slowest and smallest move fastest), the proteins migrate through the gel matrix at velocities inversely related to their size. Upon completion of the electrophoresis, proteins may be visualized by staining with compounds that bind to proteins, like Coomassie Brilliant Blue (Figure 8.17) or silver nitrate.

Non-denaturing gel electrophoresis

The SDS_PAGE technique described above is the commonest method used for electrophoretic separation of proteins. In some situations, however, proteins may be resolved on so-called "native" gels, in the absence of SDS.

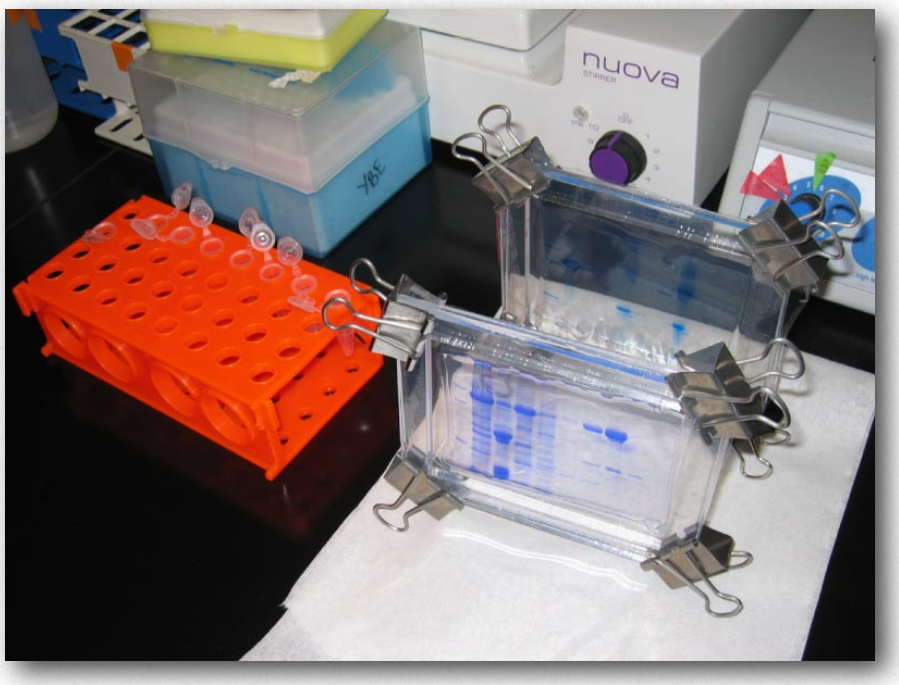

Figure 8.17 - Two SDS-PAGE gels - Proteins are the blue bands (stained with Coomassie Blue)

Wikipedia

Under these conditions, the movement of proteins through the gel will be affected not simply by their mass, but by their charge at the pH of the gel, as well. Proteins complexed with other molecules may move as single entity, allowing the isolation of the binding partners of proteins of interest.

Isoelectric focusing

Proteins vary considerably in their charges and, consequently, in their pI values (pH at which their charge is zero). This can be exploited to separate proteins in a mixture. Separating proteins by isoelectric focusing requires establishment of a pH gradient in a tube containing an acrylamide gel matrix. The pore size of the gel is adjusted to be large, to reduce the effect of sieving based on size. Molecules to be separated are applied to the gel containing the pH gradient and an electric field is applied.

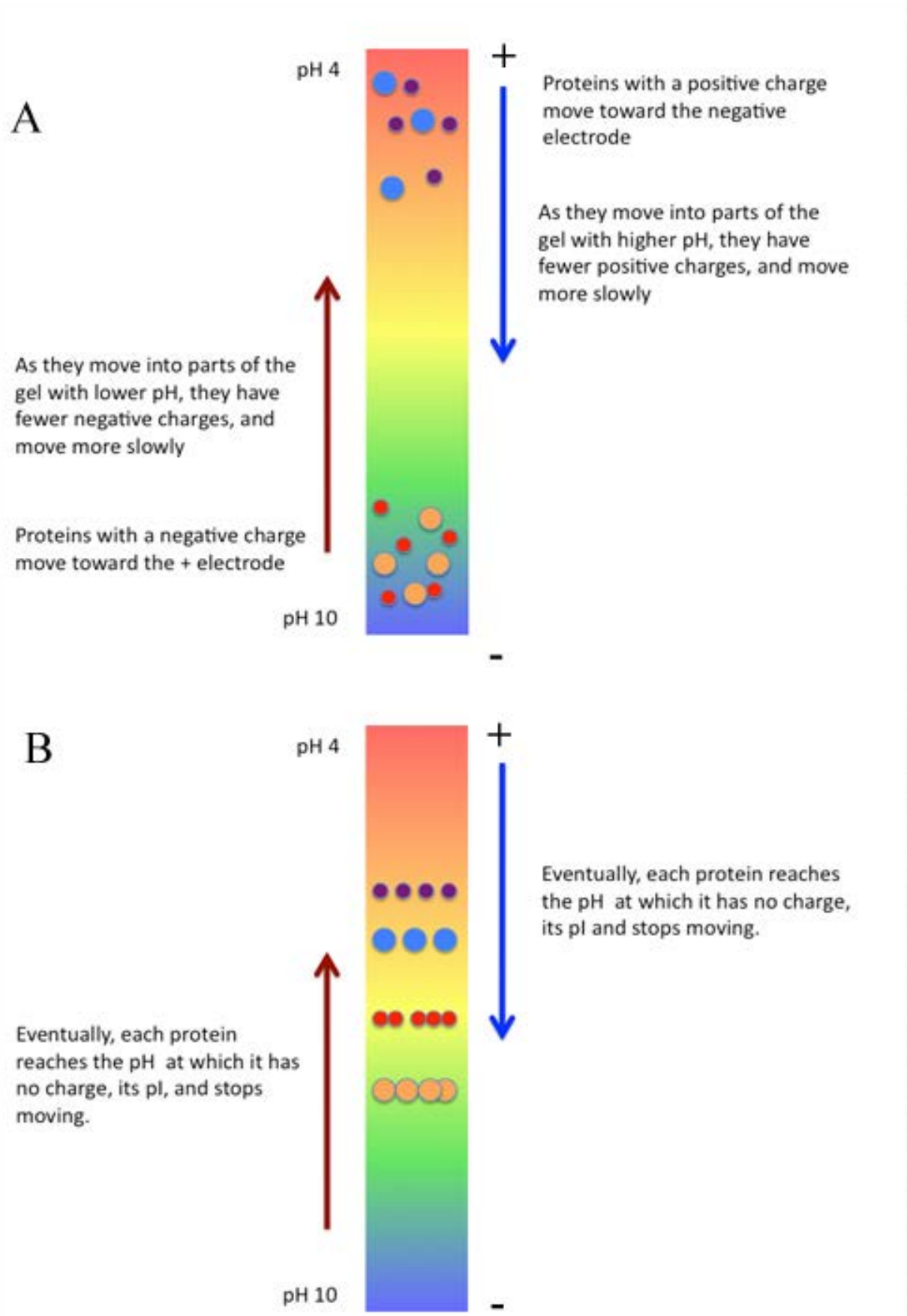

Figure 8.18 - Isoelectric focusing: A. At the start of the run; B. at the end of the run

Image by Indira Rajagopal

Under these conditions, proteins will move according to their charge.

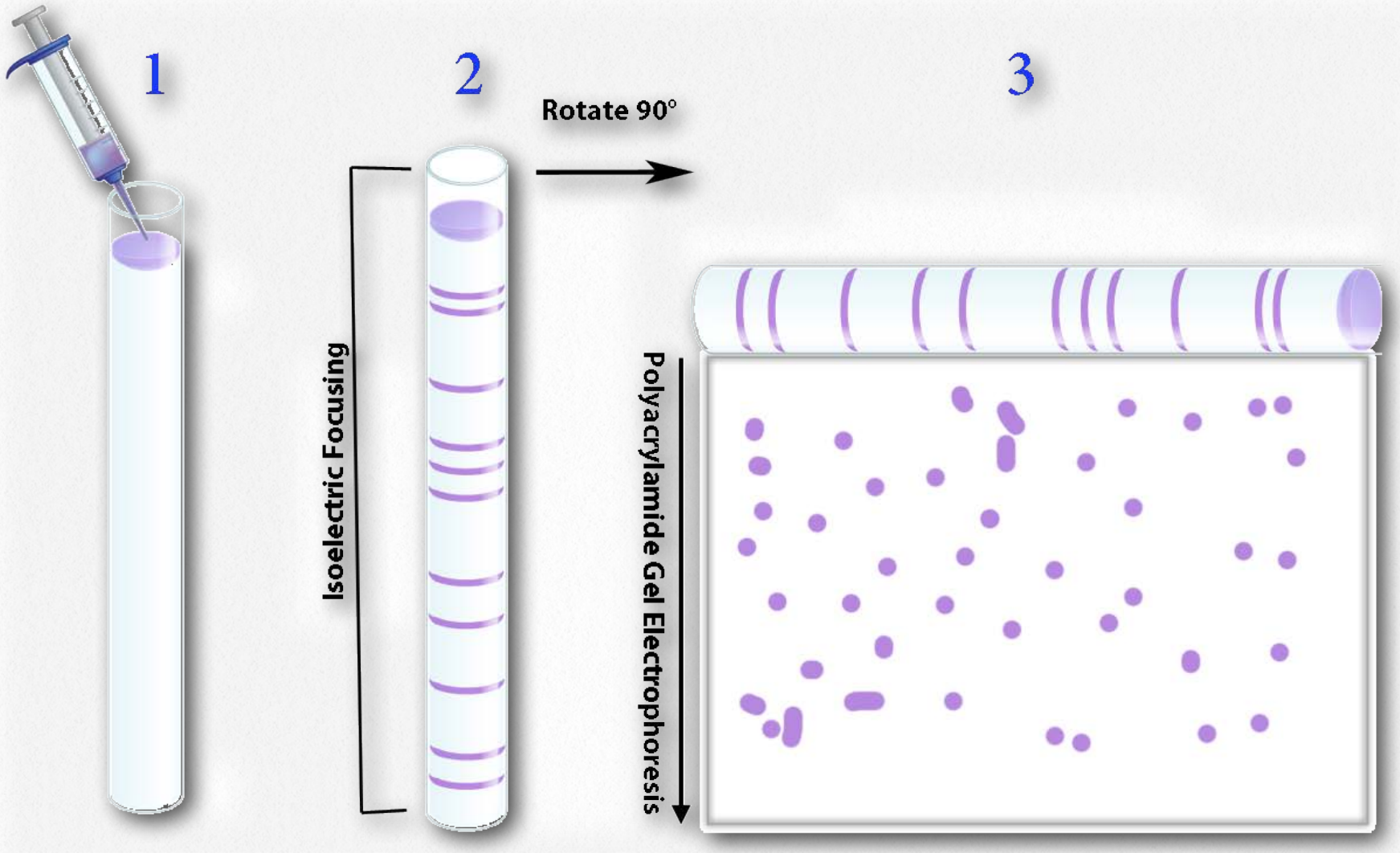

Figure 8.19 - Scheme for performing 2-D gel analysis

Image by Aleia Kim

Positively charged molecules, for example, move towards the negative electrode, but since they are traveling through a pH gradient, as they pass through it, they reach a region where their charge is zero and, at that point, they stop moving. They are at that point attracted to neither the positive nor the negative electrode and are thus "focused" at their pI (Figure 8.18). Using isoelectric focusing, it is possible to separate proteins whose pI values differ by as little as 0.01 units.

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2D gel electrophoresis

Both SDS-PAGE and isoelectric focusing are powerful techniques, but a clever combination of the two is a powerful tool of proteomics - the science of studying all of the proteins of a cell/tissue simultaneously. In 2-D gel electrophoresis, a lysate is first prepared from the cells of interest. The proteins in the lysate are separated first by their pI, through isoelectric focusing and then by size by SDS-PAGE.

The mixture of proteins is first applied to a

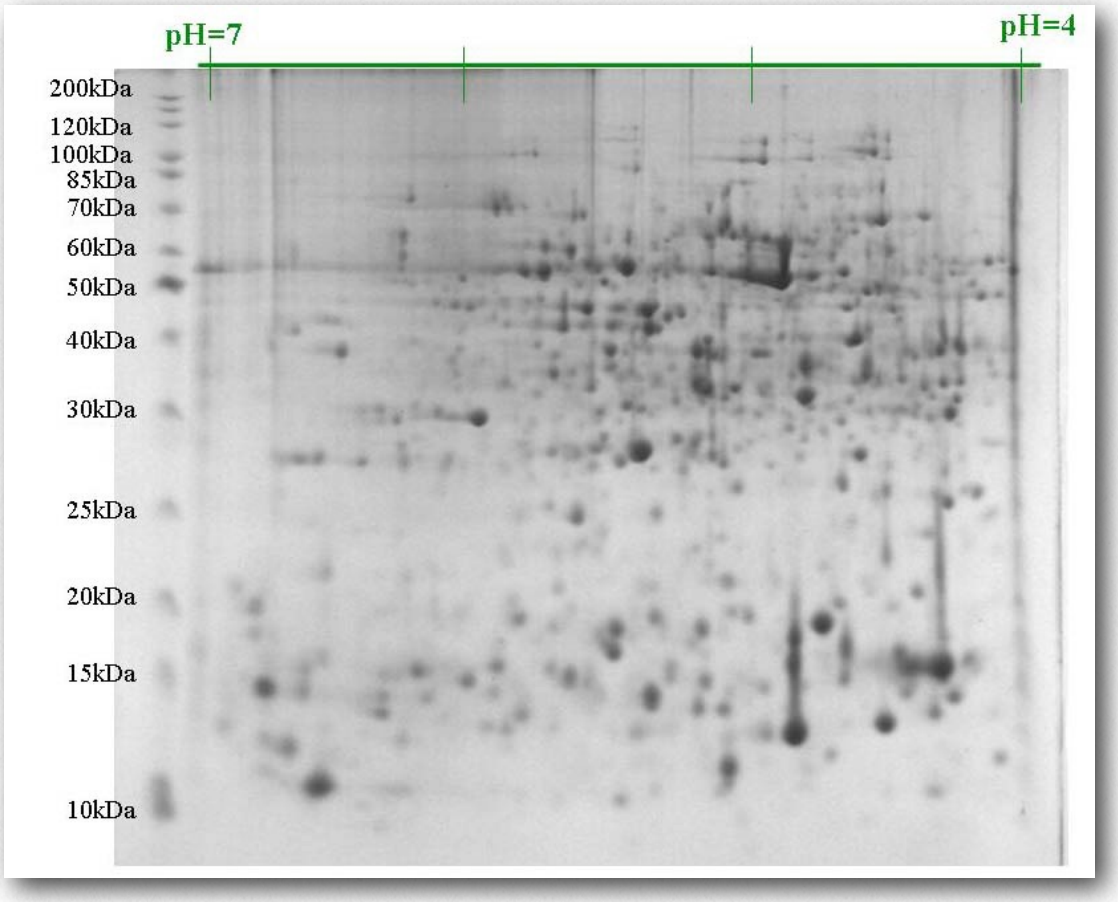

Figure 8.20 - Result of 2-D gel electrophoresis separation

Wikipedia

tube or strip (Figure 8.19, Step 1) where isoelectric focusing is performed to separate the proteins by their pI values (Step 2). Next, as shown in the figure, the gel containing the proteins separated by their pIs is turned on its side and applied along the top of a polyacrylamide slab for SDS-PAGE to separate on the basis of size (Step 3). The proteins in the isoelectric focusing matrix are electrophoresed into the polyacrylamide gel and separated on the basis of size. The product of this analysis is a 2-D gel as shown in Figure 8.20.

The power of 2-D gel electrophoresis is that virtually every protein in a cell can be separated and appear on the gel as a spot defined by its unique size and pI. In the figure, spots in the upper left correspond to large positively charged proteins, whereas those in the lower right are small negatively charged ones. Every spot on a 2-D gel can be eluted and identified by using high throughput mass spectrometry. This is particularly powerful when one compares protein profiles between different tissues or between control and treated samples of the same tissue.

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Protein profiles comparison

Comparison of 2-D gels of proteins from non-cancerous tissue and proteins from a cancerous tissue of the same type provides a quick identification of proteins whose level of expression differs between the two. Information such as this can be useful in designing treatments or in understanding the mechanism(s) by which the cancer develops.

Detection, identification and quantitation of specific nucleic acids and proteins

While gel electrophoresis can be used to resolve molecules in a mixture, by itself, the

technique does not permit the detection and identification of specific nucleic acid sequences or proteins. For example, the 2-D gel shown above clearly separates a large number of proteins in a sample into individual spots. However, if we wanted to know whether a specific protein was present, we could not tell by simply looking at the gel. Likewise, in an agarose gel, while bands of DNA could be assigned a size, one could not distinguish between two DNAs of different sequence if they were both the same length in base-pairs. One way to detect the presence of a particular nucleic acid or protein is dependent on transferring the separated molecules from the gels onto a membrane made of nitrocellulose or nylon to create a "blot" and probing for the molecule(s) of interest using reagents that specifically bind to those molecules. The next section will discuss how this can be done for nucleic acids as well as for proteins.

Southern and northern blots

The Southern blot is named for its inventor, Oxford professor, Edwin Southern, who came up with a protocol for transferring DNA fragments from a gel onto a nitrocellulose sheet and detecting a specific DNA sequence among the bands on the blot.

As shown in Figure 8.21, the method works as follows. A mixture of DNA molecules (often DNA that has been cut into smaller fragments using restriction endonucleases) is loaded on an agarose gel, as usual. After the gel run is complete, the DNA bands are transferred from the gel onto a membrane. This can be achieved by capillary transfer, where the gel is placed in contact with a piece of membrane and buffer is pulled through the gel by wicking it up into a stack of absorbent paper placed above the mem-

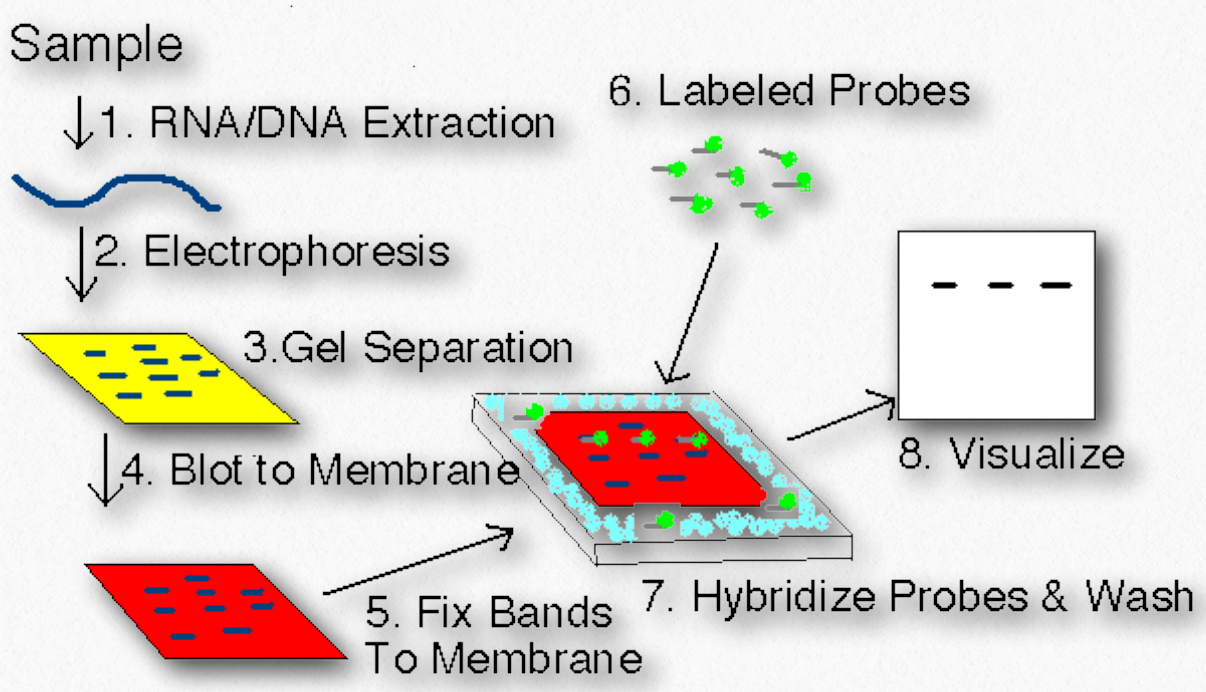

Figure 8.21 - Northern or Southern blot scheme. Southern blotting adds strand denaturation between steps 4 and 5.
Wikipedia

brane. As the buffer moves, it carries with it the DNA fragments. The DNA binds to the membrane leaving a “print” of DNA fragments that exactly mirrors their positions in the gel. The blotting membrane may be treated with UV light, heat, or chemicals to firmly attach the DNA to the membrane.

Next, a probe, or visualizing agent specific for the molecule of interest is added to the membrane. In Figure 8.21, this is called a labeled probe. The probes in a Southern blot are pieces of DNA designed to be complementary to the desired target sequence. If the sequence of interest is present on the blot, the probe, which is complementary to it, can base-pair (hybridize) with it. The blot is then washed to remove all unbound probe. Probes are labeled with radioactivity or with other chemical reagents that allow them to be easily detected when bound to the blot, so it is possible to visually determine whether the probe has bound to any of the DNA bands on the blot. Given that the Southern blot relies on specific base-pairing between the probe and the target sequence, it is easy to adapt the technique to detect specific RNA molecules, as well. The modification of this method to detect RNAs was jokingly named a “northern” blot.

Western blots

Proteins cannot, for obvious reasons, be detected through base-pairing with a DNA probe, but protein blots, made by transferring proteins, separated on a gel, onto a membrane, can be probed using specific antibodies against a particular protein of interest.

Protein detection usually employs two antibodies, the first of which is not labeled. The label is on the second antibody, which is designed to recognize only the first antibody in a piggyback fashion. The first antibody specifically binds to the protein of interest on the blot and the second antibody recognizes and binds the first antibody.

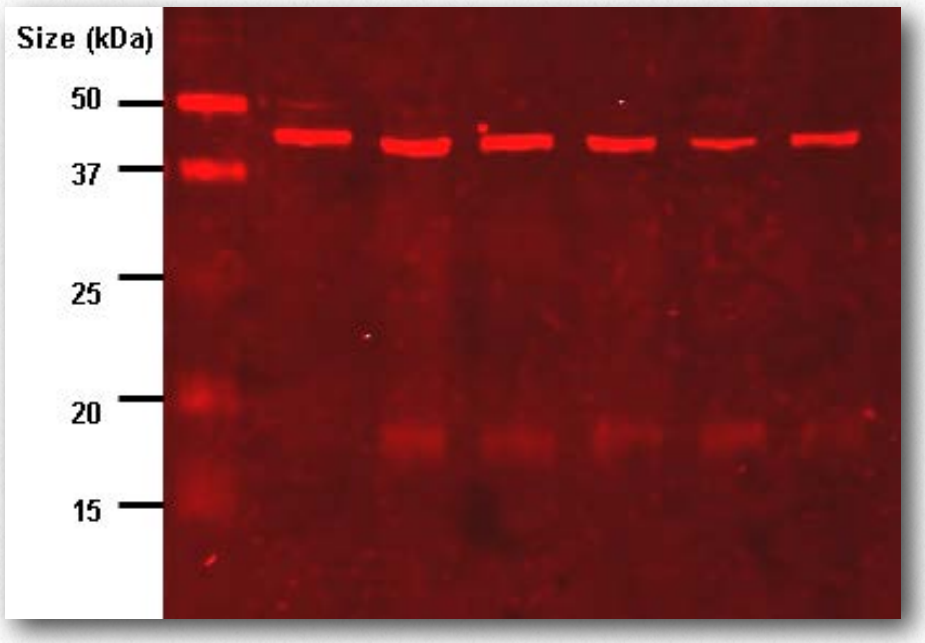

Figure 8.22 - Result of a western blot analysis

Wikipedia

The second antibody commonly carries an enzyme or reagent which can cause a reaction to produce a color upon further treatment. In the end, if the molecule of interest is in the original mixture, it will “light” up and reveal itself on the blot. This variation on the blotting theme was dubbed a western blot (Figure 8.22).

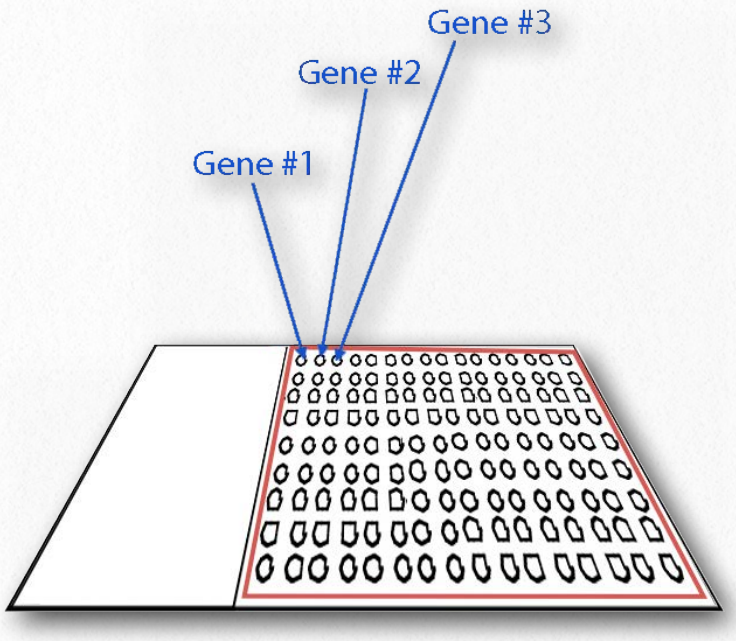

Figure 8.23 - Microarray design
Image by Taralyn Tan

In each of the blots described above, binding of the probe to the target molecule allows one to determine whether the target sequence or protein was in the sample. Although blots are designed to be used for detection, rather than for precise quantitation, it is possible to obtain estimates of the abundance of the target molecule from densitometry measurements of signal intensity.

Microarrays

2-D gels are a way of surveying a broad spectrum of protein molecules simultaneously. One approach to doing something similar with DNA or RNA involves what are called microarrays. Microarrays are especially useful for monitoring the expressions of thousands of genes, simultaneously. Where a northern blot would allow the identification of a single mRNA from a mixture of mRNAs, a microarray experiment can allow the simultaneous identification of thousands of mRNAs that may be made by a cell at a given time. It is also possible to perform quantitation much more reliably than with a blot.

Microarrays employ a glass slide, or chip, to which are attached short sequences of single-stranded DNA, arranged in a grid, or matrix (Figure 8.23) Each position in the grid corresponds to a unique gene. That is, the DNA sequence at this spot is part of the sequence of a specific gene. Each spot on the grid has multiple identical copies of the same sequence.

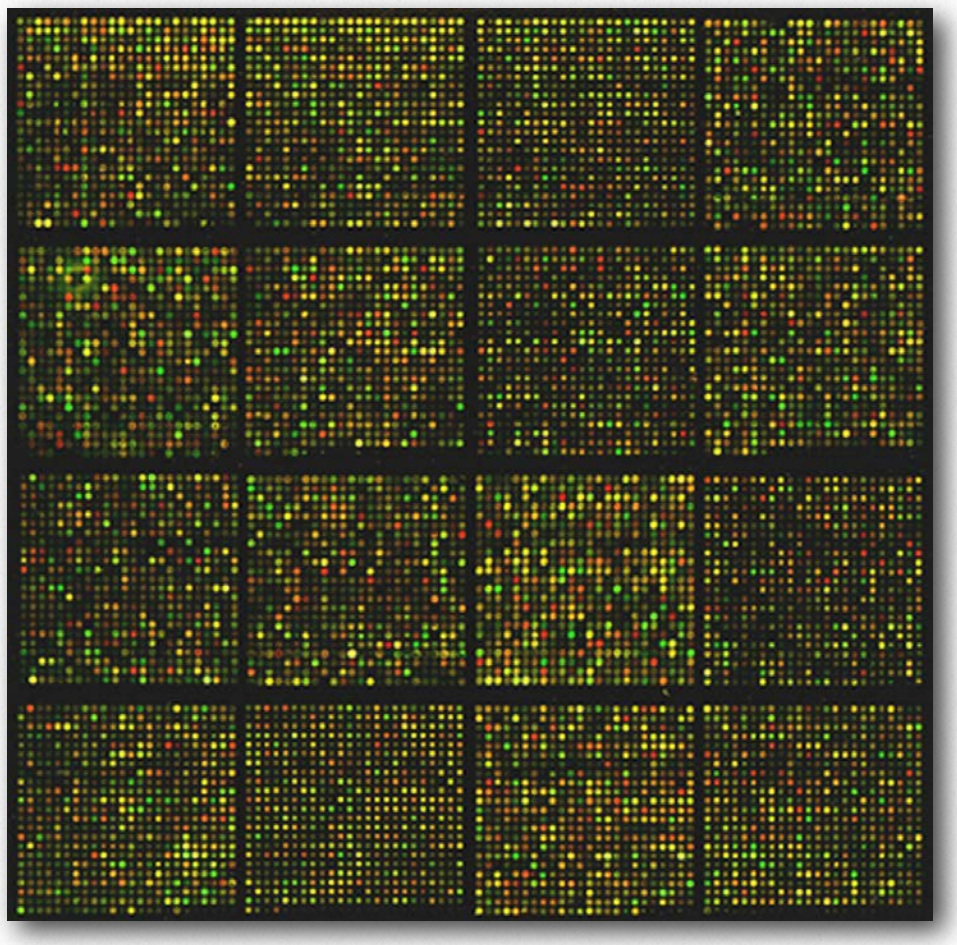

Figure 8.24 - Large scale microarray analysis of mouse transcriptome
Wikipedia

The gene sequence immobilized at each position in the grid is recorded.

Adding samples

To the slide are added a mixture of sample molecules, some of which will recognize and bind specifically to the sequences on the slide. Binding between the sample molecules and the sequences attached to the slide occurs by base pairing, in the case of DNA microarrays. The slide is then washed to remove sample molecules that are not specifically bound to the sequences in the grid.

Sample molecules are tagged with a fluorescent dye, allowing the spots where they bind to be identified. The grid is analyzed spot by spot for binding of the sample molecules to the immobilized sequences. The more sample molecules are bound at a spot, the greater the intensity of dye fluorescence that will be observed. Information from this analysis can give information about the presence/absence/abundance of molecules in the sample that bind to the sequences in the grid.

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Transcriptomics

For example, consider a matrix containing all of the known gene sequences in a genome. To make such a matrix for analysis, one would need to make copies of every gene, either by chemical synthesis or by using the polymerase chain reaction. The strands of the resulting DNAs would then be separated to obtain single-stranded sequences that could be attached to the chip. Each box of the grid would contain sequence from one gene. With this grid, one could analyze the transcriptome - all of the mRNAs being made in selected cells at a given time. For a simple analysis, one could take a tissue (say liver) and extract all the mRNAs from it. This mRNA population represents all the genes that were being expressed in the liver cells at the time the RNA was extracted. These RNAs should be able to hybridize (base-pair) with their corresponding genes on the microarray. Genes that were not being expressed would have no mRNAs to bind to their corresponding genes on the grid.

In practice, the mRNAs are not used directly, but are copied into single-stranded DNA copies called cDNAs. The cDNAs are tagged with a fluorescent dye and added to the microarray under conditions that allow base pairing so that the cDNAs can find and base pair with complementary sequences on the matrix (Figure 8.26). The matrix is then washed to remove unhybridized cDNAs. The presence/absence/abundance of each mRNA is then readily determined by measuring the amount of dye at each box of the grid.

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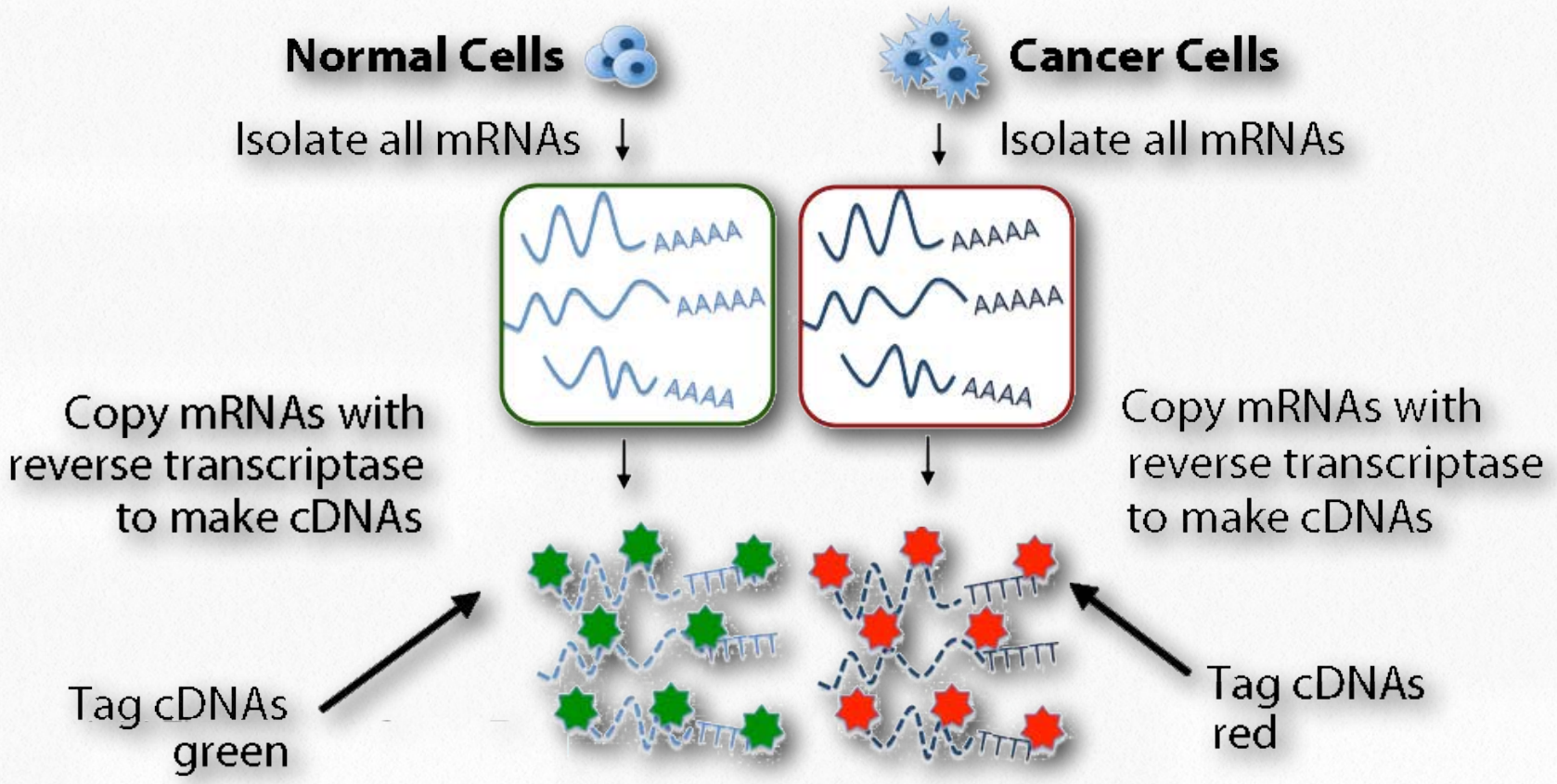

Figure 8.25 - Copying and labeling of transcriptome

Image by Taralyn Tan

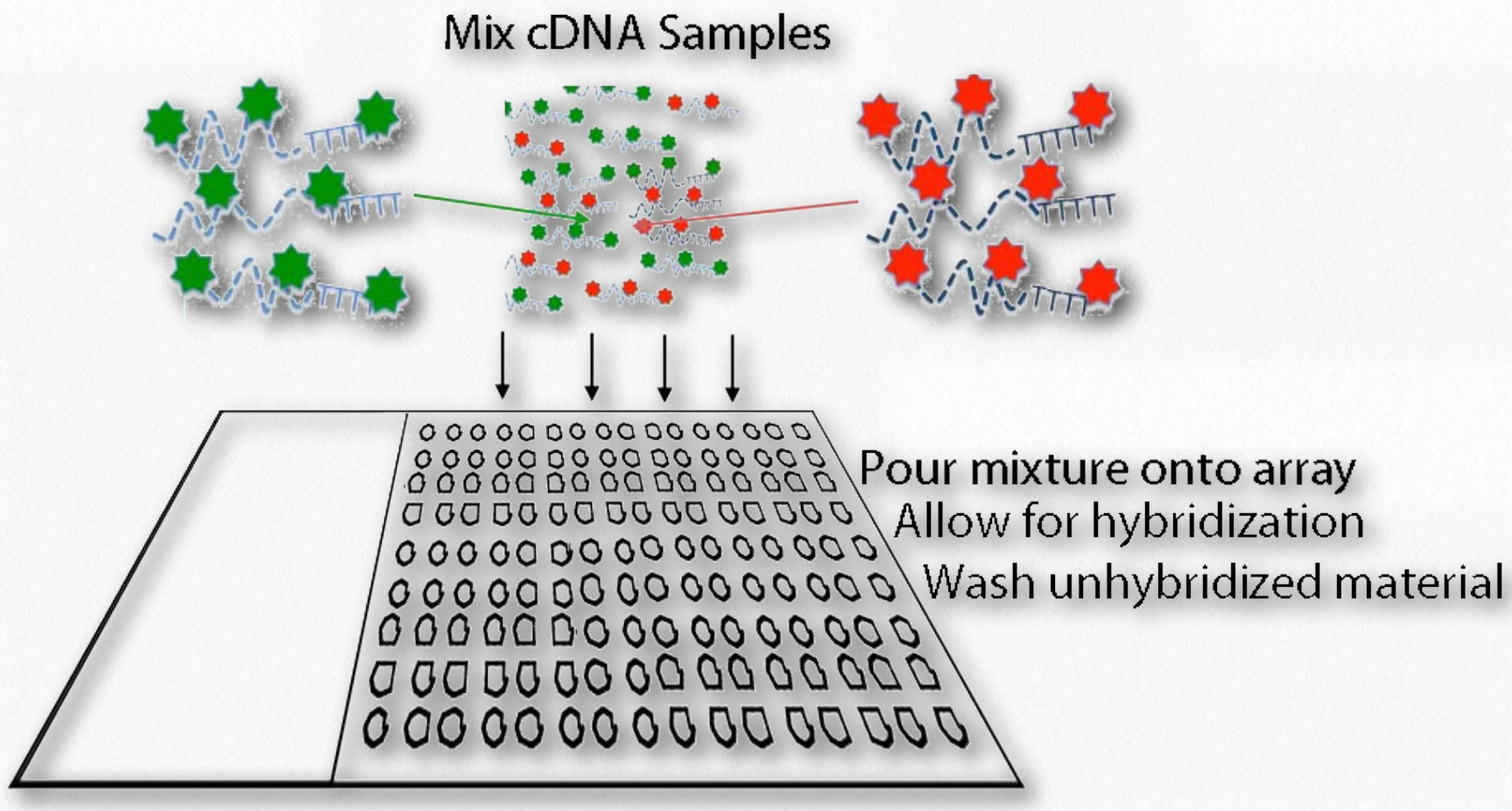

Figure 8.26 - Add labeled cDNAs to microarray plate

Image by Taralyn Tan

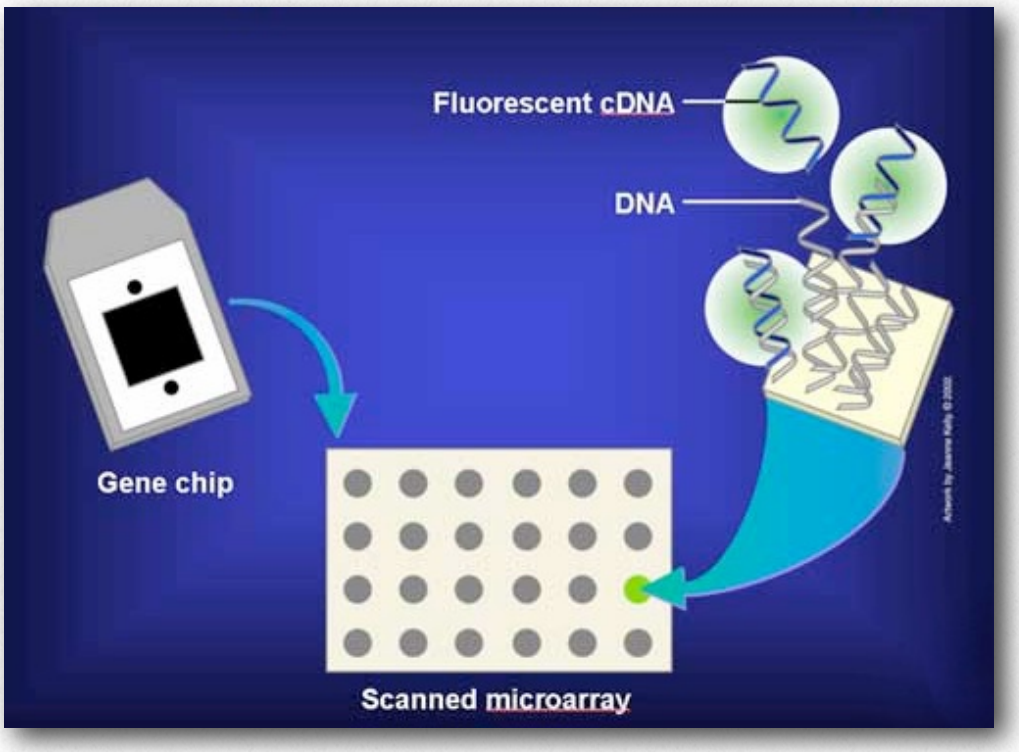

Figure 8.27 - Binding of a fluorescent cDNA copy of a specific mRNA to DNA immobilized on one spot in a microarray

Wikipedia

In Figure 8.27, a fluorescent cDNA has bound to the spot on the far right in the third row of the grid. This means that the sequence of the cDNA was complementary to the sequence of the gene sequence immobilized at that spot. Because the identity of the genes at each position on the grid is known, we then know that the sample contained mRNA that corresponded to that particular gene. In other words, that gene was being expressed in the cells from which the mRNAs were obtained.

A more powerful analysis could be performed with two sets of mRNAs simultaneously. . One set of cDNAs could come from a cancerous tissue and the other from a non-cancerous tissue, for example. The cDNAs derived from each sample is marked with a different color (say green for normal and red for cancerous) (Figure 8.25). The cDNAs are mixed and then added to the matrix and complementary sequences are once again allowed to form

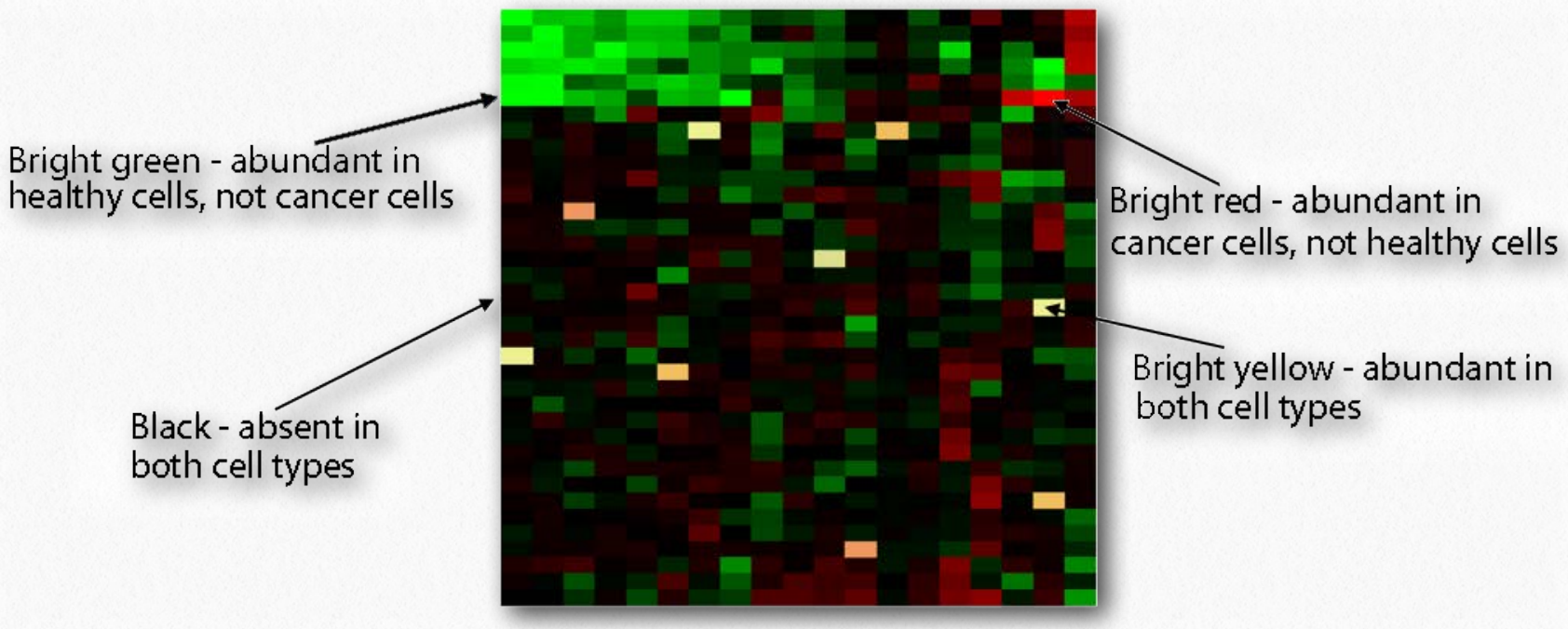

Figure 8.28 - Microarray analysis comparing gene expression in normal and cancer cells

Wikipedia

duplexes (Figure 8.27). Unhybridized cDNAs are washed away and then the plate is analyzed. Red grid boxes correspond to an mRNA present in the cancerous tissue, but not in the non-cancerous tissue. Green grid boxes correspond to an mRNA present in the non-cancerous tissue, but not in the cancerous tissue. Yellow would correspond to mRNAs present in equal abundance in the two tissues (Figure 8.28). The intensity of each spot also gives information about the relative amounts of each mRNA in each tissue.

Protein microarrays

The same principle used for nucleic acid microarrays can be adapted for analyzing other molecules. For example, polypeptides could be bonded to the glass slide instead of DNA to create a protein chip. Protein chips are useful for studying the interactions of proteins with other molecules as well as for diagnostics.

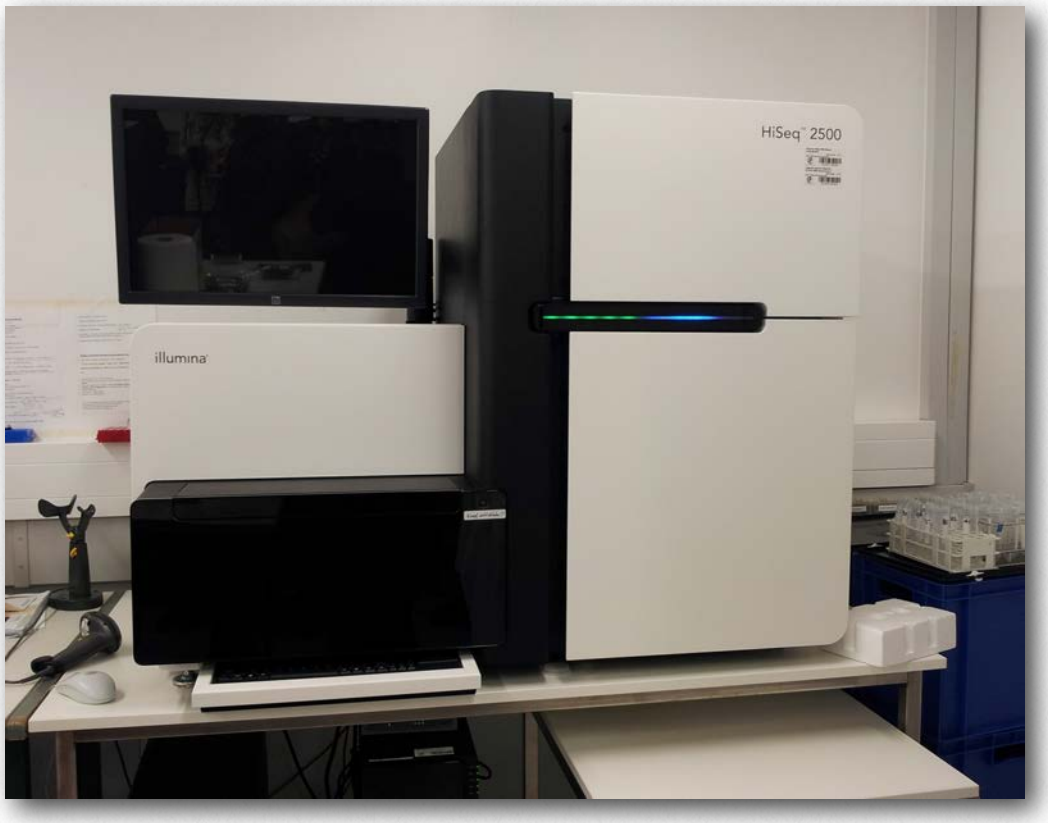

Figure 8.29 - Automated high throughput sequencer
Wikipedia

RNA-Seq

Like microarrays, a newer method called RNA-Seq, is a tool for simultaneously detecting and quantitating all of the transcripts in a given sample. This method relies on recently developed sequencing technologies called next-generation sequencing, or deep sequencing. These techniques allow for rapid, parallel sequencing of millions of DNA fragments and can, thus, be used not only for genomic DNA, but also to sequence all of the reverse-transcribed RNAs from a given sample.

To determine all the protein-coding genes that were being expressed in a particular set of cells under specific physiological conditions, all of the mRNA would first be extracted and reverse-transcribed into cDNA. This step is similar to the preparation of samples for microarrays. However, at this point, the cDNAs are fragmented into smaller pieces, and have small sequencing adapters attached at either end. The fragments are

then subjected to high-throughput sequencing, to obtain short sequences from all of the fragments. These data are aligned against the genome sequence and used to measure the level of expression of different genes. RNA-Seq offers some advantages over microarrays. With microarrays, an RNA can only be detected if the gene sequence corresponding to it is present on the grid. In RNA-Seq every RNA present in the sample is sequenced, so detection of RNAs is not limited by the probes on a chip. RNA-Seq is more sensitive than microarrays and offers a much larger range over which gene expression can be measured accurately.

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Isolating genes

Earlier in this chapter, we discussed methods such as column chromatography that are used to purify proteins of interest. Using combinations of these methods, it is possible to isolate a protein to a high degree of purity, thus enabling us to study the protein's activity and properties. This problem is harder to solve for nucleic acids. Genomic DNA can be readily obtained from cells, but is too complex to be analyzed as a whole. Individual genes are the units of DNA that correspond to proteins, and thus, it makes more sense to isolate specific genes for study. Methods to isolate genes were not available till the 1970s, when the discovery of restriction enzymes and the invention of molecular cloning provided, for the first time, ways to obtain large quantities of specific DNA fragments, for study. Although, for purposes of obtaining large amounts of a specific DNA fragment, molecular cloning has been largely replaced by direct amplification using the polymerase chain reaction described later, cloned DNAs are still very useful for a variety of reasons. The development of molecular cloning was dependent on the discovery of restriction endonucleases, described below.

Restriction enzymes

Restriction enzymes, or restriction endonucleases, are enzymes made by bacteria. These enzymes protect bacteria by degrading foreign DNA molecules that are carried into their cells by, for example, an invading bacteriophage. Each restriction enzyme recognizes a specific sequence, usually of four or six nucleotides in the DNA. These sequences, when they occur in the bacterium's own DNA, are chemically modified by methylation, so that they are not recognized and degraded. Where these sequences occur in foreign DNA, they are cut by the restriction enzyme.

The utility and importance of restriction enzymes lies in their ability to recognize specific sequences in DNA and cut near or (usually) at the site they recognize. Over 3000 such enzymes are known. Sequences recognized by these enzymes are typically 4-8 base pairs long and the most commonly used enzymes

Figure 8.30 -A restriction enzyme bound to its recognition sequence on DNA

Wikipedia

which is the same as the bottom strand (read in the same 5' to 3' direction).

While all restriction enzymes must recognize and bind to particular DNA sequences, the exact spot at which they cut the DNA varies. Some enzymes leave a staggered sequence after cutting that has an overhang at the 5' end of one strand of the duplex; some leave a staggered sequence after cutting that has an overhang at the 3' end; and some cut both strands in the same place, leaving no overhanging sequence - called blunt end cutters.

Consider cutting a DNA sequence that contains the Hind III recognition site, which is recognize sequences described as palindromic.

Palindrome

In molecular biology, the term palindrome means that the sequence of the recognition site when read in the 5' to 3' direction for the top strand is exactly the same as that of the bottom strand. Consider the sequence recognized by the restriction enzyme known as Hind III (pronounced hin-dee-three). It is

5' -A-A-G-C-T-T-3'
3' -T-T-C-G-A-A-5'

On the top strand, the recognition sequence is

5' AAGCTT 3'

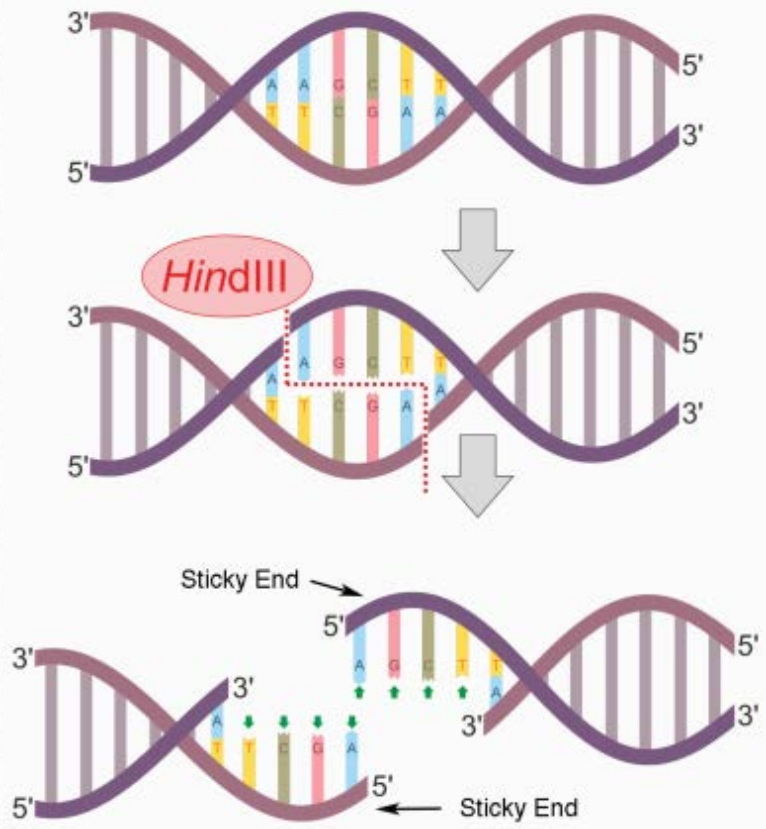

Figure 8.31 - Result of cutting DNA with Hind III

Wikipedia

5’ -A-A-G-C-T-T-3’
3’ -T-T-C-G-A-A-5’

Embedded within a DNA sequence, the Hind III sequence would look like this (Ns correspond to any base and represent all of the DNA around the recognition site).

5’ -N-N-N-A-A-G-C-T-T-N-N-N-3’
3’ -N-N-N-T-T-C-G-A-A-N-N-N-5’

After cutting with Hind III, it would look as follows:

5’ -N-N-N-A 3‘ 5’A-G-C-T-T-N-N-N-N-3’
3’ -N-N-N-T-T-C-G-A-5‘
3’ A-N-N-N-N-5’

where gaps have been inserted to illustrate where cutting has occurred. Hind III cuts between the two ‘A’ containing nucleotides near the 5’ end of the recognition sequence and thus leaves 5’ overhangs (Figure 8.31).

and cuts between the A and the G near the 3’ end of the recognition sequence.

5’ -N-N-N-C-T-G-C-A 3‘ 5’G-N-N-N-N-N 3’
3’ -N-N-N-G 5‘ 3’ A-C-G-T-C-N-N-N-N-N 5’

As you can see, cutting a DNA with Pst I leaves 3’ overhangs of the recognition sequence. The ends left after cutting by a restric-

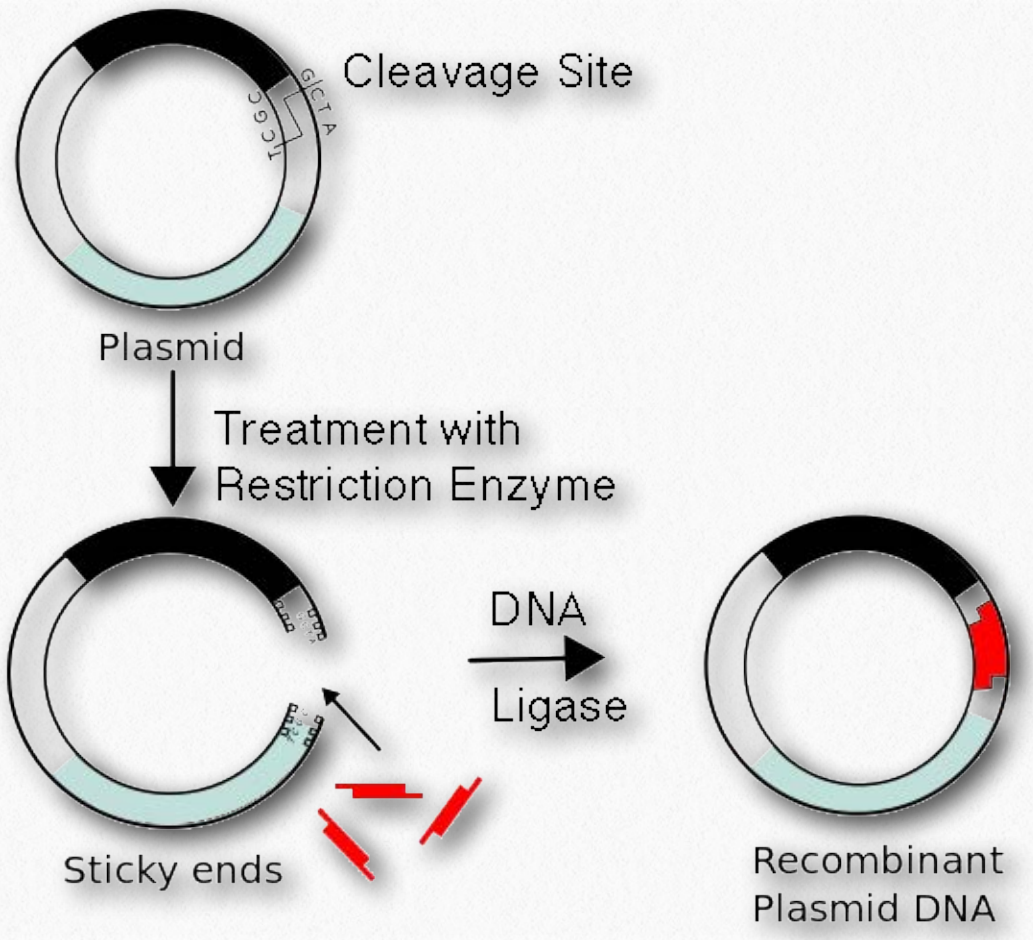

Figure 8.32 - Recombinant DNA construction

Wikipedia

The restriction enzyme Pst I, on the other hand, recognizes the following sequence

5’ -N-N-N-C-T-G-C-A-G-N-N-N-N-3’
3’ -N-N-N-G-A-C-G-T-C-N-N-N-N-5’

tion enzyme that overhang either at the 5’ end or the 3’ end are referred to as being “sticky” because they can form proper base pairs and more readily be joined to a similarly “sticky end”. This means that you can take two unrelated pieces of DNA, cut them with the same restriction enzyme so that they have

compatible sticky ends, and then "paste" them together using DNA ligase to form a new hybrid molecule, or recombinant.

Making recombinant DNAs

Joining together of DNA fragments from different sources creates recombinant DNA. The ability to cut and paste DNA might seem like purely a technical feat, but one key application that arose out of this is molecular cloning. In molecular cloning a gene of interest can be inserted into a vector, usually a plasmid, by cutting both the vector and the gene (called the insert) with the same enzyme to generate sticky ends and joining the two pieces together to generate a recombinant (Figure 8.32). A plasmid is a type of autonomously replicating, extrachromosomal DNA. It is quite simple to extract plasmids from the cells, engineer them to contain the gene of interest and re-introduce the recombinant plasmid into the bacteria. The idea was that when the plasmid DNA was replicated, the extra inserted gene would also be copied. Thus, by growing up a lot of the bacteria carrying the plasmid, many copies of the gene of interest could be obtained, to provide sufficient amounts of the gene to use in experiments. While we now have easier methods to accomplish this goal, cloned DNAs remain very useful. For example, it is possible to clone a gene that encodes a protein of interest so that it can be expressed at high levels in the cells into which the recombinant plasmid is introduced.

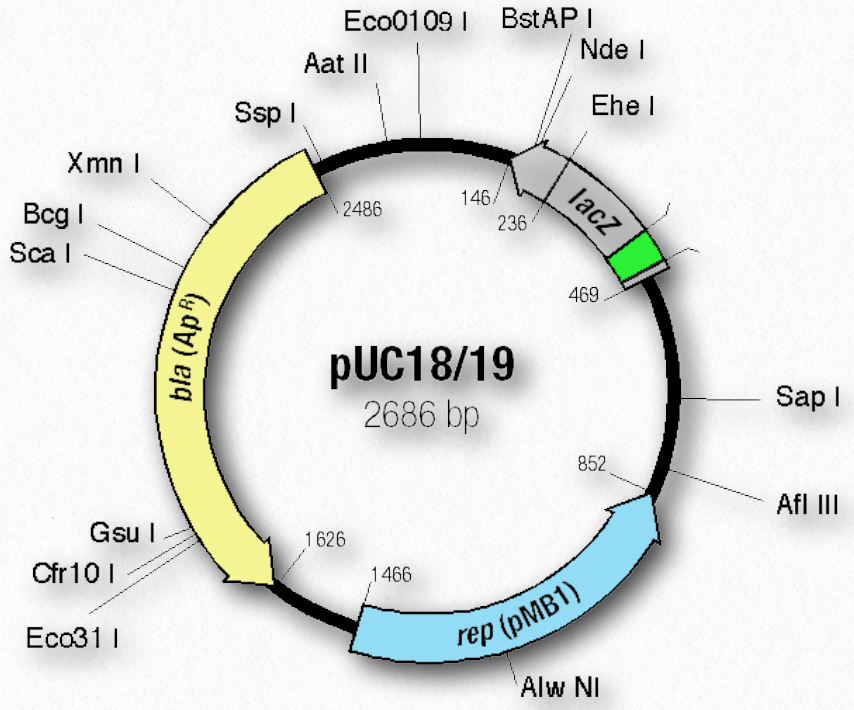

Figure 8.33 - Restriction site map for the pUC 18/19 plasmids, a classic plasmid vector. Genes identified by arrows. Numbers correspond to the pUC 18/19 numbering convention

Whatever the purpose for which the recombinant plasmid is made, it typically carries an antibiotic resistance gene (or genes), called a *selectable marker*. Cells that take up the plasmid will be able to grow in the presence of the antibiotic. If bacterial cells to which the plasmid has been added are plated on agar containing the antibiotic, the cells which took up the plasmid will be able to grow, while the others will not.

Expression cloning

As mentioned above, a gene of interest may be inserted into a vector and the recombinant plasmid be placed into a cell where the gene can be expressed. For instance, one might desire to clone the gene coding for human growth hormone or insulin or other medically important proteins and have a bacterium or yeast make large quantities of it very cheaply. Remember that these are human proteins, and thus it is not feasible to extract the proteins in any quantity from human subjects.

Expression vectors

To clone a gene so that it can be expressed, one needs to set up the proper conditions in order for the human protein to be made in the bacterial cells. This typically involves the use of specially designed plasmids. These plasmids have been engineered to 1) replicate in high numbers; 2) carry markers that allow researchers to identify cells carrying them (antibiotic resistance, for example) and 3) contain sequences (such as a promoter and Shine Dalgarno sequence) necessary for expression of the desired protein, with convenient sites for insertion of the gene of interest in the appropriate place relative to the control sequences. A plasmid which has all of these features is referred to as an expression vector. In addition to plasmids that can be used for expression in bacterial cells, expression vectors are also available that allow protein expression in a variety of eukaryotic cells.

Many sophisticated variations on such vectors have been created that have made it easy to produce and purify large amounts of any pro-

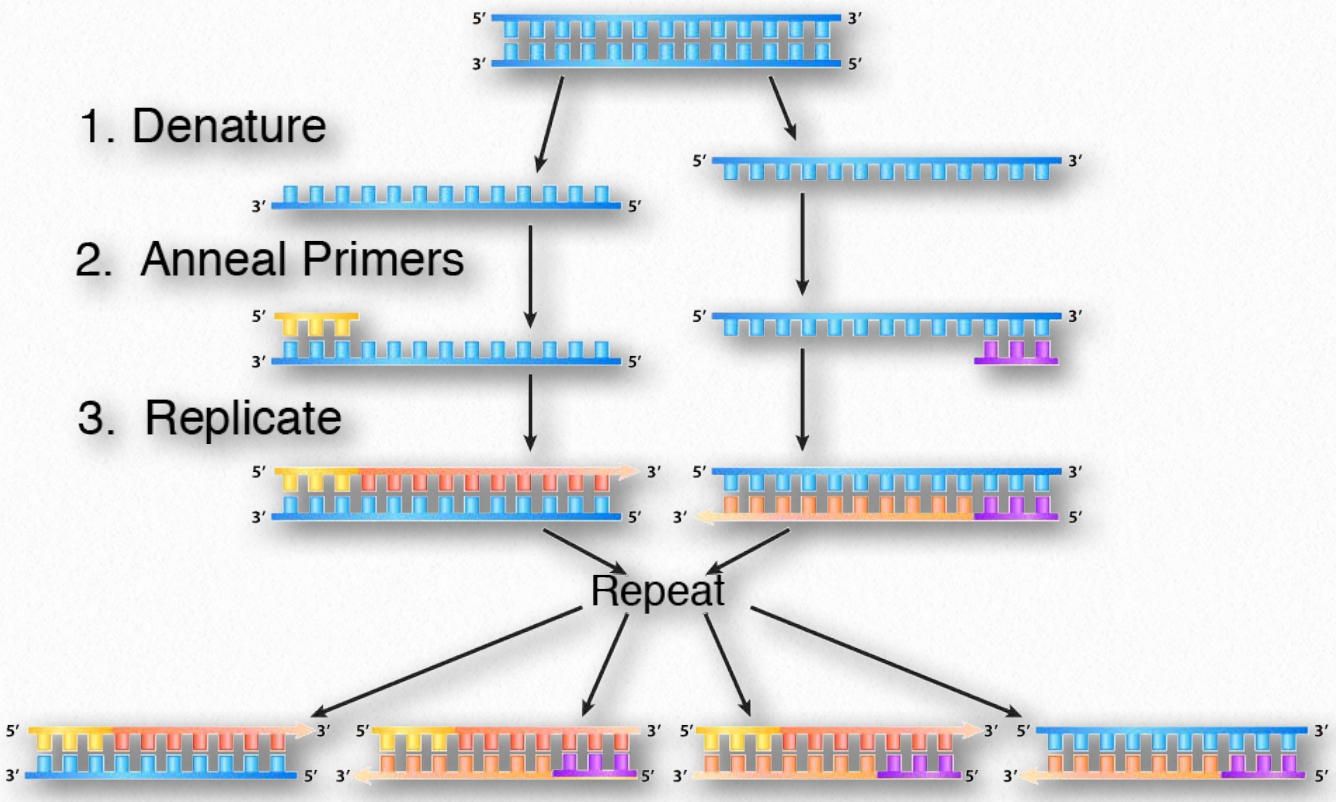

Figure 8.34 - Steps in the polymerase chain reaction

Image by Aleia Kim

tein of interest for which the gene has been cloned. A handy feature in some expression vectors is a sequence encoding an affinity tag either up- or downstream of the gene being expressed. This sequence allows a short affinity tag (such as a run of histidine residues) to be fused onto the encoded protein. The tag can be used to readily purify the protein, as described in the section on affinity chromatography.

Figure 8.35 - PCR tubes with DNA samples ready for reaction

Wikipedia

Polymerase chain reaction (PCR)

As we just saw, molecular cloning was the first method available to isolate a gene of interest and make many copies of it to obtain sufficient amounts of the DNA to study. Today, there is a faster and easier way to obtain large amounts of a DNA sequence of interest -the polymerase chain reaction, or PCR.

PCR allows one to use the power of DNA replication to amplify DNA enormously in a short period of time. As you know, cells replicate their DNA before they divide, and in doing so, double the amount of the cell's DNA. PCR essentially mimics cellular DNA replication in the test tube, repeatedly copying the target DNA over and over, to produce large quantities of the desired DNA.

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Selective replication

In contrast to cellular DNA replication, which amplifies all of a cell's DNA during a replication cycle, PCR does targeted amplification to replicate only a segment of DNA bounded by the two primers that determine where DNA polymerase begins replication. Figure 8.34 illustrates the process. Each cycle of PCR involves three steps, denaturing, annealing and extension, each of which occurs at a different temperature.

The starting materials

Since PCR is, basically, replication of DNA in a test-tube, all the usual ingredients needed for DNA replication are required:

A template (the DNA containing the target sequence that is being copied)

Primers (to initiate the synthesis of the new DNA strands)

Thermostable DNA polymerase (to carry out the synthesis). The polymerase needs to be heat stable, because heat is used to separate the template DNA strands in each cycle.

dNTPs (DNA nucleotides to build the new DNA strands).

The template is the DNA that contains the tar-

get you want to amplify (the "target" is the specific region of the DNA you want to amplify). The primers are short synthetic single-stranded DNA molecules whose sequence matches a region flanking the target sequence. It is possible to chemically synthesize DNA molecules of any given base sequence, to use as primers. To make primers of the correct sequence that will bind to the template DNA, it is necessary to know a little bit of the template sequence on either side of the region of DNA to be amplified. DNA polymerases and dNTPs are commercially available from biotechnology supply companies.

Figure 8.36 - A PCR thermocycler system

Wikipedia

First, all of the reagents are mixed together. Primers are present in millions of fold excess over the template. This is important because each newly made DNA strand starts from a primer. The first step of the process involves separating the strands of the target DNA by heating to near boiling.

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Next, the solution is cooled to a temperature that favors complementary DNA sequences finding each other and making base pairs, a process called annealing. Since the primers are present in great excess, the complementary sequences they target are readily found and base-paired to the primers. These primers direct the synthesis of DNA. Only where a primer anneals to a DNA strand will replication occur, since DNA polymerases require a primer to begin synthesis of a new strand.

Extension

In the third step in the process, the DNA polymerase replicates DNA by extension from the 3' end of the primer, making a new DNA strand. At the end of the first cycle, there are twice as many DNA molecules, just as in cellular replication. But in PCR, the process is repeated, usually for between 25 and 30 cycles. At the end of the process, there is a theoretical yield of 2^{30} (over 1 billion times) more DNA than there

was to start. (This enormous amplification power is the reason that PCR is so useful for forensic investigations, where very tiny amounts of DNA may be available at a crime scene.)

The temperature cycles are controlled in a thermocycler, which repeatedly raises and lowers temperatures according to the set program. Since each cycle can be completed in a couple of minutes, the entire amplification can be completed very rapidly. The resulting DNA is analyzed on a gel to ensure that it is of the expected size, and depending on what it is to be used for, may also be sequenced, to be certain that it is the desired fragment.

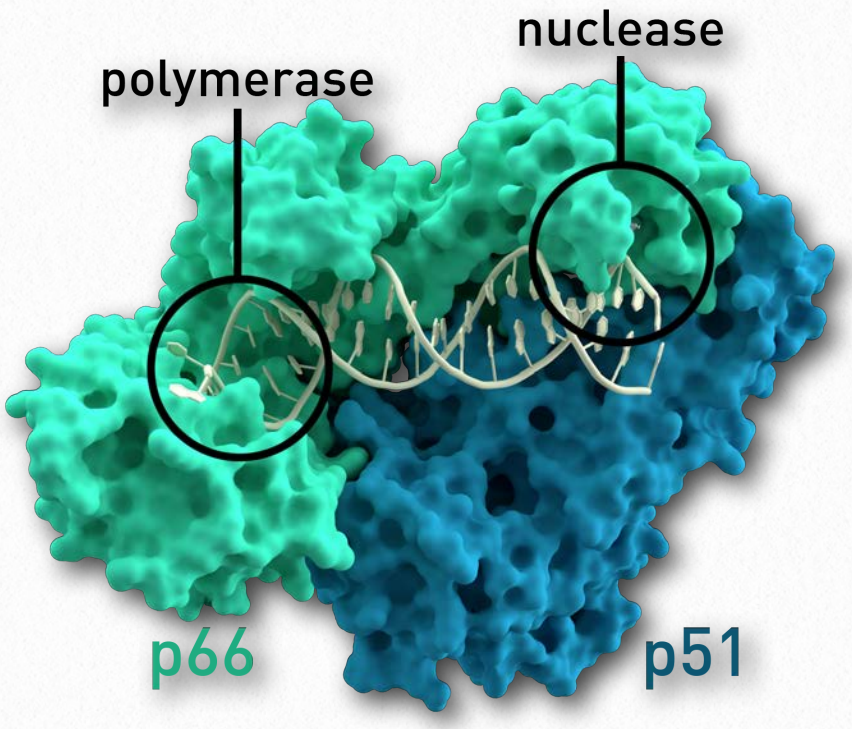


Figure 8.37 - Reverse transcriptase of HIV. The nuclease function is needed for the viral life cycle, but not for lab use.

Wikipedia

Mutagenesis

PCR is frequently used to obtain gene sequences to be cloned into vectors for protein expression, for example. Besides simplicity and speed, PCR also has other advantages. Because primers can be synthesized that differ from the template sequence at any given position, it is possible to use PCR for site-directed mutagenesis. That is, PCR can be used to mutate a gene at a desired position in the sequence. This allows the proteins encoded by the normal and mutant genes to be expressed, purified and compared.

Analysis of gene expression

PCR can also be used to measure gene expression. Where in PCR the amount of amplified product is not determined till the end of all the cycles, a variation called quantitative real-time PCR is used, in which the accumulation of product is measured at each cycle. This is possible because real-time PCR machines have a detector module that can measure the levels of a fluorescent marker in the reaction, with the amount of fluorescence proportional to the amount of amplified product. By following the accumulation of product over the cycles it is possible to calculate the amount of starting template. To measure gene expression, the template used is mRNA reverse-transcribed into cDNA (see below). This coupling of reverse transcription with quantitative real-time PCR is called qRT-PCR.

Reverse transcription

In the central dogma, DNA codes for mRNA, which codes for protein. One known exception to the central dogma is exhibited by retroviruses. These RNA-encoded viruses have a phase in their life cycle in which their genomic RNA is converted back to DNA by a virally-encoded enzyme known as reverse transcriptase. The ability to convert RNA to DNA is a method that is desirable in the laboratory for numerous reasons. For example, converting RNAs of interest to cDNA is used in RT-PCR as well as in other applications like microarray analysis.

Process

First, one creates a DNA oligonucleotide to serve as a primer for reverse transcriptase to use on a target RNA. The primer must, of course, be complementary to a segment (near the 3' end) of the RNA to be amplified. The RNA, reverse transcriptase, the primer, and four dNTPs are mixed. With one round of replication, the RNA is converted to a single strand of DNA. Denaturation frees the single stranded cDNA, which can be used as is, or converted to double-stranded cDNA, depending on the application.

Detecting molecular interactions

The study of biochemistry is basically the study of the interactions of cellular molecules. Methods for detecting interactions among biomolecules are, for this reason, very useful to biochemists. We will now discuss a couple of very different methods for detecting these inter-molecular interactions.

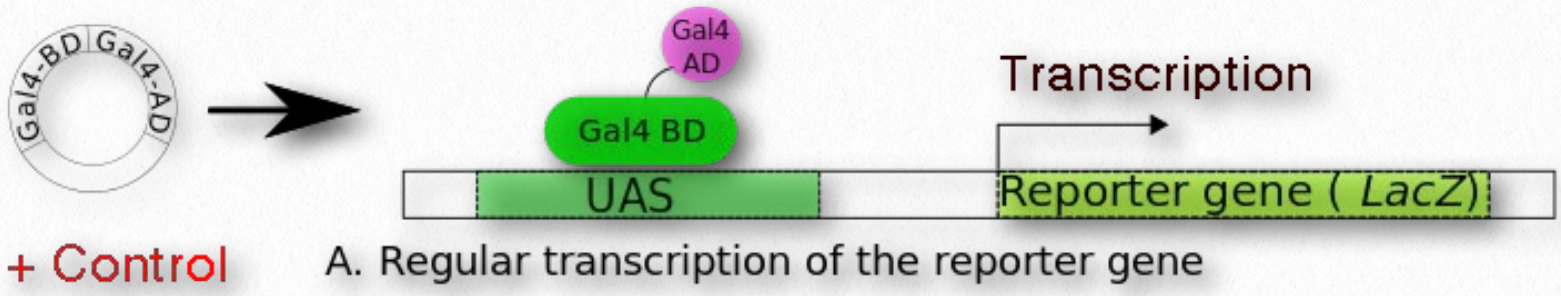
Yeast two-hybrid system (Y2H)

Yeast two-hybrid screening is a sophisticated technique for identifying which protein(s), out of a collection of all of a cell's proteins, interacts with a specific protein of interest. The method relies on the interaction between two proteins to reconstitute a functional transcriptional activator within yeast cells. You may remember that many transcriptional activators are modular proteins that have a domain that binds to DNA and another domain that activates transcription (Figure 8.38).

Figure 8.38 - Structure of a eukaryotic transcriptional activator, showing the DNA-binding domain (DBD) and transcriptional activation domain (TAD).

Wikipedia

If the transcription factor is split, so that the binding domain is attached to one protein, and the activation domain to another protein, a functional transcriptional activator can only be re-created if the two "carrier"proteins come into close proximity - that is, they inter-



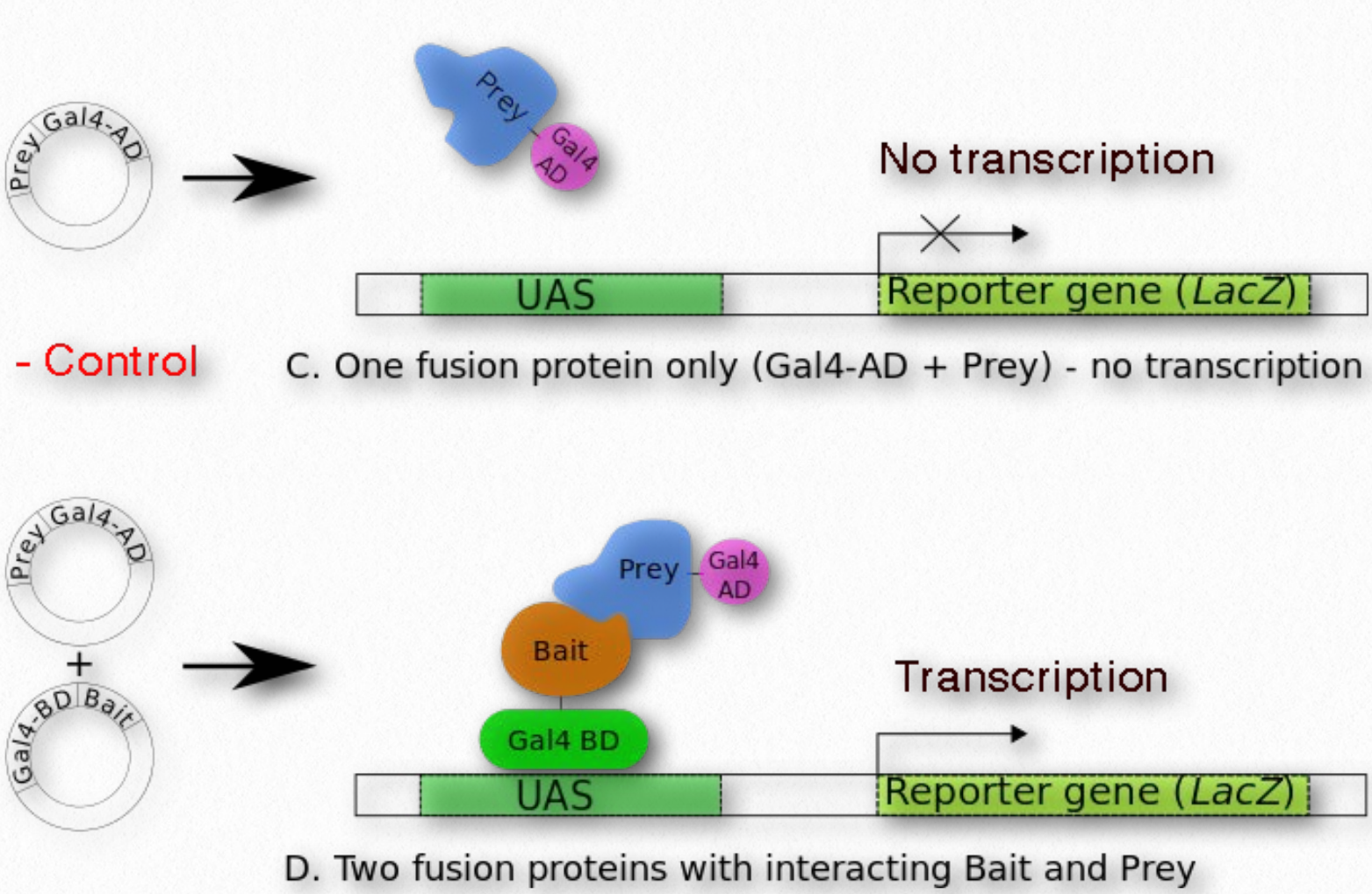


Figure 8.39 - Four scenarios for the yeast two-hybrid system. UAS = Upstream Activator Sequences - acts like a promoter. Scenario A shows that the two transcription factors start out as one protein

Wikipedia

act. The presence of this functional activator can be detected by the expression of a reporter gene.

A simple way to understand this idea is by thinking of a transcriptional activator as a device, like a flashlight, that has two parts, the battery and the lamp, that must be together in order to function. Neither a person who has just a battery nor one who has only the lamp will be able to see in a dark room. But if the two interact by coming close enough to insert the battery in the flashlight, their interaction can be detected by the fact that the flashlight will now be functional as evidenced by the light produced.

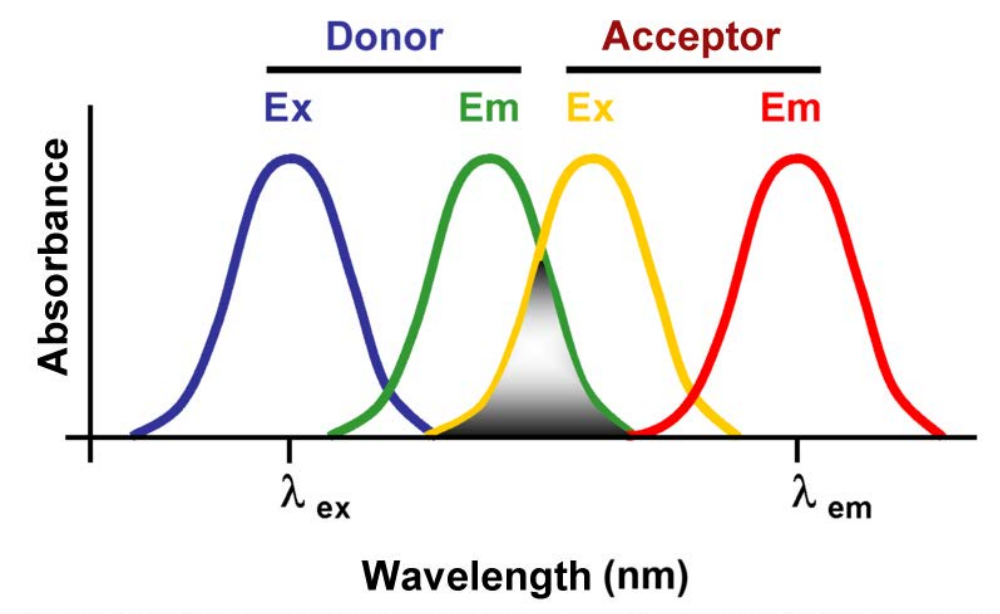


Figure 8.40 - Excitation and emission spectra for donor and acceptor fluorophores in FRET

Wikipedia

It takes two to tango

Figure 8.39 (A) shows the normal yeast transcriptional activator, GAL4, with both the DNA-binding (DBD) and Activation domains (AD). It is able to stimulate transcription of the downstream reporter gene, *lac z*. Panels B and C show constructs that produce the GAL4 DBD and AD, respectively, fused to other proteins, one of which is termed the "bait" and the other as "prey". Neither of these fusion proteins can stimulate transcription of the *lac z* gene. When constructs encoding both the bait and prey are in the same yeast cell, if the bait protein interacts with the prey, the DBD and AD of the GAL4 will be brought together to reconstitute a functional GAL4. The presence of functional GAL4 is readily detectable because it will stimulate expression of the l*ac z* reporter gene. If the bait and prey proteins do not interact, then there will be no lac z expression.

When interaction is detected through expression of the reporter gene, the specific prey protein can then be identified.

YouTube Lectures by Kevin HERE & HERE

The yeast two-hybrid system allows for simultaneous screening of many prey proteins, by constructing large collections of fusion constructs, with each potential protein partner of the bait protein fused to the GAL4 activation domain.

FRET

Another method for detecting molecular interactions is Fluorescence resonance energy transfer (FRET) - also called Förster reso-

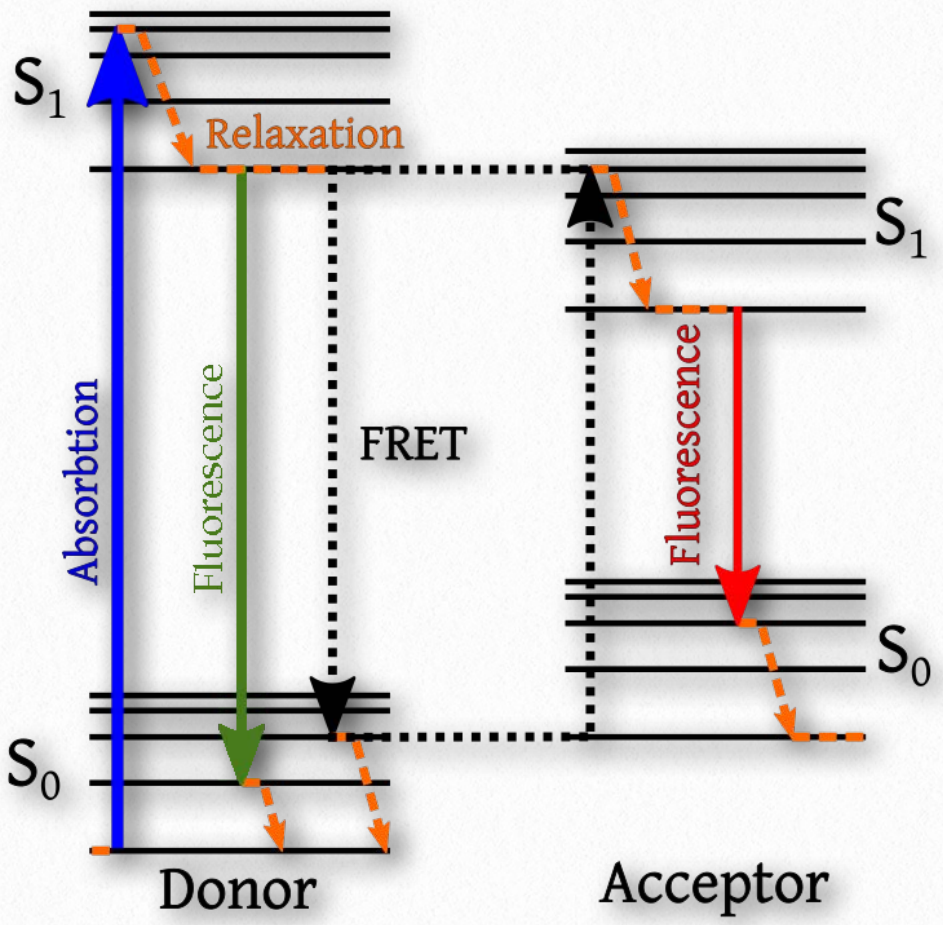


Figure 8.41 - Fluorescence resonance energy transfer between donor and acceptor chromophores

Image by Pehr Jacobson

nance energy transfer, resonance energy transfer (RET) or electronic energy transfer (EET). The technique is based on the observation that a molecule excited by the absorption of light can transfer energy to a nearby molecule if the emission spectrum of the first molecule overlaps with the excitation spectrum of the second (Figure 8.40) This transfer of energy can only take place if the two molecules are sufficiently close together (no more than a few nanometers apart).

Design

In the technique, a donor fluorophore or an acceptor fluorophore is covalently attached to two molecules of interest. The acceptor fluorophore is designed to accept energy from the donor molecule (orange dotted line in Figure 8.41) and fluoresce at a unique wavelength (red arrow) when it receives that energy from the donor.

Further, the wavelength of light that the donor absorbs is uniquely tailored for the donor fluorophore and has no effect on the acceptor fluorophore. The only way the acceptor can fluoresce is if it is close enough to receive energy transferred from the donor (red arrow). This fluorescence will have a unique wavelength, as well. If the donor and acceptor are not close enough together, the donor fluoresces and emits light corresponding to the green or black arrow. These are different wavelengths than that of the red arrow.

The experiment begins in the cell with one protein with a donor fluorophore and the other protein with an acceptor fluorophore. Light of a wavelength that excites the donor fluorophore is shined on the cell. If a protein with a donor interacts with the protein carrying an acceptor, then energy transfer occurs from the donor fluorophore to the acceptor and the unique fluorescence (red line) of the acceptor is detected. If the two proteins do not interact, then little or no fluorescence from the acceptor is detected.

Genome editing

The development of tools that would allow scientists to make specific, targeted changes in the genome has been the Holy Grail of molecular biology. An ingenious new tool that is both simple and effective in making precise changes is poised to revolutionize the field, much as PCR did in the 1980s. Known as the CRISPR/Cas9 system, and often abbreviated simply as CRISPR, it is based on a sort of bacterial immune system that allows bacteria to recognize and inactivate viral invaders.

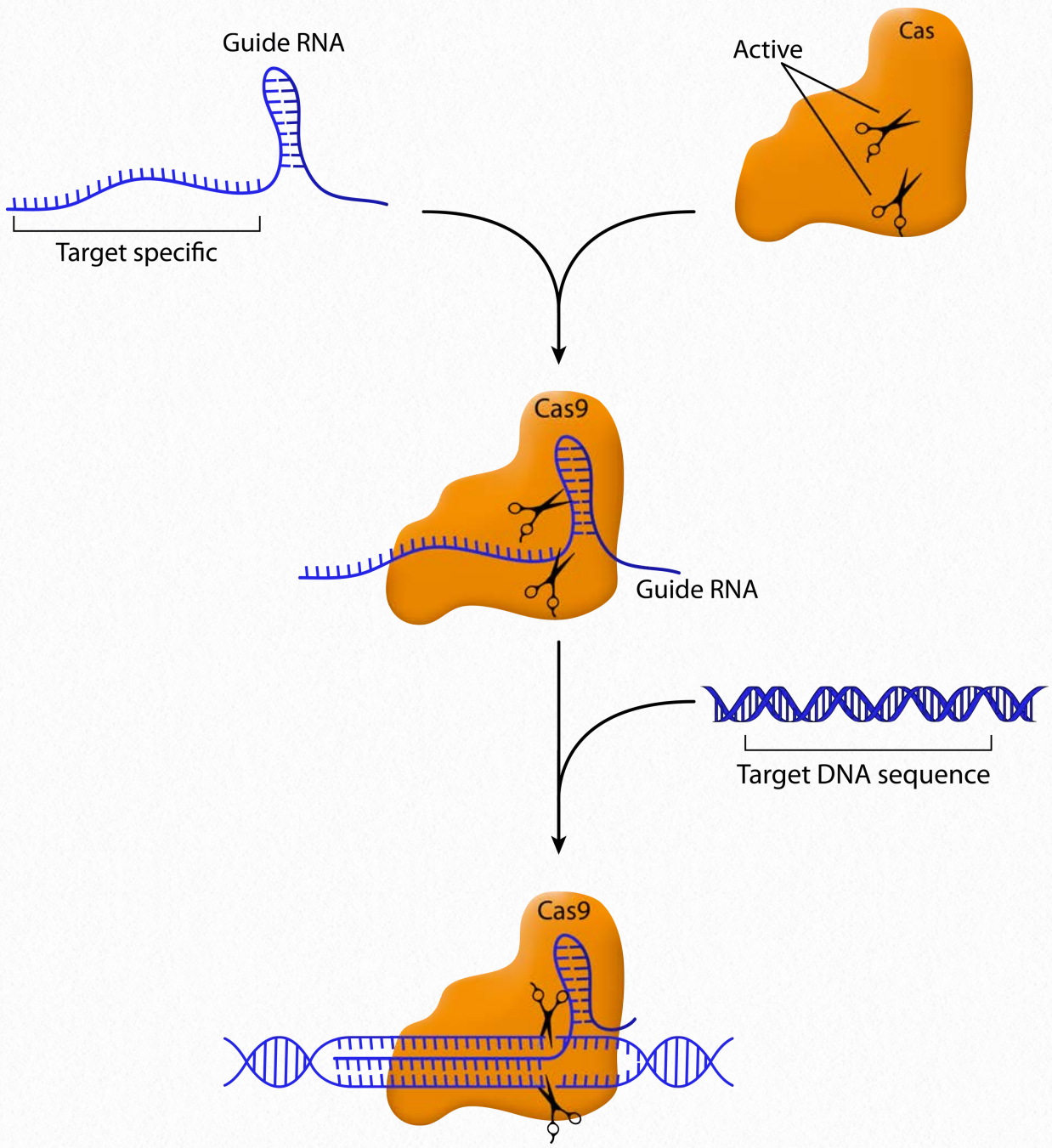


Figure 8.42 - A guide RNA directs the Cas9 nuclease to its target gene

Image by Pehr Jacobsen

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, short repeated sequences found in prokaryotic DNA, separated by spacer sequences derived from past encounters with, for example, a bacteriophage. Like the glass slipper left behind by Cinderella that was later used to identify her, the pieces of the invader's sequences are a way for the bacteria to identify the virus if it attacks again. Inserted into the bacterial genome, these sequences can later be transcribed into a guide RNA that matches, and base-pairs with, sections of the viral genome if it was encountered again. A nuclease associated with the guide RNA then cleaves the sequence base-paired with the guide RNA. (The nucleases are named Cas for CRISPR-associated.)

The essential elements of this system are a guide RNA that homes in on the target sequence and a nuclease that can make a cut

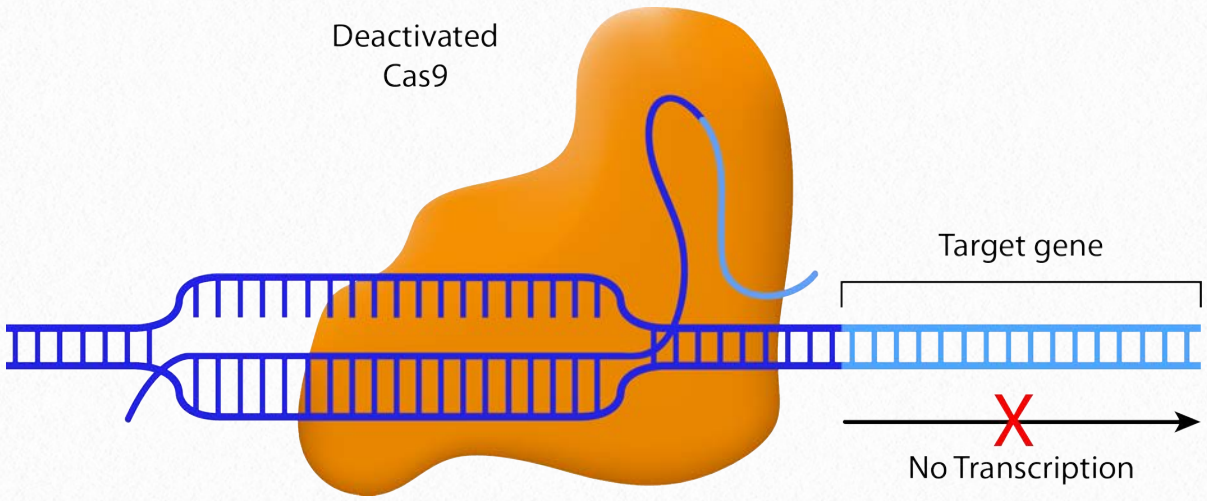


Figure 8.43 - Inactive Cas9 can block transcription of a target gene

Image by Pehr Jacobsen

in the sequence that is bound by the guide RNA. By engineering guide RNAs complementary to a target gene, it is possible to target the nuclease to cleave within that gene. In the CRISPR/Cas9 system, the Cas9 endonuclease cuts both strands of the gene sequence targeted by the guide RNA (Figure 8.42). This generates a double-strand break that the cell attempts to repair.

As you may remember, double-strand breaks in DNA can be repaired by simple, non-homologous end joining (NHEJ) or by homologous recombination. When a break is fixed by NHEJ, there is good chance that there will be deletions or insertions that will inactivate the gene they are in. Thus, targeted cleavage of a site by CRISPR/Cas9 can easily and specifically inactivate a gene, making it easy to characterize the gene's function.

Interactive Learning Module HERE

But, what if you wished to simply mutate the gene at a specific site to study the effect of the mutation? This, too, can be achieved. If a homologous sequence bearing the specific mutation is provided, homologous recombination can repair the break, and at the same time insert the ex-

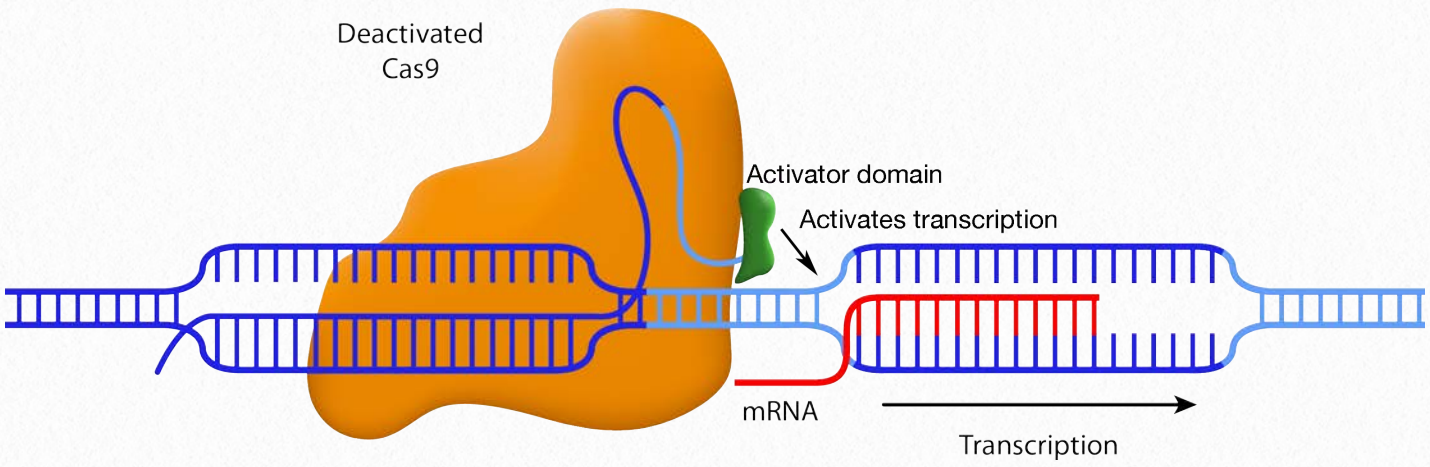


Figure 8.44 - A Cas9-activator domain fusion can activate transcription of a target gene

Image by Pehr Jacobsen

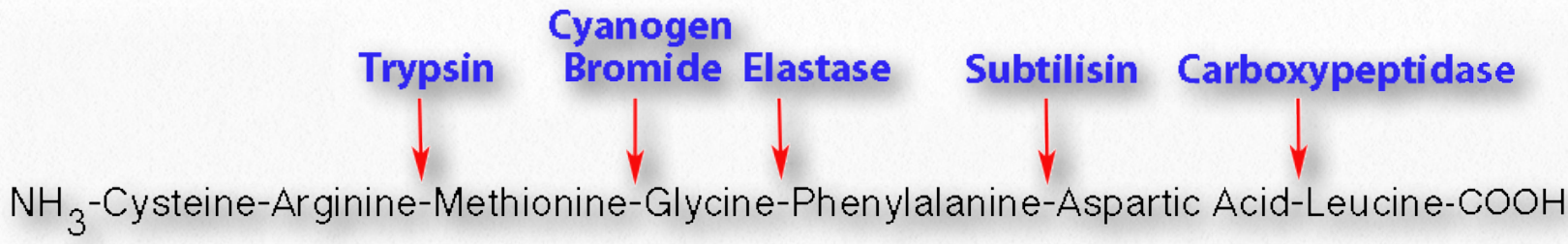


Figure 8.45 - Protease cleavage sites on a polypeptide

act mutation desired. It is obvious that if you can insert a mutation as just described, it should be possible to correct a mutation in the genome by cleaving at the appropriate spot and providing the correct sequence as a template for repair by homologous recombination. The simplicity of the system holds great promise for curing genetic diseases.

Scientists have also come up with some creative variations on the CRISPR/Cas9 system. For instance, one variant inactivates the nuclease activity of Cas9. The guide RNA in this system pairs with the target sequence, but the Cas9 does not cleave it. Instead, the Cas9 blocks the transcription of the downstream gene (Figure 8.43) This method allows specific genes to be turned off without actually altering the DNA sequence.

Another variation also uses a disabled Cas9, but this time, the Cas9 is fused to a transcriptional activation domain. In this situation, the guide RNA positions the Cas9-activator domain in a place where it can enhance transcription from a specific promoter (Figure 8.44). Other variations on this theme attach histone-modifying enzymes or DNA methylases to the inactive Cas9. Again, the guide RNA positions the Cas9 in the desired spot, and the enzyme attached to Cas9 can methylate the DNA or modify the histones in that region.

Protein Cleavage Agent Cut Sites

Subtilisin - C-terminal side of large uncharged side chains

Chymotrypsin - C terminal side of aromatics (Phe, Tyr, Trp)

Trypsin - C-terminal side of lysine and arginines (not next to proline)

Carboxypeptidase - N-terminal side of C-terminal amino acid

Elastase - Hydrolyzes C-side of small AAs (Gly, Ala)

Cyanogen Bromide (chemical) - Hydrolyzes C-side of Met

CRISPR has already been used to edit genomes in a wide variety of species (and in human cell cultures). It may not be long before the technique is approved for clinical use. In the meanwhile, CRISPR is transforming molecular biology.

Protein cleavage

Because of their large size, intact proteins can be difficult to study using analytical techniques, such as mass spectrometry. Consequently, it is often desirable to break a large polypeptide down into smaller pieces. Proteases are enzymes that typically break peptide bonds by binding to specific amino acid sequences in a protein and catalyzing their hydrolysis.

Chemical reagents, such as cyanogen bromide, which cleaves peptide bonds on the C-terminal side of a methionine residue can also be used to cut larger proteins into smaller peptides. Common proteins performing this activity are found in the digestive system and are shown in the yellow box below.

Determining mass and protein sequence

Mass spectrometry, as its name suggests, is a method that can be used to determine the masses of molecules. Once limited to analyzing small molecules, it has since been adapted and improved to allow the analysis of biologically important molecules like proteins and nucleic acids. Mass spectrometers use an electrical field to accelerate an ionized molecule toward a detector. The time taken by an ionized molecule to move from its point of ionization to the detector will depend on both its mass and its charge and is termed its time of flight (TOF).

Figure 8.46 - A desktop MALDI-TOF system

MALDI-TOF

MALDI-TOF (Matrix-assisted Laser Desorption Ionization - Time of Flight) is an analytical technique allowing one to determine the molecular masses of biologically relevant

molecules with great precision. It is commonly used in proteomics and determination of masses of large biomolecules, including nucleic acids. The development of MALDI, which permits the production of ionic forms of relatively large molecules, was crucial to the successful use of mass spectrometry of biomolecules. Figure 8.46 shows a compact MALDI-TOF system.

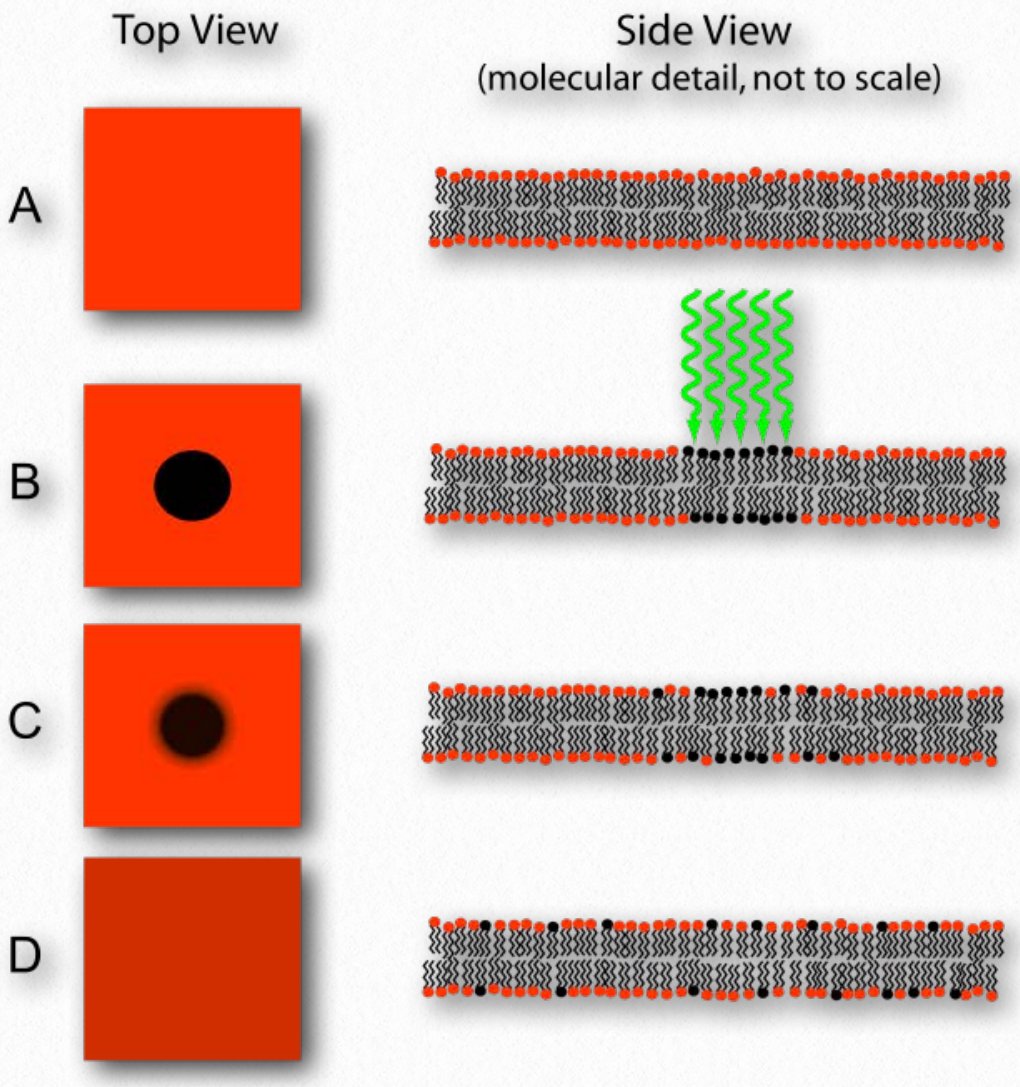
The MALDI-TOF process involves three basic steps. First, the material to be analyzed is embedded in solid support material (matrix) that can be volatilized in a vacuum chamber by a laser beam. In the second part of the process, a laser focused on the matrix volatilizes the sample, causing the molecules within it to vaporize and, in the process, to form ions by either gaining or losing protons. Third, the ions thus created in the sample are accelerated by an electric field towards a detector. Their rate of movement towards the detector is a function of the ratio of their mass to charge (m/z). An ion with a mass of 100 and a charge of +1 will move twice as fast as an ion with a mass of 200 and a charge of +1 and at the same rate as an ion with a mass of 200 and a charge of +2. Thus, by precisely determining the time it takes for an ion to go from ionization (time zero of the laser treatment) to being detected, the mass to charge ratio for all of the molecules in a sample can be readily determined.

Ionization may result in destabilization of larger molecules, which fragment into smaller ones in the MALDI-TOF detection chamber. The size of each of the sub-fragments of a larger molecule allows one to determine its identity if this is not previously known. This fragmentation can be intentionally enhanced by having the accelerated ions collide with an inert gas, like argon.

Fragmentation of a molecule may also be carried out prior to analysis, as for example, by cleaving a protein into smaller peptides by the use of enzymes or chemical agents. The amino acid sequence of a protein may be determined by using MALDI-TOF by analyzing the precise molecular masses of the many short peptide fragments obtained from a protein. When one amino acid, for example, fragments from a larger peptide, this can be detected as the difference in mass between the fragment with and without the amino acid, since each amino acid will have a characteristic molecular mass. By peptide mass fingerprinting and analysis of smaller fragments of individual peptides, the entire sequence of a polypeptide can, thus, be determined.

Membrane dynamics

Understanding the dynamics of movement in the membranes of cells is the province of the Fluorescence Recovery After Photobleaching (FRAP) technique (Figure 8.47). This optical technique is used to measure the two dimensional lateral diffusion of mole-



bleached using a laser (Step B). The spread of the bleached molecules is followed using a microscope (Step C). Information obtained in this manner provides data about the rate of lateral diffusion occurring in a lipid bilayer (Step D).

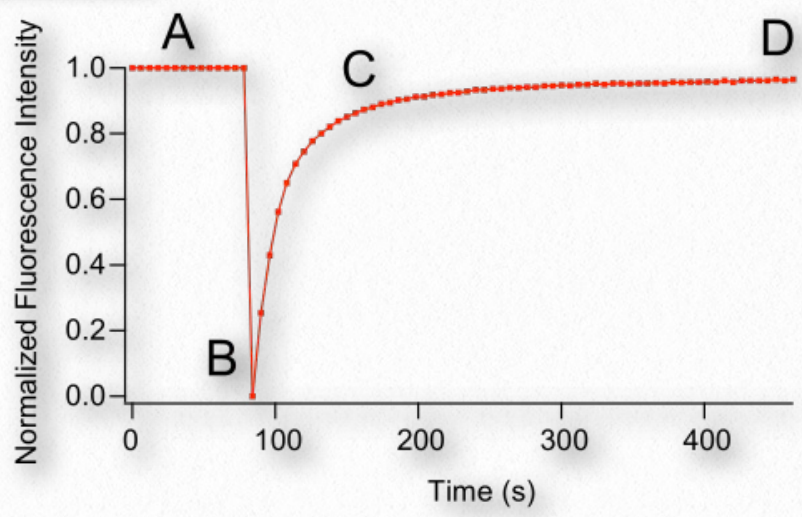


Figure 8.47 - FRAP analysis

Wikipedia

cules in thin films, like membranes, using fluorescently labeled probes. It also has applications in protein binding.

In the method, a lipid bilayer is uniformly labeled with a fluorescent tag (Figure 8.47, Step A) and then a subset of the tag is

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

Click HERE for Penelope Irving's Web Page

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The Restriction Enzyme Song

To the tune of "*Chim Chim Cher-ee*"

Metabolic Melodies Website HERE

I'm obsessed with A-A-G-C-T-T
Cuz it is the binding site of Hin-d-III
Cutting up DNA most readily
The ends are not blunt when they're cut up you see

Five prime overhangs of A-G-C-T

Bacteria don't have an immune system so
They must fight off phages or they will not grow
Protection by chopping is their strategy
And one of the cutters we call Hin-d-III

On binding to A-A-G-C-T-T
The site recognition site's bent easily
Phosphodiester attacking meanwhile
Has water behaving as nucleophile

To stave off the phage for a little while

Why don't these enzymes cut cell DNAs?
The answer's provided by their methylase
Adding a methyl group on top of what
The sequence these enzymes would otherwise cut

So cells get protected in this simple way
From nuclease chewing of their DNA
The phage is not lucky in most every case
Unless methylases win the enzyme race

If that happens then, the cell gets erased

Lyrics by Kevin Ahern

No Recording Yet For This Song

I’ve Just Run a Gel

To the tune of “*I Just Saw a Face*”

Metabolic Melodies Website HERE

I’ve just run a gel. I do not think it went too well
I may have used a bit much SDS.
The stacker’s looking like a mess. It’s true
Oh now what will I do?

The protein sample’s my last one. To purify it was not fun
I spent three weekends working late.
The middle lanes aren’t looking great. I’m screwed
Good God what will I do?

Crawling.
I’m almost bawling
The boss is calling to follow through

I just loaded all I’ve got to make this final western blot
My fingers are both crossed for sure
I hope my protein product’s pure. I do
Then my thesis is through

Hating.
All of the waiting
I’m contemplating what I should do

Staining.
My eyes are straining
There’s no complaining. I say ‘wahoo’

‘Cuz it has the band I need
I’ll go and have it scanned to speed
The writing of my thesis and
Proceed onto the post-doct’ral plan
Oh that will be so grand

Pieces make up my thesis.
No more ‘phoresis. The promised land.

Writing so unexciting.
But no more biting. My nails again.

Writing is coinciding.
With reference citing. I’m at the end.

Lyrics by Kevin Ahern

No Recording Yet For This Song

The Proteins Marching One by One

To the tune of "*The Ants Go Marching One by One*"

Metabolic Melodies Website HERE

Oh there's a method you should know that's very huge
It's spinning round and round inside the centrifuge
The supernatant, pellet too
You choose the one that's right for you
And from there we pu-ri-fy
What's inside

To size exclude filtration is the way to go
The beads have pores small proteins can go in you know
The largest ones, they come out fast
The smallest ones eluting last
And the proteins purified
By their size

Electrons power gel e-lec-tro-pho-re-sis
The protein is denatured thanks to SDS
Proteins in a minus state
Get sorted by atomic weight
Smaller ones in speedy mode
To the anode

Ion exchange is special chromatography
To switch cations, you must have a minus bead
Upon this bead, the proteins bind
They're positive, not any kind
And the others wash right through
Out to you

Oh my this song has given you a mighty list
Perhaps we'll just skip over ol' dialysis
So study HPL and C
If you have questions, talk to me
You will get through protein hell
You'll do well.

Recording by David Simmons
Lyrics by Taralyn Tan

9

Point by Point

“It is not how much we have, but how much we enjoy, that makes happiness.”

-Charles Spurgeon

Students always ask us for study guides so when we designed this book, we decided to build in chapter and section summaries to help in this capacity. That’s what follows in this chapter. We hope you find them helpful in your studies.x

Point by Point: In the Beginning

Basic Biology

- Cells are the fundamental units of life
- Three main branches of cells - prokaryotes, eukaryotes, and archaeans
- All cells have 1) plasma membrane; 2) ribosomes; 3) cytoplasm
- The plasma membrane has a lipid bilayer, proteins, and cholesterol
- Phototrophs get energy from light
- Chemotrophs get energy from oxidation of chemicals
- Autotrophs synthesize their own organic compounds from CO2
- Heterotrophs get organic compounds from other organisms
- Eukaryotic cells contain numerous organelles not found in prokaryotes and archaeans
- Eukaryotic organelles include nucleus, lysosomes, mitochondria, chloroplasts (plants), endoplasmic reticulum, nu-

cleolus, Golgi apparatus, endosomes, plastids (plants), and vacuoles.

- Archaeans similar to bacteria, but often found in extreme environments
- All bacteria are unicellular
- Most eukaryotes are multicellular
- Unicellular eukaryotes include yeast and protists
- Bacteria have a peptidoglycan cell wall not found in eukaryotes
- Eukaryotes have a cytoskeleton containing microtubules, microfilaments, and intermediate filaments.
- Eukaryotic DNAs are generally much bigger than in prokaryotes
- Eukaryotic DNAs are arranged in chromatin with histone proteins. Prokaryotic DNAs arranged in nucleoids
- The cytoskeleton has roles in signaling, endocytosis, chromosome segregation, cell division.
- Microtubules arise from polymerization of **α**- and **β**-tubulin
- Epithelial tissues line the cavities and surfaces of blood vessels and organs in the body ad are categorized by their shapes: squamous, columnar, and cuboidal.
- The underlying connective tissue is known as the basement membrane.
- Four types of tissue in animals - epithelium, connective tissue, nerve tissue, and muscle tissue.
- Connective tissue is the glue that holds all together.
- Nerve tissue has central nervous system (brain and spinal cord) and peripheral nervous system (nerves and ganglia)
- Nerve cells = neurons
- Muscle tissue - 3 types - 1) skeletal/striated muscle; 2) smooth, non-striated muscle; and 3) cardiac muscle
- Secretory pathways move proteins out of cells

Basic Chemistry

- Single bonds can rotate. Double bonds cannot
- Double-bonded carbons create a planar structure with angles of 120°
- Single-bonded carbons create tetrahedral structures with angles of 109.5°
- Important organic structures needed to understand biochemistry include alkanes, alkenes, alcohols, esters, amines, thiols, aldehydes, ketones, carboxylic acids, amides, and esters.
- Molecules or chemical groups that mix or interact well with water are called hydrophilic.
- Molecules or chemical groups that do not mix or interact well with water are called hydrophobic.

- Oxidation is the loss of electrons. Reduction is the gain of electrons.
- For every oxidation, there is also a reduction.
- Electronegativity is a measure of the "pull" a nucleus has for electrons. High electronegativity means stronger pull
- Covalent bonds involving hydrogen in which the electronegaties are not very equal give rise to unequal sharing of electrons and hydrogen bonds.
- Carboxyl groups can gain or lose a proton. When the proton is on, the charge is zero When the proton is off, the charge is -1
- Amine groups can gain or lose a proton. When the proton is on, the charge is +1 When the proton is off, the charge is 0.
- Carbons having bonds to four different chemical groups can have those groups arranged in three-dimensional space around it in two different ways. These different arrangements are called stereoisomers. Such carbons are called asymmetric centers.
- The Gibbs free energy (G) for a system is equal to the enthalpy (H) minus the absolute temperature (T) times the entropy (S) -> G = H - TS
- For a process, the change in Gibbs free energy is $\Delta G = \Delta H - T\Delta S$
- For a reaction aA + bB <=> cC + dD, the equilibrium constant, K_{eq} is equal to $\{[C]^c_{eq}[D]^d_{eq}]\} / \{[A]^a_{eq}[B]^b_{eq}\}$
- For a biological system, the standard Gibbs free energy ($\Delta G°'$) is equal to $-RT\ln K_{eq}$
- For a biological system, the change in Gibbs free energy for a process is
- $\Delta G = \Delta G°' + RT\ln K_{eq}$
- Changes in Gibbs free energy for two processes are additive.
- Changes in standard Gibbs free energy for two processes are additive
- Catalysts speed reactions without being changed.
- The change in Gibbs free energy for a catalyzed process is the same as for an uncatalyzed process.
- Enzymes are proteins that catalyze biological reactions. Ribozymes are RNAs that catalyze biological reactions.

Water & Buffers

- Water is the most abundant component of every cell.
- The electronegativity of oxygen is greater than that of hydrogen, leading to unequal sharing of electrons between the two atoms. This is the cause of the formation of hydrogen bonds.
- Polar and ionic compounds (hydrophilic) dissolve readily in water. Non-polar compounds (hydrophobic) do not.
- Amphiphilic molecules have both polar and non-polar regions. Soaps are amphiphilic.

- Non-mixing of hydrophobic molecules and water rooted in the increase in entropy favored in the unmixed state.
- Amphiphilic substances can spontaneously form different shapes in water. These include micelles, liposomes, and lipid bilayer sheets.
- Phospholipids found in cellular membranes are amphiphilic
- Cellular membranes contain lipid bilayers
- Glycerophospholipids and sphingolipids spontaneously form lipid bilayers in water.
- The non-polar portions of globular proteins arrange themselves internally to the folded protein so as to avoid/exclude water. This too is an entropy driven process.
- Hydrogens in covalent bonds with unequally shared electrons are slightly positively charged and are called hydrogen bond "donors."
- Atoms with stronger electronegativities bonded to hydrogens are partly negatively charged and are called hydrogen bond "acceptors."
- Hydrogen bonds help hold together proteins and DNA.
- Hydrogen bonds are weaker than covalent bonds. Because of this, protein structures and DNA structures can be altered without the input of too much energy.
- Non-oxidative ionization of biomolecules involves loss or gain of protons. Since a proton has a charge of +1, gains of protons increase positive charge and loss of protons decrease positive charge.
- pH is a measure of proton concentration. Specifically, pH = -log[H^+]
- pOH is the corresponding measure of the hydroxide ion concentration

  -> pOH = -log[OH^-]
- pH + pOH = 14
- For the purposes of this book acids are molecules that can lose protons and salts are molecules that can gain protons. We shall use the term 'base' only to refer to strong bases, such as NaOH
- Strong acids, such as HCl completely dissociate in water.
- Strong bases, such as NaOH completely dissociate in water
- Weak acids only partly dissociate in pure water
- The amount of dissociation of a weak acid in a solution is a function of the pH of the solution.
- The pK_a is a measure of the strength of a weak acid. Weak acids with lower pK_a values are storger than those with higher pK_a values.
- The Henderson Hasselbalch equation gives the relationship between the pH, the pKa, and the amount of ionization of a weak acid.
- The Henderson Hasselbalch equation says

  $$pH = pKa + \log \{[A^-]/[HA]\}$$

where A^- is the salt formed by ionization of the weak acid and HA is the weak acid.

- A weak acid dissociates as follows

$$HA \rightleftarrows H^+ + A^-$$

- Within one pH unit of their pK_a values, weak acids resist changes of the pH of the solutions in which they are dissolved. We call this resistance buffering, making the weak acid/salt system a buffer.

- Buffers are strongest closest to the pK_a value of the weak acid/buffer system. Maximum buffering capacity occurs when $pH = pK_a$. From the Henderson Hasselbalch equation, this is also when

$$[Salt] = [Weak\ Acid]$$

- Buffers are important in living organisms because they help to maintain pH in a narrow range and allow proteins and DNA structures to be stable.

- Addition of a strong acid to a buffer will cause salt to be converted to weak acid. Each proton converts one salt molecule to one acid molecule

- Addition of a strong base to a buffer will cause weak acid to be converted to salt. Each hydroxide converts one weak acid molecule to one salt molecule

- When the capacity of a buffer is exceeded, it no longer acts like a buffer. This generally occurs at pH values more than 1 unit above or below the pKa value.

- A reasonable estimate of the charge of an ionizable group is as follows - if the pH is one or more units above the pKa value of the R-group, the proton is off. If the pH is one or more units below the pKa, the proton is on. It is only an estimate, though.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

Click HERE for Aleia Kim's Web Page

Click HERE for Pehr Jacobson's Web Page

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Email **Kevin Ahern** / **Indira Rajagopal** / **Taralyn Tan**

Biochemistry Pie (Part I)

To the tune of "*American Pie*"
Metabolic Melodies Website HERE

A long nine weeks ago
I can still remember
How the lectures sometimes made me smile
I pushed myself to study lots
So I could fill my head with thoughts
And then I'd find the effort all worthwhile

But mid-term one, it left me jaded
I worried as exams were graded
Sad news came from Kevin
The average - forty seven

It was so bad I went in shock
I couldn't stand to hear the talk
Of Henderson and Hasselbalch
And bi-o-che-mis-try

So why why biochemistry why
Does percent misrepresent that
My attention is high?
And all the students have a rallying cry
Singin' I will be a studious guy
I will be a studious guy

Did you draw an alanine?
And can you titrate a histidine?
If you know its p-K-a
Now do you believe you'll have it made
If you can pull a decent grade
And can recitation lead me to an 'A'?

Well we learned that protein structure is
A bunch of pleats and helixes
True beauty to behold
Man I dig how proteins fold!

There are seniors in pre-pharmacy
Learning all that chromatography
Gel filtration / HPLC
For bi-o-che-mis-try

I started Singin'
Why why biochemistry why
Must performance be enormous for
My grade to be high?
And all the students have a rallying cry
Singin' I will be a studious guy
I will be a studious guy

(*continued on next page*)

Recording by Tim Karplus
Lyrics by Kevin Ahern

Biochemistry Pie (Part II)

To the tune of "*American Pie*"
Metabolic Melodies Website HERE

Now for ten weeks we've been crammin' in
The fact that nuc-le-i have spin
But that's not all there is to see
There are six enzyme classes from E-C
A cat-a-lytic triad three
And a voice that whispers Delta G

Oh, with enzymes there are lots of facts
Like low Kms and high Vmax
Some zymogens break down
If trypsin is around
And while Kevin lectured Milam Hall
His camera captured movies small
Sometimes they had no sound at all
In bi-o-che-mis-try

We were singing
Why why biochemistry why
Should I lament my last percent
If my incentive was high?
And all the students have a rallying cry
Singin' I will be a studious guy
I will be a studious guy

R state, T state metabolic soul mates
Protein forms that we appreciate
ATCase binding siiii----iiiites
They grab a C-T-P upright
The enzyme gets itself uptight
With aspartate on the sidelines out of sight

Then the stage was set for ex-am two
And some of us were feeling blue
I almost lost my nerve
Whoa, 'til I moved up on the curve
'cause my memory to me revealed
The answers that had been concealed
As if the key had been unsealed
For bi-o-che-mis-try

I'm always Singin'
Why why biochemistry why
Must a student be so prudent
Just to qua-a-lify?
And all the students have a rallying cry
Singin' I will be a studious guy
I will be a studious guy

(*two stanzas skipped here*)

We all pulled down the MP_3s
And memorized the older keys
Then I just smiled and carried on
I went down to the class web site
To download ev-e-ry highlight
But the server said the pages were all gone

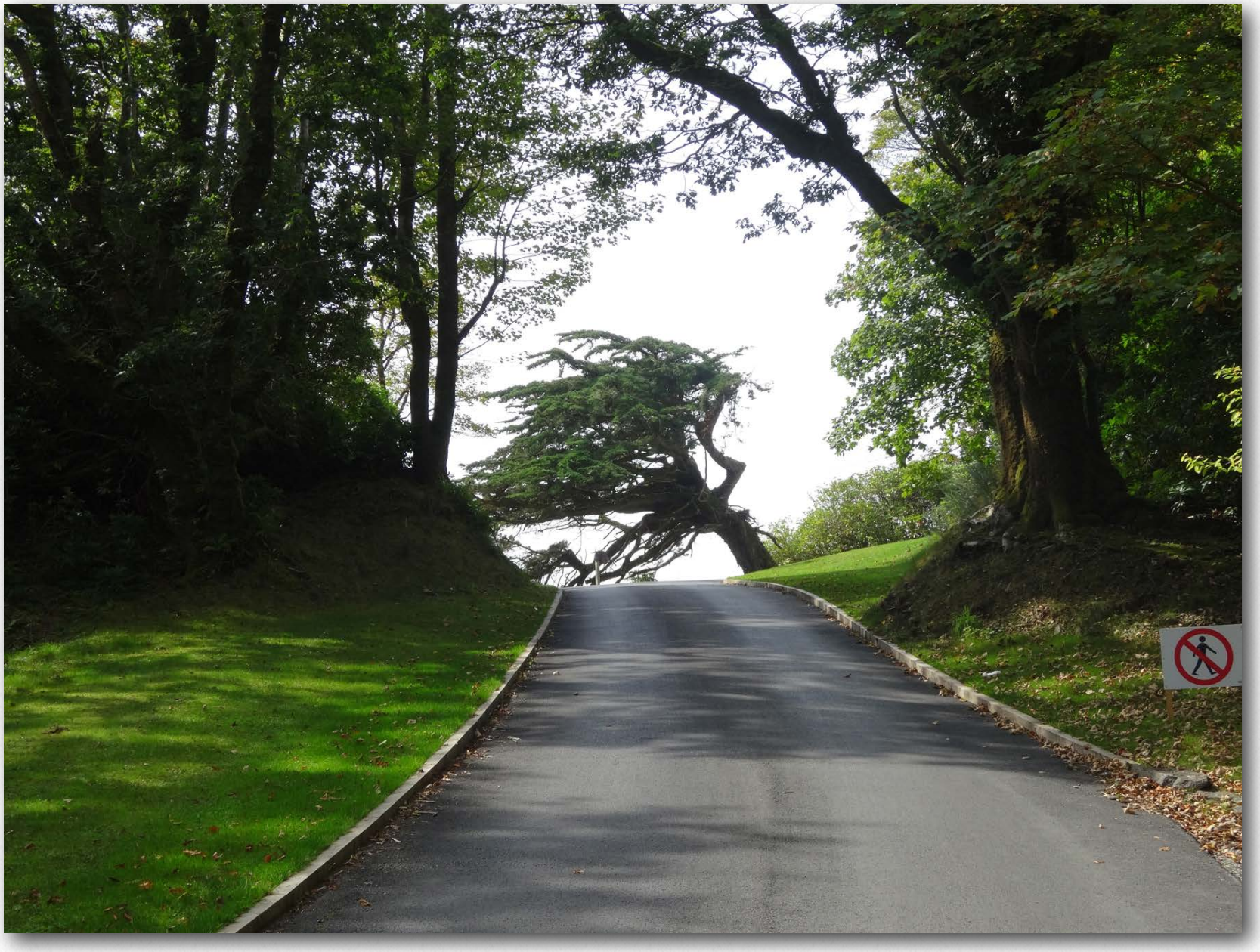
And in their rooms, the students stayed
The chemists crammed and the pre-meds prayed
There was no indecision
The end was in our vision
And the section that had made me fret
The questions for the problem set
I nailed them all without a sweat
In bi-o-che-mis-try

And I was Singin'
Bye bye biochemistry bye
You can debit all my credit
Cuz my grade is so high
And all the students have a rallying cry
Singin' there'll be a party tonight
There'll be a party tonight

Lyrics by Kevin Ahern

Entire recording is on previous page

Point by Point: Structure and Function



Amino Acids

- 20 amino acids comprise 99% of the proteins on this planet.
- Amino acids have the following general structure - a central α-carbon to which is attached the α-carboxyl, the α-amine, a hydrogen, and an R-group.
- 19 of the 20 amino acids have the α-carbon asymmetric, meaning they can exist in two different stereoisomers. With only very minor exceptions, all amino acids in proteins are in the L-configuration.
- The genetic code specifies the incorporation of the 20 amino acids into a protein during protein synthesis (translation). Specifications are via codons, which are three base sequences in tRNAs.
- Two amino acids, selenocysteine and pyrrolysine, are not encoded by the genetic code, but are put into proteins by unusual mechanisms in rare proteins involving stop codons during translation.
- Amino acids are divided into two general groups - essential (must be in the diet of the organisms) and non-essential (can be synthesized by the organism).

- Essential and non-essential amino acids vary by organisms. Humans have about 9 essential amino acids.

- Amino acids differ from each other by the composition of their R-groups.

- In this book, we categorize amino acids into six different categories based on the composition of their R-groups. They are non-polar (aliphatic R-group), carboxyl (carboxyl in R-group), amine (ionizable amino group in R-group), aromatic (contain benzene ring), hydroxyl (contain hydroxyl group), and other (contain carboxyamide, sulfhydryl, or other group).

- Alanine is one of simplest and most abundant amino acids in proteins. It is non-essential. A D-form of alanine is used to make the peptidoglycan layer of bacterial cell walls.

- Glycine is the simplest amino acid, having only a hydrogen as its R-group. It is the only amino acid to lack an asymmetric center (no stereoisomers) and is non-essential.

- Isoleucine is essential with a hydrophobic R-group.

- Leucine is the most abundant amino acid found in proteins and is also specified by the most codons (6). Its presence helps to stimulate the process of protein synthesis in muscle, however an overabundance of it is toxic.

- Methionine is one of two sulfur-containing amino acids. It is essential and is noteworthy in being the first amino acid put into all proteins. In bacteria, a modified form of it (formylated) is used only for the first amino acid in a protein.

- Proline is a non-essential only amino acid whose R-group covalently bonds to its α-amine group, creating a secondary amine. The ring leaves proline with less flexibility in a protein and often is the site of “bends” in a protein, as a result.

- Proline is often covalently modified in a protein after it is made by addition of a hydroxyl group. This happens in collagen and results in increased stability of the protein.

- Valine is an essential, non-polar amino acid. When it replaces glutamic acid in mutated formed of the globin gene in hemoglobin, the resulting hemoglobin aggregates in low oxygen conditions, giving rise to sickle cell disease.

- Aspartic acid is a non-essential amino acid readily made from oxaloacetate. Its side chain is acidic and it is negatively charged at physiological pH. Aspartate has the effect of stabilizing α-helices.

- Glutamic acid is also non-essential and chemically is very much like aspartic acid, being negatively charged at physiological pH. It is readily made from α-ketoglutarate.

- Arginine is an amino acid with an R-group that is amine-containing and positively charged at physiological pH.. It is borderline for being essential in humans. Premature infants cannot make it and may not be made in sufficient quantities in certain conditions.

- Histidine’s R-group contains an amine, but it can gain or lose a proton near physiological pH (pKa is about 6). Slight changes in physiological pH can sometimes change histidine’s charge.

- Lysine is an essential amino acid with an amine-containing R-group. It's pKa value is high, so like arginine, lysine's R-group is usually positively charged at physiological pH. Lysine is chemically modified in many ways after being incorporated into a protein.

- Phenylalanine has a non-polar aromatic R-group that is essential. Tyrosine is made from it. The genetic disease phenylketonuria arises from an inability to properly metabolize the amino acid. Phenylalanine is a component of Nutrasweet® (aspartame).

- Tryptophan is an essential amino acid containing a benzene ring in its indole R-group. It is a metabolic precursor of hormones such as serotonin and plant auxins.

- Tyrosine is a non-essential amino acid made from phenylalanine. It is both an aromatic amino acid and a hydroxyl-containing amino acid. Its hydroxyl group is a target for phosphorylation by tyrosine protein kinases in the process of signaling. Tyrosine is a precursor of neurotransmitters, such as dopamine and of hormones, such as epinephrine and thyroid hormones.

- Serine is a non-essential, hydroxyl-containing amino acid, making it a polar amino acid. It is a precursor of purines, pyrimidines, sphingolipids, folate, and of the amino acids glycine, cysteine, and tryptophan. Its hydroxyl group is also phosphorylated by cellular protein kinases.

- Threonine is a hydroxylated amino acid that is essential. Like serine and tyrosine, its hydroxyl group is a target for phosphorylation in proteins. It is also a target for O-glycosylation.

- Asparagine is a non-essential amino acid containing a carboxyamide in its R-group. Asparagine can be converted into acrylamide during the cooking of foods at high temperature. The amino acid is readily made from aspartic acid.

- Glutamine is another borderline essential amino acid. Normally it is not essential, but may be needed in the diet in some circumstances. Its carboxyamide R-group does not ionize at physiological pH, but is polar. It is made by amidation of glutamine. It is one of the few amino acids that cross the blood-brain barrier.

- Cysteine is the second amino acid with sulfur in it (methionine is the other) with the sulfur in the form of a sulfhydryl when in the reduced form. Oxidation of the sulfhydryl results in joining of two cysteines together to make cystine with a covalent disulfide bond. Cysteine is also found in glutathione.

- Selenocysteine is a component of selenoproteins and is found in all kingdoms of life, including 25 human proteins. Enzymes with it include glutathione peroxidases and thioredoxin reductases. It is incorporated into proteins by an unusual use of a stop codon.

- Pyrrolysine is a very rare amino acid found in archaeans making methane and in one methane-producing bacterium. It is a component of methane-producing enzymes and, like selenocysteine, is incorporated into proteins by an unusual use of a stop codon.

- Amino acids readily ionize at physiological pH values. In proteins, the only parts that ionize are the α-carboxyl and α-amine ends of the protein and ionizable R-groups in proteins. These include lysine, arginine, histidine, aspartic acid, glutamic acid, and cysteine.

- When amino acids are broken down into intermediates that can be made into glucose, they are called glucogenic.

- Amino acids that can be broken down into acetyl-CoA are called ketogenic. Some amino acids are both glucogenic and ketogenic.

- Covalent changes to amino acids in proteins after the protein is made are called post-translational modifications. Examples include phosphorylation (serine, threonine, and tyrosine), hydroxylation (proline and lysine), carbohydrates (asparagine, threonine, and serine), or addition to various amino acids of fatty acids, isoprenoid groups, acetyl groups, methyl groups, iodine, carboxyl groups, and sulfates.

Proteins I

- Proteins are the workhorses of cells. They are enzymes for catalysis, mediators of signaling, give structure to cells and control the proteome.

- There are four distinct levels of protein structure - primary (amino acid sequence), secondary (interactions between close amino acids that affect local protein shape), tertiary (interactions between amino acids not close in primary structure that affect folding), and quaternary (interactions between separate polypeptide subunits of a protein.

- Structure is essential for function. Proteins that lose structure lose their function.

- Proteins are flexible and very tiny changes in their structure can have large effects on their function. In hemoglobin, oxygen binding changes the protein's shape and affects its affinity for binding of other oxygens.

- The primary structure of a protein ultimately determines its shape and its properties. ‘

- Protein synthesis occurs in ribosomes and involves formation of peptide bonds between the α-carboxyl of one amino acid with the α-amine of the next one.

- The amino terminus of a protein is the end that has the free α-amino group. The carboxyl terminus is the end containing the free α-carboxyl group.

- Proteins are made starting at the amino end and ending at the carboxyl end.

- R-groups of consecutive amino acids in a protein are usually oriented on opposite sides of the polypeptide chain (*trans*). Positioning them on the same side (*cis*) often results in unfavorable steric interactions.

- Steric hindrance is an important factor driving folding of proteins.

- Common secondary structures include the **α**-helix and **β**-strands/sheets.

- α-helices have 3.6 amino acids per turn of the helix and are predominantly right-handed.

- Hydrogen bonds between carbonyl groups and amine groups four amino acids apart help to stabilize α-helices.

- The repeat of a helix is the number of amino acids in a chain before it begins to repeat its structure. This is 3.6 for an α-helix..

- The rise of a helix is the distance each step of the helix makes. For an α-helix, this is 0.15 nm per amino acid.

- The pitch of a helix is the distance between complete turns of the helix. For an α-helix, this is 0.54 nm.

- α-helices are stabilized by the presence of aspartate.

- β-strands are the equivalent of flattened helices. When β-strands are arranged together, they can form sheets, barrels, and other structures.

- Such arrangements are called supersecondary structures. These higher order structures are stabilized by hydrogen bonds.

- Chains in supersecondary structures can be parallel (same α-amino - α-carboxyl orientations) or anti-parallel (opposite α-amino - α-carboxyl orientations).

- Turns are a type of secondary structure that give rise to tertiary structure. They often connect different secondary structures, such as α-helices and β-strands.

- There are at least five types of turns - δ,γ,β,α,π - corresponding to turns spanning 1,2,3,4, or 5 amino acids, respectively.

- A 3_{10} helix is the fourth most abundant secondary structure in proteins - about 10% of all helices. It contains 10 amino acids in 3 right-handed turns. Hydrogen bonds form between amino acids that are three apart.

- **π**-helices are thought of as a special type of α-helix, as if an extra amino acid were placed in the middle. They are right-handed and have 22 amino acids in 5 turns of the helix. Most are only 7 amino acids long and occur in the middle of α-helices.

- The peptide bond has characteristics of a double bond and creates a planar structure. A polypeptide chain then can be thought of as a set of unrotatable planar structures separated by rotatable single bonds.

- Sequentially in the amino to carboxyl direction they are 1) a rotatable bond (**ψ**) between the α-carbon and α-carboxyl preceding the peptide bond, 2) an un-rotatable peptide bond (ω) between α-carboxyl and α-amine), and 3); a rotatable bond (**φ**) between the α-amine and α-carbon following the peptide bond. Note that in Figures 2.32 and 2.33 that the amino end is on the right and the carboxyl end is on the left.

- Ramachandran and colleagues performed theoretical calculations to determine the steric stability of the rotatable bonds on either side of the planar structures.

- Their results (shown in Ramachandran plots) identified three primary groups of stable rotatable angles and these correspond to the angles found in right handed α-helices, left handed α-helices, and β-strands.

- The amino acid sequence and secondary structure of thousands of proteins are known. By analyzing these sequences, it is possible to determine the frequency (likeli-

hood) of each of the amino acids occurring in any of the secondary structures. With this information, a computer can predict with about 80% accuracy where and what the regions of secondary structure are in a protein from its sequence of amino acids.

- Amino acids differ in their hydrophobicity/hydrophilicity. Hydropathy scores rate the relative hydrophobicity/hydrophilicity of each amino acid. High positive values indicate high hydrophobicity whereas high negative values correspond to high hydrophilicity.

- Proteins embedded in non-polar lipid bilayers have stretches of hydrophobic sequence (called transmembrane domains) that can be seen in a Kyte-Doolittle plot.

- Regions of proteins that have no regular, discernible structure are referred to as random coils. They may have fluid structures and exist in multiple stable forms. These may be metamorphic proteins or intrinsically disorder proteins and can be characterized by spectroscopic methods that include circular dichroism or nuclear magnetic resonance (NMR).

- Tertiary structure of proteins arises from the process known as folding and is determined ultimately by the amino acid sequence of the protein.

- Non-fibrous proteins are known as globular. Interactions between amino acids that are distant in primary sequence, but close in folded sequence stabilize tertiary structure. Chemical forces involved in the stabilization include hydrogen bonding, hydrophobic forces, ionic bonds, disulfide bonds, and metallic bonds.

- Breaking tertiary structure involves breaking the stabilizing forces. This can be accomplished by heat, pH change, detergents, urea, and mercaptoethanol. These treatments unfold proteins and destroy their function.

- Hydrogen bonds are weaker than covalent bonds. They are readily broken with boiling water or urea.

- Ionic interactions are important for structural stability and also in catalysis. pH can have a strong influence on ionization.

- Hydrophobic forces arise from interactions between hydrophobic side chains of amino acids that exclude water. They are commonly found in the interior of a protein and can readily be destroyed with detergent.

- Disulfide bonds are the only covalent bonds stabilizing tertiary structure. They form when two sulfhydryls are brought into close proximity in a folded protein. Breaking disulfide bonds requires a reducing agent, such as β-mercaptoethanol or dithiothreitol.

- van der Waals forces are forces of attraction and repulsion caused by correlations in the fluctuating polarizations of nearby particles.

- Post-translational modifications alter amino acids after a protein is made.

- There are two popular protein folding models. The first (diffusion collision model) involves a nucleation even followed by secondary structure formation. By contrast, the nucleation condensation model proposes that secondary and tertiary structures form together.

- Folding can begin before the synthesis of a protein is complete.

- A folding funnel energy landscape is hypothesized. This is an energy diagram with many local minima a folding protein can "fall into" and become trapped, thus explaining misfolding.

- Secondary structures can readily be predicted by computer from sequence. Tertiary structure prediction is much harder to predict. Leventhal's paradox presents the enormity of the problem from approach the prediction from a random basis.

- Problems arising from protein misfolding include Mad cow disease, Alzheimer's, Parkinson's, and Creutzfeld-Jacob disease.

- Misfolded proteins commonly form aggregates and become insoluble in water creating problems. They begin with a "seed" protein called prions and they act infectiously.

- Creutzfeld-Jacob diseases, Mad cow disease, and scrapie all have the same protein involved - it is a membrane protein called PrP. PrP^{c} is the properly folded form and PrP^{sc} is the folded form associated with disease. They each have the same amino acid sequence

- Amyloids are collections of misfolded protein aggregates. Examples include Alzheimer's disease (Amyloid β), Parkinson's disease (α-synuclein), Huntington's disease (huntingtin), rheumatoid arthritis (serum amyloid A), and fatal familial insomnia (PrP^{sc}).

- Huntingtin is the protein implicated in Huntington's disease. It must be mutated to misfold. Its mutation arises with formation of repeats of a glutamine coding sequence as a result of "slipping" of a repeated sequence causing additional copies of the repeat to be made during DNA replication.

- One class of proteins assist other proteins to fold properly. There are two classes of these proteins. Heat shock (Hsp) proteins use ATP hydrolysis to facilitate proper folding. They have a β-barrel structure that has affinity for hydrophobic amino acid side chains. Hsp70 binds to polypeptides as they are being synthesized on ribosomes. It largely protect proteins from aggregating with each other before they begin to properly fold. When proteins are damaged, Hsp70 binds to ubiquitinating factors to target them for destruction.

- The other class of proteins assisting folding is the chaperonins. The best studied are the GroEL/GroES complexes. They too provide a lidded chamber within which folding occurs. It may occur in a model like that of Hsp 70 or may involve a more active process of catalyzed folding.

- Proteasomes are cellular structures involved in degradation of damaged/misfolded proteins. Degradation is targeted on proteins flagged by being bound to ubiquitin. Proteasomes degrade targeted proteins into short peptides of 8 amino acids or fewer.

- Parkin is a protein involved in Parkinson's disease and is a component of ubiquitin ligase (involved in attachment of ubiquitin to proteins to be degraded).

- Intrinsically disordered proteins have more fluid structures. They are not misfolded, but may have multiple stable forms they switch between. In some cases, disor-

dered regions may become ordered upon binding to another protein.

- Metamorphic proteins have different stable structures that are in equilibrium with each other.

- A few proteins, such as ribonuclease, can properly refold after being denatured. Most, however, cannot properly refold after denaturation.

- Quaternary structure involves interactions between multiple polypeptides in a protein. Such interactions can give new properties, such as cooperativity and allosterism, in multi-subunit proteins that do not exist in similar proteins comprised of only a single subunit.

Proteins II

- Fibrous proteins have a strong structural component and mostly have primary and secondary structure - little tertiary structure.

- Fibrous proteins constitute hair, nails, hard substances like horns, and connective tissues. They include keratins, fibroin, elastin, and collagen.

- Keratins are found in hair, nails, beaks, scales, feathers, and claws. There are over 50 in the human genome. Keratins comprise the intermediate filaments of the cytoskeleton. α-keratins often have intertwined **α**-helices in coiled-coil structures. Disulfide bonds between chains add strength. Curling/uncurling hair involves breaking these bonds.

- β-keratins contain β-sheets.

- Fibroin is a component of silk and has a repeating amino acid sequence rich in glycine and alanine.

- Elastin has elastic properties and is rich in glycine and proline. Elastin is made by winding together chains of tropoelastin and then joining lysines within them in cross-linked desmosine structures.

- Collagen is the most abundant protein in mammals. It is found in tendons, skin, cornea, cartilage, bone, blood vessels and the gut.

- It contains three left-handed helical chains coiled together in a right-handed helix. On the inside of the helix, only glycines are found. In addition to glycine, collagen is also rich in proline and a modified form of it - hydroxyproline.

- Hydroxylation of proline is a post-translational modification that requires vitamin C. Deficiency of vitamin C leads to a weakened form of collagen, resulting in scurvy.

- Lamins are fibrous proteins in the cell nucleus. They help to regulate transcription and are similar to proteins in intermediate filaments. They are also involved in assembly and disassembly of the nuclear envelope relating to mitosis.

- Disassembly is mediated by phosphorylation by mitosis promoting factor. Dephosphorylation reverses the process, allowing for assembly.

- Tertiary structure includes structural domains (repeated structures in mamy proteins that are larger than secondary

structures. Structural domains are self-sustaining and can fold independently of the rest of the protein.

- One structural domain is a leucine zipper - a zipper-like structure found within and between proteins where leucines in the core of the zipper stabilize it by interacting with each other. Leucine zippers commonly interact with DNA and can be found in many transcription factors.

- Zinc fingers (often) use a coordinated zinc ion to stabilize a finger-like projection of the protein. They too can bind DNA and be found in transcription factors. Other molecules bound by zinc fingers include RNA, protein, and lipids.

- The src oncoprotein has a structural domain called SH_2 that binds to phosphorylated tyrosines in target proteins. The domain plays a role in signaling and is found in over 100 human proteins.

- The helix-turn-helix domain is commonly found in DNA binding proteins and contains two α-helices separated by a small number of amino acids. The helix parts of the domain interact with bases in the major groove of DNA.

- Pleckstrin homology domains bind to phosphorylated inositol residues (PIP_2 and PIP_3) in cell membranes. Proteins with this domain can also bind to G-proteins and protein kinase C. They play important roles in cellular signaling.

- The basement membrane is a glue that holds tissues together. It is a layered extracellular matrix of tissue comprised of protein fibers (type IV collagen) and glycosaminoglycans that separates the epithelium from other tissues.

- Structural globular proteins are globular proteins that are able to self-assemble into fiber-like structures.

- Actin is a structural globular protein comprising as much as 20% of the mass of muscles. Polymerization of actin leads to microfilaments (also called thin filaments)- a major component of the cytoskeleton. Thin filaments of actin are acted on by myosin in muscular contraction.

- Intermediate filaments are intermediate in size (average diameter = 10 nm) between that of the microfilaments (7 nm) and the microtubules (25 nm). They include the lamins in both nuclear and cytoplasmic forms. They are extremely flexible and can be stretched to several times their original length.

- There are six types of intermediate filaments and they vary considerably in the composition of proteins within them, ranging from one to four proteins. The lamins make up Type V proteins. Types I and II contain different keratins. Type III is the most complex with four proteins.

- Tubulins are monomeric units of microtubules.

- Microtubules provide rails for motor proteins to move on for transport of cargo inside of cells.

- Vimentin is the most widely distributed protein of the intermediate filaments, being found in fibroblasts, leukocytes, and the endothelial cells of blood vessels. It helps to position organelles in the cytoplasm, providing attachment to the nucleus, mitochondria, and the endoplasmic reticulum. Vimentin helps control the esterification of cholesterol.

- Mucins are proteins in epithelial tissue with numerous attached carbohydrates and are involved in lubrication, bone formation, binding of pathogens in the immune system, and mucosal secretions from mucus membranes.

- Vinculin is a protein in the cytoskeleton involved in focal adhesion structures found at the cell-cell and cell-matrix junctions. It interacts with integrin proteins as well as f-actin where it helps anchor actin microfilaments to the membrane.

- Syndecans are transmembrane proteins that facilitate G-protein coupled receptor's interaction with ligands. Syndecans typically have 3-5 heparan sulfate and chondroitin sulfate chains attached to them and cleavage of those chains at the site of a wound can help stimulate the healing process. Syndecans play a role in cell-cell adhesion. The syndecan 1 ectodomain can suppress growth of tumor cells without affecting normal epithelial cells.

- Defensins are small cationic proteins that act as ionophores to protect against infection by various bacteria, fungi, and viruses.

- Focal adhesions are structures with multiple proteins that link the cytoskeleton to the extracellular matrix. Over 100 proteins are involved. Since they are connected to the extracellular matrix, focal adhesions can communicate its status to cells containing them.

- Ankyrins are a family of membrane adaptor proteins that anchor integral membrane proteins to the spectrin-actin membrane cytoskeleton. Ankyrins are anchored to the plasma membrane by palmitoyl-CoA.

- Spectrin is a cytoskeletal protein that helps to maintain the structure and integrity of the plasma membrane. It gives red blood cells their shape and is found in the inner layer of the plasma membrane in a network of pentagonal and hexagonal shapes.

- Integrins are important transmembrane proteins for connecting cells together. They bind to collagen, fibronectin, laminin, and vitronectin and also play roles in communication, migration, viral attachments, and blood clotting. They are a bridge between the extracellular matrix and the cytoskeleton. The are important in focal adhesions.

- The binding response of integrins can be rapid - GPIbIIIa (on the surface of blood platelets) attaches to fibrin in a clot as it develops.

- Integrins can also help to recruit signaling molecules inside of the cell to activated tyrosine kinases to help them to communicate their signals.

- The class of integrin proteins is large, with 18 α- and 8 β-chains in mammals.

- Cadherins perform binding functions when bound to calcium and preferentially cluster with the same cadherins on other cells over different cadherins.

- Selectins are cell adhesion glycoproteins that bind to sugar molecules - a type of lectin. Their N-terminus binds calcium, which activates its lectin activity. Selectins are specific for endothelium (E), lymphocytes (L), or platelets (P). They help lymphocytes to bind to lymphoid organs in inflammation and have a role in metastasis. Selectins are involved in the inflammatory

processes of asthma, psoriasis, multiple scleroris, and rheumatoid arthritis.

- Laminins are extracellular matrix glycoproteins - major components of the basal lamina. They affect cell differentiation, migration, and adhesion. They are secreted into the extracellular matrix and are essential for tissue maintenance and survival. They are associated with fibronectin, entactin, and perlecan proteins in collagen and bind to integrin receptors in plasma membrane

- Vitronectin is a glycoprotein in blood serum (platelets), the extracellular matrix, and in bone that promotes cell adhesion and spreading. It binds to several protease inhibitors (serpins), integrin, and stabilizes plasminogen activator inhibitor. May play role in blood clotting and malignancy.

- Catenins interact with cadherin in cell adhesion at adherens junctions. They connect to actin fiber in the cytoskeleton and are important in contact inhibition of cells. Tumorigenesis may result from mutation in catenins.

- Glycophorins are heavily glycosylated proteins (sialic acid) on the surface of red blood cells that help them to avoid attaching to other cells. They help regulate mechanical properties and shape of the cells.

- Quaternary structure's multiple protein interactions allow for cooperative binding of substrates and allosterism to occur. Allosteric effectors that are also substrates are called homotropic, whereas those that are not substrates are called heterotropic.

- Cooperativity occurs when binding of one substrate by a multi-subunit protein favors the binding of more of the same substrate by the same protein (the term substrate here is used simply to indicate a molecule bound by any protein - not just an enzyme).

- In hemoglobin, for example, binding of the first oxygen increases the affinity of hemoglobin for binding subsequent oxygens. This happens because binding of the first oxygen in the lungs converts hemoglobin from the T-state (low affinity) to the R-state (high affinity).

- Rapidly respiring tissues have molecules they release that lower hemoglobin's affinity for oxygen and that convert it from the R to the T state. These include protons, 2,3, BPG, and carbon dioxide. Carbon dioxide is carried on amines by hemoglobin back to the lungs. Oxygen and carbon monoxide, by contrast, bind to the iron in the heme group.

- In contrast to myoglobin, which has strong affinity for oxygen, hemoglobin has varying affinity for oxygen as a function of oxygen concentration (low affinity in low oxygen, high affinity in high oxygen), thus allowing it to adapt to the boy's needs and availability of oxygen.

- As a consequence, myoglobin is better for storing oxygen and hemoglobin is better for transporting it.

- The Bohr effect describes how external molecules (protons, carbon dioxide, 2,3 BPG) decrease hemoglobin's affinity for oxygen and provide rapidly respiring tissues the oxygen that they need.

- 2,3 BPG (a byproduct of glycolysis) binds in the "donut" hole of hemoglobin, favoring the T-state and releasing oxygen. If the 2,3BPG concentration is high in the blood, it

may not get removed from hemoglobin before the returning to the lung, leaving hemoglobin in the T-state with a lower capacity for binding oxygen. Smokers have high 2,3 BPG concentrations in the blood and this is why smokers have a reduced oxygen carrying capacity.

- Smokers also have higher levels of carbon monoxide in their blood and this competes with oxygen for binding iron on the heme group, also reducing oxygen carrying capacity.

- Carbon dioxide moves from tissues to lungs in the blood by two mechanisms - 1) carried by hemoglobin and 2) dissolved as bicarbonate.

- Fetal hemoglobin is slightly different from adult hemoglobin, with two γ-chains replacing the β-chains of adult hemoglobin. The result is a hemoglobin that can bind oxygen cooperatively, but can't bind 2,3 BPG, resulting in a hemoglobin more frequently in the R-state. Fetal hemoglobin thus has a higher affinity for oxygen than adult hemoglobin so the fetus can take oxygen from the mother.

- Sickle cell disease arises from mutations in hemoglobin that cause aggregates to form under low oxygen conditions. This, in turn, causes blood cells containing the mutated hemoglobin to form sickle shapes, making it harder for them to pass through capillaries. The condition can be very painful under conditions of high exertion and may be fatal if too severe.

- People heterozygous for the sickle cell gene (one copy of the mutant and one unmutated) appear to have a selective advantage in being better able to survive malaria infections.

- Sickle cell anemia is treated with hydroxyurea, which induces expression of the fetal hemoglobin gene in adults to replace the defective mutant copy.

- Oxygen is needed more by plants than animals due to rapidly changing needs arising from muscular contraction.

- This is because oxygen is the terminal electron acceptor of electron transport, so when it and oxidative phosphorylation are running, ATP generation is much more efficient.

- Besides hemoglobin, two other oxygen binding proteins are of note - myoglobin (muscles of higher animals) and hemocyanin (molluscs and arthropods).

- Insects and unicellular organisms have other means of managing oxygen

- Myoglobin is the primary oxygen-storage protein found in animal muscle tissues. It has high affinity for oxygen and only releases it when the oxygen concentration is very low.

- Red meat gets its color from ferrous iron (Fe^{++}), which oxidizes to ferric iron (Fe^{+++}), causing browning when meat is cooked.

- Myoglobin has higher affinity for oxygen than hemoglobin.

- Mammals that dive deeply in the ocean, such as whales and seals, have muscles with particularly high abundance of myoglobin.

- Hemocyanin is a copper-containing protein that transports oxygen in the bodies of molluscs and arthropods.

- The oxygen in hemocyanin is held between two Cu^{+} ions, which are, in turn, held in place by six histidines.

- Most (but not all) oxygen binding to hemocyanin is non-cooperative. Horseshoe crabs and some arthropods bind oxygen cooperatively.

Proteins III

- Actin is a structural globular protein that exists in monomer and polymeric forms. Polymerization of actin leads to microfilaments - a major component of the cytoskeleton.

- Actin is essential for muscular contraction, cell signaling, and maintenance of cell junctions. α-actin is in the muscles, whereas the β and γ forms are components of the cytoskeleton.

- The monomeric unit of actin is called G-actin and the polymer is known as F-actin.

- Helical F-actin in muscles contains tropomyosin. In addition to tropomyosin, other proteins binding actin filaments include troponins I, T, and C.

- Actions in which actin plays a role include cell motility, cytokinesis, intracellular transport of vesicles and organelles, and it helps to establish cell shape.

- During polymerization of actin, its weak ATPase activity is stimulated to convert ATP to ADP.

- F-actin binds to structural proteins at adherens junctions, such as **α**-actinin, vinculin, catenins, and cadherins.

- The Arp 2/3 complex mimics an actin dimer and helps to initiate the process of actin polymerization. Thymosin at the end of actin filaments helps control growth of the filaments. The protein known as profilin acts to exchange ADP for ATP within actin monomers.

- Tubulins are monomeric units of microtubules. The α-tubulin and β-tubulin proteins polymerize to make microtubule structures in the cytoplasm of cells. Microtubules only grow in one direction. The end of growth is called the plus end and the other is referred to as the minus end.

- Microtubules are major components of the cytoskeleton. Stable microtubules contain tubulin units bound to GTP. Those bound to GDP are unstable and fall apart.

- Microtubules are found in the cytoplasm, the inner structure of cillia and flagella and provide rail-like structures for the movement of materials within cells. The proteins navigating these rails are dynein and kinesin, which operate in opposite directions. Centrosomes are focal points of connection of microtubules.

- Motor proteins act as their name suggests - the provide movement inside of cells. In their action, they carry cellular cargo from one location to another.

- Motor proteins navigating microtubules in cells include kinesin and dynein. Each uses hydrolysis of ATP as the fuel needed for the movement.

- Kinesin and dynein walk in opposite directions on a microtubule. Kinesin moves in the direction of synthesis of the microtubule (plus end movement, away from the cell center) whereas dynein exhibits minus end movement toward the cell center.
- Myosin proteins use ATP to enable movement along actin thin filaments. Myosin proteins form aggregated structures are called thick filaments.
- Myosin has a head, a tail, and a hinge/neck region. The head is where ATP is held and hydrolyzed.
- There are three types of muscle tissue - skeletal (striated), smooth, and cardiac.
- Muscles may be activated by the central nervous system or may contract involuntarily (smooth and cardiac only).
- Sarcomeres are the basic units of striated muscle and are comprised of thick (myosin) and thin (actin) filaments and a protein called titin.
- In muscular contraction, thick and thin filaments slide past each other fueled by myosin.
- A sarcomere is the region between the two Z-lines of striated muscle and encompasses the entire A band (See Figure 2.112). In muscular contraction, myosin heads move toward the center of the sarcomere.
- The center of the sarcomere's H-zone contains an M-line, which is attached to the cytoskeleton.
- The sarcolemma is the plasma membrane of muscle cells, with a lipid bilayer and a glycocalyx on the outside.
- Polysaccharides of the glycocalyx connect the sarcolemma with the basement membrane. Muscle fibers use the basement membrane as a scaffolding. Connections are also made by transmembrane proteins bound to the actin cytoskeleton.
- At the ends of muscle fibers, the sarcolemma is fused with a tendon fiber and the latter is adhered to bones.
- The sarcoplasmic reticulum is a muscle cell structure like the endoplasmic reticulum, serving as a calcium battery, releasing calcium to stimulate muscular contraction and absorbing it during relaxation.
- The sliding filament model is one attempt to explain muscular contraction.
- In it, a repeated set of "pulls" results in sliding of a thin actin filament over a thick myosin filament.
- The process starts with a signal from the central nervous system.
- At the end of the nerve, calcium channels open, allowing calcium to enter the neuron. This causes synaptic vesicles containing acetylcholine to fuse with the plasma membrane and be expelled into the synaptic cleft between the nerve and the muscle cell.
- Acetylcholine activates receptors on the muscle cell, allowing sodium and potassium ions to flow, depolarizing the muscle cell.
- The action potential, thus initiated spreads throughout the muscle cell.
- The sarcoplasmic reticulum responds by opening calcium channels, allowing calcium to escape.

- Calcium binds to troponin on actin filaments, causing it and the tropomyosin it is bound to to shift, allowing myosin binding sites on the tropomyosin to be exposed.
- Myosin's head binds to tropomyosin and the ATP it holds gets cleaved
- Release of ADP and P_i by the myosin head results in a bending of the hinge/neck area, pulling the actin filament over the myosin filament.
- The sarcomere thus shortens. If ATP is available, myosin binds it and continues the process.
- Tropomyosins are proteins that interact with actin filaments and regulate their ability to be used in movement. They form head to tail dimers on the α-helical groove of an actin filament. In this position they are able to control the interactions between myosin and actin and thus regulate contraction.
- Non-muscular tropomyosin helps to regulate cytoskeletal functions.
- Troponin I, C, and T form a complex and interact with tropomyosin on actin filaments. Troponin I prevents binding of myosin's head to actin, thus stopping contraction. Troponin C binds to calcium. Troponin T binds all three proteins to tropomyosin. Elevation of troponins in the blood occurs after a myocardial infarction and can remain high for up to two weeks.
- Actinin connects actin filaments to Z-lines of skeletal muscles.
- Titin is a muscle protein that is the molecular equivalent of a spring. It is the third most abundant protein in muscles and is the large protein with the largest exon known. Titin has both folded regions and unstructured domains. It serves to connect the M and Z lines to the muscle sarcomere.
- Muscle cells have an ATP battery in the form of creatine phosphate. When the oxygen concentration in a muscle cell is high, the reaction to form creatine phosphate moves in the direction of making ADP and creatine phosphate.
- ATP + Creatine <=> ADP + Creatine-P
- When the ATP concentration falls, the equation moves in the direction of making creatine and ATP, thus supplying needed ATP.

Nucleic Acids

- In the race to discover the structure of DNA, Watson and Crick combined observations of Erwin Chargaff with the data of Rosalind Franklin to determine the structure of B-DNA.
- At the core of DNA, bases are hydrogen bonded together - guanine (G) to cytosine (C) and thymine (T) to adenine (A). In RNA, uracil (U) replaces thymine (T).
- The interior of DNA is relatively hydrophobic and the exterior is hydrophilic.
- The DNA molecule is a polymer of nucleoside monophosphates with phosphodiester bonds between the phosphate on the 5' end of one deoxyribose and the 3' end of the next one.

- In the B-form, the DNA helix has a repeat of 10.5 base pairs per turn, with sugars and phosphate forming the covalent phosphodiester “backbone” of the molecule and the adenine, guanine, cytosine, and thymine bases oriented in the middle.
- B-DNA has a major and a minor groove in its structure.
- DNA strands of a double helix are anti-parallel - the 5’ end of one strand is paired to the 3’ end of the other strand.
- The building blocks of DNA and RNA are nucleotides.
- Nucleotides have a sugar (ribose in RNA, deoxyribose in DNA), at least one phosphate, and a nitrogenous base (U,T,A,G, or C). Nucleosides lack phosphate.
- Triphosphate ribonucleotides are important sources of cellular energy. ATP is most widely used for general purposes UTP is used to make glycogen. CTP is used to make glycerophospholipids, GTP is used to make proteins.
- ATP is mostly made in cells by oxidative phosphorylation or (in plants) photophosphorylation.
- Three forms of DNA predominate - A, B, and Z. A and B are right-handed. Z is left-handed.
- The A-form of DNA was discovered by Rosalind Franklin and is found in double-stranded RNA as well as DNA-RNA duplexes.
- ATP can be made from 2 ADPs by adenylate kinase -> 2ADP <=> ATP + AMP
- Nucleoside diphosphokinase (NDPK) allows interchange of all diphosphate and triphosphate nucleotides
- ATP + NDP <=> ADP + NTP
- Deoxyribonucleotides are made from nucleoside diphosphates by catalysis with ribonucleotide reductase.
- Kinases put phosphates onto molecules. Phosphatases remove phosphates from molecules.
- Superhelicity of DNA arises from tension in a duplex that alters the preferred ratio of 10.5 base pairs per turn. Tension is relieved by supercoiling in which the double strands cross over each other (Figure 2.110).
- Three terms are used to measure/describe winding of DNA strands - twists (T - number of turns of the DNA); writhes (W - number of superhelical turns where the double helix crosses over itself); and the linking number (L - number of twists and writhes).
- L = T + W
- Alteration of the superhelical density (number of writhes per base pair) is a factor in DNA replication and can affect transcription of genes.
- Topoisomerase enzymes can create or relieve DNA tension.
- Type 1 topoisomerases work by cutting one strand of a DNA helix. Type II topoisomerases work by cutting both strands of a double helix.

- Antibiotics targeting topoisomerases include fluoroquinolones and ciprofloxacin.
- RNAs come in several forms - ribosomal RNA (rRNA - makes peptide bonds); transfer RNA (tRNA - carries amino acids in protein synthesis); messenger RNA (mRNA - carries genetic message for making proteins), and several small RNAs with functions in control of gene expression and/or suppression of viruses. They include small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), and microRNAs (miRNAs). Each of these has short regions of duplex.
- In RNA, G-U base pairs are not unstable, allowing for more base-pairing possibilities. Single-stranded RNA therefore has many more ways to base-pair with itself than single-stranded DNA.
- RNAs like the rRNAs of ribosomes that catalyze reactions, are called ribozymes.
- RNA is less chemically stable than DNA.
- Cytosine can spontaneously deaminate to form uracil. Repair systems fix this in DNA.
- Denaturation of nucleic acids is accomplished by breaking the hydrogen bonds between the base pairs of the double helix. This is often accomplished with heat.
- When denatured, absorbance of light at 260 nm by single strands is greater than that of double strands, leading to the hyperchromic effect.
- Denaturation of strands is important for techniques like the polymerase chain reaction (PCR).
- The process of allowing strands to re-form a duplex is called annealing.
- Human DNA is a cell is over 7 feet long. It is wrapped in chromosomal coils (chromatin) by positively-charged proteins called histones.
- DNA is kept in the nucleus of eukaryotic cells and in a nucleoid of bacterial cells.
- Prokaryotes don't have histones, but do have nucleoid associated proteins that they wrap around.
- There are five main types of eukaryotic histones - H1, H2a, H2b, H3, and H4. Pairs of each of the last four are found as octamers in the core particle of the nucleosome - the fundamental repeating unit of chromatin. H1 binds to the DNA in the regions between core particles.
- Histones are positively charged and are rich in lysine and arginine.
- Tightly packed chromatin is called heterochromatin and is found in metaphase chromosomes of meiosis and mitosis.
- Chemical modification of lysine side chains in chromatin (acetylation, for example), changes the histones' charge and the tightness with which they are bound to the negatively charged DNA. This effectively loosens the grip of histones on DNA and is important in gene expression to allow transcription proteins to gain access to relevant DNA sequences.
- The Ames test allows one to determine the tendency of a compound to cause mutation.

- The Ames test works by using a biological assay to measure the frequency with which a specific mutation occurs in a plasmid. By comparing the mutation rate for bacteria treated with a compound compared to the mutation rate of bacteria not treated with the compound, the mutagenicity of the compound is determined.

Carbohydrates

- Carbohydrates are molecules that are literally hydrates of carbon. They are also known as sugars or saccharides and polymers of them are known as polysaccharides. Monosaccharides contain one sugar. Disaccharides contain two. Oligosaccharides contain several.
- Glucose is a monosaccharide, sucrose is a disaccharide, and glycogen is a polysaccharide.
- Sugars are names with the -ose suffix.
- Some sugars are modified, such as deoxyribose or glucose-6-phosphate.
- The most common monosaccharides include glucose, fructose, galactose, ribose, and mannose. All but fructose are sugars containing an aldehyde (aldoses). Fructose contains a ketone group (ketose).
- Glucose, fructose, galactose, and mannose all contain six carbons (hexoses). Ribose contains five carbons (pentose).
- Names can be combined. Fructose is a keto-hexose. Ribose is an aldo-pentose.
- Most sugars have multiple asymmetric centers.
- Sugars that are the same chemical type (aldoses, for example) with the same formula (hexoses, for example), but differ in only in arrangement of hydroxyls around asymmetric carbons are known as diastereomers.
- Diastereomers that differ only in configuration of one carbon are called epimers.
- Cyclization of linear sugar structures creates a new asymmetric center at the location of the carbonyl group of the linear sugar. This new asymmetric center is called the anomeric carbon.
- Diastereomers that differ only in the configuration of the anomeric carbon are called anomers. The location of the hydroxyl on the anomeric carbon determines whether it is in the α (hydroxyl down) or the β (hydroxyl up) configuration.
- Sugars that cyclize to form rings with 6 atoms are called pyranoses. Those that form rings of 5 atoms are called furanoses.
- A given form of a hexose sugar can exist in two different conformations known as the boat or the chair form (see Figure 2.127).
- Modifications to sugars can include oxidation, reduction, phosphorylation, and conversion of a hydroxyl to an amine or acetyl-amine. Alterations affecting the anomeric hydroxide create glycosides.
- A reducing sugar is a sugar that can easily be oxidized. Benedict's test determines if a sugar is a reducing sugar or not. In the test, cupric oxide (blue color) is reduced to cu-

prous oxide (orange color) if a reducing sugar is present.

- Aldoses and ketoses that can tautomerize to an aldose (such as fructose) are reducing sugars. Any sugar with a free, non-glycosidic anomeric hydroxyl group is a reducing sugar.
- Phosphorylation of sugars occurs in metabolism.
- Oxidation of a sugar creates modified sugars like glucuronic acid or galacturonic acid (oxidation of the sixth carbon in each case). The new carboxyl group can ionize easily.
- Glucuronic acid is a common constituent of glycosaminoglycans, proteoglycans, and glycoglycerolipids and is found in heparin, dermatan sulfate, chondroitin sulfate, hyaluronic acid, and keratan sulfate.
- Glucuronic acid is also a precursor of ascorbic acid (Vitamin C) in organisms that synthesize this compound.
- Reduction of sugars creates sugar alcohols, compounds widely used as thickeners of food or as artificial sweeteners.
- Common sugar alcohols (sugar progenitor in parentheses) include glycerol (glyceraldehyde), xylitol (xylose), sorbitol (glucose), galactitol (galactose), arabitol (arabinose), and ribitol (ribose).
- Most are inefficiently absorbed by the intestine.
- Artificial sweeteners are compounds that stimulate sweet receptors on the tongue.
- Disaccharides are comprised of two monosaccharides.
- The most common disaccharides include sucrose (glucose and fructose), lactose (galactose and glucose), and maltose (glucose and glucose.
- All of the common disaccharides contain at least one glycosidic bond.
- Oligosaccharides are comprised of a few (typically 3 to 9) sugar residues. Most are bound to other molecules/structures.
- Oligosaccharides in membrane glycoproteins play important roles in cellular identity/recognition - often a factor in transplanted organ rejection.
- Addition of sugar(s) to proteins is called glycosylation and the products are glycans.
- Immunoglobulin types (IgG, IgA, IgE, IgD, and IgM have distinct glycosylation patterns that confer unique functions by affecting their affinities for immune receptors.
- Blood types, arise from differential glycosylation of a blood cell membrane protein.
- Glycosylation can also play an important role in cell-cell adhesion - important in the immune system.
- Oligosaccharides that are attached to proteins may also determine their cellular destinations. I-cell disease, which arises from an oligosaccharide on a glycoprotein that lacks proper phosphorylation, results in the wrongful export of the protein from the cell instead of its intended destination in the lysosomes.

- There are five such classes - 1) N-linked (attachment to an asparagine or arginine side chain amine), 2) O-linked (attachment to the hydroxyl of serine, threonine, tyrosine, hydroxylysine, or to a lipid; 3) attachment to the phosphate of a phosphorylated amino acid, such as serine; 4) glypiations (use of a phosphatidylinositol to join proteins to lipids; or 5) c-linked (attachment to a carbon of a tryptophan side chain).

- Glycosylation may be required for proper protein folding or for stabilization.

- N-linked glycosylation is the most common type and occurs in the endoplasmic reticulum.

- The process starts on a dolichol pyrophosphate on the outside of the organelle where a core structure of seven sugars is assembled in a Y-shaped form. The structure then flips to bring the sugar structure to the inside of the endoplasmic reticulum (still attached to dolichol phosphate). Additional sugars may be added and then the oligosaccharide is attached to the target protein where additional modifications may occur.

- O-linked glycosylation is initiated primarily in the Golgi apparatus of eukaryotic cells, though a few such linkages start in the endoplasmic reticulum.

- Mucins are membrane or secreted glycoproteins that have many O-linked oligosaccharide chains and are present in most bodily secretions.

- In glypiation, a protein's carboxy terminus becomes linked to glycosylphosphatidylinositol to anchor it to a membrane. This is linked to mannose residues that are attached to GPI embedded in the membrane.

- C-linked glycosylation is the rarest and least understood protein glycosylation, occurring as a link between a mannose residue and a tryptophan side chain.

- Glycoproteins arise from glycosylation of a protein.

- Glycation refers to non-enzymatic reaction of a sugar with a protein or lipid. It is driven by the chemistry and concentration of monosaccharides.

- Exogenous glycation occurs outside of organisms and arises mostly from cooking of food (browning) where it contributes to the taste of cooked food.

- Endogenous glycation occurs inside of an organism. Most commonly it involves fructose, mannose, or glucose. It can be damaging to the endothelium or cartilage can arise from hydrogen peroxide reaction byproducts.

- Diabetes can be indicated by increased glycation of hemoglobin.

- Polysaccharides are polymers of monosaccharides. Most are homopolymers.

- Polysaccharides function in energy storage (animals), structural integrity of cells (plants, fungi, bacteria) and lubrication (joints, mucous).

- Amylose is a simple polysaccharide. It is a homopolymer of glucose units linked only with α-1,4 bonds. It is an energy storage form in plants.

- Amylopectin is related to amylose, having α-1,4 linked glucose units, but about every fifty residues, a new chain of glucoses (also linked α-1,4) branches off from carbon 6 from a glucose (the only 1,6 branch in the chain). Amylopectin is also an energy storage form in plants and a mixture of it with amylose is what we refer to as starch.

- Glycogen is an animal polysaccharide related to amylopectin. Its only difference is that the branches occur about every 8-10 residues instead of every 50 residues, meaning glycogen is more branched.

- In animals, glycogen is broken down starting at the ends, so more ends means more glucose can be released quickly.

- Cellulose is a structural polysaccharide found in plants and fungi, forming the cell wall. It is also a polymer of glucose, but the links between units are β-1,4. Cellulose cannot be digested by most animals because they lack the cellulase enzyme needed for that. Ruminants, however, contain a bacterium that has the enzyme and they can get glucose energy from plant cell walls.

- Hemicellulose is a class of molecules that encompasses several branched heteropolymers of (mostly) D-pentose sugars along with a few hexoses and L-sugars. Hemicelluloses are shorter than cellulose (500-3000 sugars versus 7000-15,000 sugars).

- Chitin is another structural polysaccharide, being comprised of N-acetylglucosamine units joined by β-1,4 linkages. It is like cellulose except for the acetyl-amine group replacing the hydroxyl on position 2.

- Pectins are structural polysaccharides rich in galacturonic acid that is present in most primary plant cell walls and abundant in non-woody parts of terrestrial plants.

- Pectins in the diet may reduce cholesterol due to its tendency to bind it and reduce absorption of cholesterol from food.

- Lectins are proteins that have high specificity of binding for certain sugars. They facilitate attached of bacteria and viruses to cellular targets. Some, such as ricin, are highly toxic.

- In the immune system, a mannan binding lectin (MBL) helps mediate the first defenses against microorganisms and may modulate inflammatory processes.

- Biofuels are fuels derived from biological sources. Most commonly, they are ethanol or methane and may be made by cellulase digestion of plant cellulose followed by fermentation or by native metabolism of methane producing organisms.

- Agar/agarose is a polysaccharide with laboratory applications. It is a polysaccharide polymer of D-galactose and 3,6-anhydro-L-galactopyranose extracted from seaweed. Agarose used to make laboratory gels for separation of DNAs. Agar, which is made by adding agaropectin to agarose, is used to make growth media for plating microorganisms or other cells.

- Glycosaminoglycans are polymers of unbranched repeating disaccharides. The repeating units of the disaccharide core of the molecules typically have an amino sugar (N-acetylglucosamine or N-acetylgalactosamine) and a uronic sugar (glucuronic acid or iduronic acid) or galactose.

- The presence of uronic acid residues and sulfates in glycosaminoglycans causes them to be polyanionic, so they can bind many cations.
- There are four groups - 1) those in connective tissues linked to collagen; 2) joint lubricants; 3) anti-clotting agents; and 4) mucus components.
- Chondroitin sulfate is a glycosaminoglycan found in cartilage and is given as a dietary supplement to reduce joint pain. It can be linked to proteins through serine residues to form proteoglycans, such as aggrecan, versican, brevican, and neurocan.
- Heparin helps prevent clotting of blood by inhibiting conversion of fibrinogen to fibrin. It is stored in the secretory granules of mast cells and released at the point of injury. The repeating disaccharide of 2-O-sulfated iduronic acid and 6-O-sulfated, N-sulfated glucosamine, occupies about 85% of the molecule and make heparin the molecule with the highest negative charge density known.
- Hyaluronic acid is a glycosaminoglycan in connective, epithelial, and nerve tissues that lacks sulfate and is formed in the plasma membrane instead of the Golgi apparatus. It has a molecular weight in the millions. Hyaluronic acid is important in joint lubrication (as a component of synovial fluid) and in the extracellular matrix, where it assists in cell proliferation and migration.
- Hyaluronic acid is also a major component of skin and has functions in tissue repair.
- Hyaluronic acid is abundant in the granulation tissue matrix that replaces a fibrin clot during the healing of wounds.
- Breakdown of hyaluronic acid is catalyzed by enzymes known as hyaluronidases. Humans have seven types of such enzymes, some of which act as tumor suppressors.
- Proteoglycans are made by linking glycosaminoglycans to proteins. Proteoglycans are made by glycosylation of target proteins in the Golgi apparatus.

Lipids

- Lipids are molecules that are significantly hydrophobic
- Many are important for energy storage or for functions in membranes
- Some, like fats are purely hydrophobic. Others, like glycerophospholipids and sphingolipids are amphipathic/ amphiphilic.
- Fatty acids are components of fats and they store a lot of energy.
- They can be saturated (no double bonds), unsaturated (at least one double bond), or polyunsaturated (more than one double bond).
- Double bonds in biologically produced fatty acids are almost exclusively in the *cis* configuration. Partial hydrogenation of vegetable oil produces *trans* fats containing fatty acids with *trans* double bonds.
- *Trans* fat increases LDL levels and lowers HDL levels.

- The Δ numbering system for fatty acids labels #1 as the carboxyl group whereas the ω numbering system calls the methyl group as #1.
- Animals lack the ability to make double bonds beyond position Δ-9, so those fatty acids are essential and must be in the diet.
- ω-3 and ω-6 fatty acids have important health considerations.
- Glycerophospholipids are components of the lipid bilayer of membranes.
- They are derived from phosphatidic acid, just as fats are.
- Glycerophospholipids often are esterified to ethanolamine, serine, choline, or inositol. These are phosphatidyl compounds.
- Phosphatidyl ethanolamine is found in all living cells and makes up 25% of the phosphatidyl compounds - up to 45% of brain tissue.
- Phosphatidyl serine is preferentially found on the inner leaflet of the plasma membrane. In apoptosis (programmed cell death), it appears on the outer leaflet and serves as a signal to macrophages to destroy the cell.
- Phosphatidly choline tends to be found more on the outer leaflet of the plasma membrane. It is positioned there by phosphatidylcholine transfer protein.
- Cardiolipin is an unusual glycerophospholipid containing two diacylglycerol backbones separated by a diphosphoglycerol. It occupies about 20% of the inner mitochondrial membrane and plays roles in facilitating electron transport through complexes III and IV.
- In apoptosis, cardiolipin gets oxidized and then moves to the outer mitochondrial membrane where it facilitates movement of cytochrome c to the cytoplasm.
- Diacylglycerol (DAG) is produced by hydrolysis of fat and hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2) by phospholipase c. It is a signaling molecule.
- Inositol is a component of many lipids. It contains six carbons and can contain 1-6 phosphates. It is a part of the signaling molecules known as PIP_2 and PIP_3.
- PIP_2 functions in the phospholipase c signaling cascade. In this signaling pathway, hydrolysis catalyzed by phospholipase c releases inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol.
- Phosphorylation of PIP_2 produces PIP_3, which helps recruit proteins in signaling cascades. Dephosphorylation of PIP_3 by phosphatase PTEN yields PIP_2.
- Plasmalogens are glycerophospholipids with a vinyl ether linkage at position 1 of glycerol, in contrast to other glycerophopsholipids, which have an ester linkage at this position. They are abundant in heart and nerve tissue (30% of total) and 70% of the ethanolamine lipids of the myelin sheath of nerve cells are plasmalogens.
- Lecithin is a generic term referring to many different lipids.
- Sphingolipids are synthesized from palmitic acid and serine. They are named for the amino alcohol known as sphin-

gosine, though they are not directly synthesized from it.

- Addition of a fatty acid to a simple sphingolipid creates a ceramide. If a phosphoethanolamine is added to the ceramide, sphingomyelin is made. It is an important component of the myelin sheath of nerve cells.

- If a simple sugar is added instead of phosphoethanolamine, a cerebroside is created and if a complex sugar is added, then a ganglioside is created.

- Sphingolipids are abundant in plasma membranes, but almost completely absent from mitochondrial and endoplasmic reticulum membranes.

- Fatty acids with 20 carbons, such as arachidonic acid, dihomo-γ-linolenic acid, and eicosapentaenoic acid are precursors of eicosanoids. Important ones include the prostaglandins, prostacyclins, thromboxanes, leukotrienes, lipoxins, and endocannabinoids.

- Prostaglandins are derived from arachidonic acid by action of cyclooxygenase enzymes (also called COX enzymes). The molecules have numerous, often conflicting physiological effects, such as constriction or dilation of vascular smooth muscle cells, induction of labor, regulation of inflammation, and action on the thermoregulatory center of the hypothalamus to induce fever, among others.

- Thromboxanes and prostacyclins are made from prostaglandins and the three are collectively known as prostanoids.

- Interesting prostaglandins include PGD_2, PGE_2, PGH_2, $PGF_{2\alpha}$, and PGI_2.

- Thromboxanes play roles in blood clotting. They are potent vasoconstrictors and facilitate platelet aggregation.

- Thromboxanes are synthesized from PGH_2 and can be reduced (blood thinning) by aspirin, which inhibits synthesis of prostaglandins from arachidonic acid.

- Prostacyclin is also known as PGI_2. It counters the effect of thromboxanes and is also made from PGH_2 by prostacyclin synthase.

- Leukotrienes are eicosanoids (from arachidonic acid) that are involved in regulating immune responses. Leukotrienes are found in numerous immune system cells. They can trigger contractions of the smooth muscles of bronchioles and may play a role in asthma and allergic responses.

- A fat is a triacylglycerol that is a solid at room temperature, whereas an oil is a triacylglycerol that is a liquid at room temperature. Increasing amounts of unsaturated fatty acids and shorter fatty acids lower the melting point of a fat.

- Adipocytes are cells specialized to store fats/oils.

- Lipases catalyze release of fatty acids from fats/oils by hydrolysis.

- Cholesterol provides membrane flexibility. It is made in many cells, but the most is made in the liver.

- The pathway responsible for cholesterol biosynthesis is known as the isoprenoid pathway. This path also leads to synthesis of other molecules, including fat soluble vitamins.

- Movement of lipids in the body is problematic due to their hydrophobic nature and the aqueous environment in which they must travel. This occurs in lipoprotein complexes made mostly in the liver and lymph system. They include chylomicrons (from small intestine), VLDLs, IDLs, LDLs, and HDLs. The last four are made in the liver.

- LDLs contain the highest concentration of cholesterol and they enter the cell via receptor-mediated endocytosis.

- Cholesterol is made into bile acids by the liver for excretion in the bile. Bile acids also help with emulsification of fats.

- Levels of *trans* fats in the diet correlate with incidence of coronary artery disease.

- Cholesterol is recycled through the digestive system. Plant equivalents of cholesterol called phytosterols compete with cholesterol in the recycling system and may lower body levels of cholesterol.

- LDLs are referred to as "bad" cholesterol because they are associated with atherosclerosis. HDLs are called good cholesterol because their levels correlate with removal of arterial debris (including cholesterol). They also help to reduce inflammation.

- Cholesterol acts an insulator for the transmission of signals in nerve tissue. It helps to manage fluidity of membranes over a wide range of temperatures and reduces the membrane's permeability. It also helps with the structure of lipid rafts in the membrane.

- Vitamin A is a fat soluble vitamin that comes in three forms - retinol (alcohol), retinal (aldehyde), and retinoic acid (acid).

- Retinol is the storage form. Retinal has a role in vision, and retinoic acid aids in stem cell differentiation through the retinoic acid receptor.

- Vitamin A is made from β-carotene. Vitamin A (retinal) is light sensitive with double bonds that isomerize (*cis-trans*) when exposed to light. Bound to a protein (rhodopsin), it initiates a nerve signal that results in detection of light by rod and cone cells in the eyes.

- Deficiency of vitamin A can result in blindness and excess vitamin A can result in death.

- Vitamin D is necessary for proper absorption of calcium and phosphorus from the diet. It behaves like a hormone and is made from cholesterol.

- Exposure of a vitamin D precursor to ultraviolet light is necessary for making an intermediate in the vitamin's synthesis.

- Vitamin D acts through a specific receptor.

- Vitamin E is a collection of stereoisomers of two compounds - tocopherols and tocotrienols that act as antioxidants.

- Vitamin E works via the glutathione peroxidase system to limit chain reactions involving lipid peroxidation in membranes. It also reduces levels of reactive oxygen species.

- After taking electrons from oxygen radicals, Vitamin E is recycled back to its original

form by a hydrogen donor - sometimes Vitamin C.

- Vitamin E can also can inhibit action of protein kinase C in smooth muscle and activate catalysis of protein phosphatase 2A to remove phosphates, stopping smooth muscle growth.

- Deficiency of vitamin E reduces the efficiency of nerve signals, can lead to low birth weights and premature deliveries.

- Excess vitamin E can reduce vitamin K levels, thus reducing the ability of the body to clot blood.

- Vitamin E may also protect by reducing harmful oxidation of LDLs - a step in atherosclerosis.

- Vitamin K also comes in multiple forms. It is used as a co-factor for enzymes that add carboxyl groups to glutamate side chains of proteins to increase their affinity for calcium. This is important in blood clotting. Proteins affected include blood proteins such as prothrombin (called Factor II), Factors VII, IX, and X, as well as proteins involved in bone metabolism - osteocalcin, also called bone Gla protein (BGP), matrix Gla protein (MGP), periostin and others.

- One strategy of blood thinning drugs (non-aspirin) is to interfere with vitamin K's role in carboxylating prothrombin. Warfarin is one such compound.

- Vitamin K is found abundantly in green, leafy vegetables. Vitamin K_1 is called phylloquinone, but has low bioavailability. Vitamin K_2 is produced by bacteria in the gut and is the primary source of the vitamin.

- Steroid hormones are all made from cholesterol and are grouped into five categories - mineralocorticoids (water/electrolyte balance), glucocorticoids (modulating immune system), progestagens (pregnancy maintenance), androgens (male sex hormones), and estrogens (female sex hormones).

- Cortisol is an important glucocorticoid with cardiovascular, metabolic, and immunologic functions.

- Progesterone is an important progestagen. It is produced primarily in the diestrus phase of the estrous cycle by the corpus luteum of mammalian ovaries.

- Androgens stimulate development and maintenance of male characteristics in vertebrates. Testosterone, dihydrotestosterone, and androstenedione are important androgens

- Estrogens are made from androgens. They play important roles in menstrual and estrous cycles by activating estrogen receptors inside of cells. These receptors, in turn, affect expression of many genes.

- Major estrogens and their primary times of importance include estrone (menopause), estradiol (reproductive years), and estriol (pregnancy).

- Estrogens are made from androgens by action of an enzyme known as aromatase. Inhibition of aromatase by specific aromatase inhibitors is used to stop estrogen production and is a strategy for stopping estrogen-responsive tumors.

- Cannabinoids are biochemicals that act on brain receptors to repress neurotransmitter release.

- Endocannabinoids are cannabinoids made in the body, whereas phytocannabinoids are made in plants, such as marijuana.

- Anandamide is an endocannabinoid neurotransmitter derived from arachidonic acid. It has roles in stimulating eating/appetite, as well as affecting motivation and pleasure. It may be responsible for "runner's high". It is found in chocolate.

- Lipoxins are eicosanoids that modulate immune responses and have anti-inflammatory effects - signaling the end of the inflammation response.

- Heme has a large heterocyclic aromatic ring known as a porphyrin ring with a ferrous (Fe^{++}) ion in the middle. It is a prosthetic group for proteins that include the globins (hemoglobin and myoglobin), cytochromes, catalase, and succinate dehydrogenase.

- Porphobilinogen is a pyrrole molecule involved in porphyrin metabolism. It is acted upon by the enzyme porphobilinogen deaminase. Deficiency of this enzyme can result in porphyria - accumulation of porphobilinogen in the cytoplasm of cells. It can cause temporary madness and may be the source of the vampire legend.

- Phosphorylated dolichols play central roles in the N-glycosylation of proteins in the endoplasmic reticulum. A membrane-embedded dolichol pyrophosphate is a point of attachment for oligosaccharides to be built for later transfer to target proteins. Sugars involved include glucose, mannose, and N-acetylglucosamine.

- Terpenes are non-polar molecules made from isoprene units (mostly by plants and some insects). They are common components of plant resins and help to protect against insects.

- The flavor of hops comes from terpenes.

- Dimethylallyl pyrophosphate and isopentenyl pyrophosphate are the two isoprenes used to make terpenes.

- Terpenes and terpenoids are classified according to how many isoprene units they contain. They are as follows - hemiterpenes (one unit), monoterpenes (two units), sesquiterpenes (three units), diterpenes (four units), sesterterpenes (five units), triterpenes (six units), sesquarterpenes (seven units), tetraterpenes (eight units), polyterpenes (many units).

- Common terpenes include terpineol (lilacs), limonene (citrus), myrcene (hops), linalool (lavender), and pinene (pine). Higher order terpenes include lycopene (tetraterpenes), carotenes (tetraterpenes), and natural rubber (polyterpenes).

- Caffeine is the world's most consumed psychoactive drug. It is closely related to adenine and guanine and this is responsible for many effects on the body. Caffeine blocks binding of adenosine to a receptor, preventing drowsiness.

- Caffeine crosses the blood-brain barrier and stimulates release of neurotransmitters. It inhibits phosphodiesterase and causes cAMP levels to rise, thus stimulating breakdown of glycogen and an increase in blood glucose. It inhibits TNF-α and leukotriene synthesis, which results in reduction of inflammation and innate immunity.

- Lipoprotein complexes are combinations of apolipoproteins and lipids bound to them that solubilize fats and other non-polar molecules, such as cholesterol, allowing them to move in the bloodstream.

- From highest density to lowest they are high density lipoproteins (HDLs), Low Density Lipoproteins (LDLs), Intermediate Density Lipoproteins (IDLs), Very Low Density Lipoproteins (VLDLs) and the chylomicrons. The particles are synthesized in the liver and small intestines.

- The apolipoproteins ApoC-II and ApoC-III are found in all of the complexes and respectively activate or inactivate lipoprotein lipase.

- ApoE helps to predict the likelihood of the occurrence of Alzheimer's disease in a patient.

- ApoB-48 and ApoB-100 are coded by the same gene, but a unique mRNA sequence editing event occurs that converts one into the other. This is a deamination of the cytosine base in nucleotide #2153. It changes C to a U and changes the codon it is in from CAA (codes for glutamine) to UAA (stop codon). The enzyme for the deamination is only present in small intestine. Thus ApoB-100 is made for chylomicrons and ApoB-48 is made for VLDLs by the liver.

- Three relevant pathways for moving lipids in the body are 1) the exogenous pathway; 2) the endogenous pathway, and 3) the reverse transport pathway.

- Dietary lipids take the exogenous pathway. These get emulsified by bile acids, pass through intestines, get packaged in chylomicrons, pass through the lymph system and enter the bloodstream.

- In the bloodstream, lipoprotein lipase breaks down the fats causing the chylomicrons to shrink and become what are known as chylomicron remnants. These are absorbed by the liver to end the exogenous pathway.

- The endogenous pathway begins with packaging of lipids into VLDLs which enter the bloodstream and travels to muscles/tissues where lipoprotein lipase cleaves fatty acids from fats. These get oxidized in muscle cells or rebuilt into fats in adipocytes. VLDLs shrink to IDLs and LDLs. Cholesterol is unaltered in this process so the cholesterol concentration increases with each shrinkage of the complexes.

- The LDLs are comprised primarily of lipids and ApoB-100. This latter protein is bound by cellular receptors for binding and internalization by the process of receptor-mediated endocytosis. LDLs not internalized by cells return to the liver where they are bound by a liver LDL receptor and internalized. The more LDLs making it back to the liver, the fewer VLDLs will be released by the liver. This ends the endogenous pathway.

- HDLs play important roles in the last lipid movement pathway - the reverse transport pathway. HDLs are synthesized in liver and small intestine with little or no lipid. They scavenge cholesterol from remnants of lipoprotein complexes (sometimes damaged) in the blood. The cholesterol causes the HDL to swell and it returns with its load to the liver where it is internalized. This ends the reverse transport pathway.

- The role of liver LDL receptors in managing LDL and cholesterol levels is critical. Non-functioning receptors leads to a condi-

tion known as familial hypercholesterolemia - dangerously high LDL levels due to the fact that the liver gets no LDLs returned to it, so it continues to release large quantities of VLDLs.

- Because of the fact that high LDL levels correlate with increased incidence of atherosclerosis, LDLs are know as bad cholesterol, whereas HDLs are known as “good” cholesterol, since it has the effect of reducing cholesterol and damaged LDLs from the blood stream.

- Foam cells arise when macrophages take up damaged LDLs. Damage may commonly arise from oxidation by reactive oxygen species arising from smoking. Foam cells are the beginnings of formation of atherosclerotic plaques.

- The lipoprotein ApoE comes in four different forms - E1, E2, E3, and E4. People homozygous for the E4 allele are 15 times more likely to contract Alzheimers disease. The cause of the association is not known.

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To the tune of "*She'll Be Comin' 'Round the Mountain*"
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Oh the students taking BB 350 - 350
Have an awful lot of things that we must know - 350
With acetic acid buffer
Kevin Ahern makes us suffer
The exams could not be tougher 3-5-0 – 350

There's amino acid side chains to recall - 350
And the things it takes to make cholesterol - 350
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I'm becoming alcoholic 3-5-0 -350

There must be a way to jam into my head - 350
All the metabolic enzyme names I dread - 350
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Where the endonucleases
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I must find a way to make a better grade
Or my GPA will truly get waylaid
I shall overcome frustration
To achieve my aspiration
On the last examination 3-5-0, 350

Here's the plan I made to help me to succeed
Fill the notecard with the knowledge I will need
I've put all of Ahern's quotes
Along with what each one denotes
Onto a massive stack of notes for 3-5-0, 350

So there's just one teensy problem I must fix
It requires some very skillful penman tricks
Squeezing info I must store
Onto the card he gave before
Will mean a font the size of zero point one four

Oh the students taking BB 350 - 350
Have an awful lot of things that we must know - 350
With acetic acid buffer
Kevin Ahern makes us suffer
The exams could not be tougher 3-5-0 – 350

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Point by Point: Membranes

Basic Concepts

- Cell membranes contain cholesterol, proteins, glycolipids, glycerophospholipids, and sphingolipids.
- Lipid bilayers form spontaneously when glycerophospholipids, and sphingolipids are mixed in an aqueous solution.
- Water, CO_2, CO, and O_2 move efficiently across the lipid bilayer. Other molecules don't move so readily and require proteins/energy to assist their movement.
- Cells need energy, export of wastes, and osmotic balance. They create chemical/ion gradients for energy purposes.
- When energy is required to move a substance across a membrane, the process is called active transport.
- Facilitated diffusion is driven by the process of diffusion and occurs through specific cellular channels made of protein.
- Surrounding cells are plasma membranes and (in some cases) cell walls.
- Bacteria, fungi, and plants all have cell walls in addition to plasma membranes.

Animal cells only have a plasma membrane.

- All plasma membranes contain amphiphilic substances, such as glycerophospholipids and sphingolipids.

- Glycerophospholipids are based on glycerol. They have two fatty acids esterified to it and the third position has a phosphate (making phosphatidic acid) to which something else is often esterified - serine, ethanolamine, choline, or inositol (making a phosphatidyl compound, such as phosphatidylserine).

- Cells tend to have more negative charges on the exterior half of the lipid bilayer (outer leaflet) and more positive charges on the interior half (inner leaflet).

- Sphingolipids are named for sphingosine, which they resemble. Attachment of a phosphoethanolamine or phosphocholine creates a sphingomyelin.

- Most sphingolipids, however, lack a phosphorylated molecule and instead have a simple sugar (cerebrosides) or a complex set of them (gangliosides).

- Glycerophospholipids and sphingolipids each have components in which one end is polar and the other is non-polar (amphiphilic).

- The components arrange themselves in aqueous solutions in a bilayer with the non-polar portions aligning in the middle of the bilayer and the polar portions projecting out on either side interacting with water.

- Plasma membranes have biases in the constituents of the inner and outer layers of the bilayer. Some, like phosphatidylcholine and sphingomyelin are predominantly found in the outer leaflet of the bilayer and others like phosphatidylserine and phosphatidylethanolamine predominate in the inner leaflet.

- Such specific arrangements are important in apoptosis (programmed cell death). Movement of biased lipids from one leaflet to another occurs during this process and may be a signal.

- Molecules with sugars attached almost always have the sugars arranged on the outside of the cell.

- Cellular organelles in eukaryotes also have biases of composition of their membrane lipids. Cardiolipin, for example, isn't commonly found in the plasma membrane or that of the endoplasmic reticulum, but is common in other organelle membranes.

- Lipids typically move freely within the layer in which they are found (called lateral diffusion), but rarely "flip" from one side to the other (transverse diffusion) without the assistance of an enzyme.

- Enzymes catalyzing transverse diffusion of membrane lipids include flippases (move from outer leaflet to inner leaflet); flippases (move from inner leaflet to outer leaflet), and scramblases (move both directions).

- Cholesterol and proteins are other important components of the lipid bilayer.

- Cholesterol is also a metabolic precursor of bile acids, and steroid hormones.

- Cholesterol influences membrane fluidity.

- Membrane fluidity is also influenced by the fatty acids within it - long and more saturated fatty acids favor higher T_m values. The T_m is the midpoint of the transition between more fluid and more solid characteristics of the lipid bilayer.

- Cholesterol does not change the T_m. Rather, it widens the range of that transition temperature.

- Cholesterol is found abundantly in membrane structures called lipid rafts. These are membrane sub-structures that are more organized that the surrounding material and often contain lipids with more saturated fatty acids and up to 5 times the amount of cholesterol. They are also rich in sphingolipids, which appears to help cholesterol to fit better into the structures.

- Prenylated proteins, such as Ras, may be excluded from lipid rafts.

- Lipid rafts may provide concentrating platforms after individual protein receptors bind to ligands in signaling and protect them from being altered (dephosporylation, for example).

- The lipid bilayer is an effective barrier to the movement of most molecules.

- Membrane proteins play roles, in some cases, with transport of molecules across the bilayer. Proteins occupy (typically) about 30-75% of the weight of a lipid bilayer.

- An integral membrane protein completely spans from one side of the bilayer to the other and often projects out from both sides. These transmembrane proteins can be 1) docking sites to the extracellular matrix; 2) as receptors of chemical signals; or 3) facilitators of the transport of molecules in or out of the cell.

- Peripheral membrane proteins interact with part of the bilayer, but do not project through it.

- Associated membrane proteins do not have hydrophobic regions and do not embed in any part of the lipid bilayer, but are found near them as a result of interaction with other proteins or molecules in the bilayer.

- Anchored membrane proteins are not embedded in the layer, but instead are attached to a non-polar molecule that is embedded in the membrane.

- Integral and anchored membrane proteins are categorized into six different types. Type I has one portion of the protein traversing the lipid bilayer. The protein's amino terminus is on the outside and the carboxy terminus is on the inside. Type II membrane proteins have this reversed. Type IIIs have a single chain that crosses the membrane multiple times to form a channel. Type IVs have multiple chains that cross multiple times. Type Vs do not cross the membrane but are anchored to something in the membrane. Type VIs have a part that crosses and they are anchored.

- Glycoproteins embedded in membranes play important roles in cellular identification. Blood types differ from each other in the structure of the carbohydrate chains projecting out from the surface of the glycoprotein in their membranes.

- The permeability of water across a lipid bilayer and the impermeability of materials inside the cell create osmotic pressure

- Osmotic pressure is a measure of the tendency of a solution to take in water by the process of osmosis.
- The osmotic pressure of a solution is the pressure difference needed to halt the flow of solvent across a semipermeable membrane.
- $P_{osmotic}$ = MR*T where M is the molarity of the dissolved molecules, R* is the gas constant expressed in (L atm)/(K mol), and T is the temperature.
- A hypotonic situation occurs if the concentration of solutes is greater inside the cell than outside. Water will tend to move into the cell, causing the cell to swell.
- It is hypertonic if the solute concentration is greater outside the cell than inside of it. Then water will exit the cell and the cell with shrink.
- When the concentrations of solutes inside and outside of the cell is equal, this is called an isotonic solution - no change will occur.
- If the osmotic pressure is greater than the forces holding together a cellular membrane, the cell will rupture. Cell walls resist rupturing due to osmotic stresses.

Membrane Transport

- Cells must internalize nutrients from their environment.
- A protein involved in moving only one molecule across a membrane is called a uniport.
- Proteins that move two molecules in the same direction across a membrane are called symports.
- If two molecules are moved in opposite directions across the bilayer, the protein is called an antiport.
- Proteins involved in moving ions are called ionophores.
- Electrogenic transport involves movements that result in a net change of charge.
- Electroneutral transport involves movements that result in no net change of charge.
- If simple diffusion is the driving force, the process is called facilitated diffusion and if the process requires other energy input, the process is active transport.
- Channels largely provide openings with some specificity and molecules pass through them at close to the rate of diffusion. Examples include sodium and potassium channels.
- Transporters have high specificity and transfer rates that are orders of magnitude slower than channels. An example is the Na+/K+ ATPase.
- At the end of the process of facilitated diffusion, molecular concentrations on either side of a lipid bilayer will be equal if nothing else is done.
- The ion channels are membrane proteins forming pores in cell membranes to regulate movement of selected ions across a membrane.
- Ion channels help to establish the resting membrane potential and to affect action

potentials and other electrical signals. They are important in nerve transmission.

- Ion channels are controlled by mechanisms that include voltage, ligands, light, temperature, and mechanical deformation.
- Ligand-gated ion channels (LGICs) are transmembrane proteins which open to selectively allow ions such as Na^+, K^+, Ca^{++}, or Cl^- to pass through the membrane in response to the binding of a ligand messenger.
- Sodium ion channels in the tongue for sugar receptors open in response to binding of sucrose, initiating a nerve signal.
- Calcium gates in the eye are open by default, but stimulation by light causes them to close, triggering a series of events that result in a signal being sent the brain about the perception of light.
- Voltage gated channels are essential for transmission of nerve signals.
- Ion channels selectively allow ions to pass based on 1) size and 2) energy of dehydration/hydration.
- Sodium channels exclude potassium ions on the basis of size, but potassium channels exclude sodium ions based on unoptimal orientation of the sphere of water around sodium ions. The potassium channel is perfectly set up for the hydration shell around potassium ions, thus making dehydration of potassium on entering the channel optimal and energetically favorable when exiting the channel, but for sodium ions, the energy of rehydration is insufficient to make dehydration of the sodium ions energetically favorable. As a result potassium ions selectively pass through a channel even though they are bigger than sodium ions.
- Ionic balance is important for cells. If the ionic balance of a cell is sufficiently disturbed by an uncontrolled ionophore, a cell may die.
- Gramicidin is an antibiotic peptide made by a soil bacterium. It is an ion channel that gets inserted in to a target cell and kills it by allowing sodium to leak in.
- Transporter proteins are slower than ion channels. They use conformational changes to move ions.
- An active transport system moves at least one molecule against a concentration gradient.
- The energy source for active transport is frequently, but not necessarily ATP. The sodium-glucose transporter, for example, uses a sodium concentration gradient to move glucose into the cell.
- The Na+/K+ ATPase is an electrogenic antiport that moves three sodium ions out of the cell and two potassium ions in the cell with every cycle of action. Each movement is against a concentration gradient. ATP is the energy source. The pump is important for balancing osmotic pressure.
- The cycle goes as follows - 1) binding of three Na^+ in the cytoplasm; 2) phosphorylation of aspartate on the pump by ATP hydrolysis; 3) conformational change of pump releases Na^+ to outside; 4) two K^+ ions bind from outside; 5) dephosphorylation of pump inverts pump pushing K^+ in.
- The Na+/K+ ATPase is a P-type ATPase.

- ATPases are put into five categories. Some work in reverse and make ATP instead of breaking it down.

1. F-type - mitochondrial, chloroplasts, bacterial membrane. A proton gradient is energy source for making ATP. Complex V of mitochondria is an F-type ATPase.

2. V-type - Uses ATP to pump protons into vacuoles and lysosomes

3. A-type - found in archaeans. Similar to F-type ATPases in function.

4. P-type - bacteria, fungi, eukaryotic membranes, and organelles. Use ATP and phosphorylated aspartate to move ions across membranes

5. E-type - found on cell surfaces. Hydrolyze extracellular nucleoside triphosphates.

- The Na+/glucose transporter is an electrogenic symporter that moves glucose into intestinal cells. The sodium ion gradient is the energy source. Referred to as a secondary active transport system.

- Calcium pumps in the plasma membrane and organelle membranes pump calcium and keep cytoplasmic concentration of it low. ATP or a sodium gradient is typically the energy source.

- Opening of calcium channels allows calcium to quickly flow into the cytoplasm to facilitate muscular contraction and/or signaling.

- The sodium/calcium pump relies on a sodium gradient for energy to move calcium out of a cell. It is an electrogenic antiport.

- When heart cells are treated with digitalis (blocks Na+/K+ ATPase), the sodium gradient is significantly reduced. As a consequence, less sodium gets pumped out of the heart cells. Since calcium stimulates muscular contraction, the heart cells are stimulated to be harder due to the higher concentration of calcium on digitalis treatment. Digitalis is used to treat congestive heart failure.

- ABC transporters are a class of transport proteins that move lipids, sterols, and drugs across membranes.

- Some ABC transport proteins can provide resistance to antibiotics in bacteria as well as resistance to chemotherapy in higher cells by exporting drugs used to treat both of these types of cells.

- There are 3 groups of ABC transporters - 1) importers; 2) exporters; and 3) non-transporters that function in DNA repair and translation.

- All ABC transporters have two membrane domains and two cytoplasmic domains and they flip between opening to cytoplasm and the extracellular space in response to ATP hydrolysis.

- The protein implicated in cystic fibrosis (CFTR) is an ABC transporter.

- It normally moves chloride and thiocyanate ions across epithelial tissue membranes exerts its effect mostly in the lungs.

- Manifestations of the disease arising from lack of CFTR function include breathing difficulty and overproduction of mucus in the lungs.

- Lactose permease facilitates the movement of the sugar lactose across the lipid bilayer of the cell membrane.
- Glucose Transport Proteins (GLUTs) are uniport, type III integral membrane proteins that facilitate transport of glucose into cells.
- The one in red blood cells is known as GLUT 1 and has 12 membrane-spanning hydrophobic helices.
- GLUT 4 is regulated by insulin and is found primarily in adipose and striated muscle tissue.
- Insulin acts to stimulate uptake of glucose by cells by favoring movement of various GLUT proteins (including GLUT 4) from intracellular vesicles to the cell membrane.
- Once inside the cell, phosphorylation of glucose by hexokinase prevents it from exiting via GLUTs.

Other Considerations

- Another means of getting material into cells is by endocytosis. This method tends to move particles, some of which are larger than could be transferred via a transporter protein.
- Materials entering this way include LDLs, iron packaged in transferrin, vitamins, hormones, proteins, and some viruses.
- Receptor mediated endocytosis uses a specific cell receptor called clathrin that binds to particles with a binding site for it.
- Cellular structures lined with clathrin are called coated pits.
- ApoB-100 of LDLs binds to clathrin and is internalized and gets targeted to the early endosome for sorting and processing of contents.
- In signaling, internalization of bound receptors may result in a response in the nucleus. It can also serve to reduce the number of receptors on the surface and thus reduce the amount of signaling.
- Other types of endocytosis include 1) caveolae-based endocytosis; 2) macropinocytosis; and 3) phagocytosis.
- Caveolae-based endocytosis uses a an integral membrane protein receptor called caveolin that creates cave-like structures in a plasma membrane.
- Caveolins appear to be involved in cellular migration.
- Caveolins inhibit cancer-related growth factor signaling pathways, but can also lead to metastasis.
- Macropinocytosis literally involves a cell invaginating and “taking a gulp” of the extracellular fluid, creating a tiny vesicle. This internalized vesicle will fuse with endosomes and lysosomes. The process is non-specific for what is internalized.
- In phagocytosis, relatively large particles are internalized.
- Cells of the immune system use this to internalize debris, apoptotic cells, and microbes.
- It uses specific cell surface receptors and the internalize structure is called a phagosome. The phagosome merges with lysosome to create a phagolysosome which

gets exposed to toxic materials to kill any contents.

- Non-phagocytic internalizations target incoming material to endosomes. They provide a sorting function and can receive materials from the *trans*-Golgi network. Materials can be delivered to lysosomes or targeted to the Golgi apparatus. There are three forms of endosomes - early, late, and recycling.

- Exocytosis is used to expel materials that won't easily pass through the plasma membrane. Within the cytosol, this internalized vesicle will fuse with endosomes and lysosomes. A a result of the fusion, contents in the membrane of the vesicles become part of the plasma membrane.

- Membrane fusion is important for both endocytosis and exocytosis and occurs when two distinct lipid bilayers merge their hydrophobic cores, producing one interconnected structure.

- Processes involving membrane fusion include fertilization of an egg by a sperm, separation of membranes in cell division, transport of waste products, neurotransmitter release, fusion of artificial liposomes to cells, and entry of pathogens.

- Fusion of vesicles in exocytosis is mediated by proteins known as SNAREs (Soluble NSF Attachment Protein REceptor).

- SNARE proteins that facilitate fusion of vesicles to release neurotransmitters can be targeted and proteolytically cleaved by neurotoxins in botulism and tetanus.

- v-SNAREs are found in the membranes of transport vesicles during the budding process, whereas t-SNARES can be found in the membranes of targeted compartments.

- Fusion in neurotransmission results in release of intracellular calcium due to activation of voltage-dependent calcium channels in the targeted cell. Calcium further helps to stimulate the fusion.

- During the fusion process, v- and t-SNAREs "zipper" themselves together to bring the membrane vesicle and the target membrane closer together. Zippering also causes flattening and lateral tension of the curved membrane surfaces, favoring hemifusion of the outer layers of each membrane. Continued tension results in subsequent fusion of the inner membranes as well, yielding opening of the contents of the vesicle chamber to its target.

- Shuttles are another way to move materials across membranes.

- Electrons from NADH are shuttled across the mitochondrial inner membrane using the glycerol-phosphate shuttle or the malate-aspartate shuttle.

- In the glycerol-phosphate shuttle, electrons from NADH are donated to DHAP to create glycerol-3-phosphate, which gets moved across the inner mitochondrial membrane by a transport protein.

- Inside the mitochondrial matrix, glycerol-3-phosphate donates electrons to FAD to make $FADH_2$ and DHAP. FADH2 does not pump as many electrons in the electron transport system as NADH, so the system is not 100% efficient.

- In the malate-aspartate shuttle, inefficiency is not a problem - starting with

NADH and ending with it. In this shuttle, NADH donates electrons to oxaloacetate to create malate, which gets moved across the inner mitochondrial membrane in exchange for α-ketoglutarate. In the mitochondrial matrix, malate donates electrons to NAD^+ to create NADH and oxaloacetate. The rest of the cycle involves regenerating the original starting contents about in the inter membrane space. Oxaloacetate gets an amine from glutamate and is converted to aspartate, which is moved to the intermembrane space in exchange for another glutamate. Aspartate in the cytoplasm donates an amine to α-ketoglutarate to create glutamate and regenerate oxaloacetate. Glutamate gets transported to the matrix in exchange for aspartate (same as above). In the matrix, glutamate is the source of the amino for making aspartate, creating α-ketoglutarate. α-ketoglutarate is transported to the intermembrane space in exchange for malate (above).

- Molecules can also be shuttled across membranes. An example is the acetyl-CoA shuttle across the mitochondrial membranes. In it, acetyl-CoA is joined to oxaloacetate to by citrate synthase to create citrate and a free CoASH. The citrate is transported to the cytoplasm where the reverse reaction occurs (catalyzed by citrate lyase), yielding oxaloacetate and acetyl-CoA. Oxaloacetate can make it back to the mitochondrial matrix by several means, completing the cycle.

- Cell junctions are found in three main categories - 1) gap junctions; 2) adherens junctions; and 3) tight junctions.

- In gap junctions two connexons (one on each cell) join and link the cytoplasms of each cell together. Similar structures in plants are called plasmodesmata.

- Adherens junctions are complexes on the cytoplasmic side of cell membranes that are linked to each other or the extracellular matrix. Proteins in adherens junctions include α-catenin, β-catenin, γ-catenin, cadherins, plakoglobin, actin filaments, vinculin, and α-actinin.

- Adherens junctions may help to maintain the actin contractile ring which forms in cytokinesis.

- Tight junctions seal cells together and restrict the flow of ions in the spaces between them. They restrict the movement of materials through tissues by requiring them to pass through cells instead of around them.

- Membrane proteins attached to glycosylphosphatidylinositol (also known as a GPI anchor) are referred to as being glypiated.

- Liposomes are artificial extracellular vesicles created by spontaneous formation of lipid bilayers of glycerophospholipids and/or sphingolipids in aqueous solution. Through membrane fusion, the contents of liposome vesicles can be delivered to a cell's cytoplasm.

- Amino acids in integral membrane proteins must have hydrophobic R-groups in the region(s) of the protein crossing the lipid bilayer. From analysis of the hydropathy index of a protein sequence, a computer can readily identify potential membrane-crossing regions of a protein. Assisting that analysis is the fact that tryptophan or tyrosine is commonly positioned

at the non-polar/polar interface of the bi-layer.

- Cell walls are found in plants, fungi, and bacteria. They provide at least some protection against bursting from osmotic pressure.

- Gram positive bacteria have the simplest ones - on the outside, there is a peptidoglycan layer, followed by a periplasmic space, a plasma membrane and then the cytoplasm.

- Gram negative bacteria have a more complicated structure with an outer lipopolysaccharide layer, a periplasmic space, the peptidoglycan cell wall, a second periplasmic space, a plasma membrane and then the cytoplasm.

- Herbaceous plants have a rigid outer cell wall primarily composed of cellulose, hemicellulose, and pectin and an inner plasma membrane. Woody plants add lignin between the cellulosic wall and the plasma membrane of herbaceous plants.

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The *E. coli* Song

To the tune of "*Rudolph the Red-Nosed Reindeer*"

Metabolic Melodies Website HERE

E. coli's very simple
That's the way the story goes
But if you worked around it
You would probably hold your nose

Most of the other cell types
Have a mitochondrion
They use to make triphosphates
By phos-phor-y-la-she-un

When there is no oxygen
Coli's got it made
Glucose breakdown products all
Wind up making ethanol

Then all the cells around it
Shout *E. coli's* name with glee
"You make us feel light-headed"
"When you act fermentally"

Recording by Tim Karplus
Lyrics by Kevin Ahern

Point by Point: Catalysis

Basic Principles

- Enzymes are protein catalysts that speed reactions enormously.
- Catalysts lower the magnitude of the energy barrier for a reaction without changing the overall energy. The energy barrier they help to overcome is the activation energy.
- At equilibrium, the concentration of products and reactants will not change over time.
- At equilibrium, the concentration of products and reactants will not be equal unless the value of $\Delta G^{\circ\prime}$ is zero.
- All reactions move in the direction of equilibrium.
- Enzymatic reactions have substrates (reactants) and products.
- The part of an enzyme where catalysis occurs is called the active site.
- In metabolic pathways, the product of one reaction is the substrate of the next reaction.

- Activation energy is the amount of energy that must be put into a reaction in order for it to begin.
- Non-catalyzed (non-enzymatic) reactions have higher activation energies than catalyzed (enzymatic) reactions.
- The overall ΔG for a reaction does not change when a reaction is catalyzed compared to an uncatalyzed reaction.
- The extent of a reaction proceeding forward is a function of the size of the energy difference between the product and reactant states. The lower the energy of the products compared to those of the reactants, the greater percentage of products that will be present at equilibrium.
- All reactions are theoretically reversible.
- When a product, such as CO_2 is volatile, it can make reversibility less likely.
- Removal of products tends to "pull" reactions forward. Addition of reactants "pushes" reactions forward.
- Enzymes differ from chemical catalysts (such as platinum) in being flexible. Flexibility allows movement and movement facilitates alteration of electronic environments necessary for catalysis. Koshland's induced fit model reflects this flexibility. It states that not only do enzymes change substrates, but substrates also transiently change enzymes. At the end of a reaction, though, an enzyme goes back to its original state.
- The Fischer lock and key model contrasts with Koshland's model in saying only that an enzyme fits its substrate like a lock fits a key. It makes no note of the flexibility of an enzyme.
- Two distinct structural states are described for enzymes. The T-state is the "tight" state and in this state, the enzyme will bind less substrate and be much less able to catalyze reactions. The R-state (R=relaxed) is a state where the enzyme is better able to bind substrate and is much more active.
- Reactions can be a) one substrate/one product; b) one substrate/multiple products; c) multiple substrates/one product; or d) multiple substrates/multiple products.
- For multiple substrate reactions, there are two ways in which substrate can sequentially bind - ordered or random. In ordered binding, one substrate must bind first or the other one will not bind. In random binding, it doesn't matter which one binds first.
- Ordered binding is consistent with the Koshland model because binding of the first substrate is likely needed to cause the enzyme to change shape in order to allow binding of the second one.
- Lactate dehydrogenase exhibits ordered binding and creatine kinase exhibits random binding.
- A third mechanism for handling multiple substrate reactions is that of double displacement (or ping-pong) reactions. In this case, the enzyme exists in two states. The first state is necessary for the reaction of the second state to occur. Transaminases exhibit ping-pong kinetics with the enzyme ferrying oxygen or an amine between two different molecules.

- Enzymatic reactions proceed as E + S ⇄ ES -> E + P. The ES state is actually more complicated and could be written as E + S ⇄ ES -> ES* -> EP -> E + P

- To study an enzymatic reaction, two parameters are considered - velocity and affinity of the enzyme for substrate. Reactions are started with substrate and enzyme only (no products). Velocity is measured by concentration of product over time.

- To measure velocity most accurately, Michaelis-Menten kinetics conditions are employed. The involves

- 1) measuring initial velocities (V_0) before product has a chance to accumulate (which would favor the reverse reaction and reduce the apparent velocity). Mathematically, V_0 = [Product]/time of reaction

- 2) using substrate in great excess to enzyme

- 3) reaction conditions corresponding to steady state

- In steady conditions, [E] and [ES] are not changing much over the time of the reaction.

- In pre-steady state conditions, [E] is rapidly decreasing and [ES] is rapidly increasing. Changing [ES] means reaction velocity will vary over the time of measurement.

- Enzymatic reactions get to equilibrium faster than non-enzymatic reactions, but equilibrium is nonetheless the same.

- For an enzyme obeying Michaelis-Menten kinetics (some don't), a plot of V0 vs [S] will result in a hyperbola. The top end of the hyperbola will approach a maximum value of V_0 called V_{max} (maximum velocity). At this point, the enzyme is saturated with substrate.

- To determine the affinity of an enzyme for a substrate, a quantity called K_m is calculated. Km corresponds the substrate concentration that gets an enzymatic reaction to $V_{max}/2$. The higher the value of K_m for an enzyme, the lower its affinity for its substrate. On the other hand, the lower the K_m value, the higher the affinity the enzyme has for its substrate.

- The velocity of a reaction, v, can be determined as follows:

- $$v = \frac{V_{max}[S]}{K_m + [S]}$$

- V_{max} is limiting for describing reaction velocities, since it depends on the quantity of enzyme used in a reaction. If one doubles the amount of enzyme, one will double V_{max}.

- Consequently, for comparing rates of reaction, the quantity K_{cat} is used. K_{cat} (also called turnover number) is calculated by dividing V_{max} by the concentration of enzyme used in a reaction. The numerical value obtained has units of inverse time (for example, seconds^{-1}) and corresponds to the number of molecules of product made per molecule of enzyme per second.

- As noted above, not all enzymes obey Michaelis-Menten kinetics. Examples include multi-subunit enzymes that change in such a way upon binding the first substrate molecule that binding of further substrate molecules by the same enzyme is affected (positively or negatively).

- Perfect enzymes are enzymes for which the ratio K_{cat}/K_m approaches a theoretical maximum. For these enzymes, the only thing limiting them in catalysis is the rate with which the substrate can diffuse to the active site of the enzyme.

- Not all enzymes have evolved to perfection because too much speed can be hard to control. One of the reasons perfection has evolved is to reduce the time an unstable intermediate is present, thus preventing it from having too much time to wreak havoc. Triose phosphate iosomerase is an example, catalyzing a reaction rapidly to prevent escape and accumulation of the toxic intermediate known as methyl glyoxal.

- To measure the "tightness" of binding of a ligand by a protein, the dissociation constant is calculated. Dissociation of a ligand-protein complex is given by the following equation:

- LP <=> L + P

- The corresponding dissociation constant (K_d) is

$K_d = [L][P]/[LP]$

where [L], [P], and [LP] are the molar concentrations of the protein, ligand and the complex when they are joined together.

Where multiple molecules bond together, such as

JxKy <=> xJ + yK

(complex JxKy is breaking down down into x subunits of J and y subunits of K)

the dissociation constant is then defined as

$K_d = [J]^x[K]^y/[JxKy]$

- Another way of analyzing enzyme kinetic data is to plot velocity/substrate data by the Lineweaver-Burk method. In these plots, the inverse of V_0 is plotted against the inverse of the [S].

- These so-called double reciprocal plots ($1/V_0$ vs $1/[S]$) give straight lines for enzymes following Michaelis Menten kinetics. The line of these plots, when extrapolated to the X-axis, give the value of $1/V_{max}$ as Y-intercept and the value of $-1/K_m$ as the X-intercept.

- The term molecularity refers to the number of molecules that must come together in order for a reaction to take place. Unimolecular reactions are when there is only one reactant molecule.

- For a bimolecular reaction where A + B <=> C, the reaction depends on the concentration of both A and B and its rate will be related to the product of the concentration of A and of B.

- Coenzymes are molecules that help enzymes to perform catalysis. These include both inorganic ions and organic molecules. If the latter is covalently or tightly bound to the enzyme, it is referred to as a prosthetic group.

- Enzymes lacking their co-factors are called apoenzymes.

- Not all biological catalysts are proteins. Ribozymes are catalytic RNA molecules. The most prominent of these are the 23S rRNA of prokaryotes and the 28S rRNA of eukaryotes. Each of these functions in the ribosome to catalyze the formation of peptide bonds in protein synthesis.

Control of Enzyme Activity

- The inhibition of specific enzymes by drugs can be medically useful.
- There are four types of inhibition that are of interest - competitive, non-competitive, uncompetitive, and suicide inhibition.
- Only suicide inhibition is not reversible.
- Competitive inhibition occurs when the inhibitor resembles the natural substrate of an enzyme and competes with it for binding at the active site.
- An example is methotrexate that resembles the folate normally acted on by the enzyme dihydrofolate reductase (DHFR).
- When methotrexate binds to DHFR, the enzyme is inhibited and won't function.
- However, since methotrexate and folate compete for binding to DHFR, the more one increases the amount of folate, the less methotrexate will be able to bind, meaning that the amount of inhibition will decrease. At infinite amounts of folate, the inhibition of methotrexate disappears. Thus, methotrexate has no effect on the V_{max} of the DHFR reaction though it can affect velocities at lower concentrations.
- On the other hand, at lower concentrations, methotrexate does have effects and thus causes an increase in the amount of substrate necessary to reach $V_{max}/2$. Since this is known as the K_m for an enzyme, it means that in competitive inhibition, K_m increases.
- On a Lineweaver-Burk plot, the line of the competitively inhibited reaction crosses the line of the uninhibited reaction at the Y-intercept - 1/Vmax. This makes sense, since the V_{max} of the uninhibited and the inhibited reaction is the same.
- In a study of competitive inhibition, the percentage of inhibited enzyme varies considerably over the range of [S] used. At low [S], the inhibition is highest and at very high [S], the percent of enzyme inhibited is negligible.
- Non-competitive inhibition occurs when an inhibitor acts by binding and inhibiting an enzyme at a site apart from the active site. In this case, the non-competitive inhibitor molecule will not resemble the substrate and will not compete with it for binding to the active site.
- In this case, the amount of inhibition of the enzyme is fixed by the amount of inhibitor used. This percentage will not change no matter how much substrate is added because the substrate cannot compete with the inhibitor. As noted above, V_{max} depends on the amount of enzyme. If you knock out a fixed percentage of an enzyme, you will reduce V_{max} accordingly.
- Thus, for non-competitive inhibition, V_{max} decreases.
- K_m for a non-competitive inhibition does not change, however. This is because the inhibited enzyme does not enter the picture. One can only measure K_m for uninhibited enzymes. This never changes. As a conse-

quence, K_m remains the same in non-competitive inhibition.

- Uncompetitive inhibition occurs when the inhibitor only binds and inhibits the ES complex, forming an ES-I complex. It cannot release product. ES (and ES-I) complex forms primarily under high substrate conditions. In fact, as the substrate concentration gets higher, more ES-I complex will form. This has the effect of reducing V_{max}.

- It may seem unintuitive, but K_m actually decreases. This is because ES-I reduces the concentration of ES. Reduced ES results in formation of more ES by Le Chatelier's principle. Thus, the enzyme appears to gain affinity for substrate since more ES is forming. Higher affinity for substrate translates to lower K_m.

- Suicide inhibition occurs when the inhibitor makes a covalent attachment to the active site of an enzyme, stopping all activity permanently. For this to occur, the suicide inhibitor must resemble the substrate. Thus suicide inhibition is somewhat like competitive inhibition, except that the binding of the inhibitor is permanent in suicide inhibition, but reversible in competitive inhibition.

- Penicillin is a suicide inhibitor. It binds to the enzyme known as D-D transpeptidase, which is responsible for making the bacterial peptidoglycan cell wall.

- Enzymes are controlled by 1) allosterism; 2) covalent modification; 3) access to substrate; and 4) control of enzyme synthesis/breakdown.

- Allosterism occurs when a molecule binding to an enzyme affects the enzyme's activity. This requires a multi-subunit enzyme, typically.

- Homotropic effectors are substrates for the enzyme.

- Heterotropic effectors are non-substrates.

- Homotropic effectors convert the hyperbola of a V_0 vs. [S] plot to a sigmoidal shape due to the conversion of the enzyme from the T-state to the R-state on binding the effector.

- Homotropic effectors have the same effect on enzymes as oxygen does on the cooperative binding property of hemoglobin.

- Allosteric effectors can act positively (favor R-state - increasing enzyme activity) or negatively (favors T-state - decreasing enzyme activity).

- One interesting use of allosteric control helps to regulate metabolic pathways. This is feedback inhibition, which occurs when the end product of a metabolic pathway allosterically inhibits an early enzyme in the same pathway.

- An example of feedback inhibition is cholesterol's inhibition of HMG-CoA reductase. Cholesterol is the end product of a long pathway and HMG-CoA reductase is an early enzyme in the pathway. By acting on an early enzyme, the entire pathway is stopped, along with many energy-requiring reactions so materials are not wasted.

- ATCase is another allosterically regulated enzyme. It has three effectors - ATP, CTP, and aspartate.

- ATCase is comprised of 12 subunits - 6 regulatory subunits and 6 catalytic subunits.

ATP (activates) and CTP (inhibits) bind to the regulatory subunits. They are heterotropic effectors.

- Aspartate (activates) is a substrate, so it binds to catalytic subunits. It is a homotropic effector.

- There are three models to explain how allosteric regulation occurs - 1) sequential; 2) MWC (concerted); and 3) morpheein.

- The sequential model of allosterism says that changing the configuration of one subunit of an enzyme (say T-state to R-state) causes the others to change in the same way. The sequential model is associated with cause and effect.

- The concerted model proposes that the entire multisubunit enzyme complex changes from T-state to R-state (and vice versa) independently of changes to any one unit. It also proposes that binding of an allosteric effector locks the enzyme in that state. Binding of inhibitors will tend to favor the T-state and binding of activators will favor the R-state.

- The morpheein model is the newest of the three and is similar to the concerted model. It proposes that the multi-subunit complex breaks down to individual units which each can flip T- and R-states. but that only subunits in the same state can reassociate into a larger complex (all in the same state). Again, activators will favor R-state and inhibitors will favor T-state.

- Enzymes are known exhibiting each of the models and most enzymes probably employ a hybrid of the models described here.

- A second means of controlling enzymes is covalent control. In this mechanism, covalent modifications are made to enzymes to activate or inhibit them. One category of activation is that of zymogens.

- Zymogens are inactive forms of enzymes (commonly proteases) that are synthesized in a state that requires a peptide bond to be cleaved for them to become active. Cleaving the bond may, for example, provide access to the active site.

- Zymogen control is employed for digestive proteases (trypsin, chymotrypsin, carboxypeptidase, elastase, etc) and proteases involved in blood clotting (fibrin, thrombin, etc).

- Nomenclature for zymogens involves (in many, but not all cases) addition of the suffix -ogen to the enzyme name to designate the inactive form of the enzyme and removal of the suffix to indicate the active form. Thus, trypsinogen is inactive and trypsin is active.

- Zymogens are commonly activated in cascades. This has the effect of activating a large number of enzymes very quickly as each enzyme in the cascade activates a large number of other enzymes that each continue the process. For a process like blood clotting, this is very important to occur quickly.

- Another common covalent modification is that of phosphorylation/dephosphorylation. In this system (commonly used in signaling pathways), addition of a phosphate to an enzyme either activates or inactivates it, depending on the enzyme. Phosphates are added by kinases and removed by phosphatases. ATP is typically the source of the phosphate added.

- Another covalent modification is that of reduction/oxidation. It is found in enzymes of photosynthetic plants. In it, when the NADPH concentration is high from light energy, the concentration of reduced ferredoxin increases. Ferredoxin can then reduce thioredoxin, which can further reduce disulfide bonds in the enzyme. Four enzymes of the Calvin cycle can be reduced and thus be activated by this method.

- A third means of controlling enzymes is access to substrate/substrate level control. Hexokinase is an example. it is largely regulated by availability of its substrate, glucose. When glucose concentration is low, the product of the enzyme's catalysis, glucose-6-phosphate, inhibits the enzyme's function.

- The last means of controlling enzymes is via control of their synthesis by regulation of gene expression.

Enzymes - Mechanism

- Chymotrypsin is a serine protease - a class of enzymes with several members.

- Some examples of serine proteases include trypsin, chymotrypsin, elastase, subtilisin, and signal peptidase I.

- Proteases catalyze the cleavage of peptide bonds.

- Serine proteases use a serine in their active site as part of the catalytic process.

- Serine is one of three amino acids in the protein that play critical roles in the catalysis. The three amino acids make up what is called the catalytic triad and they are serine, histidine, and aspartic acid.

- Activation of serine in the catalytic process creates a nucleophile called an alkoxide ion which attacks the peptide bond, causing it to be broken.

- Specificity of serine proteases is determined by a part of the enzyme called the S1 pocket. The S1 pocket has a geometry and/or chemical composition that allows only certain amino acid side chains to fit in it. Since the S1 pocket is adjacent to the active site, the amino acid that fits into the S1 pocket is the one where the peptide bond is broken.

- Trypsin has an aspartate (negatively charged) side chain at the bottom of its S1 pocket, favoring binding of positively charged amino acids, such as lysine or arginine.

- Chymotrypsin has a broad, non-polar S1 pocket favoring amino acids like phenylalanine and others.

- The process of catalysis of a serine protease begins with binding of a suitable amino acid in the S1 pocket. This induces a slight structural change in the enzyme (Koshland's induced fit model) causing the side chains of the catalytic triad to move closer to each other.

- The result of this is that the electron-rich imidazole ring pulls a proton from the hydroxyl side-chain of serine, creating a negatively charged alkoxide ion.

- The alkoxide ion makes a nucleophilic attack on the carbonyl carbon of the peptide bond involving the amino acid of the substrate protein bound in the S1 pocket.

This breaks the peptide bond after stabilization of the structure by another region in the active site known as the oxyanion hole.

- With the peptide bond broken, one piece of the protein is loosened and exits the active site. The other part of the protein is linked to the serine side chain via the carbonyl carbon. At this point, the fast phase of catalysis has completed.
- In the next phase of catalysis, the covalently bound peptide must be released from the serine side chain and the enzyme must be returned to its original state.
- This begins with entry of a molecule of water into the active site.
- Histidine abstracts a proton from the water, leaving a nucleophilic hydroxyl group. It attacks the carbon bound to the serine and releases it (again, after stabilization by the oxyanion hole).
- The proton on histidine returns to serine's oxygen, recreating the hydroxyl group and the process is complete.
- Serine proteases are in two broad categories - 1) chymotrypsin-like and 2) subtilisin-like. They both use the same mechanism, but are not related to each other by sequence and have evolved independently by convergent evolution.
- Cysteine proteases are related to serine proteases in mechanism of action, but instead have an active site with histidine and cysteine. In their catalytic mechanism, histidine removes a proton from cysteine's side chain to create a reactive, negatively charged sulfur ion that performs the same functions as serine's reactive, negatively charged oxygen.
- Some examples of cysteine proteases include papain, caspases, hedgehog protein, calpain, and cathepsin K.
- Caspases (Cysteine-ASPartic ProteASEs) are a family of cysteine proteases that function in apoptosis, necrosis, inflammation, and the immune system. They are known as the executioner enzymes and are synthesized in a zymogen form.
- Caspases come in two forms. Initiator caspases, when activated, activate the effector caspases. The effector caspases cleave other proteins in the cell beginning the process of cellular suicide.
- Metalloproteases use catalytic mechanisms for breaking peptide bonds involving a metal - usually zinc. In their catalytic mechanism, the bound metal abstracts a proton from water to create a nucleophilic hydroxyl group that attacks the peptide bond and causes it to fall apart, much like the second phase of serine protease action.
- Some carboxypeptidases are metalloproteases.
- Aspartyl proteases use aspartic acid in their catalytic mechanism. Like metalloproteases, they activate a water by abstracting a proton.
- Threonine proteases have a different mechanism of action than serine proteases. Like the serine proteases, they activate a hydroxyl to act as a nucleophile and attack the carbonyl carbon of a peptide bond. They are different in how the hydroxyl's proton is removed. Serine proteases use a catalytic triad, but threonine's own α-amine group is what removes the proton. To have a free α-amine group, threo-

nine must be at the N-terminus of the enzyme. Threonine proteases are found in proteasomes.

- Protease inhibitors stop the catalytic action of proteases. Mechanisms of their action include suicide inhibition, transition state inhibition, denaturation, and chelation. Metalloproteases, for example are sensitive to chelating agents like EDTA that remove their metal ion.

- A broad category of proteinaceous protease inhibitors is the serpins. These proteins inhibit serine proteases by altering their active sites. Serpins like antithrombin help to regulate the blood clotting process.

- Non-serpin serine protease inhibitors are competitive inhibitors of the active site.

- α-1-anti-trypsin (A1AT) functions in the lungs to inhibit the elastase protease. Reactive oxygen species produced by smoking can oxidize a critical methionine residue of A1AT, rendering it unable to inhibit elastase. Uninhibited, elastase can attack lung tissue and cause emphysema.

- Protease inhibitors are used as anti-viral agents to prohibit maturation of viral proteins - commonly viral coat proteins.

- Protease inhibitors are part of drug "cocktails" used to inhibit the spread of HIV in the body and are also used to treat other viral infections, including hepatitis C.

Blood Clotting

- Blood clotting is a process in which liquid blood is converted into a gelatinous substance which hardens.

- Steps in the process include 1) activation (wounding); 2) a cellular response (aggregation of blood platelets) and 3) a molecular response (polymerization of fibrin to create a meshwork that hardens).

- An injury to the epithelial lining of a blood vessel begins the process of clotting almost instantly.

- In the cellular response, blood platelets are activated in an initial response by exposure to collagen beneath the damaged epithelium and form a plug. Platelets do this by binding to collagen through their glycoprotein VI. In the process, platelets' integrins get activated and then bind tightly to the extracellular matrix to anchor them to the site of the wound.

- The von Willebrand factor assists by forming additional links between the platelets' glycoproteins Ib/IX/V and the collagen.

- In the amplification phase of the cellular response, platelets release factor 4, a cytokine stimulating inflammation and moderating action of the heparin anticoagulant. They also release thromboxane, a molecule that increases stickiness of platelets.

- A Gq-linked protein receptor cascade is also activated in the platelets, releasing calcium into their cytoplasms and the surrounding area. It plays a role in the molecular response.

- In the molecular response, a mesh or web comprised of polymers of the protein fibrin

is created. Two catalytic pathways called intrinsic (also known as the contact activation pathway) and extrinsic (also known as the tissue factor pathway) converge to create this. Both pathways contain a cascading series of zymogen activation of serine proteases. Cascades such as these allow for rapid activation of inactive enzymes, allowing the clot to form rapidly.

- The tissue factor pathway has an initial phase (a thrombin burst where thrombin is quickly activated) and an amplification phase where a chain reaction rapidly amplifies the amount of active thrombin

- Thrombin is a serine protease that catalyzes activation of fibrinogen to form fibrin for the clot).

- The initiation phase of the extrinsic (tissue factor) pathway begins with activation of FVII to form FVIIa as a result of the blood vessel damage. A complex of factors then act to convert a tiny amount of prothrombin (zymogen) to the active thrombin. The factors include TF, FVIIa, FIXa, and calcium from the cellular response. This is the end of the initiation phase and the product is a small amount of thrombin.

- In the amplification phase, factors of both the extrinsic and intrinsic pathways interact and the pathways converge. The aim is to make a sufficient amount of thrombin to catalyze formation of enough fibrin to make a clot.

- The small amount of thrombin made in the initiation phase is critical. It activates several factors which, in turn, help to make more thrombin. Thus, thrombin helps to stimulate production of more thrombin. Inactive factors activated by thrombin include FV, FXI, and FVIII and the products are FVa, FXIa, and FVIIIa. FIXa also helps to stimulate production of more active copies of itself.

- FIXa plus FVIIIa stimulate production of a considerable amount of FXa. FVa joins FXa and calcium to make a much larger amount of thrombin.

- Besides activation of fibrinogen to make fibrin and helping to increase production of more copies itself, thrombin also activates an enzyme known as transglutaminase (FXIIIa) that helps to harden the clot. This occurs via formation of a covalent bond between adjacent glutamine and lysine side chains in the fibrin polymers.

- Hemophilia is a hereditary (X-linked) genetic disorder affecting the blood clotting process in afflicted individuals. It is treated by exogenous provision of missing clotting factors

- A deficiency of FVIII leads to Hemophilia A and deficiency of FIX produces Hemophilia B.

- Lack of the von Willebrand factor gives rise to von Willebrand's disease, a genetically linked disease much like hemophilia.

- The von Willebrand factor binds to several things essential to the clotting process.

- First, it anchors platelets near the site of the wound in the cellular response.

- Second, it binds to the anticoagulant heparin to moderate its action.

- Third, it binds to the collagen exposed by the wound.

- Fourth, it binds to FVIII in the molecular response, playing a protective role for it. In the absence of the von Willbrand factor, FVIII is destroyed.
- Fifth, it binds to the platelets' integrin proteins.
- Vitamin K is a pro-clotting factor, serving as a coenzyme to help catalyze addition of an additional carboxyl group to the side chains of glutamic acid in several clotting enzymes.
- The additional carboxyl group allows the enzyme to bind to calcium and this is critical to the clotting process.
- Blocking action of vitamin K results in reduced clotting abilities and is referred to as blood thinning.
- In the process of the reaction above, vitamin K is oxidized and must be recycled (reduced) by vitamin K epoxide reductase in order to function. The compound known as warfarin (coumadin) interferes with vitamin K epoxide reductase and can be used to reduce blood levels of active vitamin K, thus "thinning" the blood.
- Warfarin is commonly given to patients prone to clotting to reduce their likelihood of stroke. It is very critical that the proper amount be given. Too much can result in hemorrhaging.
- Vitamin K can be obtained (inefficiently) from consumption of plants and more abundantly from action of gut bacteria.
- Plasmin is a serine protease (zymogen = plasminogen) that breaks down fibrin polymers and dissolves blood clots in the healing process.
- It can also activate collagenases (break down collagen) and this too may play a role in healing.
- Plasmin can be activated by several proteins, including tissue plasminogen activator (tPA), (using fibrin as a co-factor), urokinase plasminogen activator (using urokinase plasminogen activator receptor as a co-factor), kallikrein (plasma serine protease with many forms and blood functions), and FXIa and FXIIa of the blood clotting pathway.
- Conversion of plasminogen to plasmin can be inhibited by plasminogen activator inhibitor (inactivated tPA and urokinase plasminogen activator).
- Active plasmin can be inhibited by α2-antiplasmin and α2-macroglobulin. Thrombin also can play a role in plasmin inhibition.
- Fibronectin is a large glycoprotein found in the extracellular matrix that binds to integral cellular proteins called integrins and to extracellular proteins, including collagen, fibrin, and heparan sulfate. It is important in the healing process and in blood clot formation.
- In the repair of the wound, the damaged area is acted on by fibroblasts and macrophages, which degrade blood clot matrix proteins and replace them with a new matrix like the undamaged, surrounding tissue.
- Fibroblasts release proteases that cleave the fibronectin from the plasma, causing wound contraction. Then, fibroblasts release cellular fibronectin and integrate it with the matrix.

- Fibronectin is also essential for embryogenesis.

- Platelet Activating Factor (PAF) is a host defense chemical produced in greater quantities in inflammatory cells upon proper stimulation. It acts like a hormone and can transmit signals between cells to trigger and amplify inflammatory and clotting cascades.

- Unregulated PAF can cause severe inflammation resulting in sepsis and injury. Inflammation in allergic reactions arises partly as a result of PAF and is an important player in bronchoconstriction in asthma. In fact, at a concentration of only 10 picomolar, PAF can cause life threatening asthmatic inflammation of the airways.

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The Way They Work

To the tune of "*The Way We Were*"

Metabolic Melodies Website HERE

Enzymes
Might powerhouse peptides
Cause reactions to go faster
In the cells' insides

Tiny substrates
Bring about an induced fit
Enzyme structure is affect-ed
By what binds to it

Can it be that it's just simple zen?
How the enzymes activate
If they bind effector, will they go
To an R-State, T-State?

Folding
Gives the mechanistic might
To three-D arrangement
Of the active site

(Additional stanza)
Enzymes
Have a bias they can't hide
Hydrophobic side chains are
Mostly found inside

So it's the structure
For celebrating
Whenever there's debating
The way they work
The way they work

Recording by Liz Bacon and David Simmons
Lyrics by Kevin Ahern

Point by Point: Energy

Energy Basics

- Maintaining and creating order in cells takes the input of energy.
- Oxidation is the main form of non-photosynthetic energy in organisms.
- Carbon is the most commonly oxidized biological material.
- Energy released during the oxidative steps is “captured” in ATP.
- The more reduced a carbon atom is, the more energy can be realized from its oxidation.
- Fat is used as the primary energy storage form in animals because it is more reduced than carbohydrates and can store more energy.
- Biochemical processes that break things down from larger to smaller are catabolic processes. Catabolic processes are oxidative in nature and energy releasing.
- Energy from biological oxidation is largely captured (ultimately) as ATP.

- Uncaptured energy of metabolism is released as heat.
- Synthesizing large molecules from smaller ones is referred to as anabolism.
- Anabolic processes are reductive in nature and require energy input.
- Anabolic process counter entropy (larger things made from smaller pieces and energy required). To do this requires input of energy. Plants use energy from the sun to accomplish this.
- Cells use energy coupling to make reactions favorable that would otherwise be energetically unfavorable. A good example is phosphorylation of a sugar. By itself, this process is not energetically favorable, with the equilibrium far to the left. However, if the phosphorylation is coupled to hydrolysis of ATP, the reaction is energetically favorable. This is because the energy released by the hydrolysis is used by the enzyme catalyzing the reaction to put the phosphate onto the sugar.
- Cells that derive the metabolic energy directly from the sun are autotrophic. Those that get it from organic material in their food are heterotrophic.
- Besides using energy to counter entropy, cells also need metabolic energy for muscular contraction, synthesis of molecules, neurotransmission, signaling, thermoregulation, and subcellular movements.
- ATP is the most common energy 'currency' of the cell, but other triphosphates are also used. GTP is the energy source for protein synthesis. CTP is used to make glycerophospholipids, and UTP is used to make glycogen and other polysaccharides.
- ATP can be converted to other triphosphates by action of the enzyme NDPK.
- ATP is made by three distinct types of phosphorylation – oxidative phosphorylation (in mitochondria), photophosphorylation (in chloroplasts of plants), and substrate level phosphorylation (in enzymatically catalyzed reactions).
- Gibbs free energy is the amount of useful work obtainable in a constant temperature/ constant pressure system.
- Mathematically, the Gibbs free energy, G is measured by

$$G=H-TS$$

- where H is the enthalpy, T is the temperature in Kelvin, and S is the entropy.
- Gibbs free energy is not easy to measure directly, but the change in Gibbs free energy that occurs in a reaction is. For that reason, we typically measure the change in Gibbs free energy, ΔG.

$$\Delta G = \Delta H - T\Delta S$$

- ΔG also tells us the direction of a reaction. There are three cases:
- $\Delta G < 0$ - the reaction proceeds as written
- $\Delta G = 0$ - the reaction is at equilibrium
- $\Delta G > 0$ - the reaction runs in reverse
- For a reaction $aA \rightleftarrows bB$

where 'a' and 'b' are integers and A and B are molecules) at pH 7, ΔG can be determined by the following equation,

- $\Delta G = \Delta G^{\circ\prime} + RT\ln([B]^b/[A]^a)$
- For multiple substrate reactions, such as

$$aA + cC \rightleftarrows bB + dD$$

- $\Delta G = \Delta G^{\circ\prime} + RT\ln\{([B]^b[D]^d)/([A]^a[C]^c)\}$
- The **ΔG°'** term is the change in Standard Gibbs Free energy, which is the change in energy that occurs when all of the products and reactants are at standard conditions and the pH is 7.0. It is a constant for a given reaction.
- If we collect all of the terms of the numerator together and call them {Products} and all of the terms of the denominator together and call them {Reactants}, then

$$\Delta G = \Delta G^{\circ\prime} + RT\ln(\{Products\}/\{Reactants\})$$

- A negative $\Delta G^{\circ\prime}$ indicates an energetically favorable reaction, whereas a positive $\Delta G^{\circ\prime}$ corresponds to an unfavorable one. This is not absolute. The actual direction of a reaction is given ONLY by the value.
- Le Chatelier's Principle states that a system responds to stress by acting to alleviate the stress.
- If the amount of products increases, the ln term becomes more positive and **ΔG** becomes more positive, moving the reaction backward. Conversely, if the amount of reactants increases, then the ln term becomes more negative and and ΔG becomes more negative, moving the reaction forward. Thus, the system responds to the stress by acting to relieve it.
- From $\Delta G = \Delta H - T\Delta S$, an increase in entropy will make ΔG more negative, favoring reactions that increase entropy. The hydrophobic effect, described in protein folding, is favorable, for example, because the exclusion of water arising from interacting hydrophobic amino acids internal to a protein actually increases the entropy of the process.
- Whenever there is a difference in concentration of molecules across a membrane, there is said to be a concentration gradient across it.
- A difference in concentration of ions across a membrane creates an ionic (or electrical) gradient. When both are present, then we refer to it as an electrochemical gradient.
- Such gradients function like batteries and contain potential energy.
- For two solutions of uncharged material separated by a lipid bilayer (say inside a cell versus outside a cell, where C_1 is the concentration inside and C_2 is the concentration outside), The Gibbs free energy associated with moving material in the direction of C_2 is given by

$$\Delta G = RT\ln[C_2/C_1]$$

- To move material in the direction of C_1, the result would be

$$\Delta G = RT\ln[C_1/C_2]$$

- The last two equations assume the molecules have no charge. If they have charge, this must be taken into account with another term -> $ZF\Delta\psi$.
- Here, Z refers to the charge of the transported species (+1 for a potassium or -1 for a chloride, for example), F is the Faraday con-

stant (96,485 Coulombs/mol), and $\Delta\psi$ is the electrical potential difference (voltage difference) across the membrane. This term accounting for the charge is added to the first equation (movement in the direction of C_2) to yield

$$\Delta G = RT\ln[C_2/C_1] + ZF\Delta\psi$$

- For a situation of movement of potassium ions from outside to inside where $C_2 > C_1$, the signs of the terms would be as follows:

$$RT\ln[C_2/C_1] = \text{positive, since } C_2 > C_1$$

- $ZF\Delta\psi$ = positive, since Z is positive (K = +1) and the $\Delta\psi$ term is positive, since positive ions are moving against a positive charge gradient ($C_2 > C_1$). Thus, the ΔG term will be positive and movement in the direction of C_2 would not be favored.

- Gain and loss of electrons has an electrical component and Gibbs free energy component as well. Reduction potential measures the tendency of a chemical to be reduced by electrons.

- Reduction potential is commonly measured in volts, or millivolts.

- If two chemicals are mixed in an aqueous solution, the chemical with the greater (more positive) reduction potential will tend to take electrons away, thus being reduced, from the one with the lower reduction potential, which becomes oxidized.

- The standard of reference for measurement is the half-reaction

$$H^+ + e^- \rightarrow 1/2H2$$

- The electrode where this reaction occurs (referred to as a half-cell) is given the value of E° (Standard Reduction Potential) of 0.00 volts.

- The hydrogen electrode is connected via an external circuit to another half cell containing a mixture of the reduced and oxidized species of another molecule (for example, Fe^{++} and Fe^{+++}) at 1M each and standard conditions of temperature (25°C) and pressure (1 atmosphere).

- Electrons can either flow into the reference cell if hydrogen's reduction potential is greater than that of the ions being measured) or away from the reference cell if the reverse is true.

- Voltages for electron flow away from the reference cell are positive and voltages of flow into the reference cell are negative.

- Under standard conditions, electrons will move from compounds with lower voltages to compounds with higher (more positive) voltages.

- Actual direction of electron movement depends on concentration, just as ΔG varied with concentration.

- Thus, we can define the overall reduction potential for a system as follows

$$E = E^\circ + (RT/nF)*\ln\left(\frac{[\text{reduced molecule}]}{[\text{oxidized molecule}]}\right)$$

where E° is the standard reduction potential measured above (under standard conditions), F is the Faraday constant (96,480 J/(Volts*moles), R is the gas constant (8.315 J/(moles*K), n is the number of moles of electrons being transferred, and T is the absolute temperature in Kelvin.

- Like the Gibbs free energy, consideration is given for measuring values at conditions found in cells. This means doing measurements at pH = 7, which differs from having all species at 1M, so an alternative E°' is used in place of E° for the same reason ΔG°' is used in biological systems instead of ΔG°.

- The relationship between ΔG and reduction potential then is as follows:

$$\Delta G_{red} = -nF\Delta E$$

where ΔG_{red} is the ΔG for the reduction potential difference. Similarly, we can write

$$\Delta G_{red}{}^{\circ\prime} = -nF\Delta E^{\circ\prime}$$

- Thus in considering the overall ΔG for a chemical reaction involving electrochemical changes

$$\Delta G_{total} = \Delta G_{chemical} + \Delta G_{red}$$

- Cells mostly store energy arising from oxidation in the form of triphosphate nucleotides - most commonly ATP.

- In a given day, an average human being makes and breaks down more than its body weight in triphosphates.

- Energy in ATP is released by hydrolysis of a phosphate from the molecule.

- The three triphosphates starting with the one closest to the sugar are referred to as α, β, and γ.

- Hydrolysis between the β, and γ phosphate of ATP produces ADP and P_i

- Hydrolysis between the α, and β phosphate produces AMP and pyrophosphate (PP_i).

- All of the diphosphate nucleotides can be interchanged with triphosphate nucleotides by nucleoside diphosphate kinase (NDPK). The reaction proceeds as

$$XTP + YDP \rightleftarrows XDP + YTP$$

where X = adenosine, cytidine, uridine, thymidine, or guanosine and Y can be any of these as well.

- Cells have another way of making ATP when ADP concentrations are high. Adenylate kinase catalyzes the following reaction:

$$2\ ADP \rightleftarrows ATP + AMP$$

- The AMP produced in this reaction is an indicator to the cell that energy levels are low and it activates phosphofructokinase of glycolysis to catalyze glucose breakdown to get more energy.

- In enegy coupling, energetically favorable reactions that release energy, such as hydrolysis of ATP are coupled enzymatically to energetically unfavorable reactions in order to make the latter favorable.

- Another mechanism for moving a reaction forward is by removal of a product. An example is the orotate reaction:

$$Orotate + PRPP \ <=> \ OMP + PP_i$$

- The PP_i (pyrophosphate) product can be further broken down by pyrophosphorylase as follows

$$PP_i + H_2O <=> 2P_i$$

- Thus, the concentration of a product decreases and this helps to "pull" the reaction forward.

- From an energy perspective, removal of product (pulling a reaction) and/or increasing the concentration of reactant (pushing a reaction) decreases **Δ**G because these have the effect of making the fraction in the term below smaller and its Ln value more negative, thus reducing ΔG

$$\Delta G = \Delta G^{\circ\prime} + RT\ln(\{Products\}/\{Reactants\})$$

Electron Transport and Oxidative Phosphorylation

- The vast majority of ATP synthesis in eukaryotes occurs in the mitochondria in a process called oxidative phosphorylation.

- Oxidative phosphorylation is preceded in the mitochondria by another process known as electron transport.

- NADH and $FADH_2$ donate their electrons to the electron transport system and become NAD^+ and FAD, respectively.

- Peter Mitchell proposed the chemiosmotic hypothesis to explain oxidative phosphorylation.

- Mitchell proposed that mitochondrial ATP synthesis results from an electrochemical gradient across its inner membrane that arises ultimately from the energy of reduced electron carriers, NADH and $FADH_2$

- Mitchell said further that electron carriers transfer electrons to an electron transport system (ETS) in the inner mitochondrial membrane and movement of the electrons causes protons to be pumped out of the mitochondrial matrix across the inner mitochondrial membrane, creating a proton gradient. Flow of the electrons back into the matrix through a transmembrane ATP synthase is the driving force for synthesis of ATP from ADP and P_i.

- Tight coupling of electron transport and oxidative phosphorylation exists when the two processes are interdependent - stopping of one stops the other. This is the basis of metabolic control.

- Uncoupling of electron transport occurs when the integrity of the inner mitochondrial membrane is compromized, allowing protons to re-enter the matrix without passing through the ATP synthase. When this occurs, the proton gradient is destroyed and no ATP is made.

- In the electron transport system, electrons flow through the system via complexes and shuttles. The order of movement for electrons from NADH is NADH -> Complex I -> CoQ -> Complex III -> Cytochrome c -> Complex IV. The order of movement for electrons from $FADH_2$ is $FADH_2$ -> Complex II -> CoQ -> Complex III -> Cytochrome c -> Complex IV.

- Electrons enter the system in pairs and travel in pairs until CoQ, which passes them off singly to Complex III. CoQ is called a traffic cop for electrons.

- Movement of electrons through complexes I, III, and IV cause protons to be pumped from the mitochondrial matrix to the intermembrane space, creating the pro-

ton gradient (higher proton concentration outside the mitochondrion than in the matrix).

- Complex III is a docking station for CoQ and cytochrome C. It is the site of the Q cycle.
- Cytochrome c ferries electrons to Complex IV one at a time - Complex IV requires 4 electrons to reduce O2 to 2 H_2O molecules.
- O_2 is the terminal electron acceptor of electron transport.
- Pumping protons out of the mitochondrion creates a proton gradient - electrochemical potential energy that is later used to make ATP.
- Complex I contains 44 individual polypeptide chains, numerous iron-sulfur centers and a molecule of flavin mononucleotide (FMN)
- In the process of electron transport through it, four protons are pumped across the inner membrane into the intermembrane space and electrons move from NADH to coenzyme Q, converting it from ubiquinone to ubiquinol.
- Complex I moves electrons through seven primary iron sulfur centers within it.
- The Complex I inhibitor rotenone stops electron movement by binding to the site where CoQ would bind.
- Other complex I inhibitors include ADP-ribose, which binds to the NADH site, and piericidin A, a rotenone analog.
- Electron movement through complex I is reversible and can result in production of reactive oxygen species.
- Complex II is a membrane bound enzyme of the citric acid cycle (succinate dehydrogenase). It also transfers electrons to CoQ.
- The oxidized form of CoQ is known as ubiquinone and the fully reduced form (gain of two electrons) is ubiquinol. An intermediate form (gain of one electron) is known as either ubisemiquinone or just semiquinone. The three forms of CoQ allow it to function as a traffic cop - accepting up to two electrons and passing them off one at a time.
- Inhibitors of complex II include carboxin, malonate, malate, and oxaloacetate. The last two are thought to function as inhibitors of the production of reactive oxygen species.
- Complex III contains 11 subunits, a 2-iron ferredoxin, cytochromes b and c_1 and belongs to the family of oxidoreductase enzymes.
- Complex III accepts electrons from coenzyme Q in electron transport and passes them off to cytochrome c in the Q cycle.
- Movement of electrons through the complex can be inhibited by antimycin A, myxothiazol, and stigmatellin.
- In the Q-cycle, electrons are passed from ubiquinol (QH_2) to cytochrome c using Complex III as a docking station.
- The process starts with a ubiquinol ($CoQH_2$), a ubiquinone (CoQ), and a cyto-

chrome c (lacking an electron) docking at Complex III.

- The two electrons from $CoQH_2$ split - one to cytochrome c (which exits with the electron) and one to CoQ (creating CoQ.- - also called CoQH or ubisemiquinone).
- The $CoQH_2$ that donated electrons becomes CoQ (ubiquinone) and is replaced by another $CoQH_2$.
- The two electrons from the new $CoQH_2$ split as the last ones did - one to cytochrome c (which exits with the electron) and one to CoQH (creating $CoQH_2$). Both CoQ ($CoQH_2$ that lost its electrons) and $CoQH_2$ exit and the process is complete.
- In the overall process, two protons are consumed from the matrix and four protons are pumped into the intermembrane space.
- Cytochrome c is a small protein, conserved from unicellular species to animals, that is loosely associated with the inner mitochondrial membrane.
- It uses a heme to carry a single electron from Complex III to Complex IV.
- Mitochondrial damage in higher organisms results in release of cytochrome c that stimulates assembly of the apoptosome and programmed cell death.
- Complex IV (cytochrome c oxidase) is a 14 subunit integral membrane protein that accepts one electron each from four cytochrome c proteins. It adds them to molecular oxygen (O_2) with four protons from the mitochondrial matrix to make two molecules of water. It is inhibited by cyanide, carbon monoxide, azide, and hydrogen sulfide.
- Four protons from the matrix are also pumped into the intermembrane space.
- The complex contains two molecules of heme, two cytochromes (a and a_3), and two copper centers (called CuA ad CuB).
- Complexes I, III, and IV appear to form a supercomplex, which has been dubbed the respirasome.
- Oxidative phosphorylation uses the energy of the proton gradient to make ATP.
- Things that destroy the proton gradient destroy the mitochondrion's ability to make ATP.
- The protein complex harvesting energy from the proton gradient to make ATP from ADP is an enzyme most commonly called complex V or ATP synthase.
- Protons moving through it (from the intermembrane space back into the matrix) will only provide energy to make ATP if their concentration is greater in the intermembrane space than in the matrix.
- During periods of rest, the rate of ATP synthesis exceeds the rate of ATP usage. Then ADP concentrations fall everywhere.
- Reducing ADP concentration in the matrix reduces oxidative phosphorylation and this, in turn, reduces electron transport because protons are not moving in through the ATP synthase. As a consequence, the proton gradient grows steeply, while electron transport is still running, but it quickly stops growing, since it because it becomes too difficult for the complexes to continue

pumping protons. As a consequence, electron transport slows or stops and oxygen consumption decreases (breathing slows).

- When the electron transport system stops, the concentration of NADH and $FADH_2$ increases, since they can't put their electrons into the electron transport system. This means that the citric acid cycle will slow or stop, since it requires NAD^+.

- The scenario described above is a good example of respiratory control. It moves the other way when exercise begins. First, ATP gets used by muscles, so the ADP concentration increases. This allows ATP synthase to function and protons re-enter the mitochondrial matrix. As the proton gradient falls, electron transport starts up because it can once again pump protons, since the gradient isn't too steep.

- When electron transport starts, oxygen usage increases (heavier breathing) and NADH and $FADH_2$ get converted to NAD^+ and FAD. As NAD^+ and FAD concentrations increase, the citric acid cycle starts and you start breaking down acetyl-CoA. Thus, if you exercise, you can lose weight, by oxidizing material and if you don't exercise, you can't burn off as much material

- These controls work only when there is tight coupling (intact mitochondrial inner membrane).

- If one does not have the proper amount of exercise, reduced carriers remain high in concentration for long periods of time. This favors anabolic pathways (since NADH and NADPH are needed for many biosynthesis reactions) particularly fatty acid synthesis, are favored, so we get fatter.

- ATP made in oxidative phosphorylation is released in the mitochondrial matrix, but is needed in the rest of the cell. To get it out, an ADP-ATP translocase (antiport) in the inner membrane of the mitochondrion is used for the transfer. Phosphate is moved into the mitochondrial matrix by a proton-phosphate translocase symport.

- Movement of protons through the ATP Synthase c-ring causes it and the γ-ε stalk attached to it to spin. It is this action that is necessary for making ATP.

- The γ-ε stalk projects into the F1 head and its rotation affects the α and β units, which are a set of three dimers. The β subunits slightly change configuration as the γ-ε stalk rotates, moving from configurations called loose (L) to tight (T) to open (O). The L form binds and holds ADP and P_i. The T form squeezes them together to make ATP and the O form opens to release the ATP.

- Inhibiting electron transport and/or oxidative phosphorylation with exogenous chemicals is dangerous and can be fatal.

- ATP synthase can be physically stopped with an inhibitor known as oligomycin A. Oxidative phosphorylation can be also stopped by destroying the proton gradient. This can be accomplished with an uncoupling agent, such as 2,4 dinitrophenol (2,4 DNP), which pokes holes in the mitochondrial inner membrane, allowing an alternate way for protons to enter the matrix from the intermembrane space that does not involve ATP synthase.

- When an uncoupling agent is used, oxidative phosphorylation stops because there is no proton gradient, but electron transport, on the other hand operates rap-

idly, since no gradient accumulates to stop it. Thus oxygen consumption goes up and heat is generated, due to the increased metabolic activity. This can be very dangerous, as cells can run out of ATP.

- Some cells actually use a biological uncoupling agent known as thermogenin to generate heat. This occurs in brown fat cells. Thermogenin allows protons to flow back into the matrix. As a result, metabolism increases and heat is generated. This differs from treatment with 2,4 DNP in that it is tightly controlled and can be reversed.

- Another way some cells generate heat is by taking a shortcut through the electron transport system. This occurs in fungi, plants, and protozoa and involves a protein known as alternative oxidase. It short-circuits the electron transport system by accepting electrons from CoQ and passing them directly to oxygen, bypassing the rest of the electron transport system.

- As a result, each pair of electrons entering the system pumps much fewer protons (bypassing complexes III and IV) and fewer ATPs are made per pair of electrons. That requires increased oxidation of foodstuffs to generate ATP and increased oxidation results in generation of heat.

- Alternative oxidase is only activated by cold temperatures.

- Reactive oxygen species (ROS) are byproducts of electron transport and other cellular enzymes. Some ROS include peroxides, hydroxyl radical, superoxide, peroxynitrite, and others that are very chemically reactive.

- Some ROS, such as peroxide and nitric oxide function in signaling, but increases in reactive oxygen species in times of stress can cause significant damage in the cell. Some cells use enzymes like NADPH oxidase to generate superoxides to kill bacteria.

- Phagocytes of the immune system engulf foreign cells and then use ROS to kill them.

- Damaged tissues of zebrafish have increased levels of H_2O_2 and this is thought to signal white blood cells to converge on the site.

- Cell organelles called peroxisomes can generate ROS as a byproduct of oxidation of long chain fatty acids.

- The free radical theory of aging states that organisms age due to the accumulation of damage from free radicals in their cells.

- In yeast and *Drosophila*, there is evidence that reducing oxidative damage can increase lifespan.

- Bcl-2 proteins on the surface of mitochondria monitor damage and if they detect it, will activate proteins called Bax to stimulate the release of cytochrome c from the mitochondrial inner membrane, stimulating apoptosis (programmed cell death).

- Superoxide can be produced when movement of electrons into and out of the chain don't match well. Then CoQ can donate an electron to O_2 to form O_2^- (superoxide). Superoxide can react with many things, including DNA where it can cause damage leading to mutation.

- Countering the effects of ROS are enzymes, such as catalase, superoxide dismutase, and anti-oxidants, such as glutathione and vitamins C and E.

- Catalase catalyzes the breakdown of hydrogen peroxide into water and oxygen.
- Catalase converts up to 40,000,000 molecules of hydrogen peroxide to water and oxygen per enzyme per second. It is abundantly found in peroxisomes.
- There is evidence that reduced levels of catalase with aging may allow higher levels of H_2O_2 that are responsible for bleaching that produces gray hair.
- Superoxide dismutase (SOD) is found, like catalase, in virtually all organisms living in an oxygen environment.
- Like catalase, superoxide dismutase has a very high K_{cat} value and has the highest K_{cat}/K_m known for any known enzyme.
- It operates by ping-pong (double displacement) mechanism, shuffling between reactions 1 and 2 below
- 1. $O_2^- + \text{Enzyme-Cu}^{++}$ $O_2 + \text{Enzyme-Cu}^{+}$
- 2. $O_2^- + \text{Enzyme-Cu}^{+} + 2\ H^+$ $H_2O_2 + \text{Enzyme-Cu++}$
- As can be seen, superoxide uses a copper ion in its catalytic mechanism.
- The hydrogen peroxide produced in the second reaction is easily handled by catalase.
- Superoxide can react with nitrous oxide (NO) to form very toxic peroxynitrite ions.
- In humans, superoxide dismutase is associated with the genetically-linked form of Amyotrophic Lateral Sclerosis (ALS) and over-expression of the gene is linked to neural disorders associated with Down syndrome.
- Mixed function oxidases use molecular oxygen for two different purposes in one reaction.
- Monooygenases are one type of mixed function oxidase that catalyze reactions like the one shown below

$AH + BH_2 + O_2 <=> AOH + B + H_2O$

- Cytochrome P450 enzymes (called CYPs) are family of heme-containing mixed function oxidase enzymes. The type of reaction catalyzed by them is shown below

$RH + O_2 + NADPH + H^+ <=> ROH + H_2O + NADP^+$

- There are six different classes of P_{450} enzymes based on how they get electrons

1. Bacterial P_{450} - electrons from ferredoxin reductase and ferredoxin

- 2. Mitochondrial P_{450} - electrons from adrenodoxin reductase and adrenodoxin
- 3. CYB5R/cyb5 - electrons come from cytochrome b_5
- 4. FMN/Fd - use a fused FMN reductase
- 5. Microsomal P_{450} - NADPH electrons come via cytochrome P_{450} reductase or from cytochrome b_5 and cytochrome b5 reductase
- 6. P_{450} - only systems - do not require external reducing power

- CYP enzymes perform important functions in synthesis of steroids (cholesterol, estrogen, testosterone, Vitamin D, e.g.), breakdown of endogenous compounds (bilirubin), and in detoxification of toxic compounds including pharmaceutical drugs.

- Cytochromes are heme-containing proteins that play major roles in the process of electron transport in the mitochondrion and in photosynthesis in the chloroplast.

- An atom of iron at the center of the heme group flips between the ferrous (Fe^{++}) and ferric (Fe^{+++}) states as a result of the movement of electrons through it.

- Cytochrome c is a soluble protein loosely associated with the mitochondrion. Cytochromes a and a_3 are found in Complex IV. Complex III has cytochromes b and c_1 and the plastoquinol-plastocyanin reductase of the chloroplast contains cytochromes b6 and f. Cytochrome P_{450} enzymes (absorb light at 450 nm when heme is reduced) contain cytochromes as well.

- Iron-sulfur proteins have many configurations and functions. In the electron transport system, they function in the redox reactions involved in the movement of electrons (complexes I and II).

- Aconitase uses an iron sulfur center in catalysis.

- Ferredoxins are iron-sulfur containing proteins performing electron transfer. Some function in photosynthesis in chloroplasts.

- Some ferredoxins provide electrons to enzymes (glutamate synthase, nitrate reductase, and sulfite reductase) and others serve as electron carriers between reductase flavoproteins and bacterial dioxygenase systems.

- Ferritin is a globular protein complex with 24 subunits and is the primary intracellular iron-storage protein in eukaryotes and prokaryotes. It keeps iron in a soluble non-toxic form and keeps the concentration of free iron from going to high or falling too low.

- Monoamine oxidases (MAOs) catalyze the oxidative deamination of monoamines, such as serotonin, epinephrine, and dopamine. Removal of the amine with oxygen results in the production of an aldehyde and ammonia.

- MAO-A and MAO-B inactivate monoaminergic neurotransmitters such as dopamine, tyramine, and tryptamine.

- MAO-A is the primary enzyme for metabolizing melatonin, serotonin, norepinephrine, and epinephrine, while MAO-B is the primary enzyme for phenethylamine and benzylamine.

- MAOs have been linked to numerous psychological problems, including depression, attention deficit disorder (ADD), migraines, schizophrenia, and substance abuse.

- Excess levels of catecholamines, such as epinephrine, norepinephrine, and dopamine, can result in dangerous hypertension events.

- The DNA Damage Theory of Aging says that accumulated oxidative damage to DNA alters its ability to perform its function properly, so this can induce changes in gene expression associated with aging.

- Mouse cells are thought to cell experience 40,000 to 150,000 damage events per day. Slowly replicating cells, such as in the lens of the eye or brain, may be more susceptible to this damage.

- DNA repair systems, of course, protect against damage to DNA, but over time, unrepairable damage may accumulate.

- Oxidation of guanine by reactive oxygen species can produce 8-oxo-guanine which is capable of forming a stable base pairing interaction with adenine, potentially giving rise to a mutation when DNA replication proceeds.

- 8-oxoguanine can be repaired if recognized in time by a DNA glycosylase,

- Polycyclic aromatic hydrocarbons from cigarette smoke, diesel exhaust, or overcooked meat can covalently bind to DNA and, if unrepaired, lead to mutation.

- Diseases affecting DNA repair can lead to premature aging.

- Individuals with Werner syndrome, for whom the life expectancy is 47 years, are missing two enzymes in base excision repair.

- People suffering from Cockayne syndrome have a life expectancy of 13 years due to mutations affecting transcription-coupled nucleotide excision repair.

- Life expectancies of 13 species of mammalian organisms correlates with the level of expression of the PARP DNA repair-inducing protein.

- Antioxidants have the chemical property of protecting against oxidative damage by being readily oxidized themselves and may protect against ROS.

- Cellular antioxidant defenses include vitamins C, A, and E, glutathione, and enzymes that destroy ROS such as superoxide dismutase, catalase, and peroxidases.

- Oxidation by ROS is mutagenic and has been linked to atherosclerosis.

- However, no reduction in mortality rates as a result of supplementation with these materials has been found, so the protective effects of antioxidants on ROS in human health remain poorly understood.

- Glutathione is a tripeptide comprised of glutamate, cytsteine, and glycine that protects cells against damage caused by reactive oxygen species and heavy metals. It is important for

• Neutralization of free radicals and reactive oxygen species.

- Maintenance of exogenous antioxidants such as vitamins C and E in their reduced forms.

- Regulation of the nitric oxide cycle

- The thiol group of glutathione's cysteine is a reducing agent that reduces disulfide bonds to sulfhydryls in cytoplasmic proteins and results in it forming a disulfide bond with the sulfur of the cysteine of another glutathione.

- Glutathione is made by two enzymes rather than being synthesized in ribosomes.

- In healthy cells, 90% of glutathione is in the GSH state. Higher levels of GSSG corre-

spond to cells that are oxidatively stressed. Mice lacking glutathione die in infancy.

- Resveratrol is a phenolic stilbenoid compound produced in the skin of plants. It may improve the functioning of mitochondria by acting as an antioxidant and by causing concentration of another antioxidant, glutathione, to increase.

- Resveratrol induces expression of manganese superoxide dismutase and inhibits several phosphodiesterases. This increases cAMP concentrations which result in increases in oxidation of fatty acids, mitochondria formation, gluconeogenesis, and glycogen breakdown.

- Resveratrol has been claimed to be the cause of the French paradox in which drinking of red wine is supposed to give protection for the cardiovascular system. Research data in support of it, though, is lacking.

- Resveratrol is known to activate sirtuin proteins, which play roles in gene inactivation.

Photophosphorylation

- Photophosphorylation is the third general mechanism for synthesizing ATP (substrate level phosphorylation and oxidative phosphorylation are the others). It is a mechanism of photosynthesis, a process which occurs only in plants and some microbes.

- Photophosphorylation is similar to oxidative phosphorylation in relying on a proton gradient for making ATP, having a proton gradient being made by an electron transport system, and using an ATP synthase enzyme very similar to the one in mitochondria.

- Photophosphorylation (PP) differs from oxidative phosphorylation (OP) in several respects.

- The source of electrons in PP is H_2O (releasing oxygen), but in OP, it is $NADH/FADH_2$ (releasing NAD^+ and FAD).

- The terminal electron acceptor in PP is $NADP^+$, producing NADPH, but is O_2 for OP, producing water.

- The driving force for movement of electrons in PP is sunlight, but is oxidation for OP.

- The proton gradient is reversed for OP and PP. Protons move out of an organelle structure (thylakoid of the chloroplast) to make ATP for PP, but move into an organelle (mitochondria) for the same purpose in OP.

- Photophosphorylation is only part of the process of photosynthesis - referred to as the “light reactions or light cycle.” The other part of photosynthesis involves “fixing” of carbon dioxide from the atmosphere into organic compounds that can be used to make glucose or other carbohydrates. These reactions are known as the “dark reactions or dark cycle,” though they do not occur in the dark - it simply means light is not directly required for them to take place. The dark reactions are also known as the Calvin cycle.

- The light cycle of photosynthesis starts with energy capture from light by proteins containing chlorophyll pigments called reaction centers. Plants have these in chloroplasts, bacteria have them in the plasma membrane.

- The light reactions of photosynthesis occur inside chloroplasts in specialized structures called thylakoids. In the membranes of the thylakoids are contained the electron transporting system and the ATP synthase.

- Light energy is used to excite electrons (which ultimately come from water), thus beginning a series of electron transporting steps and releasing O_2 from the oxidized water.

- There are two photosystems for harvesting light in the membranes of the thylakoid. Chlorophyll is the most common pigment used for this purpose in plants, but carotenes and xanthophylls are also used.

- The thylakoid membrane does its magic using four major protein complexes - photosystem II (PS II), cytochrome b6f complex (Cb6f), photosystem I (PS I), and ATP synthase.

- The process of photosynthesis begins in PS II with the absorption of a photon of light at a reaction center, which excites an electron to a high energy. This electron must be replaced as it will pass through the electron transport system.

- The electron replacing the excited electron ultimately comes from water, but first is replaced by one from the oxygen evolving complex with four manganese centers (the source of the initial replacement electrons). After four electrons have been replaced, the oxygen evolving complex extracts four electrons from two water molecules, liberating oxygen and dumping four protons into the thylakoid space.

- The excited electron transfers to pheophytin and then to protein bound plastoquinones (in order - PQA to PQ). PQ waits and accepts two electrons and two protons to become PQH2.

- When PQH_2 donates the electrons to the next acceptor (Cytochrome b6f, - Cb6f), it pumps the protons into the thylakoid space. Thus, the proton gradient is growing a a result of the splitting of water and the movement of electrons. Cb6f passes off one electron at a time to plastocyanin. At this point the electron is ready to replace an excited electron in photosystem I (PS I). Also in the thylakoid membrane at this time, ATP synthase makes ATP from the proton gradient.

- Absorption of light by photosystem I begins a similar process to what occurred in PS II. Loss of an electron by absorption of light creates a positive charge in PS I and it is neutralized by the electron from PS II in plastocyanin. Meanwhile, the excited electron moves through an iron-sulfur protein, then to ferredoxin, then to the last protein in the system known as Ferredoxin:$NADP^+$ oxidoreductase, which gives the electron and a proton to the terminal electron acceptor, $NADP^+$, creating NADPH. At this point, the light cycle is complete - water has been oxidized, ATP has been created, and NADPH has been produced.

- Plants also have an alternate route electrons can take. It is known as cyclic photophosphorylation. It primarily involves PS I. in it, excited electrons of PS I are not passed to the route leading to $NADP^+$. Instead, they pass off to the proton-pumping Cb6f complex. The electrons take the route they would have taken from PS II through Cb6f

to plastocyanin, pumping protons along the way. In this method, no NADPH is made, but a proton gradient is made, thus allowing continued synthesis of ATP.

- The ability of plants to switch between non-cyclic and cyclic photosystems allows them to make the proper ratio of ATP and NADPH they need for assimilation of carbon dioxide in the dark cycle of photosynthesis.

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Student Nightmares

To the tune of "*Norwegian Wood*"

Metabolic Melodies Website HERE

I answered 3 'b'.
But then I thought. It might be 'c'
Or was the false true?
I can't undo. It makes me blue

It asked me to list all the enzymes that regulate fat
As I wrote them down I discovered I didn't know Jack

I ought to give thanks,
Scoring some points, filling in blanks
I squirmed in my seat
Feeling the heat, shuffling my feet

Professor then told me there wasn't a chance I would pass
So I started crying and fell through a big pane of glass

I suffered no harm,
'Cuz I awoke, to my alarm
Oh nothing compares
To deadly scares, of student nightmares

Recording by David Simmons
Lyrics by Kevin Ahern

Point by Point: Metabolism

Sugar Metabolism

- Glycolysis is the breakdown of sugars.
- It is a catabolic process where the oxidation of sugars begins and it occurs in the cytoplasm of cells.
- The end product of glycolysis is pyruvate.
- The reversal is the synthesis of glucose and that is called gluconeogenesis. It is reductive.
- Complete oxidation of glucose yields carbon dioxide.
- Glucose is the most abundant hexose in nature.
- Fructose is also readily metabolized in glycolysis by being converted to fructose-6-phosphate (F6P).
- Galactose can also be readily oxidized in glycolysis.
- Products of glycolysis include 2 ATP, 2 NADH, and 2 pyruvates per glucose molecule.
- Pyruvate is further oxidized to acetyl-CoA and oxidized in the citric acid cycle if oxygen is available.

- Pathways with a few common intermediates to glycolysis include the Calvin cycle and the pentose phosphate pathway (PPP). These include glucose-6-phosphate (PPP, glycogen metabolism), Fructose-6-phosphate (Calvin Cycle, PPP), Glyceraldehyde-3-phosphate (Calvin Cycle, PPP), dihydroxyacetone phosphate (PPP, glycerol metabolism, Calvin Cycle), 3-phosphoglycerate (Calvin Cycle, PPP), phosphoenolpyruvate (C_4 plant metabolism, Calvin Cycle), and pyruvate (fermentation, acetyl-CoA genesis, amino acid metabolism).

- Glycerol from fat is the only part of used in glycolysis. It must first be converted to DHAP.

- The first reaction of glycolysis is catalyzed by hexokinase and it converts glucose to G6P, using energy from ATP.

- Hexokinase is one of three regulated enzymes of glycolysis and it is inhibited by G6P.

- Hexokinase can catalyze reactions on several six carbon sugars, including fructose, mannose, and galactose.

- Phosphorylation of glucose keeps it from escaping out of the cell.

- G6P can be used in the pentose phosphate pathway and can be converted to glucose-1-P for glycogen synthesis.

- Glucokinase is an enzyme related to hexokinase and it is found in the liver. It has a much higher K_m for glucose than hexokinase, allowing liver cells to more easily export glucose without converting it to G6P.

- In the second reaction of glycolysis, G6P is converted to F6P by phosphoglucoisomerase - a readily reversible reaction.

- In reaction 3, F6P is phosphorylated to F1,6BP in a reaction catalyzed by phosphofructokinase (PFK-1) with energy provided by ATP.

- PFK-1 is an important regulatory enzyme for glycolysis - several allosteric effectors. The reaction it catalyzes is essentially irreversible.

- A variant enzyme to PFK-1 in plants and bacteria uses pyrophosphate as the energy/phosphate source and that reaction is readily reversible.

- In reaction 4, F1,6BP is split into glyceraldehyde-3-phosphate (GLYAL-3-P) and dihydroxyacetone phosphate (DHAP) in a reaction catalyzed by aldolase.

- The reaction has a large positive $\Delta G°'$ value. Cells decrease the concentration of products to help drive the reaction forward.

- Reaction 5 involves conversion of DHAP to GLYAL3P in a reaction catalyzed by the "perfect" enzyme known as triose phosphate isomerase.

- Enzymes in this category have very high ratios of K_{cat}/K_m that approach a theoretical maximum limited only by the diffusion of substrate into the active site of the enzyme.

- They do this to avoid accumulation of a toxic intermediate.

- In the 6th reaction, the only oxidation of glycolysis occurs - catalyzed by GLYAL-

3P dehydrogenase. In it, GLYAL-3P is converted to 1,3 BPG. NADH is also formed.

- The need for NAD^+ is this reaction is the reason cells go through fermentation (which produces NAD^+).
- The seventh reaction is the first substrate-level phosphorylation of glycolysis in which 1,3BPG donates a phosphate to ADP to form ATP and 3-phosphoglycerate (3-PG).
- The enzyme is phosphoglycerate kinase.
- Oxidative phosphorylation (predominant producer of ATP) and photophosphorylation (plants) are two other ways cells make ATP.
- Reaction 8 is a phosphoglycerate mutase catalyzed reaction in which 3-PG is converted to 2-PG. An intermediate in the process is 2,3BPG which is stable and can be released by the enzyme. 2,3BPG binds to hemoglobin and favors oxygen release, which helps rapidly metabolizing cells.
- 2,3BPG can also be made by the enzyme bisphophoglycerate mutase by action on 1,3BPG.
- In reaction 9, water is released from 2-PG in a reaction catalyzed by enolase to form phosphoenolpyruvate (PEP) - a high energy intermediate.
- In the last reaction of glycolysis (#10), the “big bang” occurs - PEP is converted to pyruvate, ATP is made, and there is still a lot of energy left over, which can be released as heat.
- This reaction is the second substrate level phosphorylation in glycolysis and is catalyzed by pyruvate kinase.
- Galactose is produced in cells by breakdown of lactose, catalyzed by lactase.
- To use galactose in glycolysis, it must be converted to galactose-1-phosphate by galactokinase.
- Galactose-1-phosphate swaps with glucose-6-phosphate from UDP-glucose to make UDP-galactose, which is made into UDP-glucose by an epimerase. The G6P on the UDP in the first reaction was originally a galactose-1-phosphate, so each turn of the cycle results in binding of a galactose-1-P and release of a glucose-6P, effectively converting galactose into a glycolysis intermediate.
- Deficiency of galactose conversion enzymes results in accumulation of galactose, which is converted to galactitol. Galactitol in the human eye lens causes it to absorb water and may favor formation of cataracts.
- Fructose can be phosphorylated to F6P by hexokinase or it can enter glycolysis by being converted to F1P by fructokinase. F1P can be broken down by fructose-1-phosphate aldolase to yield DHAP and glyceraldehyde.
- Phosphorylation of glyceraldehyde by triose kinase yields GLYAL3P.
- This alternative pathway for entry of fructose bypasses the PFK-1 reaction and has been proposed as an explanation for fat production in people who consume high fructose corn syrup, since bypassing PFK-1 favors production of excess pyruvate, which

is converted to acetyl-CoA, a precursor of fatty acids.

- Mannose enters glycolysis by 1) phosphorylation by hexokinase to make mannose-6-phosphate followed by its conversion to fructose-6-phosphate, catalyzed by phosphomannoisomerase.

- Glycerol is important for synthesis of fats, glycerophospholipids, and other membrane lipids. Most commonly it is made into glycerol-3-phosphate which can easily be made into DHAP and vice-versa (catalyzed by glycerol-3-phosphate dehydrogenase).

- Thanks to glycolysis, DHAP (for making glycerol-3-phosphate) can be produced by several sugars - glucose, galactose, fructose, and mannose.

- Thanks to gluconeogenesis, DHAP (for making glycerol-3-phosphate) can be produced from pyruvate, lactate, alanine, oxaloacetate, and aspartic acid.

- Animals can't use acetyl-CoA from fatty acid oxidation to make glucose in net amounts, but plants and bacteria can, since they have the glyoxylate cycle (which animals lack).

- Both glycolysis and gluconeogenesis, however, can use glycerol from fat metabolism, as noted.

- Pyruvate has three pathways, depending on the cell and the conditions it is in. It can be made into acetyl-CoA in most cells when oxygen is abundant. In animal cells, it is converted to lactate in low oxygen conditions (fermentation) and in bacteria and yeast, it is made into ethanol under the same conditions.

- The reason for the different paths depending on oxygen is because NAD^+ is needed to keep reaction 6 of glycoslysis going. In the absence of oxygen, the electron transport system (producer of NAD^+) is not operating very much. Formation of lactate from pyruvate produces NAD^+ as does conversion of pyruvate to ethanol.

- Pyruvate is readily interconverted with alanine by transamination.

- Pyruvate metabolism enzymes include include pyruvate dehydrogenase (makes acetyl-CoA), lactate dehydrogenase (makes lactate), transaminases (make alanine), pyruvate carboxylase (makes oxaloacetate), and pyruvate decarboxylase (a part of pyruvate dehydrogenase that makes acetaldehyde in bacteria and yeast).

- Gluconeogenesis occurs mostly in liver and kidney.

- Seven gluconeogenesis reactions are reversals of glycolysis reactions. Four gluconeogenesis reactions replace three essentially irreversible reactions of glycolysis.

- The four enzymes unique to gluconeogenesis are pyruvate carboxylase and PEP carboxykinase - PEPCK (catalyze reactions that bypass pyruvate kinase), F1,6BPase (bypasses PFK-1) and G6Pase (bypasses hexokinase).

- Pyruvate carboxylase and G6Pase are found in the mitochondria and endoplasmic reticulum, respectively. All of the other enzymes are found in the cytoplasm.

- Biotin (vitamin B_7) is a coenzyme used in carboxylation reactions, such as by pyruvate carboxylase.

- Biotin is readily produced by gut bacteria.
- All of the enzymes of glycolysis and nine of the eleven enzymes of gluconeogenesis are all in the cytoplasm.
- Cells avoid having anabolic and catabolic pathways occurring simultaneously, lest they produce a futile cycle.
- One method of control is called reciprocal regulation. In reciprocal regulation, things that activate catabolic pathways inactivate anabolic pathways and vice-versa. Methods can include allosteric effectors with opposite effects or covalent modifications (dephosphorylation/phosphorylation) with opposite effects.
- For example, PFK-1 is activated by F2,6BP, but F1,6BPase is inactivated by the same molecule.
- In glycogen metabolism enzymes, phosphorylation of phosphorylase kinase and glycogen phosphorylase (catabolic enzymes) has the effect of making them more active, whereas phosphorylation of glycogen synthase (anabolic enzyme) makes it less active. Dephosphorylation reverses these effects.
- Reciprocal regulation is very efficient.
- PEPCK is controlled largely at the level of synthesis, which can be controlled by hormones.
- Sequestering in an organelle is another means of regulation and is what occurs to pyruvate carboxylase - in mitochondria.
- Three regulated enzymes of glycolysis - hexokinase, PFK-1, and pyruvate kinase.
- Pyruvate kinase must be regulated to avoid creating a futile cycle when gluconeogenesis is occurring
- It takes energy from two triphosphates (ATP and GTP) to reverse the pyruvate kinase reaction.
- Feedforward activation occurs when a metabolite in a pathway activates an enzyme catalyzing a reaction ahead of it in the same pathway. F1,6BP feedforward activates pyruvate kinase to remove products so the aldolase reaction becomes favorable.
- Removing products is known as pulling a reaction.
- Increasing reactants is known as pushing a reaction.
- F2,6BP activates PFK-1 and inhibits F1,6BPase. PFK-1 is also allosterically activated by AMP, whereas F1,6BPase is inhibited. On the other hand, citrate inhibits PFK-1, but activates F1,6BPase.
- PFK-1 is also inhibited by ATP and is exquisitely sensitive to proton concentration.
- PFK-1 inhibition by ATP is due to a second ATP binding site (allosteric site separate from active site).
- F2,6BP is made from F6P by PFK-2.
- The liver is the major organ in the body for the synthesis of glucose. Muscles are major users of glucose to make the ATP they need for contraction.

- When muscles are exercising, they use oxygen faster than the blood can deliver it, causing them to go anaerobic. This causes pyruvate to be converted to lactate (to make NAD^+ for glycolysis), which is dumped into the blood. It travels to the liver where there is plenty of oxygen and is converted to pyruvate and then back to glucose, which is dumped into the blood for the muscles. This is the Cori cycle.

- The glucose-alanine cycle is a sort of parallel cycle to the Cori cycle for amines. Instead of reduction to make lactate, pyruvate is transaminated in tissues to make alanine, which travels in the blood to the liver where the amine is removed to make urea and the pyruvate is converted back to glucose.

- Glucose in high concentrations is hazardous to cells, so it is converted into polysaccharides to reduce problems and store it. This can be amylose, amylopectin (both in plants), or glycogen in animals. Cellulose is a structural polysaccharide of glucose in plants.

- Glucose (as G1P) is released from glycogen's α-1,4 bond by action of glycogen phosphorylase, which uses phosphate to clip off a glucose.

- Free glucose is released from α-1,6 bonds by action of debranching enzyme, which performs a hydrolysis reaction.

- In glycogen synthesis, G1P is converted to UDP-glucose by UDP-glucose pyrophosphorylase, using energy from UTP to make the activated intermediate.

- Glycogen synthase uses UDP-glucose to add glucose to a growing glycogen chain.

- Branching enzyme catalyzes formation of α-1,6 branches.

- Glycogen metabolism is regulated allosterically and covalently.

- Phosphorylation of glycogen phosphorylase b (GPb) creates glycogen phosphorylase a (GPa), which is considered more active.

- GPa converts from the R-state to the T-state in the presence of glucose.

- GPb converts to the R-state in the presence of AMP and to the T-state in the presence of ATP or G6P.

- Epinephrine or glucagon can activate a signaling cascade to favor phosphorylation of GPb to make GPa.

- The sequence of signaling steps are 1) hormone binding; 2) activation of a G-protein; 3) activation of adenylate cyclase to make cAMP; 4) activation of protein kinase A to phosphorylate phosphorylase kinase, activating it; 5) phosphorylation of GPb to make GPa.

- Phosphorylase kinase can be activated both by phosphorylation and by calcium.

- Phosphorylation of GPb to make GPa favors glycogen breakdown. Phosphorylation of glycogen synthase by protein kinase A inhibits glycogen synthesis (converts glycogen synthase A to glycogen synthase B).

- The G protein in the signaling cascade is activated by the hormone receptor by binding GTP. The G protein is active with GTP and over time slowly dephosphorylates GTP to make GDP, which inactivates itself.

- Phosphodiesterases break down cAMP to AMP, thus turning off that signal.
- Caffeine inhibits phosphodiesterases.
- Phosphoprotein phosphatase (PP-1) is activated by insulin binding to cell surface receptors. It catalyzes removal of phosphates from all of the phosphorylated enzymes mentioned above.
- It is regulated by an inhibitor called PI-1. PI-1 acts to inhibit when phosphorylated and this can be catalyzed by protein kinase A.
- Phosphoprotein phosphatase is carried in an inactive form by GPa in the R-state. When GPa binds glucose, it flips to the T-state, releasing PP-1 in an active state.
- Phosphoglucomutase interconverts G1P and G6P.
- Glycogen synthesis is catalyzed by glycogen synthase and starts with a protein called glycogenin.
- Phosphorylation/dephosphorylation reciprocally regulates glycogen's catabolism (phosphorylation activates) and anabolism (dephosphorylation activates).
- Glucagon/epinephrine binding favors phosphorylation. Insulin binding favors dephosphorylation.
- Cellulose formation is catalyzed by cellulose synthase. GDP-glucose or UDP-glucose can serve as substrates.
- The pentose phosphate pathway (PPP) is an multipurpose pathway involving sugars. It can produce NADPH from oxidation, ribose-5-phosphate for nucleotide synthesis and intermediates for use in other pathways.
- PPP doesn't really have a beginning, but one "starting point" is oxidation of G6P to form phosphoglucono-δ-lactone, catalyzed by G6P dehydrogenase.
- NADPH is important for anabolic pathways.
- The only decarboxylation (and last oxidation) occurs when 6-Phosphogluconate is converted to ribulose-5-phosphate (Ru5P), NADPH, and carbon dioxide. The reaction is catalyzed by 6-phosphogluconate dehydrogenase
- Ru5P interconverts with ribose-5-phosphate (R5P), catalyzed by Ru5P isomerase.
- Ru5P also interconverts with xylulose-5-P (Xu-5-P), catalyzed by Ru-5-P epimerase.
- Xu-5-P and erythrose-4-P combine (rearrange) to form GLYAL3P and F6P in a reaction catalyzed by transketolase (enzyme also in Calvin cycle).
- Thiamine pyrophosphate (TPP) is a coenzyme for transketolase. Its thiazole ring allows it to donate a proton and act as an acid, forming a carbanion.
- The carbanion is a nucleophile that attacks the carbonyl carbon of the substrate and covalently links to it, allowing it to carry the carbonyl group to the other substrate. A similar reaction occurs with sedohelptulose-7P (S-7-P) and GLYAL3P to interchange with R5P and Xu-5-P.

- The PPP allows glycolysis intermediates, such as GLYAL3P and F6P to be made into R5P for nucleotide synthesis. Thus PPP can make R5P for nucleotide metabolism even if its oxidative steps are blocked.
- Translaldolase catalyzes interconversion of GLYAL3P and S-7-P to E-4-P and F6P.
- Thiamine is vitamin B_1
- Thiamine pyrophosphate (TPP) is an enzyme cofactor found in all living systems derived from thiamine by action of the enzyme thiamine diphosphokinase.
- TPP is required for the oxidative decarboxylation of pyruvate to form acetyl-CoA and similar reactions.
- TPP is also required for oxidative decarboxylation of α-keto acids like **α**-ketoglutarate and branched-chain α-keto acids arising from metabolism of valine, isoleucine, and leucine. It is also used by transketolase.
- In the pyruvate dehydrogenase complex, TPP carries the activated acetaldehyde molecule to its attachment (and subsequent oxidation) to lipoamide.
- The Calvin cycle (dark cycle) is a metabolic pathway occurring exclusively in the chloroplasts of higher photosynthetic organisms.
- In the Calvin cycle, carbon dioxide is taken from the atmosphere and built into glycolysis intermediates that can ultimately be built into sugars.
- Reactions occur in regions of the chloroplast known as the stroma, the fluid areas outside of the thylakoid membranes.
- There are three phases to the Calvin cycle - assimilation of CO_2, reduction, and regeneration of starting materials.
- To synthesize a glucose from CO_2 requires electrons from 12 molecules of NADPH (and 18 ATPs).
- Ribulose-1,5-bisphosphate (Ru1,5BP) is the molecule that accepts the CO_2 in a reaction catalyzed by ribulose-1,5-bisphosphate carboylase (RUBISCO) - the most abundant enzyme on Earth.
- Reduction reactions in the Calvin cycle require electrons from NADPH.
- The resynthesis phase has multiple steps, but only utilizes two enzymes unique to plants - sedoheptulose-1,7 bisphosphatase and phosphoribulokinase. RUBISCO is the third (and only other) enzyme of the pathway unique to plants.
- In the resynthesis phase, Ru1,5BP is regenerated. GLYAL3P is converted to DHAP by triose phosphate isomerase. Some DHAPs are converted (via gluconeogenesis) to F6P (one phosphate is lost for each F6P).
- Two carbons from F6P are given to GLYAL3P to create E-4P and Xu-5P (reversal of PPP reaction). E-4P combines with DHAP to form sedoheptulose-1,7 bisphosphate (S1,7BP). The phosphate at position #1 is cleaved by sedoheptulose-1,7 bisphosphatase to yield S-7-P.
- Transketolase (another PPP enzyme) catalyzes transfer to two carbons from S-7-P to GLYAL3P to yield Xu-5P and R5P.
- Phosphopentose isomerase catalyzes conversion of R5P to Ru5P and phos-

phopentose epimerase similarly converts Xu-5P to Ru5P. Finally, phosphoribulokinase transfers a phosphate to Ru5P (from ATP) to yield Ru1,5BP.

- Ribulose-1,5-bisphosphate carboxylase (RUBISCO) catalyzes the addition of carbon dioxide to ribulose-1,5-bisphosphate (Ru1,5BP) to create two molecules of 3-phosphoglycerate.

- Oxygen competes with CO_2 for binding to RUBISCO. When that happens, an alternative metabolic pathway called photorespiration occurs. It involves production of 3-PG (like the CO_2 pathway) and one molecule of phosphoglycolate. The latter is converted to glyoxylate and then transaminated to form glycine. A complicated set of reactions convert glycine to serine. Serine can ultimately be converted into 3-PG, but there are significant energy costs, making the oxygen pathway less efficient than the carbon dioxide pathway.

- C4 plants differ from other plants (called C3 plants) in how they get the carbon dioxide to operate the Calvin cycle. C3 plants get it directly from the atmosphere. C4 plant assimilate it first onto PEP to make oxaloacetate, which is converted to malate and donates it to Ru1,5BP (Calvin cycle) in the bundle sheath cells of plants. This helps C4 plants to conserve oxygen and avoid photorespiration involving oxygen.

- Bacterial cell walls contain a layer of protection known as the peptidoglycan layer. The multi-step process for its synthesis begins with a modified sugar (glucosamine-6-P) and after converting it to UDP-N-acetylmuramic acid, a pentapeptide sequence of L-Ala-D-Glu-L-Lys-D-Ala-D-Ala is attached and it is linked to another pentapeptide of the same sequence. These D- amino acids are rare examples of such stereoisomers in living cells.

- Additions and rearrangements to the growing chain yields N-acetylmuramic acid-N-acetylglucosamine-decapeptide, which is added to the growing peptidoglycan chain in a reaction catalyzed by an enzyme known as DD-transpeptidase. This enzyme is the target of penicillin.

- Metabolons are cellular complexes containing multiple enzymes of a metabolic pathway that are arranged so that the product of one enzymatic reaction is passed directly to the enzyme that catalyzes the next reaction in the metabolic pathway.

- Metabolic pathways thought to use metabolons include glycolysis, the citric acid cycle, nucleotide metabolism, glycogen synthesis, steroid synthesis, DNA synthesis, RNA synthesis, the urea cycle, and the process of electron transport.

- Hypoxia occurs when the body or a region of it has an insufficient oxygen supply.

- The body's response to hypoxia is to produce Hypoxia-Inducible Factors (HIFs) - transcription factors that induce expression of genes to help cells adapt to hypoxic conditions. Many of the genes are, in fact, enzymes of glycolysis and GLUTs (glucose transport proteins).

- The hypoxia response allows cells to 1) import more glucose and 2) metabolize it when it arrives. This is important, since anaerobic glucose metabolism is only 1/15 as efficient as aerobic glucose metabolism.

- Cytoglobin facilitates transfer of oxygen from arteries to the brain.

- HIFs are regulated by oxidation. When oxygen is high, prolyl hydroxylase hydroxylates prolines in them to target them to the proteasome for destruction.

Citric Acid Cycle / Related Pathways

- The primary catabolic pathway in the body is the citric acid cycle - occurs completely in the mitochondrion.
- It is a common pathway for metabolism of the cells' major building blocks - sugars, fatty acids, and amino acids.
- The molecule "feeding" the citric acid cycle is acetyl-CoA and it can be obtained from pyruvate (from glycolysis), from fatty acid β-oxidation, from ketone bodies, and from amino acid metabolism.
- Molecules from other pathways feeding into the citric acid cycle for catabolism make the citric acid cycle 'cataplerotic'.
- Anabolically, acetyl-CoA is also very important for providing building blocks for synthesis of fatty acids, ketone bodies, amino acids and cholesterol.
- Some citric acid cycle intermediates are also important in amino acid metabolism, heme synthesis, electron shuttling, and shuttling of acetyl-CoA across the mitochondrial inner membrane.
- Anaplerotic means 'to fill up and it describes the pathway's ability to provide intermediates for use in other pathways.
- The pyruvate dehydrogenase enzyme complex has multiple copies of three subunits (E_1, E_2, and E_3) that catalyze the decarboxylation of pyruvate to form acetyl-CoA.
- The reaction mechanism requires use of five coenzymes - thiamine pyrophosphate (TPP), lipoamide, coenzyme A, NAD^+/NADH, and FAD/$FADH_2$.
- E_1 is the decarboxylase. E_2 is dihydrolipoamide acetyltransferase and E_3 is called dihydrolipoyl dehydrogenase.
- The steps, sequentially occurring on E_1, E_2, and E_3, are 1) decarboxylation of pyruvate; 2) oxidation of the decarboxylated product; and 3) transfer of electrons to ultimately form NADH.
- The process begins with formation of a nucleophilic carbanion on the TPP that attacks the electrophilic ketone carbon on the pyruvate, releasing carbon dioxide in a non-oxidative decarboxylation.
- The remaining two carbon piece is known as an activated acetaldehyde (or hydroxyethyl unit) attached to TPP.
- Next, acetylation occurs as the 2-carbon hydroxyethyl unit is transferred to lipoamide on E_2. This is an oxidation of the hydroxyethyl (to form an acetyl group) and a reduction for the lipoamide to which the unit is transferred.
- Lipoamide is a lipoic acid covalently attached to a lysine of E_2.
- Prokaryotes have the option to release the acetyl group as acetaldehyde (and form ethanol in fermentation when oxygen is limiting), but animals cannot.

- In animals and prokaryotes with abundant oxygen, the acetyl group is then transferred from lipoamide to coenzyme A in E_2 to form acetyl-CoA, which is released.
- The lipoamide is left with sulfhydryl groups and these must be converted back to disulfides to complete the cycle.
- Lipoamide transfers electrons to FAD in E_3, forming $FADH_2$ and a disulfide bond on lipoamide. $FADH_2$ transfers electrons to NAD^+, forming NADH, which is released.
- Pyruvate deyhdrogenase is regulated both allosterically and by covalent modification - phosphorylation / dephosphorylation.
- ATP, acetyl-CoA, NADH, and fatty acids (indicators of high energy) inhibit the enzyme.
- AMP, coenzyme A, NAD^+, and calcium stimulate it.
- Phosphorylation by pyruvate dehydrogenase kinase (PDK) inhibits the enzyme. PDK is itself inhibited by pyruvate.
- Dephosphorylation by pyruvate dehydrogenase phosphatase (PDP) activates it.
- Low concentrations of NADH and acetyl-CoA are necessary for PDP to dephosphorylate the enzyme and remain on it. When those concentrations rise, PDP dissociates and PDK gains access to a serine for phosphorylation.
- Insulin and calcium can also activate the PDP.
- In the citric acid cycle, acetyl-CoA combines with oxaloacetate (OAA) to form citrate (catalyzed by citrate synthase).
- The $\Delta G°'$ is fairly negative and helps to "pull" the reaction preceding it in the cycle catalyzed by malate dehydrogenase.
- In the next reaction, citrate is isomerized to isocitrate by action of the enzyme called aconitase.
- Isocitrate is a branch point for the glyoxylate cycle, which occurs in plants and bacteria.
- Oxidative decarboxylation of isocitrate by isocitrate dehydrogenase produces NADH and **α**-ketoglutarate.
- **α**-ketoglutarate is a branch point for synthesis of glutamate (by transamination).
- Decarboxylation of α-ketoglutarate yields succinyl-CoA and is catalyzed by **α**-ketoglutarate dehydrogenase, an enzyme similar to pyruvate dehydrogenase - employs the same five coenzymes.
- Succinyl-CoA is a branch point for the synthesis of heme.
- Succinyl-CoA is converted to succinate in a substrate level phosphorylation reaction catalyzed by succinyl-CoA synthetase. Cleavage of the thioester Co-A bond provide the energy for the formation of GTP.
- Succinate is also produced by metabolism of odd-chain fatty acids.
- Oxidation of succinate to fumarate is catalyzed by succinate dehydrogenase and produces $FADH_2$.

- Fumarate is also a byproduct of nucleotide metabolism and the urea cycle.
- Succinate dehydrogenase is embedded in the inner membrane of the mitochondrion and transfers electrons to coenzyme Q of the electron transport system.
- In the next reaction, fumarate gains a water to become malate (catalyzed by fumarase).
- Malate is an important shuttle molecule in the malate-aspartate shuttle for moving electrons across the mitochondrial inner membrane in ferrying carbon dioxide from mesophyll cells to bundle sheath cells in C_4 plants.
- Conversion of malate to oxaloacetate by malate dehydrogenase is a rare biological oxidation that has a $\Delta G°'$ with a positive value (29.7 kJ/mol). As noted above, it is pulled by the citrate synthase reaction.
- Oxaloacetate intersects pathways for amino acid metabolism (readily converted to aspartic acid), transamination (nitrogen movement) and gluconeogenesis.
- Reversal of the citric acid cycle provides a mechanism for assimilating CO_2 in bacteria (Arnon-Buchanan cycle).
- ATP and NADH will tend to inhibit the cycle and NAD^+, AMP, and ADP will tend to activate the cycle.
- Citrate synthase is inhibited by NADH, ATP, and succinyl-CoA.
- Isocitrate dehydrogenase is inhibited by ATP, activated by ADP and NAD^+.
- α-ketoglutarate dehydrogenase is inhibited by NADH and succinyl-CoA and activated by AMP.
- The citric acid cycle is an important source of molecules needed by cells (anaplerotic) and a mechanism for extracting energy from amino acids in protein breakdown and other breakdown products (cataplerotic).
- Transamination of α-ketoglutarate and oxaloacetate produces glutamate and aspartic acid, respectively. Oxaloacetate is needed for production of glucose in gluconeogenesis.
- Glutamate has an important role in movement of nitrogen through cells.
- Aspartate is a precursor of other amino acids and for making pyrimidine nucleotides.
- Succinyl-CoA is necessary for the synthesis of porphyrins, such as the heme groups in hemoglobin, myoglobin and cytochromes.
- Citrate carries an acetyl group for making acetyl-CoA across the inner mitochondrial membrane into the cytoplasm for fatty acid synthesis.
- Acetyl-CoA is produced by fatty acid oxidation, pyruvate decarboxylation, amino acid catabolism, and breakdown of ketone bodies.
- α-ketoglutarate is produced by amino acid metabolism.
- Succinyl-CoA comes from propionic acid metabolism.

- Fumarate is produced from the urea cycle and purine metabolism.
- Malate is made by carboxylation of PEP in plants.
- Oxaloacetate comes from many sources, including amino acid catabolism and pyruvate carboxylase action on pyruvate in gluconeogenesis.
- The glyoxylate cycle (plants and bacteria only) bypasses the decarboxylation reactions while using most of the non-decarboxylation reactions of the citric acid cycle thank to two enzymes - isocitrate lyase and malate synthase.
- Isocitrate lyase catalyzes the conversion of isocitrate into succinate and glyoxylate. Succinate continues in the cycle to form oxaloacetate.
- Glyoxylate combines with a second acetyl-CoA (one acetyl-CoA was used to start the cycle) to create malate (catalyzed by malate synthase). Malate also is converted to oxaloacetate.
- At the end of one turn of the glyoxylate cycle, two molecules of oxaloacetate are produced. Because of this, bacteria and plants can make glucose in net amounts from acetyl-CoA. Animals can't, since they only regenerate the oxaloacetate they start with in the citric acid cycle.
- The glyoxylate cycle is particularly important for plant seed germination, allowing the seedling to make glucose from stored lipids since it is not exposed to the sun.
- Each turn of the glyoxylate cycle produces one FADH2 and one NADH instead of the three NADHs, one FADH2, and one GTP made in each turn of the citric acid cycle.
- Control of the glyoxylate cycle in plants and bacteria occurs as a result of isocitrate dehydrogenase. The enzyme can be inactivated by phosphorylation by a kinase found only in plants and bacteria. Inactivation causes isocitrate to accumulate in the mitochondrion of the plants and when this happens, it gets shunted to the glyoxysome, favoring the glyoxylate cycle.
- Removal of the phosphate by a specific phosphoprotein phosphatase restores activity to the enzyme.
- In bacteria, where the enzymes for both cycles are present together in the cytoplasm, accumulation of citric acid cycle intermediates and glycolysis intermediates will tend to favor the citric acid cycle by activating the phosphoprotein phosphatase, whereas high energy conditions will tend to favor the glyoxylate cycle by inhibiting it.
- Acetyl-CoA is found in fatty acid oxidation/synthesis, pyruvate oxidation, the citric acid cycle, amino acid anabolism/catabolism, ketone body metabolism, steroid/bile acid synthesis, and (by extension from fatty acid metabolism) prostaglandin synthesis.
- Ketone bodies are molecules made in the liver when the blood levels of glucose fall very low.
- Pathways for ketone body synthesis and cholesterol biosynthesis overlap.
- In the beginning, two acetyl-CoAs are joined together by thiolase to make acetoacetyl-CoA.

- A third acetyl-CoA is added to form hydroxy-methyl-glutaryl-CoA, or HMG-CoA - the last common molecule of ketone body synthesis and cholesterol synthesis.
- For ketone body synthesis, HMG-CoA is broken down into acetyl-CoA and acetoacetate. Acetoacetate is a ketone body. It can be reduced to form another one, D-β-Hydroxybutyrate (not actually a ketone, though, but still called a ketone body).
- Acetoacetate can break down to acetone, which can be converted to pyruvate and made into glucose.
- D-β-Hydroxybutyrate can cross the blood-brain barrier. It can be then oxidized back to acetoacetate, converted to acetoacetyl-CoA, and then broken down to two molecules of acetyl-CoA for oxidation in the citric acid cycle.
- When a body is producing ketone bodies for its energy, this state in the body is known as ketosis.
- Ketone bodies can be made in animals from the breakdown of fat/fatty acids.
- Ketosis may arise from fasting, a very low carbohydrate diet or, in some cases, diabetes.
- Acidosis refers to conditions in the body where the pH of arterial blood drops below 7.35. In alkalosis, the pH of the arterial blood rises above 7.45.
- Blood pH values lower than 6.8 or higher than 7.8 can cause irreversible/deadly damage. Acidosis may have roots in metabolism (metabolic acidosis) or in respiration (respiratory acidosis).
- In metabolic acidosis, production of excess lactic acid or failure of the kidneys to excrete acid can cause blood pH to drop.
- Respiratory acidosis arises from accumulation of carbon dioxide in the blood. Causes include hypoventilation, pulmonary problems, emphysema, asthma, and severe pneumonia.

Fats and Fatty Acids

- Fat is the most important energy storage form of animals.
- Fat stores more energy per weight than carbohydrates.
- Fat's insolubility in water makes movement in the body more complicated.
- Dietary triglycerides are solubilized in the digestive system by the stomach and emulsification by the bile acids.
- In the intestines, triglycerides are acted on by lipases to release two fatty acids, leaving a monoacylglyceride, which is moved with the freed fatty acids into the lymph system where the fat is reassembled.
- Fat is stored in the body in adipocytes.
- In adipocytes, hormone sensitive triacylglycerol lipase (HSTL) removes the first fatty acid from the fat. Diacylglyceride lipase removes the second one and monoacylglyceride lipase removes the third.
- HSTL is the primary regulated enzyme in fat catabolism. It is activated by binding of epinephrine to the cell surface receptor

using the same system that activates glycogen breakdown enzymes.

- HSTL is inhibited by dephosphorylation and this is stimulated by binding of insulin to its cell membrane receptor.

- Perilipin is a protein that associates with fat droplets and helps regulate action of HSTL.

- When perilipin is not phosphorylated, it coats fat droplets and blocks HSTL from accessing it. Activation of protein kinase A in the epinephrine cascade, results in phosphorylation of perilipin and HSTL.

- Perilipin expression is high in obese organisms and some mutational variants have been associated with obesity in women.

- In fat synthesis, glycerol-3-phosphate is esterified at position 1 with a fatty acid (enzyme = glycerol-3 O-phosphate acyl transferase), followed by a duplicate reaction at position 2 to make phosphatidic acid.

- Phosphatidic acid gets dephosphorylated to diacylglycerol, which is then esterified with a third fatty acid to complete the synthesis of the fat.

- Fatty acids released from adipocytes travel in the bloodstream bound to serum albumin.

- Membrane-associated fatty acid binding proteins regulate the uptake of fatty acids by cells. These include CD36, plasma membrane-associated fatty acid-binding protein, and a family of fatty acid transport proteins (called FATP1-6).

- Fatty acids are oxidized in a process that chops off two carbons at a time to make acetyl-CoA.

- Long fatty acids (22 or more carbons) begin oxidation in peroxisomes and then move to the mitochondrion. Other ones get oxidized solely in the mitochondrion.

- In the cytoplasm, fatty acids are attached to coenzyme A and then they travel to the intermembrane space of the mitochondrion where CoA is replaced by carnitine. The enzyme catalyzing this, carnitine acyl transferase, helps to control how many fatty acids are moved into the mitocohondrial matrix. It is inhibited by malonyl-CoA, an intermediate in fatty acid synthesis.

- The acyl-carnitine is moved into the matrix where the carnitine is replaced by CoA.

- Oxidation occurs in the matrix. There are four steps -

1) dehydrogenation to form $FADH_2$ and a *trans* intermediate (enzyme = acyl-CoA dehydrogenase)

2) hydration to produce an L intermediate at position three (enzyme = enoyl-CoA hydratase)

3) oxidation of the hydroxyl group to form a ketone and NADH (enzyme = hydroxyacyl-CoA dehydrogenase)

4) thiolytic cleavage (catalyzed by thiolase). Thiolase is inhibited by acetyl-CoA.

- Acyl-CoA dehydrogenase comes in three different forms – ones specific for long, medium, or short chain length fatty acids. The one for long fatty acids is found in the peroxisomes.

- Plants and yeast perform **β**-oxidation exclusively in peroxisomes.

- The acyl-CoA dehydrogenase that works on medium length fatty acids is the one most commonly deficient in animals and has been linked to sudden infant death syndrome.

- Reversal of the thiolase reaction at the four carbon stage is the first step in ketone body synthesis.

- Oxidation of fatty acids is chemically very similar to oxidation of the four carbon compounds of the citric acid cycle.

- Oxidation of fatty acids with odd numbers of carbons ultimately produces an intermediate with three carbons - propionyl-CoA. It cannot be oxidized in the **β**-oxidation pathway.

- Oxidation of propionyl-CoA involves 1) carboxylation to make D-methylmalonyl-CoA; 2) isomerization to L-methylmalonyl-CoA; 3) rearrangement to form succinyl-CoA.

- The last reaction above requires vitamin B_{12}.

- Peroxisomal fatty acid oxidation is slightly different from mitochondrial fatty acid oxidation.

- Peroxisomes have no electron transport system, so they transfer the first set of electrons directly to oxygen to make H_2O_2.

- NADH made in the peroxisomes must be shuttled into the mitochondrion for making ATP.

- Peroxisomes are also involved in oxidation of branched chain fatty acids, leukotrienes, and some prostaglandins.

- Unsaturated fatty acids have *cis* bonds that interfere with **β**-oxidation and must be isomerized for metabolism.

- There are two relevant enzymes.

1. cis-**Δ**3-enoyl-CoA isomerase will convert a *cis* bond between carbons Δ3 and Δ4 to a *trans* bond between carbons Δ2 and Δ3, allowing β-oxidation to proceed at that point.

2. 2,4 dienoyl CoA reductase (using NADPH) will convert an intermediate with a *trans* double bond between carbons Δ2 and Δ3 and a *cis* double bond between carbons Δ4 and Δ5 to an intermediate with a single *cis* bond between carbons Δ3 and Δ4. cis-**Δ**3-enoyl-CoA isomerase will then convert it to a *trans* bond between carbons two and three, allowing **β**-oxidation to proceed

- **α**-oxidation is a peroxisomal pathway necessary for catabolism of fatty acids that have branches in their chains.

- Branched molecules like phytanic acid (from chlorophyll's phytol group) undergo hydroxylation and oxidation on carbon number two (in contrast to carbon three of **β**-oxidation), followed by decarboxylation and production of an unbranched intermediate that can be further oxidized by the β-oxidation pathway.

- Deficiency of **α**-oxidation leads to Refsum's disease.

- **ω**-oxidation is a minor oxidation pathway in the smooth endoplasmic reticulum of liver and kidney cells. In it, oxidation begins at the ω end of the fatty acid. Steps in the process involve 1) oxidation of the terminal methyl group of the fatty acid to an alcohol; 2) oxidation of the alcohol to an aldehyde, and 3) oxidation of the aldehyde group to a carboxylic acid.

- After the last oxidation, the fatty acid has carboxyl groups at each end and can be attached to coenzyme A at either end and subsequently oxidized, ultimately yielding succinate.

- Synthesis of fatty acids occurs in the cytoplasm and endoplasmic reticulum of the cell and is chemically similar to the reversal of the **β**-oxidation process.

- Transport of acetyl-CoA from the mitochondrial matrix occurs when it begins to accumulate, such as when the citric acid cycle slows or stops from lack of exercise.

- Movement of acetyl groups to the cytoplasm is done by citrate and acetylcarnitine. Carnitine can swap with CoA groups on acetyl-CoA when concentration of the latter increases. When citrate accumulates, it can be transported out of the mitochondrion to the cytoplasm where citrate lyase can cleave it to oxaloacetate and acetyl-CoA.

- In animals, six different catalytic activities necessary to fully make palmitoyl-CoA are contained in a single complex called fatty acid synthase.

- These include 1) transacylases (MAT) for swapping CoA-SH with ACP-SH on acetyl-CoA and malonyl-CoA; 2) a synthase (KS) to catalyze addition of the two carbon unit from the three carbon malonyl-ACP in the first step of the elongation process; 3) a reductase (KR) to reduce the ketone; 4) a dehydrase (DH) to catalyze removal of water; 5) a reductase (ER) to reduce the *trans* double bond and 6) a thioesterase (TE) to cleave the finished palmitoyl-ACP into palmitic acid and ACP.

- The process of making a fatty acid in the cytoplasm starts with two acetyl-CoA molecules. One is converted to malonyl-CoA by adding a carboxyl group (catalyzed by acetyl-CoA carboxylase - the only regulated enzyme of fatty acid synthesis and the only one separate from fatty acid synthase).

- Next, both acetyl-CoA and malonyl-CoA have their CoA-SH portions replaced by acyl carrier protein (ACP).

- In the next step, a fatty acyl-ACP (in this case, acetyl-ACP) is joined to malonyl-ACP which splits out the carboxyl group from malonyl-ACP and creates the acetoacyl-ACP intermediate.

- The ketone is then reduced to a hydroxyl (D-configuration) using NADPH.

- Next, water is removed from carbons 2 and 3 of the hydroxyl intermediate to form a *trans* intermediate.

- Last, the double bond is hydrogenated to yield a saturated intermediate. This completes the first round of synthesis.

- The acyl group produced at the end of the first round is the substrate for the second round of synthesis and this cycling continues until a 16-carbon acyl-ACP is produced - palmitoyl-ACP. At this point, a thioesterase on the fatty acid synthase cleaves the ACP

from the palmitoyl-ACP to yield palmitic acid and the cytoplasmic synthesis ceases.

- Acetyl-CoA carboxylase is regulated by both allosteric control and covalent modification.
- It can be phosphorylated by both AMP kinase and protein kinase A (inactivates and causes it to depolymerize).
- Dephosphorylation is stimulated by phosphatases activated by insulin binding. Dephosphorylation activates the enzyme and favors its assembly into a long polymer.
- Citrate is an allosteric activator of acetyl-CoA carboxylase and palmitoyl-CoA is an inhibitor.
- Elongation to make fatty acids longer than 16 carbons occurs in the endoplasmic reticulum catalyzed by elongases.
- The mechanism is similar to cytoplasmic synthesis (a malonyl group is used to add two carbons, for example), but CoA is attached to the intermediates and the enzymes are separable and not part of a complex.
- Desaturation of fatty acids occurs in the endoplasmic reticulum by desaturases, which make *cis*, not *trans* bonds.
- The delta (Δ) system numbers the carbon at the carboxyl end as number 1 and the omega (ω) number system numbers the carbon at the methyl end as number 1.
- Humans have desaturases named as Δ5, Δ6, and Δ9 - none greater than Δ9, making a requirement for linoleic (Δ9,12) and linolenic acid (Δ9,12,15) in the diet, since they cannot be synthesized (essential fatty acids).
- The mechanism of desaturases requires NAD(P)H, O_2, two membrane-bound cytochromes, the membrane bound desaturase, and the fatty acid.
- In the electron transfer, the O_2 is reduced to two molecules of H_2O. This reduction requires four electrons and four protons. Two electrons and two protons come from the fatty acid to form the double bond on it. Two electrons come from the NAD(P)H via the cytochromes and two protons come from the aqueous solution.
- *Trans* fatty acids found in trans fat of prepared food are produced not by biological processes, but rather by the process of partial hydrogenation of unsaturated fats.
- The pathway for making prostaglandins, leukotrienes, prostacyclin, and thromboxanes is an extension of fatty acid synthesis.
- Prostaglandins (eicosanoids) are synthesized from arachidonic acid when it has been cleaved from membrane lipids by a phospholipase - most commonly phospholipase A_2 (PLA_2). The bee venom known as mellitin activates PLA_2.
- Lipocortin (also called annexin) is a protein that inhibits PLA_2. Synthesis of lipocortin is stimulated by glucocorticoid hormones, such as cortisol.
- Synthesis of prostaglandins can be reduced by inhibiting the cyclooxygenase (also called prostaglandin synthase or COX) that catalyzes their synthesis from arachidonic acid.

- Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COX enzymes. Molecules in this class include aspirin, ibuprofen, Vioxx, and Celebrex. Aspirin is a suicide inhibitor.

- Since prostacyclin, and thromboxanes are made from arachidonic acid / prostaglandins, anything that inhibits their synthesis also reduces the amount of prostacyclins and thromboxanes. Thromboxanes are implicated in making platelets "stickier" and this is why aspirin is taken to reduce clotting, since platelet stickiness is part of the cellular response of blood clotting.

- COX enzymes come in at least two forms in humans - COX-1 and COX-2. COX-1 is synthesized constitutively whereas COX-2 enzymes are expressed in increasing amounts in areas of growth and inflammation.

- COX-2 specific inhibitors are associated with some serious side effects, including a 37% increase in incidence of major vascular events and some of the gastrointestinal problems of NSAIDs. The increased risk of heart attack, thrombosis, and stroke are apparently due to an imbalance between prostacyclin (reduced by COX-2 inhibitors) and thromboxanes (not reduced) by the same inhibitors.

- Phosphatidic acid is an intermediate in the synthesis of triacylglycerols and other lipids, including phosphoglycerides.

- Diacylglycerol (DAG), which is an intermediate in fat synthesis, also acts as a messenger in some signaling systems.

- Fatty acids twenty carbons long (eicosanoids) based on arachidonic acid are precursors of the leukotrienes, prostaglandins, thromboxanes, and endocannabinoids.

- Thiolase can join two acetyl-CoAs to make acetoacetyl-CoA - a precursor of both ketone bodies and the isoprenoids. Isoprenoids include steroid hormones, cholesterol, bile acids, and the fat soluble vitamins. In plants, acetyl-CoA can be made into carbohydrates in net amounts via the glyoxylate cycle.

- In 2014, over 600 million adults and 42 million children in the world were classified as obese.

- Adipokines are adipose tissue-synthesized cytokines.

- Examples include leptin, adiponectin (regulates glucose levels and fatty acid oxidation), apelin (control of blood pressure, angiogenesis promotion, vasodilator release, increased water intake), chemerin (stimulation of lipolysis, adipocyte differentiation, link to insulin resistance), and resistin (links to obesity, type II diabetes, LDL production in liver).

- Resistin stimulates insulin resistance, when injected. It is also linked to increased inflammation. Serum levels of it correlate with increased obesity. Resistin stimulates production of LDLs and adversely impacts the effects of statin drugs used to control levels of cholesterol in the body.

- Leptin is a peptide hormone that negatively impacts hunger and regulates energy balance. It is countered by ghrelin, also known as the hunger hormone. Both hormones act in the hypothalamus where hunger is controlled. Low levels of leptin correlate with a decrease in hunger.

- Leptin levels are highest between midnight and early morning, presumably to suppress appetite. Levels of leptin in humans do not strictly reflect levels of fat. Sleep deprivation can reduce leptin levels, as can increasing levels of testosterone and physical exercise. Estrogen increases leptin levels. Emotional stress and insulin can increase leptin levels.

- Obesity increases leptin levels, but doesn't fully suppress appetite.

- Neuropeptide Y is a potent hunger promoter whose receptors in the arcuate nucleus can be bound and blocked by leptin.

- Binding of leptin to the Ob-Rb receptor causes down-regulation of synthesis of endocannabinoids, whose normal function is to increase hunger. High fructose diets have been associated with reduced levels of leptin and of leptin receptor.

- Ghrelin exerts its effects on the central nervous system to increase appetite. It is able to cross the blood-brain barrier. The ghrelin receptor in the brain is found on the same cells as the leptin receptor (arcuate nucleus). Leptin can counter ghrelin by decreasing hunger. Stretching of the stomach reduces the expression of ghrelin.

- Circulating levels of ghrelin increase before eating and decrease afterwards.

- Ghrelin increases food seeking behavior and there is a negative correlation between levels of ghrelin and weight.

- Neuropeptide Y acts as a vasoconstrictor and favors growth of fat tissue. It appears to stimulate food intake, fat storage, relieve anxiety/stress, reduce pain perception, and lower blood pressure. Blockage of neuropeptide Y receptors in the brain of rats decreases food intake. Repeated stress and high fat, high sugar diets stimulate neuropeptide Y levels and cause abdominal fat to increase.

- High levels of neuropeptide Y may help individuals to recover from post-traumatic stress disorder and to reduce the fear response. It may also protect against alcoholism.

Other Lipids

- Acetyl-CoA is the building block of most lipids.

- Isoprenoids are molecules built from isoprene building blocks which, in turn, are built from acetyl-CoA.

- The two isoprene building blocks are isopentenyl pyrophosphate and dimethylallyl pyrophosphate.

- The pathway to make isoprene building blocks overlaps with that of ketone body synthesis.

- The first step begins with joining of two acetyl-CoAs by thiolase to make acetoacetyl-CoA.

- HMG-CoA synthase catalyzes addition of a third acetyl-CoA to form the six carbon compound known as hydroxymethyl glutaryl-CoA (HMG-CoA).

- HMG-CoA is a branch point with ketone body synthesis.

- In the direction of isoprene synthesis, HMG-CoA reductase acts on HMG-CoA to produce mevalonate

- Mevalonate gets phosphorylated twice and then decarboxylated to yield isopentenyl-pyrophosphate (IPP) - readily converted to dimethylallylpyrophosphate (DMAPP). These molecules are called isoprenes.

- HMG-CoA reductase is the most important regulated enzyme leading to cholesterol and is targeted by statin drugs, which act as competitive inhibitors of HMG-CoA for the enzyme.

- Statins also increase production of LDL receptors in the liver, which favors uptake and destruction of LDLs, thus lowering serum cholesterol levels.

- HMG-CoA reductase is feedback inhibited by cholesterol and its synthesis is favored by high levels of blood glucose.

- Phosphorylation of HMG-CoA reductase by AMP-activated protein kinase inhibits its activity.

- Transcription of the HMG-CoA reductase gene is enhanced by binding of the sterol regulatory element binding protein (SREBP) to the sterol recognition element (a promoter sequence) located near the gene coding sequence. As cholesterol levels rise, SREBP is proteolytically cleaved and transcription stops.

- Cholesterol is a precursor of steroid hormones and bile acids and its immediate metabolic precursor, 7-dehydrocholesterol, is also a precursor of vitamin D.

- The pathway leading to cholesterol is the isoprenoid pathway. Branches of it lead to fat-soluble vitamins.

- Joining of IPP and DMAPP forms geranyl-pyrophosphate (10 carbons). Addition of another IPP make farnesyl-pyrophosphate, a 15-carbon compound.

- Joining two farnesyl-PPs yields squalene, a 30 carbon compound.

- Squalene can be rearranged to form lanosterol - a cyclic intermediate resembling cholesterol

- 19 steps after lanosterol, cholesterol is made.

- Steroid hormones made from cholesterol include progestagens, androgens, estrogens, mineralocorticoids, and the glucocorticoids.

- Pregnenolone, made from cholesterol, is the precursor of all of the steroid hormones.

- Estrogens are made from androgens by formation of an aromatic (benzene) ring, catalyzed by aromatase.

- Aromatase inhibitors are use to stop cancers that are stimulated by estrogen.

- Oxidation of the terminal carbon on the side chain off the rings of cholesterol leads to bile acids. Hydroxylation of the rings and linkage to other polar compounds increases polarity.

- Bile acids include cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, and deoxycholic acid.

- The more cholesterol there is made into bile acids, the less cholesterol there is available. The fewer bile acids recycled, the less

cholesterol there is. Reduced cholesterol promotes uptake of LDLs from the blood.

- Addition of isopentenyl pyrophosphate to farnesyl pyrophosphate creates a 20 carbon intermediate - geranylgeranyl pyrophosphate (GGPP).

- Combining two GGPPs creates a 40 carbon intermediate that decomposes to form phytoene. Desaturases oxidize two single bonds in phytoene, creating lycopene.

- Cyclization of end portions of lycopene give rise to **β**-carotene, the precursor of vitamin A.

- Catalysis by β-Carotene 15,15' monooxygenase cleaves **β**-carotene to form retinal (vitamin A aldehyde). It can be reduced to retinol (alcohol) or oxidized to retinoic acid.

- Retinoic acid binds to the retinoic acid receptor (RAR). RAR binds to DNA and affects transcription of Hox genes important for differentiation.

- Sphingolipid synthesis joins palmitoyl-CoA and serine to make an 18-carbon amine called 3-keto-sphinganine.

- Reduction of 3-keto-sphinganine yields dihydrosphingosine and addition of a fatty acid from an acyl-CoA yields N-acylsphinganine - a ceramide.

- A ceramide can be made into a cerebroside by addition of a glucose from UDP-glucose . It can be turned into a globoside by addition of a few simple sugars or a ganglioside by addition of a complex set of sugars. Alternatively, addition of phosphocholine yields sphingomyelin - important for the myelin sheath of nerve cells.

- Sphingolipid catabolism is critical. Deficiencies lead to severe problems.

- GM1 glandiosidoses (arising from inability to break down GM1 gangliosides) cause severe neurodeneration and seizures.

- Synthesis of glycerophospholipids begins with addition of a fatty acid to glycerol-3-phosphate. Addition of a second fatty acid creates phosphatidic acid.

- CDP serves as part of an activated intermediate in synthesis of phosphatidyl compounds by two methods

1. CTP combines with phosphatidic acid to make CDP-diacylglcyerol (activated intermediate) with release of a pyrophosphate. The phosphatidyl part can then to added to molecules like serine (making phosphatidylserine) or inositol (making phosphatidylinositol).

2 CTP can be combined with molecules to make intermediates that can be put onto diacylglycerol. Example - CDP-choline can be joined to diacylglycerol to make phosphatidylcholine.

- Phosphatidylserine can be decarboxylated to form phosphotidylethanolamine. Tri-methylation of phosphotidylethanolamine by SAM yields phosphatidylcholine.

- Phosphotidylethanolamine and phosphatidylserine can swap groups. So can phosphatidylserine and phosphatidylcholine.

- CDP-diacylglycerol and phosphatidylglycerol can combine to make cardiolipin

- CDP-diacylglycerol and glycerol-3-phosphate can combine to for phosphatidylglycerol
- In heme synthesis, δ-aminolevulinic acid is made first from glycine and succinyl-CoA.
- Joining of two δ-aminolevulinic acid molecules together with splitting out of two molecules of water yields porphobilinogen.
- Joining of four molecules of porphobilinogen together yields hydroxylmethylbilane
- Then a series of reactions including loss of water, six carbon dioxides, oxidation, loss of six protons, and attachment of an atom of iron yields heme.
- Two enzymes in heme synthesis are sensitive to lead, leading to 1) anemia and 2) accumulation of δ-aminolevulinic acid, which can be harmful to neurons in development.
- Deficient enzymes of the heme biosynthesis pathway lead to porphyrias - lead to accumulation of pathway intermediates.
- Severe porphyrias can lead to brain damage, nerve damage, mental disturbances and skin problems on exposure to light. The "madness" of King George III may have been due to porphyria and the vampire legend may similarly have arisen from porphyria.
- Targets for degradation are hemes within damaged red blood cells, which get removed from the blood supply due to their appearance, leading to anemia when blood cells in high enough numbers appear damaged, such as in sickle cell anemia.
- The first biochemical step in catabolism of heme is conversion of heme to biliverdin in the spleen, releasing iron. Biliverdin is converted to bilirubin by biliverdin reductase and is secreted from the liver into bile.
- Bilirubin is converted to urobilinogen by bacteria. Some is absorbed by intestinal cells and transported into kidneys and excreted. The yellow color of urine arises from the compound known as urobilin - an oxidation product of urobilinogen.
- The remaining urobilinogens are converted in the intestinal tract to stercobilinogen whose oxidation product is stercobilin, which gives the color associated with feces.

Amino Acid Metabolism

- Amino acid metabolism is not a single pathway
- Nitrogen moves in cells through the process of transamination
- α-ketoglutarate, glutamate, and glutamine play major roles in transamination, differing by one amine each.
- A common transamination is α-ketoacid + glutamate <=> amino acid + α-ketoglutarate
- Transamination reactions occur by a ping-pong mechanism and involve swaps of amines and oxygens in Schiff base reactions.

- Glutamine and asparagine are the products of gaining an amine in their respective R-groups from ammonium ion.
- Essential amino acids cannot be made by an organism and must be in the diet.
- Amino acids with common metabolic pathways are grouped in families.
- The **α**-ketoglutarate family includes glutamate, arginine, glutamine, and proline.
- Glutamate can be made by transamination of α-ketoglutarate or by addition of ammonium ion to α-ketoglutarate in a reaction catalyzed by glutamate dehydrogenase. Reversing the reaction releases ammonium ions, which can be important for the urea cycle and glutamine metabolism.
- Any citric acid cycle intermediate can be a precursor of glutamate.
- Glutamine can be made from glutamate via catalysis by glutamine synthetase,
- Glutamine synthetase is one of the most important regulatory enzymes in all of amino acid metabolism. It can be regulated by many allosteric effectors and by adenylylation of a tyrosine residue in the enzyme.
- The reaction catalyzed by glutamine synthetase is

$$\text{Glutamate} + \text{ATP} + NH_4^+ \rightleftharpoons \text{Glutamine} + \text{ADP} + P_i$$

- This removes toxic ammonia (ammonium) - an important consideration in brain tissue.
- Inhibitors of glutamine synthetase include histidine, tryptophan, carbamoyl phosphate, glucosamine-6-phosphate, CTP, and AMP. The glutamate substrate site can be inhibited by alanine, glycine, and serine. The ATP substrate site is inhibited by binding GDP, AMP, and ADP.
- When all of the substrate sites in the multiunit enzyme are found, the enzyme is inhibited. Partial binding results in partial activity.
- Proline synthesis starts with glutamate and can branch to form ornithine.
- Arginine is an intermediate in the urea cycle, so all of its metabolites are precursors, as well.
- Arginine can be made from citrulline in two ways - 1) urea cycle and 2) reversing the reaction catalyzed by nitric oxide synthase:

$$\text{Citrulline} + \text{Nitric Oxide} + 3/2\ NADP^+ \rightleftharpoons \text{L-arginine} + 3/2\ NADPH + H^+ + 2\ O_2$$

- Arginine can also be made from ornithine by action of arginase. Glutamate also can lead to formation of arginine in six steps.
- The last means of making arginine is by reversing the methylation of asymmetric dimethylarginine (ADMA). ADMA is a meta-

bolic byproduct of protein modification that interferes with production of nitric oxide.

- The serine family includes the amino acids serine, cysteine, and glycine.
- Serine can be made from 3-phosphoglycerate (3-PG) in three steps starting with a reaction catalyzed by 3-PG dehydrogenase to make 3-phosphohydroxypyruvate followed by transamination to make phosphoserine and hydrolysis to remove the phosphate, yielding serine.
- Serine and glycine can be made from each other.
- Serine has a role in metabolism of purines, pyrimidines, glycine, cysteine, and tryptophan. It also is used in metabolism of sphingolipids and folate.
- Serine in the active site of serine proteases is essential for catalysis. Serine in the active site of acetylcholinesterases is the target of nerve gases and insecticides. Serine's hydroxyl group in proteins can be phosphorylated or glycosylated.
- D-serine is a neurotransmitter in humans.
- Serine and glycine can be interconverted by the enzyme serine hydroxymethyltransferase. This reaction requires a folate one-carbon donor/acceptor and is important for the recycling of folates - needed for nucleotide synthesis.
- Glycine is abundant in collagen and is used in the synthesis of purines and porphyrins. It is an inhibitory neurotransmitter and is a co-agonist of NMDA receptors with glutamate.
- Cysteine can be synthesized in several ways. For example methionine can form SAM and after donating a methyl group to form SAH, can be converted to cystathionine and then cysteine. A byproduct of that pathway is formation of serine.
- Serine can lead to cysteine in a pathway where the sulfur comes from H_2S.
- Last, cysteine can be made from L-cysteic acid by replacing the sulfite with the reduced sulfur from H_2S.
- The aspartate family includes aspartate, asparagine, lysine, methionine, and threonine.
- Metabolism of aspartic acid is similar to that of glutamate. It can arise from transamination of a citric acid cycle intermediate (oxaloacetate). Thus, all citric acid cycle molecules can be precursors of aspartate.
- Aspartate and asparagine can be interchanged by action of the enzyme asparaginase, which catalyzes the following reaction

$$\text{Asparagine} + H_2O \rightleftarrows \text{Aspartate} + NH_4^+$$

- Like glutamate metabolism, this reaction be used to use or produce ammonium ion depending on cell needs.

- Aspartate is an important intermediate for gluconeogenesis when proteins are the primary energy source.

- Asparagine can be also made by transamination of aspartate. For example,

Aspartate + Glutamine + ATP

Asparagine + Glutamate + AMP + PPi

- Metabolism of methionine overlaps with that of cysteine

- There seven reactions going from aspartate to methionine. In the process, cysteine donates a sulfhydryl to form cystathionine (a common intermediate of the two pathways), which is converted to homocysteine. Methylation of homocysteine by a folate yields methionine.

- Methionine can also be made from homocysteine in the liver with glycine betaine serving as a methyl donor

Glycine Betaine + Homocysteine

Dimethylglycine + Methionine

- Methionine is formylated to serve as the first amino acid of bacterial proteins. This occurs after methionine is on the tRNA. The enzyme methionyl-tRNA formyltransferase catalyzes the modification.

- To go from aspartate to threonine requires five reactions - phosphorylation, two reductions (one with loss of phosphate), another phosphorylation, and a final hydrolysis.

- Breakdown of threonine produces acetyl-CoA and glycine. It can also produce α-ketobutyrate, which can be converted to succinyl-CoA for oxidation in the citric acid cycle.

- The pathway from aspartate to lysine is even longer - 9 reactions. They include one phosphorylation, two reductions, two losses of water, one amination, addition of pyruvate, addition of a succinyl group, hydrolysis of a succinyl group and (finally) a decarboxylation.

- Lysine is an important target in proteins for covalent modification. It can be methylated, acetylated, hydroxylated, ubiquitinated, sumoylated, neddylated, biotinylated, pupylated, and carboxylated in proteins that contain it.

- Hydroxylation of lysine is important for strengthening collagen and acetylation/methylation of lysine in histone proteins plays roles in control of gene expression and epigenetics.

- Metabolism of tryptophan, phenylalanine, and tyrosine all starts with PEP and erythrose-4-phosphate. The branch point in their synthesis occurs with the molecule known as chorismate.

- Chorismate is made in 6 steps from PEP and erythrose-4-P. Steps include 1) joining, which includes gain of water and loss of phosphate; 2) oxidation to form a ring; 3) loss of water to form a double bond in the ring (forming shikimic acid); 4) phos-

phorylation by ATP; 5) addition of enolpyruvate from PEP; and 6) loss of phosphate to form a second bond in the ring.

- From chorismate to tryptophan, there are an addition seven steps. They include transamination by glutamine, loss of pyruvate, gain of a phosphorylated ribose from PRPP, loss of a glyceraldehyde-3-phoshate and gain of a serine. The end product, tryptophan, is a precursor of serotonin (neurotransmitter), melatonin (hormone), niacin (vitamin), and auxin (plant hormone).

- Melatonin is a hormone signaling the onset of darkness each day and affecting the timing of sleep, seasonal responses, and blood pressure, among other physiological phenomena. It is used sometimes to help in treatment of sleep disorders.

- Melatonin production is affected by blue light and may be linked to sleep abnormalities. Varying day/night lengths during the year alter melatonin production and provide biological period signals.

- Serotonin is a monoamine neurotransmitter found in the gastrointestinal tract, blood platelets, and the central nervous system of animals that can cause vasoconstriction. The compound has some cognitive functions of enhancing memory and learning. It may be a contributor to feelings of happiness. Some anti-depressant drugs modulate action of serotonin at synapses.

- Niacin (vitamin B_3) is related to pyridine and the amide form of it is nicotinamide, an important component of NAD^+/NADH and $NADP^+$/NADPH.

- Deficiency of niacin in the diet can cause nausea, anemia, headaches, and tiredness and ultimately lead to the disease known as pellagra.

- Auxins are plant hormones that can stimulate factors, such as elastins, to loosen cell walls and stimulate cell elongation. With cytokinins, auxins stimulate cell division. They also promote rooting of plants and organization of xyloem and phloem.

- *Agrobacterium tumefasciens* stimulates the growth of plant tumors by secreting auxins.

- Phenylalanine is a precursor of tyrosine and the catecholamines (through tyrosine).

- Phenylalanine is a component of the artificial sweetener known as aspartame (Nutrasweet) and is dangerous for people suffering from phenylketonuria, due to their deficiency of the enzyme phenylalanine hydroxylase.

- Synthesis of phenylalanine begins the chorismate and proceeds through a molecular rearrangement, decarboxylation / loss of water, and transamination from either glutamate or alanine to produce the final product.

- Tyrosine is made from phenylalanine by hydroxylation by phenylalanine hydroxylase. Plants can synthesize tyrosine by oxidation of prephenate followed by transamination of the resulting 4-hydroxyphenylpyruvate

- Tyrosine is a phosphorylation target for protein kinase enzymes involved in signal transduction pathways.

- Tyrosine is an electron donor in plants' photosystem II to reduce oxidized chlorophyll during the photoexcitation phase of photosynthesis.

- Tyrosine forms a stable radical in the catalytic action of the enzyme ribonucleotide reductase.

- Tyrosine is a precursor of catecholamines, such as L-dopa, dopamine, norepinephrine, and epinephrine and thyroid hormones - triiodothyronine (T_3) and thyroxine (T_4).

- Thyroid hormone formation involves a series of iodinations to tyrosines bound on a protein known as thyroglobulin.

- Oxidation and polymerization of tyrosine occurs in synthesis of the family of melanin pigments and the benzoquinone ring of coenzyme Q is derived from it. Metabolism of CoQ depends on HMG-CoA reductase of cholesterol metabolism.

- Dopamine is a neurotransmitter made in brain and kidney (also in plants) that plays a major role in the brain's reward-mediated behavior. It is also involved in motor control and in managing the release of various hormones. In blood vessels, dopamine inhibits norepinephrine release and causes vasodilation. In the kidneys, it increases sodium excretion and urine output. In the pancreas, it reduces insulin production.

- Epinephrine (adrenalin) is used to treat anaphylaxis, cardiac arrest, croup, and, in some cases, asthma, when other treatments are not working, due to its ability to favor bronchodilation.

- Epinephrine exerts its effects on α- and **β**-adrenergic receptors and is produced and released by adrenal glands and some neurons.

- Norepinephrine is chemically related to epinephrine - it also is released into the blood stream from adrenal glands and affects α- and **β**-adrenergic receptors. Its primary function is to increase alertness, enhance memory functions, help to focus attention, increase heart rate and blood pressure, increase blood glucose and blood flow to skeletal muscle and decrease flow of blood to the gastrointestinal system.

- The pyruvate family of amino acids includes alanine, leucine, isoleucine, and valine. The last three are known as the branched chain amino acids (BCAAs).

- Transamination catalyzed by alanine transaminase produces alanine from pyruvate.

Glutamate + Pyruvate

Alanine + **α**-ketoglutarate

- Alanine can also be produced by catabolism of valine, leucine, and isoleucine.

- The glucose alanine cycle is an important means of moving amines in the body. In amine-rich tissue, pyruvate is converted to alanine, which travels in the blood to the liver where it is converted back to pyruvate, which is used to make glucose for export back to the blood. The amine from alanine is put on **α**-ketoglutarate to make glutamate, which can be used to make urea for excretion.

- The glucose alanine cycle provides an alternative means of reducing amine/ammonium concentration in cells beyond the removal by transaminating glutamate.

- Leucine may stimulate muscle synthesis. In aged rats, it slows muscle degradation. It is an activator of mTOR, a protein which, when inhibited, increases life span in *Saccharomyces cerevisiae*, *C. elegans*, and *Drosophila melanogaster*.

- Metabolism of BCAAs starts with decarboxylation of pyruvate and attachment of the resulting two-carbon hydroxyethyl fragment to thiamine pyrophosphate.

- Valine and leucine handle the hydroxyethyl fragment differently from isoleucine, making α-acetolactate.

- α-acetolactate is then rearranged, reduced, and loses water to make α-ketoisovalerate - a branch point for valine and leucine metabolism.

- To make leucine, an acetyl group is added, followed by rearrangement, oxidation, and transamination to give leucine.

- Making valine from α-ketoisovalerate requires only a transamination reaction.

- Isoleucine metabolism attaches the two carbon hydroxethyl fragment on TPP to α-ketobutyrate (a byproduct of threonine metabolism) to form α-aceto-α-hydroxybutyrate. Rearrangement, loss of water, and transamination yields isoleucine. Several of the enzymes of valine metabolism catalyze reactions in the isoleucine pathway. Though the substrates are slightly different, they are enough like the valine intermediates that they are recognized by the enzymes.

- The key molecule regulating BCAA synthesis is α-ketobutyrate. It is a breakdown product of threonine, catalyzed by threonine deaminase (an allosterically regulated enzyme). It is inhibited by its own product (isoleucine) and activated by valine.

- When valine is abundant, production favors isoleucine and since isoleucine competes with valine and leucine for hydroxyethyl-TPP, less valine and leucine are made.

- When isoleucine concentration increases, threonine deaminase is inhibited, stopping production of α-ketobutyrate and shifting the balance back to production of valine and leucine.

- Another control method used in bacteria to regulate amino acid levels is attenuation. Here, accumulation of leucine speeds the process of translation of a portion of the mRNA transcript of the leucine operon (coding sequences for enzymes necessary to make leucine). This, in turn, causes transcription of the operon to terminate prematurely, thus stopping production of the enzymes necessary to make leucine. On the other hand, when leucine levels fall, translation slows, preventing transcription from terminating prematurely and allowing leucine metabolic enzymes to be made.

- Histidine's metabolism is so distinct, it is in a family all by itself. There are ten steps to the synthesis of histidine, starting with ribose-5-phosphate. PRPP is an intermediate and glutamine and glutamate each serve as amine donors. Histidine itself is a feedback inhibitor of the second enzyme in the pathway - ATP-phosphoribosyltransferase.

- Selenocysteine, the “21st amino acid”, is a derivative of cysteine. It is incorporated into a protein as it is being made by using a tRNA that recognizes what normally is a stop codon.

- Human proteins known to contain selenocysteine include five glutathione peroxidases, three thioredoxin reductases, and a protein known as selenoprotein P with 10 selenocysteine residues.

- Other selenium containing amino acids include selenomethionine and Se-methylselenocysteine.

- The tRNA carrying selenocysteine (gene = sel C) starts with a serine on it, but the hydroxyl group on it is substituted using selenium in selenophosphate.

- The coding regions for selenocysteine-containing proteins have unusual mRNA structures around the UGA codon that make the ribosome “miss” it as a stop codon and use the tRNA with selenocysteine instead.

- Pyrrolysine is another rare, unusual, amino acid built into proteins during translation. The mechanism used is similar to that for incorporation of selenocysteine. A different stop codon (UAG) is used, but the result is the same - pyrrolysine gets incorporated during translation.

- Synthesis of pyrrolysine begins with two lysines. One is converted to (3R)-3-Methyl-D-ornithine, which is attached to the second lysine. After elimination of an amine group, cyclization, and dehydration, L-pyrrolysine is produced.

- The urea cycle was the first metabolic cycle discovered.

- It is important for balancing nitrogen and takes place primarily in the liver and kidney.

- Urea-excreting organisms are called ureotelic. Those that excrete uric acid are uricotelic and those that excrete ammonia are ammonotelic.

- Liver failure can lead to accumulation of nitrogenous waste.

- The cycle contains five reactions (three in cytoplasm, two in mitochondria), with each turn of the cycle producing a molecule of urea. The reaction making carbamoyl phosphate, a molecule that enters the cycle, is not counted by some as part of the cycle.

- The urea cycle doesn’t really have a starting point, but a common place to begin is with ornithine. Ornithine intersects the metabolic pathways of arginine and proline and is moved into the mitochondrion by the ornithine-citrulline antiport of the inner mitochondrial membrane.

- In the matrix, carbamoyl phosphate is made from bicarbonate, ammonia, and ATP - catalyzed by carbamoyl phosphate synthetase I.

- Next, carbamoyl phosphate joins with ornithine to make citrulline (enzyme = ornithine transcarbamoylase)

- Citrulline is transported out to the cytoplasm by the ornithine-citrulline antiport (same as above).

- In the cytoplasm, citrulline reacts with ATP and combines with AMP, yielding

citrullyl-AMP, a transient intermediate that combines with aspartate, releasing the AMP, and forming argininosuccinate (enzyme = argininosuccinate synthetase).

- Argininosuccinate lyase catalyzes the next reaction, which splits out a fumarate and produces arginine.

- The enzyme arginase then splits off a urea (less toxic than ammonia) for excretion and produces an ornithine to complete the cycle.

- In summary of the urea cycle, 1) ammonia is converted to urea using bicarbonate and an amine from aspartate; 2) aspartate is converted to fumarate; and 3) glutamate and aspartate are acting as shuttles to funnel ammonia into the cycle.

- The cycle requires N-acetylglutamate (NAG) for activation of carbamoyl phosphate synthetase I. The enzyme that makes NAG, NAG synthetase (reaction below), is activated by arginine and glutamate.

Acetyl-CoA + L-glutamate

CoA-SH + N-acetyl-L-glutamate (NAG)

- Reduction of ammonia concentrations relies on the glutamate dehydrogenase reaction

α-ketoglutarate + NH_3 + NAD(P)H

Glutamate + $NADP^+$

- Additional ammonia can be taken up by glutamate in the glutamine synthetase reaction,

Glutamate + NH_3 + ATP

Glutamine + ADP + P_i

- These reactions reduct the concentrations of glutamate (brain neurotransmitter), α-ketoglutarate (energy source), and ammonia (toxic substance), so while removing the toxic substance is good, loss of an energy source and a neurotransmitter may be problematic in the brain.

- The urea cycle is even or generates a small amount of energy, if one includes the energy produced in releasing ammonia from glutamate (one NADH). The cycle either breaks even in the worst case or generates 2 ATPs in the best case.

- Amino acids whose catabolic products yield intermediates in the glycolysis pathway are called glucogenic and those that produce intermediates of acetyl-CoA or acetoacetate are called ketogenic. Some are both.

- Citric acid cycle intermediates and glycolysis intermediates are common degradation products of amino acids.

- Amino acids like tryptophan, phenylalanine, and tyrosine yield hormones or neurotransmitters on further metabolism.

- Cysteine and methionine must dispose of their sulfur and all of the amino acids must rid themselves of nitrogen, which can

happen via the urea cycle, transamination, or both.

- Breakdown of tyrosine is a five step process that yields acetoacetate and fumarate.
- Leucine breakdown is a multi-step process ultimately yielding the ketone body acetoacetate and acetyl-CoA.
- BCAAs rely on branched chain amino transferase (BCAT) and (after that) branched chain α-ketoacid dehydrogenase (BCKD) for catabolism.
- Isoleucine catabolism yields intermediates that are both ketogenic and glucogenic. These include acetyl-CoA and propionyl-CoA.

Nucleotide Metabolism

- Nucleotide metabolism is organized by metabolism of 1) purines; 2) pyrimidines; and 3) deoxyribonucleotides.
- These pathways can make nucleotides from simple precursors (*de novo* pathways). Others use pieces of nucleotides to reassemble full ones (salvage pathways).
- De novo synthesis pathways for all nucleotides begins with synthesis of ribonucleotides.
- Deoxyribonucleotides are made from the ribonucleotides.
- Purines are made by building the purine rings on a ribose.
- Purine synthesis by the *de novo* pathway begins with addition of a pyrophosphate to carbon 1 of ribose-5-phosphate, creating phosphoribosylpyrophosphate (PRPP). It proceeds with amination by glutamine, addition of a glycine with loss of a phosphate, addition of a carbon from a folate, another amination by glutamine, ring closure (with ATP hydrolysis), a carboxylation, addition of an aspartate, loss of a fumarate (net gain of amine), addition of another carbon from a folate, and loss of water to close the second ring. The intermediate at that point is inosine monophosphate (IMP).
- Atoms in the purine ring come from folates, glutamine, glycine, bicarbonate, and aspartate.
- PRPP amidotransferase (PPAT), which catalyzes addition of the first amine in the pathway, is the most important regulatory enzyme of the pathway.
- AMP and GMP both inhibit the enzyme and PRPP activates it. Full inhibition of the enzyme requires binding of both AMP and GMP.
- At IMP synthesis of AMP and GMP branches. Each branch has two reactions and the first enzyme of each branch is feedback regulated.
- On the route to GMP, IMP dehydrogenase (inhibited by GMP) catalyzes oxidation of IMP followed by a transamination (from glutamine) that produces GMP. ATP energy is required and AMP is produced.
- For making AMP, adenylosuccinate synthetase (inhibited by AMP) catalyzes addition of an aspartate, using energy of GTP

and then fumarate is lost in the second reaction to produce AMP.

- Synthesis of GMP from IMP requires energy from ATP and that synthesis of AMP from IMP requires energy from GTP.
- Purine nucleotide levels are balanced by the combined regulation of PRPP amidotransferase, IMP dehydrogenase, adenylosuccinate synthetase and the nucleotides AMP and GMP.
- When AMP and GMP both are abundant, PPAT is fully inhibited. When one is abundant and the other is not, PPAT remains partly active so synthesis can proceed to IMP. The branch of the abundant nucleotide will be blocked and the other branch will remain active, allowing synthesis of it to catch up.
- Properly balancing nucleotide levels in cells is critical, because imbalances favor mutation.
- GMP reductase can catalyze conversion of GMP to IMP using electrons from NADPH.
- AMP can also be converted back to IMP by the enzyme AMP deaminase.
- From IMP, either AMP or GMP could be made, thus providing cells with another mechanism of balancing AMP and GMP.
- To convert AMP to ATP and GMP to GTP requires nucleoside monophosphate kinase enzymes.
- Adenylate kinase catalyzes the reaction that follows

AMP + ATP

2 ADP

- In reverse, this reaction is used to generate ATP when the cell's ATP concentration is low. When ATP is made in reverse reaction, AMP levels increase and this is one way the cell senses that it is low on energy.
- GMP has its own monophosphate kinase and it catalyzes this reaction

GMP + ATP

GDP + ADP

- To make triphosphates, NDPK catalyzes reactions of the form

(d)XTP + (d)YDP

(d)XDP + (d)YTP

- where X and Y refer to any base.
- Salvage reactions to make purine nucleotides start with attachment of ribose to purine bases using phosphoribosylpyrophosphate.
- Hypoxanthine/guanine phosphoribosyltransferase (HGPRT) catalyzes the following reactions

Hypoxanthine + PRPP

IMP + PPi

and

Guanine + PRPP

GMP + PPi

- Reduction in levels of HGPRT leads to hyperuricemia, a condition where uric acid concentration increases in the body, causing gout. Complete lack of HGPRT is linked to Lesch-Nyhan syndrome.

- Adenine phosphoribosyltransferase (APRT) catalyzes the reaction corresponding to HGPRT for salvaging adenine bases.

Adenine + PRPP

AMP + PPi

- *De novo* synthesis of pyrimidine bases occurs apart from the ribose and then they are attached later. The first reaction is catalyzed by carbamoyl phosphate synthetase. It is the rate limiting step in pyrimidine biosynthesis. The enzyme is activated by ATP and PRPP and is inhibited by UMP.

- The second reaction is catalyzed by ATCase, a classic enzyme exhibiting allosteric regulation and feedback inhibition, having both homotropic and heterotropic effectors.

- ATCase exists in two states - a low activity T-state and a high activity R-state.

- Binding of the aspartate substrate (homotropic effector) to the active site shifts the equilibrium in favor of the R-state.

- Binding of ATP (heterotropic effector) to the regulatory units favors the R-state, whereas binding of CTP (heterotropic effector) to the regulatory units favors the T-state. The latter is an example of feedback inhibition.

- Thus, regulation of the first two enzymes of the pathway is consistent - a high concentration of purine nucleotides stimulates synthesis of pyrimidines and high concentration of pyrimidines turns off the pathway that synthesizes them.

- The remaining reactions involve loss of water, oxidation, addition of ribose-5-phosphate from PRPP, and decarboxylation to form UMP. The last reaction is catalyzed by OMP decarboxylase, an enzyme that speeds its reaction by 10^{17}, compared to the uncatalyzed reaction.

- UMP/CMP kinase catalyzes conversion of UMP to UDP, CMP to CDP, and dCMP to dCDP, using energy from ATP in each case.

- NDPK, of course, converts UDP to UTP.

- UTP is the substrate for synthesis of CTP via catalysis by CTP synthase.

UTP + Glutamine + ATP

CTP + Glutamate + ADP + P_i

- CTP synthase is inhibited by its product, CTP and activated by ATP, GTP, and glutamine. It exists as an inactive monomer at low enzyme concentrations or in the absence of UTP and ATP.
- CTP is the only nucleotide synthesized *de novo* as a triphosphate, It needs to be converted to CDP for dCDP synthesis. One enzyme, apyrase, sequentially converts CTP to CDP and then CMP.
- Pyrimidine salvage synthesis allows cells to remake pyrimidine triphosphate nucleotides starting from either the C or U pyrimidine bases, nucleosides, or nucleotides.
- The enzymes of pyrimidine salvage are rather flexible. Seven of them can work on both uracil and cytosine containing molecules.
- Cytidine and uridine can be interconverted by cytidine deaminase, providing an alternative to the CTP synthase reaction.
- Both UTP and CTP are converted in the breakdown process to UMP and CMP, respectively and then these can be phosphorylated to UDP and CDP for dUDP and dCDP synthesis by ribonucleotide reductase.
- dCDP and dUDP are converted to dCTP and dUTP by NDPK, but dUTP is then converted to dUMP, which is converted by thymidylate synthase to dTMP. It then gets converted to dTDP by a monophosphate kinase and to dTTP by NDPK.
- Ribonucleotide reductase (RNR) converts all ribonucleoside diphosphates to equivalent deoxyribonucleoside diphosphates.
- Class I RNRs (in humans) use a ferrous iron center that loses an electron to generate a free radical on a tyrosine ring and only work in aerobic conditions.
- Class II RNRs use 5'-deoxyadenosyl cobalamin (vitamin B12) to generate a radical and work under aerobic or anaerobic conditions.
- Class III RNRs generate a glycine radical using S-adenosyl methionine (SAM) and an iron-sulfur center. They work under anaerobic conditions.
- In class I enzymes, RNR is an iron-dependent dimeric enzyme with each monomeric unit containing a large subunit (known as α or R1) and a small subunit (known as β or R2). R1 contains regulatory binding sites. The R2 subunit houses a tyrosine residue that forms a radical critical to the reaction mechanism of the enzyme.
- Electrons needed in the reaction come from NADPH and start by reducing a sulfhydryl in the enzyme.
- A tyrosine side chain in the R2 subunit must be radicalized to start. This electronic change is transmitted through the small R2 subunit to the active site of the large R1 subunit.
- The tyrosine radical contains an unpaired electron delocalized across its aromatic ring.

- Transfer of the electronic instability to the R1 unit radicalizes a cysteine side chain (to form a thiyl radical) at the active site.

- The thiyl radical abstracts a proton plus electron from carbon 3 of ribose on the bound ribonucleoside diphosphate, creating a radical carbon atom. Radicalization of carbon #3 favors release of the hydroxyl group on carbon #2 as water. The extra proton comes from the sulfhydryl of the enzyme's cysteine. Next, a proton and two electrons from the same cysteine are transferred to carbon #2. Then carbon #3 takes back the proton originally removed from it to yield a deoxyribonucleoside diphosphate. The enzyme's thiyl group gains an electron from R2 and the disulfide bond created in the reaction must be reduced by electrons from NADPH again in order to catalyze again.

- RNR has a complex system of regulation, with two sets of allosteric binding sites, both in the R1 subunit.

- RNR is allosterically regulated via two molecular binding sites - a specificity binding site (binds dNTPs and induces structural changes in the enzyme that determines which substrates preferentially bind at the active site) and an activity control site (controls whether or not enzyme is active).

- At the activity control site, ATP activates catalysis, dATP inactivates it.

- In Severe Combined Immunodeficiency Disease (SCID), the salvage enzyme adenosine deaminase is deficient, leading to a rise in concentration of dATP in cells of the immune system, resulting in little or no immune cells for fighting infection.

- dTTP binds to RNR's specificity site and inhibits binding and reduction of CDP and UDP but stimulates binding and reduction of GDP. Binding of ATP or dATP at the specificity site stimulates binding and reduction of CDP and UDP. Binding of dGTP to the specificity site induces binding and reduction of ADP.

- Notable enzymes in the dTTP synthesis pathway include dUTPase and thymidylate synthetase. dUTPase keeps the concentration of dUTP low so it does not end up in DNA. DNA polymerase recognizes dUTP the same as dTTP.

- Thymidylate synthetase is an important target for anticancer therapies. The enzyme requires a reduced tetrahydrofolate to convert dUMP to dTMP.

- Methotrexate is a competitive inhibitor of DHFR, the enzyme that recycles tetrahydrofolate from dihydrofolate. By inhibiting DHFR, tetrahydrofolate can't be remade, so thymidylate synthetase runs out of substrate. For a rapidly dividing cancer cell, that is deadly.

- 5-fluorouracil is a suicide inhibitor of thymidylate synthetase.

- Purine nucleotide catabolism starts with nucleoside monophosphates. Metabolism of AMP and GMP converge at xanthine.

- AMP is dephosphorylated by nucleotidase to create adenosine, which is then deaminated by adenosine deaminase to yield inosine. Alternatively, AMP can be deaminated by AMP deaminase to yield IMP.

- Dephosphorylation of IMP yields inosine. Ribose is removed from it by purine nucleotide phosphorylase to release hypoxanthine. Hypoxanthine is oxidized to xanthine in a hydrogen peroxide-generating reaction catalyzed by xanthine oxidase.
- For GMP, phosphate is removed by nucleotidase to yield guanosine. Guanosine is cleaved from ribose to yield a free guanine base, which is deaminated by guanine deaminase (also called guanase) to produce xanthine.
- Xanthine can be oxidized by xanthine oxidase (same enzyme as above) to yield uric acid and H_2O_2.
- Uric acid is problematic because it is only not very soluble in water. Consequently it precipitates out of solution, forming crystals in joints and (frequently) in the big toe, causing gout.
- There may be a negative correlation between gout and contracting multiple sclerosis.
- Gout is treated with allopurinol. It inhibits xanthine oxidase, which favors an increase in the concentration of hypoxanthine and purine salvage synthesis.
- Uric acid can be excreted into the urine (in humans) or broken down into allantoin by the uricase enzyme.
- Catabolism of cytidine nucleotides proceeds through uridine by deamination of cytosine.
- Free bases of thymine and uracil are released by the enzyme ribosylpyrimidine nucleosidase.
- Uracil and thymine reduction gives dihydrothymine and dihydrouracil respectively. Addition of water to these creates 3-ureidoisobutyrate and 3-ureidopropionate respectively. Hydrolysis of these yields ammonia and carbon dioxide for both (which are made into urea) plus 3-aminoisobutyrate for the thymine pathway and **β**-alanine for the products of the uracil pathway. 3-aminoisobutyrate is produced during exercise and activates expression of thermogenic genes in white fat cells.
- **β**-alanine is a rate-limiting precursor of carnosine, a dipeptide of histidine and β-alanine. Carnosine functions as an antioxidant that scavenges reactive oxygen species and may play a role in aging.
- Ribose and deoxyribose can be recycled (ribose) or catabolized (ribose and deoxyribose).
- Ribose an be reattached to bases by phosphorylase enzymes, such as uridine phosphorylase, or converted into PRPP for the same purpose to create nucleosides. Ribose-5-phosphate can be metabolized to other sugars in the pentose phosphate pathway.
- Deoxyribose-5-phosphate can be broken into glyceraldehyde-3-phosphate and acetaldehyde by deoxyribose-5-phosphate aldolase.

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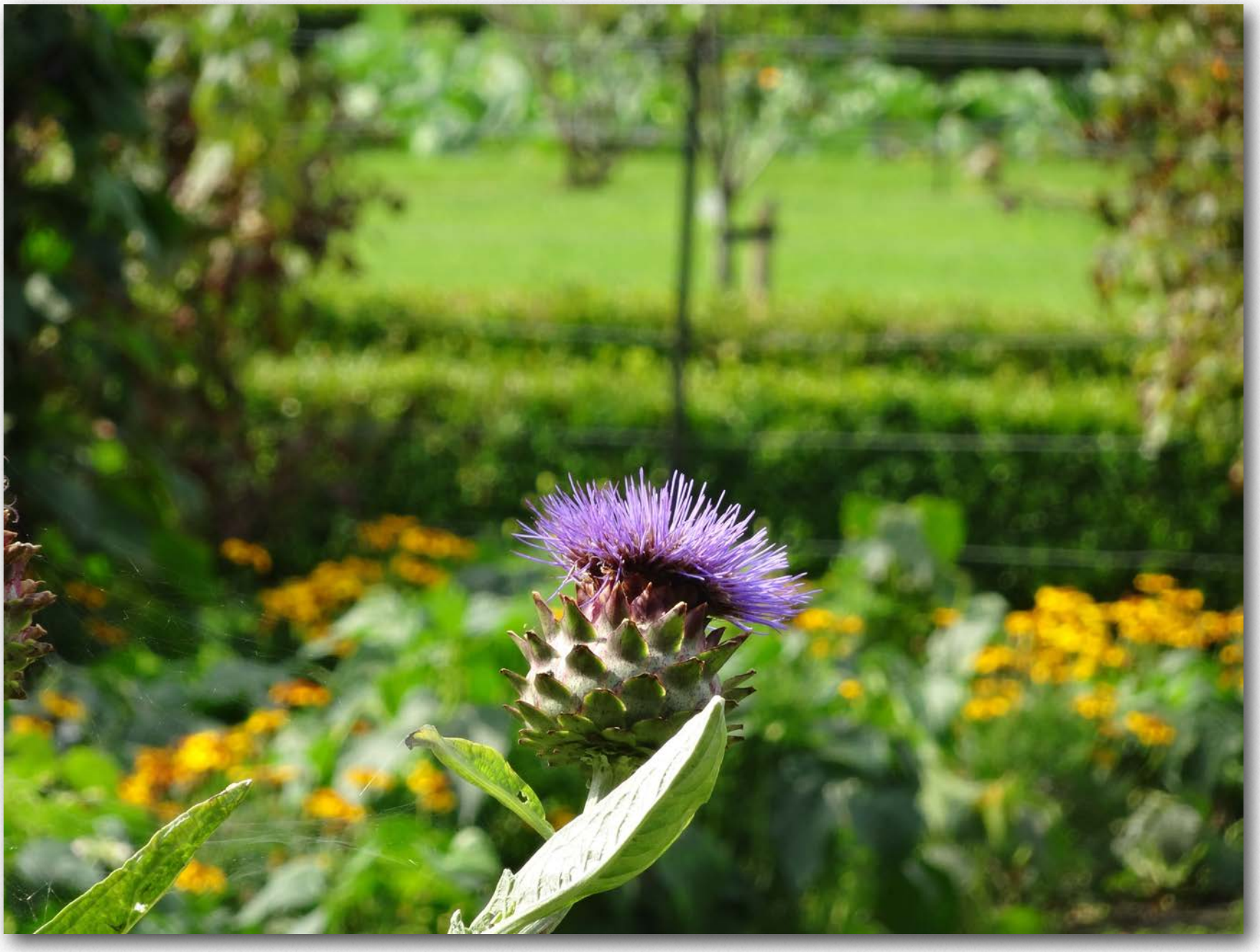

Genes and Genomes

- Key experiments, done between the 1920s and the 1950s, established convincingly that genetic information was carried by DNA.
- The word genome describes all of the genetic material of a cell.
- A genome includes all of the DNA sequences found in chromosomes.
- Eukaryotic cells have organelles like mitochondria and chloroplasts with their own DNA. These are referred to as the mitochondrial or chloroplast genomes to distinguish them from the nuclear genome.
- The complete genome sequences have been determined for thousands of species from all domains of life.
- The Global Genome Initiative is a collaborative effort to sequence at least one species from each of the 9,500 described invertebrate, vertebrate, and plant families.
- Phenotypic traits are controlled by specific regions of the DNA that were termed genes.

- Genes are separated by non-coding regions that are simply referred to as intergenic sequences.
- Early experiments in molecular biology suggested a simple relationship between the DNA sequence of a gene and its product, and led scientists to believe that each gene carried the information for a single protein.
- This simple picture has been modified by subsequent discoveries that demonstrated that the use of genetic information by cells is somewhat more complicated.
- There is not a simple relationship between the complexity of an organism and the size of its genome.
- While genes are made up of DNA, all DNA does not consist of genes (gene = a section of DNA that encodes an RNA or protein product).
- Less than 2% of the total human DNA seems to be the sort of coding sequence that directs the synthesis of proteins.
- Non-coding genomic DNA was believed to be useless, and was described as “junk DNA”.
- We now know much of this so-called junk DNA may play important roles in evolution and in regulation of gene expression.
- In almost all eukaryotes, coding regions in DNA are interrupted by non-coding sequences called introns.
- Non-coding intron sequences can be much longer than the coding sections of the gene (exons).
- Introns can vary in size from several hundred base-pairs to many thousands of base pairs versus only a few hundred bases for most exons.
- Intron sequences account for roughly a quarter of the entire genome in humans.
- Other non-coding DNA in genomes specifies when and to what extent a gene is used, or expressed - these are called regulatory sequences.
- Almost half of the human genome appears to consist of several kinds of repetitive sequences.
- Many of the repetitive sequences are transposons - sections of DNA that can move around within the genome.
- Some transposon movements are simple “cut and paste” events that cut the sequence out of one region of the DNA and inserts it into another location. Others move via a process called retrotransposition involving an RNA intermediate.
- There are two major classes of such transposable elements, the LINEs (Long Interspersed Elements) and SINEs (Short Interspersed Elements) in our genomes.
- LINEs and SINEs are both a kind of transposable element called retrotransposons, sequences that are copied into RNA, then reverse transcribed back into DNA before being inserted into new locations.
- Transposons tend to be inserted randomly in the genome, in many cases within coding regions, causing problems.

- Transposons are a major cause of mutation in genomes and play a role in evolution.

- Much of the genome is transcribed into RNAs, even though only about 2% encodes proteins.

- RNAs that do not encode proteins include ribosomal RNAs, transfer RNAs, small nuclear RNAs that function in splicing, and regulatory RNAs, which are small RNA molecules that play an important role in controlling gene expression.

DNA Replication

- Each time a cell divides, all of its DNA must be copied faithfully - a process called DNA replication.

- Watson and Crick's DNA structure suggested a mechanism by which double-stranded DNA could be copied to give two identical copies.

- Meselson and Stahl demonstrated that DNA replication was semi-conservative - resulting in two DNA molecules each made up of one old strand and one new strand.

- In DNA replication, a parental DNA molecule serves as the template and a new strand is assembled across from it. Base pairing rules dictate joining together of nucleotides to make the new strand.

- Nucleotides used in DNA synthesis are deoxyribonucleoside triphosphates (dNTPs).

- dNTPs have a deoxyribose sugar and three phosphates, in addition to one of the four DNA bases, A, T, C or G.

- DNA polymerases catalyze creation of phosphodiester linkages between one nucleotide and the next.

- Several challenges to DNA replication - 1) genomes are very large; 2) double stranded DNA must be unwound for replication; 3) unwinding must not distort molecule topologically; 4) unwound strands must be kept apart during replication; 5) DNA polymerases must work from a 3' OH; 6) DNA polymerases only work 5' to 3'; 7) short RNAs serve as primers and must be removed.

- In eukaryotes, DNA is broken up into many chromosomes, each of which is composed of a linear strand of DNA. Most bacteria have smaller, circular chromosomes.

- DNA replication is initiated at sites called origins of replication where special proteins called initiator proteins bind the DNA.

- *E.coli* replication origins have small regions of A-T-rich sequences that are "melted" to separate the strands, when the initiator proteins bind to the origin or replication.

- *E. coli* has a single origin of replication on its circular chromosome. Eukaryotes have thousands.

- Unwinding of the DNA duplex requires the enzyme called helicase, which uses energy from ATP hydrolysis to break hydrogen bonds between bases.

- A replication bubble is made up of two replication forks that "move" or open up, in opposite directions.
- Local unwinding of the double helix causes over-winding (increased positive supercoiling) ahead of the unwound region
- Enzymes called topoisomerases relieve the topological stress caused by local “unwinding” of of the double helix.
- Topoisomerases cut one or both strands of the DNA and strands to swivel around each other to release the tension before rejoining the ends.
- A topoisomerase in *E. coli* that does this is called gyrase.
- When the two strands of the parental DNA molecule are separated, they must be blocked from re-forming double-stranded DNA with each other.
- To prevent this, separated strands of the parental DNA are bound by many molecules of a protein called single-strand DNA binding protein (SSB).
- DNA polymerases cannot begin synthesis of a complementary strand *de novo* and can only add new nucleotides on to the 3' end of a pre-existing chain.
- Some enzyme other than a DNA polymerase must first make a small region of nucleic acid, complementary to the parental strand to provide a free 3' OH.
- Primase is an enzyme which makes a short base-paired region, called the RNA primer, with a free 3'OH group to which a DNA polymerase can add the first new DNA nucleotide.
- A protein called clamp loader helps to load a protein complex called the sliding clamp onto the DNA at the replication fork.
- The sliding clamp is a multi-subunit ring-shaped protein joined to the DNA polymerase to help it stay bound at the replication fork.
- The property of staying associated with the template for a long time before dissociating is known as the processivity of the enzyme.
- DNA polymerases linked to sliding clamps are much more processive than those that are not linked.
- DNA polymerase catalyzes addition of a deoxyribonucleotide to a growing chain by facilitating a nucleophilic attack by the 3’OH group at the end of a nucleic acid strand on the α phosphate of the incoming dNTP.
- A pyrophosphate is released by the reaction and a phosphodiester bond is created between the new nucleotide and the growing chain. Its 3’ end becomes the addition site for the next nucleotide.
- Parental strands of DNA are antiparallel and DNA polymerases can only synthesize DNA in the 5’ to 3’ direction. This requires two different types of bidirectional DNA replication at each fork - a continuous leading strand and a discontinuous lagging strand, both being catalyzed by the same DNA polymerase.
- Discontinuous replication on the lagging strand leads to creation of DNA pieces about 1000-2000 nucleotides long, each with an RNA primer at the 5’ end. The

DNA pieces are called Okazaki fragments.

- To complete DNA synthesis, RNA nucleotides must be removed and the gaps must be filled in with DNA nucleotides, a task accomplished by DNA Polymerase I.
- DNA polymerase I has an exonuclease activity acting in the 5' to 3' direction that removes the RNA nucleotides ahead of it, while the 5' to 3' polymerase activity replaces the RNA nucleotides with dNTPs. After the DNA nucleotides have replaced the RNA, DNA ligase seals the gap between the 3' end of the new strand and the 5' end of the strand ahead of it.
- Many DNA polymerases have a proofreading function that enables them to detect when the wrong base has been inserted across from a template strand, back up and remove the mistakenly inserted base, before continuing with synthesis.
- Proofreading is a function of a 3' to 5' exonuclease activity possessed by a DNA polymerase.
- Proofreading reduces by about a 100-fold the mistakes made when DNA is copied.
- In *E.coli*, DNA polymerase III is the major replicative polymerase.
- DNA polymerase I is responsible for DNA repair and removal of RNA primers and replacement with DNA nucleotides.
- DNA polymerase II plays a role in restarting replication after DNA damage stalls replication. DNA polymerase IV and DNA polymerase V are both required in translesion, or bypass synthesis, which allows replication around sites of DNA damage.
- Eukaryotes have over fifteen different DNA polymerases - the primary one are DNA polymerase **∂** and DNA polymerase **ε**. DNA polymerase **α** is also important because it has primase and repair activities.
- Replication is initiated in eukaryotic cells by DNA polymerase **α**. It binds to the initiation complex at the origin and makes an RNA primer plus about 25 nucleotides of DNA. It is then replaced by another polymerase, in a step called the pol switch. DNA polymerase **∂** or **ε** then continues synthesizing DNA, depending on the strand - polymerase **ε** on the leading strand and polymerase **∂** on the lagging strand.
- Protein RFC plays the role of clamp loader, while another protein, PCNA acts like the sliding clamp.
- Other DNA polymerases like β, γ and μ function in repairing gaps. Yet others are involved in *trans*-lesion synthesis following DNA damage.
- DNA polymerases have a structure that has been compared to a human right hand. The palm region forms a cleft where the DNA lies and the polymerase activity resides. Here incoming nucleotides are added on to the growing chain. The fingers region positions the DNA in the active site, while the thumb holds the DNA as it exits the polymerase. A separate domain contains the proofreading activity.
- When a mismatched base pair is in the polymerase catalytic site, the 3'end is moved from the polymerase site to the 3' exonu-

clease site. The mispair at the end is removed followed by repositioning of the 3' end in the polymerase active site to continue synthesis.

- In bidirectional, circular bacterial chromosome replication, binding of a protein called Tus, at a Ter (termination) site on the chromosome prevents further movement of the replication fork *at a site opposite the origin) and ends replication.

- There is no fixed site for termination in linear eukaryotic chromosomes. Leading strand synthesis goes all the way to the end of its template strand. On the lagging strand, the RNA primer at the end (needed to start synthesis) creates a challenge. When it is removed, there is a small stretch of the template strand that cannot be copied (no primer). As a result, in each round of replication a short sequence at the ends of linear chromosomes will be lost.

- Over time, chromosomes can become noticeably shorter.

- The ends of linear chromosomes are characterized by structures called telomeres.

- Telomeres contain many copies of short repeated sequences and special proteins that bind to them. Losing some of the repeats does not lead to loss of important coding information. Thus, the repeats act as a buffer zone, where the loss of non-coding sequence does not doom the cell.

- Shortening of the telomeres may act like a clock, with the extent of shrinkage of the chromosomes serving as a measure of aging.

- At the end of a chromosome, the original template strand has a 3' overhang resulting from the removal of the RNA primer across from it. To fill in this region, another primer would be needed, situated past the end of the template strand. But in order to build such a primer, it would be necessary for the template overhang to be longer.

- The parental template strand is extended by the enzyme telomerase, which adds telomere repeats and lengthens the template.

- Telomerase contains a piece of RNA (used as a template) and a reverse transcriptase (used to copy the RNA).

- A reverse transcriptase is an RNA-dependent DNA polymerase (copies an RNA template to make DNA).

- A part of the RNA carried by telomerase can base-pair with the last telomere repeat on the parental DNA strand, while a portion of it remains unpaired. Thus the extended template strand gets replicated.

- After replication, the telomerase can then dissociate, and repeat the process multiple times to add many repeats of the telomere sequence.

- Once the overhang has been extended by the addition of at least several telomere repeats, there is then room for the synthesis of an RNA primer complementary to the newly extended overhang (pointing back towards the rest of the chromosome). The primer can be extended and replication back towards the duplex region results in double stranded chromosomal lengthening.

- This happens in reproductive cells, explaining why each generation does not have shorter chromosomes than the parental generation.

- DNA is found in eukaryotic cells as chromatin. Chromatin contains DNA wrapped around histone protein cores to make nucleosomes. The nucleosomes must be disrupted to make DNA open for replication and restored after replication is completed.
- Ahead of the replication fork, chromatin structure is disassembled by ATP-dependent chromatin remodeling complexes, allowing access to the DNA template.
- After replication, both the original nucleosomes and new nucleosomes must be reassembled behind the replication fork.
- It appears that newly synthesized DNA is packaged into nucleosomes using the original histones that were displaced to allow the replication fork to pass, plus newly synthesized histones
- Post-translational modifications like acetylation, methylation or phosphorylation can regulate the degree to which a given region of the genome is accessible for use.

DNA Repair

- DNA is the master copy of instructions for an organism so it is important not to make mistakes when copying it to pass on to new cells.
- Minor changes in DNA sequence, such as point mutations can sometimes have far-reaching consequences.
- Damage caused by radiation, environmental chemicals or even normal cellular chemistry can interfere with the accurate transmission of information in DNA.
- Not all mistakes are fixed on the fly by DNA polymerases using proofreading.
- Errors that slip by proofreading during replication can be corrected by a mechanism called mismatch repair.
- Mismatch repair scans newly made DNA to 1) identify mispaired bases; 2) remove the region around the mismatch; and 3) correctly fill in the gap created by the excision of the mismatch region.
- A mismatch repair system must have a means to distinguish the newly made DNA strand from the template strand.
- Bacteria identify the parental strand in newly replicated DNA with methylation of GATC sequences.
- DNA adenine methylase (Dam) that adds methyl groups onto the adenines in GATC sequences. Newly replicated DNA has not yet undergone methylation, so can be distinguished from the template strand, which is methylated.
- The mismatch repair proteins selectively replace the strand lacking methylation.
- Mismatch repair proteins are encoded by a group of genes collectively known as the mut genes.
- Mut gene products include MutS (acts to recognize the mismatch and binds to it); MutL (binds to MutS); and MutH (an endonuclease that binds MutS/MutL and cuts the newly synthesized (unmethylated) DNA strand at a GATC.
- DNA helicase and an exonuclease that help unwind and remove the region containing the mismatch. DNA polymerase III

fills in the gap and DNA ligase joins the ends, to restore a continuous strand.

- The eukaryotic mismatch repair system repairs single base mismatches and also insertions and deletions. Human gene homologs (in parentheses) to the *E. coli* mut genes are MutS (hMSH1 and hMSH2) and MutL (hMLH 1). These, together with additional proteins, carry out mismatch repair in eukaryotic cells.

- It is not yet completely understood how the eukaryotic mismatch repair system "knows" which strand to repair.

- DNA that is not being replicated can get damaged or mutated at any time.

- Major causes of DNA damage are 1) radiation (e.g., UV rays in sunlight and in tanning booths, or ionizing radiation); 2) exposure to damaging environmental chemicals, such as nitrosamines or polycyclic aromatic hydrocarbons; and 3) chemical reactions within the cell (such as the deamination of cytosine to give uracil, or the methylation of guanine to produce methylguanine)

- Two adjacent pyrimidine bases one the same strand of DNA can be cross-linked by UV light to form cyclobutane pyrimidine dimers.

- Another type of UV damage is formation of a (6-4) photoproduct

- Ionizing radiation can cause breaks in the DNA backbone, in one or both strands.

- Molecules like benzopyrene can attach themselves to bases, forming bulky DNA adducts in which large chemical groups are linked to bases in the DNA.

- These types of damage can physically distort the DNA, causing DNA and RNA polymerases to stall when they attempt to copy those regions of DNA.

- Other types of chemical alterations don't physically change the shape of DNA, but can favor mispairing during replication. These include deamination of cytosine to uracil or formation of oxidized bases like 8-oxo-guanine or alkylated bases like O^6-methylguanine.

- Many organisms (not humans) contain photolyase enzymes that can repair UV damage. They work work through a process called photoreactivation using blue light energy to catalyze a photochemical reaction that breaks the problem bonds in the damaged DNA.

- O6-methylguanine methyltransferase acts directly to remove the methyl group from the guanine and transfers it onto a cysteine residue in the enzyme. This results in enzyme inactivation, meaning that each enzyme can only be used once.

- There are several different kinds of excision repair, but they all involve cutting out the portion of the DNA that is damaged, followed by repair synthesis using the other strand as template, and finally, ligation to restore continuity to the repaired strand.

- Nucleotide excision repair (NER) fixes damage such as the formation of chemical adducts, as well as UV damage.

- NER proteins cut the damaged strand on either side of the lesion. A short portion of the DNA strand containing the damage is then removed and a DNA polymerase fills in the gap with the appropriate nucleotides.

- Recognition and excision of the damaged DNA in *E. coli* is carried out by a group of proteins encoded by the uvrABC and uvrD genes. uvrA, uvrB and uvrC genes function together as the so-called UvrABC exinuclease. UvrA and UvrB proteins recognize the damage. After they bind, the UvrA dissociates, leaving the UvrB attached to the DNA, where it is then joined by the UvrC protein. UvrB and C then acts to cut the phosphodiester backbone on either side of the damage, creating nicks in the strand about 12-13 nucleotides apart.

- Then uvrD (a helicase) unwinds the region containing the damage, displacing it from the double helix together with UvrBC. The gap in the DNA is filled in by DNA polymerase I and the nick is sealed with DNA ligase.

- Nucleotide excision repair is important in eukaryotes, particularly in the removal of UV damage in humans, since we lack photolyases.

- Mutations in the genes encoding human NER proteins lead to a number of genetic diseases, like Xeroderma pigmentosum, which leaves people extremely sensitive to UV light.

- Nucleotide excision repair operates in two modes- 1) global genomic repair and 2) transcription-coupled repair.

- In global genomic repair, damage is identified by scanning the entire genome for helix distorting lesions.

- In transcription-coupled repair, stalling of the RNA polymerase at a site of DNA damage is what flags nucleotide excision repair.

- Base excision repair (BER) is a repair system dealing with damage that does not typically distort the DNA helix - for example, deamination of cytosine to uracil or the methylation of a purine base.

- In base excision repair a single damaged base is first removed from the DNA, followed by removal of a region of the DNA surrounding the missing base. The gap is then repaired by DNA polymerase and DNA ligase.

- Removal of uracil from DNA is catalyzed by uracil-DNA glycosylase. It recognizes uracil in DNA and breaks the glycosidic bond between the uracil and the sugar in the nucleotide, leaving an apyrimidinic site (AP site).

- Next, an AP endonuclease cuts the strand with the AP site 5' to the AP site and then a DNA polymerase uses its exonuclease and polymerase activities to remove and replace nucleotides around the damage site. DNA ligase seals the strands at the end.

- Double strand breaks (DSB) in DNA are a potentially lethal form of damage that, in addition to blocking replication and transcription, can also lead to chromosomal translocations.

- Two cellular mechanisms exist to help repair DSBs - 1) homologous recombination (HR) and 2) non-homologous end joining (NHEJ).

- Homologous recombination repair commonly occurs in the late S and G2 phases of the cell after chromosome replication.

- Here, a sister chromatid can be used as a template to achieve error-free repair.

- Detection of the double-strand break triggers nuclease activity that chews back one strand on each end of the break, resulting in the production of single-stranded 3' overhangs on each end.

- These single-stranded ends are bound by several proteins, creating a nucleoprotein filament that can then "search" for homologous (matching) sequences on a sister chromatid.

- When homologous sequences are found, the nucleoprotein filament invades the undamaged sister chromatid, forming a crossover and creating heteroduplexes made up of DNA strands from different chromatids.

- Branch migration follows, during which the Holliday junction moves along the DNA, extending the heteroduplex away from the original site of the crossover.

- Branch migration in *E.coli* depends on the activity of two proteins, RuvA and RuvB. RuvC resolves the structure, giving complete, error-free strands.

- Non-homologous end joining (NHEJ) is error-prone. It does not use or require a homologous template to copy, and works by simply chewing back the broken ends of DSBs and ligating them together.

- NHEJ introduces deletions in the DNA as a result.

- Translesion synthesis occurs when a DNA polymerase encounters DNA damage on the template strand, but instead of stalling or skipping past the damage, replication switches to an error-prone mode, ignoring the template and incorporating random nucleotides into the new strand.

- Translesion synthesis depends on proteins encoded by the umuC and umuD genes.

- SOS repair refers to a cellular response to UV damage. It involves activating/ synthesizing a large number of genes necessary for DNA repair.

- Genes activated in SOS repair inclue uvr genes (nucleotide excision repair) and recA (involved in homologous recombination). These can perform error free repair. In addition, the SOS response can also induce the expression of translesion polymerases encoded by the dinA, dinB and umuCD genes.

- All of the genes induced in the SOS response are regulated by two components acting ahead of their coding regions.

- The first is a short DNA sequence upstream of their coding region, called the SOS box.

- The second is a protein, the LexA repressor, that binds to the SOS box and prevents transcription of the downstream genes.

- The presence of single-stranded DNA regions resulting from DNA breaks triggers the activation and binding of RecA proteins to them. Interaction of the activated RecA with the LexA repressor leads to autocleavage of the repressor, which falls off the DNA, allowing the downstream gene(s) to be expressed.

- These are expressed in a specific order - nucleotide excision repair genes, followed by homologous recombination genes. These are both error-free mechanisms for repair.

- If the damage is too extensive to be repaired by these systems, error-prone repair genes are activated as a last resort.

Transcription

- The flow of information from DNA to RNA to protein is the central dogma of molecular biology.
- All cells in a multicellular organism have the same DNA.
- Cells with identical DNA can turn out different because of differences that arise in gene expression.
- Each different cell type uses a different subset of the genes in that DNA to direct the synthesis of a distinctive set of RNAs and proteins.
- The first step in gene expression is transcription.
- Transcription is the process of copying DNA to make RNA.
- Only one of the two DNA strands is copied into RNA.
- Not all of a cells' DNA is copied in transcription. Transcription copies short stretches of the coding regions of DNA to make RNA.
- RNAs are, essentially, temporary copies of the information in DNA and different sets of instructions are copied for use at different times and by different cells.
- The primary RNAs are 1) mRNAs that code for proteins; 2) rRNAS that form part of ribosomes; 3) tRNAs that serve as adaptors between mRNA and amino acids during translation; Small RNAs that regulate gene expression and control splicing, including miRNAs and siRNAs; 4) other small RNAs that have a variety of functions, including the small nuclear RNAs that are part of the splicing machinery; and 5) Long noncoding RNAs (lncRNAs)
- Transcription is catalyzed by an RNA polymerase - there are several different kinds in eukaryotes, but only one in prokaryotes.
- RNA polymerases synthesize new strands only in the 5' to 3' direction using ribonucleotides - ATP, GTP, CTP, and UTP.
- RNA polymerases do not require a primer to make RNA.
- In humans, there are 20,000 to 30,000 genes in each cell.
- Patterns in the DNA sequence indicate where RNA polymerase should start and end transcription.
- The DNA sequence at which the RNA polymerase binds to start transcription is called a promoter.
- The DNA sequence that indicates where the RNA polymerase should stop adding nucleotides and dissociate from the template is known as a terminator sequence.
- The promoter and terminator, thus, bracket the region of the DNA that is to be transcribed.
- The promoter sequence is "before" or "upstream" of the gene - on the side of the gene opposite to the direction of transcription.

- Expression of the gene is dependent on the binding of RNA polymerase to the promoter sequence to begin transcription, so a promoter is said to "control" a gene.
- Common sequence patterns are present in many promoters.
- The transcription start site is the base in the DNA across from which the first RNA nucleotide is paired
- Bacteria have a "-10 sequence" - a 6 bp region centered about 10 bp upstream of the start site. The consensus sequence at this position is TATAAT. In other words, if you count back from the transcription start site, which by convention, is called the +1, the sequence found at roughly -10 in the majority of bacterial promoters studied is TATAAT.
- The -35 sequence is a 6 bp sequence at about 35 basepairs upstream from the start of transcription. The consensus sequence at this position is TTGACA.
- Sequences at -10 and -35 are necessary for recognition of the promoter region by RNA polymerase.
- It is only when the RNA polymerase has stably bound at the promoter that transcription can begin.
- *E. coli* RNA polymerase is made up of a core enzyme of four subunits ($\alpha 2\beta\beta'$) and an additional subunit called the σ (sigma) subunit. The together make up the RNA polymerase holoenzyme.
- The σ subunit helps the core polymerase specifically bind to promoter sequences.
- The initial binding of the holoenzyme at the promoter results in what is called a "closed" complex - DNA has not unwound for transcription to begin.
- The "open" complex is marked by the separation of the DNA strands to create a transcription bubble about 12-14 base-pairs long. The σ subunit is required for the conversion.
- After the open complex has formed, the DNA template can begin to be copied, and the core polymerase adds nucleotides complementary to one strand of the DNA.
- At this stage, known as initiation, the RNA polymerase adds several nucleotides while still bound to the promoter, and without moving along the DNA template.
- Elongation occurs when an RNA of 8-9 bases is made and the enzyme moves beyond the promoter region. When this occurs, the σ subunit is no longer necessary and may dissociate from the core enzyme.
- The core polymerase then can move along the template, unwinding the DNA ahead of it to maintain a transcription bubble of 12-15 base-pairs while copying DNA to make RNA.
- RNA polymerase joins the 5' phosphate of an incoming ribonucleotide to the 3' OH on the last nucleotide of the growing RNA.
- A sequence of nucleotides called the terminator site is the signal to the RNA polymerase to stop transcription and dissociate from the template.
- There are two kinds of terminator - 1) intrinsic terminators, allow termination by

RNA polymerase without the help of any additional factors and 2) rho-dependent terminators, require the assistance of a protein factor called rho (ρ).

- The terminator sequence precedes the last nucleotide of the transcript.
- In intrinsic terminators, the terminator sequence in the RNA has self-complementary regions that can base-pair with each other to form a hairpin structure. It is followed by a single-stranded region that is rich in U's.
- Folding of the end of the RNA into the hairpin causes the RNA polymerase to pause.
- The run of U's at the end of the hairpin permits the RNA-DNA duplex in this region to come apart and the transcript to be released from the DNA template and from the RNA polymerase.
- In rho-dependent termination, an additional protein factor, rho, is necessary for termination.
- Rho is a helicase that separates the transcript from the template it is paired with.
- Rho-dependent termination also requires the formation of a hairpin structure in the RNA that causes pausing of the RNA polymerase.
- Rho binds to a region of the transcript called the rho utilization site (rut) and moves along the RNA till it reaches the paused RNA polymerase where it unwinds the RNA-DNA duplex and releases the transcript and RNA polymerase from the DNA.
- In prokaryotes (but not eukaryotes) mRNA is immediately available to the translation machinery, as the transcript is coming off the template DNA. Translation can begin before the entire gene has been transcribed.
- In eukaryotes, the DNA template exists as chromatin, where the DNA is tightly associated with histones and other proteins
- DNA must therefore be opened up to allow the RNA polymerase access to the template for transcription to occur.
- Eukaryotes have multiple, specialized RNA polymerases.
- RNA polymerase I transcribes the ribosomal RNA genes.
- RNA polymerase II transcribes protein-coding genes to make mRNAs.
- RNA polymerase III copies tRNA genes.
- All eukaryotic RNA polymerases need additional proteins called transcription factors to help get transcription started.
- Transcription happens in the nucleus in eukaryotes, and the mRNAs produced are processed further before they are sent into the cytoplasm for translation.
- Transcription starts about 25 bp downstream of the eukaryotic TATA box, and creates a transcript that begins with a 5' untranslated region (5' UTR) followed by the coding region which may include multiple introns and ending in a 3' untranslated region or 3' UTR.

- Eukaryotic genes also have promoters that determine where transcription will begin.
- Specific sequences in the promoter regions are recognized and bound by proteins involved in the initiation of transcription.
- Eukaryotic promoters commonly have a TATA box (similar to the -10 sequence in prokaryotic promoters) about 25-35 base-pairs upstream of the start of transcription (+1).
- Eukaryotic promoters that lack TATA boxes have, instead, other recognition sequences, known as downstream promoter elements.
- The TATA box is not directly recognized and bound by RNA polymerase II. Instead, this sequence is bound by other proteins that, together with the RNA polymerase, form the transcription initiation complex.
- Other short stretches of sequences within about 100 to 200 base-pairs upstream of the transcription start site affect eukaryotic transcription.
- These upstream elements or promoter-proximal upstream elements, are bound by activator proteins that interact with the transcription complex at the TATA box. Examples include the CAAT box and the GC box.
- General transcription factors are proteins that help eukaryotic RNA polymerases find promoter sites and initiate transcription.
- These transcription factors that assist RNA polymerase II are named TFIIA, TFIIB and so on.
- A complex between general transcription factors and the RNA polymerase at the TATA box is called the basal transcription complex or transcription initiation complex.
- The first step in the formation of the complex is binding by TFIID to the TATA box. TFIID has several proteins, one of which is called the TATA Binding Protein or TBP. Binding of the TBP causes the DNA to bend at this spot and favor binding of additional transcription factors and RNA polymerase.
- Binding of TBP is a necessary step in forming a transcription initiation complex even when the promoter lacks a TATA box.
- The order of binding of additional proteins appears to be TFIIB, followed by TFIIF and RNA polymerase II, then TFIIE. The final step in the assembly of the basal transcription complex is binding of a general transcription factor called TFIIH.
- The presence of all of these general transcription factors and RNA Polymerase II at the promoter is necessary for the initiation of transcription.
- In order for RNA polymerase II to move down the template and elongate the transcript, TFIIH must act. It is a multifunctional protein with a helicase activity and a kinase activity. The kinase activity of TFIIH adds phosphates onto the C-terminal domain of the RNA polymerase II. This phosphorylation by TFIIH appears to be the signal releasing the RNA polymerase II from the transcrip-

tion initiation complex and allow it to move forward on the template.

- For termination, the polyadenylation signal in the 3' UTR of the transcript appears to play a role in RNA polymerase pausing, and subsequent release of the completed primary transcript. Recognition of the polyadenylation signal triggers the binding of proteins involved in 3'end processing and termination.

RNA Processing

- Both prokaryotes and eukaryotes process their rRNAs and tRNAs.
- Prokaryotes and eukaryotes differ in the processing of mRNAs.
- In bacterial cells, the mRNA is translated directly as it comes off the DNA template.
- RNA synthesis in eukaryotes occurs in the nucleus, apart from translation in the cytoplasm.
- After RNA processing in the nucleus, RNAs exported to the cytoplasm are called mature mRNAs.
- The three main processing steps for mRNAs are 1) capping at the 5' end; 2) splicing to remove introns; and 3) addition of a polyA tail at the 3' end.
- There is evidence that some of the processing occurs co-transcriptionally.
- Proteins involved with mRNA processing are associated with the phosphorylated C-terminal domain (CTD) of RNA polymerase II.
- The addition of an mRNA cap at the 5' end is the first step in mRNA processing.
- Capping occurs once the first 20-30 nucleotides of the RNA have been synthesized.
- Addition of the cap involves removal of a phosphate from the 5' nucleotide in the mRNA creating a diphosphate which gets joined to a guanosine monophosphate that is subsequently methylated at N7 of the guanine to form the 7mG cap structure.
- The cap protects the 5' end of the mRNA from degradation by nucleases and also helps to position the mRNA correctly on ribosomes for translation.
- Introns are noncoding regions that interrupt a gene.
- These introns must be removed before the mRNA is sent out of the nucleus to be used to direct protein synthesis.
- Introns are removed from the pre-mRNA by a complex called the spliceosome.
- The spliceosome contains proteins and small RNAs that are associated to form protein-RNA enzymes called small nuclear ribonucleoproteins or snRNPs.
- The splicing machinery recognizes splice junctions (where each exon ends and its associated intron begins) in order to correctly remove the introns and make the mature, spliced mRNA.
- The consensus sequence at the junction of 5' exon-introns (also called the 5' splice site) is AG*GURAGU, where the * indicates the boundary between the end of the exon (on the left) and the beginning of the intron (on the right).

- The 3' splice junction (at the other end of the intron) has the consensus sequence YAGRNNN, where YAG is the end of the intron, and RNNN is the beginning of the next exon. (Y = pyrimidine and N = any nucleotide).

- Another important splicing sequence within the intron, about a hundred nucleotides from the 3' splice site, is called a branch site. It is defined by the presence of an A followed by a string of pyrimidines. This site plays an important role in the mechanism of splicing.

- The first step in splicing is the nucleophilic attack by the 2'OH of the A at the branch point on the 5' splice site (the junction of the exon and the 5' end of the intron). This makes a lariat structure composed of the second exon still linked to the intron sequence.' The intron containing the lariat is completely released in the second step.

- In the second step of splicing, the 3' OH of the first exon (the one freed in the first reaction) attacks the 3' splice site, resulting in the two exons being joined together and the lariat-shaped intron is released in the process.

- Five small RNAs (snRNAs) are crucial to the spliceosome complex. They are U1, U2, U4, U5 and U6 and are found associated with proteins, as snRNPs.

- Components of the splicing machinery associate with the CTD of the RNA polymerase II for improved splicing efficiency.

- The initial step in spliceosome assembly is the interaction of the U1 snRNP with the 5' splice site. This is followed sequentially by binding of U2AF (U2 associated factor) near the branch site; U2 snRNA (to the branch site); and U4/U6 and U5 snRNPs. This creates the pre-catalytic complex.

- Rearrangements displace U4 and U2 snRNPs, resulting in the catalytically active spliceosome. It is this structure that catalyzes the splicing reactions above.

- On average, human genes have about 9 exons each.

- Exons in a pre-mRNA can be spliced together in different combinations to generate different mature mRNAs in a process known as alternative splicing.

- A single mRNA with many exons can, by combining different exons during splicing, create many different protein coding messages.

- Because of alternative splicing, each gene in our DNA gives rise, on average, to three different proteins, which can be made at different developmental stages or in different cell types.

- The 3' end of a processed eukaryotic mRNA typically has a "poly(A) tail" consisting of about 200 adenine-containing nucleotides.

- The poly(A) tail is added by a template-independent enzyme, poly(A)polymerase, following cleavage of the RNA at a site near the 3' end of the new transcript.

- C Components of the polyadenylation machinery are also associated with the phosphorylated CTD of the RNA polymerase.

- The polyA tail plays a role in efficient translation of the mRNA, as well as in the stability of the mRNA.
- The cap and the polyA tail on an mRNA are also indications that the mRNA is complete.
- After these processing events, mRNAs are transported out of the nucleus for translation in the cytoplasm.
- RNA editing is another type of mRNA processing that occurs to some messages and to rRNAs and tRNAs.
- In RNA editing, the sequence of the transcript is altered post-transcriptionally.
- The apolipoprotein B mRNA is one that gets edited.
- The editing here results in the deamination of a cytosine in the transcript to form a uracil, at a specific location in the mRNA, converting the codon at this position, CAA, which encodes a glutamine, into UAA, a stop codon.
- As a result, a shorter version of the protein is made, when the edited transcript is translated.
- Notably, editing of this mRNA occurs in intestinal cells but not in liver cells. Thus, the protein product of the apolipoprotein B gene is longer in the liver than it is in the intestine.
- Mitochondrial RNAs of trypanosome undergoes a different kind of editing in which nucleotides are inserted or deleted. These are specified by guide RNAs that indicate the sites of insertion or deletion.
- Editing changes the properties of proteins made from a transcript and provide another point at which the product of expression of a gene can be controlled.
- tRNAs are synthesized as pre-tRNAs by RNA polymerase III. They must undergo processing to generate mature tRNAs.
- Initial transcripts contain extra RNA sequences at both the 5' and 3' ends and some contain introns. All these extra sequences must be removed from the transcript during processing.
- The 5' end (leader sequence) of the pre-tRNA is cleaved by a catalytic RNA (ribozyme) - an endonuclease called ribonuclease P.
- Extra 3' end sequences (trailer sequence) are later removed by a different nucleases.
- All tRNAs must have a 3' CCA sequence for the charging of the tRNAs with amino acids. In bacteria, this CCA sequence is encoded in the tRNA genes. In eukaryotes, the CCA sequence is added post-transcriptionally by an enzyme called tRNA nucleotidyl transferase.
- Introns in tRNAs are spliced out with the help of a tRNA splicing endonuclease and a ligase.
- Mature tRNAs contain a high proportion of bases other than the usual A,G,C, and U.
- They are produced by chemically modifying the bases in the tRNA to form variants, such as pseudouridine or dihydrouridine. Modifications occur at the final processing step by a variety of specialized enzymes.

- Cells contain many copies of rRNA genes (between 100 and 2000 copies for mammalian cells).

- Each transcription unit contains rRNA sequences coding for 18S, 5.8S and 28S rRNA, and it is transcribed by RNA polymerase I into a single long transcript.

- Sizes of rRNAs are, by convention, indicated by their sedimentation coefficients (Svedberg units, given by the letter S), which is a measure of their rate of sedimentation during centrifugation. Higher values indicate greater mass.

- The primary transcript is first trimmed at both ends by nucleases to give a 45S pre-rRNA.

- Further processing of the pre-rRNA through cleavages is guided by RNA-protein complexes containing snoRNAs (small nucleolar RNAs). This yields the mature 18S, 5.8S and 28S rRNAs.

- rRNAs are also modified on the ribose sugars (methylation and acetylation) and on various alterations to the bases. The modified base pseudouridine is also common in rRNA.

- Modifications may be important in modulating ribosome function.

Translation

- Translation is the process by which information in mRNAs is used to direct the synthesis of proteins.

- Translation occurs in the cytoplasm of cells and is carried out by ribosomes.

- Ribosomes contain ribosomal RNA (rRNA) and proteins organized into a large subunit and a small subunit.

- Ribosomes bind mRNAs and hold them to allow amino acids (carried by tRNAs) encoded by the RNA to be joined sequentially.

- The mRNA sequence, copied from a gene, directly specifies the sequence of amino acids in the protein it encodes.

- Each amino acid in a protein is specified by a sequence of 3 bases called a codon in the mRNA coding for it.

- With the exception of the amino acids methionine and tryptophan, all the other amino acids are encoded by multiple codons - degeneracy.

- Codons for the same amino acid are often related, with the first two bases the same and the third being variable.

- Three of the 64 codons are stop codons - they indicate the end of a protein coding sequence.

- The codon for methionine, AUG, is used as the initiation or start codon for the majority of proteins.

- tRNAs are small RNA molecules, about 75-90 nucleotides long, that function to 'interpret' the instructions in the mRNA during protein synthesis.

- tRNAs are extensively modified post-transcriptionally and contain a large number of unusual bases.

- tRNAs have several self complementary regions, where the single-stranded tRNA folds on itself and base-pairs to form what is

sometimes described as a clover leaf structure.

- tRNAs contain sites for attachment of the appropriate amino acid and for recognition of codons in the mRNA at opposite molecular ends.
- A given tRNA is specific for a particular amino acid - corresponding to the anticodon it carries.
- A tRNA is linked covalently to its specific amino acid at its 3' end by aminoacyl tRNA synthetase, which “reads” the anticodon and attaches the proper amino acid.
- A tRNA with an amino acid attached to it is said to be charged.
- The amino acid sequence of the protein is determined by the order of the codons in the mRNA.
- The RNA sequence is converted into amino acid sequence by the appropriate charged tRNAs’ antiparallel base pairing of their anticodons with the codons in the mRNA. This occurs in special sites in the ribosome.
- Thus, base-pairing of the anticodon of a charged tRNA with the codon on the mRNA is what brings the correct amino acids in to the ribosome to be added on to the growing protein chain.
    - Ribosomes have two sites (P-site and A-site) for binding and positioning charged tRNAs so each can form base pairs between their anticodon and a codon from the mRNA.
- The start codon (AUG) is positioned to base pair with the tRNA in the P-site (peptidyl site).
- Then, the charged tRNA complementary to the second codon binds and occupies the A-site (aminoacyl site).
- The ribosome then joins the amino acids carried on each tRNA by making a peptide bond, leaving the two amino acids attached to the tRNA in the A-site.
- The ribosome then moves one codon further down the mRNA, with the first (empty) tRNA exiting through the E site. The process continues until a stop codon is reached.
- When a stop codon is reached, a release factor binds at the A-site, and helps to free the completed polypeptide from the ribosome and the two ribosomal subunits come apart, releasing the mRNA as well.
- Examining translation more closely, it occurs in three steps - initiation, elongation, and termination.
- In the initiation process, small and large subunits of ribosomes assemble on mRNAs to form complete ribosomes that carry out translation.
- The small subunit of prokaryotic cells is called the 30S ribosomal subunits (40S subunit in eukaryotes). The large ribosomal subunit in prokaryotes is the 50S subunit (60S in eukaryotes).
- rRNA components of ribosomes help to orient the 5’ end of the mRNA, and catalyze formation of peptide bonds.

- mRNAs have non-coding sequences at the 5’ end (5’ UTR) and 3' end (3’ UTR) with the protein-coding region between them.
- The ribosome must recognize the mRNA’s 5' end, bind to it, then determine where the start codon is located.
- Ribosomes assemble at the 5’ end of a transcript by the stepwise binding of the small and large subunits.
- The small subunit binds first at specific sequences in the 5’ UTR. Binding of the first tRNA to the ribosome occurs next and then the large subunit binds to the complex of the mRNA, initiator tRNA, and small subunit, to form the complete ribosome.
- In bacteria, the methionine on the initiator tRNA is modified by the addition of a formyl group, and is designated $tRNA^{fmet}$. it is different from the tRNAs carrying methionine intended for other places in the protein.
- The Shine-Dalgarno sequence in the mRNA helps to properly orient the 5’ end of the mRNA on the small subunit of the ribosome. This happens as a result of complementarity between the Shine-Dalgarno sequence and a separate sequence on the 16S rRNA of the small ribosomal subunit.
- When this pairing occurs, the AUG start codon is properly positioned at the P-site.
- Three initiation factors, IF1, IF2, and IF3 facilitate the initial ribosome/mRNA complex.
- IF3 facilitates binding of the small subunit to the mRNA.
- IF2 brings the initiator tRNA to the partial P-site of the small ribosomal subunit.
- IF1 occupies the A-site, preventing binding of the initiator tRNA at that site.
- Binding of the 50S ribosomal subunit (which occurs next) is accompanied by the dissociation of all three initiation factors.
- Translation initiation in eukaryotes is similar in many ways, but differs in some.
- Eukaryotes have a large number of IFs that are known as eIFs and they together perform the same functions carried out by IFs.
- Binding of the small subunit of the eukaryotic ribosome to the mRNA requires the assistance of eIF2 and eIF3. Next, the small subunit with the initiator tRNA binds to the mRNA’s 7-methyl G cap.
- The 40S subunit then moves along the mRNA, scanning for a proper start codon, since eukaryotes do not have a Shine Dalgarno sequence. They do have a Kozak sequence that includes a few specific bases around the proper AUG.
- After the small subunit is properly positioned, the large subunit binds.
- Elongation of translation in prokaryotes and eukaryotes requires proteins called elongation factors (EFs). EF-Tu (bound to GTP) in bacteria brings the second charged tRNA to the A-site for proper pairing and orientation.
- When the charged tRNA has been loaded at the A-site, EF-Tu hydrolyzes the GTP to GDP and dissociates from the ribosome.

eEF1α.GTP performs the same function in eukaryotes.

- Next, the methionine carried by the tRNA in the P-site is joined to the amino acid carried by tRNA in the A-site, forming a peptide bond.
- The reaction occurs in the ribosomal peptidyl transferase center of the large ribosomal subunit, catalyzed by rRNA components.
- The result of the peptidyl transferase activity is that the tRNA in the A-site now has a dipeptide attached to it, while the tRNA at the P-site has nothing.
- This “empty” tRNA is moved to the E-site on the ribosome, where it exits. The tRNA in the A-site, moves to occupy the vacated P-site, leaving the A-site open for the next incoming charged tRNA.
- EF-G complexed with GTP translocates the ribosome along the mRNA one codon further (in bacteria - eEF2.GTP in eukaryotes), ending one cycle of the elongation phase.
- The elongation cycle repeats until a stop codon appears in the A-site to begin termination.
- In termination, release factors (RFs) recognize the stop codon and cleave and release the newly made polypeptide. In bacteria, RF1 acts when UAG or UAA are in the A-site, whereas RF2 acts when UGA or UAA are in the A-site.
- RF3, works with RF1 and RF2 to hydrolyze the polypeptide from the final tRNA and release the newly synthesized protein. The ribosomal subunits then dissociate.
- The released polypeptide must fold properly in order to function. It may also undergo modifications such as the addition of phosphates, sugars, lipids,and/or may be cleaved by proteases to remove inactivating precursor sequences.
- Proteins made in the cytoplasm must be delivered to the appropriate cellular compartment in which it functions.
- Some proteins are delivered to their destinations in an unfolded state, and are folded within the compartment in which they function. Others are fully folded and may be post-translationally modified before they are sent to their cellular (or extracellular) destinations.
- Some proteins are delivered as they are being synthesized. Others are sent post-translationally. With the exception of cytosolic proteins, all proteins must cross membrane barriers, through membrane channels or other "gates", or by transport within membrane vesicles that fuse with the membrane of the target organelle to deliver their contents.
- Folding of a protein is largely influenced by hydrophobic interactions that position hydrophobic residues in the interior of the protein.
- As a polypeptide emerges from the ribosome, the N-terminal region may begin to fold on itself, with adjacent parts of the chain interacting in inappropriate ways, before the entire protein has been made. This can result in misfolding of the protein and consequent malfunction.
- Protein chaperones bind to and shield regions of polypeptides as they emerge from

the ribosome to keep them from improperly interacting until they can fold properly.

- Some chaperones sequester proteins to permit unfolding and refolding of misfolded polypeptides.

- Protein sorting is the process by which proteins are identified and delivered to a proper compartment.

- Proteins have "address labels" or sorting signals (also called signal sequences) in their amino acid sequences that indicate which cellular compartment they are destined for.

- Signal sequences may be found at the N-terminal or C-terminal region of proteins, or they may be within the amino acid sequence of the proteins.

- Signal sequences targeting proteins to the endoplasmic reticulum, mitochondrion, or chloroplast are at the N-terminus of a protein. Nuclear proteins, by contrast, have the signal internal to the polypeptide.

- Proteins are synthesized by ribosomes in the cytoplasm or by those that associate with membranes temporarily (membrane-bound ribosomes). The latter make proteins that are destined for the nucleus, as well as those going to chloroplasts, mitochondria and peroxisomes.

- Nuclear proteins are delivered in their folded state, while chloroplast and mitochondrial proteins are folded at their destination.

- Proteins destined for the ER, the Golgi apparatus, lysosomes and those that are to be secreted from the cell are first delivered to the ER by ribosomes that associate with the membrane of the rough ER and synthesize the protein directly into the ER.

- All proteins delivered to the ER, regardless of their final destination, have an ER N-terminal signal sequence of 15-30 amino acids.

- If the sequences that emerges first from a ribosome in translation of a protein is an ER signal, it will be recognized and bound by a ribonucleoprotein complex called the Signal Recognition Particle (SRP) and translation will pause.

- The SRP, in turn, is bound by an SRP receptor in the ER membrane, effectively anchoring the ribosome to the membrane.

- When the ribosome is docked over the channel, the SRP releases the signal sequence, which is threaded through the channel, with its hydrophobic residues interacting with the hydrophobic interior of the membrane. Translation resumes at this point and the rest of the protein is delivered into the lumen of the ER as it is made.

- The signal sequence is cleaved off by a membrane associated signal peptidase, releasing the completed protein into the ER lumen.

- Integral membrane proteins differ in that they do not pass all the way through to the lumen, but, instead, are anchored in the membrane of the ER by hydrophobic stop transfer sequences.

- Chaperones in the ER lumen help proteins to fold properly. The ER environment is more oxidizing than the cytosol, and permits the formation of disulfide bonds more readily to stabilize the folded proteins.

- Protein disulfide isomerase in the ER lumen helps to make disulfide bonds and removes bonds that were incorrectly made during folding.
- Proteins in the ER undergo modifications such as glycosylation and addition of glycolipids. Multimeric proteins are also assembled from subunits in the ER.
- Correctly folded and modified proteins are transported in membrane vesicles to their final destinations. Improperly folded proteins are sent back to the cytoplasm to be degraded in proteasomes.

Gene Expression

- Gene expression is the process by which information in DNA directs the production of the proteins needed by the cell.
- The first step in gene expression is transcription.
- The basic mechanism by which transcription is regulated depends on highly specific interactions between transcription regulating proteins and regulatory sequences on DNA.
- Besides the promoter, genes have additional *cis* regulatory sequences that control when it is transcribed.
- Transcriptional regulators are proteins that can recognize DNA sequences and bind to them, affecting transcription.
- In bacteria, genes are often clustered in groups that need to be expressed at the same time. Many are controlled as a single unit (operon) by the same promoter.
- Transcription regulator DNA binding proteins act as either repressors (preventing transcription) or activators (increasing transcription of genes).
- Binding of these proteins to DNA targets is allosterically controlled by the binding of specific small molecules that signal the state of the cell.
- The *lac* operon is a group of coordinately regulated genes that encode proteins needed for the uptake and breakdown of the sugar lactose.
- *E.coli* cells prefer glucose for energy, but if glucose is unavailable and lactose is present, they will take up lactose and use it for energy
- Proteins for utilizing lactose are only needed when glucose is absent and lactose is available. The cells need to express the genes of the *lac* operon only under those conditions.
- The default state of the *lac* operon is OFF.
- A repressor protein that binds to a region of the DNA just downstream of the -10 sequence of the *lac* promoter is the primary regulator of operon's transcription.
- The location on the DNA where the *lac* repressor binds is called the operator.
- The lac repressor's binding here physically blocks the RNA polymerase from transcribing the genes.
- When lactose is present, a small amount of it is taken up by the cells and converted to allolactose, which binds to the lac repressor, changing its conformation so that it no longer binds to the operator.

- When the lac repressor is gone, the roadblock to transcription is gone. Only when lactose is present can transcription of the operon to make proteins to break down lactose be activated. Thus, these genes are not expressed unless they are needed.

- Glucose too is a factor - if it is present, lactose will not be used.

- A second protein involved in *lac* operon regulation is the Catabolite Activator Protein (CAP).

- It binds on the side of the promoter opposite that of the *lac* repressor and its binding is necessary for RNA polymerase to begin transcription of the operon.

- CAP binds to its site only when glucose levels are low.

- When glucose levels are low, adenylate cyclase makes a molecule called cyclic AMP (cAMP), which can bind to CAP. CAP binds to its site ahead of the *lac* promoter only when bound to cAMP. Thus, only when glucose levels are low will CAP bind and favor RNA polymerase to bind and start transcription of the *lac* operon.

- For genes whose default state is ON, they are expressed unless conditions turn the signal OFF. An example is the trp operon. The trp operon makes proteins that allow the cell to synthesize tryptophan. Unless tryptophan is available from the cell's surroundings, the genes in the trp operon are always expressed. When tryptophan is abundant, the trp operon is turned off. This is achieved by a repressor protein that will bind to the operator only in the presence of tryptophan. Tryptophan is a co-repressor of the operon.

- The trp operon has two systems of regulation. The second is called attenuation.

- Attenuation is a process by which the expression of an operon is controlled by termination of transcription before the first gene of the operon.

- This functions as follows: Transcription begins upstream of the first gene in the operon, producing what is termed a 5' leader sequence. This leader sequence contains an intrinsic terminator that can form a transcriptional terminator when high levels of tryptophan are available to the cells. It can also form a different structure that permits continued transcription of the genes in the operon when tryptophan levels are low.

- The 5' end of the mRNA is the first part of the transcript to be made and since bacterial translation is linked to transcription, the 5' end of the RNA begins to be translated before the entire transcript is made.

- The 5' leader sequence of the trp operon mRNA encodes a short peptide that contains two tryptophan codons. When tryptophan is abundant, the leader sequence is easily translated and it forms a transcriptional terminator, which stops transcription immediately - long before the entire transcript is made.

- If tryptophan levels are low, the ribosome stalls at the tryptophan codons. In this case, the leader sequence adopts a different structure that allows transcription to continue.

- Thus, when tryptophan levels are high, transcription of the trp operon is stopped quickly and when tryptophan levels are low, transcription of the complete

operon occurs, allowing the cell to make the proteins necessary to synthesize tryptophan.

- Riboswitches are sequences that can control transcription of the downstream genes based on the conformation they adopt. Two features are important for their function.
- One is a region of the sequence called an aptamer. It folds into a three-dimensional shape that can bind a small effector molecule. The second is an adjacent region of the RNA, called the expression platform. It can fold into different conformations depending on whether or not the aptamer is bound to the effector.
- The guanine riboswitch of bacteria controls the expression of genes required for purine biosynthesis. The aptamer region binds to guanine when levels are high.
- Binding of guanine triggers causes the downstream expression platform to adopt a conformation that terminates transcription of the genes needed for the synthesis of guanine.
- In the absence of guanine, the expression platform assumes a different conformation that allows transcription of the purine biosynthesis genes.
- Thus, when guanine it high, transcription of genes for making guanine is turned off and when guanine is low, transcription of these genes progresses.
- For most eukaryotic genes, general transcription factors and RNA polymerase are necessary but not sufficient for high levels of transcription.
- Distant DNA sequences like the CAAT box and GC box bind proteins that interact with the transcription initiation complex, influencing its formation.
- Enhancers and the proteins that bind to them are needed to achieve high levels of eukaryotic transcription.
- Enhancers are short DNA sequences that regulate the transcription of genes, but may be located a long distance away from the gene they control (upstream, downstream, or within).
- Enhancers work by binding transcriptional activator proteins that can, in turn, interact with the proteins bound at the promoter.
- Transcriptional activator(s) on enhancers can come in contact with the promoter that is a long distance away by looping of the DNA.
- This interaction can assist in recruiting proteins necessary for transcription, like the general transcription factors and RNA polymerase to the promoter.
- Enhancers may also play a role in facilitating the transition of the RNA polymerase to the elongation phase of transcription.
- Enhancers can also affect transcription by recruiting to the promoter proteins to modify the chromatin structure of that region of the chromosome to allow access of transcription proteins to promoters.
- In addition to enhancers, there are also negative regulatory sequences called silencers.

- Silencers bind to transcriptional repressor proteins that interact with the transcription initiator complex and reduce transcription.

- Transcriptional activators and repressors are modular proteins- they have a part that binds DNA and a part that activates or represses transcription through interactions with the transcription initiation complex.

- The DNA binding domain of the protein confers specificity for determining which gene(s) will be activated or repressed (which sequences are bound - usually through the major groove of DNA).

- The activation domain is the part of the protein that stimulates or represses transcription through interactions with the transcription initiation complex.

- Combinatorial regulation provides great versatility, with different combinations of regulatory elements and proteins working together in response to a wide variety of conditions and signals.

- Alternative splicing and editing of transcripts can also modify the proteins that are produced by the cell and thus affect gene expression.

- Another way of affecting gene expression is through histone modification because for a gene to be transcribed, the relevant regions of the chromatin must be opened up to allow access to the RNA polymerase and transcription factors.

- Chromatin remodeling factors assist in reorganizing the nucleosome structure at regions that need to be made accessible.

- Transcriptional activator proteins bound at enhancers, sometimes work by recruiting histone modifying enzymes to the promoter region. Histone acetyl transferase (HAT), for example works to acetylate specific amino acid residues in the tails of the histones forming the nucleosome core.

- Acetylation of histones may be responsible for loosening interactions between histones and DNA in nucleosomes and help to make the DNA more readily accessible for transcription.

- Histone deacetylases which remove acetyl groups from the tails of the histones in the nucleosome may reverse the activation by leading to tighter packing of the chromatin.

- Other enzymes may add or remove methyl groups, phosphate groups, and other chemical moieties to specific amino acid side chains on the histone tails. The patterns of these covalent modifications are called the histone code.

- Histone methyltransferases are “writers” that add the chemical groups on to the histone tails. Other enzymes, like the histone demethylases, may act as "erasers", removing the chemical groups added by the "writers".

- “Readers” are proteins that bind to specific combinations of the modifications and assist in either silencing gene expression in the vicinity or making the region more transcriptionally active.

- Gene expression can also be regulated by methylation of DNA.

- DNA methyltransferases (DNMTs) catalyze the covalent addition of a methyl group to C5 of cytosines in DNA.

- In vertebrates, cytosines that are methylated are generally next to a guanine (referred to as CpG).

- Methylation of DNA seems to correlate with gene silencing while demethylation is associated with increased transcription

- Methylation might block the binding of proteins necessary for transcription or the binding of transcriptional activators at enhancers. Proteins that bind to methylated CpG sites also seem to interact with histone deacetylases - favoring tighter packing of chromatin and less access for transcription proteins to DNA.

- MicroRNAs (miRNAs) and Short Interfering RNAs (siRNAs) are small, non-coding RNAs that act at the post-transcriptional level to regulate gene expression.

- They appear to silence genes by base-pairing with target mRNAs and marking them for degradation, or by blocking their translation.

- The functional forms of both miRNAs and siRNAs are from 20-30 nucleotides long and are derived by processing from longer primary transcripts.

- miRNAs are transcribed from specific genes by RNA polymerase II. The primary transcript, known as a pri-miRNA folds on itself to form double-stranded hairpin structures that are cleaved by the Drosha RNase in the nucleus to about 60-70 nucleotides (pre-miRNAs). These are exported to the cytoplasm where the enzyme known as Dicer cuts them to

- 20-30 nucleotides are the sizes of mature double-stranded miRNAs. The RNAs contain loops and mismatches.

- siRNAs also derive from double-stranded RNAs, but they may arise from either endogenous or exogenous (viral) sources

- These double-stranded RNAs are also processed in the cytoplasm by Dicer to generate mature miRNAs - 20-30 nucleotide double-stranded RNAs. Mature siRNAs are perfectly base-paired along their lengths.

- Both miRNAs and siRNAs then are assembled with Argonaute proteins to form a silencing complex called RISC (RNA-induced silencing complex).

- One strand of each of these double-stranded RNAs is referred to as the guide RNA, while the other is called the passenger RNA.

- During the process of loading the RNA onto the Argonaute protein, the guide strand of the RNA remains associated with the protein, while the passenger strand is removed.

- The guide RNA associated with the Argonaute protein is the functional gene silencing complex.

- Sequence specific base-pairing of the guide RNA with a complementary mRNA sequence leads to either the degradation of the mRNA by the Argonaute protein (in the case of the siRNAs) or in suppression of translation of the mRNA (for miRNAs).

- The expression of at least a third of all human genes has already been shown to be modulated by miRNAs.

- Long noncoding RNAs (lncRNAs) are RNAs of greater than 200 nucleotides that do not code for proteins. Some come from introns or antisense transcripts of coding genes. Others from intergenic sequences. The last ones are called lincRNAs.

- lncRNAs appear to affect gene expression by 1) modification of chromatin structure, 2) regulation of splicing, 3) serving as structural scaffolds for the assembly of nucleoprotein complexes or 4) other unknown ways.

- Gene expression can also be regulated by mechanisms that alter the rate of mRNA degradation.

- Regulation of translation is used to control the production of many proteins. Examples are ferritin and the transferrin receptor.

- Ferritin is an iron-binding protein that sequesters iron atoms in cells to keep them from reacting. When iron levels are high, there is a need for more ferritin than when iron levels are low.

- The 5'UTR of the ferritin mRNA contains a sequence called the Iron Response Element (IRE). When iron levels are low, the IRE is bound by a protein. The presence of the IRE-binding protein at the 5'UTR blocks translation of the ferritin mRNA. When iron levels are high, it binds to the IRE-binding protein, which undergoes a conformational change and dissociates from the IRE. This frees up the 5' end of the ferritin mRNA for ribosome assembly and translation, producing more ferritin.

- The transferrin receptor is required for uptake of iron into cells - when intracellular iron levels are low. It is only when iron levels are low that more transferrin receptor is needed.

- The mRNA encoding the transferrin receptor also has multiple IRE sequences in the 3'UTR of the transcript.

- When cell iron levels are high, the iron binds the IRE-binding protein, which dissociates from IRE, leaving the 3'UTR susceptible to attack by RNases and to degradation of the transferrin receptor mRNA.

- When iron levels are low, the IRE-binding protein remains bound to the 3' UTR of the mRNA, stabilizing it and permitting more transferrin receptor to be made by translation.

Signaling

- Cells must know when to divide, when to undergo apoptosis (programmed cell death), when to store food, and when to break it down.

- Signaling is dependent on molecular recognition.

- In signaling, a molecule, sent by a signaling cell, is recognized and bound by a receptor protein in (or on the surface of) a target cell.

- Signals may be proteins, short peptides, lipids, nucleotides or catecholamines, to name a few.

- Signal molecules that are small and hydrophobic can cross the cell membrane and bind a receptor inside the cell.

- Signal molecules that are charged, or very large, are not be able to diffuse through the plasma membrane and need receptors on the cell surface - usually transmembrane proteins.

- In the transmembrane receptor proteins, the extracellular portion binds the signal and an intracellular part passes on the message within the cell.

- Different cells have different sets of receptors, so they respond to different signals or combinations of signals.

- Binding of a signal molecule to a receptor sets off a chain of events (called signal transduction) in the target cell that include, but are not limited to, alterations in metabolic pathways or gene expression.

- Signal transduction pathways all have some features in common - 1) binding of a signal to its receptor is usually followed by the generation of a new signal(s) within the cell; 2) most have multiple steps involving a series of molecular messengers that amplify and distribute the message to various parts of the cell; and 3) the last of the messengers usually interacts with a target protein(s) and changes its activity, often by phosphorylation.

- When a signal sets a particular pathway in motion, it is acting like an ON switch. This means that once the desired result has been obtained, the cell must have a mechanism that acts as an OFF switch.

- The simplest and fastest of signal pathways are where receptors are gated ion channels.

- Each ion channel is specific to the passage of a particular ionic species. Gates are opened by the binding of an incoming signal (ligand) to the receptor, allowing the almost instantaneous passage of millions of ions from one side of the membrane to the other.

- Changes in the interior environment of the cell are thus brought about in microseconds and in a single step.

- This type of swift response is seen in neuromuscular junctions, where muscle cells respond to a message from the neighboring nerve cell.

- Nerve cells release a neurotransmitter signal (acetylcholine, for example) into the synaptic cleft. It diffuses rapidly till reaching receptors on the membrane of the muscle cell. Its binding causes the gate in the ion channel to open, resulting in ion flow that immediately changes the membrane potential of the cell. This, in turn, can trigger other changes in the cell.

- Sensory neurons carry information to the brain. Motor neurons send signals to muscles.

- Receptors for signals like steroid hormones are part of a large group of proteins known as the nuclear hormone receptor superfamily.

- They recognize and bind not only steroid hormones, but also retinoic acid, thyroid hormone, and vitamin D.

- Nuclear hormone receptors that bind steroid hormones are intracellular proteins.
- Steroid hormones are able to cross the cell membrane by themselves.
- Inside the cell, steroid hormones bind to their receptors, which may reside in the cytoplasm or in the nucleus.
- Steroid hormone receptors are transcriptional regulating proteins that are inactive till a steroid hormone binds and causes a conformational change in them. Receptors, with the hormone bound, bind to regulatory sequences in DNA and regulate gene expression.
- Responses to steroid hormones are slow, since gene expression is a relatively slow process.
- Steroid receptors have a DNA-binding domain (DBD), an activation domain, and a ligand binding domain for the hormone.
- Glucocorticoid receptors are examples.
- In the absence of the signal, glucocorticoid receptors are bound to a protein chaperone, Hsp90, which keeps the receptors from moving to the nucleus.
- Binding of a glucocorticoid molecule causes it to undergo a conformational change, dissociate from the Hsp90, and translocate into the nucleus.
- There it increase the transcription of target genes by binding to specific regulatory sequences (called HRE for hormone-response elements).
- Binding of the hormone-receptor complex to the regulatory elements of hormone-responsive genes modulates their expression. Many such genes encode anti-inflammatory proteins, thus causing the physiological effect of corticosteroid therapies.
- Most other signaling pathways involve multiple steps in which the original signal is passed on and amplified through a number of intermediate steps.
- G-protein coupled receptors (GPCRs) are involved in responses of cells to many different kinds of signals, from epinephrine, to odors, to light.
- GPCRs are cell surface receptors that pass on signals they receive with the help of guanine nucleotide binding proteins (a.k.a. G-proteins).
- GPCRs all have the same basic structure - a single polypeptide chain that threads back and forth seven times through the lipid bilayer of the plasma membrane (called 7TMs).
- One end of the polypeptide forms the extracellular domain that binds the signal. The other end is in the cytosol of the cell.
- Binding of a a ligand (signal) causes the receptor to undergo a conformational change on its cytoplasmic side allowing it to interact with a G-protein which then passes the signal on to other intermediates in the signaling pathway.
- G-proteins are associated with the cytosolic side of the plasma membrane, where they interact with the tail of the GPCR

- All G-proteins share a characteristic structure- they are composed of three subunits called α, β and γ.

- The guanine nucleotide binding site is on the α subunit of the G-protein. It can bind GDP or GTP. It also has a GTPase activity to convert GTP to GDP.

- In the absence of a signal bound to GPCR, G-proteins are in the trimeric form (α-β-γ bound together) and the α subunit has a GDP molecule bound to it. In this form, the α subunit is inactive.

- Binding of a signal molecule by the extracellular part of the GPCR causes its cytosolic tail alter the conformation of a G-protein on the inner face of the plasma membrane. The α subunit then swaps GDP for GTP and it splits into the GTP-bound α part and the β-γ part.

- The now activated α subunit can diffuse freely along the cytosolic face of the plasma membrane and act upon its targets.

- G-proteins interact with different kinds of target proteins.

- Some targets for G-proteins are gated ion channels. The change in the distribution of ions across the plasma membrane causes a change in the membrane potential.

- G-proteins also interact and affect the activity of specific enzymes. The change in activity of the target enzyme resulting from G-protein interaction causes downstream changes in other proteins in the cell, and alters the metabolic state of the cell.

- An example is binding of epinephrine (a catecholamine signal), mediated through the **β**-adrenergic receptor (GPCR).

- In response to stressful stimuli, epinephrine is secreted into the blood, to be carried to target organs whose cells will respond to this signal.

- Binding of epinephrine to the **β**-adrenergic receptor causes the receptor to activate a G-protein with its cytoplasmic tail. This leads to the α subunit exchanging its GDP for GTP and dissociating from the β-γ subunits. The activated α subunit then interacts with the enzyme adenylate cyclase, stimulating it to produce cyclic AMP (cAMP) from ATP.

- cAMP is a second messenger. It binds to an enzyme, protein kinase A (PKA). Upon binding of cAMP, the catalytic subunits of PKA are released from the regulatory subunits, allowing the latter to carry out their function - phosphorylating other proteins.

- One protein activated by PKA is the enzyme, phosphorylase kinase, which can then activate glycogen phosphorylase, the enzyme ultimately responsible for breaking glycogen down into glucose-1-phosphate, a molecule that can readily be converted to glucose.

- So, epinephrine binding ultimately increases glucose concentration, providing energy to escape dangerous situations.

- Simultaneously, PKA also phosphorylates the enzyme glycogen synthase, inactivating it, and preventing free glucose from being used up for glycogen synthesis, thus ensuring cells are amply supplied with glucose they can use.

- Amplification of the signal occurs at every step of the pathway - binding of one epinephrine molecule to its receptor results in the activation of a million glycogen phosphorylase enzyme molecules.

- Turning off of the GPCR signal involves several actions.

- First, G-protein receptor kinase phosphorylates the cytoplasmic tail of the receptor. The phosphorylated tail is then bound by a protein called arrestin, preventing further interaction with a G-protein.

- Second, the α subunit of the G-protein's GTPase activity enables it to hydrolyze the GTP it carries to GDP, causing it to reassociate with the β-γ part and become inactive again.

- Third, cAMP is broken down by an enzyme called phosphodiesterase. When cAMP levels drop, PKA returns to its inactive state, putting a halt to the changes brought about by the activation of adenylate cyclase by an activated G-protein.

- Receptor tyrosine kinases (RTKs) are part of other signaling systems. They are cell surface receptors with tyrosine kinase activity (phosphorylate tyrosine side chains).

- The ligand binding domain of the receptor tyrosine kinase is on the cell surface, while the tyrosine kinase enzymatic activity is in the cytoplasmic part of the protein. A transmembrane α helix connects these two regions.

- Binding of signal molecules to the extracellular domains of two receptor tyrosine kinase proteins causes them to dimerize (come together and associate). It also causes the tyrosine kinase activity of their tails to be turned on and they phosphorylate tyrosine residues in each other (autophosphorylation).

- This phosphorylation triggers the assembly of an intracellular signaling complex on the tails since the phosphorylated tyrosines serve as binding sites for a variety of signaling proteins.

- RTKs mediate responses to a large number of signals, including peptide hormones like insulin and growth factors like epidermal growth factor (EGF).

- Insulin increases glucose uptake by cells by stimulating the movement of glucose receptor GLUT4 to their plasma membranes.

- Binding of insulin to the insulin receptor (IR), results in dimerization of the receptor monomers and subsequent autophosphorylation of the cytosolic kinase domains. The activated tyrosine kinase domains also phosphorylate intracellular proteins called Insulin Receptor Substrates or IRS proteins.

- These proteins interact with, and activate PI_3-kinase which then catalyzes the formation of the molecule PIP_3, which activates yet another kinase, PDK_1, which in turn, activates the Akt group of kinases. It is this group of enzymes that appears to increase the translocation of the GLUT4 to the plasma membrane, as cells that lack functional Akts exhibit poor glucose uptake and insulin resistance.

- Epidermal growth factor (EGF) is an important signaling molecule involved in growth, proliferation and differentiation in mammalian cells. EGF acts through the

EGF receptor, EGFR, a receptor tyrosine kinase.

- EGF binding to the EGFR is followed by receptor dimerization and stimulation and autophosphorylation of the tyrosine kinase domains of the cytosolic domains of the EGFR. This is followed by assembly of a signaling complex nucleated by the binding of proteins that recognize phosphotyrosine residues.
- An important protein activated by the EGFR signaling complex is called RAS. RAS is a monomeric guanine nucleotide binding protein associated with the cytosolic face of the plasma membrane. Like the α subunit of a G-protein, RAS is active when GTP is bound to it and inactive when GDP is bound to it. Also, like the α subunit, RAS can hydrolyze the GTP to GDP.
- Activation of RAS accompanies the exchange of the GDP bound to the inactive RAS for a GTP. Activated RAS then triggers a phosphorylation cascade of three protein kinases (MAP kinases), which relay and distribute the signal.
- The final kinase in the cascade phosphorylates enzymes (alters activities) and transcriptional activators (alters gene expression).
- To turn off RTK signaling, several steps are involved.
- First, RTKs with the signal bound can be endocytosed into the cell and broken down.
- Second, RAS, which is activated by GTP binding, can be deactivated by its hydrolysis of GTP to GDP. Cells that have a mutant Ras gene make RAS proteins with defective GTPase activity that can't shut off RAS. These cells continue to receive a signal to proliferate. More than 30% of human cancers are driven by mutations in Ras genes.
- Binding of EGF to its receptor triggers a signaling pathway that results in the activation of a series of Mitogen Activated Protein Kinases (MAP kinases).
- The final kinase in the MAP kinase cascade phosphorylates a number of target proteins, many of them transcription factors, that when activated, cause cell proliferation.
- Malfunctions in EGF pathway lead to uncontrolled cell proliferation, or cancer.
- The human EGF receptor (HER) family has four members, HER1, HER2, HER3 and HER4 - all receptor tyrosine kinases.
- A crucial step in the signal transduction pathway is the dimerization of the receptors following binding of the signal, EGF, to the receptor.
- The structure of the HER2 receptor allows the receptor monomers to dimerize independently of EGF binding.
- Thus, downstream events of the signaling pathway can be triggered even in the absence of a growth signal.
- In normal cells, only a few HER2 receptors are expressed at the cell surface, so this property of HER2 plays a relatively minor role in stimulating cell division.
- However, overexpression of HER2 leads to increased dimerization and subsequent uncontrolled cell proliferation.

- Herceptin, a monoclonal antibody against the HER2 receptor, has been shown to be an effective treatment against Her2-positive breast cancers.
- Herceptin works by binding specifically to the extracellular domain of the HER2 receptor preventing dimerization of the receptor and thus blocks downstream signaling.
- Additionally, the binding of the Herceptin antibody to the receptor acts signals the immune system to destroy the HER2-positive cells.
- Defects in an RTK signaling pathway lead to chronic myeloid leukemia (CML).
- Patients with CML have an abnormal receptor tyrosine kinase that is the product of a hybrid gene called bcr-abl, formed by the breakage and rejoining of chromosomes 9 and 22.
- The abnormal tyrosine kinase formed is constitutively dimerized, even when there is no signal to bind. As a result, it continuously signals cells to divide, leading to the massive proliferation of a type of blood cells called `.
- The approach to treating CML is to target the tyrosine kinase domain of the receptor.
- In the case of the bcr-abl RTK, the drug Gleevec (imatinib) was designed to bind near the ATP-binding site of the tyrosine kinase domain. This "locks" the site in a conformation that inhibits the enzymatic activity of the tyrosine kinase and thus blocks downstream signaling. With no "grow" signal passed on, cells stop proliferating.

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To the tune of "*Feelin' Groovy*"

Metabolic Melodies Website HERE

Oh no! I missed my class
Someone ought to kick my ass.
Per-haps there is some hope for me
Did Ahern make an
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Nanananana Online Movie

Doctor Kevin's
Always blowin'
Tellin' me I should be knowin'
All that biochemistry
I hope there is a
Online Movie

Got sweat on my brow
I'm starting to weep
I fire up my laptop. I'm white as a sheet
As Firefox is downloading I'm feeling neat
'Cause I just found the
Online Movie

Recording by David Simmons
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Point by Point: Techniques

Techniques

- The traditional approach used for the study of biochemistry is to isolate molecules, enzymes, DNAs, RNAs, and other items of interest so they can be analyzed independently of the millions of other processes occurring simultaneously.
- To separate compounds from cellular environments, one must first burst open (lyse) the cells. There are several ways to do this. Variables to consider include 1) sample size; 2) number of samples; 3) toughness of cells; 4) disruption efficiency; and 5) stability of material being isolated.
- Lysis methods include lowering the ionic strength of the media cells are kept in - can cause cells to swell and burst. Mild surfactants may improve the efficiency.
- Most bacteria, yeast, and plant tissues are resistant to osmotic shocks, however, and stronger disruption techniques are usually required.
- The enzyme lysozyme is very useful for breaking down bacterial walls. Other enzymes commonly employed include cellulase (plants), proteases, and mannases.

- Mechanical agitation may be employed in the form of beads shaken with cells.

- Sonication (20-50 kHz sound waves) provides an alternative type of agitation that can be effective, but it generates heat that can be problematic for heat-sensitive compounds.

- The “cell bomb” method involves placing cells under very high pressure (up to 25,000 psi) and then releasing it rapidly. The rapid pressure change causes dissolved gases in cells to be released as bubbles which, in turn, break open cells.

- Cryopulverization is often employed for samples having a tough extracellular matrix, such as connective tissue, seed, and cartilage. In this technique tissues are frozen with liquid nitrogen and then impact pulverization is performed.

- Whatever method is employed, crude fractions obtained from it must be further processed via fractionation.

- Fractionation of samples is typically initiated with steps involving centrifugation. Using a centrifuge, one can remove cell debris, and fractionate organelles, and cytoplasm.

- Depending upon where in the cell a desired compound is found, it can be collected in a tube along with a multitude of other cellular products using different speeds to precipitate different components.

- Separating the item of interest from the milieu of other materials is where chromatography comes into play.

- Chromatography is commonly performed in columns. Materials performing the separation are called supports and they are commonly contained within columns through which a buffer/solvent containing the items to be separated flows.

- Molecules in the sample interact differentially with the support and travel through it consequently at different speeds, thus enabling separation.

- In ion exchange chromatography, the support consists of tiny beads to which are attached chemicals possessing a charge. Each charged molecule has a counterion that can be replaced by a similarly charged molecule in the sample.

- A cation exchange resin has a negative molecule on the support and a positive counterion. Positively charged sample molecules will be attracted to the negatively charged support molecule and replace (exchange) with the positive counterion.

- Negatively charged and neutrally charged sample molecules will not be attracted to the support molecules and will quickly pass through the column.

- The positively charged molecules “stuck” to the column can be eluted with an excess of positively charged counterion.

- Anion exchange chromatography has the same principle, except that the support has a positive charge, the counterions are negatively charged, and the molecules retained by the resin are negatively charged.

- Size exclusion chromatography (also called molecular exclusion chromatography, gel exclusion chromatography, or gel filtration chromatography) is a low resolution isolation method that employs support beads with tiny “tunnels” in them that each have a precise opening.

- The size of the opening is referred to as an "exclusion limit," which means that molecules above a certain molecular weight will not typically fit into the tunnels.
- Molecules with physical sizes larger than the exclusion limit do not enter the tunnels and pass through the spaces between the beads and exit column relatively quickly. Smaller molecules take a longer path through the column because they pass through both the beads and the spaces between the beads.
- Affinity chromatography exploits the binding affinities of sample molecules for substances covalently linked to the support beads.
- To separate all of the proteins in a sample that bound to ATP from proteins that do not bind ATP, one could covalently link ATP to support beads and then elute the sample through a column of these beads.
- All proteins that bind ATP will "stick" to the column, whereas those that do not bind ATP will pass quickly through it. The proteins are then released from the column by adding ATP.
- Histidine tagging (his-tagging) is a special kind of affinity chromatography
- It relies on altering the DNA coding region for a protein to fuse a series of at least six histidine residues at one end of it (carboxyl or amino terminus) to the amino acids in the remainder of the protein.
- The segment of histidine side chains will bind to nickel or cobalt ions. By passing the sample mixture through a column with nickel or cobalt attached to beads allows the his-tagged proteins to "stick," while the remaining cell proteins all pass quickly through.
- The his-tagged proteins are then eluted by addition of imidazole (same structure as histidine side chain) to the column.
- Histidine tags can be cleaved off of the purified protein by treatment with a protease that excises the added histidines.
- High performance liquid chromatography (HPLC) is a powerful tool for separating smaller molecules based on their differential polarities.
- HPLC employs columns with tightly packed supports and very tiny beads such that flow of solvents/buffers through the columns requires high pressures.
- The supports used in HPLC can be polar (normal phase separation) or non-polar (reverse phase separation).
- In normal phase separations, non-polar molecules elute first followed by the more polar compounds. This order is switched in reverse phase chromatography.
- Separation methods for large molecules, such as DNA, RNA, and proteins use charge and size as means of separating them.
- For DNA and RNA, this is trivial, as the length of the nucleic acid is proportional to the charge coming from the phosphate backbone.
- The charge of proteins varies enormously and is not a function of the size of the protein.

- To use charge and size as a basis of protein separation, they are denatured, disulfide bonds are cleaved, and the protein is treated with a detergent (SDS) coats it and gives it uniform negative charge (SDS is negatively charged).

- Treated in this way, proteins have a size that is related to their charge - longer proteins have more SDS and more charge. Shorter ones have less SDS and less negative charge.

- Separating DNA and RNA molecules is usually accomplished using gel electrophoresis.

- Agarose gel electrophoresis is a technique used to separate nucleic acids. Agarose is a polysaccharide that provides a matrix which encases a buffer. The matrix provides openings for macromolecules to move through and the largest macromolecules have the most difficult time navigating through the matrix, whereas the smallest macromolecules slip through it the fastest.

- Electrophoresis uses electricity as a force to move molecules through the matrix. This is why they must be charged.

- Since the size to charge ratios for DNA and RNA are constant for all sizes of these nucleic acids, the size per force is also constant (since force is directly proportional to charge), so the molecules simply sort on the basis of their size - the smallest move fastest and the largest move slowest. Visualization of the DNA fragments is enabled by addition of a dye, such as ethidium bromide with viewing under ultraviolet light.

- Polyacrylamide is the support material used to separate proteins and small nucleic acids. To make it for a gel, monomeric acrylamide is polymerized and the polymers are cross-linked using N,N'-Methylene-bisacrylamide to create a mesh-like structure. One can adjust the size of the openings of the matrix/mesh by changing the percentage of acrylamide in the reaction. Higher percentages of acrylamide give smaller openings and are more effective for separating smaller molecules, whereas lower percentages of acrylamide reverse that.

- A small "stacking gel" may be employed at the top of a polyacrylamide gel to provide a way of compressing the samples into a tight band before they enter the main polyacrylamide gel (called the resolving gel).

- The buffer and sample for polyacrylamide gel electrophoresis (PAGE) contains SDS and mercaptoethanol, as noted above, to denature and give the proteins a uniform charge per size. The resulting technique is called SDS-PAGE.

- Just like DNA fragments in agarose gel electrophoresis get sorted on the basis of size (largest move slowest and smallest move fastest), the proteins migrate through the gel matrix in an electric field at velocities inversely related to their size.

- Proteins can be visualized on the gel by staining with Coumassie Brilliant Blue or silver nitrate (50 times more sensitive).

- Separating proteins by isoelectric focusing requires establishment of a pH gradient in a tube containing an acrylamide gel matrix. The matrix's pores are adjusted to be large to avoid size separations.

- When the matrix is placed in an electric field, positively charged molecules, for example, move towards the negative electrode, but since they are traveling through a pH

gradient, as they pass through it, their charge changes and they ultimately reach a pH region where their charge is zero. At that point, their pI, they stop moving. Using isoelectric focusing, it is possible to separate proteins whose pI values differ by as little as 0.01 units.

- SDS-PAGE and isoelectric focusing are combined in the technique of 2-D gel electrophoresis - a powerful tool of proteomics. The method has two steps. First, proteins are separated in a tube by isoelectric focusing. Then the tube is treated with SDS and laid on top of a polyacrylamide gel and SDS-page is performed. The first separation is on the basis of pI and the second is on the basis of size.

- The power of 2-D gel electrophoresis is that virtually every protein in a cell can be separated and appear on the 2-D gel array as spots.

- For cancer analysis, comparison a 2-D plot of proteins from a non-cancerous tissue with proteins from a cancerous tissue of the same type provides a quick identification of those proteins whose level of expression differs between the the different tissues.

- Working with intact proteins in analytical techniques, such as mass spectrometry, can be problematic.

- Consequently, it is often desirable to break a large polypeptide down into smaller pieces.

- Proteases are enzymes that (typically) break peptide bonds by binding to specific amino acid sequences in a protein and catalyzing their hydrolysis.

- Chemical reagents can also be used. A protein sample treated with cyanogen bromide, for example will have fragments of proteins each one terminating at a methionine, since cyanogen bromide breaks proteins uniformly at that amino acid.

- Fluorescence Recovery After Photobleaching (FRAP) is used to measure the two dimensional lateral diffusion of molecules in thin films, like membranes, using fluorescently labeled probes.

- In the method, a lipid bilayer is uniformly labeled with a fluorescent tag and then a portion of the tag is bleached using a laser. The spread of the bleached molecules is followed using a microscope. Information obtained in this manner provides data about the rate of lateral diffusion occurring in a lipid bilayer.

- Fluorescence resonance energy transfer (FRET - also called Förster resonance energy transfer, resonance energy transfer (RET) or electronic energy transfer (EET)) is a method for determining interactions between biomolecules.

- In the technique, a donor chromophore or an acceptor chromophore is covalently attached to separate molecules of interest. The acceptor chromophore is designed to accept energy through from the donor molecule and fluoresce at a unique wavelength when it receives that energy from the donor. Only if the proteins containing the donor and acceptor chromophores are physically close in the cell will the unique fluorescence resulting from the transfer occur and be detected.

- Microarrays employ a matrix of “boxes” on a glass slide containing support materials, each box containing thousands of copies

of the same support material covalently linked to the slide. For DNA/RNA microarrays, the support materials would be short sequences of nucleic acid. The position of each set of materials on the grid is known.

- To the slide matrix are added sample molecules that recognize and bind specifically to the support materials. Binding between the sample molecules and support materials occurs by base pairing, for example in the case of DNA or RNA. The slide is washed to remove sample molecules not specifically bound to the support materials.

- Consider a matrix containing all of the known mRNA sequences of a genome. Each box of the grid would contain the sequence from one gene. With this grid, one could analyze the transcriptome - all of the mRNAs being made in selected cells. For a simple analysis, one could take a tissue (say liver) and extract the mRNAs from it. Each sample mRNA can easily be tagged with a color (blue, for example) and then the mixture of tagged mRNAs would added to the matrix on the slide and base pairing conditions are created to allow each mRNA molecule to find and base pair with its complementary sequence on the matrix.

- The matrix is then washed to remove unhybridized mRNAs. The presence/absence/abundance of each mRNA is then readily determined by measuring the amount of blue dye at each box of the grid.

- Such analyses can also be performed with two different sets of mRNAs, each one marked with a different dye color. One set of mRNAs could come from a cancerous tissue (red) and the other from a non-cancerous tissue (green), for example. The mRNAs are mixed and then added to the matrix and complementary sequences are once again allowed to form duplexes, followed by washing of unhybridized mRNAs.

- On analysis, red grid boxes correspond to mRNAs present in the cancerous tissue, but not in the non-cancerous tissue (Figure 7.23 and 7.24). Green grid boxes correspond to mRNAs present in the non-cancerous tissue, but not in the cancerous tissue. Yellow would correspond to mRNAs present in equal abundance in the two tissues. The intensity of each spot also gives information about the relative amounts of each mRNA in each tissue.

- Blotting provides a means of identifying and quantitating specific molecules in of a mixture. A sample is collected and the mixture of molecules is separated by gel electrophoresis. The mixture could be DNA, RNA, or protein and the gel could be either agarose (DNA/RNA) or polyacrylamide (protein).

- After the gel run is complete, the material in the gel is transferred onto a membrane/paper that physically binds to the material.

- The composition of the material that is blotted gives rise to different blot names. Analysis of DNA by this method is known as a Southern Blot (named for the person who invented it). Analysis of RNA is called a Northern Blot and analysis of protein is called a Western Blot.

- The blotting membrane may be treated by UV light, heating, or chemicals to make covalent bonds between the membrane and the material on it.

- Next, a visualizing agent called a labeled probe that is specific for the molecule of interest in the mixture is added to the membrane.

- Labeled probes are designed to be complementary to (DNA/RNA) or have binding affinity for (proteins) the desired target sequence bound to the membrane.

- Binding of the probe to the target sequence allows one to determine 1) if target sequence was in the sample and 2) an estimate of abundance of the target sequence based on the intensity of the probe binding.

- Labels in probes can be radioactive or chemical reagents that give colored light. For DNA/RNA, a probe might be a complementary nucleic acid sequence that is labeled in some fashion (^{32}P in DNA, for example).

- For a protein, a probe would typically involve an antibody that specifically binds to the target protein of interest. Protein analysis usually employs two antibodies and the first one is not labeled. The label is on the second antibody, which is designed to recognize only the first antibody in a piggyback fashion. The first antibody specifically binds to the protein of interest on the blot and the second antibody recognizes the first antibody.

- The second antibody commonly carries an enzyme or reagent which can cause a reaction to produce a color upon further treatment. So, if the molecule of interest is in the original mixture, it will "light" up and reveal itself. The utility and importance of restriction enzymes for making recombinant DNAs lies in their ability to recognize sequences in DNA and cut near or (usually) at the site they recognize. Over 3000 such enzymes are known. Sequences recognized by these enzymes are typically 4-8 base pairs long and the most commonly used enzymes recognize sequences described as palindromic.

- Restriction enzymes recognize sequences (typically 4-8 palindromic base pairs) in DNA and cut near or (usually) at the site they recognize.

- In molecule biology, the term palindrome means that the sequence of a DNA, when read in the 5‘ to 3‘ direction for the top strand is exactly the same as that of the bottom strand. The following sequence is a palindrome

5’ -A-A-G-C-T-T-3’
3’ -T-T-C-G-A-A-5’

- There are four categories of restriction enzymes:

Type I - cut at sites a random distance away from the recognition site
Type II - cut within or near the recognition site.
Type III - cut a short distance away from the recognition site and must bind ATP for action
Type IV - cut modified DNAs

- The cut sites of Type II enzymes vary from enzyme to enzyme. They are grouped into three categories - 1) those that leave a staggered sequence after cutting that has an overhang at the 5’ end of one strand of the duplex; 2) those that leave a staggered sequence after cutting that has an overhang at the 3’ end; and 3) those that cut both strands in the same place, leaving no overhanging sequence - called blunt end cutters.

- HindIII is a type 2 restriction enzyme in the first category. It cuts and leaves a 5’ overhang

5’ -N-N-N-A 3‘ 5’A-G-C-T-T-N-N-N-N-3’
3’ -N-N-N-T-T-C-G-A-5‘ 3’ A-N-N-N-N-5’

- Pst I is a type 2 restriction enzyme of the second category. It cuts and leaves a 3' overhang

5' -N-N-N-C-T-G-C-A 3' 5'G-N-N-N-N 3'
3' -N-N-N-G 5' 3' A-C-G-T-C-N-N-N-N 5'

- Ssp I is a type 2 enzyme of the third category. It cuts and leaves a blunt end

5' -N-N-N-A-A-T 3' 5' A-T-T-N-N-N-N 3'
3' -N-N-N-T-T-A 5' 3' T-A-A-N-N-N-N 5'

- If they have the same overhanging sequence, the ends of different DNAs can be joined together using an enzyme called DNA ligase.

- If one took different DNAs cut with the same enzyme, such as Hind III and tried to join them together, they would react and get joined easily, since they would have the same overhanging (called sticky) ends.

- If one tried to join a DNA cut with Hind III to one cut with either Pst I or Ssp I, then virtually none of the ends would get joined, since the ends of their DNAs are not the same (said to be incompatible).

- Bacteria use restriction enzymes as protection against invading DNA viruses. Viruses that infect bacteria are known as bacteriophages. When a DNA-containing virus injects its DNA into a bacterial cell, if it contains a recognition for the restriction enzyme contained in the bacterium, the enzyme will cut it, thus disabling the virus.

- Restriction enzymes do not cut cellular DNA because bacterial cells protect their genomes with a modification system. This is another enzyme that recognizes exactly the same sequence as the restriction enzyme except that instead of cutting it, the modification system alters the cellular DNA so that the restriction enzyme cannot work.

- The modifying enzyme in a modification system is known as a methyl transferase (or a methylase), since it puts one or more methyl groups on the same sequence that the restriction enzyme would otherwise cut. When the methyl group is added, the restriction enzyme no longer can recognize the sequence and therefore no longer cuts the DNA. As a result, the genome gets protected from cutting, but invading DNAs from viruses lack those methyl groups and get cut.

- Creating recombinant DNA typically involves the use of plasmids.

- Plasmids are circular, autonomously replicating DNAs found commonly in bacterial cells.

- Plasmids have been adapted to 1) replicate in high numbers; 2) carry genes that allow researchers to identify cells carrying them (antibiotic resistance, for example) and 3) contain sequences (such as a promoter and Shine Dalgarno sequence) necessary for expression of the desired protein in the target cell.

- A plasmid which has all of these features is referred to as an expression vector .

- Some plasmids contain what is called a "polylinker" which is a short stretch of DNA within a selectable marker that contains numerous recognition sites for restriction enzymes. Each of these sites occurs only once in the plasmid, ensuring DNA gets placed precisely in the plasmid where desired.

- Making a recombinant DNA with such a plasmid is a relatively simple process. It involves 1) cutting the DNA of interest with a restriction enzyme; 2) similarly cutting the plasmid DNA to generate ends that are compatible; 3) ligating the DNA of interest into the plasmid DNA using an enzyme called DNA ligase; 4) inserting the ligated material into a bacterial cell; and 5) growing cells that contain the plasmid.

- Steps 3 and 4 are tricky. Let's start with step 4. Cells take up plasmid DNAs very inefficiently.

- It is for this reason that plasmids carry a selectable marker, such as antibiotic resistance. With it can easily identify the bacteria that take up a plasmid by virtue of the fact that the rare bacteria that get a plasmid are resistant to the antibiotic, whereas those bacteria that don't take up the plasmid will be killed by the antibiotic and don't grow.

- The second consideration (step 3) is that getting the DNA of interest inserted into the expression vector is also inefficient. Consequently, the most common thing that occurs is that most re-ligated expression vectors have no DNA insertions, so a selection method is desirable for identifying which of those cells that got a plasmid contain one with an insert. One solution this is to use blue-white screening.

- To understand the strategy of blue-white screening, one must first understand the *lacZ* gene of the *lac* operon.

- The enzyme coded by the *lacZ* gene is **β**-galactosidase. It catalyzes the hydrolysis of lactose into glucose and galactose. An artificial substrate called X-gal has been created that the enzyme also cleaves.

- The result of this cleavage is that one of the product molecules of X-gal cleavage has a blue color. Thus, if one adds X-gal to cells expressing the *lacZ* gene, blue color will be produced and the amount of blue color is a measure of the amount of Lac-Z gene present.

- Another tool for blue-white screening is an artificial "inducer" of expression of the *lac* operon (including *lacZ*) known as isopropyl β-D-1-thiogalactopyranoside or, as it's more commonly called, IPTG.

- Induction of Lac operon expression is important because mRNA for the operon is normally produced in bacterial cells at a very low level.

- In the presence of IPTG, transcription and translation of the Lac-Z gene increases dramatically.

- Thus, when you treat cells containing the lac operon (and lac Z) with X-gal and IPTG, blue color will be produced. If the cells are not making functional lac Z, no blue color will be produced and the cells will be white.

- To use blue-white screening, one must start with *E. coli* cells that lack the *lacZ* gene.

- Functional *lacZ* gene coding sequences have been placed on a plasmid. The coding sequence has been altered slightly to contain a "polylinker" in the middle of the coding. The polylinker does not interfere, though with making a completely functional *lacZ* protein.

- The polylinker is a short region containing several restriction enzyme cutting sites,

each of which is unique in the plasmid containing it (See Figure 7.32).

- There is, for example, a BamHI site in the polylinker. If DNA is inserted into the BamHI site of the polylinker, it disrupts the coding for *lac*Z so cells can no longer make functional LacZ enzyme. Thus, when the cells that take up plasmids with an insert are treated with X-Gal and IPTG, they do not produce a blue color and instead remain white.

- On the other hand, if the plasmid's sticky ends simply ligate to each other and do not get an inserted gene, then the lac-Z gene coding sequence is restored intact (no interruption) and functional LacZ enzyme is made. Treating these cells with X-Gal and IPTG will yield a blue color.

- It is trivial then to identify cells with a plasmid with an insert from those with a plasmid having no insert. The ones with the insert will have a white color. The ones with no insert will have a blue color.

- Some RNA-encoded viruses have a phase in their life cycle in which their genomic RNA is converted to DNA by a virally-encoded enzyme known as reverse transcriptase. The ability to convert RNA to DNA is a method that is desirable in the laboratory.

- To use reverse transcriptase to make DNA from RNA, one creates a DNA oligonucleotide to serve as a primer for reverse transcriptase to use on a target RNA. The primer must, of course, be complementary to a segment (near the 3' end) of the RNA to be amplified.

- The RNA, reverse transcriptase, the primer, and four dNTPs are mixed. Replication converts RNA to a single strand of DNA.

- Denaturation frees the single stranded DNA, which can then be amplified by PCR or simply replicated using a primer specific for the other end of the DNA.

- PCR allows one to use DNA replication to amplify DNA enormously in a short period of time.

- In contrast to cellular DNA replication, which amplifies all of a cell's DNA during a replication cycle, PCR does targeted amplification to replicate only a segment of DNA bounded by the two primers used to direct DNA polymerase where to start.

- PCR involves three cycles, each of which occurs at a different temperature. The process also requires four things - a target DNA to be amplified, 4 dNTPs, 2 primers complementary to sequences around the region of DNA to be amplified, and a DNA polymerase stable at high temperatures (thermostable).

- The thermostability of the DNA polymerase is necessary because the first step requires near boiling temperatures to separate the DNA strands.

- First, all of the reagents are mixed together. Primers are present in millions of fold excess of the target sequence to be amplified. This is important because each double stranded DNA made requires two primers.

- The first cycle of the process involves separating the strands of the target DNA by heating to near boiling.

- Second, the solution is cooled to a temperature that favors complementary DNA se-

quences finding each other and making base pairs.

- Since the primers are present in millions of fold excess, the complementary sequences they target are readily found and base-paired to the primers.

- These primers direct the synthesis of DNA. Only where a primer anneals to a DNA strand will replication occur, since all DNA polymerases require a primer to begin.

- In the third step in the process, the DNA polymerase replicates DNA by extending from the 3' end of the primer forward, making a new DNA strand.

- Then the process repeats itself, usually about 30 times. At the end of the process, there is a theoretical yield of 2^{30} (over 1 billion times) more DNA than there was to start.

- Yeast two-hybrid screening is a sophisticated technique for identifying which protein(s) out of a collection of all of a cell's proteins interacts with a specific protein of interest. To understand this method, it is important to understand what a library is, in biological terms.

- Biological libraries contain collections of DNAs (called a genomic library) or mRNAs (called a cDNA library), typically, though there are many different kinds of libraries.

- Imagine you had collected together all of the mRNAs of a cell type (for example, bone cells), and made double-stranded cDNA copies of them using reverse transcriptase.

- If you ligated those cDNAs into expression vectors and transformed the mixture into cells, then the collection of cells that arose from that experiment would be a cDNA library of the bone cells expressing every protein that a bone cell makes.

- Making a cDNA library is the first step (and primary step) in a yeast two-hybrid analysis.

- Instead of fusing the cDNA coding regions into an ordinary expression vector, one inserts it into an expression vector that has a coding region for a transcription factor - a protein that binds to DNA and helps to start transcription.

- This creates a library of cDNAs, each one fused to the coding of this transcription factor. Each bone cell protein would be fused to the transcription factor coding region meaning that the protein made would be partly composed of the transcription factor and partly composed of each protein. These proteins would be called the bait.

- Now, imagine that you took your protein of interest - let's call it XYZ protein. You are interested in learning which of the proteins in your cDNA fusion library interacts with XYZ protein. So, you make a second fusion protein - this one is partly a transcriptional activator protein and part XYZ protein. It is called the prey.

- At this point you have two collections - A) a library of cDNA proteins fused to transcription factor and B) XYZ protein fused to a transcription activator.

- The transcription factor (collection A) can't start transcription of a particular gene by itself. Neither can the transcription activator (collection B). These two proteins

can only function to activate transcription when you put the pieces into close enough proximity.

- Any cDNA proteins fused to transcription factors in A that are bound by the XYZ protein fused to the transcriptional activator of B will activate transcription, since that puts the transcription factor together with the transcriptional activator.

- The gene that the two pieces activate is chosen to be a "reporter gene" and a promoter is selected that will respond to the combination of transcription factors 1 and 2, but to neither one alone.

- The reporter gene's protein gives a phenotype that is easy to identify. For example, it could be β-galactosidase which, if it is produced on treating the cells with X-gal, will make a blue color.

- When collections A and B are transformed together into yeast, most of the cells will have no color because they have no means of putting the fusion proteins containing transcription factors 1 and 2 together (no interaction between XYZ and most of the cDNA proteins).

- If there are protein(s) that bind to XYZ protein, then they will be in the mixed libraries and when they appear together in a cell, they they will interact and physically put transcription factors 1 and 2 together. As a result, transcription will start, translation will make the β-galactosidase protein and blue color will be produced when X-gal is present. Then it will be a simple matter of retrieving the plasmids from the blue cells to identify the coding of the protein(s) that interact with XYZ protein.

- CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats (short repeated sequences found in prokaryotic DNA)

- The short repeats are separated by spacer sequences derived from past encounters with, for example, a bacteriophage.

- Inserted into the bacterial genome, these sequences can be transcribed into a guide RNA that matches, and base-pairs with, sections of the viral genome if it is encountered again.

- A nuclease associated with the guide RNA cleaves the sequence base-paired with the guide RNA. (The nucleases are named Cas for CRISPR-associated.)

- The essential elements of this system are a guide RNA that homes in on the target sequence and a nuclease that can make a cut in the sequence that is bound by the guide RNA.

- In the CRISPR/Cas9 system, the Cas9 endonuclease cuts both strands of the gene sequence targeted by the guide RNA. This generates a double-strand break that the cell attempts to repair.

- Double-strand breaks in DNA can be repaired by simple, nonhomologous end joining (NHEJ) or by homologous recombination. When a break is fixed by NHEJ, there is good chance that there will be deletions or insertions that will inactivate the gene they are in.

- Targeted cleavage of a site by CRISPR/Cas9 can easily and specifically inactivate a gene, making it easy to characterize the gene's function.

- If a homologous sequence bearing the specific mutation is provided with the CRISPR system, homologous recombination can repair the break, and at the same time insert the exact mutation desired.

- There are some creative variations on the CRISPR/Cas9 system.

- One variant inactivates the nuclease activity of Cas9. The guide RNA in this system pairs with the target sequence, but the Cas9 does not cleave it. Instead, the Cas9 blocks the transcription of the downstream gene, allowing specific genes to be turned off without actually altering the DNA sequence.

- Another variation also uses a disabled Cas9, but this time, the Cas9 is fused to a transcriptional activation domain.

- Here, the guide RNA positions the Cas9-activator domain in a place where it can enhance transcription from a specific promoter.

- Other variations on this theme attach histone modifying enzymes or DNA methylases to the inactive Cas9. Again, the guide RNA positions the Cas9 in the desired spot, and the enzyme attached to Cas9 can methylate the DNA or modify the histones in that region.

- MALDI-TOF (Matrix-assisted Laser Desorption Ionization - Time of Flight) is an analytical technique allowing one to determine the molecular masses of molecules with great precision.

- The MALDI-TOF process involves three basic steps. First, the material to be analyzed is embedded in solid support material (matrix) that can be volatilized in a vacuum chamber by a laser beam.

- In the second part of the process, a laser focused on the matrix volatilizes the sample, causing the molecules within it to vaporize and, in the process, to form ions by either gaining or losing protons.

- Third, the ions thus created in the sample are accelerated by an electric field towards a detector. Their rate of movement towards the detector is a function of the ratio of their mass to charge.

- An ion with a mass of 100 and a charge of +1 will move twice as fast as an ion with a mass of 200 and a charge of +1 and at the same rate as an ion with a mass of 200 and a charge of +2.

- By precisely determining the time it takes for an ion to go from ionization (time zero of the laser treatment) to being detected, the mass to charge ratio for all of the molecules in a sample can be readily determined.

- Ionization can also result in destabilization of larger molecules, which fragment into smaller ones in the MALDI-TOF detection chamber.

- Precise determination of the size of each of the sub-fragments of a larger molecule allows one to determine its identity and structure if this is not previously known.

- Polypeptides can have their amino acid sequence determined by a computer in MALDI-TOF by analyzing precise molecular mass of the many pieces they contain.

- When one amino acid, for example, fragments from a larger peptide, this can be detected as the difference in mass between the fragment with and without the amino acid, since each amino acid will have a characteristic molecular mass. By determining the iden-

tity of each amino acid breaking off of a larger polypeptide, the structure of the larger polypeptide is realized.

- When a larger polypeptide fragments into all of its pieces in MALDI-TOF, the composition of each of the pieces can be determined from their masses and the entire sequence of a peptide can thus be determined.

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To the tune of "*Green Acres*"

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(*Male voice*)
450 is the course for me
With all its biochemistry
I soak up what this course provides
Structure and function and info about peptides

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10

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Suresh, A.; Verma, C. (2006). "Modelling study of dimerization in mammalian defensins". BMC Bioinformatics 7: S17. DOI:10.1186/1471-2105-7-S5-S17. Anita Suresh and Chandra Verma

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Nucleosome detailed structure
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Alpha-1-antitrypsin in Europe
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Based on extrapolated data from “Worldwide racial and ethnic distribution of __-antitrypsin deficiency : summary of an analysis of published genetic epidemiologic surveys” by Frederick J. de Serres. (Orig. publ. in Chest, Nov. 2002

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Blood coagulation in vivo
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Obesity worldwide males
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Figure # 6.181
OMP Decarboxylase
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CTP Synthase Dimer
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CTP Synthase Mechanism
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Nucleic acid catabolism and salvage
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Pyrimidine salvage
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dUMP to dTTP
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Thymidylate Synthase mechanism
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DHFR to THF Methtrexate
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Folate Metabolism
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Methotrexate vs DHF
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Purine Catabolism
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Purine Catabolism 2
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Hypoxanthine and Allopurinol
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Pyrimidine Catabolism
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Carnosine
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Human Genome by Function
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Genome sizes
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Components of the Human Genome WCCSA 3.0
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Watson Crick DNA
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DNA Replication
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Replication Bubble
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Prokaryotic vs Eukaryotic Replication
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Multiple Replication Bubbles
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DNA Replication
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Replication fork
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Sliding clamp side view
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DNA Chain Growth
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Replication Fork Okazaki
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RNA Primers Okazaki Fragments
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DNA Polymerase Hand
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Mammalian DNA polymerases
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Chromosomes with Telomere caps
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Linear Chromosome Problem
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Telomerase Structure
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Telomerase illustration
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Telomerase in action
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DNA replication through nucleosomes
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Broken chromosomes
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DNA Damage
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Hemimethylation
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Histidine

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Mismatch Repair
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Thymine dimer structures
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DNA Adduct
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Thymine Dimer Repair
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Nucleotide Excision Repair
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Cytosine deamination to Uracil
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DNA Excision Repair
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Non-homologous end joining
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Homologous Recombination
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Emw - Products of meiotic recombination for human chromosome 1. The process shuffles genetic material between homologous chromosomes (i.e., between non-sister chromatids) as shown. Graphic uses an adapted version of File:Chromosome_1.svg. Inspired by Figure 10-18 in Watson, JD et al (2003) Molecular Biology of the Gene (5th ed.), Pearson/Benjamin Cummings, p. 283 ISBN: 978-0805346350

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Strand invasion
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Lex A structure
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Lex A gene activation
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SOS Response Antibiotic Resistance
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Michel B (2005). "After 30 Years of Study, the Bacterial SOS Response Still Surprises Us". PLoS Biology 3 (7): e255. DOI:10.1371/journal.pbio.0030255

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Transcriptioni
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DNA to Protein or NCR
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RNA being synthesized
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Central Dogma Genetic Code
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RNA Polymerase on Promoter
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Bacterial RNA Polymerase
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Transcription elongation
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Transcription termination
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Chromatin Organization
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Citation: Sha, K. and Boyer, L. A. The chromatin signature of pluripotent cells (May 31, 2009), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.45.1.
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Eu transcription initiation complex
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Capping mRNA
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Splicing of introns
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Splicing of introns
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Spliceosome Assembly
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Alternative Splicing
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Alternative polyadenylation
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Mature eukaryotic mRNA
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RNA Editing
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5S rRNA
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Pseudouridine synthesis
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Bacterial Central Dogma

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Standard Genetic Code
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mRNA with codons
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tRNA structure
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tRNA Charging
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Translation with codons, anticodons
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A,P,E sites on Ribosome
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Elongation of Translation
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Kozak sequences in humans
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50S ribosome subunit
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Yikrazuul / large ribosomal subunit (50S) of Haloarcula marismortui, facing the 30S subunit. The ribosomal proteins are shown in blue, the rRNA in ochre, the active site (A 2486) in red. Data were taken from PDB 3CC2, redered with PyMOL

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Translation
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Translation
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N-terminal signal sequence
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Ribosome protein delivery
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Multiple levels of gene regulation
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Prokaryotic Gene Structure
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CAP region of Lac Operator
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Lac Operon
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Lac Repressor binding
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Allolactose and Lactose
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CAP bound to DNA
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David Goodsell / RCSB Molecule of the Month doi: 10.2210/rcsb_pdb/mom_2003_12

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Lac Repressor +- glucose
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Trp operon
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Histidine

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Trp operon attenuation
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Histidine

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Trp operon sequence
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Gene Structure
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C-myc binding to target

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Eukaryotic Combinatorial control
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WCCA 3.0
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Figure # 7.119
Histones and Transc. Activation & Deactivation
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Bassett, SA and Barnett, MPG Nutrients 2014, 6(10), 4273-4301; doi:10.3390/nu6104273

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pre-miRNAs miRNAs
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siRNA and RNAi
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siRNA Duplex
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Transferrin regulation
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Signal transduction pathway features
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Nerve System function
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Glucocorticoid receptor
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Glucocorticoid signaling
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Steroid hormone action
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GPCR in membrane
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G-protein
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G-protein cycle
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Beta2 adrenergic receptor
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David Goodsel / "Molecule of the Month: Adrenergic Receptors". RCSB Protein Data Bank. doi: 10.2210/rcsb_pdb/mom_2008_4

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Epinephrine
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PDB reference:
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Metabolic Melodies

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My 'A'

To the tune of "*My Way*"

Metabolic Melodies Website HERE

And now, the course is done
Except for all that final testing
Dear friends, let's have some fun
There surely won't be much protesting

We've had a busy term
Addressing all the content swiftly
And so I sit and squirm
B-B three fif-ty

Exams, there's been a few
Our averages were somewhat lower
The grades are all askew
I wish that Ahern would go slower

I studied hard each time
And even though my grades were iffy
Oh no, I did not whine
B-B three fif-ty

Yes it was tough
You knew it too
I memorized
My knowledge grew
And through it all
I did not frown

I thought it up
And wrote it down
I fought the fight
I hope it's right
B-B three fif-ty

I laughed, I cried, I swore
Just as I did here on the first day
But since, the term is o'er
Let's all go out for thirsty Thursday

I guess I have to face
The fact that I am not a swifty
But oh, I need to ace
B-B three fif-ty

The end arrives
Our grades are out
As I log in
To my account
I say some things
I truly feel
I hope I don't
Have to appeal
There's no dismay
I made my 'A'
B-B three fif-ty

Recording by David Simmons
Lyrics by Kevin Ahern

The End

To the tune of "*The End*"

Hoc est finis

This is the end

Of Free and Easy Biiiiiii-o-chem

Recorded by David Simmons
Lyrics by Kevin Ahern

-10 sequence

The Pribnow box (also known as the Pribnow-Schaller box or the -10 sequence) is the sequence TATAAT of six nucleotides (thymine-adenine-thymine-etc.) that is an essential part of a promoter site on DNA for transcription to occur in bacteria. It is an idealized or consensus sequence—that is, it shows the most frequently occurring base at each position in a large number of promoters analyzed. Individual promoters often vary from the consensus at one or more positions. It is also commonly called the -10 sequence, because it is centered roughly 10 base pairs upstream from the site of initiation of transcription.

The Pribnow box has a function similar to the TATA box that occurs in promoters in eukaryotes and archaea: it is recognized and bound by a subunit of RNA polymerase during initiation of transcription. This region of the DNA is also the first place where base pairs separate during prokaryotic transcription to allow access to the template strand. The AT-richness is important to allow this separation, since adenine and thymine are easier to break apart (not due to the hydrogen bond count).
It is named after David Pribnow and Heinz Schaller. The frequency of occurrence of each nucleotide in the Pribnow box is shown below.

T	A	T	A	A	T
82%	89%	52%	59%	49%	89%

https://en.wikipedia.org/wiki/Pribnow_box

Related Glossary Terms

Drag related terms here

Index Find Term

-35 sequence

In bacterial transcription, RNA polymerase (RNAP) binds to one of several factors, σ, to form a holoenzyme. In this form, it can recognize and bind to s moter regions in the DNA. The -35 region and the -10 ("Pribnow box") regi the core prokaryotic promoter. The DNA on the template strand between th and the terminator sequence at the 3' end is transcribed into RNA, which is lated into protein. At this stage, the DNA is double-stranded ("closed"). Thi holoenzyme/wound-DNA structure is referred to as the closed complex.

https://en.wikipedia.org/wiki/Bacterial_transcription

Related Glossary Terms

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Index

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Chapter 9 - Point by Point: Information Processing

Chapter 9 - Point by Point: Information Processing

(*Cis*-Δ3-)Enoyl-CoA Isomerase

Enoyl-CoA-(Δ) isomerase, also known as dodecenoyl-CoA-(Δ) isomerase, 3
enoyl-CoA isomerase, Δ3(*cis*),Δ2(*trans*)-enoyl-CoA isomerase, or acetylene
isomerase, (EC 5.3.3.8) is an enzyme that catalyzes the conversion of *cis*-or
double bonds of fatty acids at γ-carbon (position 3) to *trans* double bonds a
(position 2). It plays a particularly important role in the metabolism of unsa
fatty acids.

Since the key step in the degradation of fatty acids with double bonds at eve
numbered carbon positions also produces 3-trans-enoyl-CoA in mammals a
enoyl-CoA isomerase is technically required for their metabolism as well.

https://en.wikipedia.org/wiki/Enoyl_CoA_isomerase

Related Glossary Terms

Drag related terms here

Δ3-Enoyl-CoA Isomerase

Enoyl-CoA isomerase is involved in the β-oxidation, one of the most frequently used pathways in fatty acid degradation, of unsaturated fatty acids with double bonds at odd-numbered carbon positions. It does so by shifting the position of the double bonds in the acyl-CoA intermediates and converting 3-*cis* or *trans*-enoyl-CoA to 2-*trans*-enoyl-CoA. Since the key step in the degradation of fatty acids with double bonds at even-numbered carbon positions also produces 3-*trans*-enoyl-CoA in mammals and yeasts, enoyl-CoA isomerase is technically required for their metabolism as well.

As it functions in the step immediately preceding the actual β-oxidation and forms a double bond extending from the β-carbon (position 2), enoyl-CoA isomerase is involved in both the NADPH-dependent and NADPH-independent pathways of β-oxidation. The double bond serves as the target of oxidation and carbon-to-carbon bond cleavage, thereby shortening the fatty acid chain.

https://en.wikipedia.org/wiki/Enoyl_CoA_isomerase

Related Glossary Terms

Drag related terms here

Index Find Term

ΔG

In thermodynamics, the Gibbs free energy (IUPAC recommended name: Gibbs energy or Gibbs function - also known as free enthalpy to distinguish it from Helmholtz free energy) is a thermodynamic potential that measures the maximum or reversible work that may be performed by a thermodynamic system at a constant temperature and pressure (isothermal, isobaric). Just as in mechanics, where potential energy is defined as capacity to do work, similarly different potentials have different meanings. The Gibbs free energy (kJ in SI units) is the maximum amount of non-expansion work that can be extracted from a thermodynamically closed system (one that can exchange heat and work with its surroundings, but not matter). This maximum can be attained only in a completely reversible process.

https://en.wikipedia.org/wiki/Gibbs_free_energy

Related Glossary Terms

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Index Find Term

1-alkyl-dihydroxyacetone-3-phosphate

1-alkyl-dihydroxyacetone-3-phosphate is an intermediate in synthesis of pl
It is a precursor of 1-alkyl-glycerol-3-phosphate.

Related Glossary Terms

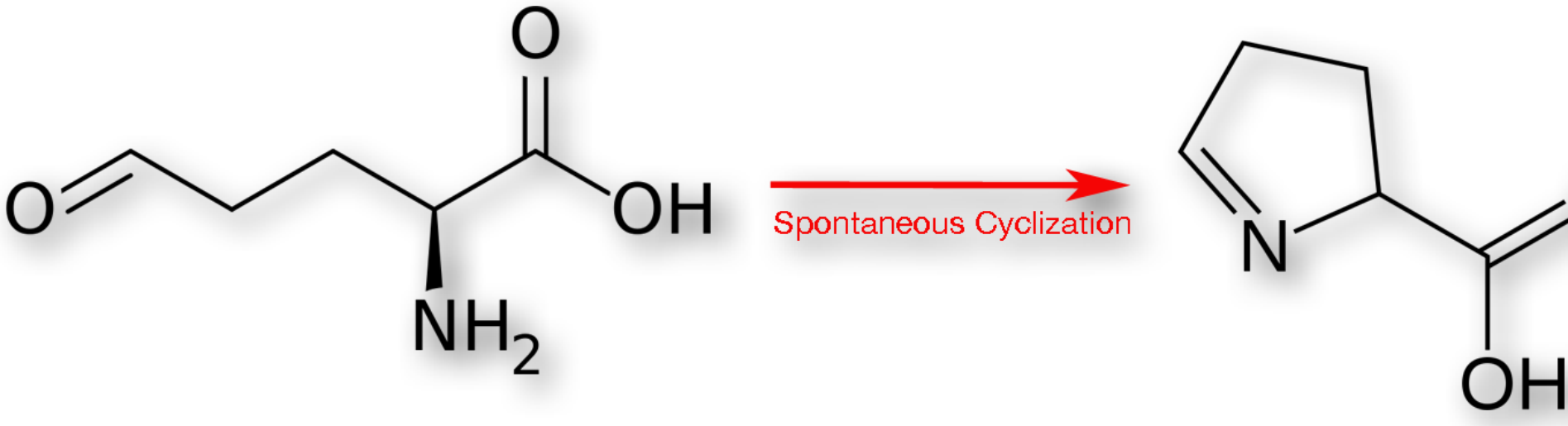
Drag related terms here

Index

Find Term

1-pyrroline-5-carboxylic Acid

1-pyrroline-5-carboxylic acid is an intermediate in the synthesis of proline. vant reaction is shown in the figure below. 1-pyrroline-5-carboxylic acid (o below) is converted directly to proline by 1-pyrroline-5-carboxylic acid redu



Related Glossary Terms

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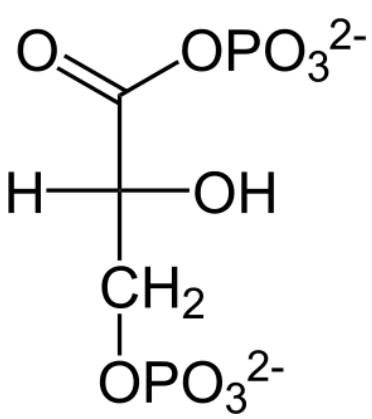
1,3-bisphosphoglycerate

1,3-bisphosphoglyceric acid (1,3-bisphosphoglycerate or 1,3BPG) is a 3-carbon organic molecule present in most, if not all, living organisms. It primarily exists as a metabolic intermediate in both glycolysis during respiration and the Calvin cycle during photosynthesis. 1,3BPG is a transitional stage between glycerate 3-phosphate and glyceraldehyde 3-phosphate during the fixation/reduction of CO_2. 1,3BPG is also a precursor to 2,3-bisphosphoglycerate which in turn is a reaction intermediate in the glycolytic pathway.



https://en.wikipedia.org/wiki/1,3-Bisphosphoglyceric_acid

Related Glossary Terms

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Index Find Term

2-D Gel Electrophoresis

Two-dimensional gel electrophoresis, abbreviated as 2-DE or 2-D electrophoresis, is a form of gel electrophoresis commonly used to analyze proteins. Mixtures of proteins are separated by two properties in two dimensions on 2D gels. 2-DE was first independently introduced by O'Farrell and Klose in 1975.

2-D electrophoresis begins with electrophoresis in the first dimension and then separates the molecules perpendicularly from the first to create an electropherogram in the second dimension. In electrophoresis in the first dimension, molecules are separated linearly according to their isoelectric point. In the second dimension, the molecules are then separated at 90 degrees from the first electropherogram according to molecular mass. Since it is unlikely that two molecules will be similar in two distinct properties, molecules are more effectively separated in 2-D electrophoresis than in 1-D electrophoresis.

The two dimensions that proteins are separated into using this technique can be isoelectric point, protein complex mass in the native state, and protein mass.
Separation of the proteins by isoelectric point is called isoelectric focusing (IEF). Thereby, a gradient of pH is applied to a gel and an electric potential is applied across the gel, making one end more positive than the other. At all pH values other than their isoelectric point, proteins will be charged. If they are positively charged, they will be pulled towards the more negative end of the gel and if they are negatively charged they will be pulled to the more positive end of the gel. The proteins applied in the first dimension will move along the gel and will accumulate at their isoelectric point. That is, the point at which the overall charge on the protein is 0 (a neutral charge).

For the analysis of the functioning of proteins in a cell, the knowledge of their cooperation is essential. Most often proteins act together in complexes to be fully functional. The analysis of this sub organelle organization of the cell requires techniques conserving the native state of the protein complexes. In native polyacrylamide gel electrophoresis (native PAGE), proteins remain in their native state and are separated in the electric field following their mass and the mass of their complexes respectively. To obtain a separation by size and not by net charge, as in IEF, an additional charge is transferred to the proteins by the use of Coomassie Brilliant Blue or lithium dodecyl sulfate. After completion of the first dimension the complexes are destroyed by applying the denaturing SDS-PAGE in the second dimension, where the proteins of which the complexes are composed of are separated by their mass.

Before separating the proteins by mass, they are treated with sodium dodecyl sulfate (SDS) along with other reagents (SDS-PAGE in 1-D). This denatures the proteins (that is, it unfolds them into long, straight molecules) and binds a number of SDS molecules roughly proportional to the protein's length. Because a protein's length (when unfolded) is roughly proportional to its mass, this is equivalent to saying that it attaches a number of SDS molecules roughly proportional to the protein's mass. Since the SDS molecules are negatively charged, the result of this is that all of the proteins will have approximately the same mass-to-charge ratio as each other. In addition, proteins will not migrate when they have no charge (a result of the isoelectric focusing step) therefore the coating of the protein in SDS (negatively charged) allows migration of the proteins in the second dimension (SDS-PAGE, it is not compatible for use in the first dimension as it is charged and a nonionic or zwitterionic detergent needs to be used). In the second dimension, an electric potential is again applied, but at a 90 degree angle from the first field. The proteins will be attracted to the more positive side of the gel (because SDS is negatively charged) proportionally to their mass-to-charge ratio. As previously explained, this ratio will be nearly the same for all proteins. The proteins' progress will be slowed by frictional forces. The gel therefore acts like a molecular sieve when the current is applied, separating the proteins on the basis of their molecular weight with larger proteins being retained higher in the gel and smaller proteins being able to pass through the sieve and reach lower regions of the gel.

https://en.wikipedia.org/wiki/Two-dimensional_gel_electrophoresis

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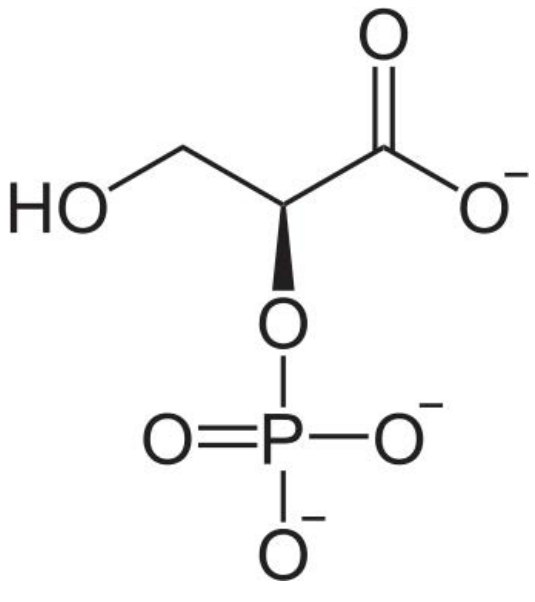
2-phosphoglycerate

2-phosphoglyceric acid (2PG), or 2-phosphoglycerate, is a glyceric acid whi
the substrate in the ninth step of glycolysis. It is catalyzed by enolase into p
nolpyruvate (PEP), the penultimate step in the conversion of glucose to pyr



https://en.wikipedia.org/wiki/2-Phosphoglyceric_acid

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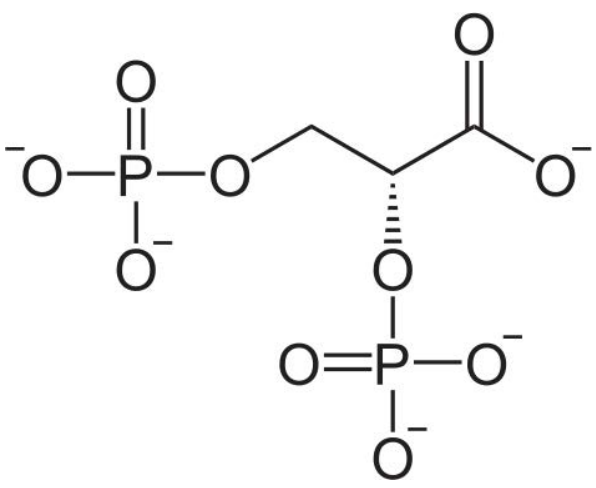
2,3-BPG

2,3-bisphosphoglyceric acid (2,3-bisphosphoglycerate or 2,3-BPG, also known as 2,3-diphosphoglycerate or 2,3-DPG) is a three-carbon isomer of the glycolytic intermediate 1,3-bisphosphoglyceric acid (1,3-BPG). 2,3-BPG is present in human red blood cells (RBC/erythrocyte) at approximately 5 mmol/L. It binds with greater affinity to deoxygenated hemoglobin (e.g. when the red blood cell is near respiring tissue) than it does to oxygenated hemoglobin (e.g., in the lungs) due to spatial changes: 2,3-BPG (with an estimated size of about 9 angstroms) fits in the deoxygenated hemoglobin configuration (11 Å), but not as well in the oxygenated (5 Å). It interacts with deoxygenated hemoglobin β subunits by decreasing their affinity for oxygen, so it allosterically promotes the release of the remaining oxygen molecules bound to the hemoglobin, thus enhancing the ability of RBCs to release oxygen near tissues that need it most. 2,3-BPG is thus an allosteric effector.

Its function was discovered in 1967 by Reinhold Benesch and Ruth Benesch.



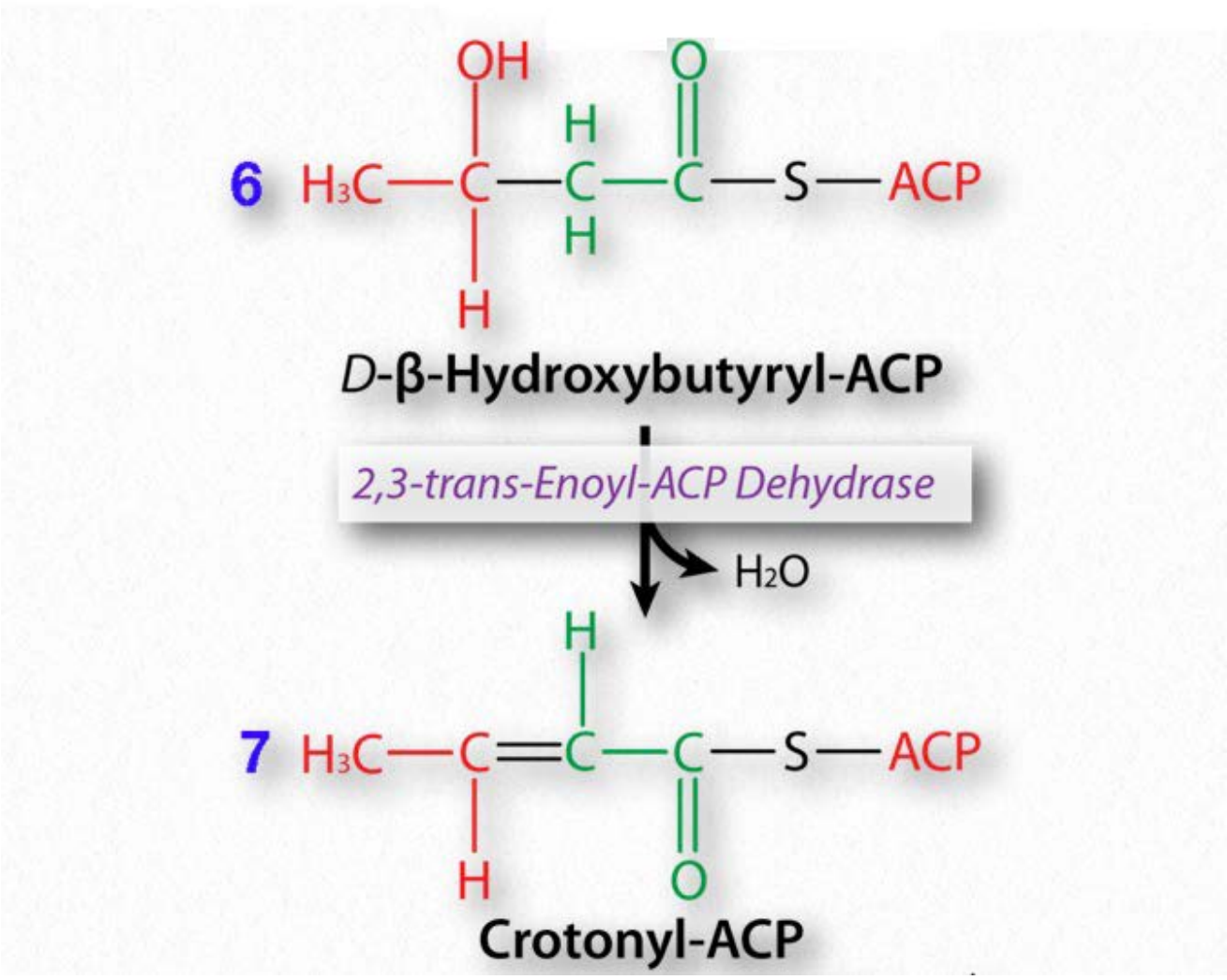
https://en.wikipedia.org/wiki/2,3-Bisphosphoglyceric_acid

Related Glossary Terms

Drag related terms here

2,3-trans-enoyl-ACP Dehydrase

2,3-*trans*-enoyl-ACP dehydrase is an enzyme that catalyzes the removal of wat
from D-β-hydroxybutyryl-ACP in the synthesis of fatty acids. It is depicted in the re
tion below. The product is a *trans* doubled-bonded molecule.



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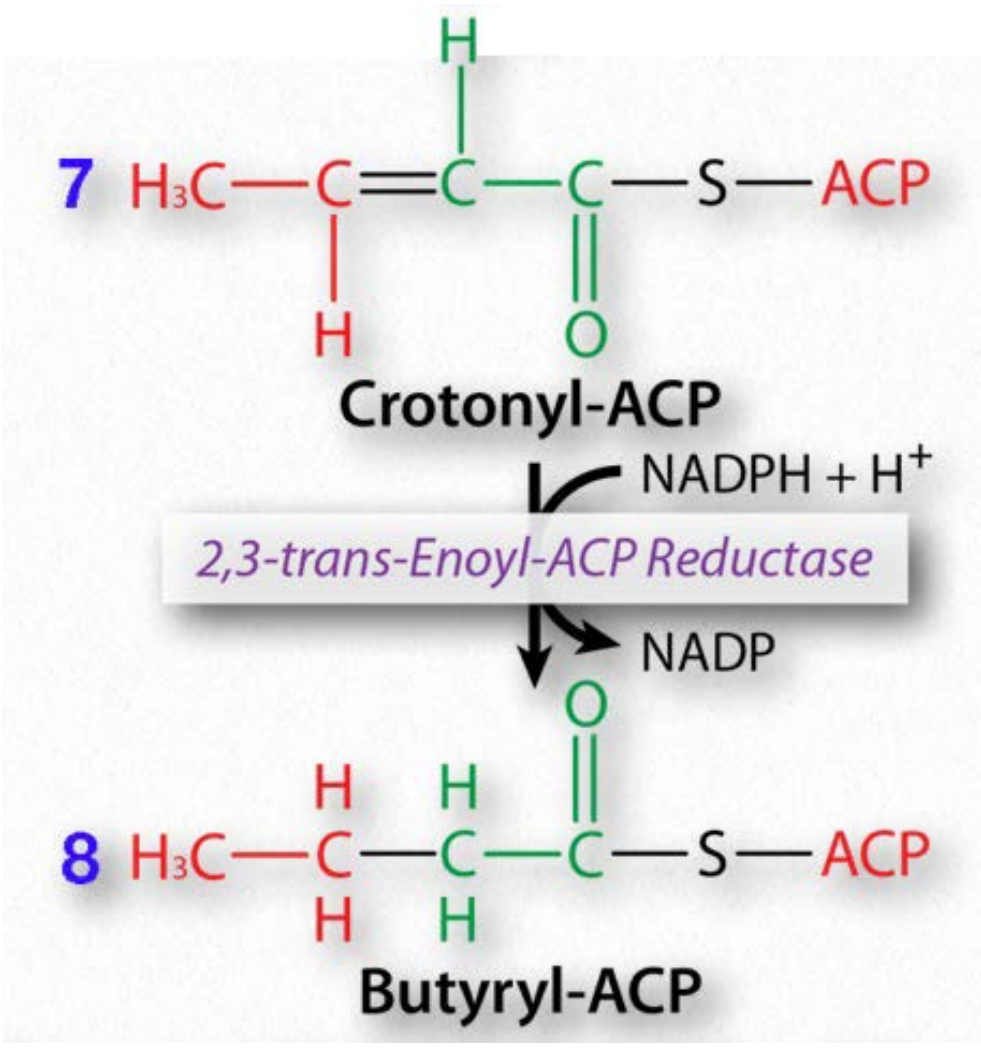
Chapter 6 - Metabolism: Fats and Fatty Acids

2,3-trans-enoyl-ACP Reductase

2,3-*trans*-enoyl-ACP reductase is an enzyme that catalyzes the hydrogenation
crotonyl-ACP in the synthesis of fatty acids. It is depicted in the reaction below. T
product is a saturated fatty acid that is ready for the next round of synthesis.



Related Glossary Terms

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2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase

2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase (EC 2.3.1.117) is an enzyme that catalyzes the chemical reaction:

Succinyl-CoA + (S)-2,3,4,5-tetrahydropyridine-2,6-dicarboxylate + H_2O
<->
CoASH + N-succinyl-L-2-amino-6-oxoheptanedioate

The reaction is the fifth step in the metabolic synthesis of lysine from arginine.

This enzyme belongs to the family of transferases, specifically those acyltransferases transferring groups other than aminoacyl groups. The systematic name of this enzyme class is succinyl-CoA:(S)-2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase. Other names in common use include tetrahydropicolinate succinylase, tetrahydrodipicolinate N-succinyltransferase, tetrahydrodipicolinate succinyltransferase, succinyl-CoA:tetrahydrodipicolinate N-succinyltransferase, succinyl-CoA:2,3,4,5-tetrahydropyridine-2,6-dicarboxylate, and N-succinyltransferase. This enzyme participates in lysine biosynthesis.

https://en.wikipedia.org/wiki/2,3,4,5-tetrahydropyridine-2,6-dicarboxylate_N-succinyltransferase

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2,4 dienoyl CoA Reductase

This gene encodes an accessory enzyme that participates in the β oxidation
lism of polyunsaturated fatty enoyl-CoA esters. Specifically, it catalyzes the
of 2,4 Dienoyl-CoA thioesters of varying length by NADPH cofactor to 3-tra
CoA of equivalent length. Unlike the breakdown of saturated fat, *cis* and *tra*
saturated fatty acid degradation requires three additional enzymes to gener
uct compatible with the standard beta oxidation pathway. DECR is the secc
zyme (The others being Enoyl CoA isomerase and Dienoyl CoA isomerase)
rate limiting step in this auxiliary flow. DECR is capable of reducing both 2
cis-dienoyl-CoA and 2-*trans*,4-*trans*-dienoyl-CoA thioesters, as well as dou
at odd carbon positions, with equal efficiency. At this time, there is no clear
tion for this of lack of stereo-specificity.

https://en.wikipedia.org/wiki/2,4_Dienoyl-CoA_reductase

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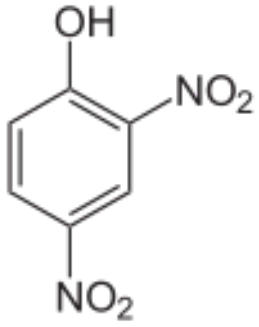
Chapter 9 - Point by Point: Metabolism

2,4 DNP

2,4-dinitrophenol (2,4-DNP or simply DNP) is an organic compound with the formula $HOC_6H_3(NO_2)_2$. It is a yellow, crystalline solid that has a sweet, musty odor. It sublimes, is volatile with steam, and is soluble in most organic solvents as well as aqueous alkaline solutions. It is a precursor to other chemicals and is biochemically active, inhibiting energy (adenosine triphosphate, ATP) production in cells with mitochondria. Its use in high doses as a dieting aid has been identified with severe side-effects, including a number of deaths.

In living cells, DNP acts as a proton ionophore, an agent that can shuttle protons (hydrogen cations) across biological membranes. It dissipates the proton gradient across mitochondria and chloroplast membranes, collapsing the proton motive force that the cell uses to produce most of its ATP chemical energy. Instead of producing ATP, the energy of the proton gradient is lost as heat.

DNP is often used in biochemistry research to help explore the bioenergetics of chemiosmotic and other membrane transport processes.



https://en.wikipedia.org/wiki/2,4-Dinitrophenol

Related Glossary Terms

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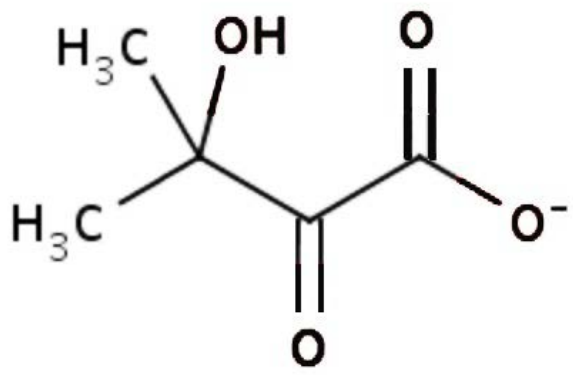
3-hydroxy-3-methyl-2-oxobutanoate

3-hydroxy-3-methyl-2-oxobutanoate is an intermediate in synthesis of valine and leucine. Relevant reactions are shown below.



α-acetolactate

⇅

3-hydroxy-3-methyl-2-oxobutanoate

3-hydroxy-3-methyl-2-oxobutanoate + NADP(P)H

⇅

α,β-dihydroxyisovalerate + NAD(P)⁺

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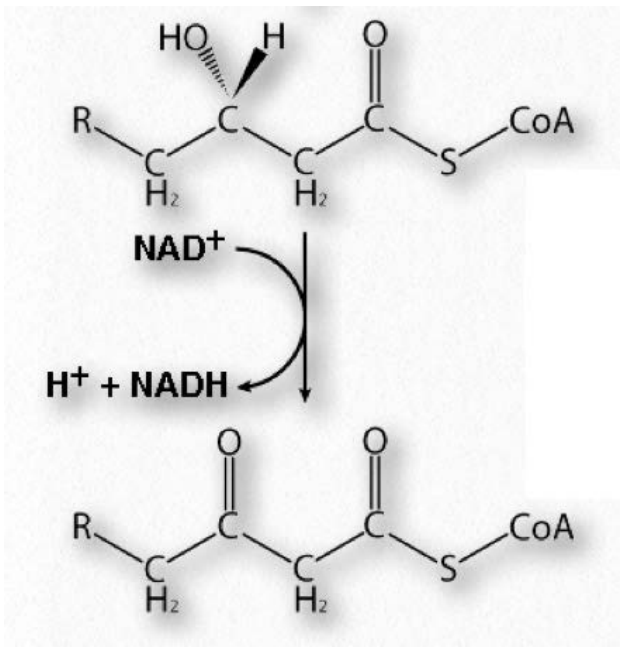
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

3-hydroxyacyl-CoA Dehydrogenase

3-hydroxyacyl-CoA dehydrogenase is an enzyme that catalyzes the third reaction int he β-oxidation of fatty acids. It catalyzes the chemical reaction:

(S)-3-hydroxyacyl-CoA + NAD^+ <-> 3-oxoacyl-CoA + NADH + H^+

3-hydroxyacyl CoA dehydrogenase is classified as an oxidoreductase. It is involved in fatty acid metabolic processes. Specifically it catalyzes the third step of β oxidation - the oxidation of L-3-hydroxyacyl CoA by NAD^+. The reaction converts the hydroxyl group into a keto group.



https://en.wikipedia.org/wiki/3-hydroxyacyl-CoA_dehydrogenase

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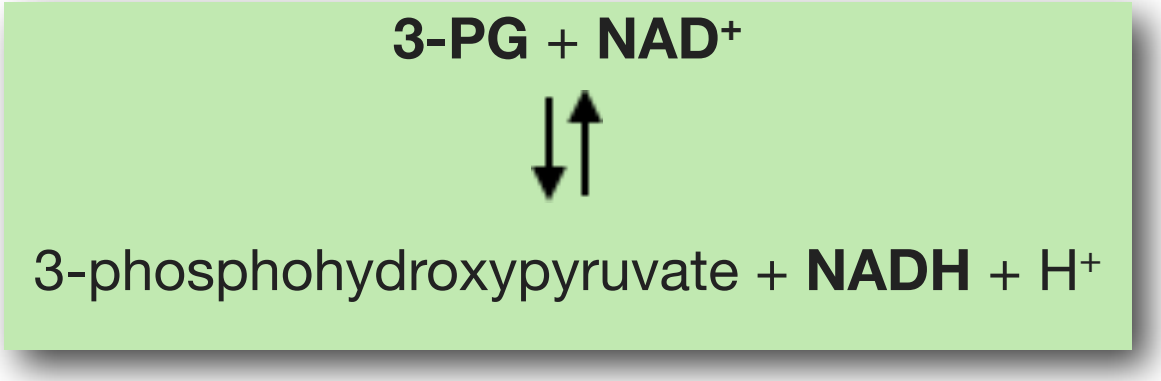
Chapter 6 - Metabolism: Fats and Fatty Acids

3-PG Dehydrogenase

3-phosphoglycerate (3-PG) dehydrogenase is an enzyme involved in the syn
serine. It catalyzes the oxidative reaction shown below.



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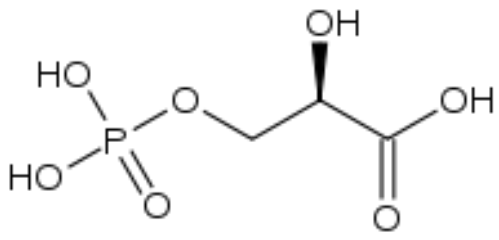
3-phosphoglycerate

3-phosphoglyceric acid (3PG), or glycerate 3-phosphate (GP), is a biochemically significant 3-carbon molecule that is a metabolic intermediate in both glycolysis and the Calvin cycle. This chemical is often termed PGA when referring to the Calvin cycle. In the Calvin cycle, 3-phosphoglycerate is the product of the spontaneous split of an unstable 6-carbon intermediate formed by CO_2 fixation. Thus, two 3-phosphoglycerate molecules are produced for each molecule of CO_2 fixed.



https://en.wikipedia.org/wiki/3-Phosphoglyceric_acid

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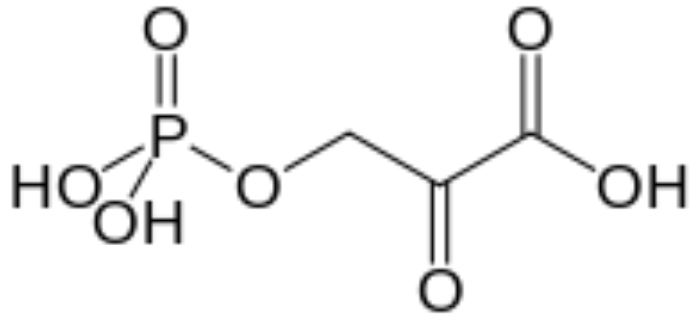
3-phosphohydroxypyruvate

Phosphohydroxypyruvic acid is an intermediate in the synthesis of serine.



https://en.wikipedia.org/wiki/Phosphohydroxypyruvic_acid

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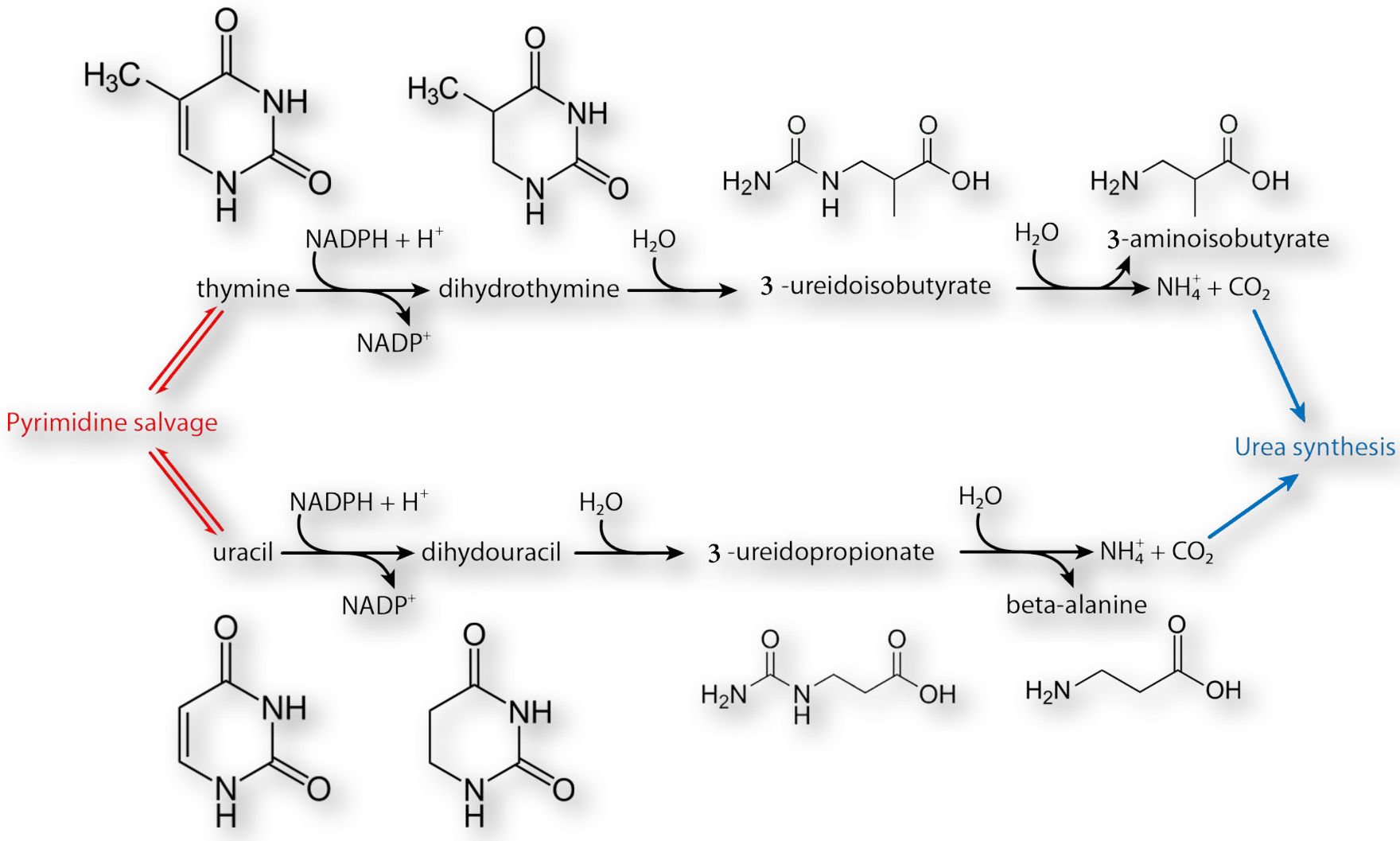
3-ureidoisobutyrate

In the reduction pathway of pyrimidine catabolism, uracil and thymine reduction by NADPH gives dihydrothymine and dihydrouracil respectively. Addition of water to these creates 3-ureidoisobutyrate and 3-ureidopropionate respectively, shown in the figure below.



Related Glossary Terms

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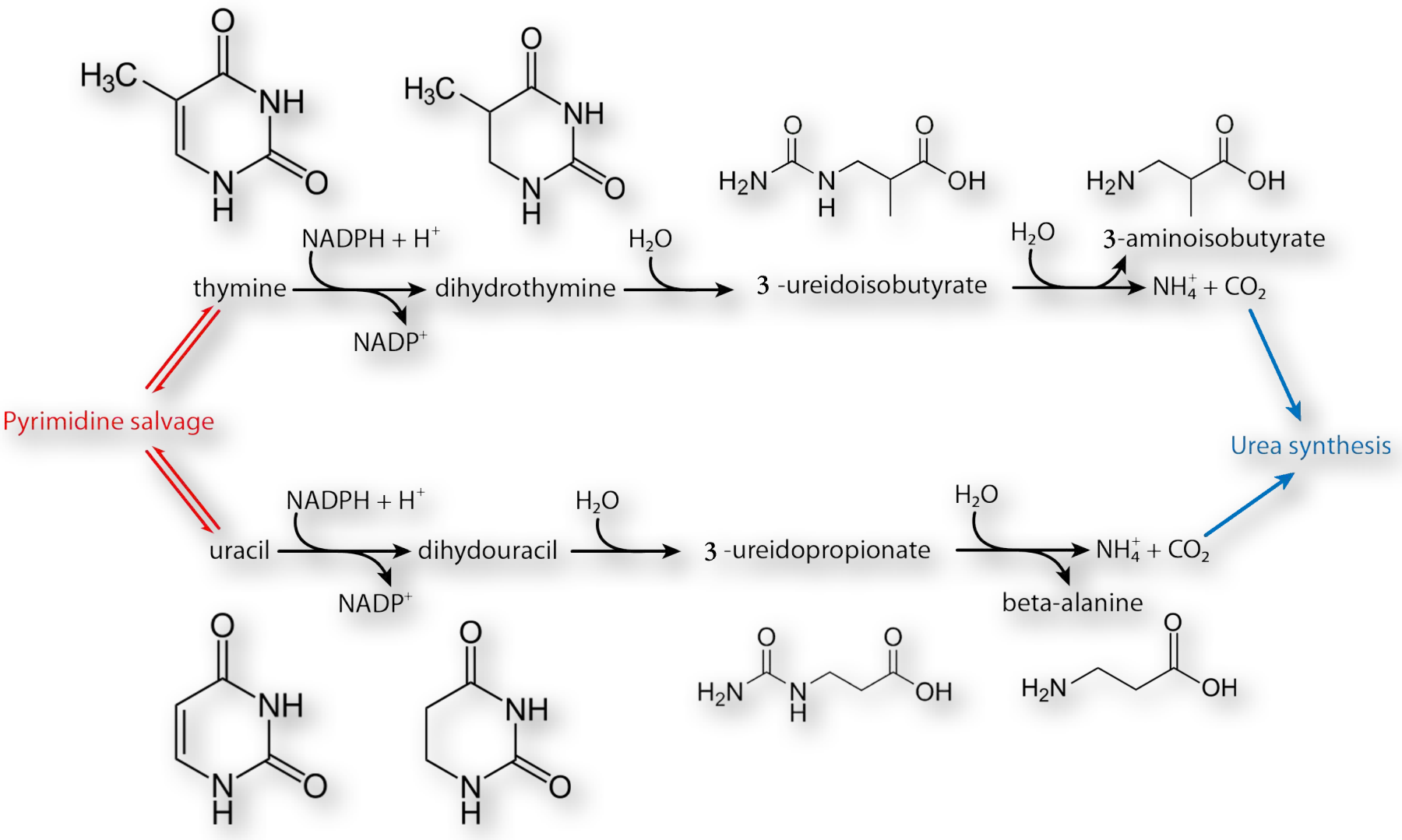
3-ureidopropionate

In the reduction pathway of pyrimidine catabolism, uracil and thymine reduction by NADPH gives dihydrothymine and dihydrouracil respectively. Addition of water to these creates 3-ureidoisobutyrate and 3-ureidopropionate respectively, shown in the figure below.



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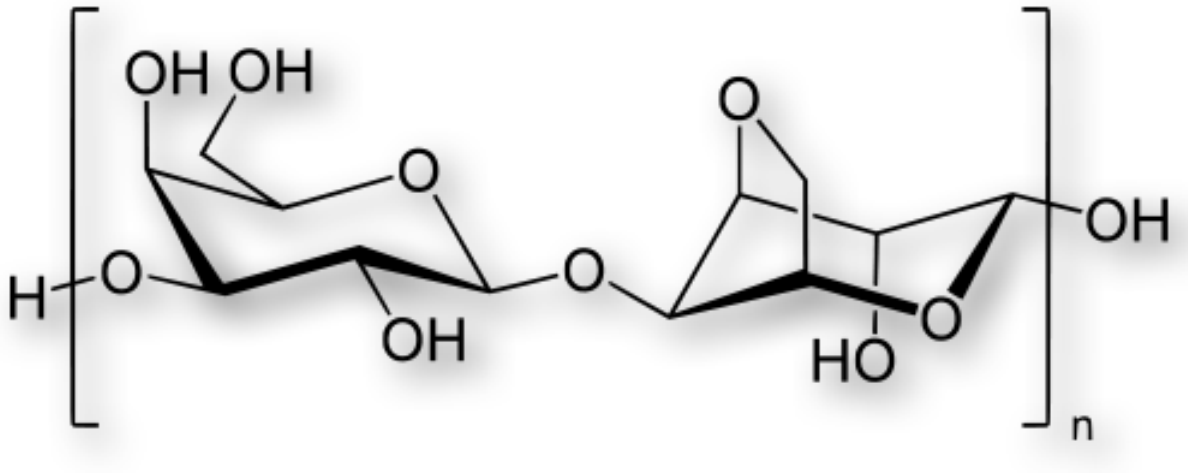
3,6-anhydro-L-galactopyranose

3,6-anhydro-L-galactopyranose is part of the repeating structure of the aga
mer used in making gels.



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3' to 5' Exonuclease

In bacteria, all three DNA polymerases (I, II and III) have the ability to pro
ing 3’ → 5’ exonuclease activity. When an incorrect base pair is recognized,
lymerase reverses its direction by one base pair of DNA and excises the mis
base. Following base excision, the polymerase can re-insert the correct base
cation can continue.

In eukaryotes only the polymerase that deal with the elongation (Δ, and ε) h
reading ability (3’ → 5’ exonuclease activity).

https://en.wikipedia.org/wiki/Proofreading_(biology)

Related Glossary Terms

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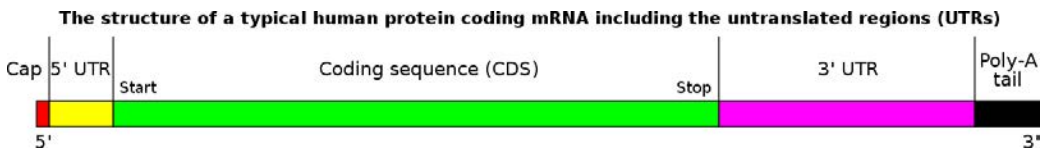
3' UTR

The three prime untranslated region (3'-UTR) is the section of messenger RNA (mRNA) that immediately follows the translation termination codon. An mRNA molecule is transcribed from the DNA sequence and is later translated into protein. Several regions of the mRNA molecule are not translated into protein including the 5' cap, 5' untranslated region, 3' untranslated region, and the poly(A) tail. The 3'-UTR often contains regulatory regions that post-transcriptionally influence gene expression.

Regulatory regions within the 3'-untranslated region can influence polyadenylation, translation efficiency, localization, and stability of the mRNA. The 3'-UTR contains both binding sites for regulatory proteins as well as microRNAs (miRNAs). By binding to specific sites within the 3'-UTR, miRNAs can decrease gene expression of various mRNAs by either inhibiting translation or directly causing degradation of the transcript. The 3'-UTR also has silencer regions which bind to repressor proteins and will inhibit the expression of the mRNA.

Many 3'-UTRs also contain AU-rich elements (AREs). Proteins bind AREs to affect the stability or decay rate of transcripts in a localized manner or affect translation initiation. Furthermore, the 3'-UTR contains the sequence AAUAAA that directs addition of several hundred adenine residues called the poly(A) tail to the end of the mRNA transcript. Poly(A) binding protein (PABP) binds to this tail, contributing to regulation of mRNA translation, stability, and export. For example, poly (A) tail bound PABP interacts with proteins associated with the 5' end of the transcript, causing a circularization of the mRNA that promotes translation. The 3'-UTR can also contain sequences that attract proteins to associate the mRNA with the cytoskeleton, transport it to or from the cell nucleus, or perform other types of localization. In addition to sequences within the 3'-UTR, the physical characteristics of the region, including its length and secondary structure, contribute to translation regulation. These diverse mechanisms of gene regulation ensure that the correct genes are expressed in the correct cells at the appropriate times.



https://en.wikipedia.org/wiki/Three_prime_untranslated_region

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Related Glossary Terms

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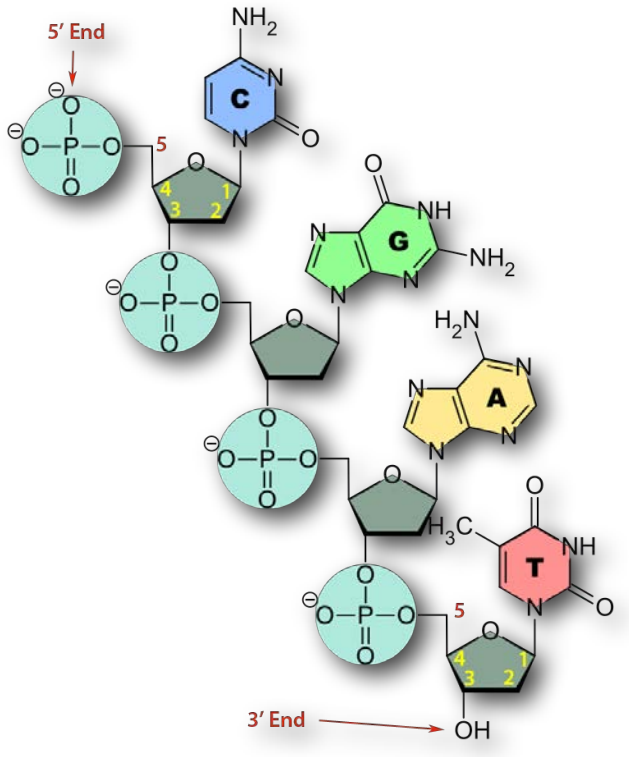
3’ end

The 3’ end of a nucleotide or nucleic acid is a position determined by the numbering system for the sugars of the nucleotides composing it. The 3’ end of a nucleotide has a hydroxyl to which phosphate can be linked in the formation of a nucleic acid.



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4-hydroxy-tetrahydrodipicolinate Reductase

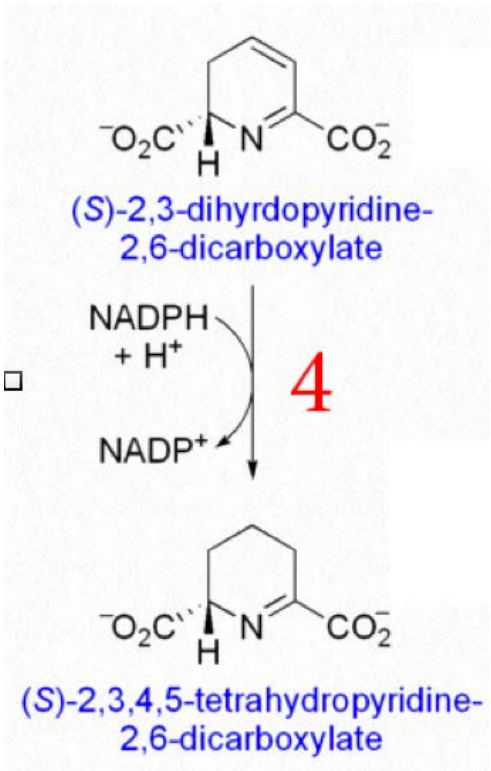
4-hydroxy-tetrahydrodipicolinate reductase (EC 1.17.1.8) is an enzyme that catalyzes the fourth reaction in the biosynthesis of lysine from aspartate.

(S)-2,3,4,5-tetrahydropyridine-2,6-dicarboxylate + $NAD(P)^+$ + H_2O <-> (2S,4S)-4-hydroxy-2,3,4,5-tetrahydrodipicolinate + $NAD(P)H$ + H^+

This enzyme belongs to the family of oxidoreductases, specifically those acting on CH or CH2 groups with NAD^+ or $NADP^+$ as acceptor. The systematic name of this enzyme class is (S)-2,3,4,5-tetrahydropyridine-2,6-dicarboxylate:NAD(P)+ 4-oxidoreductase. Other names in common use include:

- dihydrodipicolinate reductase,
- dihydrodipicolinic acid reductase, and
- 2,3,4,5-tetrahydrodipicolinate:NAD(P)+ oxidoreductase.

This enzyme participates in lysine biosynthesis.



https://en.wikipedia.org/wiki/4-hydroxy-tetrahydrodipicolinate_reductase

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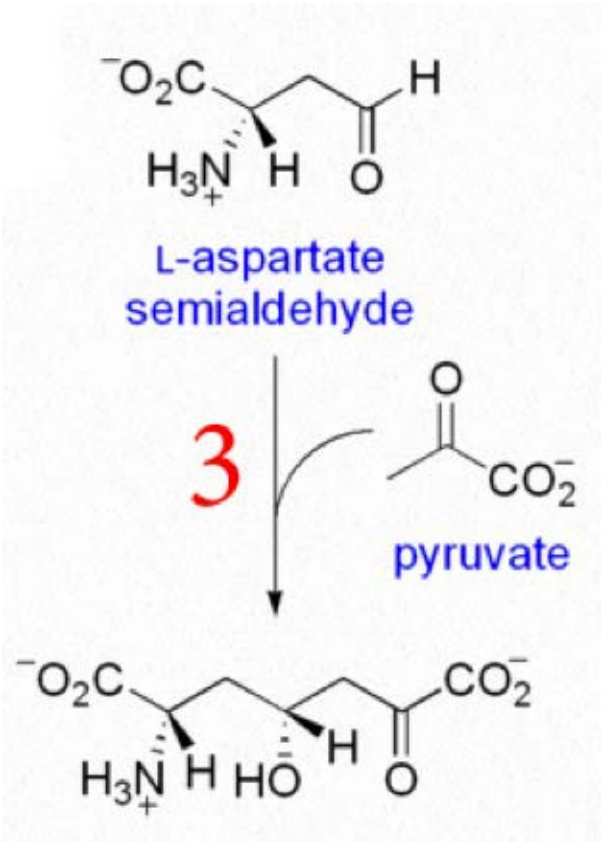
4-hydroxy-tetrahydrodipicolinate Synthase

4-hydroxy-tetrahydrodipicolinate synthase is an enzyme that catalyzes the third reaction in the synthesis of lysine from aspartate.

This enzyme catalyzes the following chemical reaction:

Pyruvate + L-aspartate-4-semialdehyde <-> (2S,4S)-4-hydroxy-2,3,4,5-tetrahydrodipicolinate + H_2O



https://en.wikipedia.org/wiki/Dihydrodipicolinate_synthase

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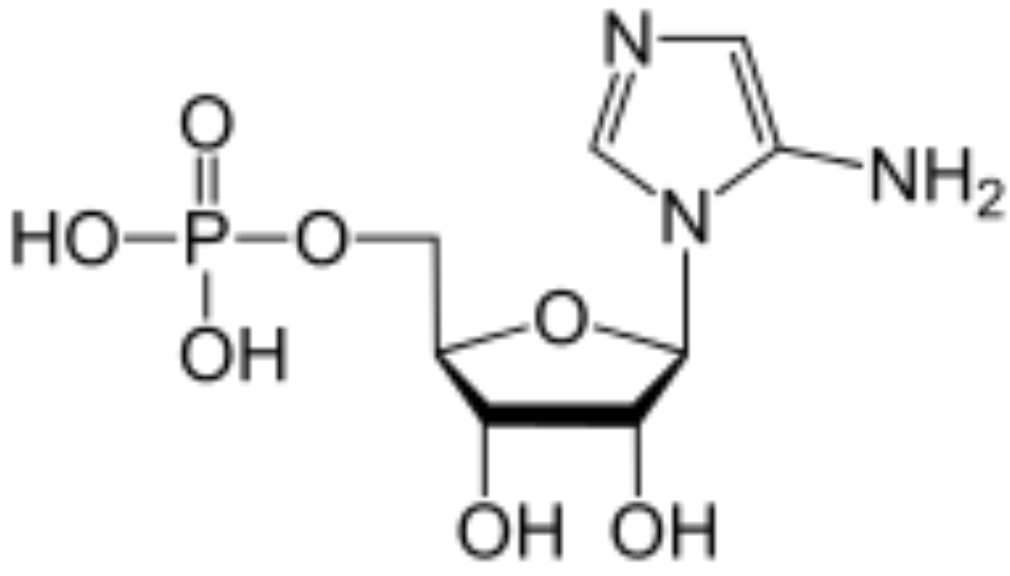
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

5-Aminoimidazole Ribotide

5'-Phosphoribosyl-5-aminoimidazole (or aminoimidazole ribotide) is an intermediate in the formation of purines. Thus, it is an intermediate in the adenine pathway, and is synthesized from 5'-phosphoribosylformylglycinamidine by AIR synthetase.



https://en.wikipedia.org/wiki/5-Aminoimidazole_ribotide

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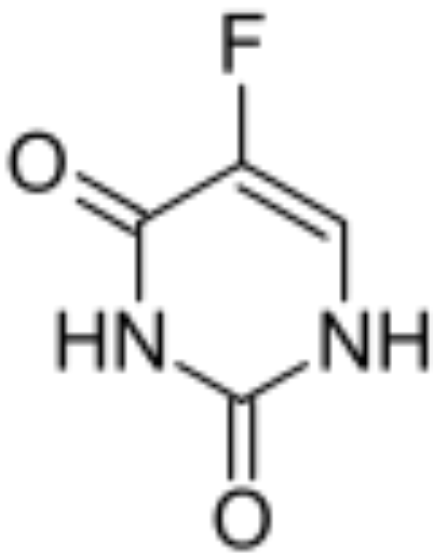
5-fluorouracil

Fluorouracil (5-FU) (trade name Adrucil among others) a medication which
the treatment of cancer. It is a suicide inhibitor and works through irreversi
tion of thymidylate synthase. It belongs to the family of drugs called the anti
lites. It is also a pyrimidine analog.



https://en.wikipedia.org/wiki/Fluorouracil

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Chapter 6 - Metabolism: Nucleotides

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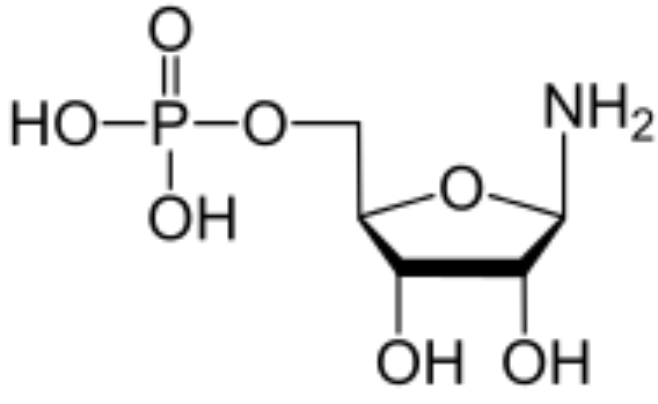
5-phosphoribosylamine

Phosphoribosylamine (5PRA) is an intermediate in purine metabolism. It is a sor to IMP and is generated from phosphoribosyl pyrophosphate (PRPP).



https://en.wikipedia.org/wiki/Phosphoribosylamine

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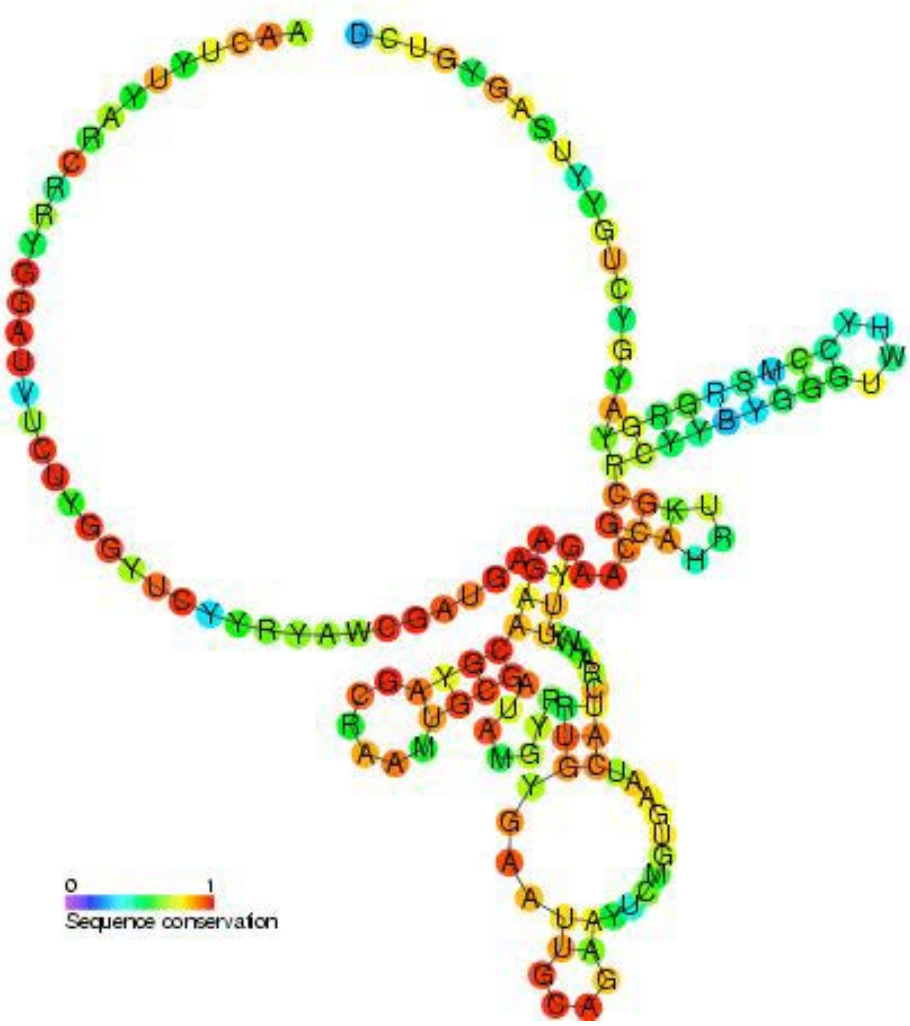
5.8S rRNA

The 5.8S ribosomal RNA (5.8S rRNA) is a non-coding RNA component of the large subunit of the eukaryotic ribosome and so plays an important role in protein translation. It is transcribed by RNA polymerase I as part of the 45S precursor that also contains 18S and 28S rRNA. Its function is thought to be in ribosome translocation. It is also known to form covalent linkage to the p53 tumor suppressor protein.



https://en.wikipedia.org/wiki/5.8S_ribosomal_RNA

Related Glossary Terms

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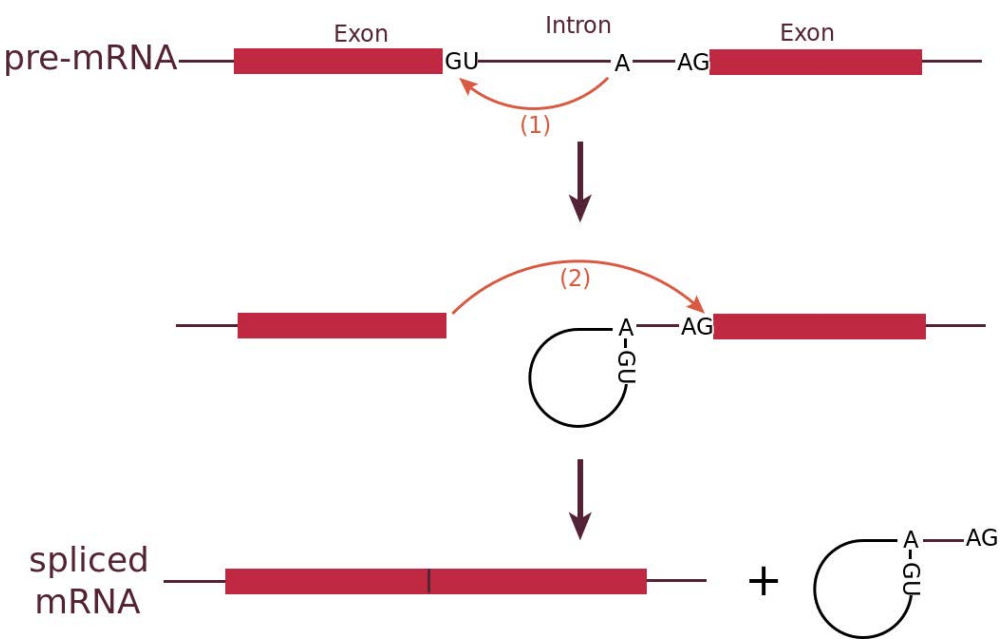
5' Splice Site

Spliceosomal splicing and self-splicing involve a two-step biochemical process. Both steps involve transesterification reactions that occur between RNA nucleotides. tRNA splicing, however, is an exception and does not occur by transesterification.

Spliceosomal and self-splicing transesterification reactions occur via two sequential transesterification reactions. First, the 2'OH of a specific branchpoint nucleotide within the intron, defined during spliceosome assembly, performs a nucleophilic attack on the first nucleotide of the intron at the 5' splice site, forming the lariat intermediate. Second, the 3'OH of the released 5' exon then performs a nucleophilic attack at the last nucleotide of the intron at the 3' splice site, thus joining the exons and releasing the intron lariat.



https://en.wikipedia.org/wiki/RNA_splicing

Related Glossary Terms

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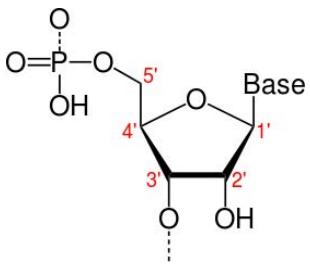
5' to 3’

Directionality, in molecular biology and biochemistry, is the end-to-end chemical orientation of a single strand of nucleic acid. In a single strand of DNA or RNA, the chemical convention of naming carbon atoms in the nucleotide sugar-ring means that there will be a 5′-end, which frequently contains a phosphate group attached to the 5′ carbon of the ribose ring, and a 3′-end (usually pronounced "five prime end" and "three prime end"), which typically is unmodified from the ribose -OH substituent. In a DNA double helix, the strands run in opposite directions to permit base pairing between them, which is essential for replication or transcription of the encoded information.

Nucleic acids can only be synthesized *in vivo* in the 5′-to-3′ direction, as the polymerases that assemble various types of new strands generally rely on the energy produced by breaking nucleoside triphosphate bonds to attach new nucleoside monophosphates to the 3′-hydroxyl (-OH) group, via a phosphodiester bond. The relative positions of structures along a strand of nucleic acid, including genes and various protein binding sites, are usually noted as being either upstream (towards the 5′-end) or downstream (towards the 3′-end). (See also upstream and downstream.)

Directionality is related to, but independent from sense. Transcription of single-stranded RNA from a double-stranded DNA template requires the selection of one strand of the DNA template as the template strand that directly interacts with the nascent RNA due to complementary sequence. The other strand is not copied directly, but necessarily its sequence will be similar to that of the RNA. Transcription initiation sites generally occur on both strands of an organism's DNA, and specify the location, direction, and circumstances under which transcription will occur. If the transcript encodes one or (rarely) more proteins, translation of each protein by the ribosome will proceed in a 5′ to 3′ direction, and will extend the protein from its N terminus toward its C terminus. For example, in a typical gene a start codon (5′-ATG-3′) is a DNA sequence within the sense strand.

Transcription begins at an upstream site (relative to the sense strand), and as it proceeds through the region it copies the 3′-TAC-5′ from the template strand to produce 5′-AUG-3′ within a messenger RNA. The mRNA is scanned by the ribosome from the 5′ end, where the start codon directs the incorporation of a methionine (in eukaryotes) at the N terminus of the protein. By convention, single strands of DNA and RNA sequences are written in a 5′-to-3′ direction except as needed to illustrate the pattern of base pairing.



https://en.wikipedia.org/wiki/Directionality_(molecular_biology)

Related Glossary Terms

Drag related terms here

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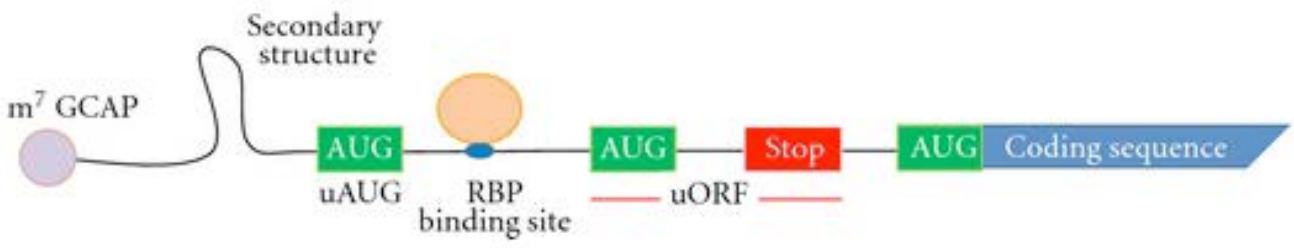
5' UTR

The 5' untranslated region (5′ UTR) (also known as a Leader Sequence or Leader RNA) is the region of an mRNA that is directly upstream from the initiation codon. This region is important for the regulation of translation of a transcript by differing mechanisms in viruses, prokaryotes and eukaryotes. While called untranslated, the 5′ UTR or a portion of it is sometimes translated into a protein product. This product can then regulate the translation of the main coding sequence of the mRNA. In many other organisms, however, the 5′ UTR is completely untranslated, instead forming complex secondary structure to regulate translation. The 5′ UTR has been found to interact with proteins relating to metabolism and proteins translate sequences within the 5′ UTR. In addition, this region has been involved in transcription regulation, such as the sex-lethal gene in *Drosophila*. Regulatory elements within 5' UTRs have also been linked to mRNA export.



https://en.wikipedia.org/wiki/Five_prime_untranslated_region

Related Glossary Terms

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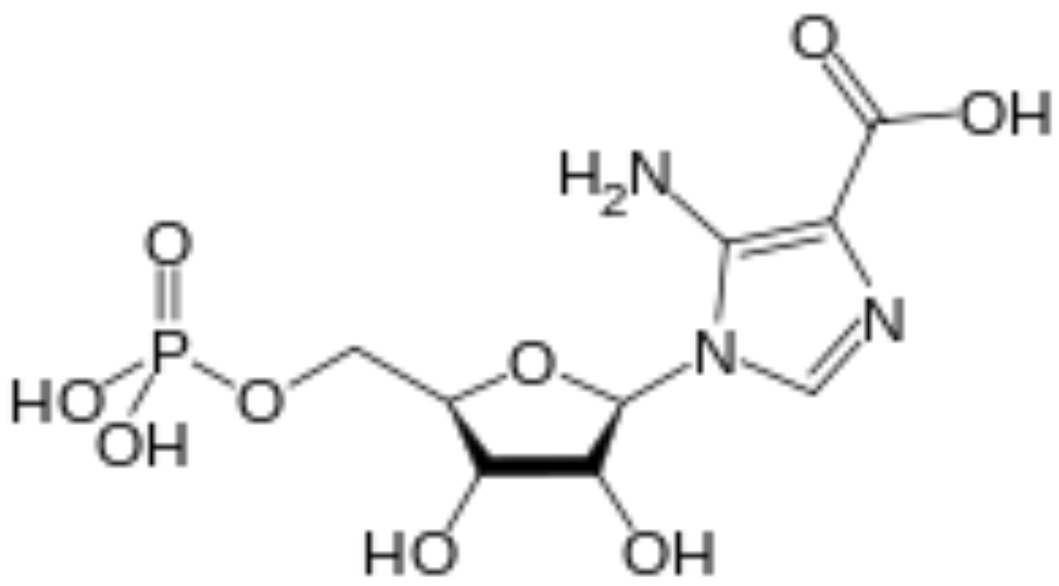
5'-Phosphoribosyl-4-carboxy-5-aminoimidazole

5'-Phosphoribosyl-4-carboxy-5-aminoimidazole (or CAIR) is an intermedia
mation of purines. It is formed by phosphoribosylaminoimidazole carboxy



https://en.wikipedia.org/wiki/5%27-Phosphoribosyl-4-carboxy-5-aminoim

Related Glossary Terms

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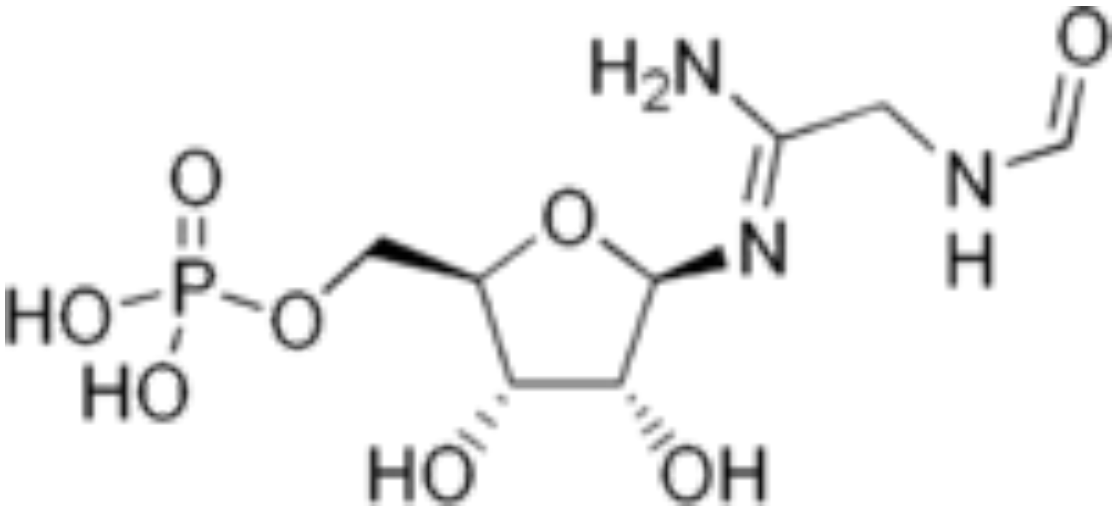
5'-Phosphoribosylformylglycinamidine

5'-Phosphoribosylformylglycinamidine (or FGAM) is an intermediate in the
of purines.



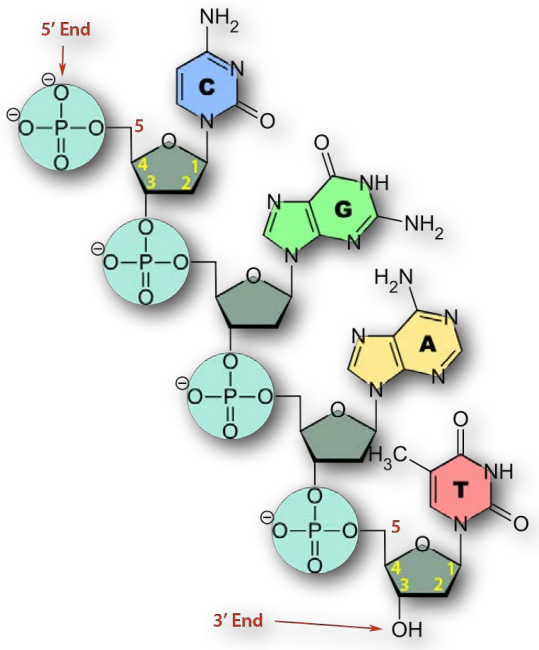
https://en.wikipedia.org/wiki/5%27-Phosphoribosylformylglycinamidine

Related Glossary Terms

Drag related terms here

5’ End

The 5’ end of a nucleotide or nucleic acid is a position determined by the numbering system for the sugars of the nucleotides composing it. The 5’ end of a nucleotide has phosphate can be linked to a 3’ hydroxyl in the formation of a nucleic acid.



Related Glossary Terms

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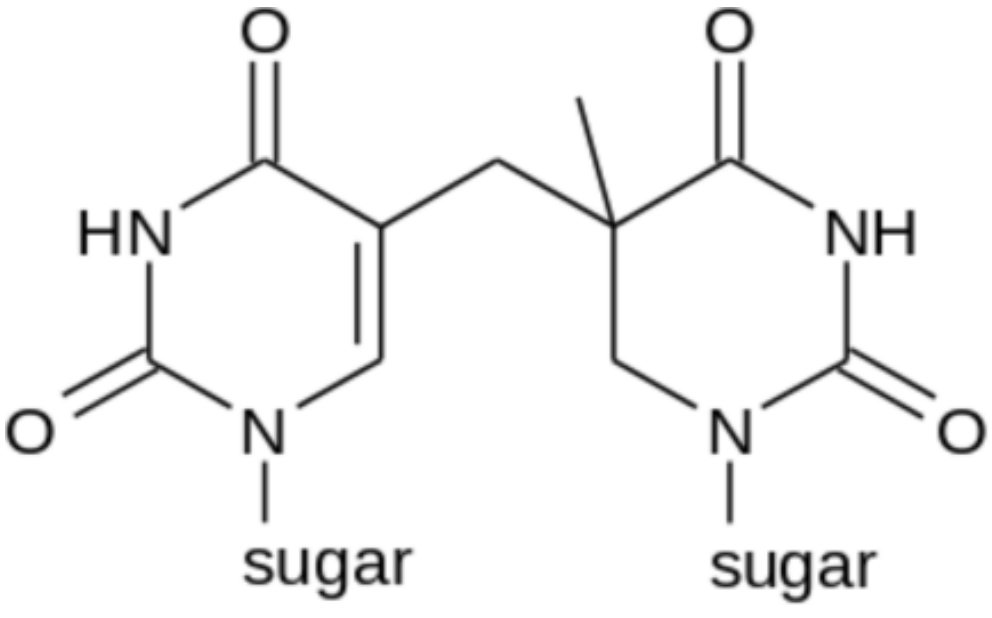
6-4PP

A 6-4 photoproduct (6-4PP) refers to a chemical product of DNA damage o
a result of exposure to UV light. As seen in the figure below a 6-4PP is a co
formed between two adjacent bases in a strand of DNA.



https://en.wikipedia.org/wiki/(6-4)DNA_photolyase

Related Glossary Terms

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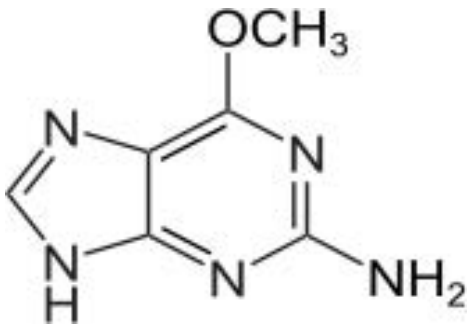
Chapter 7 - DNA Repair

6-O-methylguanine

6-O-methylguanine (also called O^6-methylguanine) is a derivative of the nucleobase guanine in which a methyl group is attached to the oxygen atom. It base-pairs to thymine rather than cytidine, causing a G:C to A:T transition in DNA.

6-O-methylguanine is formed in DNA by alkylation of the oxygen atom of guanine, most often by N-nitroso compounds (NOC) and sometimes due to methylation by other compounds such as endogenous S-adenosyl methionine. NOC are alkylating agents formed by the reaction of nitrite or other nitrogen oxides with secondary amines and N-alkylamides, yielding N-alkylnitrosamines and N-alkylnitrosamides.

NOC are found in some foods (bacon, sausages, cheese) and tobacco smoke, and are formed in the gastrointestinal tract, especially after consumption of red meat. In addition, endogenous nitric oxide levels were found to be enhanced under chronic inflammatory conditions, and this could favor NOC formation in the large intestine.



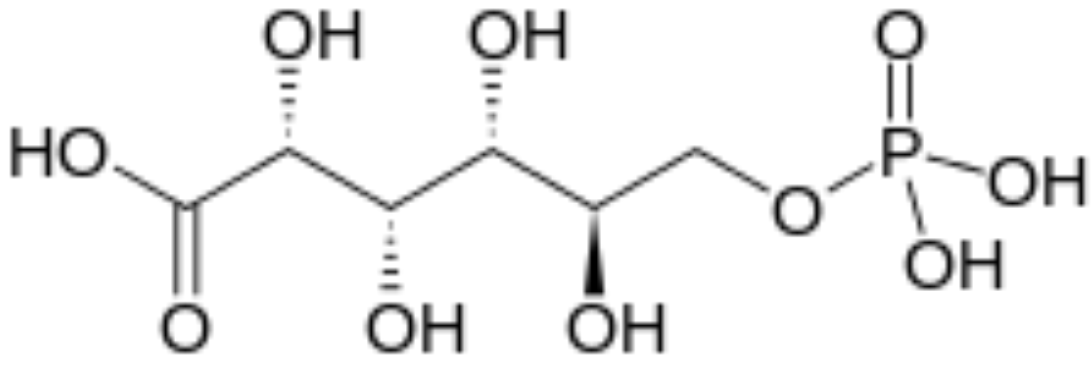
https://en.wikipedia.org/wiki/6-O-Methylguanine

Related Glossary Terms

Drag related terms here

6-phosphogluconate

6-Phosphogluconic acid (6-phosphogluconate) is an intermediate in the pentose ph
phate pathway and the Entner–Doudoroff pathway. It is formed by 6-
phosphogluconolactonase, and acted upon by phosphogluconate dehydrogenase to
duce ribulose 5-phosphate. It may also be acted upon by 6-phosphogluconate dehyc
tase to produce 2-keto-3-deoxy-6-phosphogluconate.



https://en.wikipedia.org/wiki/6-Phosphogluconic_acid

Related Glossary Terms

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Find Term

6-phosphogluconate Dehydrogenase

Phosphogluconate dehydrogenase is an enzyme in the pentose phosphate p
forms ribulose 5-phosphate from 6-phosphogluconate. It is an oxidative ca
that catalyzes the decarboxylating reduction of 6-phosphogluconate into rib
phosphate in the presence of $NADP^+$. This reaction is a component of the h
mono-phosphate shunt and pentose phosphate pathways (PPP).

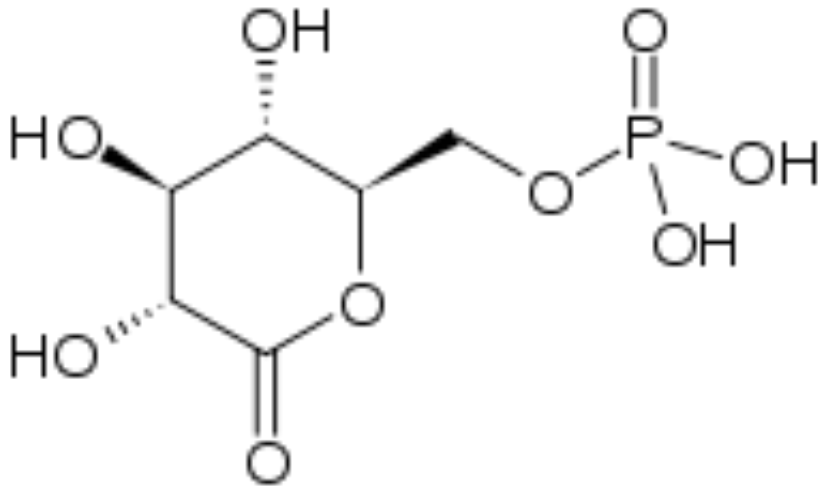
https://en.wikipedia.org/wiki/Phosphogluconate_dehydrogenase

Related Glossary Terms

Drag related terms here

6-Phosphoglucono-δ-lactone

6-Phosphogluconolactone is an intermediate in the pentose phosphate path
It is produced from glucose-6-phosphate by glucose-6-phosphate dehydrog



https://en.wikipedia.org/wiki/6-Phosphogluconolactone

Related Glossary Terms

Drag related terms here

6-phosphogluconolactonase

6-Phosphogluconolactonase (6PGL, PGLS) is a cytosolic enzyme found in a
isms that catalyzes the hydrolysis of 6-phosphogluconolactone to 6-phosph
acid in the oxidative phase of the pentose phosphate pathway.

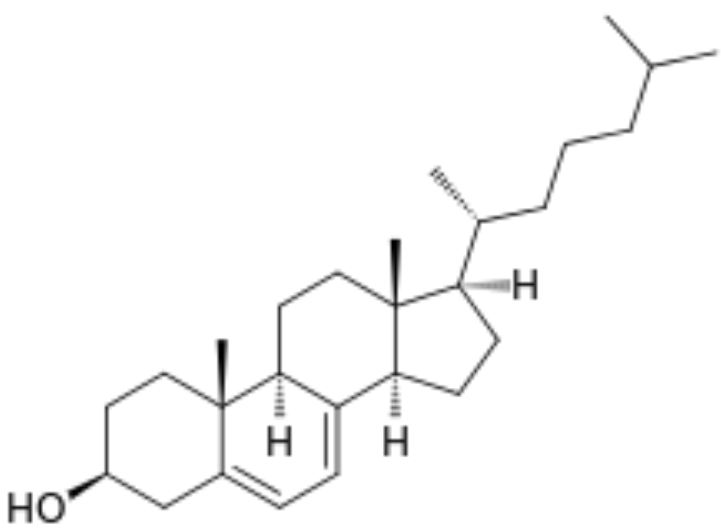
https://en.wikipedia.org/wiki/6-phosphogluconolactonase

Related Glossary Terms

Drag related terms here

7-dehydrocholesterol

7-dehydrocholesterol is a zoosterol that functions in the serum as a cholesterol pr
sor, and is converted to vitamin D_3 in the skin, therefore functioning as provitami
The presence of this compound in human skin enables humans to manufacture vi
min D_3 from ultraviolet rays in the sun light, via an intermediate isomer pre-vitar
D_3.



https://en.wikipedia.org/wiki/7-Dehydrocholesterol

Related Glossary Terms

Drag related terms here

7-transmembrane Domain Family

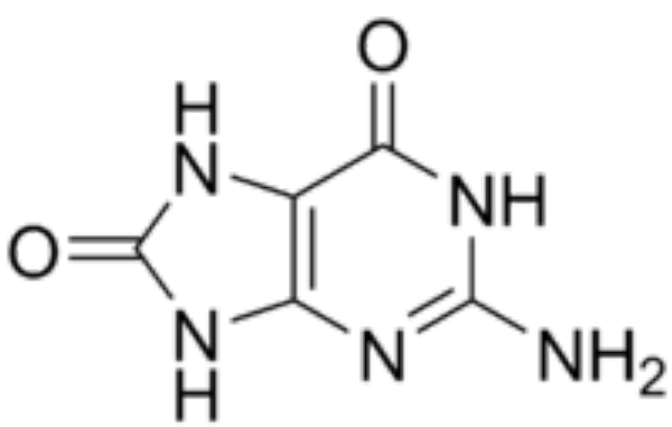
Transmembrane proteins are of several types. The most common ones hav
(domains) that cross the membrane repeatedly. One of the most common t
brane proteins is the group of them that crosses the membrane precisely se
These are known as 7-transmembrane domain proteins or 7-TMs. A good e
the class of G-protein coupled receptors, such as the β-adrenergic receptors

Related Glossary Terms

Drag related terms here

8-oxo-guanine

8-oxoguanine (8-hydroxyguanine, 8-oxo-Gua, or OH8Gua) is one of the most co
DNA lesions resulting from reactive oxygen species and can result in a mismatch
pairing with adenine resulting in G to T and C to A substitutions in the genome.
mans, it is primarily repaired by DNA glycosylase OGG1. It can be caused by ioni
radiation, in connection with oxidative metabolism.



https://en.wikipedia.org/wiki/8-Oxoguanine

Related Glossary Terms

Drag related terms here

10.5 Base Pairs per Turn

In the B-form the DNA helix has a repeat of 10.5 base pairs per turn, with s
phosphate forming the covalent phosphodiester “backbone” of the molecul
adenine, guanine, cytosine, and thymine bases oriented in the middle wher
the now familiar base pairs that look like the rungs of a ladder. DNA with s
sity of base pairs per turn is referred to as “relaxed”. Altering that density c
sults in supercoiling of the DNA molecule.

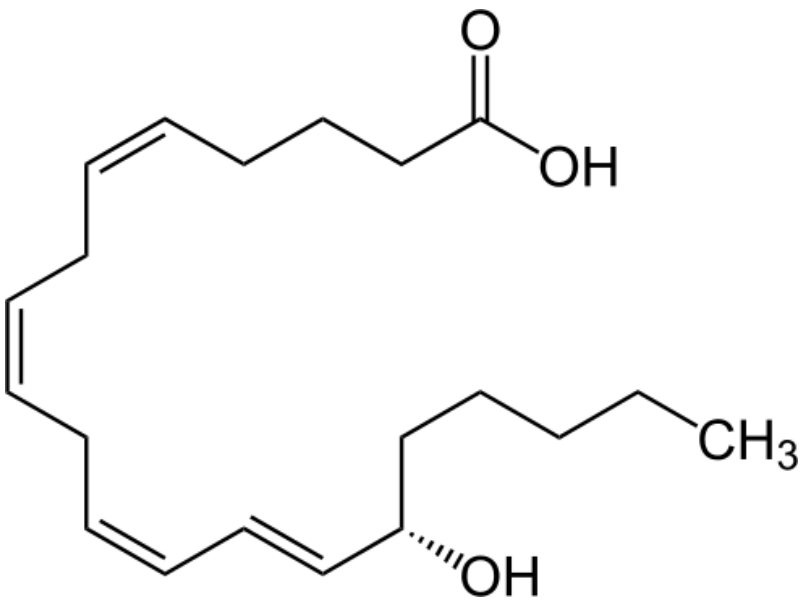
Related Glossary Terms

Drag related terms here

15R-hydroxyeicosatetraenoic acid

15-Hydroxyicosatetraenoic acid (also termed 15-HETE, 15(S)-HETE, and 15S-HETE) is an endogenous eicosanoid, i.e. a metabolite of arachidonic acid. Various cell types and tissues first produce 15-Hydroperoxyicosatetraenoic acid (15-HpETE). These initial hydroperoxy products are extremely short lived in cells. If not otherwise metabolized, they are reduced to 15-HETE. Both these molecules are are hormone-like autocrine and paracrine signaling agents, involved in inflammation response, but often are further metabolized to a wide range of products that are much more potent, including eoxins.

The production and actions of these molecules and their metabolites often differ greatly depending on cell-type or tissue-type studied. In many ways they are analogous to the more abundant 5-HETE and 5-HPETE.



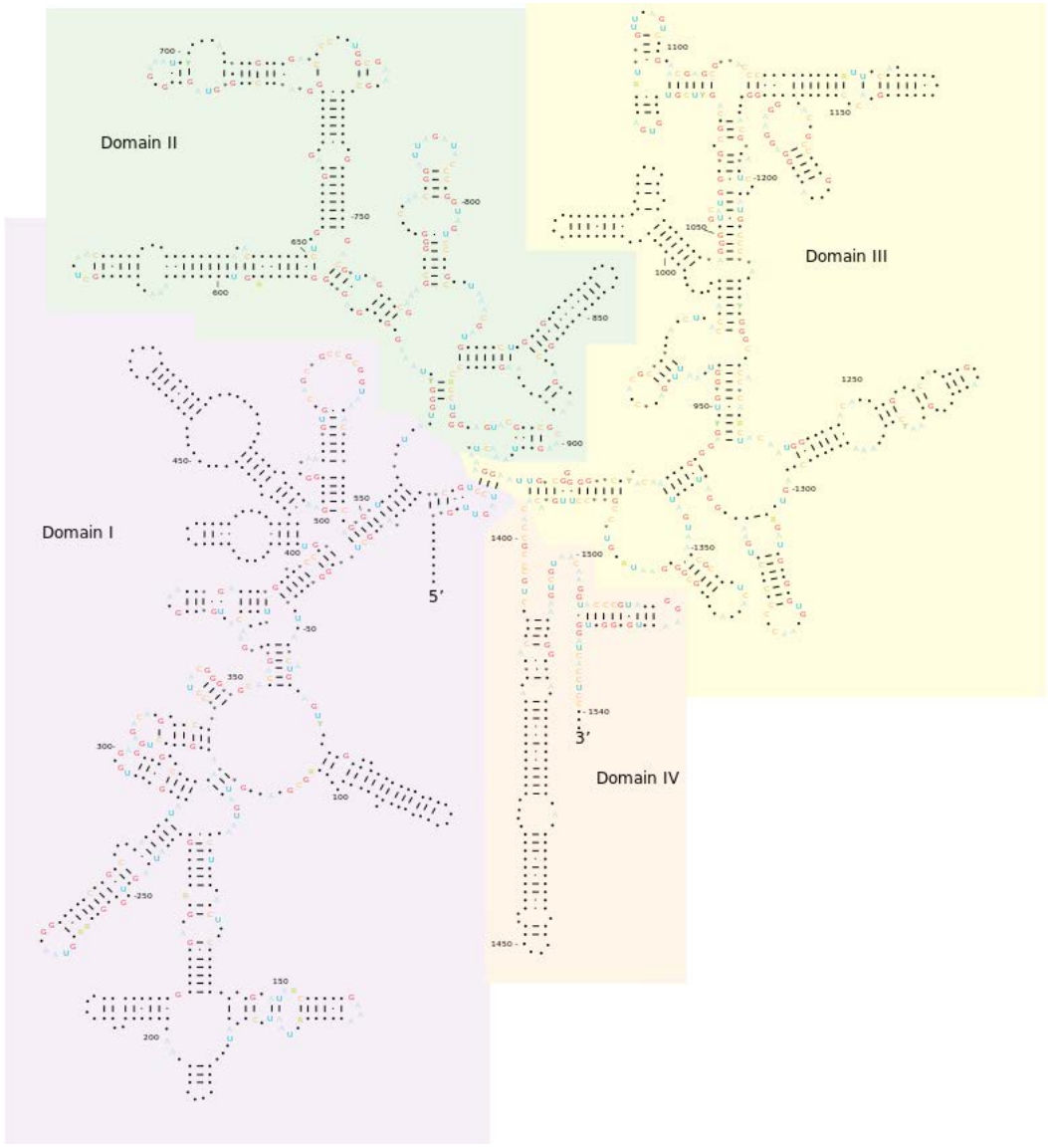
https://en.wikipedia.org/wiki/15-Hydroxyicosatetraenoic_acid

16S rRNA

16S ribosomal RNA (or 16S rRNA) is a component of the 30S small subunit of prokaryotic ribosomes. The genes coding for it are referred to as 16S rRNA gene and are used in reconstructing phylogenies, due to the slow rates of evolution of this region of the gene. Carl Woese and George E. Fox were two of the people who pioneered the use of 16S rRNA in phylogenies

The 16S rRNA has several functions:

- Like the large (23S) ribosomal RNA, it has a structural role, acting as a scaffold defining the positions of the ribosomal proteins.
- The 3' end contains the anti-Shine-Dalgarno sequence, which binds upstream to the AUG start codon on the mRNA. The 3'-end of 16S RNA binds to the proteins S1 and S21 known to be involved in initiation of protein synthesis
- Interacts with 23S, aiding in the binding of the two ribosomal subunits (50S+30S)
- Stabilizes correct codon-anticodon pairing in the A site, via a hydrogen bond formation between the N1 atom of Adenine residues 1492 and 1493 and the 2'OH group of the mRNA backbone.



https://en.wikipedia.org/wiki/16S_ribosomal_RNA

Related Glossary Terms

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18S rRNA

18S ribosomal RNA (abbreviated 18S rRNA) is a part of the ribosomal RNA. The S in 18S represents Svedberg units. 18S rRNA is a component of the small eukaryotic ribosomal subunit (40S). 18S rRNA is the structural RNA for the small component of eukaryotic cytoplasmic ribosomes, and thus one of the basic components of all eukaryotic cells.

It is the eukaryotic nuclear homologue of 16S ribosomal RNA in Prokaryotes and mitochondria. The genes coding for 18S rRNA are referred to as 18S rDNA. Sequence data from these genes is widely used in molecular analysis to reconstruct the evolutionary history of organisms, especially in vertebrates, as its slow evolutionary rate makes it suitable to reconstruct ancient divergences.

The small subunit (SSU) 18S rRNA gene is one of the most frequently used genes in phylogenetic studies and an important marker for random target polymerase chain reaction (PCR) in environmental biodiversity screening. In general, rRNA gene sequences are easy to access due to highly conserved flanking regions allowing for the use of universal primers. Their repetitive arrangement within the genome provides excessive amounts of template DNA for PCR, even in the smallest organisms. The 18S gene is part of the ribosomal functional core and is exposed to similar selective forces in all living beings. Thus, when the first large-scale phylogenetic studies based on 18S sequences were published - first and foremost phylogeny of the animal kingdom by Field et al. (1988) - the gene was celebrated as the prime candidate for reconstructing the metazoan tree of life. And in fact, 18S sequences later provided evidence for the splitting of *Ecdysozoa* and *Lophotrochozoa*, thus contributing to the most recent revolutionary change in our understanding of metazoan relationships.

https://en.wikipedia.org/wiki/18S_ribosomal_RNA

Related Glossary Terms

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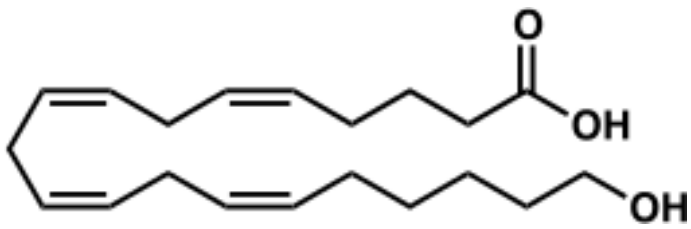
20-HETE

20-Hydroxyeicosatetraenoic acid, also known as 20-HETE or 20-hydroxy-5Z,8Z,11Z,14Z-eicosatetraenoic acid, is an eicosanoid metabolite of arachidonic acid that has a wide range of effects on the vascular system including the regulation of vascular tone, blood flow to specific organs, sodium and fluid transport in the kidney, and vascular pathway remodeling. These vascular and kidney effects of 20-HETE have been shown to be responsible for regulating blood pressure and blood flow to specific organs in rodents. Genetic and preclinical studies suggest that 20-HETE may similarly regulate blood pressure and contribute to the development of stroke and heart attacks.

Additionally the loss of its production appears to be one cause of the human neurological disease, Hereditary spastic paraplegia. Preclinical studies also suggest that the overproduction of 20-HETE may contribute to the progression of certain human cancers, particularly those of the breast.



https://en.wikipedia.org/wiki/20-Hydroxyeicosatetraenoic_acid

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Related Glossary Terms

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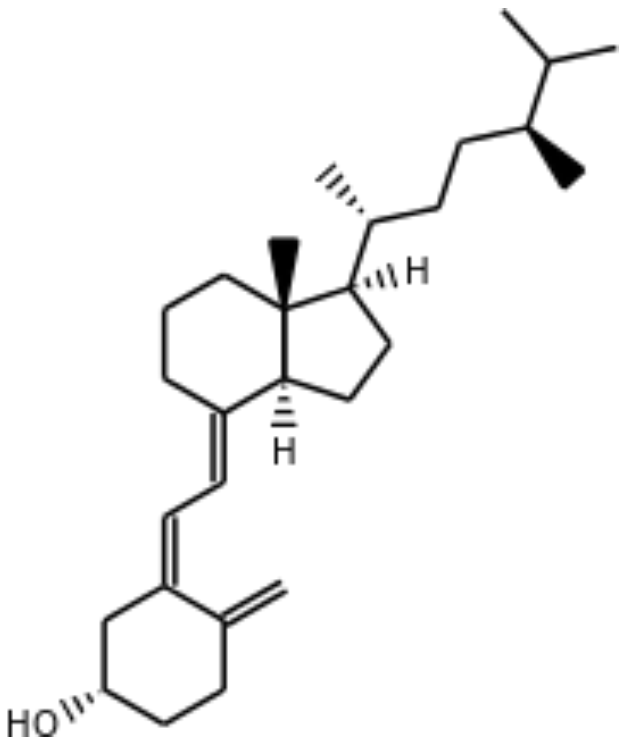
Chapter 6 - Metabolism: Fats and Fatty Acids

22-Dihydroergocalciferol

22-dihydroergocalciferol is a form of vitamin D, also known as vitamin D_4. It ha
systematic name (5Z,7E)-(3S)-9,10-seco-5,7,10(19)-ergostatrien-3-ol.



https://en.wikipedia.org/wiki/22-Dihydroergocalciferol

Related Glossary Terms

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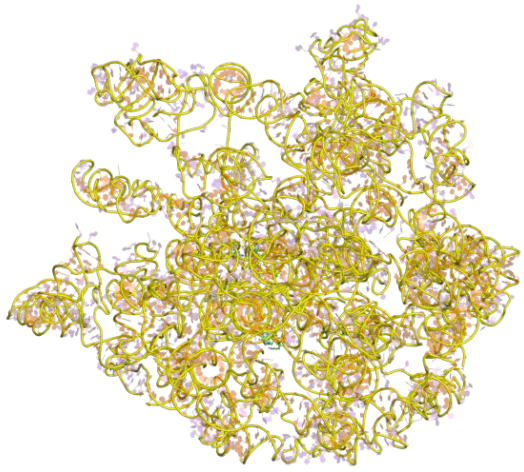
Chapter 2 - Structure & Function: Lipids

23S rRNA

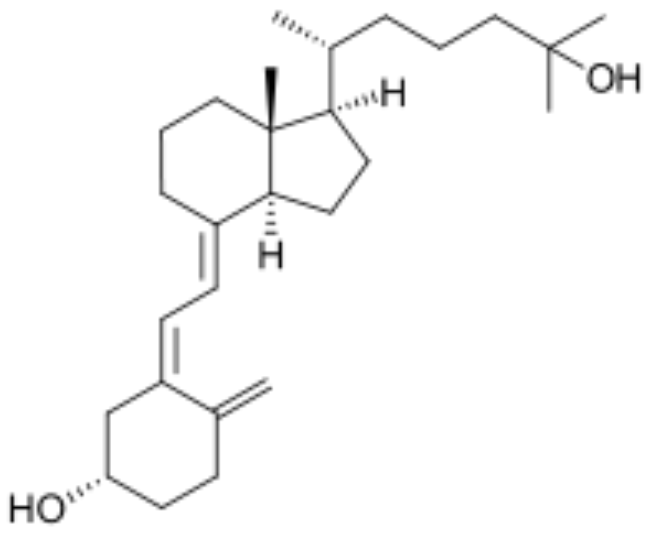
The 23S rRNA is a 2904 nucleotide long (in *E. coli*) component of the large subunit (50S) of the bacterial ribosome. The ribosomal peptidyl transferase activity resides in domain V of this rRNA, and this domain is the most common binding site for antibiotics that inhibit translation. A well-known member of this antibiotic class, Chloramphenicol, acts by inhibiting peptide bond formation, with recent 3D-structural studies showing two different binding sites depending on the species of ribosome. Linezolid and quinupristin-dalfopristin also bind to the 23S rRNA, and cross-resistance has been demonstrated between these antibiotics.



https://en.wikipedia.org/wiki/23S_ribosomal_RNA

25-hydroxycholecalciferol

Calcifediol (INN), also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D (abbreviated 25(OH)D), is a prehormone that is produced in th liver by hydroxylation of vitamin D_3 (cholecalciferol) by the enzyme cholecalcifero hydroxylase which was isolated by Michael F. Holick.



https://en.wikipedia.org/wiki/Calcifediol

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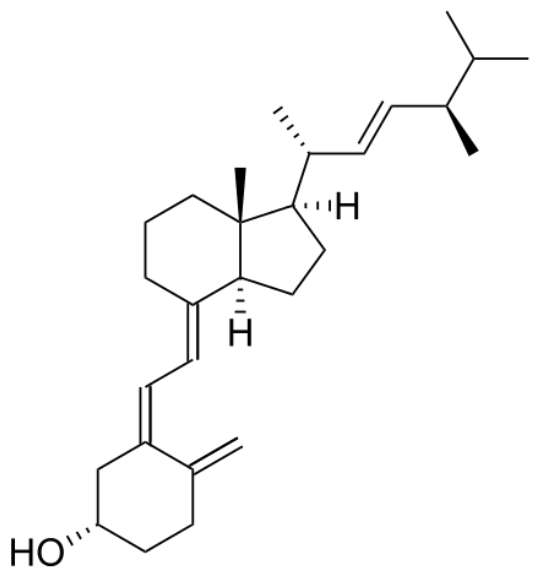
25-hydroxyergocalciferol

25-hydroxyergocalciferol is an important metabolite in vitamin D metabolism in the body. In the liver, cholecalciferol (vitamin D_3) is converted to calcidiol, which is also known as calcifediol (INN), 25-hydroxycholecalciferol (aka 25-hydroxyvitamin D_3 — abbreviated 25(OH)D3). Ergocalciferol (vitamin D_2) is converted in the liver to 25-hydroxyergocalciferol (aka 25-hydroxyvitamin D_2 — abbreviated 25(OH) D_2). These two specific vitamin D metabolites are measured in serum to determine a person's vitamin D status. Part of the calcidiol is converted by the kidneys to calcitriol, the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of bone. Calcitriol also affects neuromuscular and immune function. The structure of ergocalciferol follows.



https://en.wikipedia.org/wiki/Vitamin_D

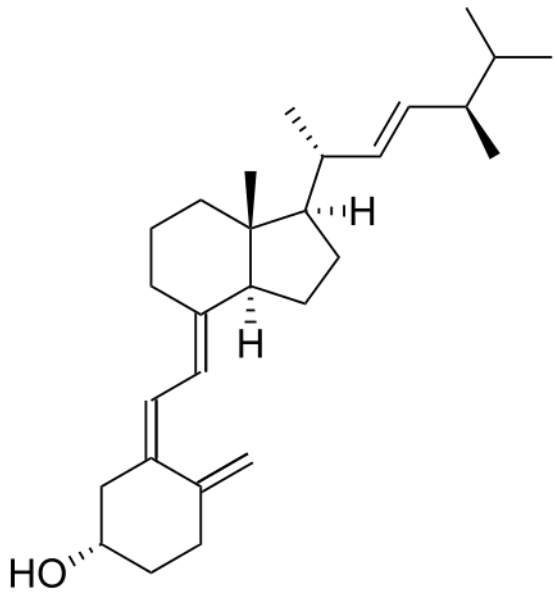
Related Glossary Terms

Drag related terms here

25-hydroxyvitamin D_2

25-hydroxyvitamin D_2 is an important metabolite in vitamin D metabolism in the body.

In the liver, cholecalciferol (vitamin D_3) is converted to calcidiol, which is also known as calcifediol (INN), 25-hydroxycholecalciferol (aka 25-hydroxyvitamin D_3 — abbreviated 25(OH)D_3). Ergocalciferol (vitamin D_2) is converted in the liver to 25-hydroxyergocalciferol (aka 25-hydroxyvitamin D_2 — abbreviated 25(OH) D_2). These two specific vitamin D metabolites are measured in serum to determine a person's vitamin D status. Part of the calcidiol is converted by the kidneys to calcitriol, the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of bone. Calcitriol also affects neuromuscular and immune function. The structure of ergocalciferol follows.



https://en.wikipedia.org/wiki/Vitamin_D

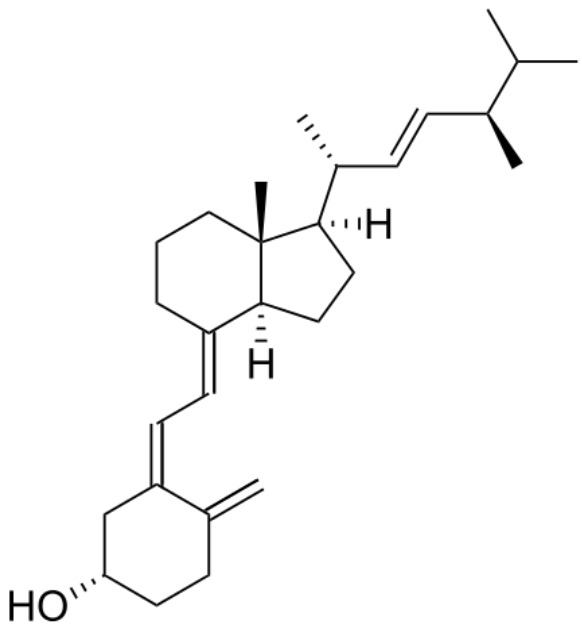
Related Glossary Terms

Drag related terms here

Index Find Term

25(OH)D_2

25(OH)D_2 is an important metabolite in vitamin D metabolism in the body. In the liver, cholecalciferol (vitamin D_3) is converted to calcidiol, which is also known as calcifediol (INN), 25-hydroxycholecalciferol (aka 25-hydroxyvitamin D_3 — abbreviated 25(OH)D_3). Ergocalciferol (vitamin D_2) is converted in the liver to 25-hydroxyergocalciferol (aka 25-hydroxyvitamin D_2 — abbreviated 25(OH) D_2). These two specific vitamin D metabolites are measured in serum to determine a person's vitamin D status. Part of the calcidiol is converted by the kidneys to calcitriol, the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of bone. Calcitriol also affects neuromuscular and immune function. The structure of ergocalciferol follows.



https://en.wikipedia.org/wiki/Vitamin_D

Related Glossary Terms

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Index Find Term

28S rRNA

28S ribosomal RNA is the structural RNA for the large component, or large
(LSU) of eukaryotic cytoplasmic ribosomes, and thus one of the basic comp
all eukaryotic cells. It is the eukaryotic nuclear homologue of the prokaryot
somal RNA.

The genes coding for 28S rRNA are referred to as 28S rDNA. The sequence
genes are sometimes used in molecular analysis to construct phylogenetic t

https://en.wikipedia.org/wiki/28S_ribosomal_RNA

Related Glossary Terms

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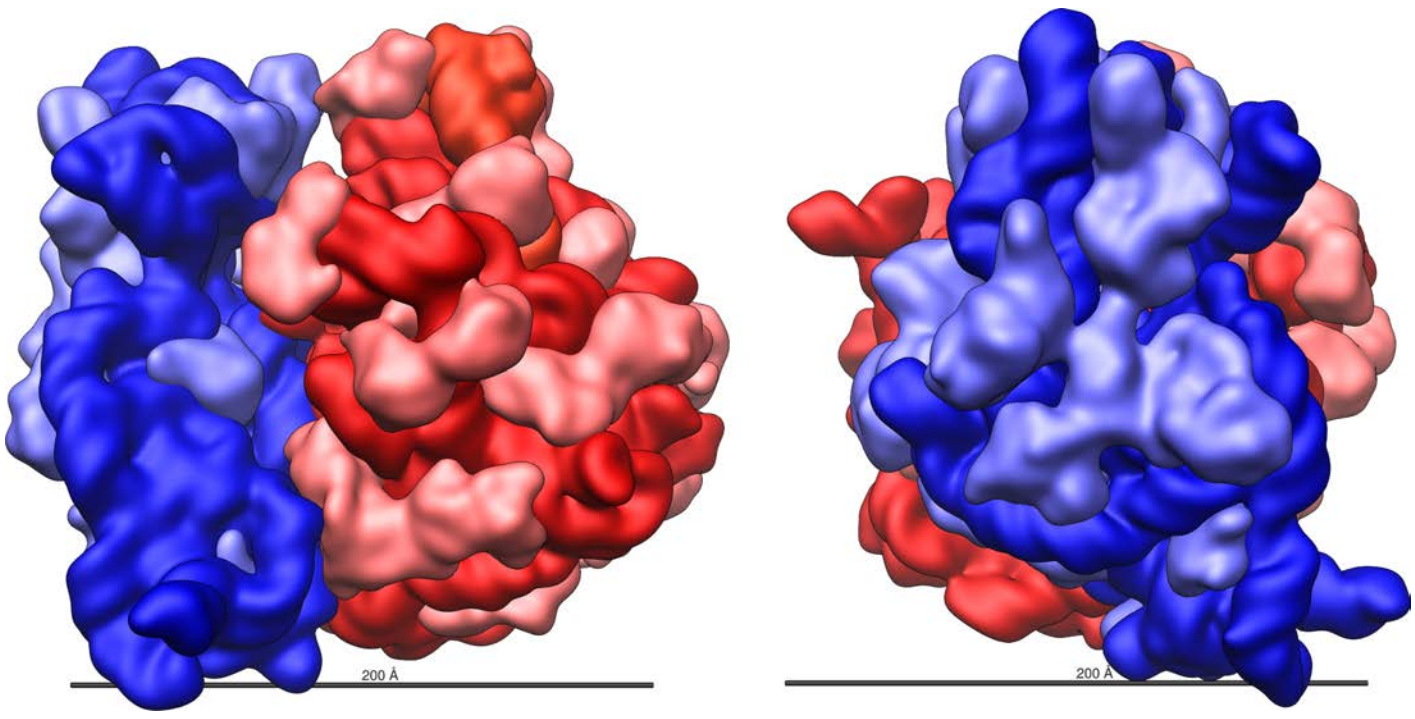
30S Subunit

Ribosomes contain two subunits, a large subunit and a small subunit. In bacteria, the large subunit has a size of 50S and the small subunit has a size of 30S. It is the 30S subunit that holds the 16S rRNA and also the one that is the first one to bind mRNA in the initiation phase of translation. The small subunit below is shown in blue.

The 30S subunit is the site of inhibition for antibiotics such as tetracycline and amino-glycosides.



https://commons.wikimedia.org/wiki/File:Ribosome_shape.png

Related Glossary Terms

Drag related terms here

40S Subunit

The eukaryotic small ribosomal subunit (40S) is the smaller subunit of the eukaryo
80S ribosomes, with the other major component being the large ribosomal subuni
(60S). The "40S" and "60S" names originate from the convention that ribosomal p
cles are denoted according to their sedimentation coefficients in Svedberg units. It
structurally and functionally related to the 30S subunit of 70S prokaryotic ribosom
However, the 40S subunit is much larger than the prokaryotic 30S subunit and co
tains many additional protein segments, as well as rRNA expansion segments.

The 40S subunit contains the decoding center which monitors the complementarit
tRNA and mRNA in protein translation. It is the largest component of several tran
tion initiation complexes, including the 43S and 48S preinitiation complexes (PICs
being bound by several eukaryotic initiation factors, including eIF1, eIF1A, and eIF

https://en.wikipedia.org/wiki/Eukaryotic_small_ribosomal_subunit_(40S)

Related Glossary Terms

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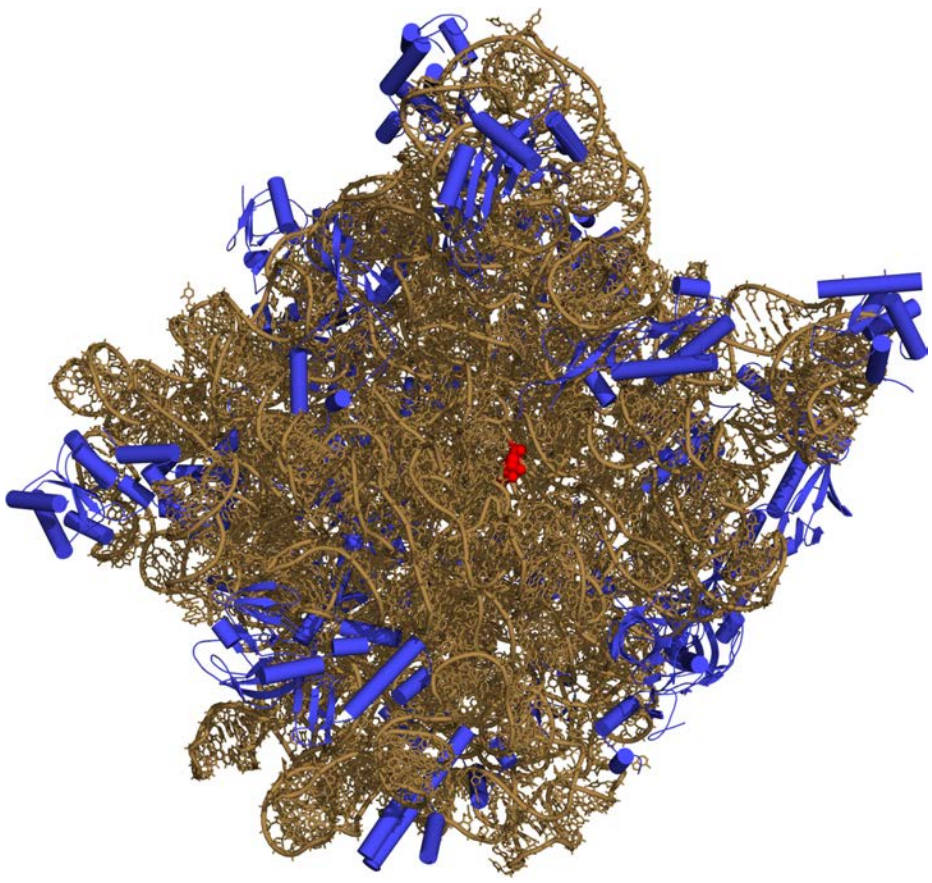
50S Subunit

50S is the larger subunit of the 70S ribosome of prokaryotes. It is the site of inhibition for antibiotics such as macrolides, chloramphenicol, clindamycin, and the pleuromutilins. It includes the 5S ribosomal RNA and 23S ribosomal RNA.

50S includes the activity that catalyzes peptide bond formation (peptidyl transfer reaction), prevents premature polypeptide hydrolysis, provides a binding site for the G-protein factors (assists initiation, elongation, and termination), and helps protein folding after synthesis.



https://en.wikipedia.org/wiki/50S

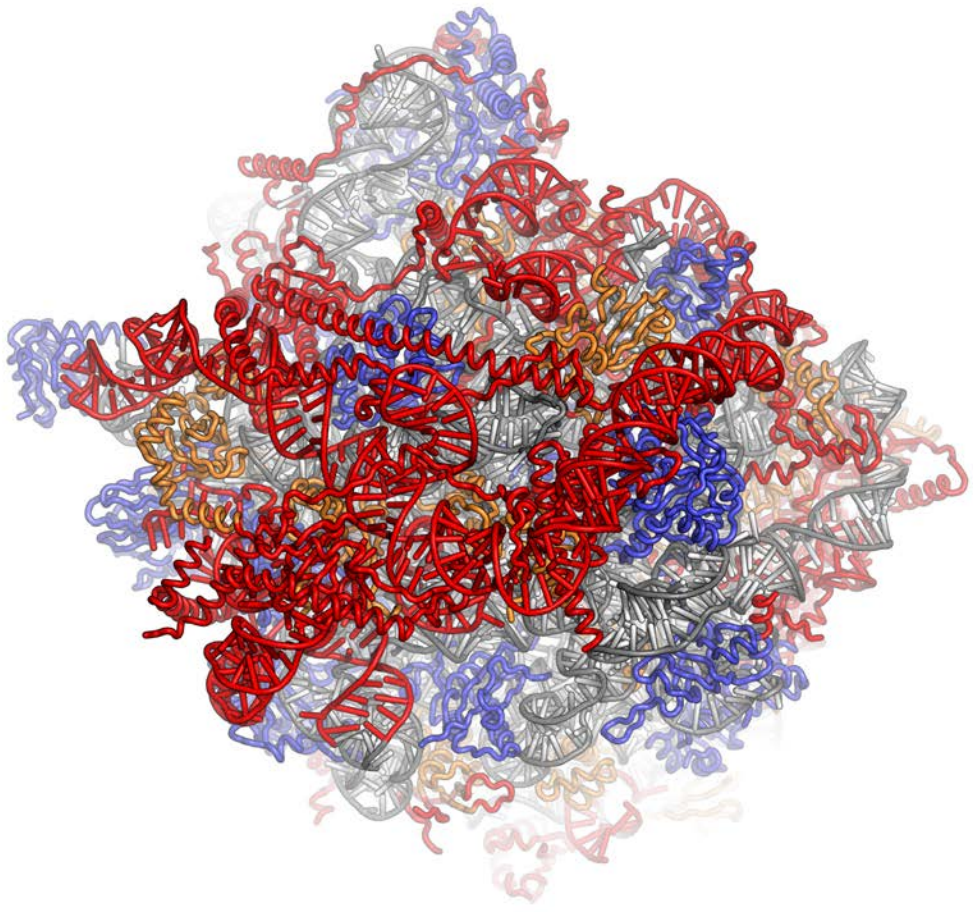
Related Glossary Terms

Drag related terms here

60S Subunit

The 60S subunit is the large subunit of eukaryotic 80S ribosomes. It is structurally and functionally related to the 50S subunit of 70S prokaryotic ribosomes. However, the 60S subunit is much larger than the prokaryotic 50S subunit and contains many additional protein segments, as well as ribosomal RNA expansion segments.

There are three binding sites for tRNA, the A-site, P-site and E-site (see article on protein translation for details). The core of the 60S subunit is formed by the 28S ribosomal RNA (abbreviated 28S rRNA), which is homologous to the prokaryotic 23S rRNA, which also contributes the active site (peptidyl transferase center, PTC) of the ribosome. The rRNA core is decorated with dozens of proteins.



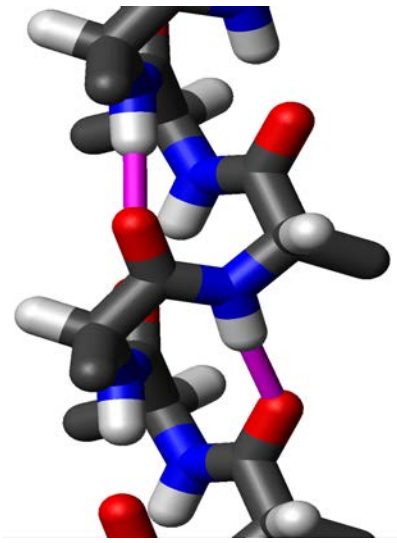
https://en.wikipedia.org/wiki/Eukaryotic_large_ribosomal_subunit_(60S)

Related Glossary Terms

Drag related terms here

3_{10} helix

A 3_{10} helix is a type of secondary structure found in proteins and polypeptides.Of the countless protein secondary structures present, the 3_{10}-helix is the fourth most common type observed, following α-helices, β-sheets and reverse turns. 3_{10}-helices constitute nearly 10-15% of all helices in protein secondary structures, and are typically observed as extensions of α-helices found at either their N- or C- termini. Because of the α-helices tendency to consistently fold and unfold, it has been proposed that the 3_{10}-helix serves as an intermediary conformation of sorts, and provides insight into the initiation of α-helix folding.



https://en.wikipedia.org/wiki/310_helix

Related Glossary Terms

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A2β2

$\alpha_2\beta_2$ is known as the adult form of hemoglobin. Various forms of hemoglobin are described below.

In the embryo:
• Gower 1 ($\zeta_2\varepsilon_2$)
• Gower 2 ($\alpha_2\varepsilon_2$) (PDB: 1A9W)
• Hemoglobin Portland I ($\zeta_2\gamma_2$)
• Hemoglobin Portland II ($\zeta_2\beta_2$).

In the fetus:
• Hemoglobin F ($\alpha_2\gamma_2$) (PDB: 1FDH).

After birth:
• Hemoglobin A ($\alpha_2\beta_2$) (PDB: 1BZ0) – The most common with a normal amount over 95%
• Hemoglobin A2 ($\alpha_2\delta_2$) – δ chain synthesis begins late in the third trimester and, in adults, it has a normal range of 1.5–3.5%
• Hemoglobin F ($\alpha_2\gamma_2$) – In adults hemoglobin F is restricted to a limited population of red cells called F-cells. However, the level of Hb F can be elevated in persons with sickle-cell disease and β-thalassemia.

https://en.wikipedia.org/wiki/Hemoglobin

Related Glossary Terms

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A2γ2

$\alpha_2\gamma_2$ is a description of the subunit composition of fetal hemoglobin. In contrast to the adult form of hemoglobin, the $A_2\gamma_2$ form holds oxygen more tightly.

Various forms of hemoglobin are described below.

In the embryo:
• Gower 1 ($\zeta_2\varepsilon_2$)
• Gower 2 ($\alpha_2\varepsilon_2$) (PDB: 1A9W)
• Hemoglobin Portland I ($\zeta_2\gamma_2$)
• Hemoglobin Portland II ($\zeta_2\beta_2$).

In the fetus:
• Hemoglobin F ($\alpha_2\gamma_2$) (PDB: 1FDH).

After birth:
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https://en.wikipedia.org/wiki/Hemoglobin

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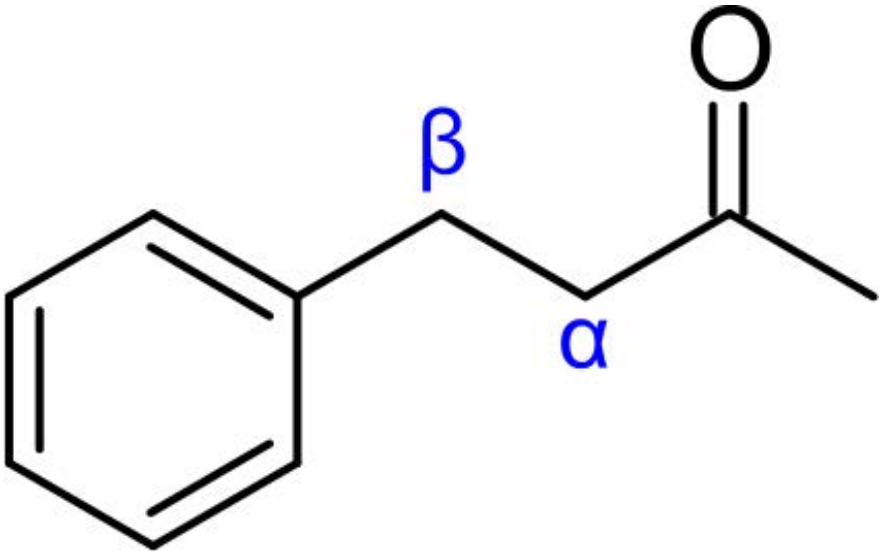
Alpha Carbon

The α carbon (C_α) in organic molecules refers to the first carbon atom that atta
a functional group, such as a carbonyl. The second carbon atom is called the β
(C_β), and the system continues naming in alphabetical order with Greek letters



https://en.wikipedia.org/wiki/Alpha_and_beta_carbon

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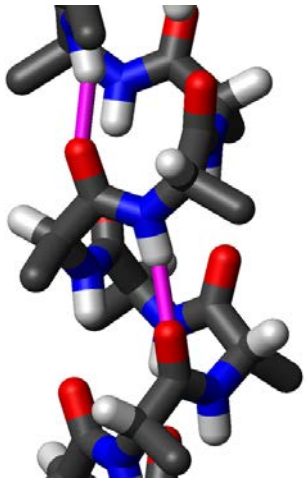
Alpha Helix

The α helix (alpha-helix) is a common secondary structure of proteins and is a righthand-coiled or spiral conformation (helix) in which every backbone N-H group donates a hydrogen bond to the backbone C=O group of the amino acid four residues earlier (hydrogen bonding). This secondary structure is also sometimes called a classic Pauling–Corey–Branson α-helix (see below). The name 3.613-helix is also used for this type of helix, denoting the number of residues per helical turn, and 13 atoms being involved in the ring formed by the hydrogen bond. Among types of local structure in proteins, the α-helix is the most regular and the most predictable from sequence, as well as the most prevalent.

The amino acids in an α-helix are arranged in a right-handed helical structure where each amino acid residue corresponds to a 100° turn in the helix (i.e., the helix has 3.6 residues per turn), and a translation of 1.5 Å (0.15 nm) along the helical axis. Pauling's first article on the theme in fact shows a left-handed helix, the enantiomer of the true structure. Short pieces of left-handed helix sometimes occur with a large content of achiral glycine amino acids, but are unfavorable for the other normal, biological L-amino acids. The pitch of the α-helix (the vertical distance between consecutive turns of the helix) is 5.4 Å (0.54 nm), which is the product of 1.5 and 3.6. What is most important is that the N-H group of an amino acid forms a hydrogen bond with the C=O group of the amino acid four residues earlier; this repeated hydrogen bonding is the most prominent characteristic of an α-helix. Official international nomenclature specifies two ways of defining α-helices, rule 6.2 in terms of repeating φ,ψ torsion angles and rule 6.3 in terms of the combined pattern of pitch and hydrogen bonding. The α-helices can be identified in protein structure using several computational methods, one of which being DSSP (Dictionary of Protein Secondary Structure).

Similar structures include the 3_{10} helix and the π-helix. The α-helix can be described as a 3.613 helix, since the i + 4 spacing adds 3 more atoms to the H-bonded loop compared to the tighter 3_{10} helix, and on average, 3.6 amino acids are involved in one ring of α-helix. The subscripts refer to the number of atoms (including the hydrogen) in the closed loop formed by the hydrogen bond.



https://en.wikipedia.org/wiki/Alpha_helix

Alpha Helix duplicate

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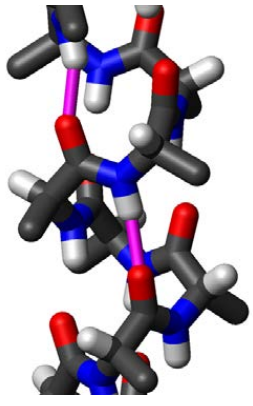

https://en.wikipedia.org/wiki/Alpha_helix

Related Glossary Terms

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Alpha Subunit

When a ligand activates a G protein-coupled receptor, it induces a conformatio
change in the receptor that allows the receptor to function as a guanine nucleot
change factor (GEF) that exchanges GDP for GTP - thus turning the GPCR "on"
GTP (or GDP) is bound to the Gα subunit in the traditional view of heterotrime
GPCR activation. This exchange triggers the dissociation of the Gα subunit (wh
bound to GTP) from the Gβγ dimer and the receptor as a whole. However, mod
which suggest molecular rearrangement, reorganization, and pre-complexing o
tor molecules are beginning to be accepted.

Both Gα-GTP and Gβγ can then activate different signaling cascades (or second
senger pathways) and effector proteins, while the receptor is able to activate th
protein.

Related Glossary Terms

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Alpha-1-Anti-trypsin

α-1 αntitrypsin (A1AT) is a protease inhibitor belonging to the serpin superfamily. It is generally known as serum trypsin inhibitor. α 1-antitrypsin is also referred to as α-1 proteinase inhibitor (A1PI) because it inhibits a wide variety of proteases. It protects tissues from enzymes of inflammatory cells, especially neutrophil elastase, and has a reference range in blood of 1.5 - 3.5 gram/liter (in US the reference range is generally expressed as mg/dL or micromoles), but the concentration can rise manyfold upon acute inflammation. In its absence (such as in α 1-antitrypsin deficiency), neutrophil elastase is free to break down elastin, which contributes to the elasticity of the lungs, resulting in respiratory complications such as emphysema, or COPD (chronic obstructive pulmonary disease) in adults and cirrhosis in adults or children.

Disorders of this protein include α 1-antitrypsin deficiency, an autosomal codominant hereditary disorder in which a deficiency of α 1-antitrypsin leads to a chronic uninhibited tissue breakdown. This causes the degradation especially of lung tissue, and eventually leads to characteristic manifestations of pulmonary emphysema. Evidence has shown that cigarette smoke can lead to oxidation of methionine 358 of α1-antitrypsin (382 in the pre-processed form containing the 24 amino acid signal peptide), a residue essential for binding elastase. This is thought to be one of the primary mechanisms by which cigarette smoking (or second-hand smoke) can lead to emphysema. Because A1AT is expressed in the liver, certain mutations in the gene encoding the protein can cause misfolding and impaired secretion, which can lead to liver cirrhosis.

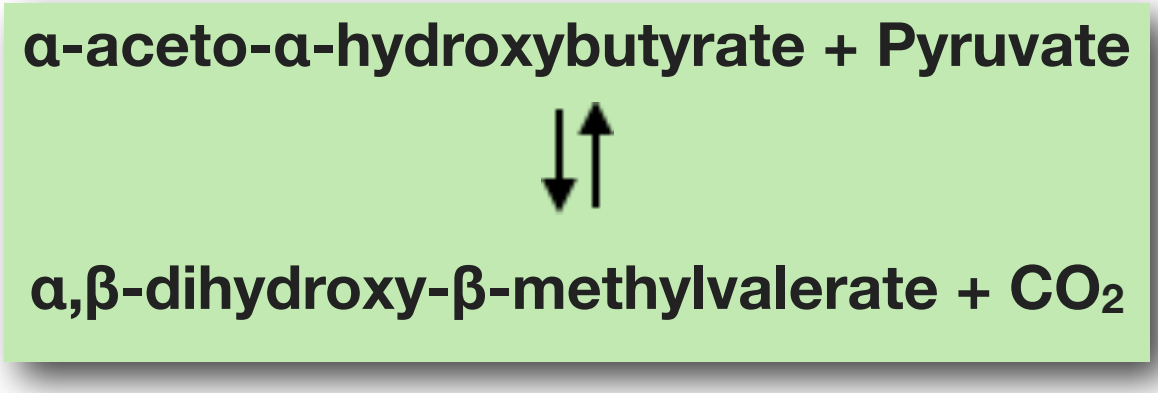
An extremely rare form of Pi, termed PiPittsburgh, functions as an antithrombin (a related serpin), due to a mutation (Met358Arg). One person with this mutation has been reported to have died of a lethal bleeding diathesis.

https://en.wikipedia.org/wiki/Alpha-1_antitrypsin

Related Glossary Terms

Alpha-aceto-α-hydroxybutyrate

α-aceto-α-hydroxybutyrate is an intermediate in the biosynthesis of isoleu



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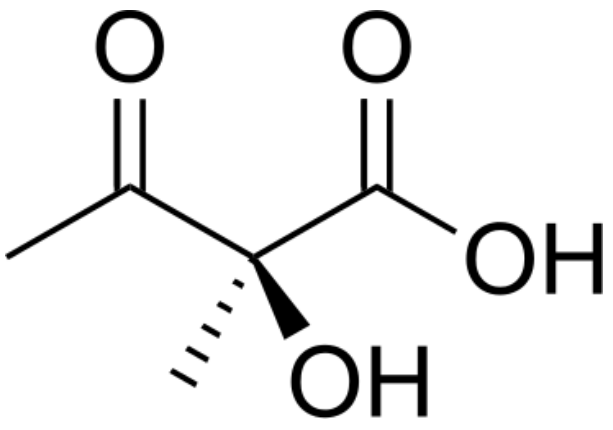
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 9 - Point by Point: Metabolism

Alpha-acetolactate

α-αcetolactic acid (α-acetolactate) is a precursor in the biosynthesis of the branc
chain amino acids valine and leucine. α-αcetolactic acid is produced from two m
cules of pyruvic acid by acetolactate synthase. α-αcetolactic acid can also be deca
lated by α-acetolactate decarboxylase to produce acetoin.



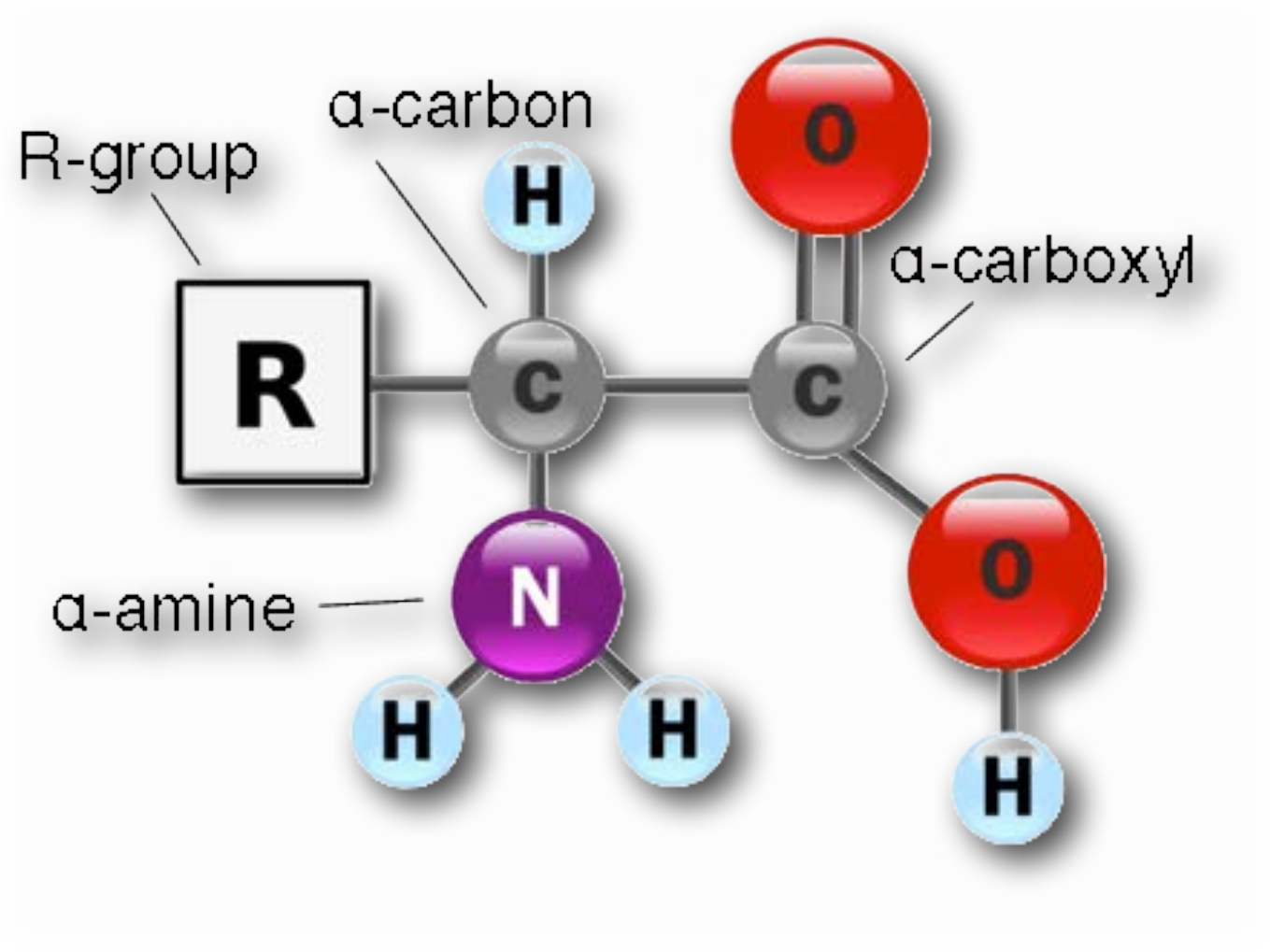
https://en.wikipedia.org/wiki/Acetolactic_acid

Related Glossary Terms

Drag related terms here

Alpha-amine

The α carbon of every amino acid has four groups attached to it - a hydroger
carboxyl group, an α-amine group, and an R-group.



Related Glossary Terms

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Alpha-carboxyl

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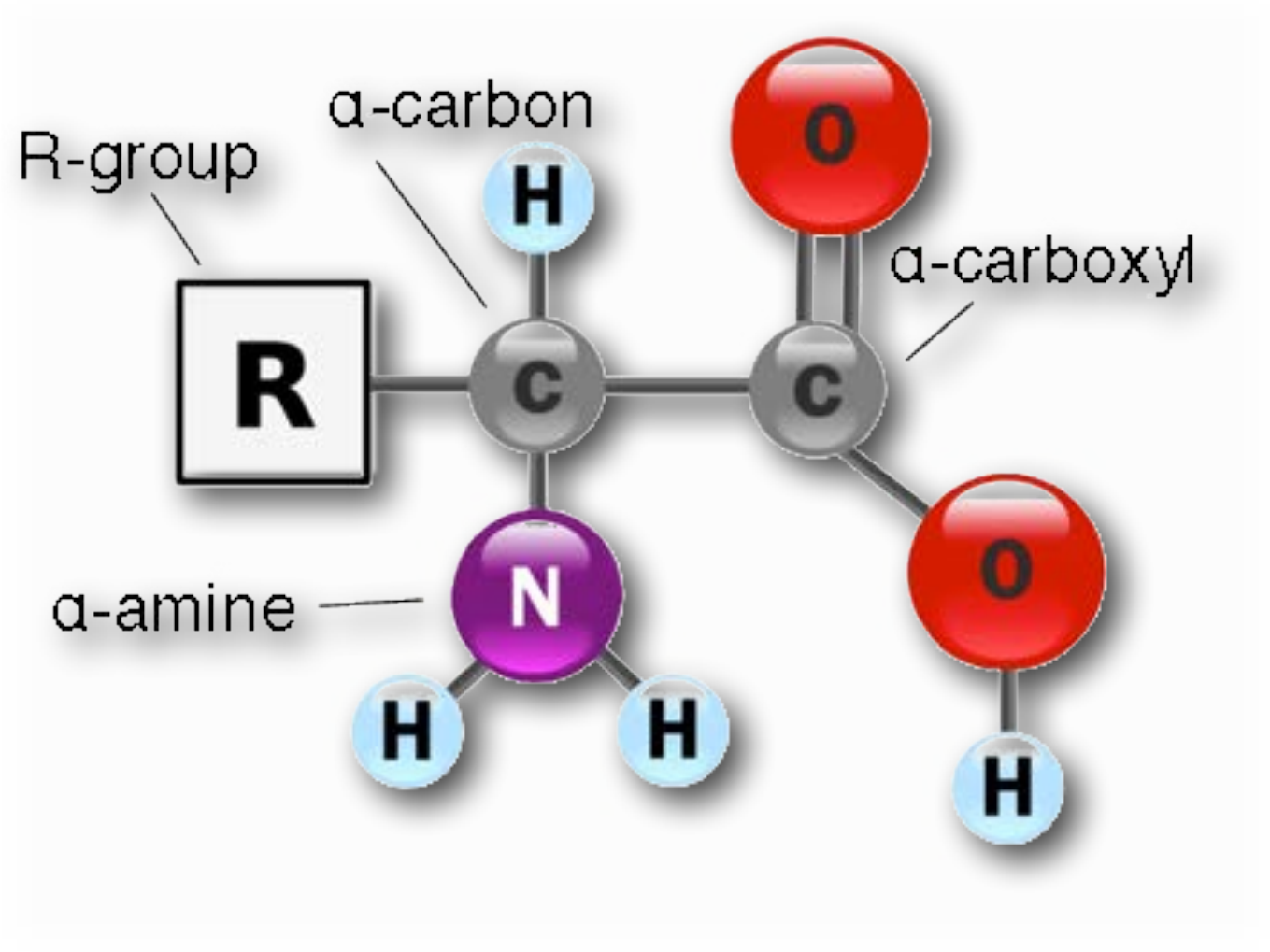
carboxyl group, an α-amine group, and an R-group.



Related Glossary Terms

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Alpha-helix Duplicate

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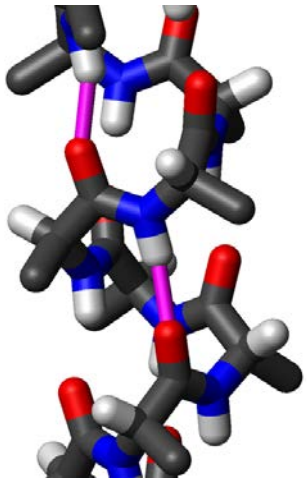
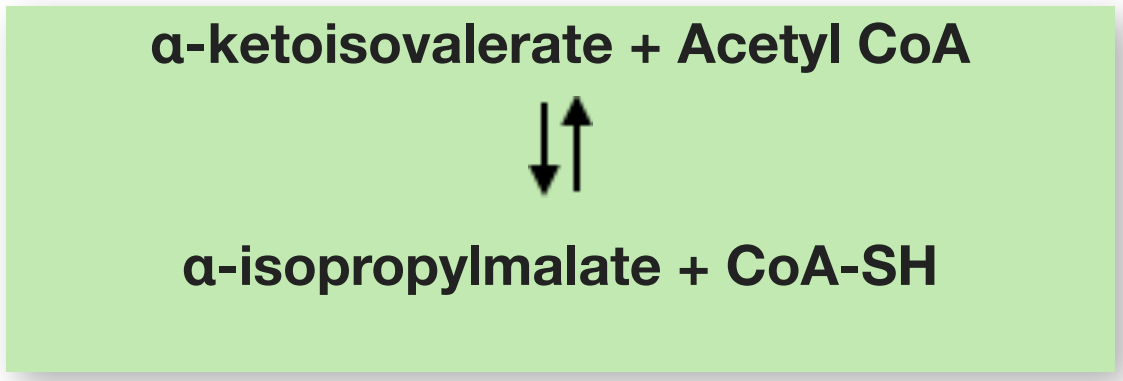
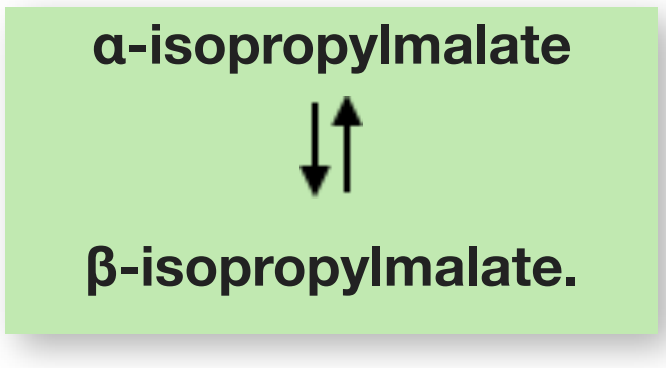


https://en.wikipedia.org/wiki/Alpha_helix

Alpha-isopropylmalate

α-isopropylmalate is an intermediate in the biosynthesis of leucine.





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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Alpha-keto-β-methylvalerate

Branched chain aminotransferases in mammals catalyze the first step in branched-chain amino acid metabolism, a reversible transamination followed by the oxidative decarboxylation of the transamination products α-ketoisocaproate, α-keto-β-methylvalerate, and α-ketoisovalerate to isovaleryl-CoA, 3-methylbutyryl-CoA, and isobutyryl-CoA, respectively. This reaction regulates metabolism of amino acids and is a crucial step in nitrogen shuttling throughout the whole body.

https://en.wikipedia.org/wiki/Branched_chain_aminotransferase

The mechanism of threonine ammonia-lyase is analogous to other deaminating PLP enzymes in its use of Schiff base intermediates. Initially, the amine group of threonine attacks the lysine/PLP Schiff base, displacing lysine. After deprotonation of the amino acid alpha carbon and subsequent dehydration (hence the common name threonine dehydratase), a new Schiff base is formed. This Schiff base is replaced by lysine attack, reforming the catalytically active PLP and releasing an initial alkene-containing product. This product tautomerizes, and after hydrolysis of the Schiff base, the final products are generated. After the final α-ketobutyrate product is generated, isoleucine is synthesized by progressing through the intermediates α-acetohydroxybutyrate to α-β-dihydroxy-β-methylvalerate, then to α-keto-β-methylvalerate.

https://en.wikipedia.org/wiki/Threonine_ammonia-lyase

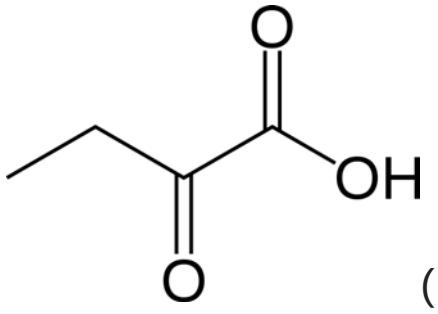
Related Glossary Terms

Drag related terms here

Alpha-ketobutyrate

α-ketobutyric acid is a product of the lysis of cystathionine. It is also one of the degradation products of threonine, produced by the catabolism of the amino acid by threonine dehydratase. It is also produced by the degradation of homocysteine and the metabolism of methionine.

α-ketobutyric acid is transported into the mitochondrial matrix, where it is converted to propionyl-CoA by branched-chain α-keto acid dehydrogenase complex. Further mitochondrial reactions produce succinyl CoA.



(note - this is an image of the acid)

https://en.wikipedia.org/wiki/Alpha-Ketobutyric_acid

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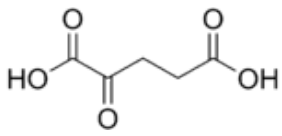
Alpha-ketoglutarate

α-κetoglutaric acid is one of two ketone derivatives of glutaric acid.
Its anion, α-ketoglutarate (α-KG, also called oxo-glutarate) is an important biological compound. It is the keto acid produced by deamination of glutamate, and is an intermediate in the citric acid cycle.

α-ketoglutarate is a key intermediate in the citric acid cycle, coming after isocitrate and before succinyl CoA. Anaplerotic reactions can replenish the cycle at this juncture by synthesizing α-ketoglutarate from transamination of glutamate, or through action of glutamate dehydrogenase on glutamate.



(note - this is an image of the acid)

https://en.wikipedia.org/wiki/Alpha-Ketoglutaric_acid

Related Glossary Terms

Drag related terms here

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Alpha-ketoglutarate Dehydrogenase

The oxoglutarate dehydrogenase complex (OGDC) or α-ketoglutarate dehydr
complex is an enzyme complex, most commonly known for its role in the citri
cle.

Oxoglutarate dehydrogenase is a key control point in the citric acid cycle. It is
by its products, succinyl CoA and NADH. A high energy charge in the cell will
inhibitive. ADP and calcium ions are allosteric activators of the enzyme.

By controlling the amount of available reducing equivalents generated by the
cycle, oxoglutarate dehydrogenase has a downstream regulatory effect on oxi
phosphorylation and ATP production.

https://en.wikipedia.org/wiki/Oxoglutarate_dehydrogenase_complex

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Related Glossary Terms

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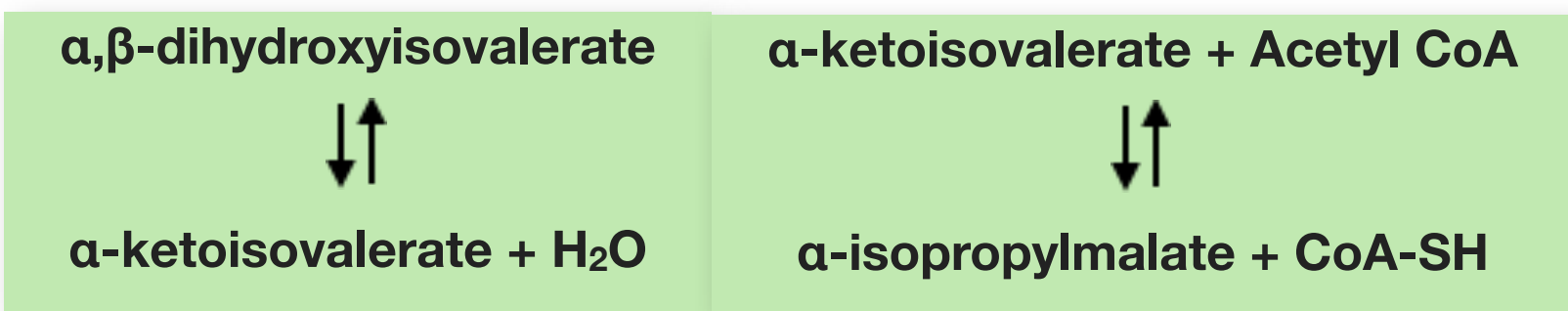
Alpha-ketoisovalerate

α-ketoisovaleric acid is a metabolite of valine. This molecule is a branch point for synthesis of leucine and valine. Addition of an acetyl group from acetyl-CoA yields α-isopropylmalate (catalyzed by α-isopropylmalate synthase).



https://en.wikipedia.org/wiki/Alpha-Ketoisovaleric_acid

Related Glossary Terms

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Alpha-oxidation

α-oxidation of phytanic acid is believed to take place entirely within peroxisome

1 Phytanic acid is first attached to CoA to form phytanoyl-CoA.
2 Phytanoyl-CoA is oxidized by phytanoyl-CoA dioxygenase, in a process using F
and O_2, to yield 2-hydroxyphytanoyl-CoA.
3 2-hydroxyphytanoyl-CoA is cleaved by 2-hydroxyphytanoyl-CoA lyase in a TP
dependent reaction to form pristanal and formyl-CoA (in turn later broken dow
formate and eventually CO_2).
4 Pristanal is oxidized by aldehyde dehydrogenase to form pristanic acid (which
then undergo β-oxidation).

(Propionyl-CoA is released as a result of β oxidation when the β carbon is substi

https://en.wikipedia.org/wiki/Alpha_oxidation

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Alpha-synuclein

α-synuclein is a protein that is abundant in the human brain. Smaller amou
found in the heart, muscles, and other tissues. In the brain, α-synuclein is f
mainly at the tips of nerve cells (neurons) in specialized structures called pr
terminals. Within these structures, α-synuclein interacts with phospholipic
teins. Presynaptic terminals release chemical messengers, called neurotran
from compartments known as synaptic vesicles. The release of neurotransm
lays signals between neurons and is critical for normal brain function.

https://en.wikipedia.org/wiki/Alpha-synuclein

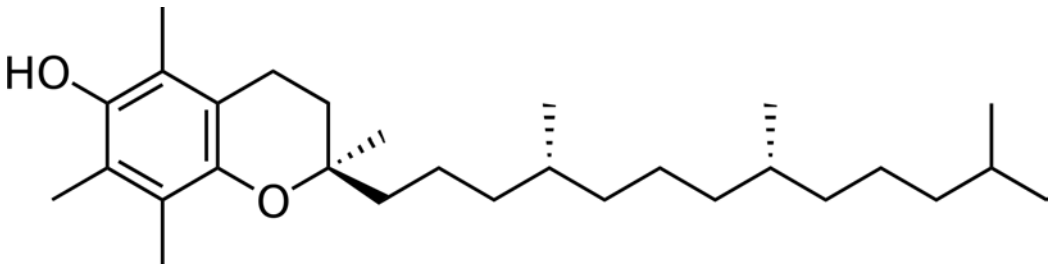
Related Glossary Terms

Drag related terms here

Alpha-tocopherol

α-tocopherol is a type of tocopherol or vitamin E. α-tocopherol is a form of vitamin E that is preferentially absorbed and accumulated in humans.

There are three stereocenters in α-tocopherol, so this is a chiral molecule. The eight stereoisomers of α-tocopherol differ in the arrangement of groups around these stereocenters. In the image of RRR-α-tocopherol, all three stereocenters are in the R form. However, if the middle of the three stereocenters were changed (so the hydrogen was now pointing down and the methyl group pointing up), this would become the structure of RSR-α-tocopherol. RSR-α-tocopherol and RRR-α-tocopherol are diastereomers of each other. These stereoisomers can also be named in an alternative older nomenclature, where the stereocenters are either in the d or l form.



https://en.wikipedia.org/wiki/Alpha-Tocopherol

Related Glossary Terms

Drag related terms here

Alpha-tubulin

Tubulin in molecular biology can refer either to the tubulin protein superfamily of globular proteins, or one of the member proteins of that superfamily. α- and β-tubulins polymerize into microtubules, a major component of the eukaryotic cytoskeleton. Microtubules function in many essential cellular processes, including mitosis. Tubulin-binding drugs kill cancerous cells by inhibiting microtubule dynamics, which are required for DNA segregation and therefore cell division.

α- and β-tubulin polymerize into dynamic microtubules. In eukaryotes, microtubules are one of the major components of the cytoskeleton, and function in many processes, including structural support, intracellular transport, and DNA segregation.

Microtubules are assembled from dimers of α- and β-tubulin. These subunits are slightly acidic with an isoelectric point between 5.2 and 5.8. Each has a molecular weight of approximately 50,000 Daltons.

To form microtubules, the dimers of α- and β-tubulin bind to GTP and assemble onto the (+) ends of microtubules while in the GTP-bound state. The β-tubulin subunit is exposed on the plus end of the microtubule while the α-tubulin subunit is exposed on the minus end. After the dimer is incorporated into the microtubule, the molecule of GTP bound to the β-tubulin subunit eventually hydrolyzes into GDP through inter-dimer contacts along the microtubule protofilament.

Whether the β-tubulin member of the tubulin dimer is bound to GTP or GDP influences the stability of the dimer in the microtubule. Dimers bound to GTP tend to assemble into microtubules, while dimers bound to GDP tend to fall apart. Thus, this GTP cycle is essential for the dynamic instability of the microtubule.

https://en.wikipedia.org/wiki/Tubulin

Related Glossary Terms

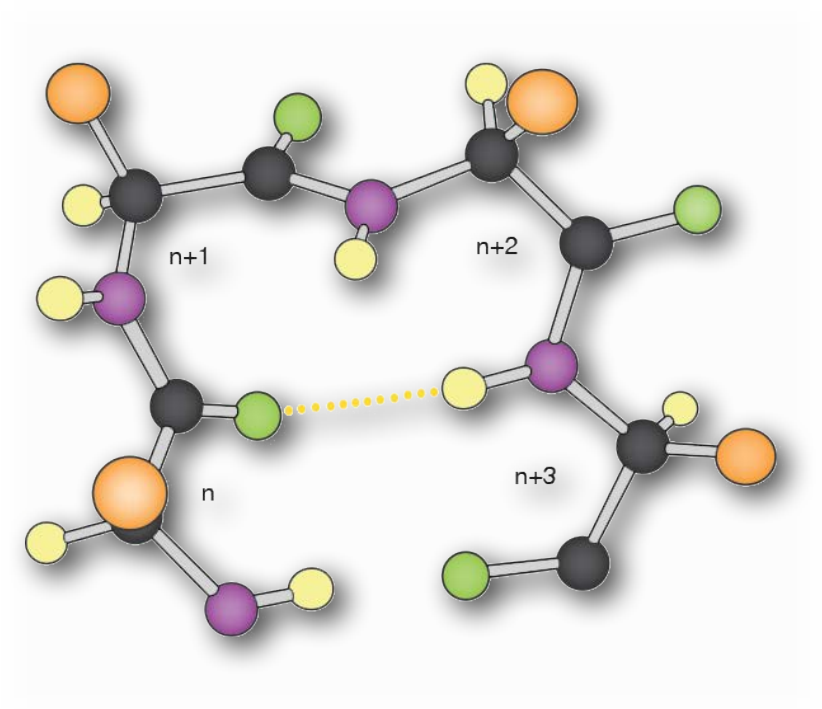
Drag related terms here

Alpha-turns

Turns are elements of secondary structure in proteins where the polypeptide chain reverses its overall direction and they are classified according to the separation between the two end residues.

In an α-turn the end residues are separated by four peptide bonds
(i --> i +/- 4).

Pictured below is a β-turn



https://en.wikipedia.org/wiki/Turn_(biochemistry)

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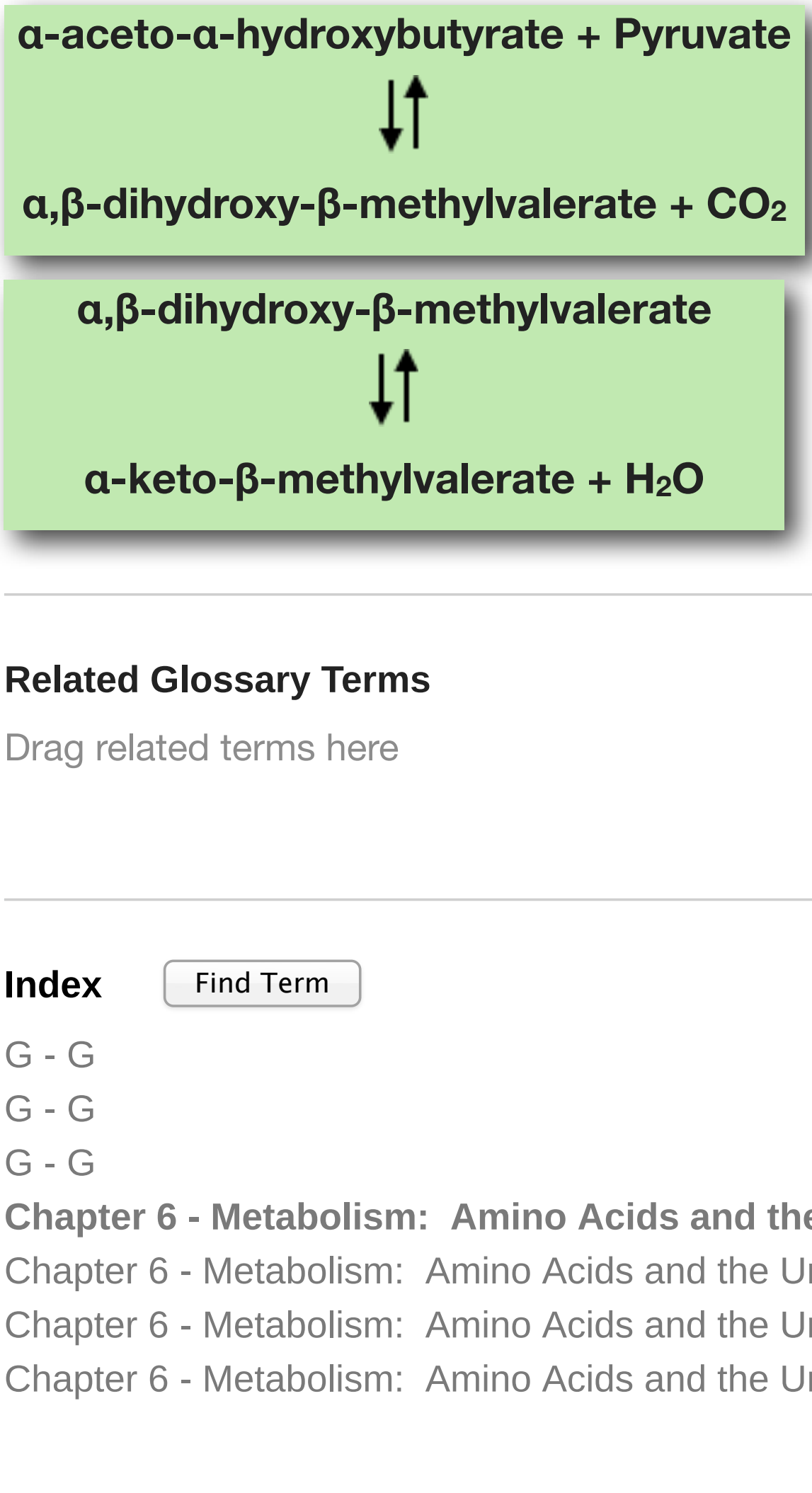
Chapter 2 - Structure & Function: Proteins I

Alpha,beta-dihydroxy-β-methylvalerate

α,β-dihydroxy-β-methylvalerate is an intermediate in metabolism of iso



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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Alpha,beta-dihydroxyisovalerate

Valine is produced by a four-enzyme pathway. It begins with the reaction of two pyruvate molecules catalyzed by acetohydroxy acid synthase yielding α-acetolactate. Step two is the $NADPH^+ + H^+$ - dependent reduction of α-acetolactate and migration of the methane groups to produce α, β-dihydroxyisovalerate. This is catalyzed by acetohydroxy isomeroreductase. The third reaction is the dehydration reaction of α, β-dihydroxyisovalerate catalyzed by dihydroxy acid dehydrase resulting in α-ketoisovalerate. Finally, a transamination catalyzed either by an alanine-valine transaminase or a glutamate-valine transaminase results in valine.

3-hydroxy-3-methyl-2-oxobutanoate + NADP(P)H

α,β-dihydroxyisovalerate + **$NAD(P)^+$**

α,β-dihydroxyisovalerate

α-ketoisovalerate + H_2O

https://en.wikipedia.org/wiki/Amino_acid_synthesis

Related Glossary Terms

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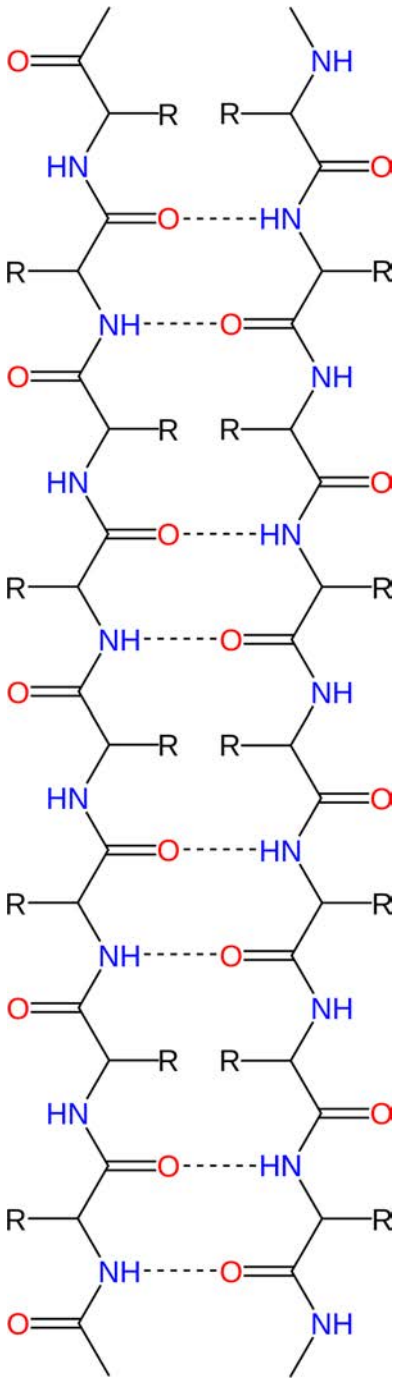
Beta Strands

The supersecondary protein structure known as β sheets consist of β strands connected laterally by at least two or three backbone hydrogen bonds, forming a generally twisted, pleated sheet. A β-strand is a stretch of polypeptide chain typically 3 to 10 amino acids long with backbone in an extended conformation. Shown below are two β-strands interacting as part of a β-sheet.



https://en.wikipedia.org/wiki/Beta_sheet

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Beta-adrenergic Receptor

The adrenergic receptors (or adrenoceptors) are a class of G protein-coupled receptors that are targets of the catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline).

Many cells possess these receptors, and the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system. The sympathetic nervous system is responsible for the fight-or-flight response, which includes widening the pupils of the eye, mobilizing energy, and diverting blood flow from non-essential organs to skeletal muscle.

There are two main groups of adrenergic receptors, α and β, with several subtypes.
• α receptors have the subtypes α_1 (a Gq coupled receptor) and α_2 (a G_i coupled receptor). Phenylephrine is a selective agonist of the α receptor.
• β receptors have the subtypes β_1, β_2 and β_3. All three are linked to G_s proteins (although β_2 also couples to G_i), which in turn are linked to adenylate cyclase.

Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA), which mediates some of the intracellular events following hormone binding. Isoprenaline is a non-selective agonist.

https://en.wikipedia.org/wiki/Adrenergic_receptor

Related Glossary Terms

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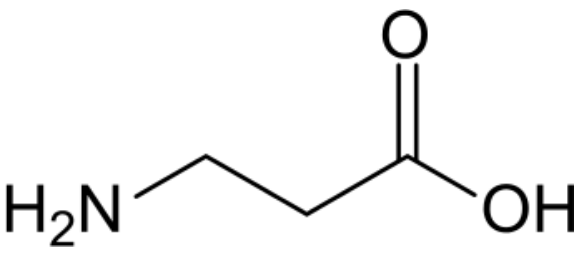
Beta-alanine

β-alanine (or beta-alanine) is a naturally occurring β amino acid, which is an amino acid in which the amino group is at the β-position from the carboxylate group. The IUPAC name for β-alanine is 3-aminopropanoic acid. Unlike its counterpart α-alanine, β-alanine has no stereocenter.

β-alanine is not used in the biosynthesis of any major proteins or enzymes. It is formed *in vivo* by the degradation of dihydrouracil and carnosine. It is a component of the naturally occurring peptides carnosine and anserine and also of pantothenic acid (vitamin B5), which itself is a component of coenzyme A. Under normal conditions, β-alanine is metabolized into acetic acid.

β-alanine is the rate-limiting precursor of carnosine, which is to say carnosine levels are limited by the amount of available β-alanine, not histidine. Supplementation with β-alanine has been shown to increase the concentration of carnosine in muscles, decrease fatigue in athletes and increase total muscular work done. Simply supplementing with carnosine is not as effective as supplementing with β-alanine alone since carnosine, when taken orally, is broken down during digestion to its components, histidine and β-alanine. Hence, by weight, only about 40% of the dose is available as β-alanine.



https://en.wikipedia.org/wiki/Beta-Alanine

Related Glossary Terms

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Beta-aminoisobutyrate

3-aminoisobutyric acid (or β-aminoisobutyric acid, BAIBA) is a product for
catabolism of thymine.

During exercise, the increase of PGC-1α protein triggers the secretion of BA
exercizing muscles to blood (concentration 2 to 3 µM in human serum). Wh
reaches the white fat tissue, it activates the expression of thermogenic gene
PPARα receptors, resulting in a browning of white fat cells. One of the cons
of the BAIBA activity is the increase of the background metabolism of the B
cells.

It has recently been postulated to play a role in cell metabolism, how body l
and regulates insulin, triglycerides, and total cholesterol.

https://en.wikipedia.org/wiki/3-Aminoisobutyric_acid

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Beta-aspartate Semialdehyde Dehydrogenase

Aspartate-semialdehyde dehydrogenase is an enzyme that is very important in the bi synthesis of amino acids in prokaryotes, fungi, and some higher plants. It forms an early branch point in the metabolic pathway forming lysine, methionine, leucine and isoleucine from aspartate. This pathway also produces diaminopimelate which plays an essential role in bacterial cell wall formation. There is particular interest in ASAD as disabling this enzyme proves fatal to the organism giving rise to the possibility of new class of antibiotics, fungicides, and herbicides aimed at inhibiting it.

The enzyme catalyzes the reversible chemical reaction:

L-aspartate 4-semialdehyde + Phosphate + $NADP^+$ <---> L-4-aspartyl phosphate + NADPH + H^+

This enzyme participates in glycine, serine and threonine metabolism and lysine bio- synthesis.

https://en.wikipedia.org/wiki/Aspartate-semialdehyde_dehydrogenase

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Related Glossary Terms

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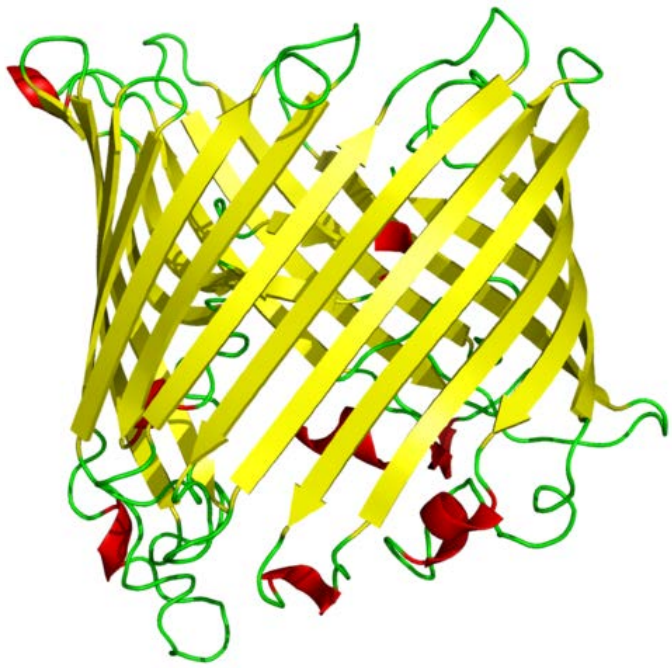
Beta-barrel

A β barrel is a large β-sheet that twists and coils to form a closed structure in which the first strand is hydrogen bonded to the last. β-strands in β-barrels are typically arranged in an antiparallel fashion. Barrel structures are commonly found in porins and other proteins that span cell membranes and in proteins that bind hydrophobic ligands in the barrel center, as in lipocalins. Porin-like barrel structures are encoded by as many as 2–3% of the genes in Gram-negative bacteria.



https://en.wikipedia.org/wiki/Beta_barrel

Related Glossary Terms

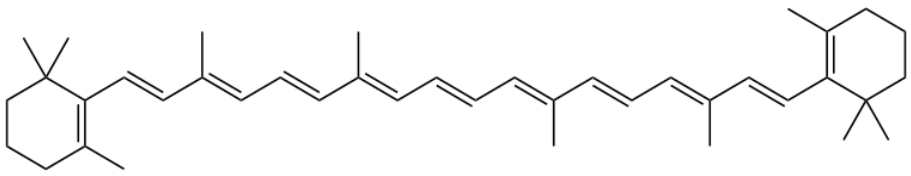
Drag related terms here

Beta-carotene

β-Carotene is an organic, strongly colored red-orange pigment abundant in plants and fruits. It is a member of the carotenes, which are terpenoids (isoprenoids), synthesized biochemically from eight isoprene units and thus having 40 carbons. Among the carotenes, β-carotene is distinguished by having β-rings at both ends of the molecule. β-Carotene is biosynthesized from geranylgeranyl pyrophosphate.

Plant carotenoids are the primary dietary source of provitamin A worldwide, with β-carotene as the most well-known provitamin A carotenoid. Others include α-carotene and β-cryptoxanthin. Carotenoid absorption is restricted to the duodenum of the small intestine and dependent on Class B scavenger receptor (SR-B1) membrane protein, which are also responsible for the absorption of vitamin E (α-tocopherol). One molecule of β-carotene can be cleaved by the intestinal enzyme β,β-carotene 15,15'-monooxygenase into two molecules of vitamin A.

Absorption efficiency is estimated to be between 9–22%. The absorption and conversion of carotenoids may depend on the form that the β-carotene is in (e.g., cooked vs. raw vegetables, or in a supplement), the intake of fats and oils at the same time, and the current stores of vitamin A and β-carotene in the body.



https://en.wikipedia.org/wiki/Beta-Carotene

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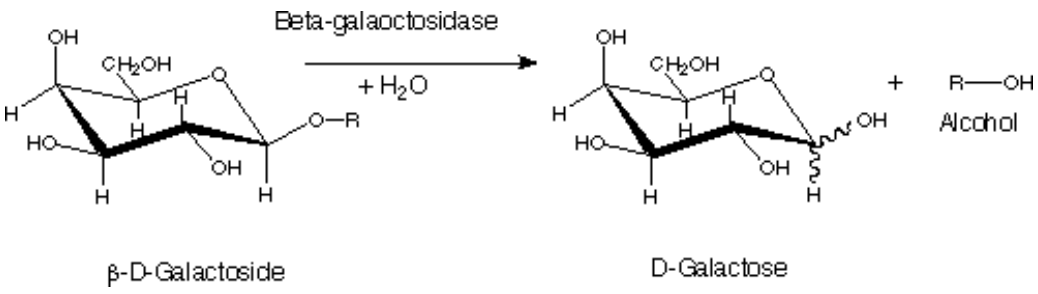
Beta-galactosidase

β-galactosidase, also called β-gal or β-gal, is a glycoside hydrolase enzyme that catalyzes the hydrolysis of β-galactosides into monosaccharides through the breaking of a glycosidic bond. β-galactosides include carbohydrates containing galactose where the glycosidic bond lies above the galactose molecule. Substrates of different β-galactosidases include ganglioside GM_1, lactosylceramides, lactose, and various glycoproteins.

The β-galactosidase assay is used frequently in genetics, molecular biology, and other life sciences. An active enzyme may be detected using X-gal, which forms an intense blue product after cleavage by β-galactosidase, and is easy to identify and quantify. It is used, for example, in blue white screen. Its production may be induced by a non-hydrolyzable analog of allolactose, IPTG, which binds and releases the lac repressor from the lac operator, thereby allowing the initiation of transcription to proceed.

It is commonly used in molecular biology as a reporter marker to monitor gene expression. It also exhibits a phenomenon called α-complementation which forms the basis for the blue/white screening of recombinant clones. This enzyme can be split in two peptides, $LacZ_\alpha$ and $LacZ_\Omega$, neither of which is active by itself but when both are present together, spontaneously reassemble into a functional enzyme. This property is exploited in many cloning vectors where the presence of the $LacZ_\alpha$ gene in a plasmid can complement in trans another mutant gene encoding the $LacZ_\Omega$ in specific laboratory strains of *E. coli*. However, when DNA fragments are inserted in the vector, the production of $LacZ_\alpha$ is disrupted, the cells therefore show no β-galactosidase activity. The presence or absence of an active β-galactosidase may be detected by X-gal, which produces a characteristic blue dye when cleaved by β-galactosidase, thereby providing an easy means of distinguishing the presence or absence of cloned product in a plasmid.



https://en.wikipedia.org/wiki/Beta-galactosidase

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Chapter 9 - Point by Point: Techniques

Beta-hairpin

The β hairpin (sometimes also called β-ribbon or β-β unit) is a simple protein structural motif involving two β strands that look like a hairpin. The motif consists of two strands that are adjacent in primary structure, oriented in an antiparallel direction (the N-terminus of one sheet is adjacent to the C-terminus of the next), and linked by a short loop of two to five amino acids. β hairpins can occur in isolation or as part of a series of hydrogen bonded strands that collectively comprise a β sheet.

https://en.wikipedia.org/wiki/Beta_hairpin

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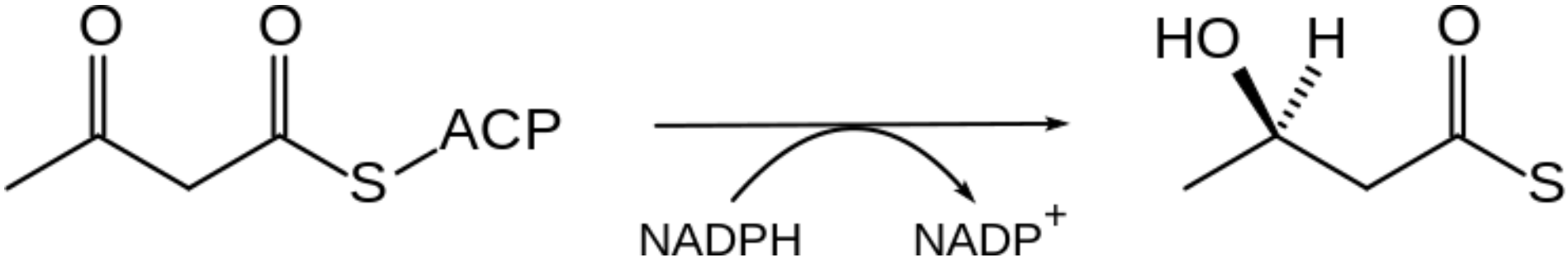
Beta-hydroxyacl-ACP Reductase

3-oxoacyl-[acyl-carrier-protein] reductase is an enzyme that catalyzes the chem
action:

(3R)-3-hydroxyacyl-[acyl-carrier-protein] + $NADP^+$ <---> 3-oxoacyl-[acyl-carr
protein] + NADPH + H^+



This enzyme participates in fatty acid biosynthesis and polyunsaturated fatty a
synthesis.

https://en.wikipedia.org/wiki/3-oxoacyl-(acyl-carrier-protein)_reductase

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Related Glossary Terms

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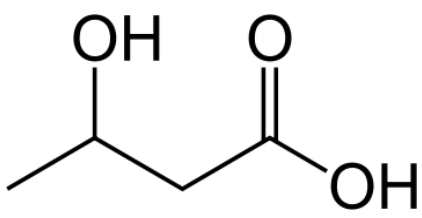
Beta-Hydroxybutyrate

β-Hydroxybutyric acid (also known as β-hydroxybutyrate, 3-hydroxybutyric acid or 3-hydroxybutyrate) is an organic compound with the formula $CH_3CH(OH)CH_2CO_2H$. It is a β hydroxy acid and a keto acid. It is a chiral compound having two enantiomers, D-3-hydroxybutyric acid and L-3-hydroxybutyric acid. Its oxidized and polymeric derivatives occur widely in nature.

In humans, β-hydroxybutyrate is synthesized in the liver from acetoacetate, the first ketone produced in the fasting state. The biosynthesis is catalyzed by the enzyme β-hydroxybutyrate dehydrogenase.

Although not a ketone itself, the concentration of β-hydroxybutyrate, like that of other ketone bodies, is raised in ketosis. This elevated β-hydroxybutyrate level seen in ketosis is naturally expected due to the fact that, as mentioned above, it is formed from acetoacetate. The compound can be used as an energy source by the brain when blood glucose is low. Diabetic patients can have their keto acid levels tested via urine or blood to indicate diabetic ketoacidosis. In alcoholic ketoacidosis, this ketone body is produced in greatest concentration. Both types of ketoacidosis result in an increase β-hydroxybutyrate to oxaloacetate ratio, resulting in TCA cycle stalling and shifting of glucose towards ketone body production.



https://en.wikipedia.org/wiki/Beta-Hydroxybutyric_acid

Related Glossary Terms

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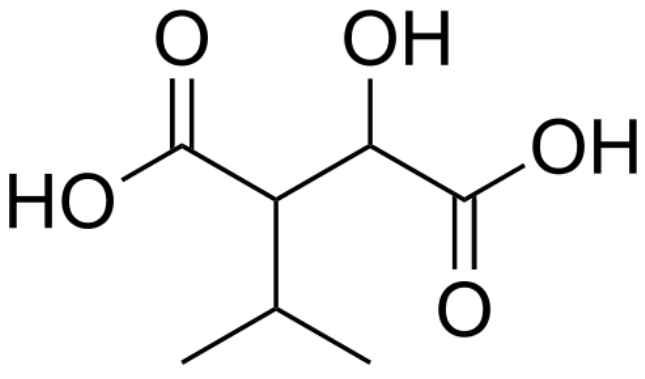
Beta-isopropylmalate

Isopropylmalic acid (isopropylmalate) is an intermediate in the biosynthesis of leuc
synthesized from oxoisovalerate by 2-isopropylmalate synthase and converted into
isopropyl-3-oxosuccinate by 3-isopropylmalate dehydrogenase.



https://en.wikipedia.org/wiki/Isopropylmalic_acid

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Beta-ketoacyl-ACP Synthase

β-ketoacyl-ACP synthase is an enzyme involved in fatty acid synthesis. It ca
formation of acetoacetyl ACP.

β-ketoacyl-ACP synthase is a highly conserved enzyme that is found in almo
on earth as a domain in fatty acid synthase (FAS).

β-ketoacyl-ACP synthase III, perhaps the most well known of this family of
catalyzes a Claisen condensation between acetyl CoA and malonyl ACP.

https://en.wikipedia.org/wiki/Beta-ketoacyl-ACP_synthase

Related Glossary Terms

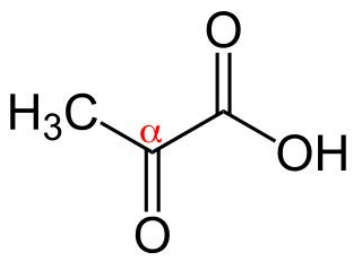
Drag related terms here

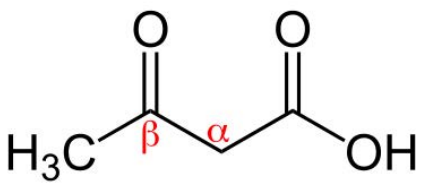
Beta-ketobutyrate

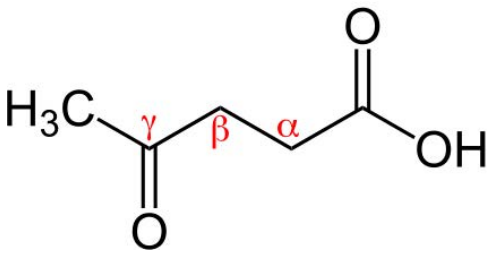
Keto acids or ketoacids (also called oxo acids or oxoacids) are organic compounds that contain a carboxylic acid group and a ketone group. The α-keto acids are especially important in biology as they are involved in the citric acid cycle and in glycolysis.

β-keto acids, or 3-oxoacids, such as acetoacetic acid, have the ketone group at the second carbon from the carboxylic acid. They can be formed by the Claisen condensation.

Three different keto acids are shown below.



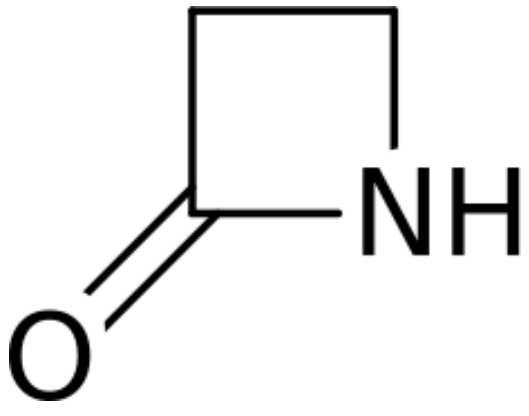




https://en.wikipedia.org/wiki/Keto_acid

Beta-lactam

A β-lactam (β-lactam) ring is a four-membered lactam. (A lactam is a cyclic
is named as such because the nitrogen atom is attached to the β-carbon ato
to the carbonyl. The simplest β-lactam possible is 2-azetidinone (shown bel



https://en.wikipedia.org/wiki/B-Lactam

Related Glossary Terms

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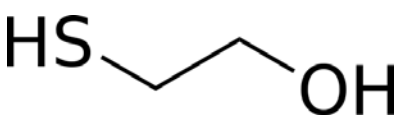
Beta-mercaptoethanol

2-µercaptoethanol (also β-mercaptoethanol, BME, 2BME, 2-ME or β-met) is the
cal compound with the formula $HOCH_2CH_2SH$.

ME or βME, as it is commonly abbreviated, is used to reduce disulfide bonds and
act as a biological antioxidant by scavenging hydroxyl radicals (amongst others).
widely used because the hydroxyl group confers solubility in water and lowers th
tility.

Due to its diminished vapor pressure, its odor, while unpleasant, is less objectior
than related thiols.



https://en.wikipedia.org/wiki/2-Mercaptoethanol

Related Glossary Terms

Drag related terms here

Beta-oxidation

In metabolism, β-oxidation is the catabolic process by which fatty acid molecules are broken down in the cytosol in prokaryotes and in the mitochondria in eukaryotes to generate acetyl-CoA, which enters the citric acid cycle, and NADH and $FADH_2$, which are co-enzymes used in the electron transport chain. It is named as such because the β carbon of the fatty acid undergoes oxidation to a carbonyl group. Various mechanisms have evolved to handle the large variety of fatty acids.

The process of β-oxidation consists of 4 steps.
1 - A long-chain fatty acid is dehydrogenated to create a *trans* double bond between C_2 and C_3. This is catalyzed by acyl CoA dehydrogenase to produce *trans*-Δ2-enoyl CoA. It uses FAD as an electron acceptor and it is reduced to $FADH_2$.
2 - *Trans*-Δ2-enoyl CoA is hydrated at the double bond to produce L-3-hydroxyacyl CoA by enoyl-CoA hydratase.
3 - L-3-hydroxyacyl CoA is dehydrogenated again to create 3-ketoacyl CoA by 3-hydroxyacyl CoA dehydrogenase. This enzyme uses NAD^+ as an electron acceptor.
4 - Thiolysis occurs between C_2 and C_3 (α and β carbons) of 3-ketoacyl CoA. Thiolase enzyme catalyzes the reaction when a new molecule of coenzyme A breaks the bond by nucleophilic attack on C_3. This releases the first two carbon units, as acetyl CoA, and a fatty acyl CoA minus two carbons. The process continues until all of the carbons in the fatty acid are turned into acetyl CoA.

Fatty acids are oxidized by most of the tissues in the body. However, some tissues such as the red blood cells (which do not contain mitochondria), and cells of the central nervous system (because fatty acids cannot cross the blood-brain barrier into the interstitial fluids that bathe these cells) do not use fatty acids for their energy requirements, but instead use carbohydrates.

Because many fatty acids are not fully saturated or do not have an even number of carbons, several different mechanisms have evolved, described below.

https://en.wikipedia.org/wiki/Beta_oxidation

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Beta-secretase

β-secretase 1 ($BACE_1$) is an enzyme that in humans is encoded by the $BACE_1$ gene. $BACE_1$ is an aspartic-acid protease important in the formation of myelin sheaths in peripheral nerve cells. The transmembrane protein contains two active site aspartate residues in its extracellular protein domain and may function as a dimer.

Generation of the 40 or 42 amino acid-long amyloid-β peptides that aggregate in the brain of Alzheimer's patients requires two sequential cleavages of the amyloid precursor protein (APP). Extracellular cleavage of APP by $BACE_1$ creates a soluble extracellular fragment and a cell membrane-bound fragment referred to as C99. Cleavage of C99 within its transmembrane domain by γ-secretase releases the intracellular domain of APP and produces amyloid-β. Since γ-secretase cleaves APP closer to the cell membrane than BACE1 does, it removes a fragment of the amyloid-β peptide. Initial cleavage of APP by γ-secretase rather than $BACE_1$ prevents eventual generation of amyloid-β.

Unlike APP and the presenilin proteins important in γ-secretase, no known mutations in the gene encoding $BACE_1$ cause early-onset, familial Alzheimer's disease, which is a rare form of the disorder. However, levels of this enzyme have been shown to be elevated in the far more common late-onset sporadic Alzheimer's. The physiological purpose of BACE's cleavage of APP and other transmembrane proteins is unknown. $BACE_2$ is a close homolog of $BACE_1$ with no reported APP cleavage *in vivo*. However a single residue mutation in APP reduces the ability of $BACE_1$ to cleave it to produce amyloid-β and reduces the risk of Alzheimers and other cognitive declines.

https://en.wikipedia.org/wiki/Beta-secretase_1

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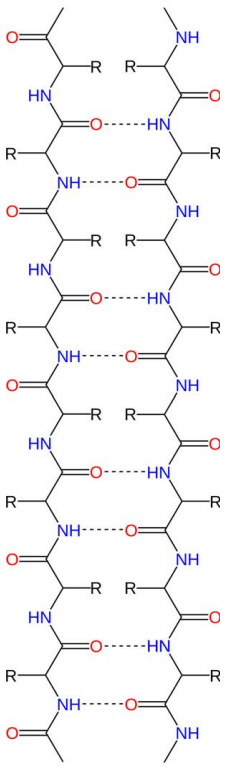
Chapter 2 - Structure & Function: Proteins I

Beta-strand

In protein structure, the β-sheet (also β-pleated sheet) is the second form of regular secondary structure in proteins. β sheets consist of β strands (also β-strand) connected laterally by at least two or three backbone hydrogen bonds, forming a generally twisted, pleated sheet. A β-strand is a stretch of polypeptide chain typically 3 to 10 amino acids long with backbone in an extended conformation. The higher-level association of β-sheets has been implicated in formation of the protein aggregates and fibrils observed in many human diseases, notably the amyloidoses such as Alzheimer's disease.

Shown below are two β-strands aligned antiparallel to form part of a β-sheet.



https://commons.wikimedia.org/wiki/File:Beta_sheet_bonding_antiparallel-color.svg

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Beta-tubulin

In molecular biology, tubulin can refer either to the tubulin protein superfamily of globular proteins, or one of the member proteins of that superfamily. α- and β-tubulins polymerize into microtubules, a major component of the eukaryotic cytoskeleton. Microtubules function in many essential cellular processes, including mitosis. Tubulin-binding drugs kill cancerous cells by inhibiting microtubule dynamics, which are required for DNA segregation and therefore cell division. Tubulin was long thought to be specific to eukaryotes. More recently, however, several prokaryotic proteins have been shown to be related to tubulin.

α- and β-tubulin polymerize into dynamic microtubules. In eukaryotes, microtubules are one of the major components of the cytoskeleton, and function in many processes, including structural support, intracellular transport, and DNA segregation.

Microtubules are assembled from dimers of α- and β-tubulin. These subunits are slightly acidic with an isoelectric point between 5.2 and 5.8. Each has a molecular weight of approximately 50,000 Daltons.

To form microtubules, the dimers of α- and β-tubulin bind to GTP and assemble onto the (+) ends of microtubules while in the GTP-bound state. The β-tubulin subunit is exposed on the plus end of the microtubule while the α-tubulin subunit is exposed on the minus end. After the dimer is incorporated into the microtubule, the molecule of GTP bound to the β-tubulin subunit eventually hydrolyzes into GDP through inter-dimer contacts along the microtubule protofilament. Whether the β-tubulin member of the tubulin dimer is bound to GTP or GDP influences the stability of the dimer in the microtubule. Dimers bound to GTP tend to assemble into microtubules, while dimers bound to GDP tend to fall apart. Thus, this GTP cycle is essential for the dynamic instability of the microtubule.

https://en.wikipedia.org/wiki/Tubulin

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Chapter 9 - Point by Point: In the Beginning

Beta-turns

A turn is an element of secondary structure in proteins where the polypeptide chain reverses its overall direction.

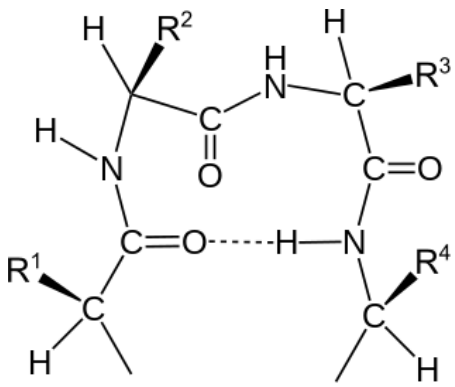
Turns are classified according to the separation between the two end residues:
In an α-turn the end residues are separated by four peptide bonds

(i --> i +/- 4).

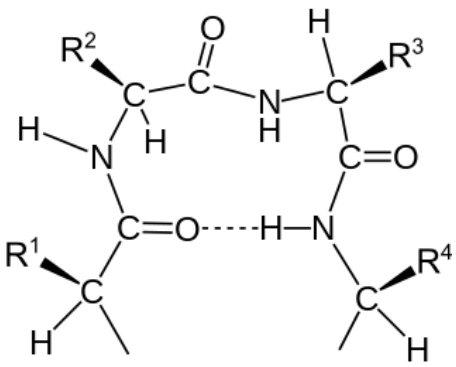
In a β-turn (the most common form), by three bonds

(i --> i +/- 3).

Shown below is a β turn



ß turn: Type I



ß turn: Type II

https://en.wikipedia.org/wiki/Turn_(biochemistry)

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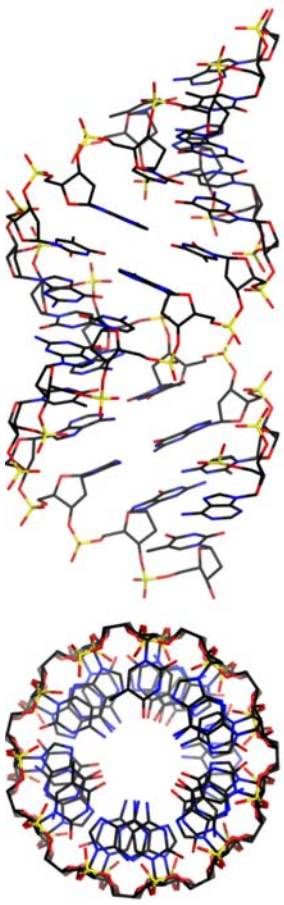
Chapter 2 - Structure & Function: Proteins I

A-form DNA

A-DNA (A-form DNA) is one of the possible double helical structures which DNA can adopt. A-DNA is thought to be one of three biologically active double helical structures along with B-DNA and Z-DNA. It is a right-handed double helix fairly similar to the more common B-DNA form, but with a shorter, more compact helical structure whose base pairs are not perpendicular to the helix-axis as in B-DNA. It was discovered by Rosalind Franklin, who also named the A and B forms. She showed that DNA is driven into the A form when under dehydrating conditions. Such conditions are commonly used in to form crystals, and many DNA crystal structures are in the A form. The same helical conformation occurs in double-stranded RNAs, and in DNA-RNA hybrid double helices.



https://en.wikipedia.org/wiki/A-DNA

https://upload.wikimedia.org/wikipedia/commons/thumb/1/14/Adna3.ogv/200px--Adna3.ogv.jpg

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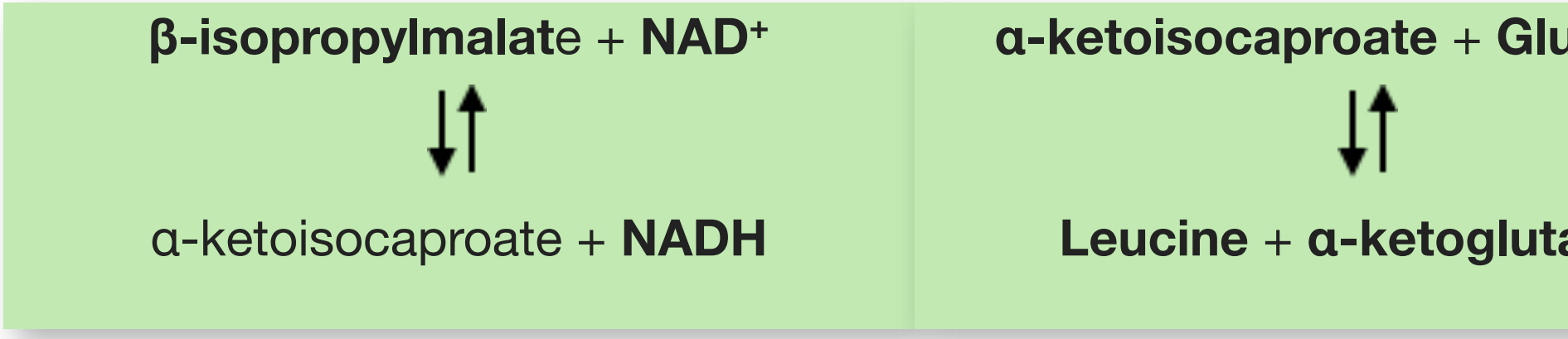
A-ketoisocaproate

α-Ketoisocaproic acid is an intermediate in the metabolism of leucine.



https://en.wikipedia.org/wiki/Alpha-Ketoisocaproic_acid

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

A-site

The A-site is the location in a ribosome where incoming charged tTRNAs enter the ribosome in preparation for incorporating the amino acid they carry into a growing polypeptide chain. After peptide bond synthesis, the tRNA in the A-site, now carrying the growing polypeptide chain, translocates to the P site so that a new charge tRNA can enter the A-site. When a STOP codon enters the A-site, release factors factilitate dissassembly of the translational complex and release of the completed polypeptide chain.

https://en.wikipedia.org/wiki/Prokaryotic_translation

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ABC Transporters

ATP-binding cassette transporters (ABC transporters) are members of a transport system superfamily that is one of the largest and is possibly one of the oldest families with representatives in all extant phyla from prokaryotes to humans.

ABC transporters often consist of multiple subunits, one or two of which are transmembrane proteins and one or two of which are membrane-associated ATPases. The ATPase subunits that utilize the energy of adenosine triphosphate (ATP) binding and hydrolysis to energize the translocation of various substrates across membranes, either for uptake or for export of the substrate.

Most but not all uptake systems also have an extracytoplasmic receptor, a solute binding protein. Some homologous ATPases function in non-transport-related processes such as translation of RNA and DNA repair. ABC transporters are considered to be with the ABC superfamily based on the sequence and organization of their ATP-binding cassette (ABC) domains, even though the integral membrane proteins may have evolved independently several times, and thus comprise different protein families. The integral membrane proteins of ABC exporters appear to have evolved independently at least three times. ABC1 exporters evolved by intragenic triplication of a 2 TMS precursor to give 6 TMS proteins. ABC2 exporters evolved by intragenic duplication of a 3 TMS precursor, and ABC3 exporters evolved from a 4 TMS precursor which duplicated either extragenicly to give two 4 TMS proteins, both required for transport function, or intragenicly to give 8 or 10 TMS proteins. The 10 TMS proteins appear to have two extra TMSs between the two 4 TMS repeat units. Similarly, it is possible that the integral membrane proteins of ABC uptake systems evolved at least 3 times independently, based on their high resolution 3-dimensional structures. ABC uptake porters take up a large variety of nutrients, biosynthetic precursors, trace metals and vitamins, while exporters transport lipids, sterols, drugs, and a large variety of primary and secondary metabolites. Some of these exporters in humans are involved in tumor resistance, cystic fibrosis and a range of other inherited human diseases. High level expression of the genes encoding some of these exporters in both prokaryotic and eukaryotic organisms (including human) result in the development of resistance to multiple drugs such as antibiotics and anti-cancer agents.

https://en.wikipedia.org/wiki/ATP-binding_cassette_transporter

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ABCA-1

ABCA-1 is a transport protein in a foam cell, ABCA-1 that transports extra c
from inside the cell to the plasma membrane where it is taken up into the H
turned to the liver or to LDLs by the reverse transport cholesterol pa

Deficiency of the ABCA-1 gene leads to Tangier disease. In this condition, I
almost totally absent because they remain empty as a result of not being ab
cholesterol from foam cells, so they are destroyed by the body.

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Chapter 2 - Structure & Function: Lipids

Acceptor Chromophore

Fluorescence resonance energy transfer (FRET - also called Förster resonan
transfer, resonance energy transfer (RET) or electronic energy transfer (EE
method for determining interactions between biomolecules. In the techniq
chromophore and an acceptor chromophore are covalently attached to mol
terest.

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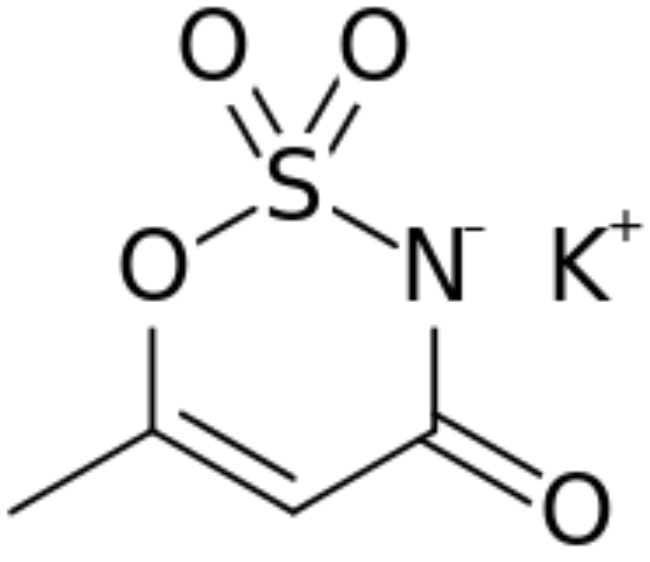
Acesulfame Potassium

Acesulfame potassium (ace-SUHL-faym), also known as acesulfame K (K is th for potassium) or Ace K, is a calorie-free sugar substitute (artificial sweetener marketed under the trade names Sunett and Sweet One.



https://en.wikipedia.org/wiki/Acesulfame_potassium

Related Glossary Terms

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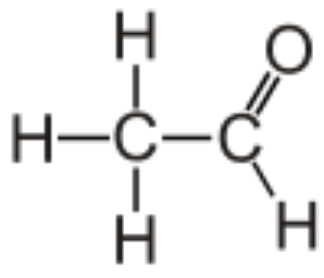
Acetaldehyde

Acetaldehyde (systematic name ethanal) is an organic chemical compound with the
mula CH_3CHO, sometimes abbreviated by chemists as MeCHO (Me = methyl). It is
one of the most important aldehydes, occurring widely in nature and being produce
on a large scale in industry.



https://en.wikipedia.org/wiki/Acetaldehyde

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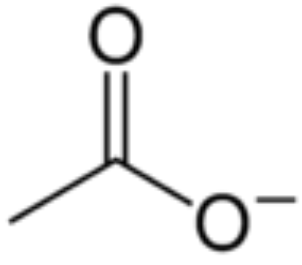
Acetate

An acetate is a salt formed by the combination of acetic acid with an alkaline, earthy, metallic base. “Acetate” also describes the conjugate base or ion (specifically, the negatively charged ion called an anion) typically found in the aqueous solution and written with the chemical formula $C_2H_3O_2^-$.



https://en.wikipedia.org/wiki/Acetate

Related Glossary Terms

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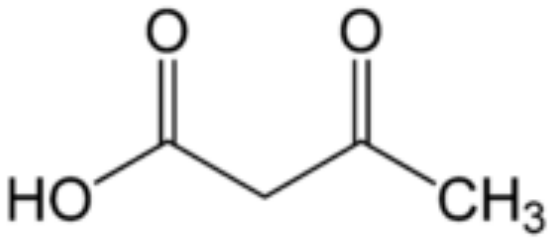
Acetoacetate

Acetoacetic acid is a weak acid. It is of biochemical importance in various animals, including humans, as one of the endogenous ketone bodies produced by the liver when it breaks down fatty acids for ATP production. It can be viewed as the product of joining two acetic acid molecules via a condensation reaction that ejects a water molecule in the process, although that is only one of the ways of forming it.



https://en.wikipedia.org/wiki/Acetoacetic_acid

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Acetoacetate Decarboxylase

Acetoacetate decarboxylase (AAD or ADC) is an enzyme involved in both th
body production pathway in humans and other mammals, and solventogen
teria. Acetoacetate decarboxylase plays a key role in solvent production by c
the decarboxylation of acetoacetate, yielding acetone and carbon dioxide.

https://en.wikipedia.org/wiki/Acetoacetate_decarboxylase

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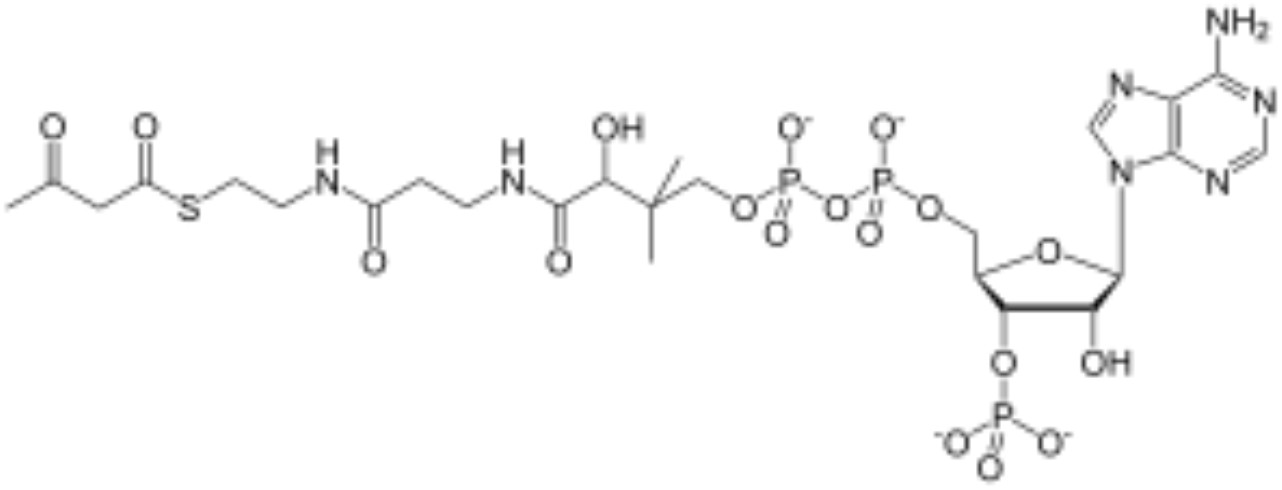
Acetoacetyl-CoA

Acetoacetyl CoA is the precursor of HMG-CoA in the mevalonate pathway, which is essential for cholesterol biosynthesis. It also takes a similar role in the ketone bodies synthesis (ketogenesis) pathway of the liver. In the ketone bodies digestion pathway (in the tissue), it is no longer associated with having HMG-CoA as a product or as a reactant.



https://en.wikipedia.org/wiki/Acetoacetyl-CoA

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Acetoacyl-ACP

Joining of a fatty acyl-ACP (in this case, acetyl-ACP) with malonyl-ACP spli
carboxyl group from malonyl-ACP that was added to it and creates an ac
intermediate (catalyzed by β-ketoacyl-ACP synthase). For the structure of t
tyl group, see acetoacetate.

Related Glossary Terms

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Acetohydroxy Acid Isomeroreductase

Acetohydroxy acid isomeroreductase is an enzyme catalyzing the reaction b
metabolic pathway from pyruvate to leucine, isoleucine, and valine.

3-hydroxy-3-methyl-2-oxobutanoate + NADP(P)H

α,β-dihydroxyisovalerate + **NAD(P)$^+$**

Related Glossary Terms

Drag related terms here

Acetolactate Mutase

2-acetolactate mutase (EC 5.4.99.3) is an enzyme that catalyzes the chemic

2-acetolactate <-> 3-hydroxy-3-methyl-2-oxobutanoate

This enzyme belongs to the family of isomerases, specifically those intramo transferases transferring other groups. The systematic name of this enzyme acetolactate methylmutase. Other names in common use include acetolacta and acetohydroxy acid isomerase. This enzyme participates in valine, leucin leucine biosynthesis. It employs one cofactor, ascorbate.

https://en.wikipedia.org/wiki/2-acetolactate_mutase

Related Glossary Terms

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Acetolactate Synthase

The acetolactate synthase (ALS) enzyme (also known as acetohydroxy acid
AHAS) is a protein found in plants and micro-organisms. ALS catalyzes the
the synthesis of the branched-chain amino acids (valine, leucine, and isoleu

It is a human protein of yet unknown function, sharing some sequence sim
bacterial ALS, and is encoded by the ILVBL gene.

https://en.wikipedia.org/wiki/Acetolactate_synthase

Related Glossary Terms

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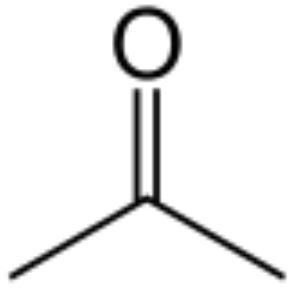
Acetone

Acetone (systematically named propanone) is the organic compound with t
$(CH_3)_2CO$. It is a colorless, volatile, flammable liquid, and is the simplest k

Acetone is miscible with water and serves as an important solvent in its ow
cally for cleaning purposes in the laboratory.

https://en.wikipedia.org/wiki/Acetone



Related Glossary Terms

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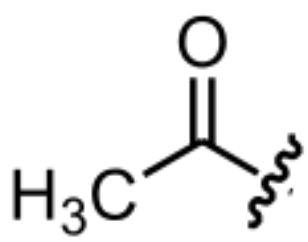
Acetyl

In organic chemistry, acetyl is a functional group, the acyl with chemical formula CH_3CO. It is sometimes represented by the symbol Ac (not to be confused with the element actinium). The acetyl group contains a methyl group single-bonded to a carbonyl. The carbonyl center of an acyl radical has one non-bonded electron with which it forms a chemical bond to the remainder R of the molecule. In IUPAC nomenclature, acetyl is called ethanoyl, although this term is rarely heard.



https://en.wikipedia.org/wiki/Acetyl

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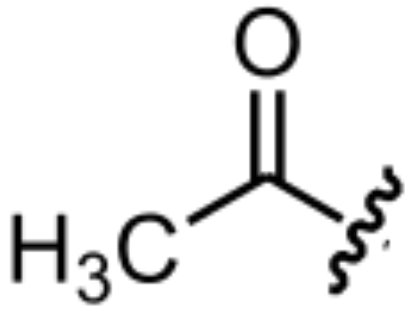
Acetyl-ACP

Acetyl-ACP is a starting point for synthesis of a fatty acid. The acetyl group
linked to two carbons of malonyl-CoA in the first step of the process. Aceto
and carbon dioxide are products of the reaction.



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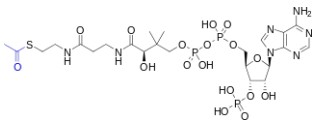
Acetyl-CoA

Acetyl coenzyme A or acetyl-CoA is an important molecule in metabolism, used in many biochemical reactions. Its main function is to convey the carbon atoms within the acetyl group to the citric acid cycle to be oxidized for energy production. The structure of coenzyme A (CoASH or CoA) consists of a β-mercaptoethylamine group linked to the vitamin pantothenic acid through an amide linkage. The acetyl group (indicated in blue in the structural diagram on the right) of acetyl-CoA is linked by a "high energy" thioester bond to the sulfhydryl substituent of the β-mercaptoethylamine group. Acetyl-CoA is an allosteric effector for pyruvate dehydrogenase.



https://en.wikipedia.org/wiki/Acetyl-CoA

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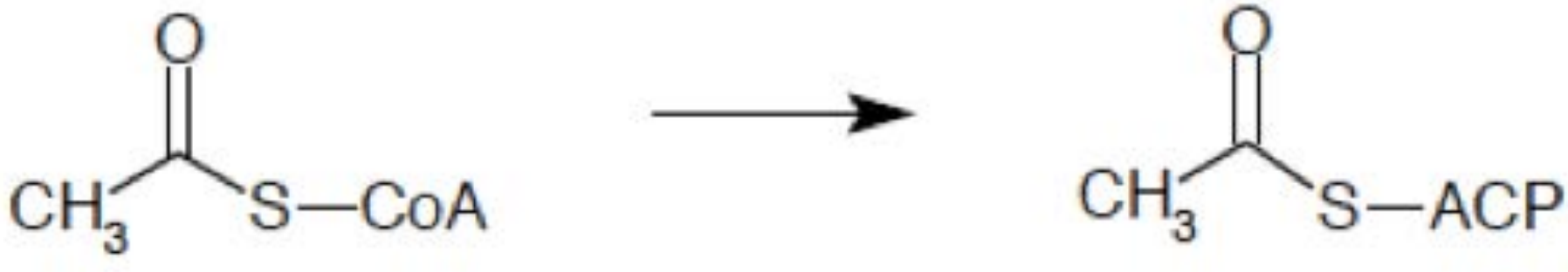
Acetyl-CoA : ACP transacylase

Acetyl-CoA : ACP transacylase is an enzyme involved in fatty acid synthesis the process is to activate acetyl CoA for reaction with malonyl-ACP. This is step in making a fatty acid. The reaction it catalyzes is below.



https://en.wikipedia.org/wiki/Fatty_acid_synthesis

Related Glossary Terms

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Chapter 6 - Metabolism: Fats and Fatty Acids

Acetyl-CoA Carboxylase

Acetyl-CoA carboxylase (ACC) is a biotin-dependent enzyme that catalyzes th
versible carboxylation of acetyl-CoA to produce malonyl-CoA through its two
activities, biotin carboxylase (BC) and carboxyltransferase (CT). ACC is a mu
subunit enzyme in most prokaryotes and in the chloroplasts of most plants a
whereas it is a large, multi-domain enzyme in the endoplasmic reticulum of
eukaryotes. The most important function of ACC is to provide the malonyl-C
strate for the biosynthesis of fatty acids. The activity of ACC can be controlle
transcriptional level as well as by small molecule modulators and covalent m
tion.

https://en.wikipedia.org/wiki/Acetyl-CoA_carboxylase

Related Glossary Terms

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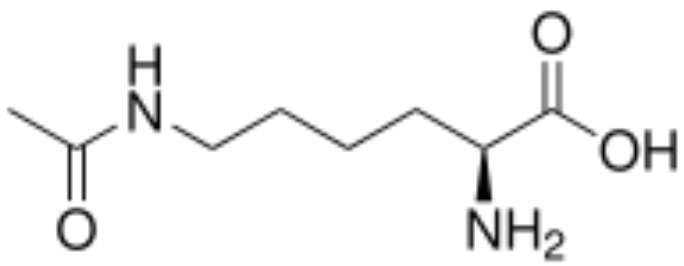
Acetyl-lysine

Acetyllysine (or acetylated lysine) is an acetyl-derivative of the amino acid l
There are multiple forms of acetyllysine - this article refers to N-ε-acetyl-L-
other form is N-α-acetyl-L-lysine.

In histone proteins, the acetylation of lysine residues is an important mecha
genetics. It functions by regulating the binding of histones to DNA in nucle
thereby controlling the expression of genes on that DNA.



https://en.wikipedia.org/wiki/Acetyllysine

Related Glossary Terms

Drag related terms here

Acetylation

Acetylation refers to the process of introducing an acetyl group (resulting in
group) into a compound, namely the substitution of an acetyl group for an a
gen atom.

https://en.wikipedia.org/wiki/Acetylation

Related Glossary Terms

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Acetylcarnitine

Acetyl-L-carnitine, ALCAR or ALC, is an acetylated form of L-carnitine. In citrate, acetyl carnitine plays an important role in transporting acetyl-CoA plasm for fatty acid synthesis

https://en.wikipedia.org/wiki/Acetylcarnitine

Related Glossary Terms

Drag related terms here

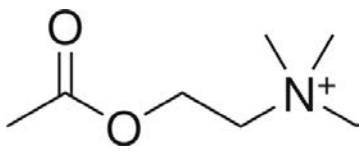
Acetylcholine

Acetylcholine is an organic chemical that functions in the brain and body of many types of animals, including humans, as a neurotransmitter—a chemical released by nerve cells to send signals to other cells. Its name is derived from its chemical structure: it is an ester of acetic acid and choline. Parts in the body that use or are affected by acetylcholine are referred to as cholinergic. Substances that interfere with acetylcholine activity are called anticholinergics.

Acetylcholine is the neurotransmitter used at the neuromuscular junction—in other words, it is the chemical that motor neurons of the nervous system release in order to activate muscles. This property means that drugs that affect cholinergic systems can have very dangerous effects ranging from paralysis to convulsions. Acetylcholine is also used as a neurotransmitter in the autonomic nervous system, both as an internal transmitter for the sympathetic nervous system and as the final product released by the parasympathetic nervous system.

Inside the brain acetylcholine functions as a neuromodulator—a chemical that alters the way other brain structures process information rather than a chemical used to transmit information from point to point. The brain contains a number of cholinergic areas, each with distinct functions. They play an important role in arousal, attention, and motivation.

Partly because of its muscle-activating function, but also because of its functions in the autonomic nervous system and brain, a large number of important drugs exert their effects by altering cholinergic transmission. Numerous venoms and toxins produced by plants, animals, and bacteria, as well as chemical nerve agents such as Sarin, cause harm by inactivating or hyperactivating muscles via their influences on the neuromuscular junction. Drugs that act on muscarinic acetylcholine receptors, such as atropine, can be poisonous in large quantities, but in smaller doses they are commonly used to treat certain heart conditions and eye problems. Scopolamine, which acts mainly on muscarinic receptors in the brain, can cause delirium and amnesia. The addictive qualities of nicotine derive from its effects on nicotinic acetylcholine receptors in the brain.



https://en.wikipedia.org/wiki/Acetylcholine

Acetylcholinesterase

Acetylcholinesterase (HGNC symbol ACHE), also known as AChE or acetylhydr
is the primary cholinesterase in the body. It is an enzyme that catalyzes the brea
of acetylcholine and of some other choline esters that function as neurotransmit

During neurotransmission, acetylcholine (ACh) is released from the presynaptic
ron into the synaptic cleft and binds to ACh receptors on the post-synaptic mem
relaying the signal from the nerve. AChE, also located on the post-synaptic mem
terminates the signal transmission by hydrolyzing ACh. The liberated choline is
up again by the pre-synaptic neuron and ACh is synthesized by combining with a
CoA through the action of choline acetyltransferase.

A cholinomimetic drug disrupts this process by acting as a cholinergic neurotran
ter that is impervious to acetylcholinesterase's lysing action.

https://en.wikipedia.org/wiki/Acetylcholinesterase

Related Glossary Terms

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Acetylglutamate Synthetase

N-acetylglutamate synthase (NAGS) is an enzyme that catalyzes the production of N-Acetylglutamate (NAG) from glutamate and acetyl-CoA.
It catalyzes the following reaction:

Acetyl-CoA + L-glutamate → CoA + N-acetyl-L-glutamate

Most prokaryotes (bacteria) and lower eukaryotes (fungi, green algae, plants, etc.) produce NAG through orinithine acetyltransferase (OAT), which is part of a 'cyclic' ornithine production pathway. NAGS is therefore used in a supportive role, replenishing NAG reserves as required. In some plants and bacteria, however, NAGS catalyzes the first step in a 'linear' arginine production pathway.

The protein sequences of NAGS between prokaryotes, lower eukaryotes and higher eukaryotes have shown a remarkable lack of similarity. Sequence identity between prokaryotic and eukaryotic NAGS is largely <30%, while sequence identity between lower and higher eukaryotes is ~20%.

Enzyme activity of NAGS is modulated by L-arginine, which acts as an inhibitor in plant and bacterial NAGS, but an effector in vertebrates. While the role of arginine as an inhibitor of NAG in ornithine and arginine synthesis is well understood, there is some controversy as to the role of NAG in the urea cycle. The currently accepted role of NAG in vertebrates is as an essential allosteric cofactor for CPS1, and therefore it acts as the primary controller of flux through the urea cycle. In this role, feedback regulation from arginine would act to signal NAGS that ammonia is plentiful within the cell, and needs to be removed, accelerating NAGS function. As it stands, the evolutionary journey of NAGS from essential synthetic enzyme to primary urea cycle controller is yet to be fully understood.

https://en.wikipedia.org/wiki/N-Acetylglutamate_synthase

Related Glossary Terms

Acid

The term acid refers to a molecule that donates a proton in solution or to a
that has a pH lower than 7. Chemists use the term “acid” to refer to a subst
has protons that can dissociate (come off) when dissolved in water. There a
acids, such as HCl that completely dissociate when placed in water. Weak a
contrast release protons as a function of the pH of the solution in which the
placed. The Henderson Hasselbalch equation below shows the relationship
the the amount of ionization (proton loss) and the pH and the pKa of the ac

For an acid HA, which dissociates as

$HA <=> H^+ + A^-$,

$pH = pKa + Log \{[A^-]/[HA]\}$

Related Glossary Terms

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Acidosis

Acidosis is an increased acidity in the blood and other body tissue (i.e. an in
drogen ion concentration). If not further qualified, it usually refers to acidit
blood plasma.

The rate of cellular metabolic activity affects and, at the same time, is affect
pH of the body fluids. In mammals, the normal pH of arterial blood lies bet
and 7.50 depending on the species (e.g. healthy human-arterial blood pH va
tween 7.35 and 7.45). Blood pH values compatible with life in mammals are
a pH range between 6.8 and 7.8. Changes in the pH of arterial blood (and th
extracellular fluid) outside this range result in irreversible cell damage.

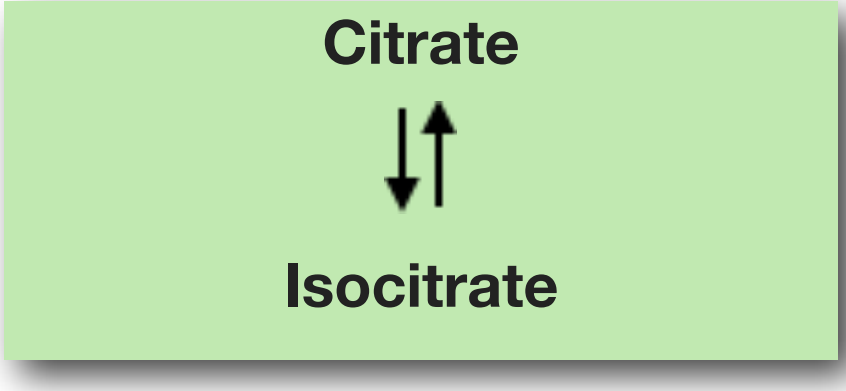
https://en.wikipedia.org/wiki/Acidosis

Related Glossary Terms

Drag related terms here

Aconitase

Aconitase (aconitate hydratase; EC 4.2.1.3) is an enzyme that catalyzes the specific isomerization of citrate to isocitrate via *cis*-aconitate in the citric ac non-redox-active process. The reaction it catalyzes is shown below.



https://en.wikipedia.org/wiki/Aconitase

Related Glossary Terms

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ACP

The acyl carrier protein (ACP) is an important component in both fatty acid etide biosynthesis with the growing chain bound during synthesis as a thiol distal thiol of a 4'-phosphopantetheine moiety. The protein is expressed in apo form and the 4'-phosphopantetheine moiety must be post-translationa to a conserved serine residue on the ACP by the action of holo-acyl carrier p thase (ACPS), a phosphopantetheinyl transferase.

https://en.wikipedia.org/wiki/Acyl_carrier_protein

Related Glossary Terms

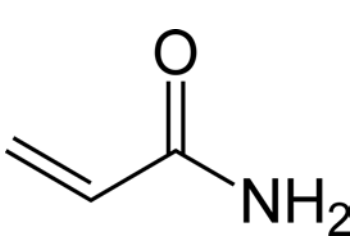
Drag related terms here

Acrylamide

Acrylamide is a compound formed from asparagine in foods cooked at high temperatures (deep frying) when it reacts with reducing sugars or other molecules with carbonyl groups. From Wikipedia - Acrylamide “is a white odorless crystalline solid, soluble in water, ethanol, ether, and chloroform. Acrylamide decomposes in the presence of acids, bases, oxidizing agents, iron, and iron salts. It decomposes non-thermally to form ammonia, and thermal decomposition produces carbon monoxide, carbon dioxide, and oxides of nitrogen.

Acrylamide was discovered in foods in April 2002 by Eritrean scientist Eden Tareke in Sweden when she found the chemical in starchy foods, such as potato chips (potato crisps), French fries (chips), and bread that had been heated higher than 120 °C (248 °F) (production of acrylamide in the heating process was shown to be temperature-dependent). It was not found in food that had been boiled or in foods that were not heated.

Acrylamide levels appear to rise as food is heated for longer periods of time. Although researchers are still unsure of the precise mechanisms by which acrylamide forms in foods, many believe it is a byproduct of the Maillard reaction. In fried or baked goods, acrylamide may be produced by the reaction between asparagine and reducing sugars (fructose, glucose, etc.) or reactive carbonyls at temperatures above 120 °C (248 °F).”



https://en.wikipedia.org/wiki/Acrylamide

Related Glossary Terms

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Actin

Actin is a globular multi-functional protein that forms microfilaments. It is found in essentially all eukaryotic cells (the only known exception being nematode sperm), where it may be present at concentrations of over 100 µM. An actin protein's mass is roughly 42-kDa and it is the monomeric subunit of two types of filaments in cells: microfilaments, one of the three major components of the cytoskeleton, and thin filaments, part of the contractile apparatus in muscle cells. It can be present as either a free monomer called G-actin (globular) or as part of a linear polymer microfilament called F-actin (filamentous), both of which are essential for such important cellular functions as the mobility and contraction of cells during cell division.

https://en.wikipedia.org/wiki/Actin

Related Glossary Terms

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Actinin

Actinin is a microfilament protein. α-Actinin is necessary for the attachmer
filaments to the Z-lines in skeletal muscle cells, and to the dense bodies in s
cle cells. The functional protein is an anti-parallel dimer, which cross-links
ments in adjacent sarcomeres, and therefore coordinates contractions betw
comeres in the horizontal axis.

https://en.wikipedia.org/wiki/Actinin

Related Glossary Terms

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Action Potential

In physiology, an action potential is a short-lasting event in which the elect
brane potential of a cell rapidly rises and falls, following a consistent trajec
potentials occur in several types of animal cells, called excitable cells, whic
neurons, muscle cells, and endocrine cells, as well as in some plant cells. In
they play a central role in cell-to-cell communication. In other types of cells
function is to activate intracellular processes. In muscle cells, for example,
tential is the first step in the chain of events leading to muscular contractio

https://en.wikipedia.org/wiki/Action_potential

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Activated Intermediate

An activated intermediate is a molecule that contains a high energy bond a
ergy from that bond to transfer a part of itself to another molecule. An exa
UDP-Glucose. The energy of the bond between the UDP and glucose is use
fer glucose to a growing glycogen chain by the enzyme glycogen synthase.
bonds between acyl groups and coenzyme A are also high energy, which ma
CoA an activated intermediate as well.

Related Glossary Terms

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Activation Domain

An activation domain is a part of a protein that interacts with transcription facilitate transcription of a eukaryotic gene.

https://en.wikipedia.org/wiki/Transcription_factor

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Activation Energy

Activation energy is a term introduced in 1889 by the Swedish scientist Sva
rhenius to describe the minimum energy which must be available to a chem
with potential reactants to result in a chemical reaction. Activation energy
defined as the minimum energy required to start a chemical reaction. The a
energy of a reaction is usually denoted by Ea and given in units of kilojoules
(kJ/mol) or kilocalories per mole (kcal/mol).

Enzymes lower activation energy for reactions and this is the way they spee

https://en.wikipedia.org/wiki/Activation_energy

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Activators

A transcriptional activator is a protein (transcription factor) that increases gene transcription of a gene or set of genes. Most activators are DNA-binding proteins that bind to enhancers or promoter-proximal elements.

Most activators function by binding sequence-specifically to a DNA site located in or near a promoter and making protein–protein interactions with the general transcription machinery (RNA polymerase and general transcription factors), thereby facilitating the binding of the general transcription machinery to the promoter. The DNA site bound by the activator is referred to as an "activator site." The part of the activator that makes protein–protein interactions with the general transcription machinery is referred to as an "activating region." The part of the general transcription machinery that makes protein–protein interactions with the activator is referred to as an "activation target."

The catabolite activator protein (CAP; also known as cAMP receptor protein, CRP) activates transcription at the lac operon of the bacterium *Escherichia coli*. Cyclic adenosine monophosphate (cAMP) is produced during glucose starvation, binds to CAP, causes a conformational change that allows CAP to bind to a DNA site located adjacent to the lac promoter. CAP then makes a direct protein–protein interaction with RNA polymerase that recruits RNA polymerase to the lac promoter.

https://en.wikipedia.org/wiki/Activator_(genetics)

Related Glossary Terms

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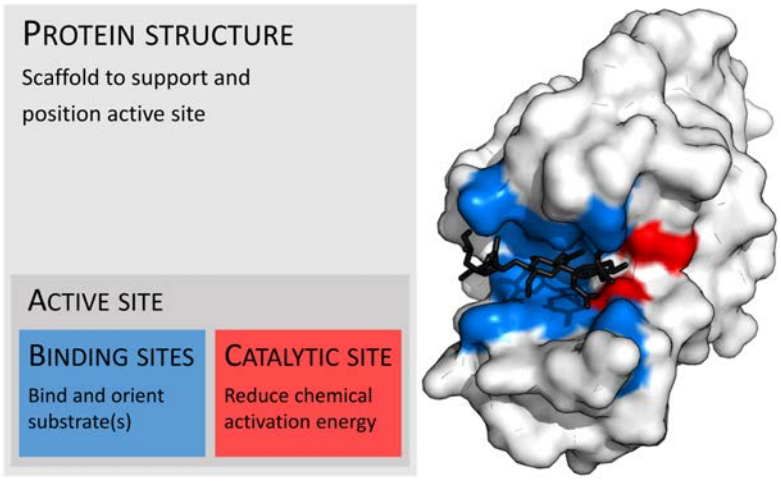
Active Site

The active site of an enzyme is the region where substrate molecules bind and undergo a chemical reaction. The active site consists of residues that form temporary bonds with the substrate (binding site) and residues that catalyze a reaction of that substrate (catalytic site). The active site is usually a groove or pocket of the enzyme which can be located in a deep tunnel within the enzyme, or between the interfaces of multimeric enzymes. An active site can catalyze a reaction repeatedly as its residues are not altered at the end of the reaction (they may change during the reaction, but are regenerated by the end).

Usually, an enzyme molecule has only one active site, and the active site fits with one specific type of substrate. An active site contains a binding site that binds the substrate and orients it for catalysis. Residues in the binding site form hydrogen bonds, hydrophobic interactions, or temporary covalent interactions (van der Waals) with the substrate to make an enzyme-substrate complex. In order to function, the active site needs to be in a specific conformation and so denaturation of the protein by high temperatures or extreme pH values will destroy its catalytic activity. A tighter fit between an active site and the substrate molecule is believed to increase efficiency of a reaction. Most enzymes have deeply buried active sites, which can be accessed by a substrate via access channels.



https://en.wikipedia.org/wiki/Active_site

Related Glossary Terms

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Active Transport

Active transport is the movement of molecules across a cell membrane from a region of their lower concentration to a region of their higher concentration in the direction against some gradient or other obstructing factor (often a concentration gradient). Unlike passive transport, which uses the kinetic energy and natural entropy of molecules moving down a gradient, active transport uses cellular energy to move them against a gradient, polar repulsion, or other resistance. Active transport is usually associated with accumulating high concentrations of molecules that the cell needs, such as ions, glucose and amino acids. If the process uses chemical energy, such as from adenosine triphosphate (ATP), it is termed primary active transport. Secondary active transport involves the use of an electrochemical gradient. Examples of active transport include the uptake of glucose in the intestines in humans and the uptake of mineral ions into root hair cells of plants."

https://en.wikipedia.org/wiki/Active_transport

Related Glossary Terms

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Activity Control Site

The activity control site is an allosteric control site found on the ribonucleo
tase enzyme. It is capable of binding ATP (activates enzyme) or dATP (inac
zyme). Students sometimes confuse the active site of RNR with the activity
(sometimes called the activity site). The active site is where the reaction is c
and could better be called the catalytic site.

https://en.wikipedia.org/wiki/Ribonucleotide_reductase

Related Glossary Terms

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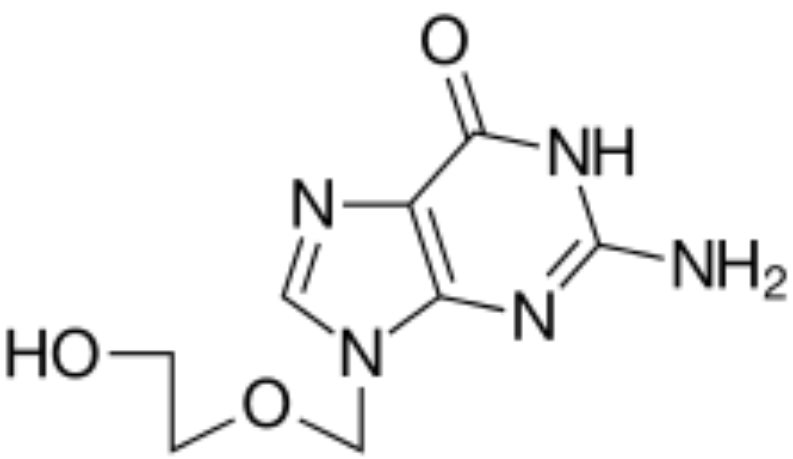
Acyclovir

Aciclovir (ACV), also known as acyclovir, is an antiviral medication. It is pr
used for the treatment of herpes simplex virus infections, chickenpox, and s
Other uses include prevention of cytomegalovirus infections following trans
infections due to Epstein-Barr virus.



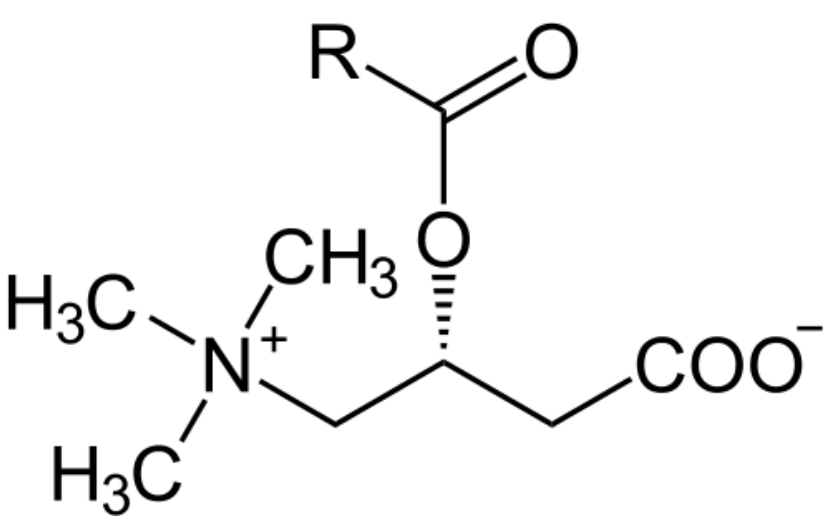
https://en.wikipedia.org/wiki/Aciclovir

Related Glossary Terms

Drag related terms here

Acyl-carnitine

Fatty acyl-CoA molecules being transported into mitochondrion for oxidation m
transported across the inner mitochondrial membrane in the form of acyl-carni
This requires replacement of the CoA with carnitine by Carnitine acyltransferas
side the mitochondrial matrix, a similar enzyme reverses the reaction to replace
nitine with a CoASH so β-oxidation can proceed.



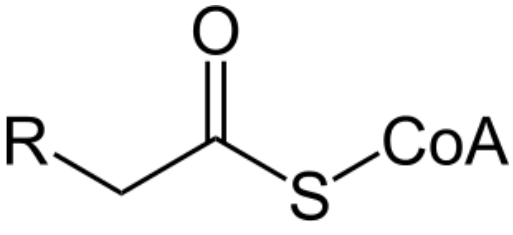
https://en.wikipedia.org/wiki/Carnitine

Related Glossary Terms

Drag related terms here

Acyl-CoA

Acyl-CoA is a name for molecules involved in the metabolism of fatty acids. pound formed when coenzyme A (CoA) attaches to the end of a long-chain side living cells. The compound undergoes β oxidation, forming one or mor of acetyl-CoA. This, in turn, enters the citric acid cycle, eventually forming A



https://en.wikipedia.org/wiki/Acyl-CoA

Related Glossary Terms

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Acyl-CoA Dehydrogenase

Acyl-CoA dehydrogenases (ACADs) are a class of enzymes that function to catalyze the initial step in each cycle of fatty acid β-oxidation in the mitochondria of cells. Their action results in the introduction of a trans double-bond between C_2 (α) and C_3 (β) of the acyl-CoA thioester substrate. Flavin adenine dinucleotide (FAD) is a required co-factor in addition to the presence of an active site glutamate in order for the enzyme to function.

Deficiencies in acyl-CoA dehydrogenases result in decreased ability to oxidize fatty acids, thereby causing metabolic dysfunction. Medium-chain acyl-CoA dehydrogenase deficiencies (MCADD) are well known and characterized because they occur most commonly among acyl-CoA dehydrogenases, leading to fatty acid oxidation disorders and the potential of life-threatening metabolic diseases. Some problems associated with medium-chain acyl-CoA dehydrogenase deficiency include intolerance to fasting, hypoglycemia, and sudden infant death syndrome.

https://en.wikipedia.org/wiki/Acyl_CoA_dehydrogenase

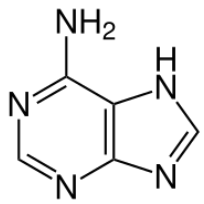
Related Glossary Terms

Drag related terms here

Adenine

Adenine is a nucleobase (a purine derivative). Its derivatives have a variety of roles in biochemistry including cellular respiration, in the form of both the energy-rich adenosine triphosphate (ATP) and the cofactors nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). It also has functions in protein synthesis and as a chemical component of DNA and RNA. The shape of adenine is complementary to either thymine in DNA or uracil in RNA.

The image right shows pure adenine, as an independent molecule. When connected into DNA, a covalent bond is formed between deoxyribose sugar and the bottom left nitrogen, so removing the hydrogen. The remaining structure is called an adenine residue, as part of a larger molecule. Adenosine is adenine reacted with ribose as used in RNA and ATP. Deoxyadenosine's adenine is attached to deoxyribose, as is used to form DNA.



https://en.wikipedia.org/wiki/Adenine

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Adenine Nucleotide Translocase

The adenine nucleotide translocase/translocator (ANT) is an antiport that transpo
ATP out of the matrix in exchange for ADP moving into the matrix. This transport
tem, which does not require input of energy is driven by the concentration of ADP
ATP.

ANT has long been thought to function asymmetrically as a homodimer of subuni
the inner mitochondrial membrane. The dimer was thought to be a gated pore thr
which ADP and ATP were exchanged between the mitochondrial matrix and the cy
plasm. The dimer hypothesis was first challenged when the three-dimensional stru
ture of ANT was discovered to be a monomer. Further work has shown that ANT
tions a monomer in detergents and in mitochondrial membranes.

ANT is an important structural component of the mitochondrial permeability tran
tion pore which can open and lead to cell death through apoptosis or necrosis.

https://en.wikipedia.org/wiki/Adenine_nucleotide_translocator

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Adenine Phosphoribosyltransferase

Adenine phosphoribosyltransferase (APRTase) is an enzyme encoded by the APRT gene, found in humans on chromosome 16. It is part of the Type I PRTase family and is involved in the nucleotide salvage pathway, which provides an alternative to nucleotide biosynthesis *de novo* in humans and most other animals.

In organisms that can synthesize purines *de novo*, the nucleotide salvage pathway provides an alternative that is energetically more efficient. It can salvage adenine from the polyamine biosynthetic pathway or from dietary sources of purines. Although APRTase is functionally redundant in these organisms, it becomes more important during periods of rapid growth, such as embryogenesis and tumor growth. It is constitutively expressed in all mammalian tissue.

In protozoan parasites, the nucleotide salvage pathway provides the sole means for nucleotide synthesis. Since the consequences of APRTase deficiency in humans is comparatively mild and treatable, it may be possible to treat certain parasitic infections by targeting APRTase function.

In plants, as in other organisms, ARPTase functions primarily for the synthesis of adenylate. It has the unique ability to metabolize cytokinins—a plant hormone that can exist as a base, nucleotide, or nucleoside—into adenylate nucleotides.

APRT is functionally related to hypoxanthine-guanine phosphoribosyltransferase (HPRT).

https://en.wikipedia.org/wiki/Adenine_phosphoribosyltransferase

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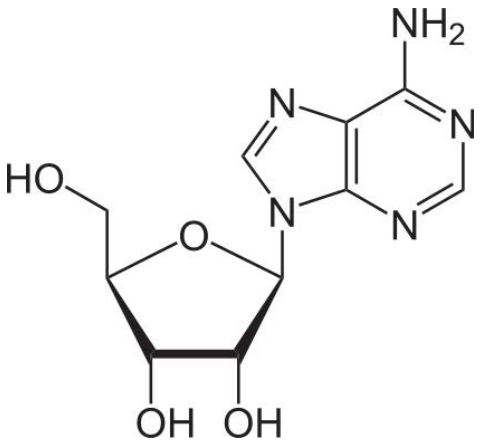
Related Glossary Terms

Drag related terms here

Adenosine

Adenosine is a purine nucleoside composed of a molecule of adenine attached to a ribose sugar molecule (ribofuranose) moiety via a β-N_9-glycosidic bond. Adenosine is widely found in nature and plays an important role in biochemical processes, such as energy transfer — as adenosine triphosphate (ATP) and adenosine diphosphate (ADP) — as well as in signal transduction as cyclic adenosine monophosphate (cAMP). It is also a neuromodulator, believed to play a role in promoting sleep and suppressing arousal. Adenosine also plays a role in regulation of blood flow to various organs through vasodilation.



https://en.wikipedia.org/wiki/Adenosine

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Adenosine Deaminase

Adenosine deaminase (also known as adenosine aminohydrolase, or ADA) zyme (EC 3.5.4.4) involved in purine metabolism. It is needed for the breakadenosine from food and for the turnover of nucleic acids in tissues. Its prition in humans is the development and maintenance of the immune system

ADA irreversibly deaminates adenosine, converting it to the related nucleosby the substitution of the amino group for a keto group.

https://en.wikipedia.org/wiki/Adenosine_deaminase

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Adenylate Cyclase

Adenylyl cyclase (EC 4.6.1.1, also commonly known as adenyl cyclase and adenylate cyclase, abbreviated AC) is an enzyme with key regulatory roles in essentially all cells. It is the most polyphyletic known enzyme. Six distinct classes have been described, all catalyzing the same reaction but representing unrelated gene families with no known sequence or structural homology. The best known class of adenylyl cyclases is class III or AC-III (Roman numerals are used for classes). AC-III occurs widely in eukaryotes and has important roles in many human tissues.

All classes of adenylyl cyclases catalyze the conversion of adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate. Magnesium ions are generally required and appears to be closely involved in the enzymatic mechanism. The cAMP produced by AC then serves as a regulatory signal via specific cAMP-binding proteins, either transcription factors, enzymes (e.g., cAMP-dependent kinases), or ion transporters.

https://en.wikipedia.org/wiki/Adenylyl_cyclase

Related Glossary Terms

Drag related terms here

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Adenylate Kinase

Adenylate kinase (EC 2.7.4.3) (also known as ADK or myokinase) is a phosp
rase enzyme that catalyzes the interconversion of adenine nucleotides, and
portant role in cellular energy homeostasis. The reaction catalyzed is:

ATP + AMP ⇔ 2 ADP

The equilibrium constant varies with condition, but is close to 1. Thus, the Δ
reaction is close to zero.

https://en.wikipedia.org/wiki/Adenylate_kinase

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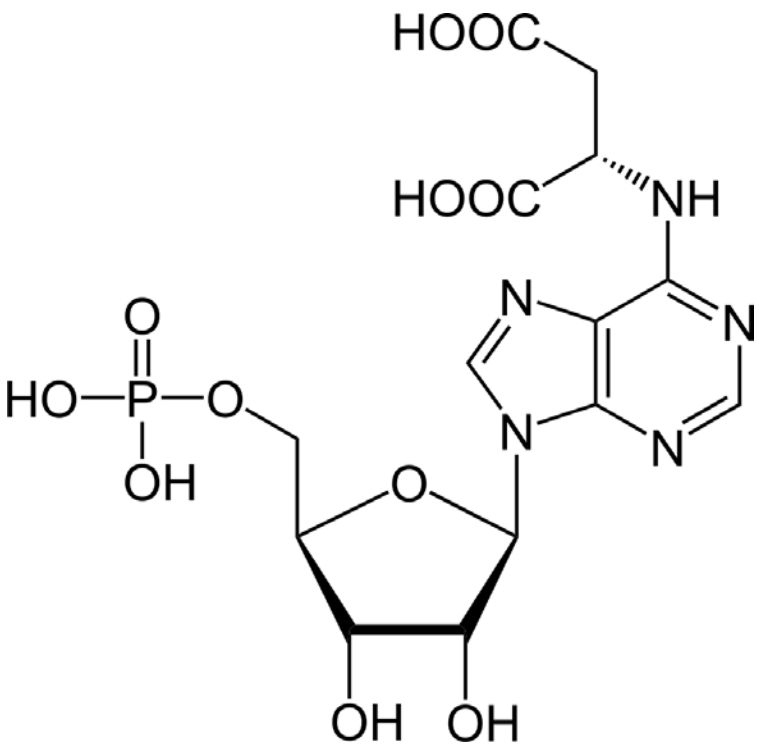
Adenylosuccinate

Adenylosuccinate is an intermediate in the interconversion of purine nucleotides inosine monophosphate (IMP) and adenosine monophosphate (AMP). The enzyme adenylosuccinate synthase carries out the reaction by the addition of aspartate to IMP and requires the input of energy from a phosphoanhydride bond in the form of guanosine triphosphate (GTP). GTP is used instead of adenosine triphosphate (ATP), so the reaction is not dependent on its products.



https://en.wikipedia.org/wiki/Adenylosuccinate

Related Glossary Terms

Drag related terms here

Adenylosuccinate Lyase

Adenylosuccinate lyase (or adenylosuccinase) is an enzyme that in humans
by the ADSL gene. Adenylosuccinate lyase converts adenylosuccinate to AM
marate as part of the purine nucleotide cycle. ASL catalyzes two reactions i
biosynthetic pathway that makes AMP. ASL cleaves adenylosuccinate into
fumarate, and cleaves SAICAR into AICAR and fumarate.

https://en.wikipedia.org/wiki/Adenylosuccinate_lyase

Related Glossary Terms

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Chapter 6 - Metabolism: Nucleotides

Chapter 6 - Metabolism: Nucleotides

Adenylosuccinate Synthetase

Adenylosuccinate synthase (or adenylosuccinate synthetase) (EC 6.3.4.4.) is an enzyme that plays an important role in purine biosynthesis, by catalyzing the guanosine triphosphate (GTP)-dependent conversion of inosine monophosphate (IMP) and aspartic acid to guanosine diphosphate (GDP), phosphate and N(6)-(1,2-dicarboxyethyl)-AMP. Adenylosuccinate synthetase has been characterized from various sources ranging from *Escherichia coli* (gene purA) to vertebrate tissues. In vertebrates, two isozymes are present: one involved in purine biosynthesis and the other in the purine nucleotide cycle.

The crystal structure of adenylosuccinate synthetase from *E. coli* reveals that the dominant structural element of each monomer of the homodimer is a central β-sheet of 10 strands. The first nine strands of the sheet are mutually parallel with right-handed crossover connections between the strands. The 10th strand is antiparallel with respect to the first nine strands. In addition, the enzyme has two antiparallel β-sheets, composed of two strands and three strands each, 11 α-helices and two short 3_{10}-helices. Further, it has been suggested that the similarities in the GTP-binding domains of the synthetase and the p21ras protein are an example of convergent evolution of two distinct families of GTP-binding proteins. Structures of adenylosuccinate synthetase from *Triticum aestivum* and *Arabidopsis thaliana* when compared with the known structures from *E. coli* reveals that the overall fold is very similar to that of the *E. coli* protein.

https://en.wikipedia.org/wiki/Adenylosuccinate_synthase

Related Glossary Terms

Drag related terms here

Adenylylation

Adenylylation, also known as AMPylation, is a process in which adenosine
phate (AMP) molecule is covalently attached to a protein side chain, alterin
tion of the protein. This covalent addition of AMP to a hydroxyl side chain
tein is posttranslational modification that is stable and reversible. Adenyly
volves a phosphodiester bond between a hydroxyl group of the molecule un
adenylylation and the phosphate group of the adenosine monophosphate n
(i.e. adenylic acid). This process can occur to molecules such as tyrosine res
zymes that are capable of catalyzing this process are called AMPylators.

https://en.wikipedia.org/wiki/Adenylylation

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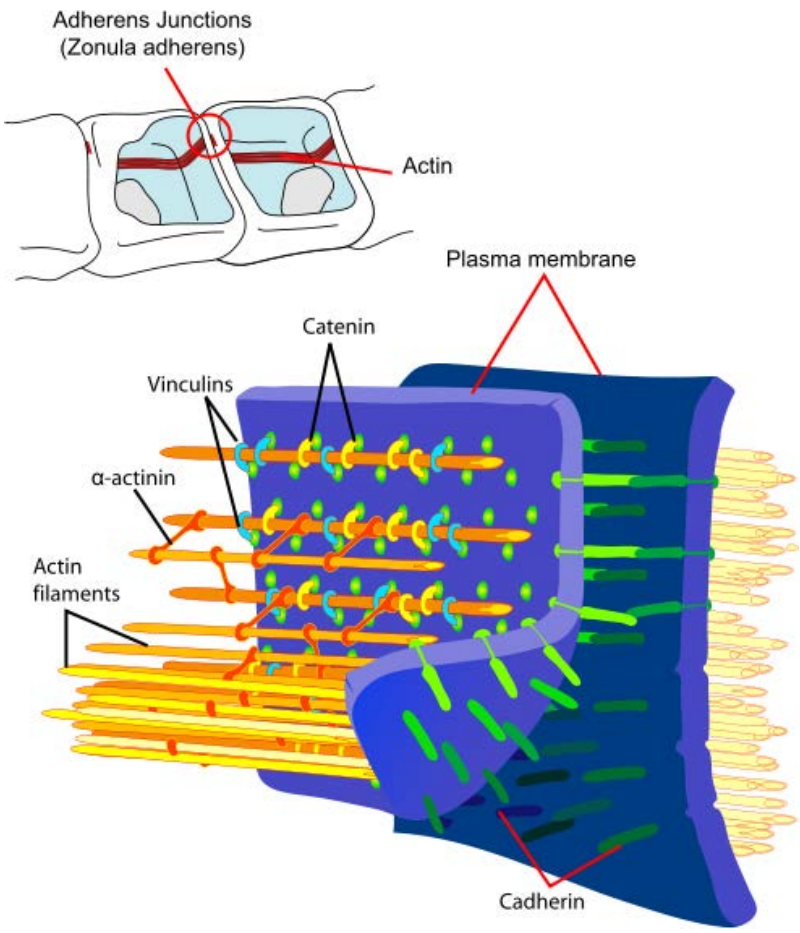
Adherens Junction

Adherens junctions (or zonula adherens, intermediate junction, or "belt desmosome") are protein complexes that occur at cell–cell junctions in epithelial and endothelial tissues, usually more basal than tight junctions. An adherens junction is defined as a cell junction whose cytoplasmic face is linked to the actin cytoskeleton. They can appear as bands encircling the cell (zonula adherens) or as spots of attachment to the extracellular matrix (adhesion plaques). A similar cell junction in non-epithelial, non-endothelial cells is the fascia adherens. It is structurally the same, but appears in ribbonlike patterns that do not completely encircle the cells. One example is in cardiomyocytes.



https://en.wikipedia.org/wiki/Adherens_junction

Related Glossary Terms

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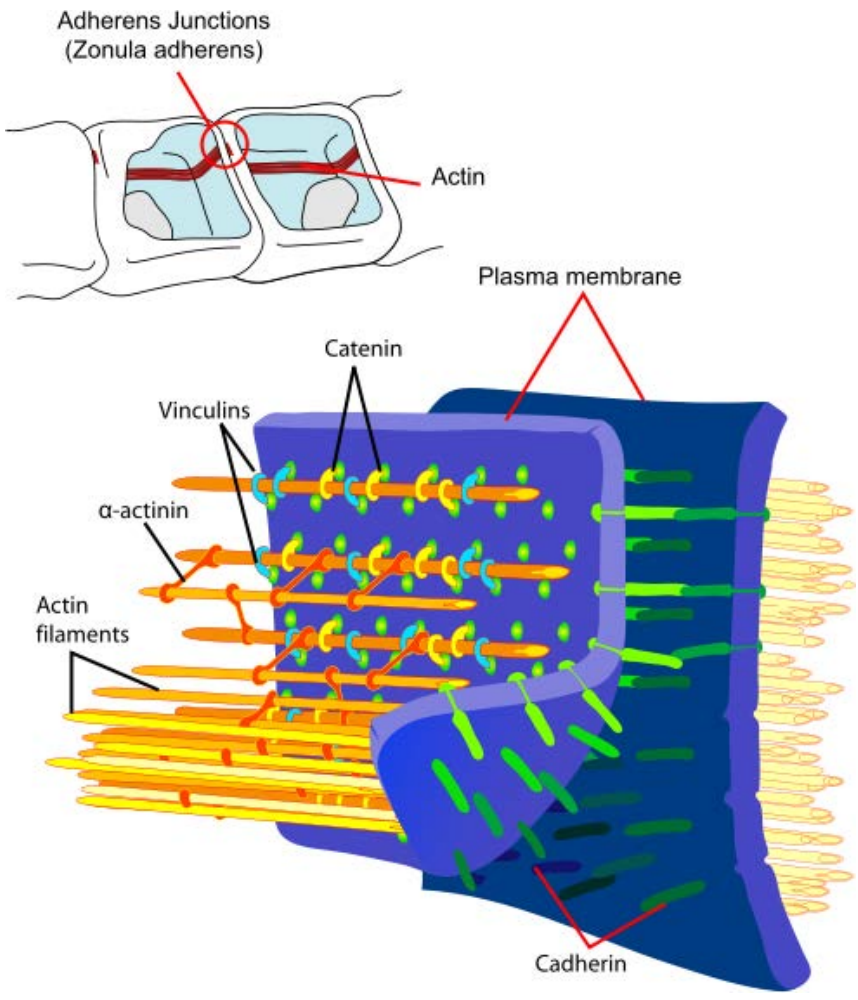

https://en.wikipedia.org/wiki/Adherens_junction

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Adipocytes

Adipocytes, also known as lipocytes and fat cells, are the cells that primarily compose adipose tissue, specialized in storing energy as fat. There are two types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), which are also known as white fat and brown fat, respectively, and comprise two types of fat cells. Most recently, the presence of beige adipocytes with a gene expression pattern distinct from either white or brown adipocytes has been described.

White fat cells or monovacuolar cells contain a large lipid droplet surrounded by a layer of cytoplasm. The nucleus is flattened and located on the periphery. A typical fat cell is 0.1 mm in diameter with some being twice that size and others half that size. The fat stored is in a semi-liquid state, and is composed primarily of triglycerides and cholesteryl ester. White fat cells secrete many proteins acting as adipokines such as resistin, adiponectin, leptin and apelin. An average human adult has 30 billion fat cells with a weight of 30 lbs or 13.5 kg. If excess weight is gained as an adult, fat cells increase in size about fourfold before dividing and increasing the absolute number of fat cells present.

Brown fat cells or plurivacuolar cells are polygonal in shape. Unlike white fat cells, these cells have considerable cytoplasm, with lipid droplets scattered throughout. The nucleus is round, and, although eccentrically located, it is not in the periphery of the cell. The brown color comes from the large quantity of mitochondria. Brown fat, also known as "baby fat," is used to generate heat.

https://en.wikipedia.org/wiki/Adipocyte

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Adipokines

The adipokines, or adipocytokines (Greek adipo-, fat; cytos-, cell; and -kinos, movement) are cytokines (cell signaling proteins) secreted by adipose tissue. The first adipokine to be discovered was leptin in 1994.

Members include:

- Leptin
- Adiponectin
- Apelin
- chemerin
- interleukin-6 (IL-6)
- monocyte chemotactic protein-1 (MCP-1)
- plasminogen activator inhibitor-1 (PAI-1)
- retinol binding protein 4 (RBP4)
- tumor necrosis factor-α (TNFα)
- visfatin

In addition, interleukin 8 (IL-8), interleukin 10 (IL-10), interferon γ (IFN-γ) and inducible protein 10 (IP-10 or CXCL10) have been shown to be associated with excessive body weight.

https://en.wikipedia.org/wiki/Adipokine

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Adiponectin

Adiponectin is a protein hormone that modulates a number of metabolic pro
cluding glucose regulation and fatty acid oxidation. Adiponectin is exclusivel
from adipose tissue (and also from the placenta in pregnancy) into the blood
and is very abundant in plasma relative to many hormones. Levels of the hor
inversely correlated with body fat percentage in adults. However, a meta ana
not able to confirm this association in healthy adults. The association in infa
young children is less clear. Similarly, circulating adiponectin concentrations
during caloric restriction in animals and humans, such as in patients with an
vosa. This observation is surprising, given that adiponectin is produced by ad
sue. However, a recent study suggests that adipose tissue within bone marro
increases during caloric restriction, contributes to elevated circulating adipo
this context.

https://en.wikipedia.org/wiki/Adiponectin

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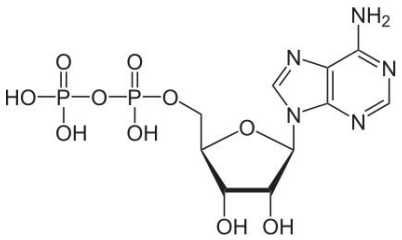
ADP

Adenosine diphosphate (ADP) (Adenosine pyrophosphate (APP)) is an important organic compound in metabolism and is essential to the flow of energy in living cells. A molecule of ADP consists of three important structural components: a sugar backbone attached to a molecule of adenine and two phosphate groups bonded to the 5 carbon atom of ribose. The carbon molecules that make up the ring structure of a sugar can be named in a way that more specifically designates the location of the phosphate and adenosine attachments: The sugar backbone of ADP is known as a pentose sugar and consists of five carbon molecules. The two phosphate groups of ADP are added in series to the 5' carbon of the sugar backbone, while the adenosine molecule attaches to the 1' carbon.

ADP is the precursor of dADP in the reaction catalyzed by ribonucleotide reductase.



https://en.wikipedia.org/wiki/Adenosine_diphosphate

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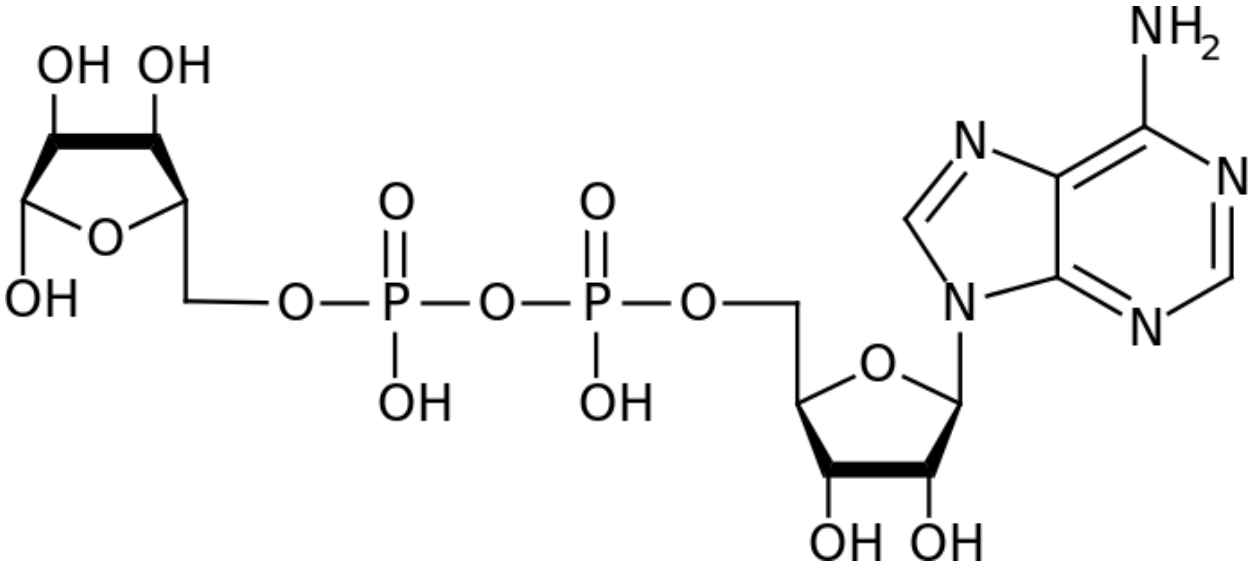
ADP-ribose

Adenosine diphosphate ribose is an ester molecule formed into chains by th
poly ADP ribose polymerase. It binds to and activates the TRPM$_2$ ion chann



https://en.wikipedia.org/wiki/Adenosine_diphosphate_ribose

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Chapter 9 - Short & Sweet: Energy

Adrenodoxin

Adrenal ferredoxin also known as adrenodoxin or adrenodoxin, mitochond
toredoxin or ferredoxin-1 (FDX1) is a protein that in humans is encoded by
gene. In addition to the expressed gene at this chromosomal locus (11q22),
pseudogenes located on chromosomes 20 and 21.

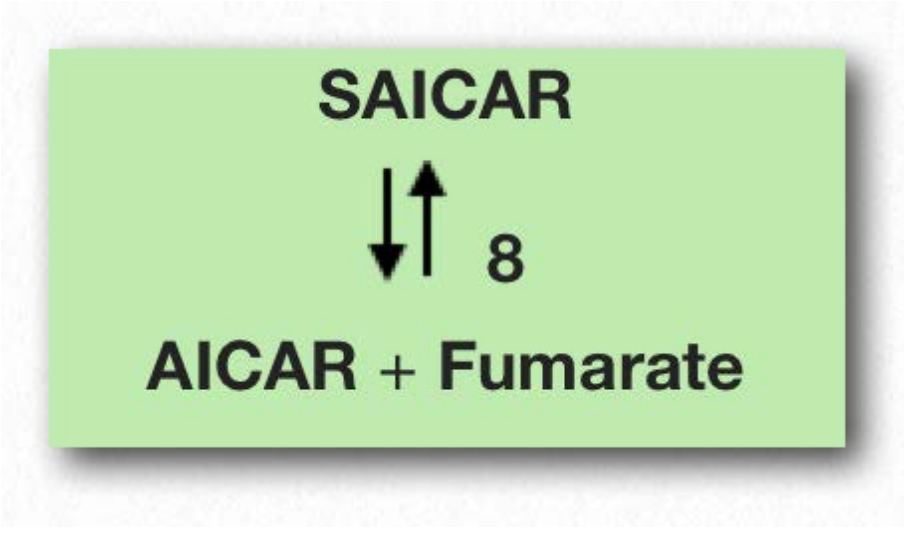
Ferredoxin-1 is a small iron-sulfur protein that transfers electrons from NA
through ferredoxin reductase to a terminal cytochrome P450. This particul
oxidation/reduction system is found in steroidogenic tissues, and is involve
synthesis of bile acid and vitamin D. Ferredoxin-1 has been identified in a r
different tissues but all forms have been shown to be identical and are not t
cific.

Related Glossary Terms

Drag related terms here

ADSL

ADSL is an acronym for the enzyme adenylosuccinate lyase, which catalyze
tion below in purine biosynthesis. ADSL is the eighth enzyme in this metab
way.



Related Glossary Terms

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Adult Hemoglobin

Hemoglobin A (HbA), also known as adult hemoglobin or $\alpha_2\beta_2$, is the most
man hemoglobin tetramer, comprising over 97% of the total red blood cell
It consists of two α chains and two β chains.

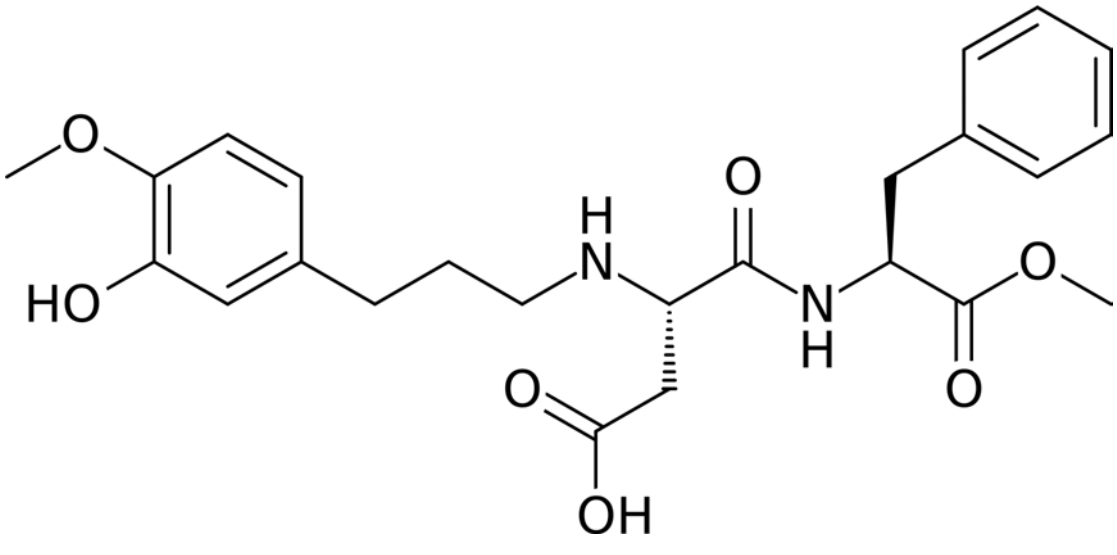
https://en.wikipedia.org/wiki/Hemoglobin_A

Related Glossary Terms

Drag related terms here

Advantame

Advantame is a non-caloric sweetener from Japan's Ajinomoto Co. The U.S. F
Drug Administration has approved advantame for general use in foods and be
except meat and poultry as a food additive. It is synthesized from isovanillin a
tame.



https://en.wikipedia.org/wiki/Advantame

Related Glossary Terms

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Aerobic

Aerobic means "requiring air," in which "air" usually means oxygen. Aerobic respiration requires oxygen (O_2) in order to create ATP. Although carbohydrates, fats, and proteins are consumed as reactants, it is the preferred method of pyruvate breakdown in glycolysis and requires that pyruvate enter the mitochondria in order to be fully oxidized by the citric acid cycle. The products of this process are carbon dioxide and water, but the energy transferred is used to break strong bonds in ADP as the third phosphate group is added to form ATP (adenosine triphosphate), by substrate-level phosphorylation, NADH and $FADH_2$

Simplified reaction:
$C_6H_{12}O_6$ (s) + 6 O_2 (g) → 6 CO_2 (g) + 6 H_2O (l) + heat
$\Delta G = -2880$ kJ per mol of $C_6H_{12}O_6$

The negative ΔG indicates that the reaction can occur spontaneously. The potential of NADH and $FADH_2$ is converted to more ATP through an electron transport chain with oxygen as the "terminal electron acceptor". Most of the ATP produced by aerobic cellular respiration is made by oxidative phosphorylation. This works by the energy released in the consumption of pyruvate being used to create a chemiosmotic potential by pumping protons across a membrane. This potential is then used to drive ATP synthase and produce ATP from ADP and a phosphate group. Biology textbooks often state that 38 ATP molecules can be made per oxidized glucose molecule during cellular respiration (2 from glycolysis, 2 from the citric acid cycle, and about 34 from the electron transport system). However, this maximum yield is never quite reached because of losses due to leaky membranes as well as the cost of moving pyruvate and ADP into the mitochondrial matrix, and current estimates range around 29 to 30 ATP per glucose.

Aerobic metabolism is up to 15 times more efficient than anaerobic metabolism (which yields 2 molecules ATP per 1 molecule glucose). However some anaerobic organisms, such as methanogens are able to continue with anaerobic respiration, yielding more ATP by using other inorganic molecules (not oxygen) as final electron acceptors in the electron transport chain. They share the initial pathway of glycolysis but aerobic metabolism continues with the citric cycle and oxidative phosphorylation. The post-glycolytic reactions take place in the mitochondria in eukaryotic cells, and in the cytoplasm in prokaryotic cells.

https://en.wikipedia.org/wiki/Aerobic

Related Glossary Terms

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Affinity

The interaction of most ligands with their binding sites can be characterized in term
of a binding affinity. In general, high-affinity ligand binding results from greater int
molecular force between the ligand and its receptor while low-affinity ligand bindin
involves less intermolecular force between the ligand and its receptor. In general, hi
affinity binding involves a longer residence time for the ligand at its receptor bindin
site than is the case for low-affinity binding. High-affinity binding of ligands to rece
tors is often physiologically important when some of the binding energy can be used
cause a conformational change in the receptor, resulting in altered behavior of an as
ciated ion channel or enzyme.

https://en.wikipedia.org/wiki/Ligand_(biochemistry)#Receptor.2Fligand_binding
finity

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Affinity Chromatography

Affinity chromatography is a method of separating biochemical mixtures based on a highly specific interaction such as that between antigen and antibody, enzyme and substrate, or receptor and ligand.

For example, if one wanted to separate all of the proteins in a sample that bound to ATP from proteins that do not bind ATP, one could covalently link ATP to support beads and then elute the sample through column. All proteins that bind ATP will "stick" to the column, whereas those that do not bind ATP will pass quickly through it. The proteins are then released from the column by adding ATP.

The stationary phase is typically a gel matrix, often of agarose, a linear sugar molecule derived from algae. Usually the starting point is an undefined heterogeneous group of molecules in solution, such as a cell lysate, growth medium or blood serum. The molecule of interest will have a well known and defined property, and can be exploited during the affinity purification process. The process itself can be thought of as an entrapment, with the target molecule becoming trapped on a solid or stationary phase or medium. The other molecules in the mobile phase will not become trapped as they do not possess this property. The stationary phase can then be removed from the mixture, washed and the target molecule released from the entrapment in a process known as elution. Possibly the most common use of affinity chromatography is for the purification of recombinant proteins.

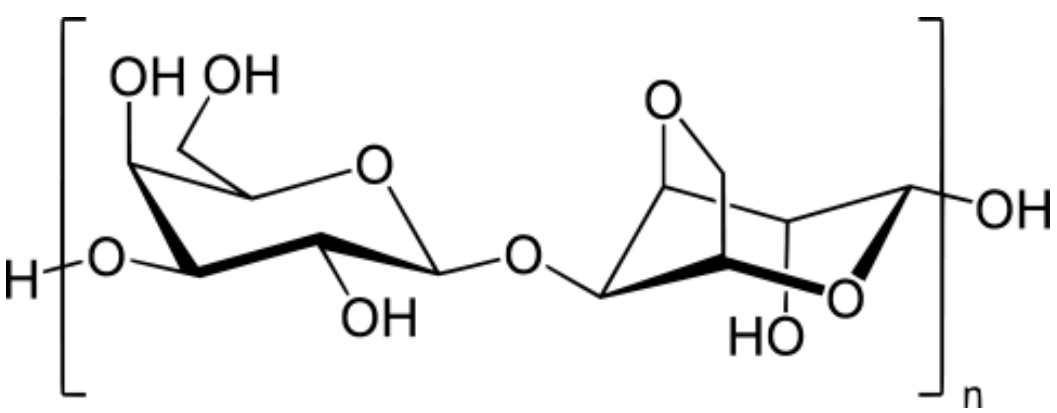
https://en.wikipedia.org/wiki/Affinity_chromatography

Related Glossary Terms

Drag related terms here

Agarose

Agarose is a polysaccharide polymer material, generally extracted from seaweed. Agarose is a linear polymer made up of the repeating unit of agarobiose, which is a disaccharide made up of D-galactose and 3,6-anhydro-L-galactopyranose. Agarose is one of the two principal components of agar, and is purified from agar by removing agar's other component, agaropectin. Below is shown the repeating unit of an agarose polymer.



https://en.wikipedia.org/wiki/Agarose

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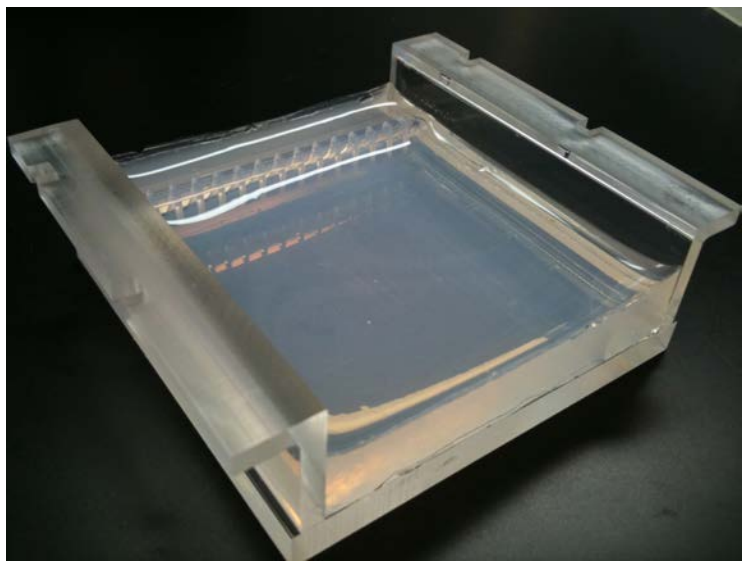
Agarose Gel Electrophoresis

Agarose gel electrophoresis is a method of gel electrophoresis used in biochemistry, molecular biology, genetics, and clinical chemistry to separate a mixed population of DNA or proteins in a matrix of agarose. The proteins may be separated by charge and/or size (isoelectric focusing agarose electrophoresis is essentially size independent), and the DNA and RNA fragments by length. Biomolecules are separated by applying an electric field to move the charged molecules through an agarose matrix, and the biomolecules are separated by size in the agarose gel matrix.



https://en.wikipedia.org/wiki/Agarose_gel_electrophoresis

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Aggrecan

Aggrecan, also known as cartilage-specific proteoglycan core protein (CSPC
droitin sulfate proteoglycan 1, is a protein that in humans is encoded by the
gene. This gene is a member of the lectican (chondroitin sulfate proteoglyc
The encoded protein is an integral part of the extracellular matrix in cartila
sue and it withstands compression in cartilage. Aggrecan is a proteoglycan,
tein modified with large carbohydrates. The human form of the protein is 2
acids long and can be expressed in multiple isoforms due to alternative spli

https://en.wikipedia.org/wiki/Aggrecan

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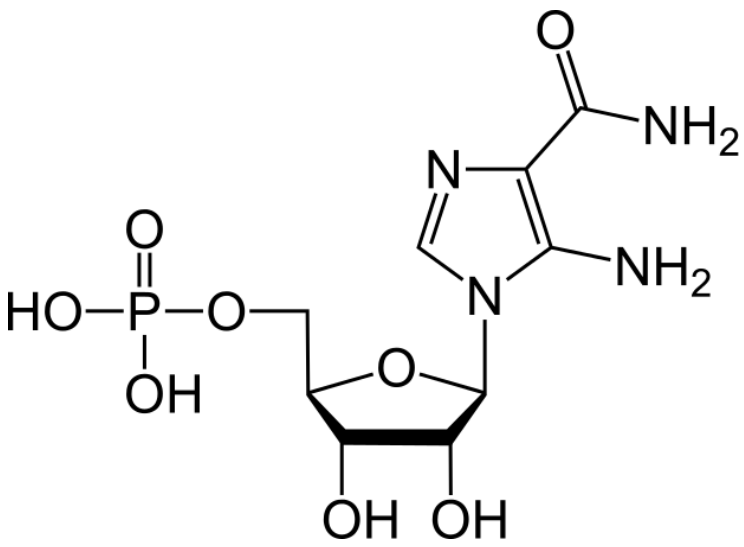
AICAR

5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) is an intermediate in the generation of inosine monophosphate. AICAR is an analog of adenosine monophosphate (AMP) that is capable of stimulating AMP-dependent protein kinase (AMPK) activity. AICAR has been used clinically to treat and protect against cardiac ischemic injury. The drug was first used in the 1980s as a method to preserve blood flow to the heart during surgery. Currently, the drug has also been shown as a potential treatment for diabetes by increasing the metabolic activity of tissues by changing the physical composition of muscle.



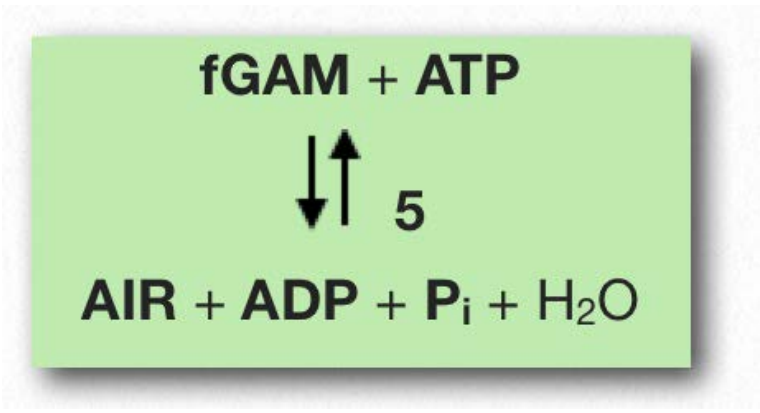
https://en.wikipedia.org/wiki/AICA_ribonucleotide

Related Glossary Terms

Drag related terms here

AIR Synthetase

AIR synthetase is the fifth enzyme in the *de novo* synthesis of purine nucleotides. It catalyzes the reaction to form 5-aminoimidizole ribonucleotide (AIR) from formylglycinamidine-ribonucleotide FGAM. This reaction closes the ring and produce a 5-membered imidazole ring of the purine nucleus (AIR). AIR synthetase catalyzes th transfer of the oxygen of the formyl group to phosphate. It is a sequential mechanism in which ATP binds first to the enzyme and ADP is released last. This enzyme hydro- lyzes ATP to activate the oxygen of the amide in order to carry out a nucleophilic attac by a nitrogen. In humans and many other organisms, this enzyme is contained within the trifunctional purine biosynthetic protein adenosine-3 polypeptide.



https://en.wikipedia.org/wiki/AIR_synthetase_(FGAM_cyclase)

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Chapter 6 - Metabolism: Nucleotides

Akt

Protein kinase B (PKB), also known as Akt, is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration.

Akt1 is involved in cellular survival pathways, by inhibiting apoptotic processes. Akt1 is also able to induce protein synthesis pathways, and is therefore a key signaling protein in the cellular pathways that lead to skeletal muscle hypertrophy, and general tissue growth. Mouse model with complete deletion of Akt1 manifests growth retardation and increased spontaneous apoptosis in tissues such as testes and thymus. Since it can block apoptosis, and thereby promote cell survival, Akt1 has been implicated as a major factor in many types of cancer. Akt (now also called Akt1) was originally identified as the oncogene in the transforming retrovirus, AKT8.

Akt2 is an important signaling molecule in the insulin signaling pathway. It is required to induce glucose transport. In a mouse which is null for Akt1 but normal for Akt2, glucose homeostasis is unperturbed, but the animals are smaller, consistent with a role for Akt1 in growth. In contrast, mice which do not have Akt2, but have normal Akt1, have mild growth deficiency and display a diabetic phenotype (insulin resistance), again consistent with the idea that Akt2 is more specific for the insulin receptor signaling pathway. Akt isoforms are overexpressed in a variety of human tumors, and, at the genomic level, are amplified in gastric adenocarcinomas (Akt1), ovarian (Akt2), pancreatic (Akt2) and breast (Akt2) cancer.

The role of Akt3 is less clear, though it appears to be predominantly expressed in the brain. It has been reported that mice lacking Akt3 have small brains.

https://en.wikipedia.org/wiki/Protein_kinase_B

Related Glossary Terms

Drag related terms here

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https://en.wikipedia.org/wiki/Protein_kinase_B

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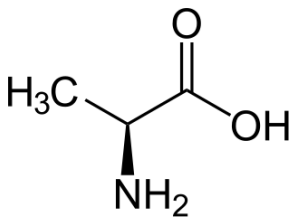
Chapter 2 - Structure & Function: Lipids

Alanine

Alanine (abbreviated as Ala or A; encoded by the codons GCU, GCC, GCA, and GCG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain methyl group, classifying it as a nonpolar (at physiological pH), aliphatic amino acid. It is non-essential in humans, meaning the body can synthesize it. The L-isomer (left-handed) of alanine is one of the 20 amino acids encoded by the human genetic code. L-Alanine is second only to leucine in rate of occurrence, accounting for 7.8% of the primary structure in a sample of 1,150 proteins. The right-handed form, D-Alanine occurs in bacterial cell walls and in some peptide antibiotics.



https://en.wikipedia.org/wiki/Alanine

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Alanine Aminotransferase

Alanine aminostransferase (ALT, also called alanine transaminase) catalyze
fer of an amino group from L-alanine to α-ketoglutarate, the products of th
transamination reaction being pyruvate and L-glutamate.

L-glutamate + Pyruvate ⇌ α-ketoglutarate + L-alanine

ALT (and all transaminases) require the coenzyme pyridoxal phosphate, wh
verted into pyridoxamine in the first phase of the reaction, when an amino
verted into a keto acid.

https://en.wikipedia.org/wiki/Alanine_transaminase

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Chapter 6 - Metabolism: Sugars

Alanine Transaminase

Alanine transaminase (ALT) catalyzes the transfer of an amino group from L-alanine to α-ketoglutarate, the products of this reversible transamination reaction being pyruvate and L-glutamate.

L-glutamate + Pyruvate ⇌ α-ketoglutarate + L-alanine

ALT (and all transaminases) require the coenzyme pyridoxal phosphate, which is converted into pyridoxamine in the first phase of the reaction, when an amino acid is converted into a keto acid.

When elevated ALT levels are found in the blood, the possible underlying causes can be further narrowed down by measuring other enzymes. For example, elevated ALT levels due to hepatocyte damage can be distinguished from bile duct problems by measuring alkaline phosphatase. Also, myopathy-related elevations in ALT should be suspected when the aspartate transaminase (AST) is greater than ALT. The possibility of muscle disease causing elevations in liver tests can be further explored by measuring muscle enzymes, including creatine kinase. Many drugs may elevate ALT levels, including Zileuton, ω-3-acid ethyl esters (Lovaza), anti-inflammatory drugs, antibiotics, cholesterol medications, some antipsychotics such as risperidone, and anticonvulsants.. Paracetamol may also elevate ALT levels.

https://en.wikipedia.org/wiki/Alanine_transaminase

Related Glossary Terms

Alcohol

An alcohol is any organic compound in which the hydroxyl functional group
bound to a saturated carbon atom.

https://en.wikipedia.org/wiki/Alcohol

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Alcohol Dehydrogenase

Alcohol dehydrogenases (ADH) (EC 1.1.1.1) are a group of dehydrogenase e
occur in many organisms and facilitate the interconversion between alcoho
hydes or ketones with the reduction of nicotinamide adenine dinucleotide (
NADH). In humans and many other animals, they serve to break down alco
otherwise are toxic, and they also participate in generation of useful aldehy
or alcohol groups during biosynthesis of various metabolites. In yeast, plan
many bacteria, some alcohol dehydrogenases catalyze the opposite reaction
fermentation to ensure a constant supply of NAD^+.

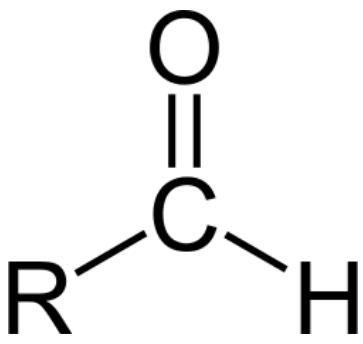
https://en.wikipedia.org/wiki/Alcohol_dehydrogenase

Related Glossary Terms

Drag related terms here

Aldehyde

An aldehyde is an organic compound containing a formyl group, a functional group with the structure -CHO, consisting of a carbonyl center (a carbon double bonded to oxygen) bonded to hydrogen that is bonded to an R group, which is any generic alkyl or side chain. The group without R is the aldehyde group or formyl group. Aldehydes differ from ketones in that the carbonyl is placed at the end of a carbon skeleton rather than between two carbon atoms. Aldehydes are common in organic chemistry. Many fragrances are aldehydes.



https://en.wikipedia.org/wiki/Aldehyde

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Aldolase

An aldolase is an enzyme that performs an aldol reaction (creating an aldol verse (cleaving an aldol). The word often refers to any type of fructose-bisp dolase, but can also refer to other enzymes, such as the one that forms sialic glycolysis, aldolase catalyzes the following reaction:

F1,6BP <=> Glyal3P + DHAP

https://en.wikipedia.org/wiki/Aldolase

Related Glossary Terms

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Aldose

An aldose, like a ketose, is a monosaccharide (a simple sugar) that contains only one aldehyde (−CH=O) group per molecule, whereas ketose contains a ketone group. The chemical formula takes the form $Cn(H_2O)n$. The simplest possible aldose is the diose glycolaldehyde, which only contains two carbon atoms.

Because they have at least one asymmetric carbon center, aldoses with three or more carbon atoms exhibit stereoisomerism. Aldoses containing stereogenic centers can exist in either a d- form or l- form. The determination is made based on the chirality of the penultimate carbon (the second-furthest from the aldehyde), where alcohol groups on the right of the Fischer projection result in d-aldoses, and epimers with alcohols on the left result in l-aldoses. Biological systems tend to recognize d-aldoses more than l-aldoses.

Examples of aldose include glycolaldehyde, glyceraldehyde, erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, talose, and galactose. All of these examples contain one group of aldehyde. They only differ in numbers of carbons in carbon skeleton. All of these complex sugars serve an important role in biochemistry.

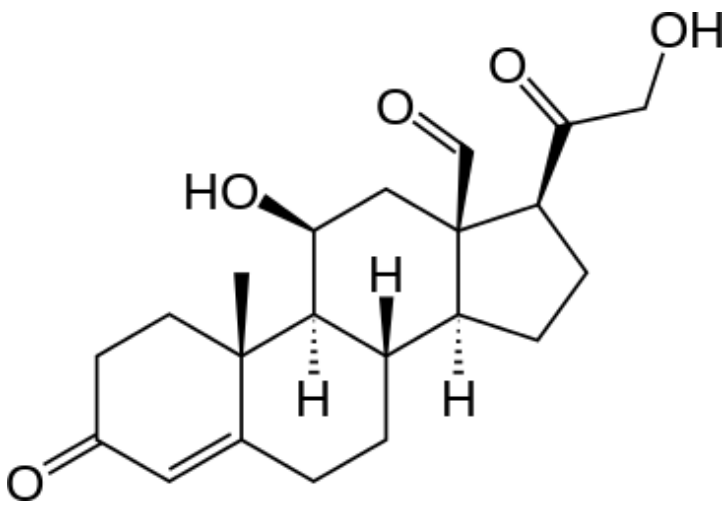
An aldose differs from a ketose in that it has a carbonyl group at the end of the carbon chain instead of in the middle. This allows ketoses and aldoses to be chemically differentiated through Seliwanoff's test. In Seliwanoff's test, aldoses tend to react in a slow pace, and produce a light pink color, while ketoses react with resorcinol to produce a dark red color. With different color of production, aldoses can be differentiate from the ketoses. An aldose may isomerize to a ketose through the Lobry-de Bruyn-van Ekenstein transformation. Aldose and ketose, also perform in different roles. Aldoses tend to isomerise into ketoses.

https://en.wikipedia.org/wiki/Aldose

Related Glossary Terms

Aldosterone

Aldosterone is a steroid hormone, "the main mineralocorticoid hormone", produced by the outer section (zona glomerulosa) of the adrenal cortex in the adrenal gland. It plays a central role in the regulation of blood pressure mainly by acting on the distal tubules and collecting ducts of the nephron, increasing reabsorption of ions and water in the kidney, to cause the conservation of sodium, secretion of potassium, increase in water retention, and increase in blood pressure and blood volume. When dysregulated, aldosterone is pathogenic and contributes to the development and progression of cardiovascular and renal disease. Aldosterone has exactly the opposite function of the atrial natriuretic hormone secreted by the heart.



https://en.wikipedia.org/wiki/Aldosterone

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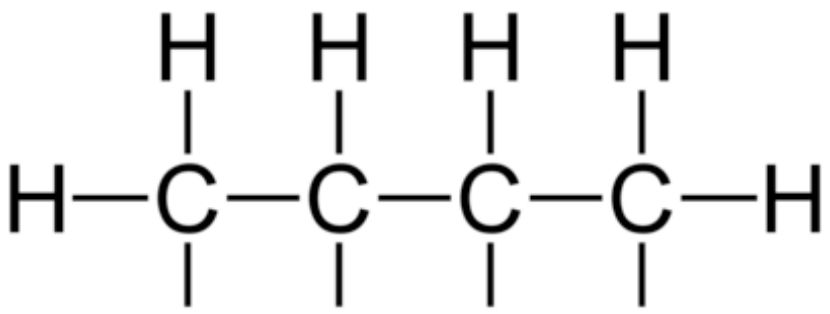
Chapter 2 - Structure & Function: Lipids

Aliphatic

In organic chemistry, hydrocarbons (compounds composed of carbon and hydrog
are divided into two classes: aromatic compounds and aliphatic compounds also
known as non-aromatic compounds. Aliphatics can be cyclic, but only aromatic co
pounds contain an especially stable ring of atoms, such as benzene. Aliphatic com
pounds can be saturated, like hexane, or unsaturated, like hexene. Open-chain co
pounds (whether straight or branched) contain no rings of any type, and are thus
phatic. An example of an aliphatic compound is shown below.



https://en.wikipedia.org/wiki/Aliphatic_compound

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Alkaline

Alkalinity is the name given to the quantitative capacity of an aqueous solu
tralize an acid. Measuring alkalinity is important in determining a stream's
neutralize acidic pollution from rainfall or wastewater. It is one of the best
the sensitivity of the stream to acid inputs. There can be long-term changes
linity of streams and rivers in response to human disturbances.

https://en.wikipedia.org/wiki/Alkalinity

Related Glossary Terms

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Alkaloid

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties. Some synthetic compounds of similar structure are also termed alkaloids. In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and, more rarely, other elements such as chlorine, bromine, and phosphorus.

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals. They can be purified from crude extracts of these organisms by acid-base extraction. Alkaloids have a wide range of pharmacological activities including antimalarial (e.g. quinine), antiasthma (e.g. ephedrine), anticancer (e.g. homoharringtonine), cholinomimetic (e.g. galantamine), vasodilatory (e.g. vincamine), antiarrhythmic (e.g. quinidine), analgesic (e.g. morphine), antibacterial (e.g. chelerythrine), and antihyperglycemic activities (e.g. piperine).

Many have found use in traditional or modern medicine, or as starting points for drug discovery. Other alkaloids possess psychotropic (e.g. psilocin) and stimulant activities (e.g. cocaine, caffeine, nicotine, theobromine), and have been used in entheogenic rituals or as recreational drugs. Alkaloids can be toxic too (e.g. atropine, tubocurarine). Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly evoke a bitter taste.

The boundary between alkaloids and other nitrogen-containing natural compounds is not clear-cut. Compounds like amino acid peptides, proteins, nucleotides, nucleic acid, amines, and antibiotics are usually not called alkaloids. Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually classified as amines rather than as alkaloids. Some authors, however, consider alkaloids a special case of amines.

https://en.wikipedia.org/wiki/Alkaloid

Alkoxide

An alkoxide is the conjugate base of an alcohol and therefore consists of an group bonded to a negatively charged oxygen atom. They can be written as R is the organic substituent. Alkoxides are strong bases and, when R is not nucleophiles and good ligands. Alkoxides, although generally not stable in p vents such as water, occur widely as intermediates in various reactions, inc Williamson ether synthesis.

An alkoxide ion of serine plays an important role the the catalytic mechanis proteases.

https://en.wikipedia.org/wiki/Alkoxide

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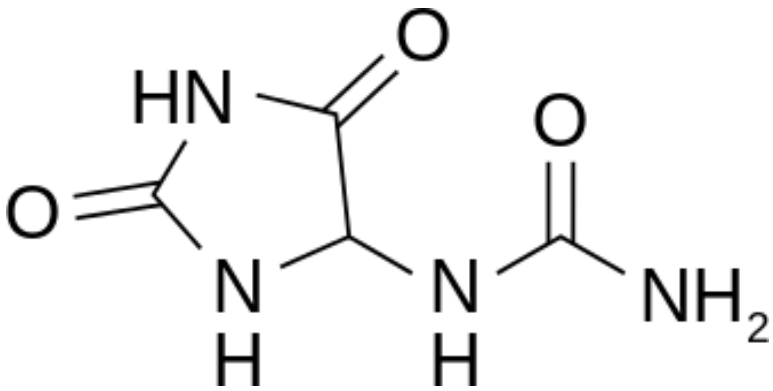
Allantoin

Named after the allantois (an amniote embryonic excretory organ in which it concentrates during development in most mammals except humans and higher apes[vague]), allantoin is a product of oxidation of uric acid by purine catabolism. After birth, it is the predominant means by which nitrogenous waste is excreted in the urine of these animals. In humans and higher apes, the metabolic pathway for conversion of uric acid to allantoin is not present, so the former is excreted. Recombinant rasburicase is sometimes used as a drug to catalyze this metabolic conversion in patients. In fish, allantoin is broken down further (into ammonia) before excretion. Allantoin is a major metabolic intermediate in many other organisms including plants and bacteria.

Allantoin has been shown to improve insulin resistance when administered to rats and increased lifespan when administered to the nematode worm *C.elegans*.



https://en.wikipedia.org/wiki/Allantoin

Related Glossary Terms

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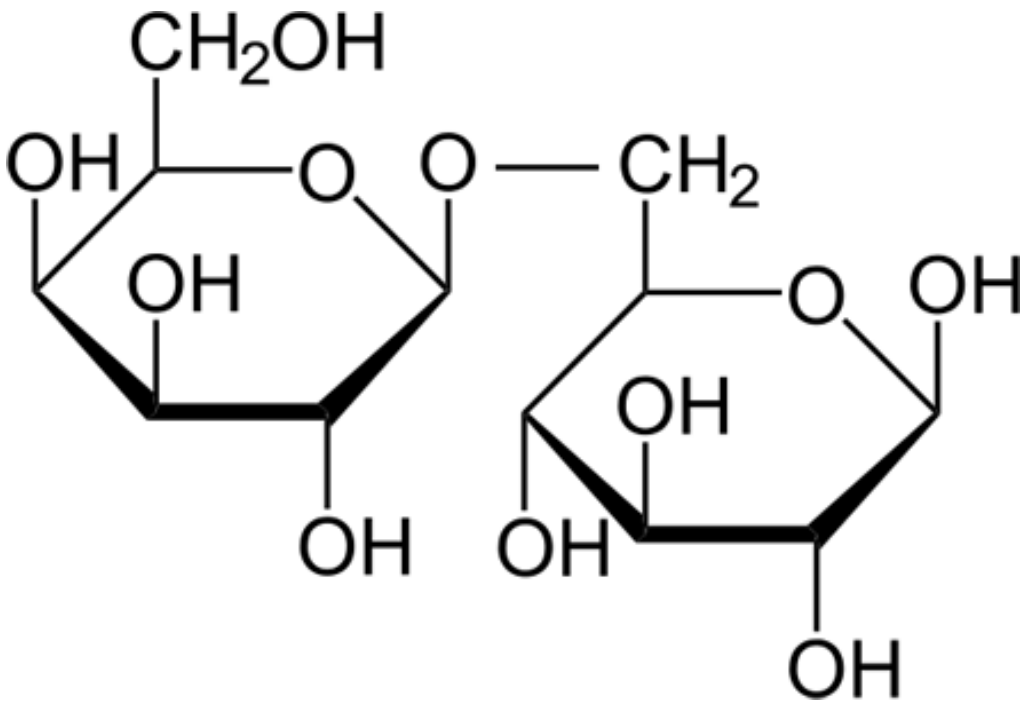
Allolactose

Allolactose is a disaccharide similar to lactose. It consists of the monosaccharides D-galactose and D-glucose linked through a β1-6 glycosidic linkage instead of the β1-4 linkage of lactose. It may arise from the occasional transglycosylation of lactose by β-galactosidase. It is the isomer of spermatiglogen.

Allolactose is an inducer of the *lac* operon in *Escherichia coli*. It binds to a subunit of the tetrameric *lac* repressor, which results in conformational changes and reduces the binding affinity of the *lac* repressor to the *lac* operator, thereby dissociating it from the *lac* operator. The absence of the repressor allows the transcription of the *lac* operon to proceed. A non-hydrolyzable analog of allolactose, isopropyl β-D-1-thiogalactopyranoside (IPTG), is normally used in molecular biology to induce the lac operon.



https://en.wikipedia.org/wiki/Allolactose

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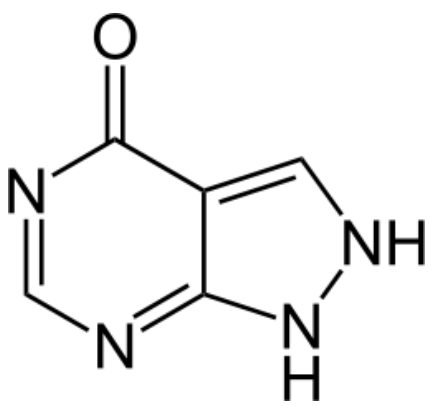
Allopurinol

Allopurinol, sold under the brand name Zyloprim and generics, is a medication us
primarily to treat excess uric acid in the blood and its complications, including ch
gout. It is a xanthine oxidase inhibitor which is administered orally.

Allopurinol is used in chronic gout to prevent future attacks. It does not alleviate a
attacks of gout and there is currently controversy over the issue of whether it can a
ally make acute gout attacks worse initially.



https://en.wikipedia.org/wiki/Allopurinol

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Chapter 6 - Metabolism: Nucleotides

Chapter 9 - Point by Point: Metabolism

Allosteric

Allosteric regulation (or allosteric control) is the regulation of an enzyme by binding an effector molecule. Effectors that bind at the active site are known as homotropic effectors, whereas those that bind elsewhere are known as heterotropic effectors.

The site to which the effector binds is termed the allosteric site. Allosteric sites allow effectors to bind to the protein, often resulting in a conformational change involving protein dynamics. Effectors that enhance the protein's activity are referred to as allosteric activators, whereas those that decrease the protein's activity are called allosteric inhibitors.

Allosteric regulations are a natural example of control loops, such as feedback from downstream products or feedforward from upstream substrates. Long-range allostery is especially important in cell signaling. Allosteric regulation is also particularly important in the cell's ability to adjust enzyme activity.

Most allosteric effects can be explained 1) by the concerted MWC model put forth by Monod, Wyman, and Changeux, 2) by the sequential model described by Koshland, Nemethy, and Filmer or 3) by the dossociative concerted Morpheein model. All models postulate that enzyme subunits exist in one of two conformations, tensed (T) or relaxed (R), and that relaxed subunits bind substrate more readily than those in the tense state.

https://en.wikipedia.org/wiki/Allosteric_regulation

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Allosteric Control

In biochemistry, allosteric regulation (or allosteric control) is the regulation of a protein by binding an effector molecule at a site other than the enzyme's active site.

The site to which the effector binds is termed the allosteric site. Allosteric sites allow effectors to bind to the protein, often resulting in a conformational change involving protein dynamics. Effectors that enhance the protein's activity are referred to as allosteric activators, whereas those that decrease the protein's activity are called allosteric inhibitors.

Allosteric regulations are a natural example of control loops, such as feedback from downstream products or feedforward from upstream substrates. Long-range allostery is especially important in cell signaling. Allosteric regulation is also particularly important in the cell's ability to adjust enzyme activity.

The term allostery comes from the Greek allos (ἄλλος), "other," and stereos (στερεός), "solid (object)." This is in reference to the fact that the regulatory site of an allosteric protein is physically distinct from its active site.

https://en.wikipedia.org/wiki/Allosteric_regulation

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Allosterism

In biochemistry, allosteric regulation (or allosteric control) is the regulation of a protein by binding an effector molecule at a site other than the enzyme's active site.

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https://en.wikipedia.org/wiki/Allosteric_regulation

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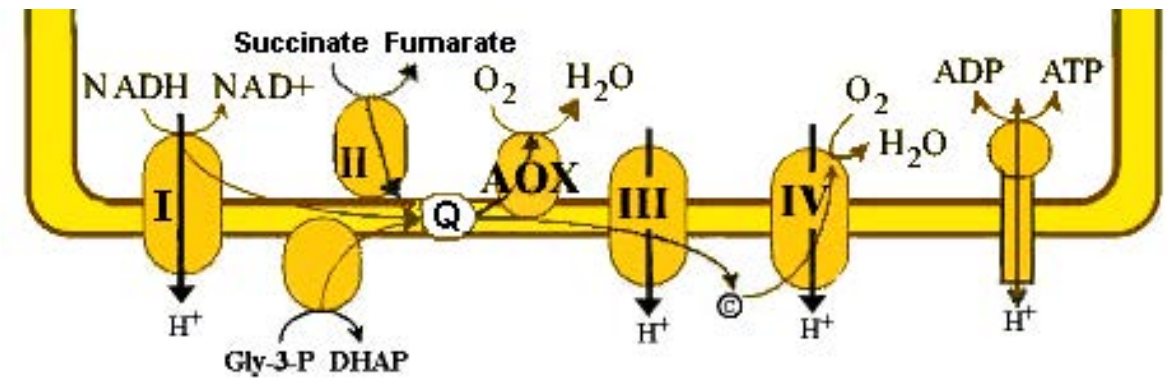
Alternative Oxidase

The alternative oxidase (AOX) is an enzyme that forms part of the electron transport chain in mitochondria of different organisms. Proteins homologous to the mitochondrial oxidase have also been identified in bacterial genomes.

The oxidase provides an alternative route for electrons passing through the electron transport chain to reduce oxygen. However, as several proton-pumping steps are bypassed in this alternative pathway, activation of the oxidase reduces ATP generation. This enzyme was first identified as a distinct oxidase pathway from cytochrome c oxidase as the alternative oxidase is resistant to inhibition by the poison cyanide.



https://en.wikipedia.org/wiki/Alternative_oxidase

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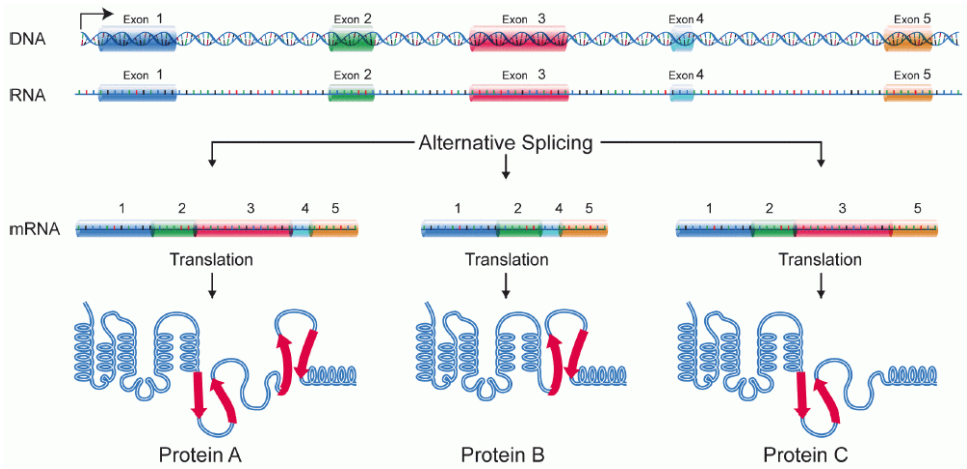
Alternative Splicing

Alternative splicing is a regulated process during gene expression that results in a single gene coding for multiple proteins. In this process, particular exons of a gene may be included within or excluded from the final, processed messenger RNA (mRNA) produced from that gene. Consequently, the proteins translated from alternatively spliced mRNAs will contain differences in their amino acid sequence and, often, in their biological functions. Notably, alternative splicing allows the human genome to direct the synthesis of many more proteins than would be expected from its 20,000 protein-coding genes. Alternative splicing is sometimes termed differential splicing.

Alternative splicing occurs as a normal phenomenon in eukaryotes, where it greatly increases the biodiversity of proteins that can be encoded by the genome. In humans, ~95% of multi-exonic genes are alternatively spliced. There are numerous modes of alternative splicing observed, of which the most common is exon skipping. In this mode, a particular exon may be included in mRNAs under some conditions or in particular tissues, and omitted from the mRNA in others.

The production of alternatively spliced mRNAs is regulated by a system of trans-acting proteins that bind to cis-acting sites on the primary transcript itself. Such proteins include splicing activators that promote the usage of a particular splice site, and splicing repressors that reduce the usage of a particular site. Mechanisms of alternative splicing are highly variable, and new examples are constantly being found, particularly through the use of high-throughput techniques. Researchers hope to fully elucidate the regulatory systems involved in splicing, so that alternative splicing products from a given gene under particular conditions could be predicted by a "splicing code".

Abnormal variations in splicing are also implicated in disease. A large proportion of human genetic disorders result from splicing variants. Abnormal splicing variants are also thought to contribute to the development of cancer, and splicing factor genes are frequently mutated in different types of cancer.



https://en.wikipedia.org/wiki/Alternative_splicing#/media/File:DNA_alternative_splicing.gif

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Alzheimer’s Disease

Alzheimer's disease (AD), also known as Alzheimer disease, or just Alzheim
counts for 60% to 70% of cases of dementia. It is a chronic neurodegenerat
that usually starts slowly and gets worse over time. The most common early
is difficulty in remembering recent events (short-term memory loss). As the
vances, symptoms can include problems with language, disorientation (incl
ily getting lost), mood swings, loss of motivation, not managing self care, an
ioral issues. As a person's condition declines, they often withdraw from fam
ety. Gradually, bodily functions are lost, ultimately leading to death. Althou
speed of progression can vary, the average life expectancy following diagno
to nine years.

https://en.wikipedia.org/wiki/Alzheimer%27s_disease

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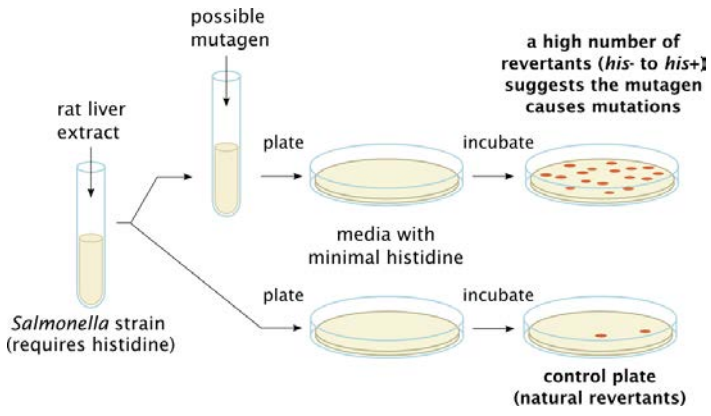
Ames Test

The Ames test is a widely employed method that uses bacteria to test whether a given chemical can cause mutations in the DNA of the test organism. More formally, it is a biological assay to assess the mutagenic potential of chemical compounds. A positive test indicates that the chemical is mutagenic and therefore may act as a carcinogen, because cancer is often linked to mutation. The test serves as a quick and convenient assay to estimate the carcinogenic potential of a compound because standard carcinogen assays on mice and rats are time-consuming (taking two to three years to complete) and expensive. However, false-positives and false-negatives are known.

The Ames test uses several strains of the bacterium *Salmonella typhimurium* that carry mutations in genes involved in histidine synthesis. These strains are auxotrophic mutants, i.e. they require histidine for growth, but cannot produce it. The method tests the capability of the tested substance in creating mutations that result in a return to a "prototrophic" state, so that the cells can grow on a histidine-free medium.
The tester strains are specially constructed to detect either frameshift (e.g. strains TA-1537 and TA-1538) or point (e.g. strain TA-1531) mutations in the genes required to synthesize histidine, so that mutagens acting via different mechanisms may be identified. Some compounds are quite specific, causing reversions in just one or two strains. The tester strains also carry mutations in the genes responsible for lipopolysaccharide synthesis, making the cell wall of the bacteria more permeable, and in the excision repair system to make the test more sensitive. Rat liver extract is optionally added to simulate the effect of metabolism, as some compounds, like benzo[a]pyrene, are not mutagenic themselves but their metabolic products are.

The bacteria are spread on an agar plate with small amount of histidine. This small amount of histidine in the growth medium allows the bacteria to grow for an initial time and have the opportunity to mutate. When the histidine is depleted only bacteria that have mutated to gain the ability to produce its own histidine will survive. The plate is incubated for 48 hours. The mutagenicity of a substance is proportional to the number of colonies observed.

The procedure was described in a series of papers in the early 1970s by Bruce Ames and his group at the University of California, Berkeley.



https://en.wikipedia.org/wiki/Ames_test

Amine

In organic chemistry, amines are compounds and functional groups that contain a basic nitrogen atom with a lone pair. Amines are formally derivatives of ammonia, wherein one or more hydrogen atoms have been replaced by a substituent such as an alkyl or aryl group.

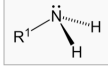
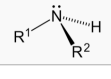
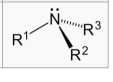
An aliphatic amine has no aromatic ring attached directly to the nitrogen atom. Aromatic amines have the nitrogen atom connected to an aromatic ring as in the various anilines. The aromatic ring decreases the alkalinity of the amine, depending on its substituents. The presence of an amine group strongly increases the reactivity of the aromatic ring, due to an electron-donating effect.

Amines are organized into four subcategories:

- Primary amines — Primary amines arise when one of three hydrogen atoms in ammonia is replaced by an alkyl or aromatic. Important primary alkyl amines include methylamine, ethanolamine (2-aminoethanol), and the buffering agent tris, while primary aromatic amines include aniline.
- Secondary amines — Secondary amines have two organic substituents (alkyl, aryl or both) bound to N together with one hydrogen (or no hydrogen if one of the substituent bonds is double). Important representatives include dimethylamine and methylethanolamine, while an example of an aromatic amine would be diphenylamine.
- Tertiary amines — In tertiary amines, all three hydrogen atoms are replaced by organic substituents. Examples include trimethylamine, which has a distinctively fishy smell, or triphenylamine.

Cyclic amines — Cyclic amines are either secondary or tertiary amines. Examples of cyclic amines include the 3-membered ring aziridine and the six-membered ring piperidine. N-methylpiperidine and N-phenylpiperidine are examples of cyclic tertiary amines.

It is also possible to have four organic substituents on the nitrogen. These species are not amines but are quaternary ammonium cations and have a charged nitrogen center. Quaternary ammonium salts exist with many kinds of anions.

Primary amine	Secondary amine	Tertiary amine
		

https://en.wikipedia.org/wiki/Amine

Related Glossary Terms

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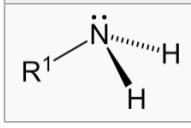
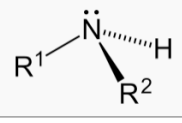
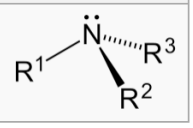
It is also possible to have four organic substituents on the nitrogen. These species are not amines but are quaternary ammonium cations and have a charged nitrogen center. Quaternary ammonium salts exist with many kinds of anions.

Primary amine	Secondary amine	Tertiary amine
		

https://en.wikipedia.org/wiki/Amine

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Amino Acid

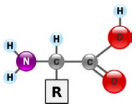
Amino acids are biologically important organic compounds containing amine ($-NH_2$) and carboxylic acid (-COOH) functional groups, usually along with a side-chain specific to each amino acid. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen, though other elements are found in the side-chains of certain amino acids.

In biochemistry, amino acids having both the amine and the carboxylic acid groups attached to the first (α-) carbon atom have particular importance. They are known as 2-, α-, or α-amino acids (generic formula $H_2NCHRCOOH$ in most cases, where R is an organic substituent known as a "side-chain"). Often the term "amino acid" is used to refer specifically to these. They include the 23 proteinogenic ("protein-building") amino acids, which combine into peptide chains ("polypeptides") to form the building-blocks of a vast array of proteins. These are all L-stereoisomers ("left-handed" isomers), although a few D-amino acids ("right-handed") occur in bacterial envelopes, as a neuromodulator (D-serine), and in some antibiotics.

Twenty of the proteinogenic amino acids are encoded directly by triplet codons in the genetic code and are known as "standard" amino acids. The other three ("non-standard" or "non-canonical") are selenocysteine (present in many noneukaryotes as well as most eukaryotes, but not coded directly by DNA), pyrrolysine (found only in some archea and one bacterium) and N-formylmethionine (which is often the initial amino acid of proteins in bacteria, mitochondria, and chloroplasts). Pyrrolysine and selenocysteine are encoded via variant codons. For example, selenocysteine is encoded by a stop codon and SECIS element which allows the stop codon to be "read" instead of protein synthesis stopping. Codon–tRNA combinations not found in nature can also be used to "expand" the genetic code and create novel proteins known as alloproteins incorporating non-proteinogenic amino acids.

Many important proteinogenic and non-proteinogenic amino acids also play critical non-protein roles within the body. For example, in the human brain, glutamate (standard glutamic acid) and γ-amino-butyric acid ("GABA", non-standard γ-amino acid) are, respectively, the main excitatory and inhibitory neurotransmitters. Hydroxyproline (a major component of the connective tissue collagen) is synthesized from proline. The standard amino acid glycine is used to synthesize porphyrins used in red blood cells. The non-standard carnitine is used in lipid transport.

Nine proteinogenic amino acids are called "essential" for humans because they cannot be created from other compounds by the human body and so must be taken in as food. Others may be conditionally essential for certain ages or medical conditions. Essential amino acids may also differ between species.



https://en.wikipedia.org/wiki/Amino_acid

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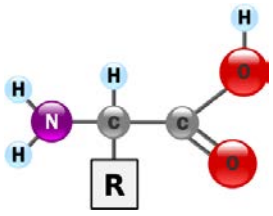

https://en.wikipedia.org/wiki/Amino_acid

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Amino Terminus

Proteins have a specific orientation (called polarity, though it has nothing t
charge) associated with them. The end of the protein that has the free α-am
is referred to as the amino terminus.

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Aminoacyl tRNA Synthetase

An aminoacyl tRNA synthetase (aaRS) is an enzyme that attaches the appropriate amino acid onto its tRNA. It does so by catalyzing the esterification of a specific cognate amino acid or its precursor to one of all its compatible cognate tRNAs to form an aminoacyl-tRNA.

This is sometimes called "charging" or "loading" the tRNA with the amino acid. Once the tRNA is charged, a ribosome can transfer the amino acid from the tRNA onto a growing peptide, according to the genetic code.

There are two classes of aminoacyl tRNA synthetase:

- Class I has two highly conserved sequence motifs. It aminoacylates at the 2'-OH of a terminal adenosine nucleotide on tRNA, and it is usually monomeric or dimeric (one or two subunits, respectively).
- Class II has three highly conserved sequence motifs. It aminoacylates at the 3'-OH of a terminal adenosine on tRNA, and is usually dimeric or tetrameric (two or four subunits, respectively). Although phenylalanine-tRNA synthetase is class II, it aminoacylates at the 2'-OH.

The amino acids are attached to the hydroxyl (-OH) group of the adenosine via the carboxyl (-COOH) group. Regardless of where the aminoacyl is initially attached to the nucleotide, the 2'-O-aminoacyl-tRNA will ultimately migrate to the 3' position via transesterification.

https://en.wikipedia.org/wiki/Aminoacyl_tRNA_synthetase

Related Glossary Terms

Aminopeptidases

Aminopeptidases are enzymes that catalyze the cleavage of amino acids fro
amino terminus (N-terminus) of proteins or peptides. They are widely distr
throughout the animal and plant kingdoms and are found in many subcellu
elles, in cytosol, and as membrane components. Aminopeptidases are used
cellular functions. Many, but not all, of these peptidases are zinc metalloen

One important aminopeptidase is a zinc-dependent enzyme produced and s
glands of the small intestine. It helps the enzymatic digestion of proteins. A
digestive enzymes produced by these glands include dipeptidases, maltase,
tase, and enterokinase.

https://en.wikipedia.org/wiki/Aminopeptidase

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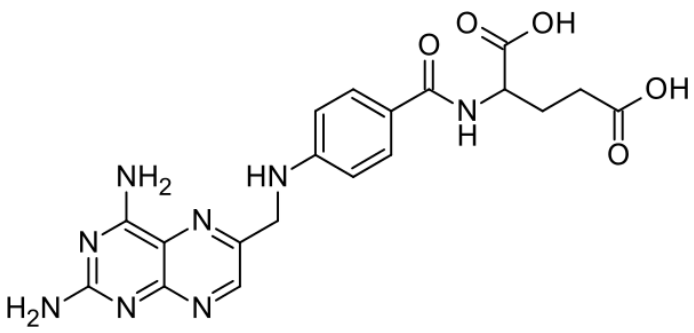
Chapter 4 - Catalysis: Mechanism

Aminopterin

Aminopterin (or 4-aminopteroic acid), the 4-amino derivative of folic acid, is an anti-neoplastic drug with immunosuppressive properties often used in chemotherapy. Aminopterin is a synthetic derivative of pterin. Aminopterin works as an enzyme inhibitor by competing for the folate binding site of the enzyme dihydrofolate reductase. Its binding affinity for dihydrofolate reductase effectively blocks tetrahydrofolate synthesis. This results in the depletion of nucleotide precursors and inhibition of DNA, RNA, and protein synthesis.

Discovered by Dr. Yellapragada Subbarow, the drug was first used by Sidney Farber in 1947 to induce remissions among children with leukemia. Aminopterin was later marketed by Lederle Laboratories (Pearl River, New York) in the United States from 1953 to 1964 for the indication of pediatric leukemia. The closely related antifolate methotrexate was simultaneously marketed by the company during the same period. Aminopterin was discontinued by Lederle Laboratories in favor of methotrexate due to manufacturing difficulties of the former.

During the period Aminopterin was marketed, the agent was used off-label to safely treat over 4,000 patients with psoriasis in the United States, producing dramatic clearing of lesions. The use of aminopterin in cancer treatment was supplanted in the 1950s by methotrexate due to the latter's better therapeutic index in a rodent tumor model. Now in a more pure preparation and supported by laboratory evidence of superior tumor cell uptake *in vitro*, aminopterin is being investigated in clinical trials in leukemia as a potentially superior antifolate to methotrexate.



https://en.wikipedia.org/wiki/Aminopterin

Ammonia

Ammonia or azane is a compound of nitrogen and hydrogen with the formula NH_3. In water, ammonia readily forms the ammonium ion (NH_4^+) It is a colorless gas with a characteristic pungent smell. Ammonia contributes significantly to the nutritional needs of terrestrial organisms by serving as a precursor to food and fertilizers. Ammonia, either directly or indirectly, is also a building block for the synthesis of many pharmaceuticals and is used in many commercial cleaning products. Although common in nature and in wide use, ammonia is both caustic and hazardous in its concentrated form.

Ammonia is both a metabolic waste and a metabolic input throughout the biosphere. It is an important source of nitrogen for living systems. Although atmospheric nitrogen abounds (more than 75%), few living creatures are capable of using this atmospheric nitrogen in its diatomic form, N_2 gas. Therefore, nitrogen fixation is required for the synthesis of amino acids, which are the building blocks of protein. Some plants rely on ammonia and other nitrogenous wastes incorporated into the soil by decaying matter. Others, such as nitrogen-fixing legumes, benefit from symbiotic relationships with rhizobia that create ammonia from atmospheric nitrogen.

In certain organisms, ammonia is produced from atmospheric nitrogen by enzymes called nitrogenases. The overall process is called nitrogen fixation. Although it is unlikely that biomimetic methods that are competitive with the Haber process will be developed, intense effort has been directed toward understanding the mechanism of biological nitrogen fixation. The scientific interest in this problem is motivated by the unusual structure of the active site of the enzyme, which consists of an Fe_7MoS_9 ensemble.

Ammonia is also a metabolic product of amino acid deamination catalyzed by enzymes such as glutamate dehydrogenase 1. Ammonia excretion is common in aquatic animals. In humans, it is quickly converted to urea, which is much less toxic, particularly less basic. This urea is a major component of the dry weight of urine. Most reptiles, birds, insects, and snails excrete uric acid solely as nitrogenous waste.

Ammonia also plays a role in both normal and abnormal animal physiology. It is biosynthesized through normal amino acid metabolism and is toxic in high concentrations. The liver converts ammonia to urea through a series of reactions known as the urea cycle. Liver dysfunction, such as that seen in cirrhosis, may lead to elevated amounts of ammonia in the blood (hyperammonemia). Likewise, defects in the enzymes responsible for the urea cycle, such as ornithine transcarbamylase, lead to hyperammonemia. Hyperammonemia contributes to the confusion and coma of hepatic encephalopathy, as well as the neurologic disease common in people with urea cycle defects and organic acidurias.

Ammonia is important for normal animal acid/base balance. After formation of ammonium from glutamine, α-ketoglutarate may be degraded to produce two molecules of bicarbonate, which are then available as buffers for dietary acids. Ammonium is excreted in the urine, resulting in net acid loss. Ammonia may itself diffuse across the renal tubules, combine with a hydrogen ion, and thus allow for further acid excretion.

Ammonium ions are a toxic waste product of metabolism in animals. In fish and aquatic invertebrates, it is excreted directly into the water. In mammals, sharks, and amphibians, it is converted in the urea cycle to urea, because it is less toxic and can be stored more efficiently. In birds, reptiles, and terrestrial snails, metabolic ammonium is converted into uric acid, which is solid, and can therefore be excreted with minimal water loss.

https://en.wikipedia.org/wiki/Ammonia

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Ammonotelic

An ammonotelic (sometimes spelled ammoniotelic) organism excretes solu
nia as a result of deamination. Ammonia is highly toxic to tissues and extre
ble in water. A proportion of 0.5 L of water is required per 1 g of nitrogen to
ammonia levels in the excretory fluid below the level in body fluids, otherw
may result. Ammonotelic animals include protozoans, crustaceans, platyhe
darians, poriferans, echinoderms, and other aquatic invertebrates, among o

Ammonotelism is one of the three major forms of excretion of nitrogenous
ganisms, the others being ureotelism and uricotelism.

https://en.wikipedia.org/wiki/Ammonotelic

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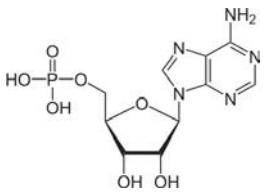
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 9 - Point by Point: Metabolism

AMP

Adenosine monophosphate (AMP), also known as 5'-adenylic acid, is a nucleotide that is used as a monomer in RNA. It is an ester of phosphoric acid and the nucleoside adenosine. AMP consists of a phosphate group, the sugar ribose, and the nucleobase adenine. As a substituent it takes the form of the prefix adenylyl-.

AMP can also be cylized to form a structure known as cyclic AMP (or cAMP). Within certain cells the enzyme adenylate cyclase makes cAMP from ATP, and typically this reaction is regulated by hormones such as adrenaline or glucagon. cAMP plays an important role in intracellular signaling.



https://en.wikipedia.org/wiki/Adenosine_monophosphate

Image - https://en.wikipedia.org/wiki/Adenosine_monophosphate#/media/File:Adenosinmonophosphat_protoniert.svg

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AMP Deaminase

Adenosine monophosphate deaminase 1 catalyzes the deamination of AMP
skeletal muscle and plays an important role in the purine nucleotide cycle.
genes have been identified, AMPD2 and AMPD3, for the liver- and erythroc
isoforms, respectively. Deficiency of the muscle-specific enzyme is apparen
mon cause of exercise-induced myopathy and probably the most common c
metabolic myopathy in the human.

A new research report shows that the widely prescribed diabetes medicatio
formin works on AMP kinase by directly inhibiting AMP deaminase, thereb
ing cellular AMP.

https://en.wikipedia.org/wiki/AMP_deaminase

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AMP Kinase

5' AMP-activated protein kinase or AMPK or 5' adenosine monophosphate-activated (AMP) protein kinase is an enzyme that plays a role in cellular energy homeostasis. It consists of three proteins (subunits) that together make a functional enzyme, conserved from yeast to humans. It is expressed in a number of tissues, including the liver, brain, and skeletal muscle. The net effect of AMPK activation is stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis, and triglyceride synthesis, inhibition of adipocyte lipolysis and lipogenesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and modulation of insulin secretion by pancreatic β-cells.

AMPK acts as a metabolic master switch regulating several intracellular systems including the cellular uptake of glucose, the β-oxidation of fatty acids and the biogenesis of glucose transporter 4 (GLUT4) and mitochondria. The energy-sensing capability of AMPK can be attributed to its ability to detect and react to fluctuations in the AMP:ATP ratio that take place during rest and exercise (muscle stimulation). During muscle stimulation, AMP increases while ATP decreases, which changes AMPK into a good substrate for activation via an upstream kinase complex, AMPKK, or better, where binding of AMP renders activated AMPK that is phosphorylated at Thr-172 a worse substrate for protein phosphatase 2Cα.

AMPKK is a complex of three proteins, STE-related adaptor (STRAD), mouse protein 25 (MO25), and LKB1 (a serine/threonine kinase). During a bout of exercise, AMPK activity increases while the muscle cell experiences metabolic stress brought about by an extreme cellular demand for ATP. Upon activation, AMPK increases cellular energy levels by inhibiting anabolic energy consuming pathways (fatty acid synthesis, protein synthesis, etc.) and stimulating energy producing, catabolic pathways (fatty acid oxidation, glucose transport, etc.).

https://en.wikipedia.org/wiki/AMP-activated_protein_kinase

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https://en.wikipedia.org/wiki/AMP-activated_protein_kinase

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Amphipathic

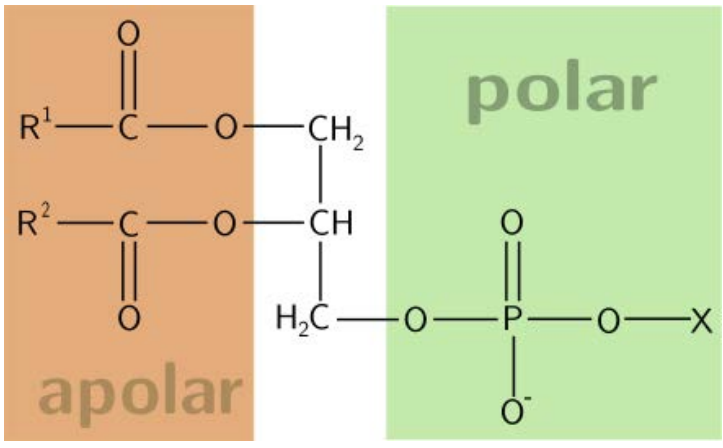
Amphiphile (from the Greek αμφις, amphis: both and φιλία, philia: love, friendship) is a term describing a chemical compound possessing both hydrophilic (water-loving, polar) and lipophilic (fat-loving) properties. Such a compound is called amphiphilic or amphipathic.

Phospholipids, a class of amphiphilic molecules, are the main components of biological membranes. The amphiphilic nature of these molecules defines the way in which they form membranes. They arrange themselves into bilayers, by positioning their polar groups towards the surrounding aqueous medium, and their lipophilic chains towards the inside of the bilayer, defining a non-polar region between two polar ones.

Although phospholipids are principal constituents of biological membranes, there are other constituents, such as cholesterol and glycolipids, which are also included in these structures and give them different physical and biological properties.

Many other amphiphilic compounds, such as pepducins, strongly interact with biological membranes by insertion of the hydrophobic part into the lipid membrane, while exposing the hydrophilic part to the aqueous medium, altering their physical behavior and sometimes disrupting them.

Shown below an amphipathic/amphiphilic compound - a glycerophospholipid



https://en.wikipedia.org/wiki/Amphiphile

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Chapter 2 - Structure & Function: Lipids

Amphiphilic

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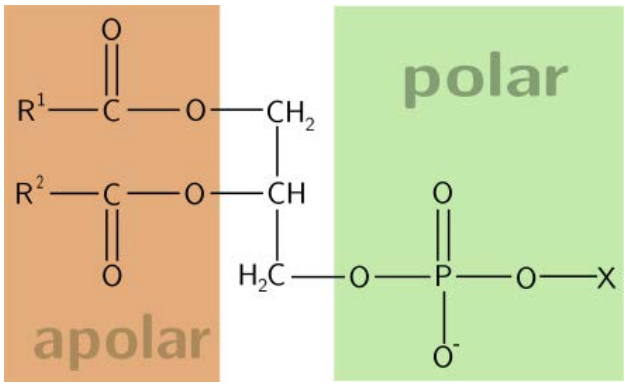

https://en.wikipedia.org/wiki/Amphiphile

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Amyloid β

Amyloid β (Aβ or Abeta) denotes peptides of 36–43 amino acids that are crucially involved in Alzheimer's disease as the main component of the amyloid plaques found in the brains of Alzheimer patients. The peptides result from the amyloid precursor protein (APP), which is cleaved by β secretase and γ secretase to yield Aβ.

Aβ molecules can aggregate to form flexible soluble oligomers which may exist in several forms. It is now believed that certain misfolded oligomers (known as "seeds") can induce other Aβ molecules to also take the misfolded oligomeric form, leading to a chain reaction akin to a prion infection. The seeds or the resulting amyloid plaques are toxic to nerve cells. The other protein implicated in Alzheimer's disease, tau protein, also forms such prion-like misfolded oligomers, and there is some evidence that misfolded Aβ can induce tau to misfold.

The normal function of Aβ is not well understood. Though some animal studies have shown that the absence of Aβ does not lead to any loss of physiological function, several potential activities have been discovered for Aβ, including activation of kinase enzymes, protection against oxidative stress, regulation of cholesterol transport, functioning as a transcription factor, and anti-microbial activity (potentially associated with Aβ's pro-inflammatory activity).

The glymphatic system clears metabolic waste from the mammalian brain, and in particular β amyloids. The rate of removal is significantly increased during sleep. However the significance of the glymphatic system is unknown in clearance of Aβ.

https://en.wikipedia.org/wiki/Amyloid_beta

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Amyloid Plaques

Amyloids are aggregates of proteins that become folded into the wrong shape, allowing many copies of that protein to stick together. These previously healthy proteins most often lose their normal function and form large fibrils. These fibrils disrupt the healthy physiological function of nearby tissues and organs.

Amyloids have been known to arise from at least 18 different proteins and polypeptides, and have been associated with more than 20 human diseases, known as amyloidosis, and may play a role in some neurodegenerative disorders.

The reasons for amyloid association disease are unclear. In some cases, the deposits physically disrupt tissue architecture, suggesting disruption of function by some bulk process. An emerging consensus implicates prefibrillar intermediates rather than mature amyloid fibers in causing cell death.

Calcium dysregulation has been observed in cells exposed to amyloid oligomers. These small aggregates can form ion channels planar lipid bilayer membranes. Channel formation has been hypothesized to account for calcium dysregulation and mitochondrial dysfunction by allowing indiscriminate leakage of ions across cell membranes. Studies have shown that amyloid deposition is associated with mitochondrial dysfunction and a resulting generation of reactive oxygen species (ROS), which can initiate a signalling pathway leading to apoptosis.

There are reports that indicate amyloid polymers (such as those of huntingtin, associated with Huntington's disease) can induce the polymerization of essential amyloidogenic proteins, which should be deleterious to cells. Also, interaction partners of these essential proteins can also be sequestered.

https://en.wikipedia.org/wiki/Amyloid

Related Glossary Terms

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Chapter 2 - Structure & Function: Proteins I

Amyloid Precursor Protein

Amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated as a regulator of synapse formation, neural plasticity and iron export. APP is best known as the precursor molecule whose proteolysis generates β amyloid (Aβ), a polypeptide containing 37 to 49 amino acid residues whose amyloid fibrillar form is the primary component of amyloid plaques found in the brains of Alzheimer's disease patients.

The most-substantiated role for APP is in synaptic formation and repair. Its expression is upregulated during neuronal differentiation and after neural injury. Roles in cell signaling, long-term potentiation, and cell adhesion have been proposed and supported by as-yet limited research. In particular, similarities in post-translational processing have invited comparisons to the signaling role of the surface receptor protein Notch.

APP knockout mice are viable and have relatively minor phenotypic effects including impaired long-term potentiation and memory loss without general neuron loss. On the other hand, transgenic mice with upregulated APP expression have also been reported to show impaired long-term potentiation.

https://en.wikipedia.org/wiki/Amyloid_precursor_protein

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Chapter 2 - Structure & Function: Proteins I

Amyloids

Amyloids are aggregates of proteins that become folded into the wrong shape, allowing many copies of that protein to stick together. These previously healthy proteins most often lose their normal function and form large fibrils. These fibrils disrupt the healthy physiological function of nearby tissues and organs.

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https://en.wikipedia.org/wiki/Amyloid

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Amylopectin

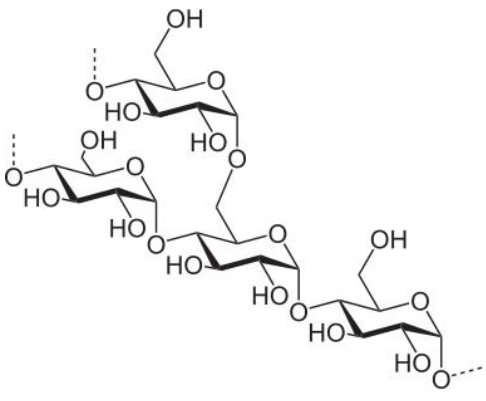
Amylopectin is a soluble polysaccharide and branched polymer of glucose found in plants. It is one of the two components of starch, the other being amylose.

Glucose units are linked in a linear way with α(1→4) glycosidic bonds. Branching takes place with α(1→6) bonds occurring every 24 to 30 glucose units, resulting in a soluble molecule that can be quickly degraded as it has many end points onto which enzymes can attach. In contrast, amylose contains very few α(1→6) bonds, or even none at all. This causes amylose to be hydrolyzed more slowly, but have higher density and be insoluble.

Its counterpart in animals is glycogen, which has the same composition and structure, but with more extensive branching that occurs every eight to 12 glucose units.

Plants store starch within specialized organelles called amyloplasts. When energy is needed for cell work, the plant hydrolyzes the starch, releasing the glucose subunits. Humans and other animals that eat plant foods also use amylase, an enzyme that assists in breaking down amylopectin.

Starch is made of about 70% amylopectin by weight, though it varies depending on the source (higher in medium-grain rice to 100% in glutinous rice, waxy potato starch, and waxy corn, and lower in long-grain rice, amylomaize, and russet potatoes, for example). Amylopectin is highly branched, being formed of 2,000 to 200,000 glucose units. Its inner chains are formed of 20-24 glucose subunits.



https://en.wikipedia.org/wiki/Amylopectin

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Amylose

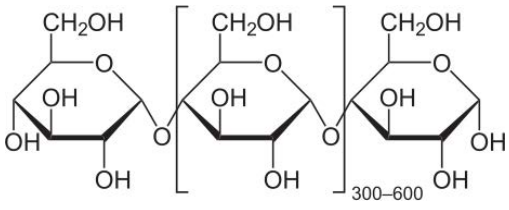
Amylose is a helical polymer made of α-D-glucose units, bound to each other through α(1→4) glycosidic bonds. This polysaccharide is one of the two components of starch, making up approximately 20-30% of the structure. The other component is amylopectin, which makes up 70–80% of the structure.

Because of its tightly packed structure, amylose is more resistant to digestion than other starch molecules and is therefore an important form of resistant starch, which has been found to be an effective prebiotic.

Amylose is important in plant energy storage. It is less readily digested than amylopectin; however, because it is more linear than amylopectin, it takes up less space. As a result, it is the preferred starch for storage in plants. It makes up about 30% of the stored starch in plants, though the specific percentage varies by species. The digestive enzyme α-amylase is responsible for the breakdown of the starch molecule into maltotriose and maltose, which can be used as sources of energy.

Amylose is also an important thickener, water binder, emulsion stabilizer, and gelling agent in both industrial and food-based contexts. Loose helical amylose chains have a hydrophobic interior that can bind to hydrophobic molecules such as lipids and aromatic compounds. The one problem with this is that, when it crystallizes or associates, it can lose some stability, often releasing water in the process (syneresis). When amylose concentration is increased, gel stickiness decreases but gel firmness increases. When other things including amylopectin bind to amylose, the viscosity can be affected, but incorporating κ-carrageenan, alginate, xanthan gum, or low-molecular-weight sugars can reduce the loss in stability. The ability to bind water can add substance to food, possibly serving as a fat replacement. For example, amylose is responsible for causing white sauce to thicken, but, upon cooling, some separation between the solid and the water will occur.

In a laboratory setting, it can act as a marker. Iodine molecules fit neatly inside the helical structure of amylose, binding with the starch polymer that absorbs certain known wavelengths of light. Hence, a common test is the iodine test for starch. Mix starch with a small amount of yellow iodine solution. In the presence of amylose, a blue-black color will be observed. The intensity of the color can be tested with a colorimeter, using a red filter to discern the concentration of starch present in the solution. It is also possible to use starch as an indicator in titrations involving iodine reduction. It is also used in amylose magnetic beads and resin to separate maltose-binding protein.



https://en.wikipedia.org/wiki/Amylose

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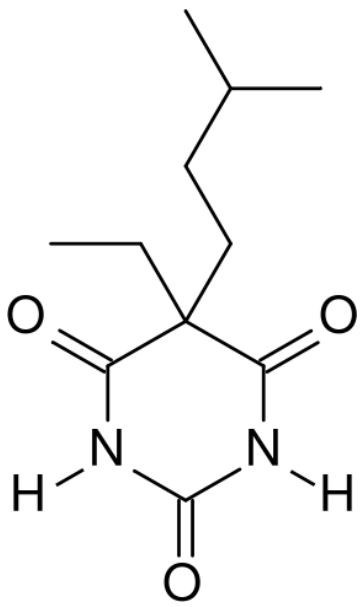
Amytal

Amobarbital (formerly known as amylobarbitone or sodium amytal) is a drug that is a barbiturate derivative. It has sedative-hypnotic properties. It is a white crystalline powder with no odor and a slightly bitter taste. It was first synthesized in Germany in 1923. If amobarbital is taken for extended periods of time, physical and psychological dependence can develop. Amobarbital withdrawal mimics delirium tremens and may be life-threatening.

Amobarbital has been used in a study to inhibit mitochondrial electron transport in the rat heart as it is an inhibitor of the movement of electrons through complex I.



https://en.wikipedia.org/wiki/Amobarbital

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Anabolic

Anabolism (from Greek: ἀνά "upward" and βάλλειν "to throw") is the set of metabolic pathways that construct molecules from smaller units. These reactions require energy. One way of categorizing metabolic processes, whether at the cellular, organ or organism level, is as "anabolic", or as "catabolic" which is the opposite. Anabolism is powered by catabolism, where large molecules are broken down into smaller parts and then used up in respiration. Many anabolic processes are powered by the hydrolysis of adenosine triphosphate (ATP).

Anabolic processes tend toward "building up" organs and tissues. These processes produce growth and differentiation of cells and increase in body size, a process that involves synthesis of complex molecules. Examples of anabolic processes include the growth and mineralization of bone and increases in muscle mass. Endocrinologists have traditionally classified hormones as anabolic or catabolic, depending on which part of metabolism they stimulate. The classic anabolic hormones are the anabolic steroids, which stimulate protein synthesis, muscle growth, and insulin. The balance between anabolism and catabolism is also regulated by circadian rhythms, with processes such as glucose metabolism fluctuating to match an animal's normal periods of activity throughout the day.

https://en.wikipedia.org/wiki/Anabolism

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Anaerobic

Anaerobic means "living without air", as opposed to aerobic which means "living in the presence of air".

An anaerobic organism or anaerobe is any organism that does not require oxygen for growth. It may react negatively or even die if oxygen is present. (In contrast, an aerobic organism (aerobe) is an organism that can survive and grow in an oxygenated environment.)

An anaerobic organism may be unicellular (e.g. protozoans, bacteria) or multicellular. For practical purposes, there are three categories of anaerobe: obligate anaerobes, which are harmed by the presence of oxygen; aerotolerant organisms, which cannot use oxygen for growth but tolerate its presence; and facultative anaerobes, which can grow without oxygen but use oxygen if it is present.

Some obligate anaerobes use fermentation, while others use anaerobic respiration. Aerotolerant organisms are strictly fermentative. In the presence of oxygen, facultative anaerobes use aerobic respiration. Without oxygen, some of them ferment. Some use anaerobic respiration.

https://en.wikipedia.org/wiki/Anaerobic

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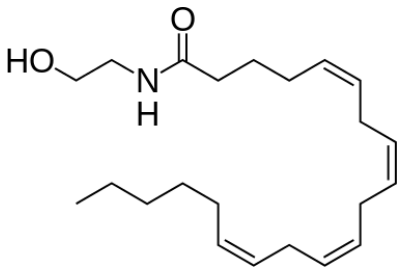
Anandamide

Anandamide, also known as N-arachidonoylethanolamine or AEA, is a fatty acid neurotransmitter derived from the non-oxidative metabolism of eicosatetraenoic acid (arachidonic acid) an essential ω-6 polyunsaturated fatty acid. The name is taken from the Sanskrit word ananda, which means "joy, bliss, delight", and amide. It is synthesized from N-arachidonoyl phosphatidylethanolamine by multiple pathways. It is degraded primarily by the fatty acid amide hydrolase (FAAH) enzyme, which converts anandamide into ethanolamine and arachidonic acid. As such, inhibitors of FAAH lead to elevated anandamide levels and are being pursued for therapeutic use.

Anandamide's effects can occur in either the central or peripheral nervous system. These distinct effects are mediated primarily by CB1 cannabinoid receptors in the central nervous system, and CB2 cannabinoid receptors in the periphery. The latter are mainly involved in functions of the immune system. Cannabinoid receptors were originally discovered as being sensitive to Δ9-tetrahydrocannabinol (Δ9-THC, commonly called THC), which is the primary psychoactive cannabinoid found in cannabis. The discovery of anandamide came from research into CB1 and CB2, as it was inevitable that a naturally occurring (endogenous) chemical would be found to affect these receptors.

Anandamide has been shown to impair working memory in rats. Studies are under way to explore what role anandamide plays in human behavior, such as eating and sleep patterns, and pain relief.

Anandamide plays a role in the regulation of feeding behavior, and the neural generation of motivation and pleasure. In addition, anandamide injected directly into the forebrain reward-related brain structure nucleus accumbens enhances the pleasurable responses of rats to a rewarding sucrose taste, and enhances food intake as well. Moreover, the acute beneficial effects of exercise (termed as runner's high) seem to be mediated by anandamide in mice. In 1996, researchers discovered anandamide in chocolate. They also detected the presence of two substances that might mimic the effects of anandamide, N-oleoylethanolamine and N-linoleoylethanolamine.



https://en.wikipedia.org/wiki/Anandamide

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Anaplerotic

Anaplerotic reactions (from the Greek ἀνά= 'up' and πληρόω= 'to fill') are c
actions that form intermediates of a metabolic pathway. Examples of such a
the citric acid cycle (TCA cycle). In normal function of this cycle for respira
trations of TCA intermediates remain constant. However, many biosynthet
also use these molecules as a substrate. Anaplerosis is the act of replenishin
intermediates that have been extracted for biosynthesis (in what are called
reactions).

https://en.wikipedia.org/wiki/Anaplerotic_reactions

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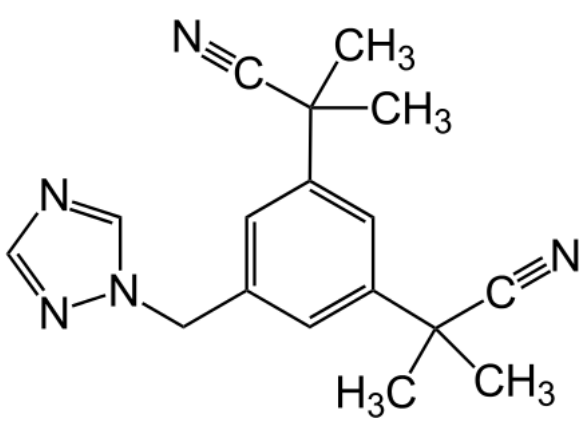
Anastrozole

Anastrozole (INN) (marketed under the trade name Arimidex by AstraZenec
non-steroidal aromatase-inhibiting drug approved for treatment of breast ca
surgery, as well as for metastasis in both pre and post-menopausal women. T
ity of breast cancer can be increased by estrogen, as sex hormones cause hyp
and differentiation at estrogen receptor sites. Anastrozole works by inhibitin
thesis of estrogen.



https://en.wikipedia.org/wiki/Anastrozole

Related Glossary Terms

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Anchored Membrane Proteins

Lipid-anchored proteins (also known as lipid-linked proteins or anchored proteins) are proteins located on the surface of the cell membrane that are covalently attached to lipids embedded within the cell membrane. These lipids insert and assume a place in the bilayer structure of the membrane alongside the similar fatty acid tails. The lipid-anchored protein can be located on either side of the cell membrane.Thus, the lipid serves to anchor the protein to the cell membrane.

The lipid groups plays a role in protein interaction and can contribute to the function of the protein to which it is attached. Furthermore, the lipid serves as a mediator of membrane associations or as a determinant for specific protein-protein interactions. For example, lipid groups can play an important role in increasing molecular hydrophobicity. This allows for the interaction of proteins with cellular membranes and protein domains.

Overall, there are three main types of lipid-anchored proteins which include prenylated proteins, fatty acylated proteins and glycosylphosphatidylinositol-linked proteins (GPI). A protein can have multiple lipid groups covalently attached to it, but the site where the lipid binds to the protein depends both on the lipid group and protein.

https://en.wikipedia.org/wiki/Lipid-anchored_protein

Related Glossary Terms

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https://en.wikipedia.org/wiki/Lipid-anchored_protein

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Androgens

Androgen (from Greek andro meaning male), also called androgenic hormone or testoid, is any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of male characteristics in vertebrates by binding to androgen receptors. This includes the activity of the primary male sex organs and development of male secondary sex characteristics. Androgens were first discovered in 1936. Androgens increase in both boys and girls during puberty. Androgens are also the original anabolic steroids and the precursor of all estrogens. The primary and most well-known androgen is testosterone. Dihydrotestosterone (DHT) and androstenedione are less known generally, but are of equal importance in male development. DHT in the embryo life causes differentiation of penis, scrotum and prostate. Later in life DHT contributes to male balding, prostate growth and sebaceous gland activity. Although androgens are described as male sex hormones, both males and females have them to varying degrees, as is also true of estrogens.

Testosterone is the best known androgen. Besides testosterone, other androgens include:

• Dehydroepiandrosterone (DHEA) is a steroid hormone produced in the adrenal cortex from cholesterol. It is the primary precursor of natural estrogens. DHEA is also called dehydroisoandrosterone or dehydroandrosterone.

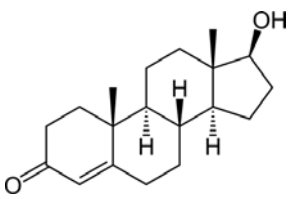
• Androstenedione (Andro) is an androgenic steroid produced by the testes, adrenal cortex, and ovaries. While androstenediones are converted metabolically to testosterone and other androgens, they are also the parent structure of estrone. Use of androstenedione as an athletic or bodybuilding supplement has been banned by the International Olympic Committee, as well as other sporting organizations.

• Androstenediol is the steroid metabolite thought to act as the main regulator of gonadotropin secretion.

• Androsterone is a chemical byproduct created during the breakdown of androgens, or derived from progesterone, that also exerts minor masculinizing effects, but with one-seventh the intensity of testosterone. It is found in approximately equal amounts in the plasma and urine of both males and females.

• Dihydrotestosterone (DHT) is a metabolite of testosterone, and a more potent androgen than testosterone in that it binds more strongly to androgen receptors. It is produced in the skin and reproductive tissue.

Show below - testosterone



https://en.wikipedia.org/wiki/Androgen

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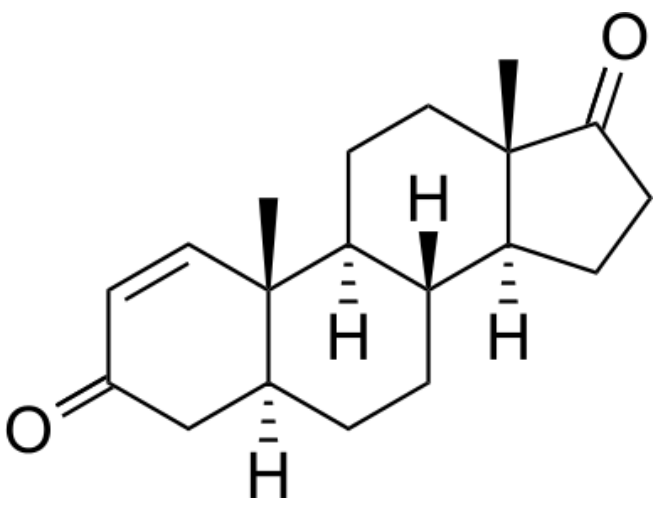
Androstenedione

Δ1-Androstenedione is a synthetic androgen and anabolic steroid. It is an is
endogenous steroid Δ4-androstenedione. It behaves as a prodrug to the tes
isomer, Δ1-testosterone.

Δ1-Androstenedione is on the World Anti-Doping Agency's list of prohibite
stances, and is therefore banned from use by athletes in most major sports.



https://en.wikipedia.org/wiki/1-Androstenedione

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Anemia

Anemia, also spelled anaemia, is usually defined as a decrease in the amount of red blood cells (RBCs) or hemoglobin in the blood. It can also be defined as a lowered ability of the blood to carry oxygen. When anemia comes on slowly, the symptoms are often vague and may include: feeling tired, weakness, shortness of breath or a poor ability to exercise. Anemia that comes on quickly often has greater symptoms, which may include: confusion, feeling like one is going to pass out, loss of consciousness, or increased thirst. Anemia must be significant before a person becomes noticeably pale. Additional symptoms may occur depending on the underlying cause.

There are three main types of anemia: that due to blood loss, that due to decreased red blood cell production, and that due to increased red blood cell breakdown. Causes of blood loss include trauma and gastrointestinal bleeding, among others. Causes of decreased production include iron deficiency, a lack of vitamin B12, thalassemia, and a number of neoplasms of the bone marrow. Causes of increased breakdown include a number of genetic conditions such as sickle cell anemia, infections like malaria, and certain autoimmune diseases. It can also be classified based on the size of red blood cells and amount of hemoglobin in each cell. If the cells are small, it is microcytic anemia. If they are large, it is macrocytic anemia while if they are normal sized, it is normocytic anemia. Diagnosis in men is based on a hemoglobin of less than 130 to 140 g/L (13 to 14 g/dL), while in women, it must be less than 120 to 130 g/L (12 to 13 g/dL). Further testing is then required to determine the cause.

https://en.wikipedia.org/wiki/Anemia

Related Glossary Terms

Angiogenic

Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels. This is distinct from vasculogenesis, which is the de novo formation of endothelial cells from mesoderm cell precursors. The first vessels in the developing embryo form through vasculogenesis, after which angiogenesis is responsible for most, if not all, blood vessel growth during development and in disease.

Angiogenesis is a normal and vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, it is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer.

Tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (e.g. VEGF). Growth factors such as bFGF and VEGF can induce capillary growth into the tumor, which some researchers suspect supply required nutrients, allowing for tumor expansion. Unlike normal blood vessels, tumor blood vessels are dilated with an irregular shape. In 2007, it was discovered that cancerous cells stop producing the anti-VEGF enzyme PKG. In normal cells (but not in cancerous ones), PKG apparently limits beta-catenin, which solicits angiogenesis. Other clinicians believe angiogenesis really serves as a waste pathway, taking away the biological end products secreted by rapidly dividing cancer cells. In either case, angiogenesis is a necessary and required step for transition from a small harmless cluster of cells, often said to be about the size of the metal ball at the end of a ball-point pen, to a large tumor.

Angiogenesis is also required for the spread of a tumor, or metastasis. Single cancer cells can break away from an established solid tumor, enter the blood vessel, and be carried to a distant site, where they can implant and begin the growth of a secondary tumor. Evidence now suggests the blood vessel in a given solid tumor may, in fact, be mosaic vessels, composed of endothelial cells and tumor cells. This mosaicity allows for substantial shedding of tumor cells into the vasculature, possibly contributing to the appearance of circulating tumor cells in the peripheral blood of patients with malignancies. The subsequent growth of such metastases will also require a supply of nutrients and oxygen and a waste disposal pathway.

https://en.wikipedia.org/wiki/Angiogenesis

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Chapter 2 - Structure & Function: Carbohydrates

Chapter 9 - Point by Point: Metabolism

Angiostatin

Angiostatin is a naturally occurring protein found in several animal species, humans. It is an endogenous angiogenesis inhibitor (i.e., it blocks the growth blood vessels).

Angiostatin is known to bind many proteins, especially to angiomotin and en cell surface ATP synthase but also integrins, annexin II, C-met receptor, NG2 can, tissue-type plasminogen activator, chondroitin sulfate proteoglycans, an Additionally, smaller fragments of angiostatin may bind several other protei is still considerable uncertainty on its mechanism of action, but it seems to in bition of endothelial cell migration, proliferation and induction of apoptosis. been proposed that angiostatin activity is related, among other things, to the of its mechanical and redox properties.

https://en.wikipedia.org/wiki/Angiostatin

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Chapter 4 - Catalysis: Blood Clotting

Anion Exchange Chromatography

Anion-exchange chromatography is a process that separates substances based on their charges using an ion-exchange resin containing positively charged groups, such as diethyl-aminoethyl groups (DEAE). In solution, the resin is coated with negatively charged counter-ions (anions). Anion exchange resins will bind to negatively charged molecules, displacing the counter-ion. Anion exchange chromatography is commonly used to purify proteins, amino acids, sugars/carbohydrates and other acidic substances with a negative charge at higher pH levels. The tightness of the binding between the substance and the resin is based on the strength of the negative charge of the substance.

A slurry of resin, such as DEAE-Sephadex is poured into the column. After it settles, the column is pre-equilibrated in buffer before the protein mixture is applied. Unbound proteins are collected in the flow-through and/or in subsequent buffer washes. Proteins that bind to the resin are retained and can be eluted in one of two ways. First, the salt concentration in the elution buffer is gradually increased. The negative ions in the salt solution (e.g. Cl^-) compete with protein in binding to the resin. Second, the pH of the solution can be gradually decreased which results in a more positive charge on the protein, releasing it from the resin. As buffer elutes from the column, the samples are collected using a fraction collector.

https://en.wikipedia.org/wiki/Anion-exchange_chromatography

Related Glossary Terms

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Ankyrins

Ankyrins are a family of adaptor proteins that mediate the attachment of in
brane proteins to the spectrin-actin based membrane cytoskeleton. Ankyri
binding sites for the beta subunit of spectrin and at least 12 families of inte
brane proteins. This linkage is required to maintain the integrity of the plas
branes and to anchor specific ion channels, ion exchangers and ion transpo
plasma membrane.

Ankyrins contain four functional domains: an N-terminal domain that cont
dem ankyrin repeats, a central domain that binds to spectrin, a death doma
binds to proteins involved in apoptosis, and a C-terminal regulatory domai
highly variable between different ankyrin proteins.

https://en.wikipedia.org/wiki/Ankyrin

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Annealing

Annealing, in genetics, means for complementary sequences of single-stran
or RNA to pair by hydrogen bonds to form a double-stranded polynucleotic
is often used to describe the binding of a DNA probe, or the binding of a pri
DNA strand during a polymerase chain reaction. The term is also often use
scribe the reformation (renaturation) of reverse-complementary strands th
separated by heat (thermally denatured).

https://en.wikipedia.org/wiki/Nucleic_acid_thermodynamics#Annealing

Related Glossary Terms

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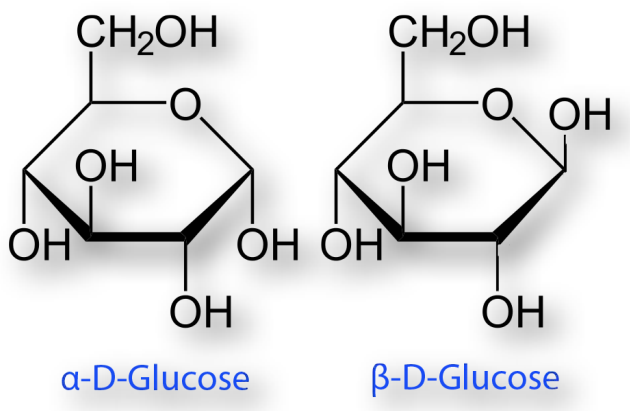
Anomeric

An anomer is a type of stereoisomer and epimer found in carbohydrate chemistry. While an epimer is a stereoisomer that differs in configuration at any single stereogenic center, an anomer is a cyclic saccharide and an epimer that differs in configuration, specifically at the hemiacetal/acetal carbon, also called the anomeric carbon. The anomeric carbon is the carbon derived from the carbonyl carbon (the ketone or aldehyde functional group) of the open-chain form of the carbohydrate molecule. Anomerization is the process of conversion of one anomer to the other.

Show below - anomers of glucose



α-D-Glucose β-D-Glucose

https://en.wikipedia.org/wiki/Anomer

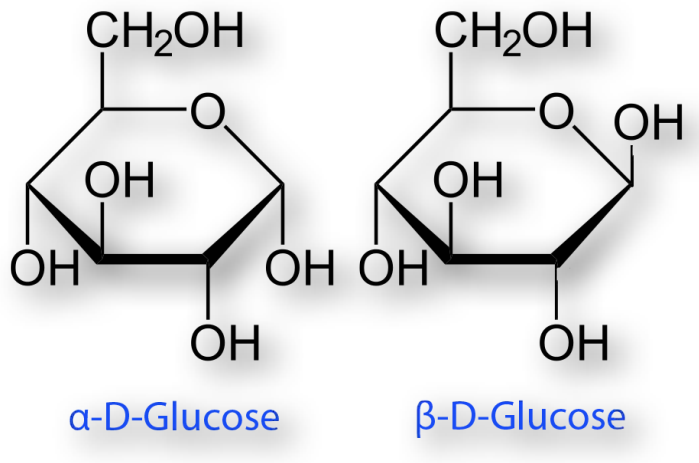
Related Glossary Terms

Drag related terms here

Anomers

An anomer is a type of stereoisomer and epimer found in carbohydrate chemistry. While an epimer is a stereoisomer that differs in configuration at any single stereogenic center, an anomer is a cyclic saccharide and an epimer that differs in configuration, specifically at the hemiacetal/acetal carbon, also called the anomeric carbon. The anomeric carbon is the carbon derived from the carbonyl carbon (the ketone or aldehyde functional group) of the open-chain form of the carbohydrate molecule. Anomerization is the process of conversion of one anomer to the other.

Show below - anomers of glucose



α-D-Glucose β-D-Glucose

https://en.wikipedia.org/wiki/Anomer

Related Glossary Terms

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Chapter 2 - Structure & Function: Carbohydrates

Chapter 9 - Point by Point: Structure and Function

Antenna Proteins

Little light reaches algae that reside at a depth of one meter or more in seawater, as light is absorbed by seawater. A phycobilisome is a light-harvesting protein complex present in cyanobacteria, glaucocystophyta, and red algae and is structured like a real antenna. The pigments, such as phycocyanobilin and phycoerythrobilin, are the chromophores that bind through a covalent thioether bond to their apoproteins at cysteins residues. The apoprotein with its chromophore is called phycocyanin, phycoerythrin, and allophycocyanin, respectively. They often occur as hexamers of α and β subunits ($\alpha 3 \beta 3$)2. They enhance the amount and spectral window of light absorption and fill the "green gap", which occur in higher plants.

The antenna pigments are predominantly chlorophyll b, xanthophylls, and carotenoids. Chlorophyll a is known as the core pigment. Their absorption spectra are non-overlapping in order to broaden the range of light that can be absorbed in photosynthesis. The carotenoids have another role as an antioxidant to prevent photo-oxidative damage of chlorophyll molecules. Each antenna complex has between 250 and 400 pigment molecules and the energy they absorb is shuttled by resonance energy transfer to a specialized chlorophyll-protein complex known as the reaction center of each photosystem. The reaction center initiates a complex series of chemical reactions that capture energy in the form of chemical bonds.

https://en.wikipedia.org/wiki/Light-harvesting_complex

Related Glossary Terms

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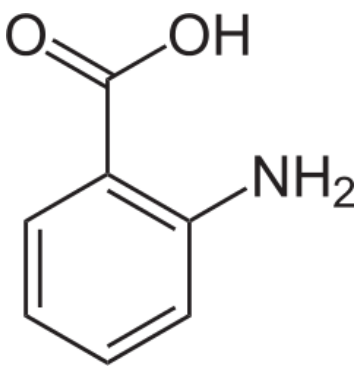
Anthranilate

Anthranilic acid (or o-amino-benzoic acid) is an aromatic acid with the formu $C_6H_4(NH_2)(CO_2H)$. The molecule consists of a substituted benzene ring, henc classed as aromatic, with two adjacent, or "ortho-" functional groups, a carbox and an amine. The compound is consequently amphoteric. In appearance, ant acid is a white solid when pure, although commercial samples may appear yel sometimes referred to as vitamin L1 and has a sweetish taste. The anion $[C_6H_4(NH_2)(CO_2)]^-$, obtained by the deprotonation of anthranilic acid, is calle nilate.



https://en.wikipedia.org/wiki/Anthranilic_acid

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Anti-clotting

Anticoagulants are a class of drugs that work to prevent blood coagulation (clotting). Such substances occur naturally in leeches and blood-sucking insects. A group of pharmaceuticals called anticoagulants can be used as an injection as a medication for thrombotic disorders. Oral anticoagulants are also available. Some anticoagulants are used in medical equipment, such as test tubes, blood transfusion bags, and renal dialysis equipment.

Anticoagulants are closely related to antiplatelet drugs and thrombolytic drugs by manipulating the various pathways of blood coagulation. Specifically, anticoagulants manipulate the coagulation cascade that builds upon the initial platelet thrombus.

A number of anticoagulants are available. The traditional ones (warfarin, other coumarins and heparins) are in widespread use. Since the 2000s a number of new agents have been introduced that are collectively referred to as the novel oral anticoagulants (NOACs) or directly acting oral anticoagulants (DOACs).

These agents include inhibitors of factor IIa (dabigatran) and factor Xa (rivaroxaban, apixaban and edoxaban) and they have been shown to be as good or possibly better than the coumarins with less serious side effects. The newer anticoagulants (NOACs/DOACs), are more expensive than the traditional ones and should be used with care in patients with kidney problems. Additionally, there is no antidote for the factor Xa inhibitors, so it is difficult to stop their effects in the body in cases of emergency (accidents, urgent surgery).

Related Glossary Terms

Drag related terms here

Anti-parallel

In biochemistry, two biopolymers are antiparallel if they run parallel to eac
with opposite alignments. An example is the two complementary strands of
ble helix, which run in opposite directions alongside each other.

https://en.wikipedia.org/wiki/Antiparallel_(biochemistry)

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Antibiotic Resistance

Antimicrobial resistance (AMR) is when a microbe evolves to become more or fully resistant to antimicrobials which previously could treat it. This broader term also covers antibiotic resistance, which applies to bacteria and antibiotics. Resistance arises through one of three ways: natural resistance in certain types of bacteria, genetic mutation, or by one species acquiring resistance from another. Resistance can appear spontaneously due to random mutations, or more commonly following gradual buildup over time, and because of misuse of antibiotics or antimicrobials. Resistant microbes are increasingly difficult to treat, requiring alternative medications or higher doses—which may be more costly or more toxic. Microbes resistant to multiple antimicrobials are called multidrug resistant (MDR) - or sometimes superbugs. Antimicrobial resistance is on the rise with millions of deaths every year. A few infections are now completely untreatable due to resistance. All classes of microbes develop resistance (fungi, antifungal resistance; viruses, antiviral resistance; protozoa, antiprotozoal resistance; bacteria, antibiotic resistance).

Rising drug resistance can be attributed to three causes use of antibiotics: in the human population, in the animal population, and spread of resistant strains between human or non-human sources. Antibiotics increase selective pressure in bacterial populations, causing vulnerable bacteria to die—this increases the percentage of resistant bacteria which continue growing. With resistance to antibiotics becoming more common there is greater need for alternative treatments. Calls for new antibiotic therapies have been issued, but new drug-development is becoming rarer. There are multiple national and international monitoring programs for drug-resistant threats. Examples of drug-resistant bacteria included in this program are: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant S. aureus (VRSA), extended spectrum beta-lactamase (ESBL), vancomycin-resistant Enterococcus (VRE), multidrug-resistant A. baumannii (MRAB).

https://en.wikipedia.org/wiki/Antimicrobial_resistance

Related Glossary Terms

Antibiotics

Antibiotics, also called antibacterials, are a type of antimicrobial drug used in the treatment and prevention of bacterial infection. They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess antiprotozoal activity. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately.

Antibacterial antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity. Most target bacterial functions or growth processes. Those that target the bacterial cell wall (penicillins and cephalosporins) or the cell membrane (polymyxins), or interfere with essential bacterial enzymes (rifamycins, lipiarmycins, quinolones, and sulfonamides) have bactericidal activities. Those that target protein synthesis (macrolides, lincosamides and tetracyclines) are usually bacteriostatic (with the exception of bactericidal aminoglycosides). Further categorization is based on their target specificity. "Narrow-spectrum" antibacterial antibiotics target specific types of bacteria, such as Gram-negative or Gram-positive bacteria, whereas broad-spectrum antibiotics affect a wide range of bacteria. Following a 40-year hiatus in discovering new classes of antibacterial compounds, four new classes of antibacterial antibiotics have been brought into clinical use in the late 2000s and early 2010s: cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigecycline), oxazolidinones (such as linezolid), and lipiarmycins (such as fidaxomicin).

Antibiotics' effectiveness and easy access has led to overuse, especially in livestock raising, prompting bacteria to develop resistance. This has led to widespread problems with antimicrobial and antibiotic resistance, so much as to prompt the World Health Organization to classify antimicrobial resistance as a "serious threat [that] is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country".

https://en.wikipedia.org/wiki/Antibiotics

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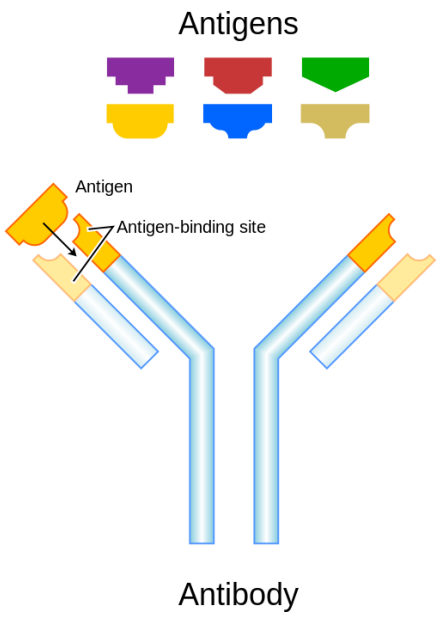
Antibodies

An antibody (Ab), also known as an immunoglobulin (Ig), is a large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses. The antibody recognizes a unique molecule of the harmful agent, called an antigen, via the variable region. Each tip of the "Y" of an antibody contains a paratope (analogous to a lock) that is specific for one particular epitope (similarly analogous to a key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can tag a microbe or an infected cell for attack by other parts of the immune system, or can neutralize its target directly (for example, by blocking a part of a microbe that is essential for its invasion and survival). Depending on the antigen, the binding may impede the biological process causing the disease or may recruit macrophages to destroy the foreign substance. The ability of an antibody to communicate with the other components of the immune system is mediated via its Fc region (located at the base of the "Y"), which contains a conserved glycosylation site involved in these interactions. The production of antibodies is the main function of the humoral immune system.

Antibodies are secreted by B cells of the adaptive immune system, mostly by differentiated B cells called plasma cells. Antibodies can occur in two physical forms, a soluble form that is secreted from the cell to be free in the blood plasma, and a membrane-bound form that is attached to the surface of a B cell and is referred to as the B-cell receptor (BCR). The BCR is found only on the surface of B cells and facilitates the activation of these cells and their subsequent differentiation into either antibody factories called plasma cells or memory B cells that will survive in the body and remember that same antigen so the B cells can respond faster upon future exposure. In most cases, interaction of the B cell with a T helper cell is necessary to produce full activation of the B cell and, therefore, antibody generation following antigen binding. Soluble antibodies are released into the blood and tissue fluids, as well as many secretions to continue to survey for invading microorganisms.



https://en.wikipedia.org/wiki/Antibody

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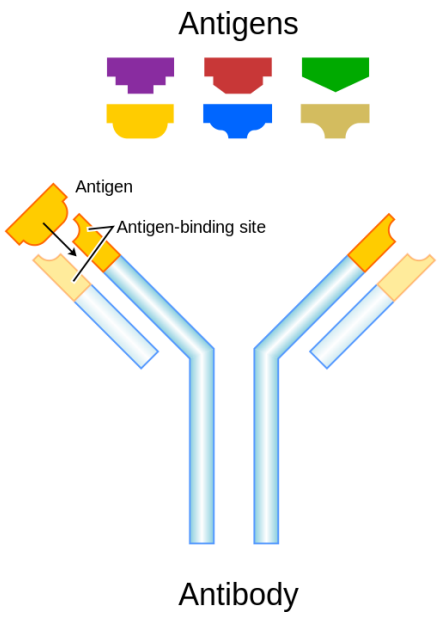

https://en.wikipedia.org/wiki/Antibody

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Anticoagulation

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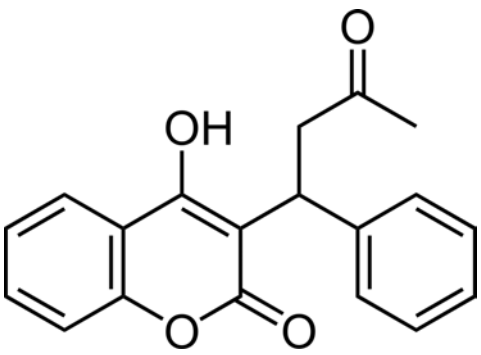
Shown below is warfarin (coumadin)



https://en.wikipedia.org/wiki/Anticoagulant

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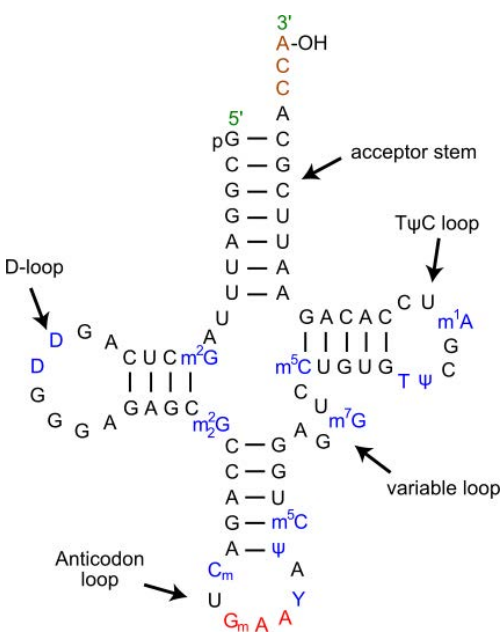
Chapter 2 - Structure & Function: Carbohydrates

Anticodon

An anticodon is a unit made up of three nucleotides that correspond to the three bases of the codon on the mRNA. Each tRNA contains a specific anticodon triplet sequence that can base-pair to one or more codons for an amino acid. Some anticodons can pair with more than one codon due to a phenomenon known as wobble base pairing. Frequently, the first nucleotide of the anticodon is one not found on mRNA: inosine, which can hydrogen bond to more than one base in the corresponding codon position. In the genetic code, it is common for a single amino acid to be specified by all four third-position possibilities, or at least by both pyrimidines and purines. For example, the amino acid glycine is coded for by the codon sequences GGU, GGC, GGA, and GGG. Other modified nucleotides may also appear at the first anticodon position - sometimes known as the "wobble position" - resulting in subtle changes to the genetic code, as for example in mitochondria.

To provide a one-to-one correspondence between tRNA molecules and codons that specify amino acids, 61 types of tRNA molecules would be required per cell. However, many cells contain fewer than 61 types of tRNAs because the wobble base is capable of binding to several, though not necessarily all, of the codons that specify a particular amino acid. A minimum of 31 tRNA are required to translate, unambiguously, all 61 sense codons of the standard genetic code.

Shown below - tRNA with anticodon. The antocodon is in red in the bottom loop.



https://en.wikipedia.org/wiki/Transfer_RNA#Anticodon

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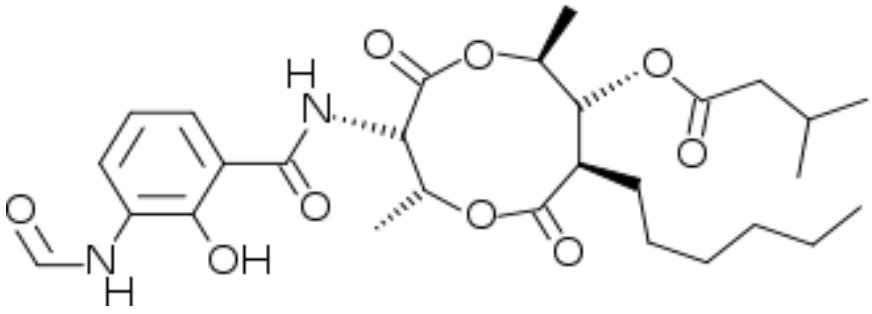
Antimycin A

Antimycins are a group of secondary metabolites produced by *Streptomyces* bacteria. Antimycin A binds to the Qi site of cytochrome c reductase in Complex III, thereby inhibiting the oxidation of ubiquinone in the Qi site thereby disrupting the Q-cycle of the electron transport system.

Cytochrome c reductase is a central enzyme in the electron transport chain of oxidative phosphorylation. The inhibition of this reaction disrupts the formation of the proton gradient across the inner membrane. The production of ATP is subsequently inhibited, as protons are unable to flow through the ATP synthase complex in the absence of a proton gradient. This inhibition also results in the formation of quantities of the toxic free radical superoxide.

Fungus-growing attine ants have been shown to use antimycins - produced by symbiotic *Streptomyces* bacteria - in their fungiculture, to inhibit non-cultivar (i.e. pathogenic) fungi.



https://en.wikipedia.org/wiki/Antimycin_A

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Antioxidants

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells. Antioxidants such as thiols or ascorbic acid (vitamin C) terminate these chain reactions.

To balance the oxidative state, plants and animals maintain complex systems of overlapping antioxidants, such as glutathione and enzymes (e.g., catalase and superoxide dismutase) produced internally or the dietary antioxidants, vitamin A, vitamin C and vitamin E.

Although certain levels of antioxidant vitamins in the diet are required for good health, there is considerable doubt as to whether antioxidant-rich foods or supplements have anti-disease activity. If they are actually beneficial, it is unknown which antioxidant(s) are needed from the diet and in what amounts beyond typical dietary intake.

The reactive oxygen species produced in cells include hydrogen peroxide (H_2O_2), hypochlorous acid (HClO), and free radicals such as the hydroxyl radical (·OH) and the superoxide anion (O_2^-). The hydroxyl radical is particularly unstable and will react rapidly and non-specifically with most biological molecules. This species is produced from hydrogen peroxide in metal-catalyzed redox reactions such as the Fenton reaction. These oxidants can damage cells by starting chemical chain reactions such as lipid peroxidation, or by oxidizing DNA or proteins. Damage to DNA can cause mutations and possibly cancer, if not reversed by DNA repair mechanisms, while damage to proteins causes enzyme inhibition, denaturation and protein degradation.

The use of oxygen as part of the process for generating metabolic energy produces reactive oxygen species. In this process, the superoxide anion is produced as a by-product of several steps in the electron transport chain. Particularly important is the reduction of coenzyme Q in complex III, since a highly reactive free radical is formed as an intermediate ($Q^{\cdot -}$). This unstable intermediate can lead to electron "leakage", when electrons jump directly to oxygen and form the superoxide anion, instead of moving through the normal series of well-controlled reactions of the electron transport chain. Peroxide is also produced from the oxidation of reduced flavoproteins, such as complex I. However, although these enzymes can produce oxidants, the relative importance of the electron transfer chain to other processes that generate peroxide is unclear. In plants, algae, and cyanobacteria, reactive oxygen species are also produced during photosynthesis, particularly under conditions of high light intensity. This effect is partly offset by the involvement of carotenoids in photoinhibition, and in algae and cyanobacteria, by large amount of iodide and selenium, which involves these antioxidants reacting with over-reduced forms of the photosynthetic reaction centers to prevent the production of reactive oxygen species.

https://en.wikipedia.org/wiki/Antioxidant

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Antiparallel

In biochemistry, two biopolymers are antiparallel if they run parallel to each ot
with opposite alignments. An example is the two complementary strands of a D
ble helix, which run in opposite directions alongside each other.

Nucleic acid molecules have a phosphoryl (5') end and a hydroxyl (3') end. This
tion follows from organic chemistry nomenclature, and can be used to define th
ment of enzymes such as DNA polymerases relative to the DNA strand in a non
arbitrary manner. In DNA, the 5' carbon is located at the top of the leading stra
the 3' carbon is located at the lower section of the lagging strand. The nucleic ac
quences are complementary and parallel, but they go in opposite directions, he
antiparallel designation. The antiparallel structure of DNA is important in DNA
tion because it replicates the leading strand one way and the lagging strand the
way. During DNA replication the leading strand is replicated continuously whe
lagging strand is replicated in segments known as Okazaki fragments.

https://en.wikipedia.org/wiki/Antiparallel_(biochemistry)

Related Glossary Terms

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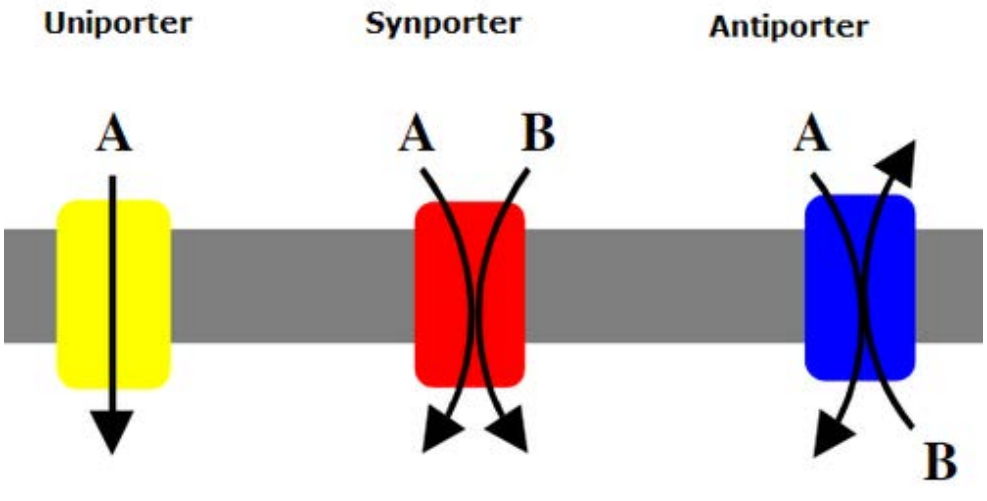
Antiport

An antiporter/antiport (also called exchanger or counter-transporter) is a cotransporter and integral membrane protein involved in transport of two or more different molecules or ions (i.e., solutes) across a phospholipid membrane such as the plasma membrane in opposite directions.



https://en.wikipedia.org/wiki/Antiporter

Related Glossary Terms

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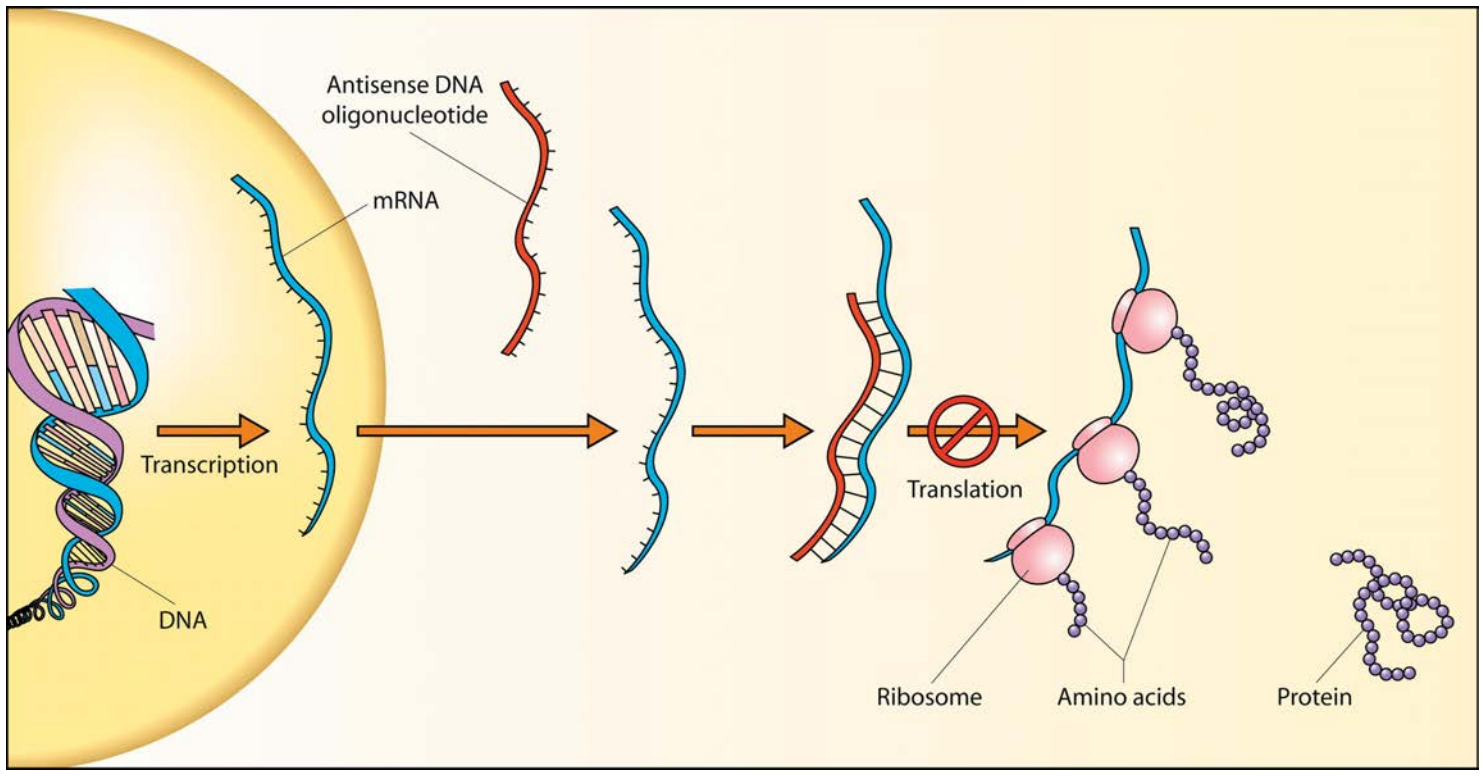
Antisense

In molecular biology and genetics, sense is a concept used to compare the polarity of nucleic acid molecules, such as DNA or RNA, to other nucleic acid molecules. Depending on the context within molecular biology, sense may have slightly different meanings.

Molecular biologists call a single strand of DNA sense (or positive (+)) if an RNA version of the same sequence is translated or translatable into protein. Its complementary strand is called antisense (or negative (-) sense). Sometimes the phrase coding strand is encountered. However, protein coding and non-coding RNAs can be transcribed similarly from both strands, in some cases being transcribed in both directions from a common promoter region, or being transcribed from within introns, on both strands.



https://commons.wikimedia.org/wiki/File:Antisense_DNA_oligonucleotide.png

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Antithrombin

Antithrombin (AT) is a small protein molecule that inactivates several enzy
coagulation system. Antithrombin is a glycoprotein produced by the liver a
of 432 amino acids. It contains three disulfide bonds and a total of four pos
sylation sites. α-Antithrombin is the dominant form of antithrombin found
plasma and has an oligosaccharide occupying each of its four glycosylation
gle glycosylation site remains consistently un-occupied in the minor form o
bin, β-antithrombin. Its activity is increased manyfold by the anticoagulan
rin, which enhances the binding of antithrombin to factor II and factor X.

https://en.wikipedia.org/wiki/Antithrombin

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AP Endonuclease

Apurinic/apyrimidinic (AP) endonuclease (BRENDA = 4.2.99.18) is an enzyme that is involved in the DNA base excision repair pathway (BER). Its main role in the repair of damaged or mismatched nucleotides in DNA is to create a nick in the phosphodiester backbone of the AP site created when DNA glycosylase removes the damaged base.

There are four types of AP endonucleases that have been classified according to their sites of incision. Class I and class II AP endonucleases incise DNA at the phosphate groups 3´ and 5´ to the baseless site leaving 3´-OH and 5´-phosphate termini. Class III and class IV AP endonucleases also cleave DNA at the phosphate groups 3´ and 5´to the baseless site, but they generate a 3´-phosphate and a 5´-OH.

Humans have two AP endonucleases, APE1 and APE2. APE1 exhibits robust AP-endonuclease activity, which accounts for >95% of the total cellular activity, and APE1 is considered to be the major AP endonuclease in human cells. Human AP Endonuclease (APE1), like most AP endonucleases, is of class II and requires an Mg2+ in its active site in order to carry out its role in base excision repair. The yeast homolog of this enzyme is APN1.

Human AP Endonuclease 2 (APE2), like most AP endonucleases, is also of class II. The exonuclease activity of APE2 is strongly dependent upon metal ions. However, APE2 was more than 5-fold more active in the presence of manganese than of magnesium ions. The conserved domains involved in catalytic activity are located at the N-terminal part of both APE1 and APE2. In addition, the APE2 protein has a C-terminal extension, which is not present in APE1, but can also be found in homologs of human APE2 such as APN2 proteins of *S.cerevisiae* and *S.pombe*.

AP Site

An AP site (apurinic/apyrimidinic site), also known as an abasic site, is a location in DNA (also in RNA but much less likely) that has neither a purine nor a pyrimidine base, either spontaneously or due to DNA damage. It has been estimated that under physiological conditions 10,000 apurinic sites and 500 apyrimidinic may be generated in a cell daily.

AP sites can be formed by spontaneous depurination, but also occur as intermediates in base excision repair. In this process, a DNA glycosylase recognizes a damaged base and cleaves the N-glycosidic bond to release the base, leaving an AP site. A variety of glycosylases that recognize different types of damage exist, including oxidized or methylated bases, or uracil in RNA. The AP site can then be cleaved by an AP endonuclease, leaving 3' hydroxyl and 5' deoxyribosephosphate termini. In alternative fashion, bifunctional glycosylase-lyases can cleave the AP site, leaving a 5' phosphate adjacent to a 3' α,β-unsaturated aldehyde. Both mechanisms form a single-strand break, which is then repaired by either short-patch or long-patch base excision repair.

If left unrepaired, AP sites can lead to mutation during semiconservative replication. They can cause replication fork stalling and are bypassed by translesion synthesis. In *E. coli*, adenine is preferentially inserted across from AP sites, known as the "A rule". The situation is more complex in higher eukaryotes, with different nucleotides showing a preference depending on the organism and experimental conditions.

https://en.wikipedia.org/wiki/AP_site

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Apelin

Apelin (also known as APLN) is a peptide that in humans is encoded by the
gene. Apelin is the endogenous ligand for the G-protein-coupled APJ recep
expressed at the surface of some cell types. It is widely expressed in various
such as the heart, lung, kidney, liver, adipose tissue, gastrointestinal tract, l
nal glands, endothelium, and human plasma.

The protein is involved in control of blood pressure, angiogenesis promotio
tor release, and increased water intake.

https://en.wikipedia.org/wiki/Apelin

Related Glossary Terms

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ApoA-I

Apolipoprotein A1 (ApoA-I) is a protein that in humans is encoded by the APOA1 gene. Apolipoprotein A1 is the major protein component of high density lipoprotein (HDL) in plasma. Chylomicrons secreted from the intestinal enterocyte also contain apo A1, but it is quickly transferred to HDL in the bloodstream. The protein promotes fat efflux, including cholesterol, from tissues to the liver for excretion. It is a cofactor for lecithin cholesterolacyltransferase (LCAT) which is responsible for the formation of most plasma cholesteryl esters. Apo A1 was also isolated as a prostacyclin (PGI2) stabilizing factor, and thus may have an anticlotting effect. Defects in the gene encoding it are associated with HDL deficiencies, including Tangier disease, and with systemic non-neuropathic amyloidosis. ApoA1 is often used as a biomarker for prediction of cardiovascular diseases and the ratio apoB- 100/apoA1 has been reported as a stronger predictor for the risk of myocardial infarction than any other lipid measurement.

As a major component of the high-density lipoprotein complex (protective "fat removal" particles), apo A1 helps to clear fats, including cholesterol, from white blood cells within artery walls, making the WBCs less likely to become fat overloaded, transform into foam cells, die and contribute to progressive atheroma.

https://en.wikipedia.org/wiki/Apolipoprotein_A1

Related Glossary Terms

Drag related terms here

ApoB-48

Apolipoprotein B is the primary apolipoprotein of chylomicrons, VLDL, IDL, and LDL particles (LDL - known commonly by the misnomer "bad cholesterol" when in reference to both heart disease and vascular disease in general), which is responsible for carrying fat molecules (lipids), including cholesterol, around the body (within the water outside cells) to all cells within all tissues. While all the functional roles of ApoB within the LDL (and all larger) particles remains somewhat unclear, it is the primary organizing protein (of the entire complex shell enclosing/carrying fat molecules within) component of the particles and is absolutely required for the formation of these particles. What is also clear is that the ApoB on the LDL particle acts as a ligand for LDL receptors in various cells throughout the body (i.e., less formally, ApoB indicates fat carrying particles are ready to enter any cells with ApoB receptors and deliver fats carried within into the cells).

The protein occurs in the plasma in 2 main isoforms, ApoB-48 and ApoB-100. The first is synthesized exclusively by the small intestine, the second by the liver. ApoB-100 is the largest of the apoB group of proteins, consisting of 4563 amino acids. Both isoforms are coded by APOB and by a single mRNA transcript larger than 16 kb. ApoB-48 is generated when a stop codon (UAA) at residue 2153 is created by RNA editing. There appears to be a trans-acting tissue-specific splicing gene that determines which isoform is ultimately produced. Alternatively, there is some evidence that a *cis*-acting element several thousand bp upstream determines which isoform is produced.

As a result of the RNA editing, ApoB-48 and ApoB-100 share a common N-terminal sequence, but ApoB-48 lacks ApoB-100's C-terminal LDL receptor binding region. In fact, ApoB-48 is so called because it constitutes 48% of the sequence for ApoB-100.

ApoB-48 is a unique protein to chylomicrons from the small intestine. After most of the lipids in the chylomicron have been absorbed, ApoB-48 returns to the liver as part of the chylomicron remnant, where it is endocytosed and degraded.

Through mechanisms only partially understood, high levels of ApoB, especially associated with the higher LDL particle concentrations, are the primary drivers of plaque formation that causes vascular disease (atherosclerosis), commonly first becoming obviously symptomatic as heart disease, stroke & many other body wide complications after decades of progression. There is considerable evidence that concentrations of ApoB and especially the NMR assay (specific for LDL-particle concentrations) are superior indicators of vascular/heart disease driving physiology than either total cholesterol or LDL-cholesterol (as long promoted by the NIH starting in the early 1970s). However, primarily for historic cost/complexity reasons, cholesterol, and estimated LDL-cholesterol by calculation, remains the most commonly promoted lipid test for the risk factor of atherosclerosis.

https://en.wikipedia.org/wiki/Apolipoprotein_B

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ApoB-100

Apolipoprotein B is the primary apolipoprotein of chylomicrons, VLDL, IDL, and LDL particles (LDL - known commonly by the misnomer "bad cholesterol" when in reference to both heart disease and vascular disease in general), which is responsible for carrying fat molecules (lipids), including cholesterol, around the body (within the water outside cells) to all cells within all tissues. While all the functional roles of ApoB within the LDL (and all larger) particles remains somewhat unclear, it is the primary organizing protein (of the entire complex shell enclosing/carrying fat molecules within) component of the particles and is absolutely required for the formation of these particles. What is also clear is that the ApoB on the LDL particle acts as a ligand for LDL receptors in various cells throughout the body (i.e., less formally, ApoB indicates fat carrying particles are ready to enter any cells with ApoB receptors and deliver fats carried within into the cells).

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ApoC-I

The protein encoded by this gene is a member of the apolipoprotein C family. This gene is expressed primarily in the liver, and it is activated when monocytes differentiate into macrophages. A pseudogene of this gene is located 4 kb downstream in the same orientation, on the same chromosome. This gene is mapped to chromosome 19, where it resides within an apolipoprotein gene cluster. Alternatively spliced transcript variants have been found for this gene, but the biological validity of some variants has not been determined.

Apolipoprotein C1 has a length of 57 amino acids normally found in plasma and responsible for the activation of esterified lecithin cholesterol with an important role in the exchange of esterified cholesterol between lipoproteins and in removal of cholesterol from tissues. Its main function is inhibition of CETP, probably by altering the electric charge of HDL molecules.

During fasting (like other apolipoprotein C), it is found primarily within HDL, while after a meal it is found on the surface of other lipoproteins. When proteins rich in triglycerides like chylomicrons and VLDL are broken down, this apoprotein is transferred again to HDL. It is one of the most positively charged proteins in the human body.

https://en.wikipedia.org/wiki/Apolipoprotein_C1

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Chapter 2 - Structure & Function: Lipids

ApoC-II

The protein encoded by this gene is secreted in plasma where it is a compon
low density lipoproteins and chylomicrons. This protein activates the enzyr
tein lipase in capillaries, which hydrolyzes triglycerides and thus provides f
ids for cells. Mutations in this gene cause hyperlipoproteinemia type IB, ch
by xanthomas, pancreatitis, and hepatosplenomegaly, but no increased risk
sclerosis. Lab tests will show elevated blood levels of triglycerides, choleste
lomicrons.

https://en.wikipedia.org/wiki/Apolipoprotein_C2

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ApoC-III

Apolipoprotein C-III also known as apo-CIII is a protein that in humans is
the APOC3 gene. Apo-CIII is a component of very low density lipoprotein (V

APOC3 inhibits lipoprotein lipase and hepatic lipase. It is thought to inhib
uptake of triglyceride-rich particles. The APOA1, APOC3 and APOA4 genes
linked in both rat and human genomes. The A-I and A-IV genes are transcr
the same strand, while the A-1 and C-III genes are convergently transcribed
crease in apoC-III levels induces the development of hypertriglyceridemia.
dences suggest an intracellular role for Apo-CIII in promoting the assembly
tion of triglyceride-rich VLDL particles from hepatic cells under lipid-rich c
However, two naturally occurring point mutations in human apoC3 coding
namely Ala23Thr and Lys58Glu have been shown to abolish the intracellula
and secretion of triglyceride-rich VLDL particles from hepatic cells.

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ApoE

Apolipoprotein E (APOE) is a class of apolipoprotein found in the chylomicron and Intermediate-density lipoprotein (IDLs) that is essential for the normal catabolism of triglyceride-rich lipoprotein constituents.

APOE transports lipoproteins, fat-soluble vitamins, and cholesterol into the lymph system and then into the blood. It is synthesized principally in the liver, but has also been found in other tissues such as the brain, kidneys, and spleen. In the nervous system, non-neuronal cell types, most notably astroglia and microglia, are the primary producers of APOE, while neurons preferentially express the receptors for APOE. There are seven currently identified mammalian receptors for APOE which belong to the evolutionarily conserved LDLR family.

APOE was initially recognized for its importance in lipoprotein metabolism and cardiovascular disease. Defects in APOE result in familial dysbetalipoproteinemia aka type III hyperlipoproteinemia (HLP III), in which increased plasma cholesterol and triglycerides are the consequence of impaired clearance of chylomicron, VLDL and LDL remnants. More recently, it has been studied for its role in several biological processes not directly related to lipoprotein transport, including Alzheimer's disease (AD), immunoregulation, and cognition. Though the exact mechanisms remain to be elucidated, isoform 4 of APOE, encoded by an APOE allele, has been associated with increased calcium ion levels and apoptosis following mechanical injury.

In the field of immune regulation, a growing number of studies point to APOE's interaction with many immunological processes, including suppressing T cell proliferation, macrophage functioning regulation, lipid antigen presentation facilitation (by CD1) to natural killer T cell as well as modulation of inflammation and oxidation. APOE is produced by macrophages and APOE secretion has been shown to be restricted to classical monocytes in PBMC, and the secretion of APOE by monocytes is down regulated by inflammatory cytokines and upregulated by TGF-β.[

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Apoenzymes

Enzymes without their co-factors are inactive and referred to as apoenzyme

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Apolipoproteins

Apolipoproteins are proteins that bind lipids (oil-soluble substances such as fat and cholesterol) to form lipoproteins. They transport the lipids through the lymphatic and circulatory systems.
The lipid components of lipoproteins are insoluble in water. However, because of their detergent-like (amphipathic) properties, apolipoproteins and other amphipathic molecules (such as phospholipids) can surround the lipids, creating the lipoprotein particle that is itself water-soluble, and can thus be carried through water-based circulation (i.e., blood, lymph).

Apolipoproteins also serve as enzyme cofactors, receptor ligands, and lipid transfer carriers that regulate the metabolism of lipoproteins and their uptake in tissues. In lipid transport, apolipoproteins function as structural components of lipoprotein particles, cofactors for enzymes and ligands for cell-surface receptors. In particular, apoA1 is the major protein component of high-density lipoproteins. ApoA4 is thought to act primarily in intestinal lipid absorption. Further, apoE is a blood plasma protein that mediates the transport and uptake of cholesterol and lipid by way of its high affinity interaction with different cellular receptors, including the low-density lipoprotein (LDL) receptor. Recent findings with apoA-I and apoE suggest that the tertiary structures of these two members of the human exchangeable apolipoprotein gene family are related. The three-dimensional structure of the LDL receptor-binding domain of apoE indicates that the protein forms an unusually elongated four-helix bundle that may be stabilized by a tightly packed hydrophobic core that includes leucine zipper-type interactions and by numerous salt bridges on the mostly charged surface. Basic amino acids important for LDL receptor binding are clustered into a surface patch on one long helix.

Apolipoproteins are
• enzyme coenzymes (C-II for lipoprotein lipase and A-I for lecithin-cholesterol acyltransferase)
• lipid transport proteins
• ligands for interaction with lipoprotein receptors in tissues (apoB-100 and apoE for LDL-receptors, apoA-I for HDL receptors)

https://en.wikipedia.org/wiki/Apolipoprotein

Apoptosis

Apoptosis (from Ancient Greek ἀπόπτωσις "falling off") is a process of programmed cell death that occurs in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and global mRNA decay. Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day.

The initiation of apoptosis is tightly regulated by activation mechanisms, because once apoptosis has begun, it inevitably leads to the death of the cell. The two best-understood activation mechanisms are of are the intrinsic pathway (also called the mitochondrial pathway) and the extrinsic pathway. The intrinsic pathway is activated by intracellular signals generated when cells are stressed and depends on the release of proteins from the intermembrane space of mitochondria. The extrinsic pathway is activated by extracellular ligands binding to cell-surface death receptors, which leads to the formation of the death-inducing signaling complex (DISC).

A cell initiates intracellular apoptotic signaling in response to a stress, which may bring about cell suicide. The binding of nuclear receptors by glucocorticoids, heat, radiation, nutrient deprivation, viral infection, hypoxia and increased intracellular calcium concentration, for example, by damage to the membrane, can all trigger the release of intracellular apoptotic signals by a damaged cell. A number of cellular components, such as poly ADP ribose polymerase, may also help regulate apoptosis.

Before the actual process of cell death is precipitated by enzymes, apoptotic signals must cause regulatory proteins to initiate the apoptosis pathway. This step allows those signals to cause cell death, or the process to be stopped, should the cell no longer need to die. Several proteins are involved, but two main methods of regulation have been identified: the targeting of mitochondria functionality, or directly transducing the signal via adaptor proteins to the apoptotic mechanisms.

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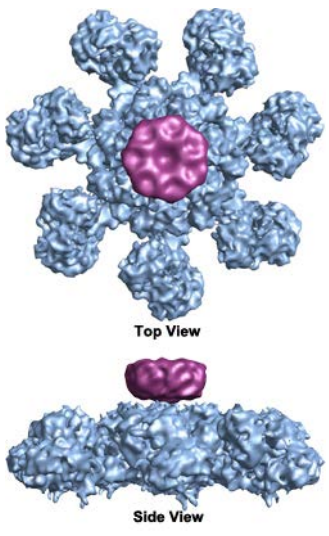
Apoptosome

The apoptosome is a large quaternary protein structure formed in the process of apoptosis. Its formation is triggered by the release of cytochrome c from the mitochondria in response to an internal (intrinsic) or external (extrinsic) cell death stimulus. Stimuli can vary from DNA damage and viral infection to developmental cues such as those leading to the degradation of a tadpole's tail in development.

In mammalian cells, once cytochrome c is released, it binds to the cytosolic protein Apaf-1 to facilitate the formation of apoptosome. An early biochemical study suggests a two-to-one ratio of cytochrome c to apaf-1 for apoptosome formation. However, recent structural studies suggest the cytochrome c to apaf-1 ratio is one-to-one. It has also been shown that the nucleotide dATP as third component binds to apaf-1, however its exact role is still debated. The mammalian apoptosome had never been crystallized, but a human APAF-1/cytochrome-c apoptosome has been imaged at lower (2 nm) resolution by cryogenic transmission electron microscopy 10 years ago, revealing a wheel-like particle with 7-fold symmetry.

Recently, a medium resolution (9.5 Ångström) structure of human apoptosome was also solved by cryo-electron microscopy, which allows unambiguous inference for positions of all the APAF-1 domains (CARD, NBARC and WD40) and cytochrome c. There is also now a crystal structure of the monomeric, inactive Apaf-1 subunit (PDB 3SFZ). Once formed, the apoptosome can then recruit and activate the inactive pro-caspase-9. Once activated, this initiator caspase can then activate effector caspases and trigger a cascade of events leading to apoptosis.



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Apoptotic

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Aptamer

Aptamers (from the Latin aptus - fit, and Greek meros - part) are oligonucleotide or peptide molecules that bind to a specific target molecule. Aptamers are usually created by selecting them from a large random sequence pool, but natural aptamers also exist in riboswitches. Aptamers can be used for both basic research and clinical purposes as macromolecular drugs. Aptamers can be combined with ribozymes to self-cleave in the presence of their target molecule. These compound molecules have additional research, industrial and clinical applications.

More specifically, aptamers can be classified as:

• DNA or RNA or XNA aptamers. They consist of (usually short) strands of oligonucleotides.
Peptide aptamers. They consist of a short variable peptide domain, attached at both ends to a protein scaffold.

Nucleic acid aptamers are nucleic acid species that have been engineered through repeated rounds of in vitro selection or equivalently, SELEX (systematic evolution of ligands by exponential enrichment) to bind to various molecular targets such as small molecules, proteins, nucleic acids, and even cells, tissues and organisms. Aptamers are useful in biotechnological and therapeutic applications as they offer molecular recognition properties that rival that of the commonly used biomolecule, antibodies. In addition to their discriminate recognition, aptamers offer advantages over antibodies as they can be engineered completely in a test tube, are readily produced by chemical synthesis, possess desirable storage properties, and elicit little or no immunogenicity in therapeutic applications.

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Apyrase

CTP is the only nucleotide synthesized *de novo* directly as a triphosphate, s
arises directly from UTP. Since deoxyribonucleotides are made from ribon
diphosphates, it means that deoxycytidine nucleotides must either be made
tially from salvage nucleotides or that CTP must be dephosphorylated first.

One enzyme that can do this is a membrane-bound enzyme known as apyra
sequentially converts CTP to CDP and then CMP.

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Aquaporins

Aquaporins are integral membrane proteins from a larger family of major intrinsic proteins (MIP) that form pores in the membrane of biological cells.

Genetic defects involving aquaporin genes have been associated with several human diseases. The 2003 Nobel Prize in Chemistry was awarded jointly to Peter Agre for the discovery of aquaporins, and Roderick MacKinnon for his work on the structure and mechanism of potassium channels. The plasma membranes of a variety of different animal and plant cells contain aquaporins through which water can flow more rapidly inside the cell than by diffusing through the phospholipid bilayer.

Aquaporins selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes. Also known as water channels, aquaporins are integral membrane pore proteins. Some of them, known as aquaglyceroporins, also transport other small uncharged solutes, such as glycerol, CO_2, ammonia and urea across the membrane, depending on the size of the pore. For example, the aquaporin 3 channel has a pore width of 8-10 Ångströms and allows the passage of hydrophilic molecules ranging between 150-200 Da. However, the water pores are completely impermeable to charged species, such as protons, a property critical for the conservation of the membrane's electrochemical potential difference.

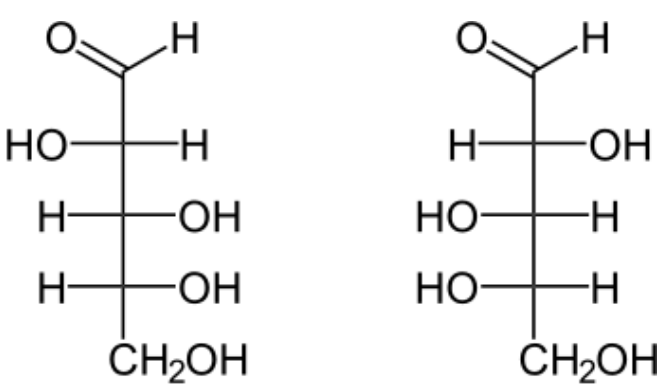
Water molecules traverse through the pore of the channel in single file. The presence of water channels increases membrane permeability to water. Many human cell types express them, as do certain bacteria and many other organisms, such as plants for which it is essential for the water transport system and tolerance to drought and salt stresses.

https://en.wikipedia.org/wiki/Aquaporin

Arabinose

Arabinose is an aldopentose – a monosaccharide containing five carbon atoms, and cluding an aldehyde (CHO) functional group.

For biosynthetic reasons, most saccharides are almost always more abundant in na as the "D"-form, or structurally analogous to D-glyceraldehyde. However, L-arabino is in fact more common than D-arabinose in nature and is found in nature as a com nent of biopolymers such as hemicellulose and pectin.



D-Arabinose L-Arabinose

https://en.wikipedia.org/wiki/Arabinose

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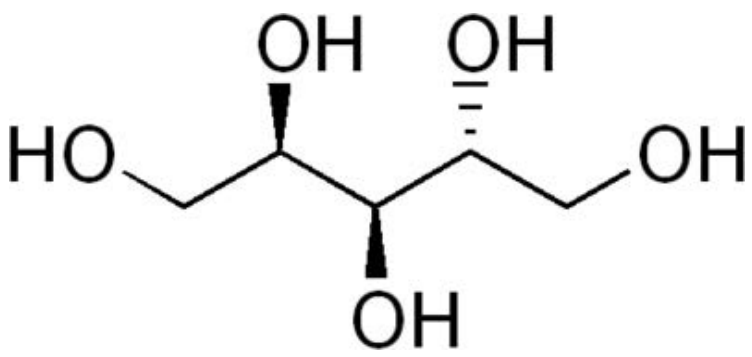
Arabitol

Arabitol or arabinitol is a sugar alcohol. It can be formed by the reduction o
binose or lyxose. Some organic acid tests check for the presence of D-arabi
may indicate overgrowth of intestinal microbes such as *Candida albicans* o
yeast/fungus species.



https://en.wikipedia.org/wiki/Arabitol

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Arachidonate

Arachidonic acid (AA, sometimes ARA) is a polyunsaturated ω-6 fatty acid 20:4(ω-6). It is structurally related to the saturated arachidic acid found in peanut oil (*L. arachis* – peanut). Arachidonic acid is a polyunsaturated fatty acid present in the phospholipids (especially phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositides) of membranes of the body's cells, and is abundant in the brain, muscles, and liver. Skeletal muscle is an especially active site of arachidonic acid retention, accounting for roughly 10-20% of the phospholipid fatty acid content on average.

In addition to being involved in cellular signaling as a lipid second messenger involved in the regulation of signaling enzymes, such as PLC-γ, PLC-δ, and PKC-α, -β, and -γ isoforms, arachidonic acid is a key inflammatory intermediate and can also act as a vasodilator.

Arachidonic acid is freed from a phospholipid molecule by the enzyme phospholipase A2 (PLA2), which cleaves off the fatty acid, but can also be generated from DAG by diacylglycerol lipase.

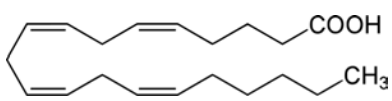
Arachidonic acid generated for signaling purposes appears to be derived by the action of a phosphatidylcholine-specific cytosolic phospholipase A_2, whereas inflammatory arachidonic acid is generated by the action of a low-molecular-weight secretory PLA_2. Arachidonic acid is the precursor that is metabolized by various enzymes to a wide range of biologically and clinically important eicosanoids and metabolites of these eicosanoids:

• The enzymes cyclooxygenase-1 and -2 (i.e. prostaglandin G/H synthase 1 and 2 {PTGS1 and PTGS2}) metabolize arachidonic acid to Prostaglandin G2 and prostaglandin H2, which in turn may be converted to various prostaglandins, to prostacyclin, to thromboxanes, and to the 17-carbon product of thromboxane metabolism of prostaglandin G_2/H_2, 12-Hydroxyheptadecatrienoic acid (12-HHT).

• The enzyme 5-lipoxygenase metabolizes arachidonic acid to 5-hydroperoxyicosatetraenoic acid (5-HPETE), which in turn is metabolized to various leukotrienes (i.e. leukotriene B4, leukotriene C4, leukotriene D_4, and leukotriene E_4 as well as to 5-hydroxyicosatetraenoic acid (5-HETE) which may then be further metabolized to 5-HETE's more potent 5-keto analog, 5-oxo-eicosatetraenoic acid (5-oxo-ETE) (also see 5-Hydroxyicosatetraenoic acid.

• The enzymes 15-lipoxygenase-1 (ALOX15 and 15-lipoxygenase-2 (ALOX15B metabolize arachidonic acid to 15-hydroperoxyicosatetraemoic acid (15-HPETE) which may then be further metabolized to 15-hydroxyicosatetraenoic acid (15-HETE) and lipoxins;. 15-Lipoxygenase-1 may also further metabolize 15-HPETE to eoxins in a pathway analogous to (and presumably using the same enzymes as used in) the pathway which metabolizes 5-HPETE to leukotrienes.

• The enzyme 12-lipoxygenase (ALOX12) metabolizes arachidonic acid to 12-hydroperoxyeicosatetraenoic acid (12-HPETE0 which may then be metabolized to 12-hydroxyeicosatetraenoic acid (12-HETE) and to hepoxilins.



https://en.wikipedia.org/wiki/Arachidonic_acid

Arachidonate 5-lipoxygenase

Arachidonate 5-lipoxygenase, also known as ALOX5, 5-lipoxygenase, 5-LOX, or
is an enzyme that in humans is encoded by the ALOX5 gene. Arachidonate 5-
lipoxygenase is a member of the lipoxygenase family of enzymes. It transforms
into leukotrienes and is a current target for pharmaceutical intervention in a nu
of diseases.

As leukotrienes are important causes of pathological symptoms in asthma, 5-LO
tors were developed as asthma treatments. The only 5-LO inhibitor currently li
for human use in asthma is zileuton.

Minocycline, although primarily a tetracycline antibiotic, is also a 5-LO inhibito
may therefore be used as a DMARD-medication in mild rheumatoid arthritis ar
rheumatic conditions.

https://en.wikipedia.org/wiki/Arachidonate_5-lipoxygenase

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Chapter 2 - Structure & Function: Lipids

Arachidonic Acid

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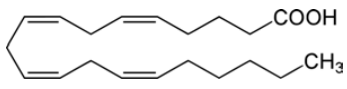

https://en.wikipedia.org/wiki/Arachidonic_acid

Related Glossary Terms

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Archaeans

The *Archaea* constitute a domain and kingdom of single-celled microorganisms. These microbes are prokaryotes, meaning that they have no cell nucleus or any other membrane-bound organelles in their cells. *Archaea* were initially classified as bacteria, receiving the name archaebacteria (in the Archaebacteria kingdom), but this classification is outdated. The *Archaea* are further divided into multiple recognized phyla. Classification is difficult because the majority have not been isolated in the laboratory and have only been detected by analysis of their nucleic acids in samples from their environment.

Archaea and bacteria are generally similar in size and shape, although a few archaea have very strange shapes, such as the flat and square-shaped cells of *Haloquadratum walsbyi*. Despite this visual similarity to bacteria, archaea possess genes and several metabolic pathways that are more closely related to those of eukaryotes, notably the enzymes involved in transcription and translation. Other aspects of archaeal biochemistry are unique, such as their reliance on ether lipids in their cell membranes, such as archaeols. *Archaea* use more energy sources than eukaryotes. These range from organic compounds, such as sugars, to ammonia, metal ions or even hydrogen gas. Salt-tolerant archaea (the *Haloarchaea*) use sunlight as an energy source, and other species of *archaea* fix carbon; however, unlike plants and cyanobacteria, no known species of archaea does both. Archaea reproduce asexually by binary fission, fragmentation, or budding; unlike bacteria and eukaryotes, no known species forms spores.

Archaea were initially viewed as extremophiles living in harsh environments, such as hot springs and salt lakes, but they have since been found in a broad range of habitats, including soils, oceans, marshlands and the human colon, oral cavity, and skin. Archaea are particularly numerous in the oceans, and the archaea in plankton may be one of the most abundant groups of organisms on the planet. *Archaea* are a major part of Earth's life and may play roles in both the carbon cycle and the nitrogen cycle. No clear examples of archaeal pathogens or parasites are known, but they are often mutualists or commensals. One example is the methanogens that inhabit human and ruminant guts, where their vast numbers aid digestion. Methanogens are also used in biogas production and sewage treatment, and enzymes from extremophile archaea that can endure high temperatures and organic solvents are exploited in biotechnology.

https://en.wikipedia.org/wiki/Archaea

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Arginase

Arginase (EC 3.5.3.1, arginine amidinase, canavanase, L-arginase, arginine transamidinase) is a manganese-containing enzyme. The reaction catalyzed by this enzyme is:

Arginine + $H_2O \rightarrow$ Ornithine + Urea.

It is the final enzyme of the urea cycle and is ubiquitous to all domains of life. Mammalian arginase is active as a trimer, but some bacterial arginases are hexameric. The enzyme requires a two-molecule metal cluster of manganese in order to maintain proper function. These Mn^{++} ions coordinate with water, orientating and stabilizing the molecule and allowing water to act as a nucleophile and attack L-arginine, hydrolyzing it into ornithine and urea.

In most mammals, two isozymes of this enzyme exist. The first, arginase I, functions in the urea cycle, and is located primarily in the cytoplasm of the liver. The second isozyme, arginase II, has been implicated in the regulation of the arginine/ornithine concentrations in the cell. It is located in mitochondria of several tissues in the body, with most abundance in the kidney and prostate. It may be found at lower levels in macrophages, lactating mammary glands, and brain. The second isozyme may be found in the absence of other urea cycle enzymes.

https://en.wikipedia.org/wiki/Arginase

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Arginine

Arginine (abbreviated as Arg or R) encoded by the codons CGU, CGC, CGA, CGG, AGA, and AGG is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain of a 3-carbon aliphatic straight chain capped by a complex guanidinium, classifying it as a charged (at physiological pH), aliphatic amino acid.

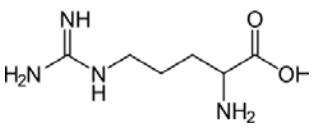
Arginine is classified as a semiessential or conditionally essential amino acid, depending on the developmental stage and health status of the individual. Preterm infants are unable to synthesize or create arginine internally, making the amino acid nutritionally essential for them. Most healthy people do not need to supplement with arginine because their body produces sufficient amounts.

Arginine is synthesized from citrulline in arginine and proline metabolism by the sequential action of the cytosolic enzymes argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL). In terms of energy, this is costly, as the synthesis of each molecule of argininosuccinate requires hydrolysis of adenosine triphosphate (ATP) to adenosine monophosphate (AMP), i.e., two ATP equivalents. In essence, taking an excess of arginine gives more energy by saving ATPs that can be used elsewhere.
Citrulline can be derived from multiple sources:

- from arginine via nitric oxide synthase (NOS)
- from ornithine via catabolism of proline or glutamine/glutamate
- from asymmetric dimethylarginine (ADMA) via DDAH

The roles of arginine include:

- Precursor for the synthesis of nitric oxide (NO). Non-L-arginine derived NO can be generated by the nitrate-nitrite-nitric oxide pathway that is monitored through saliva testing.
- Reduces healing time of injuries (particularly bone)
- Quickens repair time of damaged tissue
- Helps decrease blood pressure in clinical hypertensive subjects - NO-mediated decrease in blood pressure is influenced by both the L-arginine-dependent nitric oxide synthase pathway and non-L-arginine or alternative pathway through nitrate-rich foods such as beets and spinach.



https://en.wikipedia.org/wiki/Arginine

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Argininosuccinase

ASL (argininosuccinate lyase, also known as argininosuccinase) is an enzyme that catalyzes the reversible breakdown of argininosuccinate (ASA) producing the amino acid arginine and dicarboxylic acid fumarate. Located in liver cytosol, ASL is the fourth enzyme of the urea cycle and involved in the biosynthesis of arginine in all species and the production of urea in ureotelic species.

Ammonia (NH_3) is a toxic substance for many aerobic organisms and must be excreted. Some aquatic organisms release the toxin right directly into their environment, while other ureotelic species must convert their toxic nitrogen waste into non-toxic components, like uric acid or urea, through a series of catalyzed steps better known as the urea cycle. ASL catalyzes the fourth step in the cycle, following the action of argininosuccinate synthetase (ASS) in the liver cytosol. While ASS catalyzes the formation of argininosuccinate from citrulline and aspartate, ASL breaks the newly formed arginino-succinate into L-arginine and fumarate. L-arginine continues through the urea cycle to form urea and ornithine, while fumarate can enter the citric acid cycle. Urea, of course, can be excreted, thus reducing ammonia levels.

https://en.wikipedia.org/wiki/Argininosuccinate_lyase

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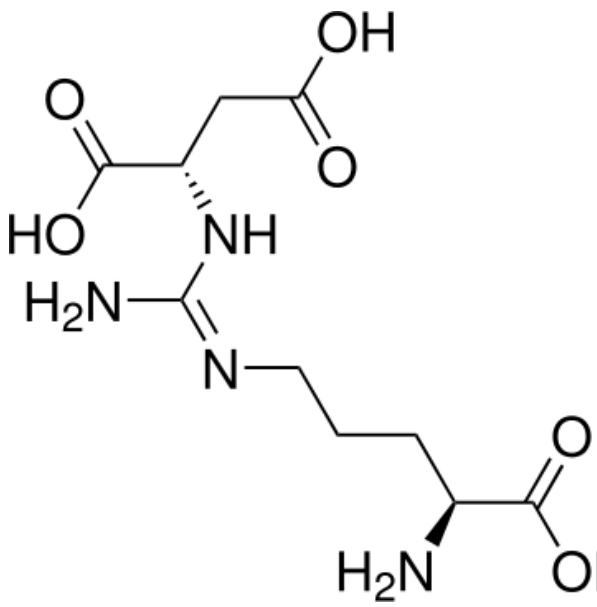
Argininosuccinate

Some cells synthesize argininosuccinic acid from citrulline and aspartic acid and use it as a precursor for arginine in the urea cycle or citrulline-NO cycle. The enzyme that catalyzes the reaction is argininosuccinate synthetase.

Argininosuccinic acid is a precursor to fumarate in the citric acid cycle via argininosuccinate lyase.



https://en.wikipedia.org/wiki/Argininosuccinic_acid

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https://en.wikipedia.org/wiki/Argininosuccinate_lyase

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Argininosuccinate Synthase

Argininosuccinate synthase or synthetase (ASS; EC 6.3.4.5) is an enzyme that catalyzes the synthesis of argininosuccinate from citrulline and aspartate. ASS is responsible for the third step of the urea cycle and one of the reactions of the citrulline-NO cycle.

The transformation of citrulline into argininosuccinate is the rate-limiting step in arginine synthesis. The activity of argininosuccinate synthetase in arginine synthesis occurs largely in at the outer mitochondrial membrane of periportal liver cells as part of the urea cycle, with some activity occurring in cortical kidney cells. Genetic defects that cause incorrect localization of argininosuccinate synthetase to the outer mitochondrial membrane cause type II citrullinemia.

In fetuses and infants, arginine is also produced via argininosuccinate synthetase activity in intestinal cells, presumably to supplement the low level of arginine found in mother's milk. Expression of argininosuccinate synthetase in the intestines ceases after two to three years of life. It is thought that regulation of argininosuccinate synthetase activity in arginine synthesis occurs primarily at the transcriptional level in response to glucocorticoids, cAMP, glucagon, and insulin. It has also been demonstrated *in vitro* that arginine down-regulates argininosuccinate synthetase expression, while citrulline up-regulates it.

Citrulline-NO cycle

The enzyme endothelial nitric oxide synthase produces nitric oxide from arginine in endothelial cells. Argininosuccinate synthetase and argininosuccinate lyase recycle citrulline, a byproduct of nitric oxide production, into arginine. Since nitric oxide is an important signaling molecule, this role of ASS is important to vascular physiology. In this role, argininosuccinate synthetase activity is regulated largely by inflammatory cellular signal molecules such as cytokines.

https://en.wikipedia.org/wiki/Argininosuccinate_synthase

Related Glossary Terms

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Argonaute

The Argonaute protein family plays a central role in RNA silencing processes, as essential catalytic components of the RNA-induced silencing complex (RISC). RISC complex is responsible for the gene silencing phenomenon known as RNA interference (RNAi). Argonaute proteins bind different classes of small non-coding RNAs, including microRNAs (miRNAs), small interfering RNAs (siRNAs) and Piwi-interacting RNAs (piRNAs). Small RNAs guide Argonaute proteins to their specific targets through sequence complementarity (base pairing), which then leads to mRNA cleavage or translation inhibition.

RNA interference (RNAi) is a significant biological process, in which the RNA molecules inhibit gene expression. The typical way of this process is causing the destruction of specific mRNA molecules. The RNA interference has a significant role in defending cells against parasitic nucleotide sequences. In many eukaryotes, including animals, the RNA interference pathway is found, and it is initiated by enzyme Dicer. Dicer cleaves long double-stranded RNA molecules into short double stranded fragments of around 20 nucleotide siRNAs. The dsRNA is then separated into two single-stranded RNAs (ssRNA) - the passenger strand and the guide strand. Consequently, the passenger strand is degraded, while the guide strand is incorporated into the RNA-induced silencing complex (RISC). The most well-studied outcome of the RNAi is post-transcriptional gene silencing, which occurs when the guide strand pairs with a complementary sequence in a messenger RNA molecule and induces cleavage by Argonaute, that lies in the core of RISC.

Argonaute proteins are the active part of RNA-induced silencing complex, cleaving the target mRNA strand complementary to their bound siRNA. Theoretically the dicer produces short double-stranded fragments so there should be also two functional single-stranded siRNA produced. But only one of the two single-stranded RNA here will be utilized to base pair with target mRNA. It is known as the guide strand, incorporated into the Argonaute protein and leads gene silencing. The other single-stranded named passenger strand is degraded during the RNA-induced silencing complex process.

Once the Argonaute is associated with the small RNA, the enzymatic activity conferred by the PIWI domain cleaves only the passenger strand of the small interfering RNA. RNA strand separation and incorporation into the Argonaute protein are guided by the strength of the hydrogen bond interaction at the 5’-ends of the RNA duplex, known as the asymmetry rule. Also the degree of complementarity between the two strands of the intermediate RNA duplex defines how the miRNA are sorted into different types of Argonaute proteins.

https://en.wikipedia.org/wiki/Argonaute

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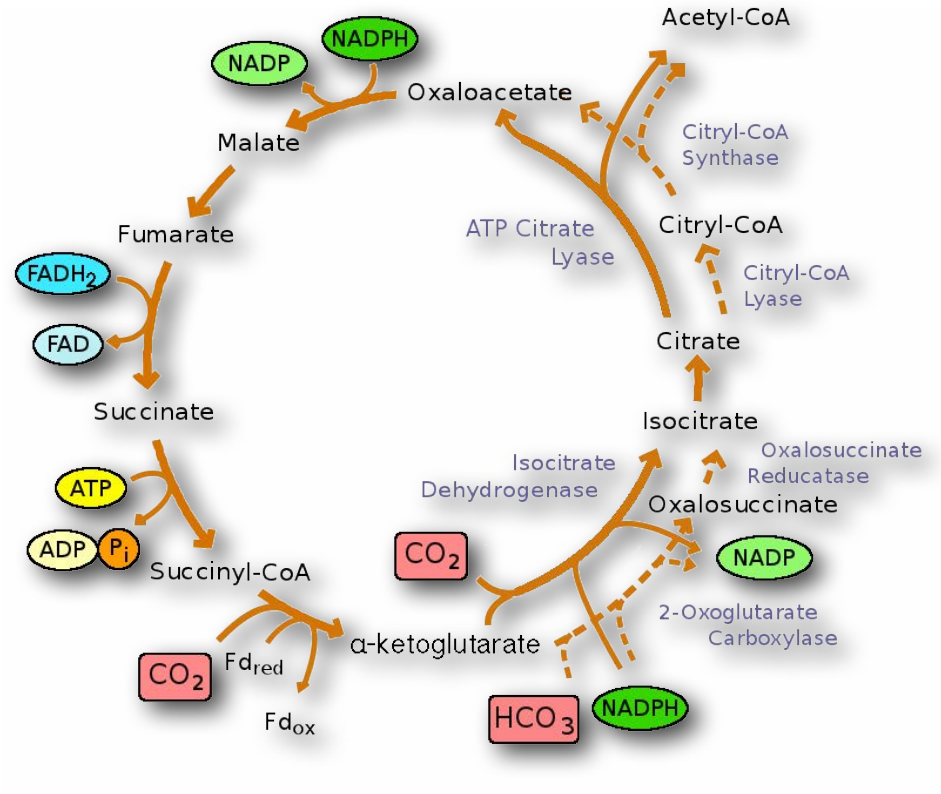
Arnon-Buchanan Cycle

The reverse Krebs cycle (also known as the reverse tricarboxylic acid cycle, the reverse TCA cycle, the reverse citric acid cycle, or the Arnon-Buchanan Cycle) is a sequence of chemical reactions that are used by some bacteria to produce carbon compounds from carbon dioxide and water.

The reaction is the citric acid cycle run in reverse: Where the Krebs cycle takes complex carbon molecules in the form of sugars and oxidizes them to CO_2 and water, the reverse cycle takes CO_2 and water to make carbon compounds. This process is used by some bacteria to synthesize carbon compounds, sometimes using hydrogen, sulfide, or thiosulfate as electron donors. In this process, it can be seen as an alternative to the fixation of inorganic carbon in the reductive pentose phosphate cycle which occurs in a wide variety of microbes and higher organisms.



https://en.wikipedia.org/wiki/Reverse_Krebs_cycle

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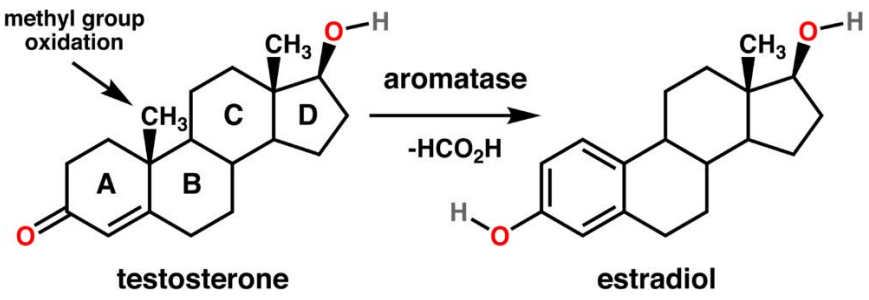
Chapter 6 - Metabolism: Citric Acid Cycle & Related Pathways

Aromatase

Aromatase, also called estrogen synthetase or estrogen synthase, is an enzyme responsible for a key step in the biosynthesis of estrogens. It is CYP19A1, a member of the cytochrome P_{450} superfamily (EC 1.14.14.1), which are monooxygenases that catalyze many reactions involved in steroidogenesis. In particular, aromatase is responsible for the aromatization of androgens into estrogens. The aromatase enzyme can be found in many tissues including gonads, brain, adipose tissue, placenta, blood vessels, skin, and bone, as well as in tissue of endometriosis, uterine fibroids, breast cancer, and endometrial cancer. It is an important factor in sexual development.

Aromatase is localized in the endoplasmic reticulum where it is regulated by tissue-specific promoters that are in turn controlled by hormones, cytokines, and other factors. It catalyzes the last steps of estrogen biosynthesis from androgens (specifically, it transforms androstenedione to estrone and testosterone to estradiol). These steps include three successive hydroxylations of the 19-methyl group of androgens, followed by simultaneous elimination of the methyl group as formate and aromatization of the A-ring.

Aromatase inhibitors, which stop the production of estrogen in postmenopausal women, have become useful in the management of patients with breast cancer whose lesion was found to be estrogen receptor positive. Inhibitors that are in current clinical use include anastrozole, exemestane, and letrozole. Aromatase inhibitors are also beginning to be prescribed to men on testosterone replacement therapy as a way to keep estrogen levels from spiking once doses of testosterone are introduced to their systems.



https://en.wikipedia.org/wiki/Aromatase

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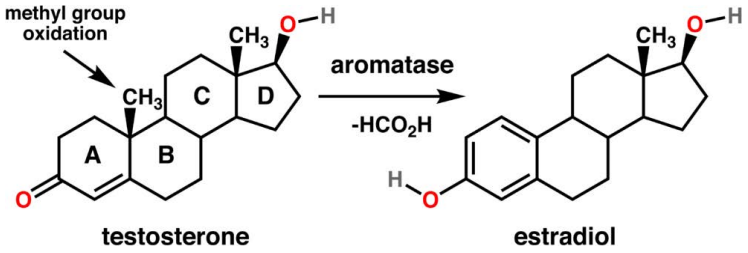
Aromatase Inhibitors

Aromatase inhibitors (AIs) are a class of drugs used in the treatment of breast cancer and ovarian cancer in postmenopausal women and gynecomastia in men. They may also be used off-label to reduce increase of estrogen conversion during cycle with external testosterone. They may also be used for chemoprevention in high risk women.

Aromatase is the enzyme that synthesizes estrogen. As breast and ovarian cancers require estrogen to grow, AIs are taken to either block the production of estrogen or block the action of estrogen on receptors.

Aromatase inhibitors work by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens by a process called aromatization. As breast tissue is stimulated by estrogens, decreasing their production is a way of suppressing recurrence of the breast tumor tissue. The main source of estrogen is the ovaries in premenopausal women, while in post-menopausal women most of the body's estrogen is produced in peripheral tissues (outside the CNS), and also a few CNS sites in various regions within the brain. Estrogen is produced and acts locally in these tissues, but any circulating estrogen, which exerts systemic estrogenic effects in men and women, is the result of estrogen escaping local metabolism and spreading to the circulatory system.



Available aromatase inhibitors (AIs) include:

Non-selective

•Aminoglutethimide, also inhibits the enzyme P450scc and so decreases synthesis of all steroid hormones.

•Testolactone (Teslac)

Selective

- Anastrozole (Arimidex)
- Letrozole (Femara)
- Exemestane (Aromasin)
- Vorozole (Rivizor)
- Formestane (Lentaron)
- Fadrozole (Afema)

https://en.wikipedia.org/wiki/Aromatase_inhibitor

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Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Metabolism

Aromatic

The term aromatic is used to describe compounds that contain a benzene ri

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Aromatic Amino Acid Hydroxylase

Aromatic amino acid hydroxylase is the name for a group of enzymes that h
aromatic amino acids. Such enzymes include phenylalanine hydroxylase, ty
droxylase and tryptophan hydroxylase.

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Arp 2/3 Complex

Arp2/3 complex is a seven-subunit protein complex that plays a major role in the regulation of the actin cytoskeleton. It is a major component of the actin cytoskeleton and is found in most actin cytoskeleton-containing eukaryotic cells. Two of its subunits, the Actin-Related Proteins ARP2 and ARP3 closely resemble the structure of monomeric actin and serve as nucleation sites for new actin filaments. The complex binds to the sides of existing ("mother") filaments and initiates growth of a new ("daughter") filament at a distinctive 70 degree angle from the mother. Branched actin networks are created as a result of this nucleation of new filaments. The regulation of rearrangements of the actin cytoskeleton is important for processes like cell locomotion, phagocytosis, and intracellular motility of lipid vesicles.

The Arp2/3 complex appears to be important in a variety of specialized cell functions that involve the actin cytoskeleton. The complex is found in cellular regions characterized by dynamic actin filament activity: in macropinocytic cups, in the leading edge of motile cells (lamellipodia), and in motile actin patches in yeast. In mammals and the social amoeba *Dictyostelium discoideum*. it is required for phagocytosis. The complex has also been shown to be involved in the establishment of cell polarity and the migration of fibroblast monolayers in a wound-healing model. In mammalian oocytes, the Arp2/3 complex is involved in oocyte asymmetric division and polar body emission, which result from the failure of spindle migration (a unique feature of oocyte division) and cytokinesis. Moreover, enteropathogenic organisms like Listeria monocytogenes and Shigella use the Arp2/3 complex for actin-polymerization- dependent rocketing movements. The Arp2/3 complex also regulates the intracellular motility of endosomes, lysosomes, pinocytic vesicles, and mitochondria. Moreover, recent studies show that the Arp2/3 complex is essential for proper polar cell expansion in plants.

https://en.wikipedia.org/wiki/Arp2/3_complex

Arrestin

Arrestins are a small family of proteins important for regulating signal tran
G protein-coupled receptors. In response to a stimulus, GPCRs activate he
G proteins. In order to turn off this response, or adapt to a persistent stimu
receptors need to be desensitized. The first step is phosphorylation by a cla
threonine kinases called G protein coupled receptor kinases (GRKs). GRK p
tion specifically prepares the activated receptor for arrestin binding. Arrest
to the receptor blocks further G protein-mediated signaling and targets rec
internalization, and redirects signaling to alternative G protein-independer
such as β-arrestin signaling. In addition to GPCRs, arrestins bind to other c
cell surface receptors and a variety of other signaling proteins.

https://en.wikipedia.org/wiki/Arrestin

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Artificial Sweetener

A sugar substitute is a food additive that provides a sweet taste like that of sugar while containing significantly less food energy. Some sugar substitutes are natural and some are synthetic. Those that are not natural are, in general, called artificial sweeteners.

An important class of sugar substitutes is known as high-intensity sweeteners. These are compounds with many times the sweetness of sucrose, common table sugar. As a result, much less sweetener is required and energy contribution is often negligible. The sensation of sweetness caused by these compounds (the "sweetness profile") is sometimes notably different from sucrose, so they are often used in complex mixtures that achieve the most natural sweet sensation.

If the sucrose (or other sugar) that is replaced has contributed to the texture of the product, then a bulking agent is often also needed. This may be seen in soft drinks or sweet tea that are labeled as "diet" or "light" that contain artificial sweeteners and often have notably different mouthfeel, or in table sugar replacements that mix maltodextrins with an intense sweetener to achieve satisfactory texture sensation.

In the United States, seven intensely sweet sugar substitutes have been approved for use. They are stevia, aspartame, sucralose, neotame, acesulfame potassium (Ace-K), saccharin, and advantame. Cyclamates are used outside the U.S., but have been prohibited in the U.S. since 1969. There is some ongoing controversy over whether artificial sweetener usage poses health risks. Others, which may or may not be approved, include allulose (psicose), and monk fruit. The U.S. Food and Drug Administration regulates artificial sweeteners as food additives. Food additives must be approved by the FDA, which publishes a Generally Recognized as Safe (GRAS) list of additives. (Stevia is exempt under FDA's GRAS policy due to its being a natural substance in wide use well before 1958, and has been approved by FDA). The conclusions about safety are based on a detailed review of a large body of information, including hundreds of toxicological and clinical studies.

https://en.wikipedia.org/wiki/Sugar_substitute

Related Glossary Terms

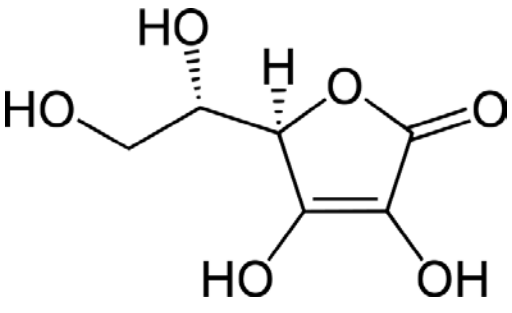
Ascorbate

Vitamin C or L-ascorbic acid, or simply ascorbate (the anion of ascorbic acid), is an essential nutrient for humans and certain other animal species. Vitamin C describes several vitamers that have vitamin C activity in animals, including ascorbic acid and its salts, and some oxidized forms of the molecule like dehydroascorbic acid. Ascorbate and ascorbic acid are both naturally present in the body when either of these is introduced into cells, since the forms interconvert according to pH.

Vitamin C is a cofactor in at least eight enzymatic reactions, including several collagen synthesis reactions that, when dysfunctional, cause the most severe symptoms of scurvy. In animals, these reactions are especially important in wound-healing and in preventing bleeding from capillaries. Ascorbate may also act as an antioxidant, protecting against oxidative stress.

Ascorbate (the anion of ascorbic acid) is required for a range of essential metabolic reactions in all animals and plants. It is made internally by almost all organisms; the main exceptions are most bats, all guinea pigs, capybaras, and the *Haplorrhini* (one of the two major primate suborders, consisting of tarsiers, monkeys, and humans and other apes). Ascorbate is also not synthesized by many species of birds and fish. All species that do not synthesize ascorbate require it in the diet. Deficiency in this vitamin causes the disease scurvy in humans.

The biological role of ascorbate is to act as a reducing agent, donating electrons to various enzymatic and a few non-enzymatic reactions. The one- and two-electron oxidized forms of vitamin C, semidehydroascorbic acid and dehydroascorbic acid, respectively, can be reduced in the body by glutathione and NADPH-dependent enzymatic mechanisms. The presence of glutathione in cells and extracellular fluids helps maintain ascorbate in a reduced state.



https://en.wikipedia.org/wiki/Vitamin_C

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Chapter 2 - Structure & Function: Amino Acids

Ascorbic acid

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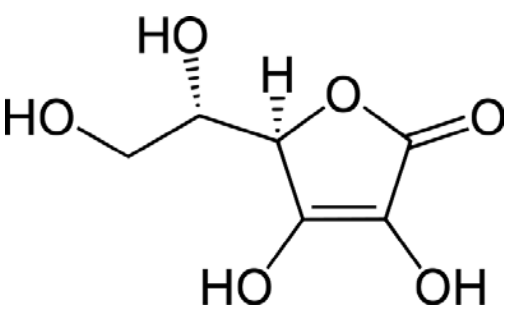

https://en.wikipedia.org/wiki/Vitamin_C

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Chapter 2 - Structure & Function: Carbohydrates

Asparaginase

Asparaginase (EC 3.5.1.1, USAN) or Colaspase (BAN) is an enzyme that cata
hydrolysis of asparagine to aspartic acid. Asparaginases are enzymes expres
produced by microorganisms. It can be used as a drug.

The rationale behind asparaginase as a drug is that it takes advantage of th
acute lymphoblastic leukemia cells and some other suspected tumor cells a
synthesize the non-essential amino acid asparagine, whereas normal cells a
make their own asparagine. Thus leukemic cells require high amount of as
These leukemic cells depend on circulating asparagine. Asparaginase, howe
lyzes the conversion of L-asparagine to aspartic acid and ammonia. This de
leukemic cell of circulating asparagine, which leads to cell death.

https://en.wikipedia.org/wiki/Asparaginase

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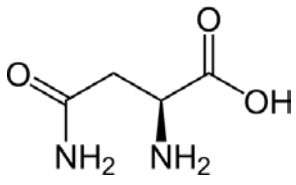
Asparagine

Asparagine (abbreviated as Asn or N) encoded by the codons AAU and AAC. is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain carboxamide, classifying it as a polar (at physiological pH), aliphatic amino acid.

Since the asparagine side-chain can form hydrogen bond interactions with the peptide backbone, asparagine residues are often found near the beginning of α-helices as asx turns and asx motifs, and in similar turn motifs, or as amide rings, in β sheets. Its role can be thought as "capping" the hydrogen bond interactions that would otherwise be satisfied by the polypeptide backbone. Glutamines, with an extra methylene group, have more conformational entropy and thus are less useful for capping.

Asparagine also provides key sites for N-linked glycosylation, modification of the protein chain with the addition of carbohydrate chains. Typically, a carbohydrate tree can solely be added to an asparagine residue if the latter is flanked on the C side by X-serine or X-threonine, where X is any amino acid with the exception of proline.



https://en.wikipedia.org/wiki/Asparagine

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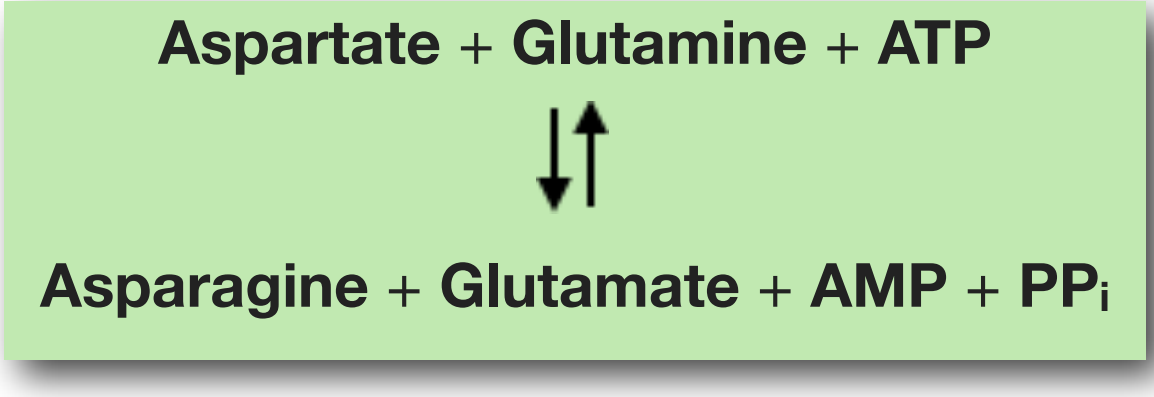
Asparagine Synthetase

Asparagine synthetase (or aspartate-ammonia ligase) is an enzyme that ger
paragine from aspartate. This amidation reaction is similar to that promote
mine synthetase.



https://en.wikipedia.org/wiki/Asparagine_synthetase

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

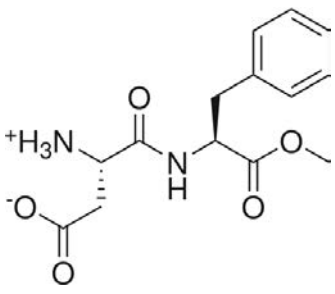
Aspartame

Aspartame is an artificial, non-saccharide sweetener used as a sugar substitute in some foods and beverages. In the European Union, it is codified as E951. Aspartame is a methyl ester of the aspartic acid/phenylalanine dipeptide. Its breakdown products include phenylalanine, so aspartame must be avoided by people with the genetic condition phenylketonuria (PKU).

Aspartame is approximately 200 times sweeter than sucrose (table sugar). Due to this property, even though aspartame produces four kilocalories of energy per gram (17 kJ/g) when metabolized, the quantity of aspartame needed to produce a sweet taste is so small that its caloric contribution is negligible. The taste of aspartame and other artificial sweeteners differs from that of table sugar in the times of onset and how long the sweetness lasts, though aspartame comes closest to sugar's taste profile among approved artificial sweeteners. The sweetness of aspartame lasts longer than that of sucrose, so it is often blended with other artificial sweeteners such as acesulfame potassium to produce an overall taste more like sugar. Aspartame can be synthesized from its constituent amino acids, L-phenylalanine and L-aspartate.

Like many other peptides, aspartame may hydrolyze (break down) into its constituent amino acids under conditions of elevated temperature or high pH. This makes aspartame undesirable as a baking sweetener, and prone to degradation in products hosting a high pH, as required for a long shelf life. The stability of aspartame under heating can be improved to some extent by encasing it in fats or in maltodextrin. The stability when dissolved in water depends markedly on pH. At room temperature, it is most stable at pH 4.3, where its half-life is nearly 300 days. At pH 7, however, its half-life is only a few days. Most soft-drinks have a pH between 3 and 5, where aspartame is reasonably stable. In products that may require a longer shelf life, such as syrups for fountain beverages, aspartame is sometimes blended with a more stable sweetener, such as saccharin.

Aspartame's major decomposition products are its cyclic dipeptide (in a 2,5-diketopiperazine, or DKP, form), the de-esterified dipeptide (aspartyl-phenylalanine), and its constituent components, phenylalanine, aspartic acid, and methanol. At 180 °C, aspartame undergoes decomposition to form a diketopiperazine derivative.



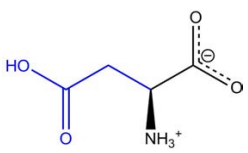
https://en.wikipedia.org/wiki/Aspartame

Aspartate

Aspartic acid (abbreviated as Asp or D; encoded by the codons [GAU and GAC]) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $–NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $–COO^−$ form under biological conditions), and a side chain CH_2COOH. It is listed by some as non-essential and others as semi-essential in humans.

Aspartate can be produced from oxaloacetate by transamination. It can also be generated from ornithine and citrulline in the urea cycle. In plants and microorganisms, aspartate is the precursor to several amino acids, including four that are essential for humans: methionine, threonine, isoleucine, and lysine.

Aspartate is also a metabolite in the urea cycle and participates in gluconeogenesis. It carries reducing equivalents in the malate-aspartate shuttle, which utilizes the ready interconversion of aspartate and oxaloacetate, which is the oxidized (dehydrogenated) derivative of malic acid. Aspartate donates one nitrogen atom in the biosynthesis of inosine, the precursor to the purine bases. In addition, aspartic acid acts as hydrogen acceptor in a chain of ATP synthase. Aspartate is also part of the catalytic triad of serine proteases.



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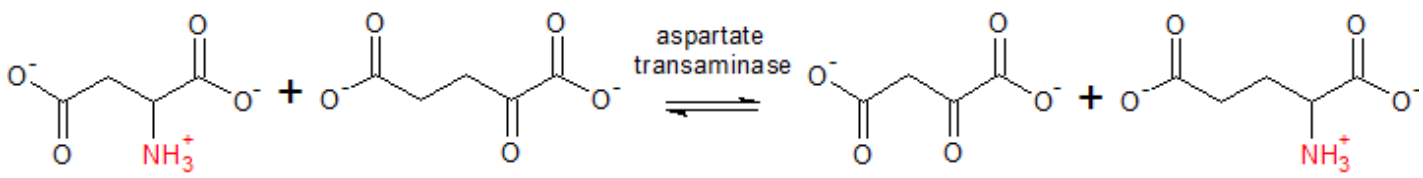
Aspartate Transaminase

Aspartate transaminase (AST) or aspartate aminotransferase, also known as AspAT/ASAT/AAT or serum glutamic oxaloacetic transaminase (SGOT), is a pyridoxal phosphate (PLP)-dependent transaminase enzyme (EC 2.6.1.1) that was first described by Arthur Karmen and colleagues in 1954. AST catalyzes the reversible transfer of an α-amino group between aspartate and glutamate and, as such, is an important enzyme in amino acid metabolism.

Aspartate transaminase catalyzes the interconversion of aspartate and α-ketoglutarate to oxaloacetate and glutamate.

Aspartate (Asp) + α-ketoglutarate ↔ Oxaloacetate + Glutamate (Glu)



As a prototypical transaminase, AST relies on PLP (Vitamin B_6) as a cofactor to transfer the amino group from aspartate or glutamate to the corresponding ketoacid. In the process, the cofactor shuttles between PLP and the pyridoxamine phosphate (PMP) form. The amino group transfer catalyzed by this enzyme is crucial in both amino acid degradation and biosynthesis. In amino acid degradation, following the conversion of α-ketoglutarate to glutamate, glutamate subsequently undergoes oxidative deamination to form ammonium ions, which are excreted as urea. In the reverse reaction, aspartate may be synthesized from oxaloacetate, which is a key intermediate in the citric acid cycle.

https://en.wikipedia.org/wiki/Aspartate_transaminase

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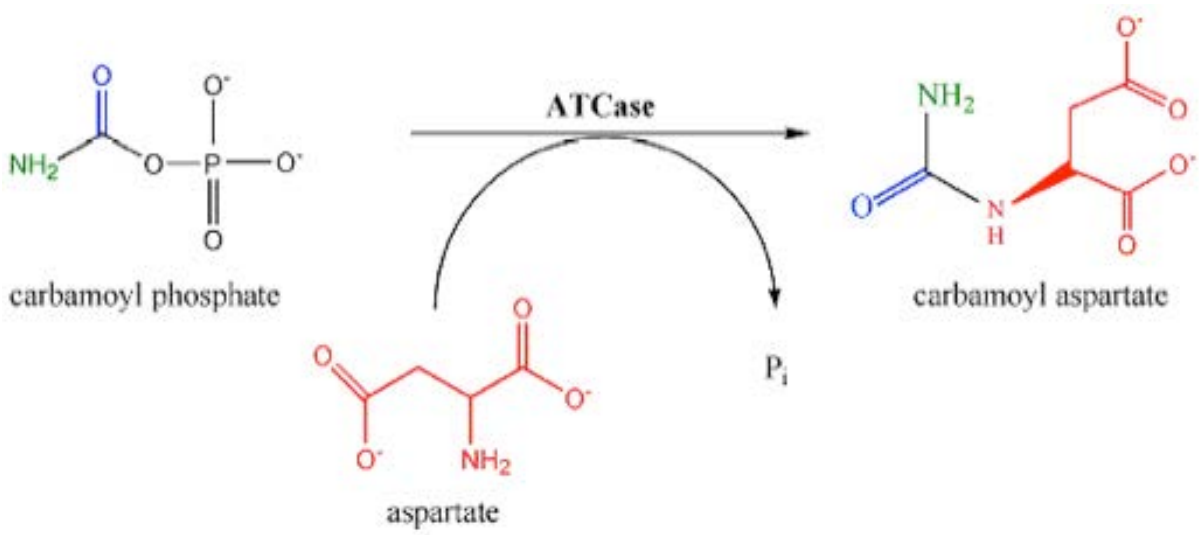
Aspartate Transcarbamoylase

Aspartate carbamoyltransferase (also known as aspartate transcarbamoylase or AT-Case) catalyzes the first step in the pyrimidine biosynthetic pathway. ATCase is a highly regulated enzyme that catalyzes the first committed step in pyrimidine biosynthesis, the condensation of l-aspartate and carbamoyl phosphate to form N-carbamyl-L-aspartate and inorganic phosphate.

ATCase controls the rate of pyrimidine biosynthesis by altering its catalytic velocity in response to cellular levels of both pyrimidines and purines. The end-product of the pyrimidine pathway, CTP, decreases catalytic velocity, whereas ATP, the end-product of the parallel purine pathway, increases catalytic velocity. The substrate, aspartate, is an allosteric (homotropic) activator of the enzyme.



ATCase does not follow Michaelis-Menten kinetics, but lies between the low-activity, low-affinity "tense" or T and the high-activity, high-affinity "relaxed" or R states. The binding of substrate to the catalytic subunits results in an equilibrium shift towards the R state, whereas binding of CTP to the regulatory subunits results in an equilibrium shift towards the T state. Binding of ATP to the regulatory subunits results in an equilibrium shift towards the R state.

https://en.wikipedia.org/wiki/Aspartate_carbamoyltransferase

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Chapter 4 - Catalysis: Control of Activity

Aspartate-semialdehyde Dehydrogenase

Aspartate-semialdehyde dehydrogenase (EC 1.2.1.11) is an enzyme that is very im
tant in the biosynthesis of amino acids in prokaryotes, fungi, and some higher pla
It forms an early branch point in the metabolic pathway leading to lysine, methio
leucine and isoleucine from aspartate.

The enzyme catalyzes the reversible chemical reaction

L-aspartate 4-semialdehyde + P_i + $NADP^+$ $\rightleftharpoons$ L-4-aspartyl Phosphate + NADPH

In physiological conditions however, the reaction runs in the opposite direction. T
enzyme belongs to the family of oxidoreductases, specifically those acting on the
hyde or oxo group of donor with NAD^+ or $NADP^+$ as acceptor.

https://en.wikipedia.org/wiki/Aspartate-semialdehyde_dehydrogenase

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Aspartic Acid

Aspartic acid (abbreviated as Asp or D; encoded by the codons [GAU and GAC]) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain CH_2COOH. It is listed by some as non-essential and others as semi-essential in humans.

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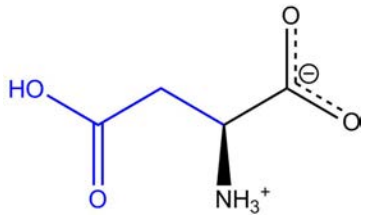
Aspartate is also a metabolite in the urea cycle and participates in gluconeogenesis. It carries reducing equivalents in the malate-aspartate shuttle, which utilizes the ready interconversion of aspartate and oxaloacetate, which is the oxidized (dehydrogenated) derivative of malic acid. Aspartate donates one nitrogen atom in the biosynthesis of inosine, the precursor to the purine bases. In addition, aspartic acid acts as hydrogen acceptor in a chain of ATP synthase. Aspartate is also part of the catalytic triad of serine proteases.



https://en.wikipedia.org/wiki/Aspartic_acid

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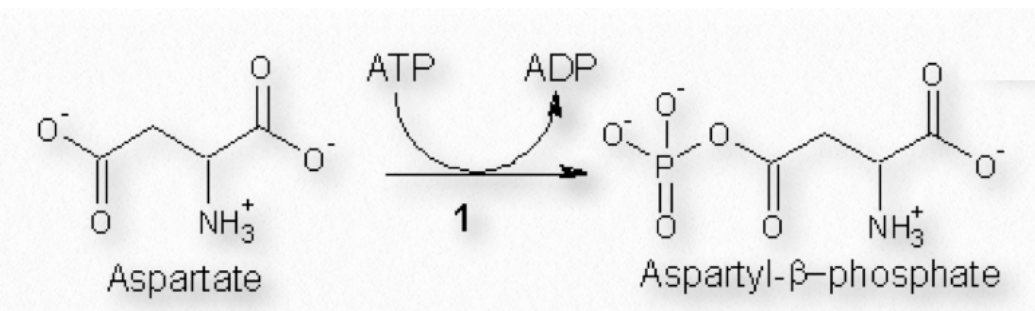
Aspartokinase

Aspartate kinase (aspartokinase, aspartic kinase) is an enzyme that catalyzes the phosphorylation of the amino acid aspartate. This reaction is the first step in the biosynthesis of three essential amino acids: methionine, lysine, and threonine, known as the "aspartate family".



The gene for aspartokinase is present only in microorganisms and plants. It is not present in animals, which must obtain aspartate-family amino acids in their diet.
In *Escherichia coli*, aspartokinase is present as three independently regulated isozymes, each of which is specific to one of the three downstream biochemical pathways. This allows the independent regulation of the rates of methionine, lysine, and threonine production. The forms that produce threonine and lysine are subject to feedback inhibition, and all three can be repressed at the level of gene expression by high concentrations of their end-products. Absence from animals makes these enzymes key targets for new herbicides and biocides and for improvements in nutritional value of crops.
This enzyme may use the morpheein model of allosteric regulation.

https://en.wikipedia.org/wiki/Aspartate_kinase

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Aspartyl Proteases

Aspartic (aspartyl) proteases are a catalytic type of protease enzymes that use an activated water molecule bound to one or more aspartate residues for catalysis of their peptide substrates. In general, they have two highly conserved aspartates in the active site and are optimally active at acidic pH. Nearly all known aspartyl proteases are inhibited by pepstatin.

Eukaryotic aspartic proteases include pepsins, cathepsins, and renins. They have a two-domain structure, arising from ancestral duplication. Retroviral and retrotransposon proteases (Pfam PF00077) are much smaller and appear to be homologous to a single domain of the eukaryotic aspartyl proteases. Each domain contributes a catalytic Asp residue, with an extended active site cleft localized between the two lobes of the molecule. One lobe has probably evolved from the other through a gene duplication event in the distant past. In modern-day enzymes, although the three-dimensional structures are very similar, the amino acid sequences are more divergent, except for the catalytic site motif, which is very conserved. The presence and position of disulfide bridges are other conserved features of aspartic peptidases.

Aspartyl proteases are a highly specific family of proteases - they tend to cleave dipeptide bonds that have hydrophobic residues as well as a β-methylene group. Unlike serine or cysteine proteases these proteases do not form a covalent intermediate during cleavage. Proteolysis therefore occurs in a single step.

https://en.wikipedia.org/wiki/Aspartic_protease

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Aspirin

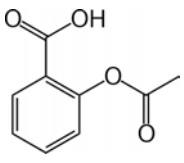
Aspirin, also known as acetylsalicylic acid (ASA), is a medication, often used to treat pain, fever, and inflammation. Aspirin is also used long-term, at low doses, to help prevent heart attacks, strokes, and blood clot formation in people at high risk of developing blood clots. Low doses of aspirin may be given immediately after a heart attack to reduce the risk of another heart attack or the death of heart tissue. Aspirin may be effective at preventing certain types of cancer, particularly colorectal cancer.

Aspirin is part of a group of medications called nonsteroidal anti-inflammatory drugs (NSAIDs), but differs from most other NSAIDs in the mechanism of action. The salicylates have similar effects (antipyretic, anti-inflammatory, analgesic) to the other NSAIDs and inhibit the same enzyme cyclooxygenase (COX), but aspirin does so in an irreversible manner and, unlike others, affects the COX-1 variant more than the COX-2 variant of the enzyme. Aspirin also has an antiplatelet effect by stopping the binding together of platelets.

Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase (COX - officially known as prostaglandin-endoperoxide synthase, PTGS) enzyme required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the PTGS enzyme. This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors.

Low-dose aspirin use irreversibly blocks the formation of thromboxane A2 in platelets, producing an inhibitory effect on platelet aggregation during the lifetime of the affected platelet (8–9 days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks. 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I_2 synthesis being little affected. However, higher doses of aspirin are required to attain further inhibition.

Prostaglandins, local hormones produced in the body, have diverse effects, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are caused primarily by blood clots, and low doses of aspirin are seen as an effective medical intervention for acute myocardial infarction.



https://en.wikipedia.org/wiki/Aspirin

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Aspirin-triggered LX4

Lipoxins are eicosanoid compounds involved in modulating immune respo
they have anti-inflammatory effects. When lipoxins appear in inflammatio
the end of the process. Lipoxins act to attract macrophages to apoptotic ce
site of inflammation and they are engulfed. Lipoxins further act to start the
phase of the inflammation process.

At least one lipoxin (aspirin-triggered LX4) has its synthesis stimulated by

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Associated Membrane Proteins

Peripheral membrane proteins interact with part of the bilayer (usually doe
volve hydrophobic interactions), but do not project through it. A good exar
pholipase A_2, which cleaves fatty acids from glycerophospholipids in memb
ciated membrane proteins typically do not have external hydrophobic reg
they cannot embed in a portion of the lipid bilayer, but are found near mem

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Asthma

Asthma is a common long term inflammatory disease of the airways of the
characterized by variable and recurring symptoms, reversible airflow obstr
bronchospasm. Symptoms include episodes of wheezing, coughing, chest ti
and shortness of breath. These episodes may occur a few times a day or a fe
week.

https://en.wikipedia.org/wiki/Asthma

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Asymmetric Center

A carbon has the ability to make four single bonds (forming a tetrahedral st
and if it bonds to four different compounds, their atoms can be arranged ar
carbon in two different ways, giving rise to stereochemical “handedness.” B
with such a property is referred to as an asymmetric center.

https://en.wikipedia.org/wiki/Stereocenter

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ATCase

Aspartate carbamoyltransferase (also known as aspartate transcarbamoylase or AT-Case) catalyzes the first step in the pyrimidine biosynthetic pathway. ATCase is a highly regulated enzyme that catalyzes the first committed step in pyrimidine biosynthesis, the condensation of l-aspartate and carbamoyl phosphate to form N-carbamyl-L-aspartate and inorganic phosphate.

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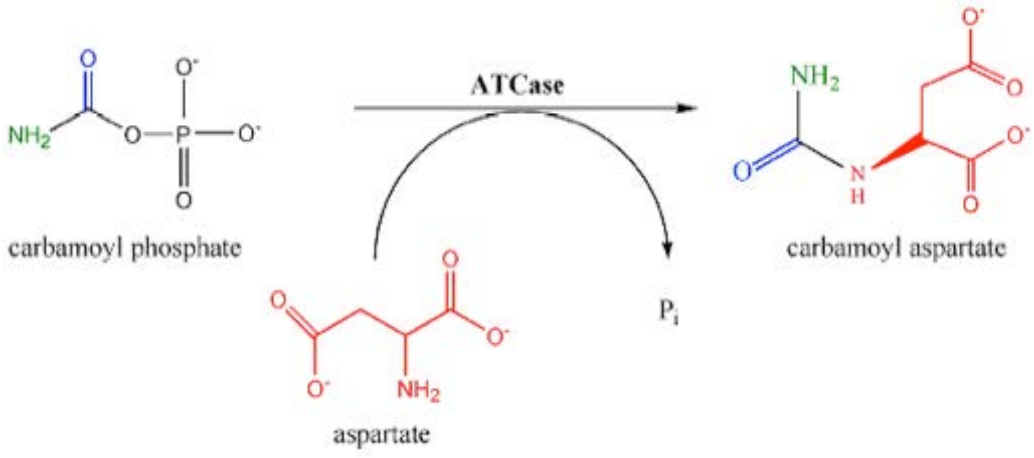

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https://en.wikipedia.org/wiki/Aspartate_carbamoyltransferase

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Atherosclerosis

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is a specific form of arteriosclerosis in which an artery-wall thickens as a result of invasion and accumulation of white blood cells (WBCs) (foam cell) and proliferation of intimal-smooth-muscle cell creating a fibrofatty plaque.

The accumulation of the white blood cells is termed "fatty streaks" early on because of the appearance being similar to that of marbled steak. These accumulations contain both living, active WBCs (producing inflammation) and remnants of dead cells, including cholesterol and triglycerides. The remnants eventually include calcium and other crystallized materials within the outermost and oldest plaque. The "fatty streaks" reduce the elasticity of the artery walls. However, they do not affect blood flow for decades because the artery muscular wall enlarges at the locations of plaque. The wall stiffening may eventually increase pulse pressure. Widened pulse pressure is one possible result of advanced disease within the major arteries.

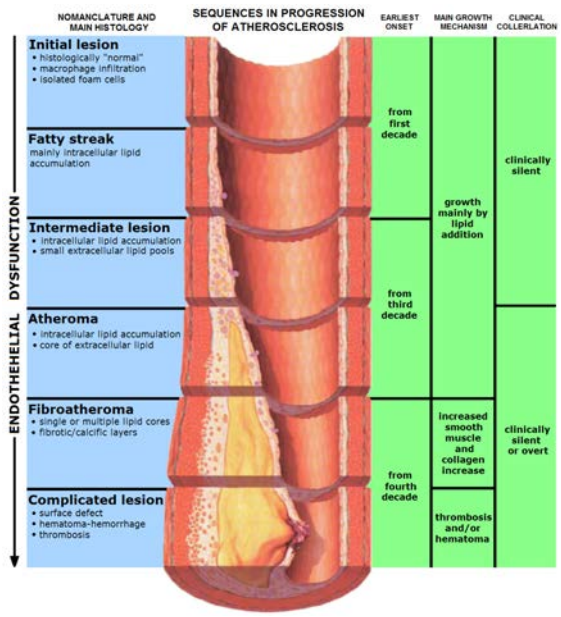
Atherosclerosis is therefore a syndrome affecting arterial blood vessels due to a chronic inflammatory response of WBCs in the walls of arteries. This is promoted by low-density lipoproteins (LDL, plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high-density lipoproteins (HDL). It is commonly referred to as a "hardening" or furring of the arteries. It is caused by the formation of multiple atheromatous plaques within the arteries.
The plaque is divided into three distinct components:

1 The atheroma ("lump of gruel", from Greek ἀθήρα (athera), meaning "gruel"), which is the nodular accumulation of a soft, flaky, yellowish material at the center of large plaques, composed of macrophages nearest the lumen of the artery
2 Underlying areas of cholesterol crystals
3 Calcification at the outer base of older or more advanced lesions.

Atherosclerosis is a chronic disease that remains asymptomatic for decades. Atherosclerotic lesions, or atherosclerotic plaques, are separated into two broad categories: Stable and unstable (also called vulnerable). The pathobiology of atherosclerotic lesions is very complicated, but generally, stable atherosclerotic plaques, which tend to be asymptomatic, are rich in extracellular matrix and smooth muscle cells. On the other hand, unstable plaques are rich in macrophages and foam cells, and the extracellular matrix separating the lesion from the arterial lumen (also known as the fibrous cap) is usually weak and prone to rupture. Ruptures of the fibrous cap expose thrombogenic material, such as collagen, to the circulation and eventually induce thrombus formation in the lumen. Upon formation, intraluminal thrombi can occlude arteries outright (e.g., coronary occlusion), but more often they detach, move into the circulation, and eventually occlude smaller downstream branches causing thromboembolism.

Apart from thromboembolism, chronically expanding atherosclerotic lesions can cause complete closure of the lumen. Chronically expanding lesions are often asymptomatic until lumen stenosis is so severe (usually over 80%) that blood supply to downstream tissue(s) is insufficient, resulting in ischemia.

These complications of advanced atherosclerosis are chronic, slowly progressive and cumulative. Most commonly, soft plaque suddenly ruptures (see vulnerable plaque), causing the formation of a thrombus that will rapidly slow or stop blood flow, leading to death of the tissues fed by the artery in approximately five minutes. This catastrophic event is called an infarction. One of the most common recognized scenarios is called coronary thrombosis of a coronary artery, causing myocardial infarction (a heart attack). The same process in an artery to the brain is commonly called stroke. Another common scenario in very advanced disease is claudication from insufficient blood supply to the legs. Atherosclerosis affects the entire artery tree, but mostly larger, high-pressure vessels such as the coronary, renal, femoral, cerebral, and carotid arteries. These are termed "clinically silent" because the person having the infarction does not notice the problem and does not seek medical help, or when they do, physicians do not recognize what has happened.



https://en.wikipedia.org/wiki/Atherosclerosis

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ATP

Adenosine triphosphate (ATP) is a nucleoside triphosphate used in cells as a coenzyme often called the "molecular unit of currency" of intracellular energy transfer.

ATP transports chemical energy within cells for metabolism. It is one of the end products of photophosphorylation, aerobic respiration, and fermentation, and is used by enzymes and structural proteins in many cellular processes, including biosynthetic reactions, motility, and cell division. One molecule of ATP contains three phosphate groups, and it is produced by a wide variety of enzymes, including ATP synthase, from adenosine diphosphate (ADP) or adenosine monophosphate (AMP) and various phosphate group donors. Substrate-level phosphorylation, oxidative phosphorylation in cellular respiration, and photophosphorylation in photosynthesis are three major mechanisms of ATP biosynthesis.

Metabolic processes that use ATP as an energy source convert it back into its precursors. ATP is therefore continuously recycled in organisms: the human body, which on average contains only 250 grams (8.8 oz) of ATP, turns over its own body weight equivalent in ATP each day.

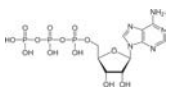
ATP is used as a substrate in signal transduction pathways by kinases that phosphorylate proteins and lipids. It is also used by adenylate cyclase, which uses ATP to produce the second messenger molecule cyclic AMP. The ratio between ATP and AMP is used as a way for a cell to sense how much energy is available and control the metabolic pathways that produce and consume ATP. Apart from its roles in signaling and energy metabolism, ATP is also incorporated into nucleic acids by polymerases in the process of transcription. ATP is the neurotransmitter believed to signal the sense of taste.

The ATP concentration inside the cell is typically 1–10 mM. ATP can be produced by redox reactions using simple and complex sugars (carbohydrates) or lipids as an energy source. For complex fuels to be synthesized into ATP, they first need to be broken down into smaller, more simple molecules. Carbohydrates are hydrolyzed into simple sugars, such as glucose and fructose. Fats (triglycerides) are metabolized to give fatty acids and glycerol.

The overall process of oxidizing glucose to carbon dioxide is known as cellular respiration and can produce about 30 molecules of ATP from a single molecule of glucose. ATP can be produced by a number of distinct cellular processes; the three main pathways used to generate energy in eukaryotic organisms are glycolysis and the citric acid cycle/oxidative phosphorylation, both components of cellular respiration; and beta-oxidation. The majority of this ATP production by a non-photosynthetic aerobic eukaryote takes place in the mitochondria, which can make up nearly 25% of the total volume of a typical cell.

ATP production in an aerobic eukaryotic cell is tightly regulated by allosteric mechanisms, by feedback effects, and by the substrate concentration dependence of individual enzymes within the glycolysis and oxidative phosphorylation pathways. Key control points occur in enzymatic reactions that are so energetically favorable that they are effectively irreversible under physiological conditions.

In glycolysis, hexokinase is directly inhibited by its product, glucose-6-phosphate, and pyruvate kinase is inhibited by ATP itself. The main control point for the glycolytic pathway is phosphofructokinase (PFK), which is allosterically inhibited by high concentrations of ATP and activated by high concentrations of AMP. The inhibition of PFK by ATP is unusual, since ATP is also a substrate in the reaction catalyzed by PFK; the biologically active form of the enzyme is a tetramer that exists in two possible conformations, only one of which binds the second substrate fructose-6-phosphate (F6P). The protein has two binding sites for ATP — the active site is accessible in either protein conformation, but ATP binding to the inhibitor site stabilizes the conformation that binds F6P poorly. A number of other small molecules can compensate for the ATP-induced shift in equilibrium conformation and reactivate PFK, including cyclic AMP, ammonium ions, inorganic phosphate, and fructose 1,6 and 2,6 biphosphate.



https://en.wikipedia.org/wiki/Adenosine_triphosphate

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ATP Hydrolysis

ATP hydrolysis is the reaction by which chemical energy that has been stored in the high-energy phosphoanhydride bonds in adenosine triphosphate (ATP) is released, for example in muscles, by producing work in the form of mechanical energy. The product is adenosine diphosphate (ADP) and an inorganic phosphate, orthophosphate (Pi). ADP can be further hydrolyzed to give energy, adenosine monophosphate (AMP), and another orthophosphate (Pi). ATP hydrolysis is the final link between the energy derived from food or sunlight and useful work such as muscle contraction, the establishment of electrochemical gradients across membranes, and biosynthetic processes necessary to maintain life.

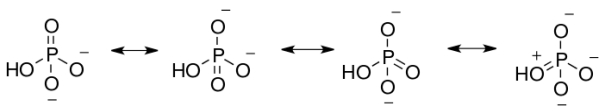
The description and typical textbook labeling anhydridic bonds as "high energy . . bonds" can be very misleading to students. These bonds are in fact relatively weak. They do involve high energy electrons but the bonds themselves are quite easy to break. As noted below, energy is released by the hydrolysis of ATP when these weak bonds are broken - requiring a small input of energy, followed by the formation of new bonds and the release of a larger amount of energy as the total energy of the system is lowered and becomes more stable.

Hydrolysis of the phosphate groups in ATP is especially exergonic, because the resulting orthophosphate group is greatly stabilized by multiple resonance structures, making the products (ADP and Pi) much lower in energy than the reactant (ATP). The high negative charge density associated with the three adjacent phosphate units of ATP also destabilizes the molecule, making it higher in energy. Hydrolysis relieves some of these electrostatic repulsions, liberating useful energy in the process by causing conformational changes in enzyme structure.

Hydrolysis of the terminal phosphoanhydridic bond is a highly exergonic process, releasing 30.5 kJ mol^{-1} energy. This reaction can then be coupled with thermodynamically unfavorable reactions to give an overall negative (spontaneous) ΔG for the reaction sequence. The actual value of ΔG for ATP hydrolysis varies, primarily depending on Mg2+ concentration, and under normal physiologic conditions is actually closer to -50 kJ mol^{-1}.

In humans, approximately 60 percent of the energy released from the hydrolysis of one mole of ATP produces metabolic heat rather than fuel the actual reactions taking place.

Due to the acid-base properties of ATP, ADP, and inorganic phosphate, the hydrolysis of ATP has the effect of lowering the pH of the reaction medium. Under certain conditions, high levels of ATP hydrolysis can contribute to lactic acidosis.



https://en.wikipedia.org/wiki/ATP_hydrolysis

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ATP Synthase

ATP synthase (EC 3.6.3.14) is an important enzyme that creates the energy currency molecule adenosine triphosphate (ATP). ATP is the most commonly used "energy currency" of cells from most organisms. It is formed from adenosine diphosphate (ADP) and inorganic phosphate (P_i), and needs energy for its formation.
The overall reaction sequence is:

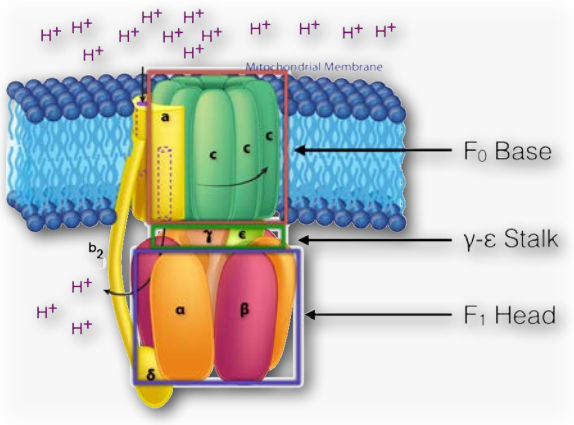
$ADP + P_i + Energy \rightarrow ATP$

where ADP and Pi are joined together by ATP synthase.

Energy used is available in the form of hydrogen ions (H^+), moving down an electrochemical gradient, such as from the thylakoid lumen through the thylakoid membrane and into the chloroplast stroma (of plants) or from the inter-membrane space and into the matrix in mitochondria.

ATP synthase consists of two regions
- the F_0 portion embedded within the membrane
- the F_1 portion of the ATP synthase is outside the membrane, but inside the matrix of the mitochondria.

In plants, ATP synthase is also present in chloroplasts (CF_1F_0-ATP synthase). The enzyme is integrated into thylakoid membrane. The CF_1-part sticks into stroma, where dark reactions of photosynthesis (also called the light-independent reactions or the Calvin cycle) and ATP synthesis take place. The overall structure and the catalytic mechanism of the chloroplast ATP synthase are almost the same as those of the mitochondrial enzyme. However, in chloroplasts, the proton motive force is generated not by respiratory electron transport chain but by primary photosynthetic proteins.



https://commons.wikimedia.org/wiki/File:Atp_synthase.PNG

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ATP-phosphoribosyltransferase

ATP phosphoribosyltransferase (EC 2.4.2.17) is an enzyme that catalyzes the chemical reaction

1-(5-phospho-D-ribosyl)-ATP + diphosphate <-> ATP + 5-phospho-alpha-D-ribose 1-diphosphate

This enzyme catalyses the first step in the biosynthesis of histidine in bacteria, fungi and plants. It is a member of the larger phosphoribosyltransferase superfamily of enzymes which catalyse the condensation of 5-phospho-alpha-D-ribose 1-diphosphate with nitrogenous bases in the presence of divalent metal ions.

Histidine biosynthesis is an energetically expensive process and ATP phosphoribosyltransferase activity is subject to control at several levels. Transcriptional regulation is based primarily on nutrient conditions and determines the amount of enzyme present in the cell, while feedback inihibition rapidly modulates activity in response to cellular conditions. The enzyme has been shown to be inhibited by 1-(5-phospho-D-ribosyl)-ATP, histidine, ppGpp (a signal associated with adverse environmental conditions) and ADP and AMP (which reflect the overall energy status of the cell). As this pathway of histidine biosynthesis is present only in prokaryotes, plants and fungi, this enzyme is a promising target for the development of novel antimicrobial compounds and herbicides.

ATP phosphoribosyltransferase is found in two distinct forms: a long form containing two catalytic domains and a C-terminal regulatory domain, and a short form in which the regulatory domain is missing. The long form is catalytically competent, but in organisms with the short form, a histidyl-tRNA synthetase paralogue, HisZ, is required for enzyme activity.

https://en.wikipedia.org/wiki/ATP_phosphoribosyltransferase

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ATPase

ATPases are a class of enzymes that catalyze the decomposition of ATP into ADP and a free phosphate ion. This dephosphorylation reaction releases energy, which the enzyme (in most cases) harnesses to drive other chemical reactions that would not otherwise occur. This process is widely used in all known forms of life.

Transmembrane ATPases import many of the metabolites necessary for cell metabolism and export toxins, wastes, and solutes that can hinder cellular processes. An important example is the sodium-potassium exchanger (or Na^+/K^+ATPase) that maintains the cell membrane potential. And another example is the hydrogen potassium ATPase (H^+/K^+ATPase or gastric proton pump) that acidifies the contents of the stomach.

Besides exchangers, other categories of transmembrane ATPase include co-transporters and pumps (however, some exchangers are also pumps). Some of these, like the Na^+/K^+ATPase, cause a net flow of charge, but others do not. These are called "electrogenic" and "nonelectrogenic" transporters, respectively.

There are different types of ATPases, which can differ in function (ATP synthesis and/or hydrolysis), structure (F-, V- and A-ATPases contain rotary motors) and in the type of ions they transport.
• F-ATPases (F1FO-ATPases) in mitochondria, chloroplasts and bacterial plasma membranes are the prime producers of ATP, using the proton gradient generated by oxidative phosphorylation (mitochondria) or photosynthesis (chloroplasts).
• V-ATPases (V1VO-ATPases) are primarily found in eukaryotic vacuoles, catalyzing ATP hydrolysis to transport solutes and lower pH in organelles like proton pump of lysosome.
• A-ATPases (A1AO-ATPases) are found in *Archaea* and function like F-ATPases
• P-ATPases (E1E2-ATPases) are found in bacteria, fungi and in eukaryotic plasma membranes and organelles, and function to transport a variety of different ions across membranes.
• E-ATPases are cell-surface enzymes that hydrolyze a range of NTPs, including extracellular ATP.

https://en.wikipedia.org/wiki/ATPase

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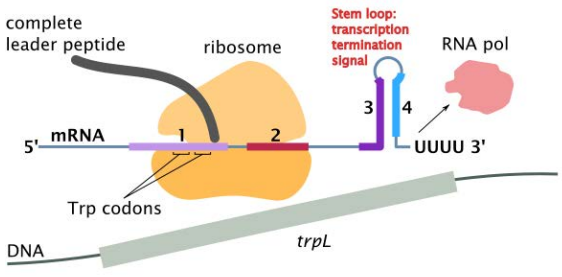
Attenuation

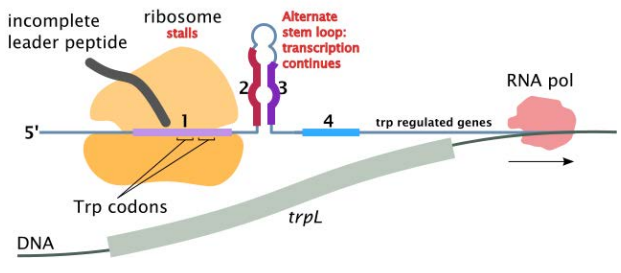
Attenuation is a means of controlling gene expression in bacteria that employs translation to help regulate transcription of operons involved in amino acid metabolism. In this method, abundance of tryptophan (or several other amino acids) during translation of a portion of the mRNA copy of the tryptophan operon (coding sequences for enzymes necessary to make leucine) causes the mRNA to form a transcriptional termination sequence. This, in turn, causes transcription of the operon coding for the genes necessary to synthesize tryptophan to terminate prematurely, thus stopping production of the enzymes necessary to make tryptophan. When tryptophan is in short supply, the transcription termination structure is unable to form and transcription of the entire operon proceeds.

Attenuation is a regulatory feature found throughout Archaea and Bacteria causing premature termination of transcription. Attenuators are 5'-*cis* acting regulatory regions which fold into one of two alternative RNA structures which determine the success of transcription. The folding is modulated by a sensing mechanism producing either a Rho-independent terminator, resulting in interrupted transcription and a non-functional RNA product, or an anti-terminator structure, resulting in a functional RNA transcript. There are now many equivalent examples where the translation, not transcription, is terminated by sequestering the Shine-Dalgarno sequence (ribosomal binding site) in a hairpin-loop structure. While not meeting the previous definition of (transcriptional) attenuation, these are now considered to be variants of the same phenomena and are included in this article. Attenuation is an ancient regulatory system, prevalent in many bacterial species providing fast and sensitive regulation of gene operons and is commonly used to repress genes in the presence of their own product (or a downstream metabolite).

High level of tryptophan



Low level of tryptophan



https://en.wikipedia.org/wiki/Attenuator_(genetics)

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Autoimmune

Autoimmunity is the system of immune responses of an organism against i
healthy cells and tissues. Any disease that results from such an aberrant im
sponse is termed an autoimmune disease.

Prominent examples include Celiac disease, diabetes mellitus type 1, Sarcoi
temic lupus erythematosus (SLE), Sjögren's syndrome, Churg-Strauss Syn
Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purp
son's Disease, rheumatoid arthritis (RA), ankylosing spondylitis, Polymyos
and Dermatomyositis (DM). Autoimmune diseases are very often treated w

https://en.wikipedia.org/wiki/Autoimmunity

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Autosomal

An autosome is a chromosome that is not an allosome (a sex chromosome). appear in pairs whose members have the same form but differ from other p loid cell, whereas members of an allosome pair may differ from one anothe thereby determine sex. The DNA in autosomes is collectively known as atD auDNA.

https://en.wikipedia.org/wiki/Autosome

Related Glossary Terms

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Autosomal Recessive

Dominance in genetics is a relationship between alleles of one gene, in whic
on phenotype of one allele masks the contribution of a second allele at the s
The first allele is dominant and the second allele is recessive. For genes on a
some (any chromosome other than a sex chromosome), the alleles and thei
traits are autosomal dominant or autosomal recessive. Dominance is a key
Mendelian inheritance and classical genetics. Often the dominant allele cod
functional protein whereas the recessive allele does not.

https://en.wikipedia.org/wiki/Dominance_(genetics)

Related Glossary Terms

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Autotrophic

An autotroph ("self-feeding", from the Greek autos "self" and trophe "nouri
producer, is an organism that produces complex organic compounds (such
drates, fats, and proteins) from simple substances present in its surroundir
ally using energy from light (photosynthesis) or inorganic chemical reactio
synthesis). They are the producers in a food chain, such as plants on land o
water, in contrast to heterotrophs as consumers of autotrophs. They do not
ing source of energy or organic carbon.

https://en.wikipedia.org/wiki/Autotroph

Related Glossary Terms

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Autotrophs

An autotroph ("self-feeding", from the Greek autos "self" and trophe "nouri
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https://en.wikipedia.org/wiki/Autotroph

Related Glossary Terms

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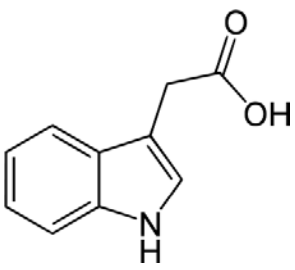
Auxin

Auxins are a class of plant hormones (or plant growth substances) with some morphogen-like characteristics. Auxins have a cardinal role in coordination of many growth and behavioral processes in the plant's life cycle and are essential for plant body development.

Auxins were the first of the major plant hormones to be discovered. They derive their name from the Greek word αυξειν (auxein – "to grow/increase"). Auxin (namely IAA) is present in all parts of a plant, although in very different concentrations. The concentration in each position is crucial developmental information, so it is subject to tight regulation through both metabolism and transport. The result is the auxin creates "patterns" of auxin concentration maxima and minima in the plant body, which in turn guide further development of respective cells, and ultimately of the plant as a whole.

On the cellular level, auxin is essential for cell growth, affecting both cell division and cellular expansion. Auxin concentration level, together with other local factors, contributes to cell differentiation and specification of the cell fate.
Depending on the specific tissue, auxin may promote axial elongation (as in shoots), lateral expansion (as in root swelling), or isodiametric expansion (as in fruit growth). In some cases (coleoptile growth), auxin-promoted cellular expansion occurs in the absence of cell division. In other cases, auxin-promoted cell division and cell expansion may be closely sequenced within the same tissue (root initiation, fruit growth). In a living plant, auxins and other plant hormones nearly always appear to interact to determine patterns of plant development.

Pictured below - Indol-3-ylacetic acid, an auxin



https://en.wikipedia.org/wiki/Auxin

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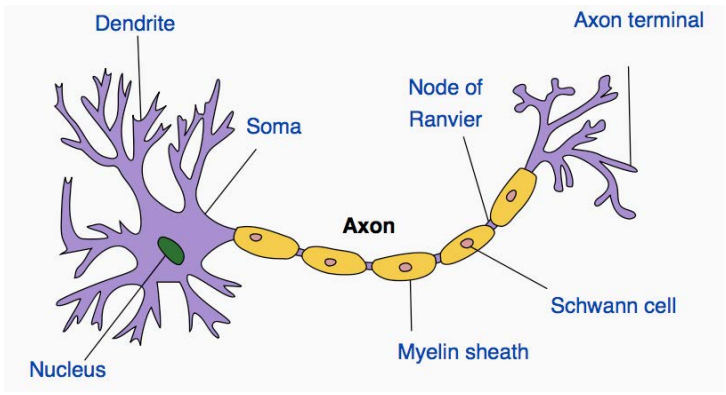
Axon

An axon is a long, slender projection of a nerve cell, or neuron, that typically conducts electrical impulses away from the neuron's cell body. Myelinated axons are known as nerve fibers. The function of the axon is to transmit information to different neurons, muscles and glands. In certain sensory neurons (pseudounipolar neurons), such as those for touch and warmth, the electrical impulse travels along an axon from the periphery to the cell body, and from the cell body to the spinal cord along another branch of the same axon. Axon dysfunction causes many inherited and acquired neurological disorders which can affect both the peripheral and central neurons.

An axon is one of two types of protoplasmic protrusions that extrude from the cell body of a neuron, the other type being dendrites. Axons are distinguished from dendrites by several features, including shape (dendrites often taper while axons usually maintain a constant radius), length (dendrites are restricted to a small region around the cell body while axons can be much longer), and function (dendrites usually receive signals while axons usually transmit them). All of these rules have exceptions, however.

Some types of neurons have no axon and transmit signals from their dendrites. No neuron ever has more than one axon; however in invertebrates such as insects or leeches the axon sometimes consists of several regions that function more or less independently of each other. Most axons branch, in some cases very profusely.

Axons make contact with other cells—usually other neurons but sometimes muscle or gland cells—at junctions called synapses. At a synapse, the membrane of the axon closely adjoins the membrane of the target cell, and special molecular structures serve to transmit electrical or electrochemical signals across the gap. Some synaptic junctions appear partway along an axon as it extends—these are called en passant ("in passing") synapses. Other synapses appear as terminals at the ends of axonal branches. A single axon, with all its branches taken together, can innervate multiple parts of the brain and generate thousands of synaptic terminals.



https://en.wikipedia.org/wiki/Axon

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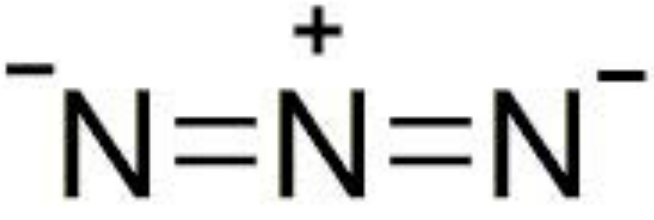
Azide

Azide is the anion with the formula N_3^-. It is the conjugate base of hydrazoi
(HN_3). N_3^- is a linear anion that is isoelectronic with CO_2 and N_2O. Per vale
theory, azide can be described by several resonance structures, an importar
N−=N+=N−. Azide is also a functional group in organic chemistry, RN_3.

Azide is an inhibitor of Complex IV in the electron transport system.



https://en.wikipedia.org/wiki/Azide

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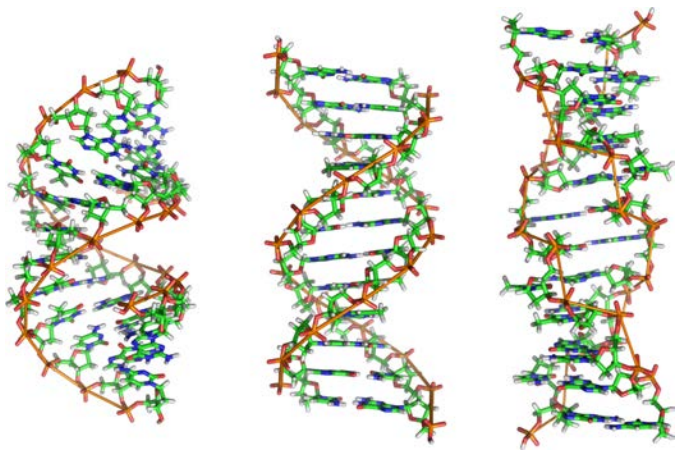
B-form DNA

At least three DNA conformations are found in nature, A-DNA, B-DNA, and Z-DNA. The "B" form described by James D. Watson and Francis Crick is believed to predominate in cells. It is 23.7 Å wide and extends 34 Å per 10 bp of sequence. The double helix makes one complete turn about its axis every 10.4-10.5 base pairs in solution. This frequency of twist (known as the helical pitch) depends largely on stacking forces that each base exerts on its neighbors in the chain.

A-DNA and Z-DNA differ significantly in their geometry and dimensions to B-DNA, although still form helical structures. It was long thought that the A form only occurs in dehydrated samples of DNA in the laboratory, such as those used in crystallographic experiments, and in hybrid pairings of DNA and RNA strands, but DNA dehydration does occur *in vivo*, and A-DNA is now known to have biological functions. Segments of DNA that cells have been methylated for regulatory purposes may adopt the Z geometry, in which the strands turn about the helical axis the opposite way to A-DNA and B-DNA. There is also evidence of protein-DNA complexes forming Z-DNA structures.

Other conformations are possible: A-DNA, B-DNA, C-DNA, E-DNA, L-DNA (the enantiomeric form of D-DNA), P-DNA, S-DNA, Z-DNA, etc. have been described so far. In fact, only the letters F, Q, U, V, and Y are now available to describe any new DNA structure that may appear in the future. However, most of these forms have been created synthetically and have not been observed in naturally occurring biological systems. There are also triple-stranded DNA forms and quadruplex forms such as the G-quadruplex.

From left to right - A, B, and Z forms of DNA



https://en.wikipedia.org/wiki/Nucleic_acid_double_helix

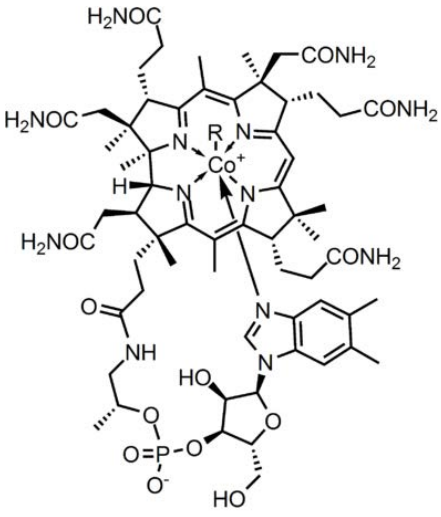
B_{12}

Vitamin B_{12} or vitamin B-12, also called cobalamin, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system, and the formation of red blood cells. It is one of eight B vitamins. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid and amino acid metabolism. No fungi, plants, nor animals (including humans) are capable of producing vitamin B_{12}. Only bacteria and archaea have the enzymes needed for its synthesis. Some plant foods are a natural source of B_{12} because of bacterial symbiosis. B_{12} is the largest and most structurally complicated vitamin and can be produced industrially only through a bacterial fermentation-synthesis. This synthetic B_{12} is used to fortify foods and sold as a dietary supplement.

Vitamin B_{12} consists of a class of chemically related compounds (vitamers), all of which show pharmacological activity. It contains the biochemically rare element cobalt (chemical symbol Co) positioned in the center of a planar tetra-pyrrole ring called a corrin ring. The vitamer is produced by bacteria as hydroxocobalamin, but conversion between different forms of the vitamin occurs in the body after consumption.

A common synthetic form of the vitamin is cyanocobalamin, produced by chemically modifying bacterial hydroxocobalamin. Because of superior stability and low cost this form is used in many pharmaceuticals and supplements as well as for fortification of foods. In the body, it is converted into the human physiological forms methylcobalamin and 5'-deoxyadenosylcobalamin. In this process a cyanide ion, (CN^{-}), is produced, but the amount is very, very small (20 µg from 1,000 µg of cyanocobalamin) compared to what would cause a toxicity risk, and is in fact less than the amount of cyanide consumed daily from food (primarily fruit, nuts, seeds, and legumes). Cyanide-free synthetic forms of the vitamin—hydroxocobalamin, methylcobalamin, and adenosylcobalamin—are being used in some pharmacological products and supplements, but their claimed superiority to cyanocobalamin is debatable.

Vitamin B_{12} was discovered from its relationship to the disease pernicious anemia, an autoimmune disease in which parietal cells of the stomach responsible for secreting intrinsic factor are destroyed. These cells are also responsible for secreting acid in the stomach. Because intrinsic factor is crucial for the normal absorption of B_{12}, its lack in the presence of pernicious anemia causes a vitamin B_{12} deficiency. Many other subtler kinds of vitamin B_{12} deficiency and their biochemical effects have since been elucidated.



R = 5'-deoxyadenosyl, Me, OH, CN

https://en.wikipedia.org/wiki/Vitamin_B12

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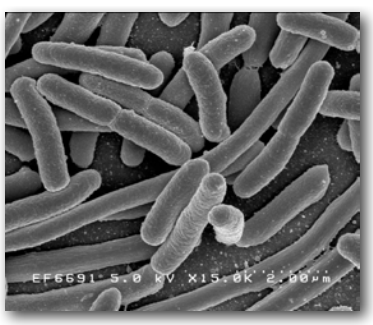
Chapter 6 - Metabolism: Fats and Fatty Acids

Bacteria

Bacteria constitute a large domain of prokaryotic microorganisms. Typically a few micrometers in length, bacteria have a number of shapes, ranging from spheres to rods and spirals. Bacteria were among the first life forms to appear on Earth, and are present in most of its habitats. Bacteria inhabit soil, water, acidic hot springs, radioactive waste, and the deep portions of Earth's crust. Bacteria also live in symbiotic and parasitic relationships with plants and animals.

There are typically 40 million bacterial cells in a gram of soil and a million bacterial cells in a milliliter of fresh water. There are approximately 5×10^{30} bacteria on Earth, forming a biomass which exceeds that of all plants and animals. Bacteria are vital in recycling nutrients, with many of the stages in nutrient cycles dependent on these organisms, such as the fixation of nitrogen from the atmosphere and putrefaction. In the biological communities surrounding hydrothermal vents and cold seeps, bacteria provide the nutrients needed to sustain life by converting dissolved compounds, such as hydrogen sulphide and methane, to energy.

On 17 March 2013, researchers reported data that suggested bacterial life forms thrive in the Mariana Trench, which with a depth of up to 11 kilometers is the deepest part of the Earth's oceans. Other researchers reported related studies that microbes thrive inside rocks up to 580 meters below the sea floor under 2.6 kilometers of ocean off the coast of the northwestern United States. According to one of the researchers, "You can find microbes everywhere — they're extremely adaptable to conditions, and survive wherever they are. Shown below - cells of *E. coli*.



https://en.wikipedia.org/wiki/Bacteria

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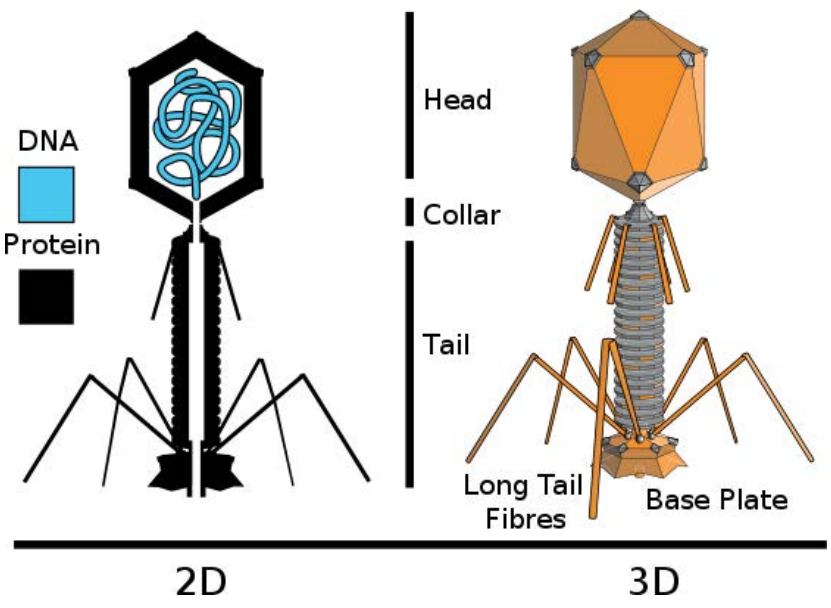
Bacteriophages

A bacteriophage is a virus that infects and replicates within a bacterium. The term is derived from "bacteria" and the Greek: φαγεῖν (phagein), "to devour". Bacteriophages are composed of proteins that encapsulate a DNA or RNA genome, and may have relatively simple or elaborate structures. Their genomes may encode as few as four genes, and as many as hundreds of genes. Phages replicate within the bacterium following the injection of their genome into its cytoplasm. Bacteriophages are among the most common and diverse entities in the biosphere.

Phages are widely distributed in locations populated by bacterial hosts, such as soil or the intestines of animals. One of the densest natural sources for phages and other viruses is sea water, where up to 9×10^8 virions per milliliter have been found in microbial mats at the surface, and up to 70% of marine bacteria may be infected by phages. They have been used for over 90 years as an alternative to antibiotics in the former Soviet Union and Central Europe, as well as in France. They are seen as a possible therapy against multi-drug-resistant strains of many bacteria (see phage therapy). Nevertheless, phages of *Inoviridae* have been shown to complicate biofilms involved in pneumonia and cystic fibrosis, shelter the bacteria from drugs meant to eradicate disease and promote persistent infection.



https://en.wikipedia.org/wiki/Bacteriophage

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BamH I

BamH I (from *Bacillus amyloliquefaciens*) is a type II restriction endonucl
the capacity for recognizing short sequences (6 b.p.) of DNA and specificall
them at a target site. Specifically, BAMH I cuts duplex DNA as shown belo
places of the vertical bars.

G|GATC C
C CTAG|G

https://en.wikipedia.org/wiki/BamHI

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Chapter 9 - Point by Point: Techniques

Base

The term ‘base’ has two meanings in biochemistry

1. Bases are substances that, in aqueous solution, are slippery to the touch, gent, change the color of indicators (e.g., turn red litmus paper blue), react to form salts, promote certain chemical reactions (base catalysis), accept pr any proton donor, and/or contain completely or partially displaceable OH– https://en.wikipedia.org/wiki/Base_(chemistry)

2. Bases are nitrogenous components of nucleotides. Adenine, guanine, ur thymine, and cytosine are all bases.

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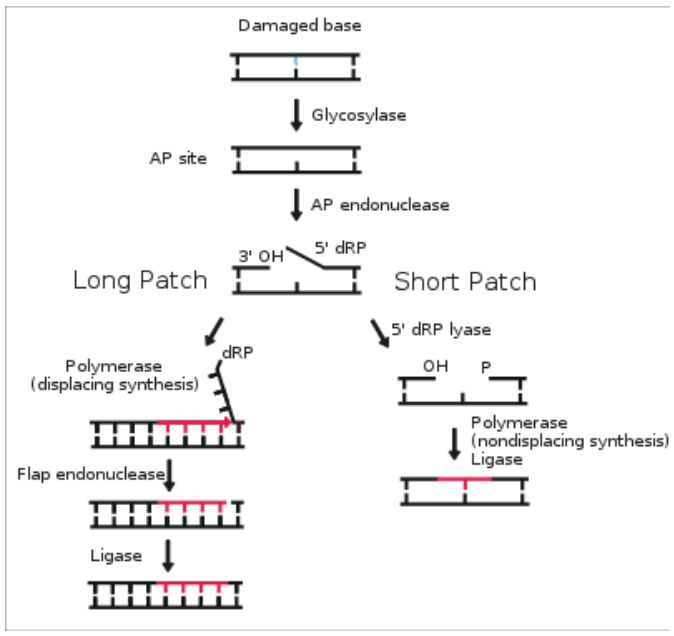
Base Excision Repair

Base excision repair (BER) is a cellular mechanism that repairs damaged DNA throughout the cell cycle. It is responsible primarily for removing small, non-helix-distorting base lesions from the genome. The related nucleotide excision repair pathway repairs bulky helix-distorting lesions. BER is important for removing damaged bases that could otherwise cause mutations by mispairing or lead to breaks in DNA during replication. BER is initiated by DNA glycosylases, which recognize and remove specific damaged or inappropriate bases, forming AP sites. These are then cleaved by an AP endonuclease. The resulting single-strand break can then be processed by either short-patch (where a single nucleotide is replaced) or long-patch BER (where 2-10 new nucleotides are synthesized).

Single bases in DNA can be chemically damaged by a variety of mechanisms, the most common ones being deamination, oxidation, and alkylation. These modifications can affect the ability of the base to hydrogen-bond, resulting in incorrect base-pairing, and, as a consequence, mutations in the DNA. For example, incorporation of adenine across from 8-oxoguanine (right) during DNA replication causes a G:C base pair to be mutated to T:A. Other examples of base lesions repaired by BER include:

• Oxidized bases: 8-oxoguanine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG, FapyA)
• Alkylated bases: 3-methyladenine, 7-methylguanosine
• Deaminated bases: hypoxanthine formed from deamination of adenine. Xanthine formed from deamination of guanine. (Thymidine products following deamination of 5-methylcytosine are more difficult to recognize, but can be repaired by mismatch-specific glycosylases)
• Uracil inappropriately incorporated in DNA or formed by deamination of cytosine.

In addition to base lesions, the downstream steps of BER are also utilized to repair single-strand breaks.



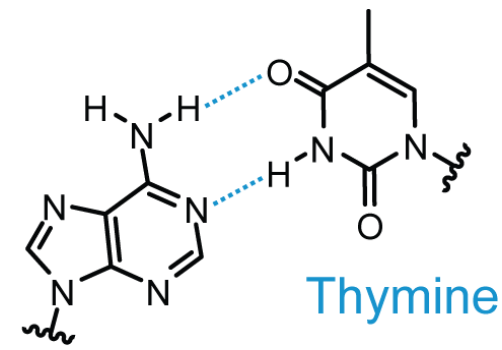
https://en.wikipedia.org/wiki/Base_excision_repair

Base Pairing

A base pair (bp) is a unit consisting of two nucleobases bound to each other by hydrogen bonds. They form the building blocks of the DNA double helix, and contribute to the folded structure of both DNA and RNA. Dictated by specific hydrogen bonding patterns, Watson-Crick base pairs (guanine-cytosine and adenine-thymine) allow the DNA helix to maintain a regular helical structure that is subtly dependent on its nucleotide sequence. The complementary nature of this based-paired structure provides a backup copy of all genetic information encoded within double-stranded DNA. The regular structure and data redundancy provided by the DNA double helix make DNA well suited to the storage of genetic information, while base-pairing between DNA and incoming nucleotides provides the mechanism through which DNA polymerase replicates DNA, and RNA polymerase transcribes DNA into RNA. Many DNA-binding proteins can recognize specific base pairing patterns that identify particular regulatory regions of genes.

Intramolecular base pairs can occur within single-stranded nucleic acids. This is particularly important in RNA molecules (e.g., transfer RNA), where Watson-Crick base pairs (G-C and A-U) permit the formation of short double-stranded helices, and a wide variety of non-Watson-Crick interactions (e.g., G-U or A-A) allow RNAs to fold into a vast range of specific three-dimensional structures. In addition, base-pairing between transfer RNA (tRNA) and messenger RNA (mRNA) forms the basis for the molecular recognition events that result in the nucleotide sequence of mRNA becoming translated into the amino acid sequence of proteins via the genetic code.

The size of an individual gene or an organism's entire genome is often measured in base pairs because DNA is usually double-stranded. Hence, the number of total base pairs is equal to the number of nucleotides in one of the strands (with the exception of non-coding single-stranded regions of telomeres). The haploid human genome (23 chromosomes) is estimated to be about 3.2 billion bases long and to contain 20,000–25,000 distinct protein-coding genes. A kilobase (kb) is a unit of measurement in molecular biology equal to 1000 base pairs of DNA or RNA. The total amount of related DNA base pairs on Earth is estimated at 5.0×10^{37}, and weighs 50 billion tonnes. In comparison, the total mass of the biosphere has been estimated to be as much as 4 TtC (trillion tons of carbon).



https://en.wikipedia.org/wiki/Base_pair

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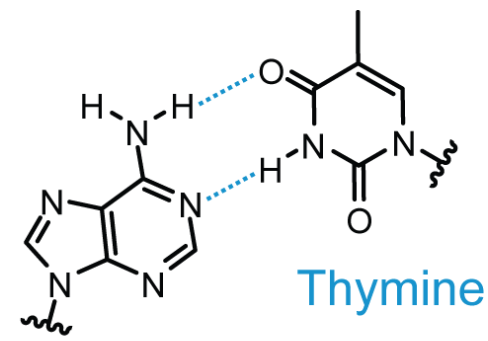

https://en.wikipedia.org/wiki/Base_pair

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Base Pairs Per Turn

In a "relaxed" double-helical segment of B-DNA, the two strands twist around the helical axis once every 10.4–10.5 base pairs per turn of the helix. Adding or subtracting twists, as some enzymes can do, imposes strain. If a DNA segment under twist strain were closed into a circle by joining its two ends and then allowed to move freely, the circular DNA would contort into a new shape, such as a simple figure-eight. Such a contortion is a supercoil. The noun form "supercoil" is often used in the context of DNA topology.

Positively supercoiled (overwound) DNA is transiently generated during DNA replication and transcription, and, if not promptly relaxed, inhibits (regulates) these processes. The simple figure eight is the simplest supercoil, and is the shape a circular DNA assumes to accommodate one too many or one too few helical twists. The two lobes of the figure eight will appear rotated either clockwise or counterclockwise with respect to one another, depending on whether the helix is over- or underwound. For each additional helical twist being accommodated, the lobes will show one more rotation about their axis. As a general rule, the DNA of most organisms is negatively supercoiled.

Lobal contortions of a circular DNA, such as the rotation of the figure-eight lobes above, are referred to as writhe. The above example illustrates that twist and writhe are interconvertible. Supercoiling can be represented mathematically by the sum of twist and writhe. The twist is the number of helical turns in the DNA and the writhe is the number of times the double helix crosses over on itself (these are the supercoils). Extra helical twists are positive and lead to positive supercoiling, while subtractive twisting causes negative supercoiling. Many topoisomerase enzymes sense supercoiling and either generate or dissipate it as they change DNA topology. DNA of most organisms is negatively supercoiled.

In part because chromosomes may be very large, segments in the middle may act as if their ends are anchored. As a result, they may be unable to distribute excess twist to the rest of the chromosome or to absorb twist to recover from underwinding—the segments may become supercoiled, in other words. In response to supercoiling, they will assume an amount of writhe, just as if their ends were joined.

Supercoiled DNA forms two structures - a plectoneme or a toroid, or a combination of both. A negatively supercoiled DNA molecule will produce either a one-start left-handed helix, the toroid, or a two-start right-handed helix with terminal loops, the plectoneme. Plectonemes are typically more common in nature, and this is the shape most bacterial plasmids will take. For larger molecules it is common for hybrid structures to form – a loop on a toroid can extend into a plectoneme. If all the loops on a toroid extend then it becomes a branch point in the plectonemic structure. DNA supercoiling is important for DNA packaging within all cells, and seems to also play a role in gene expression.

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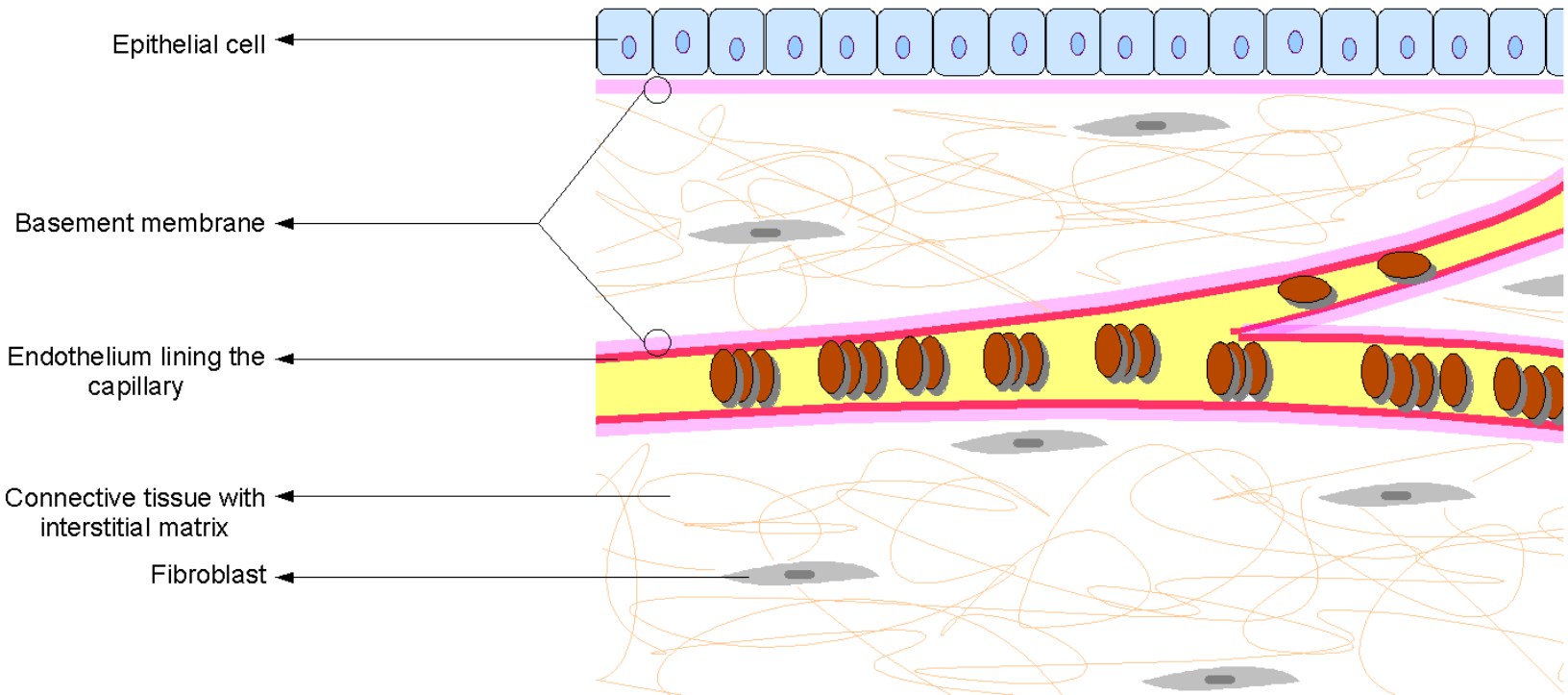
Chapter 2 - Structure and Function: Nucleic Acids

Basement Membrane

The basement membrane is a thin, fibrous, extracellular matrix of tissue that separates the epithelium (skin, respiratory tract, gastrointestinal tract, etc), mesothelium (pleural cavity, peritoneal cavity, pericardial cavity, etc) and endothelium (blood vessels, lymph vessels, etc) from underlying connective tissue.



https://en.wikipedia.org/wiki/Basement_membrane

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Bcl-2

Bcl-2 (B-cell lymphoma 2), encoded in humans by the BCL2 gene, is the founding member of the Bcl-2 family of regulator proteins that regulate cell death (apoptosis), by either inducing (pro-apoptotic) or inhibiting (anti-apoptotic) apoptosis. Bcl-2 is specifically considered an important anti-apoptotic protein and is thus classified as an oncogene.

BCL-2 is localized to the outer membrane of mitochondria, where it plays an important role in promoting cellular survival and inhibiting the actions of pro-apoptotic proteins. The pro-apoptotic proteins in the BCL-2 family, including Bax and Bak, normally act on the mitochondrial membrane to promote permeabilization and release of cytochrome C and ROS, that are important signals in the apotosis cascade. These pro-apoptotic proteins are in turn activated by BH3-only proteins, and are inhibited by the function of BCL-2 and its relative BCL-Xl.

There are additional non-canonical roles of BCL-2 that are being explored. BLC-2 is known to regulate mitochondrial dynamics, and is involved in the regulation of mitochondrial fusion and fission. Additionally, in pancreatic β-cells, BCL-2 and BCL-Xl are known to be involved in controlling metabolic activity and insulin secretion, with inhibition of BCL-2/Xl showing increasing metabolic activity, but also additional ROS production. This suggests it has a protective metabolic effect in conditions of high demand.

https://en.wikipedia.org/wiki/Bcl-2

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Bcr-abl

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Beads on a String

The basic repeat element of chromatin is the nucleosome, interconnected by sections of linker DNA, a far shorter arrangement than pure DNA in solution.
In addition to the core histones, there is the linker histone, H1, which contacts the ex entry of the DNA strand on the nucleosome. The nucleosome core particle, together with histone H1, is known as a chromatosome. Nucleosomes, with about 20 to 60 ba pairs of linker DNA, can form, under non-physiological conditions, an approximately 10 nm "beads-on-a-string" fiber.

The nucleosomes bind DNA non-specifically, as required by their function in general DNA packaging. There are, however, large DNA sequence preferences that govern nu cleosome positioning. This is due primarily to the varying physical properties of diffe ent DNA sequences: For instance, adenine and thymine are more favorably com-
pressed into the inner minor grooves. This means nucleosomes can bind preferential at one position approximately every 10 base pairs (the helical repeat of DNA)- where the DNA is rotated to maximize the number of A and T bases that will lie in the inner minor groove.

https://en.wikipedia.org/wiki/Chromatin

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Benedict’s Test

Several qualitative tests are used to detect the presence of reducing sugars. Two of them use solutions of copper(II) ions: Benedict's reagent (Cu^{++} in aqueous sodium citrate) and Fehling's solution (Cu^{++} in aqueous sodium tartrate). The reducing sugar reduces the copper(II) ions in these test solutions to copper(I), which then forms a brick red copper(I) oxide precipitate. Reducing sugars can also be detected with the addition of Tollen's reagent, which consist of silver ions (Ag^{+}) in aqueous ammonia. When Tollen's reagent is added to an aldehyde, it precipitates silver metal, often forming a silver mirror on clean glassware.

3,5-dinitrosalicylic acid is another test reagent, one that allows quantitative detection. It reacts with a reducing sugar to form 3-amino-5-nitrosalicylic acid, which can be measured by spectrophotometry to determine the amount of reducing sugar that was present.

Sugars having acetal or ketal linkages are not reducing sugars, as they do not have free aldehyde chains. They therefore do not react with any of the reducing-sugar test solutions. However, a non-reducing sugar can be hydrolyzed using dilute hydrochloric acid. After hydrolysis and neutralization of the acid, the product may be a reducing sugar that gives normal reactions with the test solutions.

https://en.wikipedia.org/wiki/Reducing_sugar

Related Glossary Terms

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Benzopyrene

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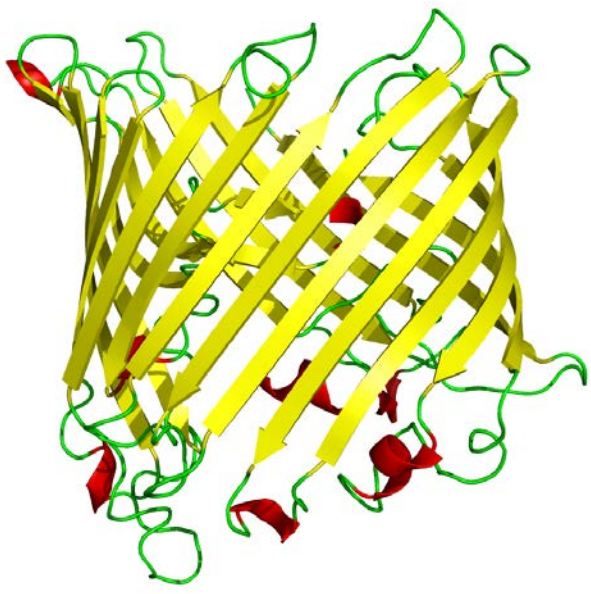
Beta Barrels

A β barrel is a large beta-sheet that twists and coils to form a closed structure in which the first strand is hydrogen bonded to the last. β-strands in beta-barrels are typically arranged in an antiparallel fashion. Barrel structures are commonly found in porins and other proteins that span cell membranes and in proteins that bind hydrophobic ligands in the barrel center, as in lipocalins. Porin-like barrel structures are encoded by as many as 2–3% of the genes in Gram-negative bacteria.

In many cases the strands contain alternating polar and hydrophobic amino acids, so that the hydrophobic residues are oriented into the interior of the barrel to form a hydrophobic core and the polar residues are oriented toward the outside of the barrel on the solvent-exposed surface. Porins and other membrane proteins containing beta barrels reverse this pattern, with hydrophobic residues oriented toward the exterior where they contact the surrounding lipids, and hydrophilic residues oriented toward the interior pore.



https://en.wikipedia.org/wiki/Beta_barrel

Betaine-homocysteine Methyltransferase

Betaine-homocysteine S-methyltransferase also known as betaine-homocys
yltransferase (BHMT) is a zinc metallo-enzyme that catalyzes the transfer o
group from betaine to homocysteine to produce dimethylglycine and methi
spectively:

Betaine + Homocysteine → Dimethylglycine + Methionine

This enzyme belongs to the family of transferases, specifically those transfe
carbon group methyltransferases. This enzyme participates in the metaboli
glycine, serine, threonine and also methionine.

https://en.wikipedia.org/wiki/Betaine%E2%80%94homocysteine_S-meth
e

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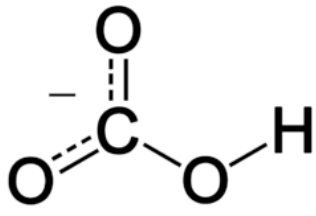
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Bicarbonate

In inorganic chemistry, bicarbonate (IUPAC-recommended nomenclature: hydrogen carbonate) is an intermediate form in the deprotonation of carbonic acid. It is a polyatomic anion with the chemical formula HCO_3^-.

Bicarbonate serves a crucial biochemical role in the physiological pH buffering system.



https://en.wikipedia.org/wiki/Bicarbonate

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Bile

Bile or gall is a dark green to yellowish brown fluid, produced by the liver o
brates, that aids the digestion of lipids in the small intestine. In humans, bi
duced continuously by the liver (liver bile), and stored and concentrated in
der (gallbladder bile). After eating, this stored bile is discharged into the du
The composition of gallbladder bile is 97% water, 0.7% bile salts, 0.2% bilir
fats (cholesterol, fatty acids and lecithin), and 200 meq/l inorganic salts.

https://en.wikipedia.org/wiki/Bile

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Chapter 2 - Structure & Function: Lipids

Bile Acid

Bile acids are steroid acids found predominantly in the bile of mammals and other vertebrates. Different molecular forms of bile acids can be synthesized in the liver by different species. Bile acids are conjugated with taurine or glycine in the liver, forming bile salts. Primary bile acids are those synthesized by the liver. Secondary bile acids result from bacterial actions in the colon. In humans, taurocholic acid and glycocholic acid (derivatives of cholic acid) and taurochenodeoxycholic acid and glycochenodeoxycholic acid (derivatives of chenodeoxycholic acid) are the major bile salts in bile and are roughly equal in concentration.

As amphipathic molecules with hydrophobic and hydrophilic regions, conjugated bile salts sit at the lipid/water interface and, at the right concentration, form micelles. The added solubility of conjugated bile salts aids in their function by preventing passive reabsorption in the small intestine. As a result, the concentration of bile acids/salts in the small intestine is high enough to form micelles and solubilize lipids. "Critical micellar concentration" refers to both an intrinsic property of the bile acid itself and amount of bile acid necessary to function in the spontaneous and dynamic formation of micelles. Bile acid-containing micelles aid lipases to digest lipids and bring them near the intestinal brush border membrane, which results in fat absorption.

Synthesis of bile acids is a major route of cholesterol metabolism in most species other than humans. The body produces about 800 mg of cholesterol per day and about half of that is used for bile acid synthesis producing 400–600 mg daily. Human adults secrete between 12-18 g of bile acids into the intestine each day, mostly after meals. The bile acid pool size is between 4–6 g, which means that bile acids are recycled several times each day. About 95% of bile acids are reabsorbed by active transport in the ileum and recycled back to the liver for further secretion into the biliary system and gallbladder. This enterohepatic circulation of bile acids allows a low rate of synthesis but with large amounts being secreted into the intestine.

Bile acids have other functions, including eliminating cholesterol from the body, driving the flow of bile to eliminate certain catabolites (including bilirubin), emulsifying fat-soluble vitamins to enable their absorption, and aiding in motility and the reduction of the bacteria flora found in the small intestine and biliary tract.

https://en.wikipedia.org/wiki/Bile_acid

Related Glossary Terms

Drag related terms here

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Bile acids are steroid acids found predominantly in the bile of mammals and other vertebrates. Different molecular forms of bile acids can be synthesized in the liver by different species. Bile acids are conjugated with taurine or glycine in the liver, forming bile salts. Primary bile acids are those synthesized by the liver. Secondary bile acids result from bacterial actions in the colon. In humans, taurocholic acid and glycocholic acid (derivatives of cholic acid) and taurochenodeoxycholic acid and glycochenodeoxycholic acid (derivatives of chenodeoxycholic acid) are the major bile salts in bile and are roughly equal in concentration.

As amphipathic molecules with hydrophobic and hydrophilic regions, conjugated bile salts sit at the lipid/water interface and, at the right concentration, form micelles. The added solubility of conjugated bile salts aids in their function by preventing passive reabsorption in the small intestine. As a result, the concentration of bile acids/salts in the small intestine is high enough to form micelles and solubilize lipids. "Critical micellar concentration" refers to both an intrinsic property of the bile acid itself and amount of bile acid necessary to function in the spontaneous and dynamic formation of micelles. Bile acid-containing micelles aid lipases to digest lipids and bring them near the intestinal brush border membrane, which results in fat absorption.

Synthesis of bile acids is a major route of cholesterol metabolism in most species other than humans. The body produces about 800 mg of cholesterol per day and about half of that is used for bile acid synthesis producing 400–600 mg daily. Human adults secrete between 12-18 g of bile acids into the intestine each day, mostly after meals. The bile acid pool size is between 4–6 g, which means that bile acids are recycled several times each day. About 95% of bile acids are reabsorbed by active transport in the ileum and recycled back to the liver for further secretion into the biliary system and gallbladder. This enterohepatic circulation of bile acids allows a low rate of synthesis but with large amounts being secreted into the intestine.

Bile acids have other functions, including eliminating cholesterol from the body, driving the flow of bile to eliminate certain catabolites (including bilirubin), emulsifying fat-soluble vitamins to enable their absorption, and aiding in motility and the reduction of the bacteria flora found in the small intestine and biliary tract.

https://en.wikipedia.org/wiki/Bile_acid

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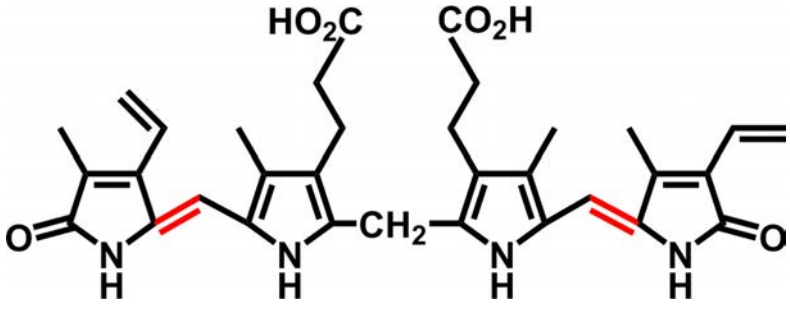
Bilirubin

Bilirubin (formerly referred to as haematoidin) is the yellow breakdown product of normal heme catabolism, caused by the body's clearance of aged red blood cells which contain hemoglobin.

Bilirubin is excreted in bile and urine, and elevated levels may indicate certain diseases. It is responsible for the yellow color of bruises and the yellow discoloration in jaundice. It is also responsible for the brown color of feces, via its conversion to stercobilin, and the background straw-yellow color of urine via its breakdown product, urobilin.



https://en.wikipedia.org/wiki/Bilirubin

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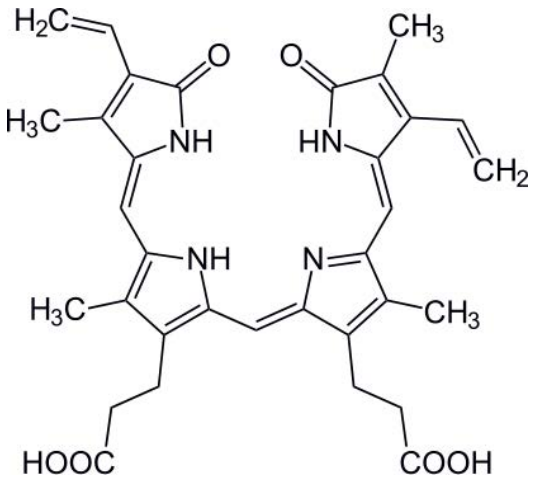
Biliverdin

Biliverdin is a green tetrapyrrolic bile pigment, and is a product of heme catabolism. It is the pigment responsible for a greenish color sometimes seen in bruises. Biliverdin results from the breakdown of the heme moiety of hemoglobin in erythrocytes. Macrophages break down senescent erythrocytes and break the heme down into biliverdin, which normally rapidly reduces to free bilirubin.

While typically regarded as a mere waste product of heme breakdown, evidence that suggests that biliverdin — and other bile pigments — has a physiological role in humans has been mounting.

Bile pigments such as biliverdin possess significant anti-mutagenic and antioxidant properties and therefore may fulfill a useful physiological function. Biliverdin and bilirubin have been shown to be potent scavengers of peroxyl radicals. They have also been shown to inhibit the effects of polycyclic aromatic hydrocarbons, heterocyclic amines, and oxidants — all of which are mutagens. Some studies have found that people with higher concentration levels of bilirubin and biliverdin in their bodies have a lower frequency of cancer and cardiovascular disease. It has been suggested that biliverdin — as well as many other tetrapyrrolic pigments — may function as an HIV-1 protease inhibitor as well as having beneficial effects in asthma though further research is needed to confirm these results. There are currently no practical implications for using biliverdin in the treatment of any disease.



https://en.wikipedia.org/wiki/Biliverdin

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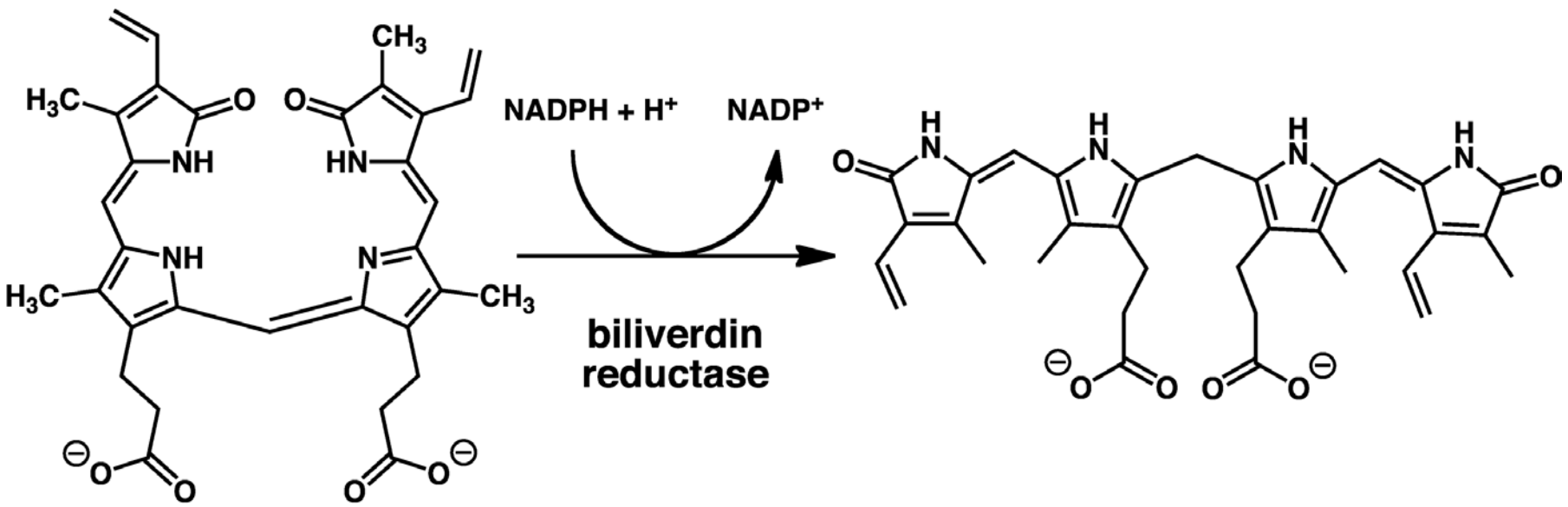
Biliverdin Reductase

Biliverdin reductase (BVR) is an enzyme (EC 1.3.1.24) found in all tissues under
mal conditions, but especially in reticulo-macrophages of the liver and spleen. B
cilitates the conversion of biliverdin to bilirubin via the reduction of a double-bo
tween the second and third pyrrole ring into a single-bond.



biliverdin **bilirubin**

https://en.wikipedia.org/wiki/Biliverdin_reductase

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Chapter 6 - Metabolism: Other Lipids

Chapter 9 - Point by Point: Metabolism

Biochemistry

Biochemistry, sometimes called biological chemistry, is the study of chemical processes within and relating to living organisms. By controlling information flow through biochemical signaling and the flow of chemical energy through metabolism, biochemical processes give rise to the complexity of life. Over the last decades of the 20th century, biochemistry has become so successful at explaining living processes that now almost all areas of the life sciences from botany to medicine to genetics are engaged in biochemical research. Today, the main focus of pure biochemistry is on understanding how biological molecules give rise to the processes that occur within living cells, which in turn relates greatly to the study and understanding of tissues, organs, and whole organisms—that is, all of biology.

Biochemistry is closely related to molecular biology, the study of the molecular mechanisms by which genetic information encoded in DNA is able to result in the processes of life. Depending on the exact definition of the terms used, molecular biology can be thought of as a branch of biochemistry, or biochemistry as a tool with which to investigate and study molecular biology.

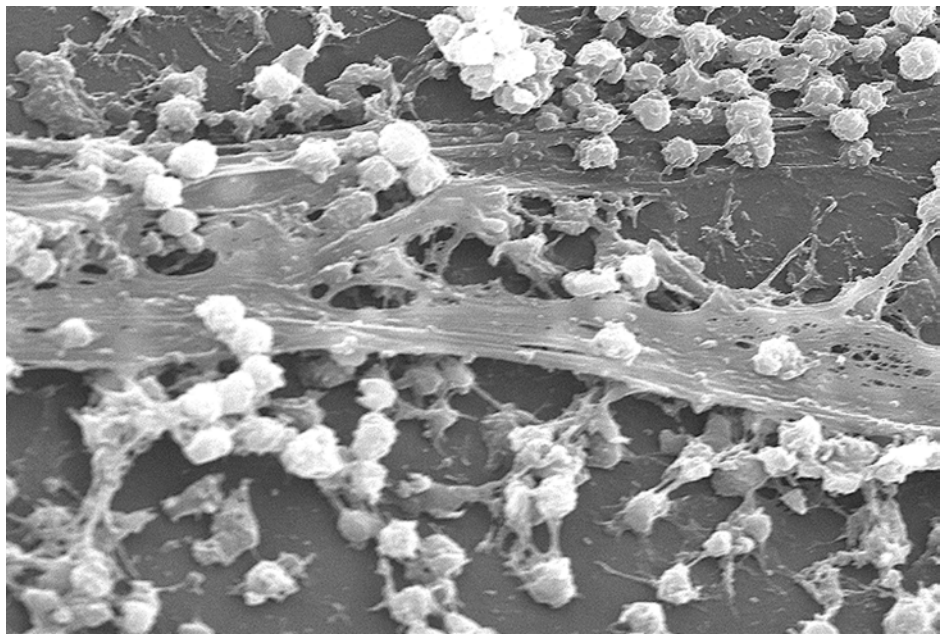
Much of biochemistry deals with the structures, functions and interactions of biological macromolecules, such as proteins, nucleic acids, carbohydrates and lipids, which provide the structure of cells and perform many of the functions associated with life. The chemistry of the cell also depends on the reactions of smaller molecules and ions. These can be inorganic, for example water and metal ions, or organic, for example the amino acids, which are used to synthesize proteins. The mechanisms by which cells harness energy from their environment via chemical reactions are known as metabolism. The findings of biochemistry are applied primarily in medicine, nutrition, and agriculture. In medicine, biochemists investigate the causes and cures of diseases. In nutrition, they study how to maintain health and study the effects of nutritional deficiencies. In agriculture, biochemists investigate soil and fertilizers, and try to discover ways to improve crop cultivation, crop storage and pest control.

https://en.wikipedia.org/wiki/Biochemistry

Related Glossary Terms

Biofilms

A biofilm is any group of microorganisms in which cells stick to each other and often these cells adhere to a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS). Biofilm extracellular polymeric substance, which is also referred to as slime (although not everything described as slime is a biofilm), is a polymeric conglomeration generally composed of extracellular DNA, proteins, and polysaccharides. Biofilms may form on living or non-living surfaces and can be prevalent in natural, industrial and hospital settings. A *Staphylococcus aureus* biofilm is shown below.



https://en.wikipedia.org/wiki/Biofilm

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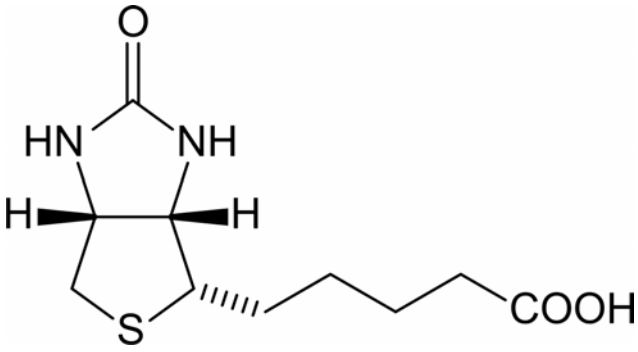
Biotin

Biotin is a water-soluble B-vitamin (vitamin B_7), formerly known as vitamin H or coenzyme R.

It is composed of a ureido (tetrahydroimidizalone) ring fused with a tetrahydrothiophene ring. A valeric acid substituent is attached to one of the carbon atoms of the tetrahydrothiophene ring. Biotin is a coenzyme for carboxylase enzymes, involved in the synthesis of fatty acids, isoleucine, and valine, and in gluconeogenesis.

Biotin deficiency can be caused by inadequate dietary intake or inheritance of one or more inborn genetic disorders that affect biotin metabolism (see multiple carboxylase deficiency). Subclinical deficiency can cause mild symptoms, whereas the inborn genetic disorders can have severe (even lethal) consequences. Neonatal screening for biotinidase deficiency began in the United States in 1984 and today many countries test for this disorder at birth. Individuals born prior to 1984 are unlikely to have been screened, thus the true prevalence of the disorder is unknown.

Biotin-thiamine-responsive basal ganglia disease is another potentially life-threatening condition that requires biotin (and thiamine, another B vitamin) for treatment.



https://en.wikipedia.org/wiki/Biotin

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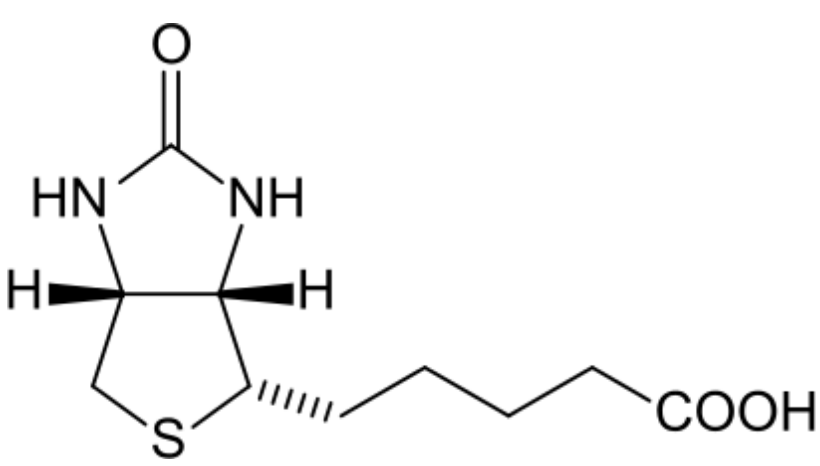
Biotinylation

In biochemistry, biotinylation is the process of covalently attaching biotin to a protein, nucleic acid or other molecule. Biotinylation is rapid, specific and is unlikely to perturb the natural function of the molecule due to the small size of biotin (MW = 244.31 g/mol). Biotin binds to streptavidin and avidin with an extremely high affinity, fast on-rate, and high specificity, and these interactions are exploited in many areas of biotechnology to isolate biotinylated molecules of interest. Biotin-binding to streptavidin and avidin is resistant to extremes of heat, pH and proteolysis, making capture of biotinylated molecules possible in a wide variety of environments. Also, multiple biotin molecules can be conjugated to a protein of interest, which allows binding of multiple streptavidin, avidin or Neutravidin protein molecules and increases the sensitivity of detection of the protein of interest. There is a large number of biotinylation reagents available that exploit the wide range of possible labelling methods. Due to the strong affinity between biotin and streptavidin, the purification of biotinylated proteins has been a widely used approach to identify protein-protein interactions and post-translational events such as ubiquitylation in molecular biology.



https://en.wikipedia.org/wiki/Biotinylation

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Bisphophglycerate Mutase

Bisphosphoglycerate mutase (BPGM) is an enzyme unique to erythrocytes and place
tal cells. It is responsible for the catalytic synthesis of 2,3-Bisphosphoglycerate (2,3-
BPG) from 1,3-bisphosphoglycerate. BPGM also has a mutase and a phosphatase fun
tion, but these are much less active, in contrast to its glycolitic cousin, phosphoglycer
ate mutase (PGM), which favors these two functions, but can also catalyze the synthe
sis of 2,3-BPG to a lesser extent.

1,3-BPG is formed as an intermediate in glycolysis. BPGM then takes this and conver
it to 2,3-BPG, which serves an important function in oxygen transport. 2,3-BPG binc
with high affinity to hemoglobin, causing a conformational change that results in the
release of oxygen. Local tissues can then pick up the free oxygen. This is also importa
in the placenta, where fetal and maternal blood come within such close proximity.
With the placenta producing 2,3-BPG, a large amount of oxygen is released from
nearby maternal hemoglobin, which can then dissociate and bind with fetal hemoglo
bin, which has a much lower affinity for 2,3-BPG.

https://en.wikipedia.org/wiki/Bisphosphoglycerate_mutase

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Blood

Blood is a bodily fluid in animals that delivers necessary substances such as nutrients and oxygen to the cells and transports metabolic waste products away from those same cells.

In vertebrates, it is composed of blood cells suspended in blood plasma. Plasma, which constitutes 55% of blood fluid, is mostly water (92% by volume), and contains dissipated proteins, glucose, mineral ions, hormones, carbon dioxide (plasma being the main medium for excretory product transportation), and blood cells themselves. Albumin is the main protein in plasma, and it functions to regulate the colloidal osmotic pressure of blood. The blood cells are mainly red blood cells (also called RBCs or erythrocytes), white blood cells (also called WBCs or leukocytes) and platelets. The most abundant cells in vertebrate blood are red blood cells. These contain hemoglobin, an iron-containing protein, which facilitates oxygen transport by reversibly binding to this respiratory gas and greatly increasing its solubility in blood. In contrast, carbon dioxide is almost entirely transported extracellularly dissolved in plasma as bicarbonate ion.

Vertebrate blood is bright red when its hemoglobin is oxygenated and dark red when it is deoxygenated. Some animals, such as crustaceans and mollusks, use hemocyanin to carry oxygen, instead of hemoglobin. Insects and some mollusks use a fluid called hemolymph instead of blood, the difference being that hemolymph is not contained in a closed circulatory system. In most insects, this "blood" does not contain oxygen-carrying molecules such as hemoglobin because their bodies are small enough for their tracheal system to suffice for supplying oxygen.

https://en.wikipedia.org/wiki/Blood

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Blood Clotting

Coagulation (also known as clotting) is the process by which blood changes from a liquid to a gel, forming a clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin. Disorders of coagulation are disease states which can result in bleeding (hemorrhage or bruising) or obstructive clotting (thrombosis).

Coagulation is highly conserved throughout biology - in all mammals, coagulation involves both a cellular (platelet) and a protein (coagulation factor) component. The system in humans has been the most extensively researched and is the best understood.

Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining the vessel. Exposure of blood to the space under the endothelium initiates two processes: changes in platelets, and the exposure of subendothilial tissue factor to plasma Factor VII, which ultimately leads to fibrin formation. Platelets immediately form a plug at the site of injury. This is called primary hemostasis. Secondary hemostasis occurs simultaneously: Additional coagulation factors or clotting factors beyond Factor VII respond in a complex cascade to form fibrin strands, which strengthen the platelet plug.

https://en.wikipedia.org/wiki/Coagulation

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Blood Thinning

The term blood thinning refers to using an anticoagulant to reduce the clotting tendency of blood in a patient. Anticoagulants occur naturally in leeches and blood-sucking insects. A group of pharmaceuticals called anticoagulants can be used as an injection as a medication for thrombotic disorders. Oral anticoagulants are also available. Some anticoagulants are used in medical equipment, such as test tubes, blood transfusion bags, and renal dialysis equipment.

Anticoagulants are closely related to antiplatelet drugs and thrombolytic drugs by manipulating the various pathways of blood coagulation. Specifically, anticoagulants manipulate the coagulation cascade that builds upon the initial platelet thrombus.

A number of anticoagulants are available. The traditional ones (warfarin, other coumarins and heparins) are in widespread use. Since the 2000s a number of new agents have been introduced that are collectively referred to as the novel oral anticoagulants (NOACs) or directly acting oral anticoagulants (DOACs). These agents include inhibitors of factor IIa (dabigatran) and factor Xa (rivaroxaban, apixaban and edoxaban) and they have been shown to be as good or possibly better than the coumarins with less serious side effects. The newer anticoagulants (NOACs/DOACs), are more expensive than the traditional ones and should be used with care in patients with kidney problems. Additionally, there is no antidote for the factor Xa inhibitors, so it is difficult to stop their effects in the body in cases of emergency (accidents, urgent surgery).

https://en.wikipedia.org/wiki/Anticoagulant

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Blood-brain Barrier

The blood–brain barrier (BBB) is a highly selective permeability barrier that separates the circulating blood from the brain extracellular fluid in the central nervous system (CNS). The blood–brain barrier is formed by brain endothelial cells, which are connected by tight junctions with an extremely high electrical resistivity of at least 0.1 Ω·m. The blood–brain barrier allows the passage of water, some gases, and lipid-soluble molecules by passive diffusion, as well as the selective transport of molecules such as glucose and amino acids that are crucial to neural function. On the other hand, the blood–brain barrier may prevent the entry of lipophilic, potential neurotoxins by way of an active transport mechanism mediated by P-glycoprotein. Astrocytes are necessary to create the blood–brain barrier. A small number of regions in the brain, including the circumventricular organs (CVOs), do not have a blood–brain barrier.

The blood–brain barrier occurs along all capillaries and consists of tight junctions around the capillaries that do not exist in normal circulation. Endothelial cells restrict the diffusion of microscopic objects (e.g., bacteria) and large or hydrophilic molecules into the cerebrospinal fluid (CSF), while allowing the diffusion of small or hydrophobic molecules (O_2, CO_2, hormones). Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins. This barrier also includes a thick basement membrane and astrocytic endfeet.

https://en.wikipedia.org/wiki/Blood%E2%80%93brain_barrier

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Blotting

A blot, in molecular biology and genetics, is a method of transferring proteins, DNA or RNA, onto a carrier (for example, a nitrocellulose PVDF or nylon membrane). In many instances, this is done after a gel electrophoresis, transferring the molecules from the gel onto the blotting membrane, and other times adding the samples directly onto the membrane.

After the blotting, the transferred proteins, DNA or RNA are then visualized by colorant staining (for example, silver staining of proteins), autoradiographic visualization of radioactive labelled molecules (performed before the blot), or specific labelling of some proteins or nucleic acids. The latter is done with antibodies or hybridization probes that bind only to some molecules of the blot and have an enzyme joined to them.

After proper washing, this enzymatic activity (and so, the molecules we search in the blot) is visualized by incubation with proper reactive, rendering either a colored deposit on the blot or a chemiluminiscent reaction which is registered by photographic film. Three commons blots and the material separated/identified by them are Southern (DNA), Northern (RNA), and Western (proteins).

https://en.wikipedia.org/wiki/Blot_(biology)

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Blue/White Screening

The blue-white screen is a screening technique that allows for the rapid and convenient detection of recombinant bacteria in vector-based molecular cloning experiments. DNA of interest is ligated into a vector. The vector is then inserted into a competent host cell viable for transformation, which are then grown in the presence of X-gal. Cells transformed with vectors containing recombinant DNA will produce white colonies. Cells transformed with non-recombinant plasmids (i.e. only the vector) grow into blue colonies. This method of screening is usually performed using a suitable bacterial strain, but other organisms such as yeast may also be used.

The correct type of vector and competent cells are important considerations when planning a blue white screen. The plasmid must contain the lacZα, and examples of such plasmids are pUC19 and pBluescript. The *E. coli* cell should contain the mutant lacZ gene with deleted sequence (i.e. lacZΔM15), and some of the commonly used cells with such genotype are JM109, DH5α, and XL1-Blue.
It should also be understood that the lac operon is affected by the presence of glucose. The protein EIIAGlc, which is involved in glucose import, shuts down lactose permease when glucose is being transported into the cell. The media used in agar plate therefore should not include glucose.

X-gal is light-sensitive and therefore its solution and plates containing X-gal should be stored in the dark. Isopropyl β-D-1-thiogalactopyranoside (IPTG), which functions as the inducer of the lac operon, may be used in the media to enhance the expression of LacZ.

https://en.wikipedia.org/wiki/Blue_white_screen

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Bohr Effect

The Bohr effect is a physiological phenomenon first described in 1904 by the Danish physiologist Christian Bohr, stating that haemoglobin's oxygen binding affinity (see Oxygen–haemoglobin dissociation curve) is inversely related both to acidity and to the concentration of carbon dioxide. That is, an increase in blood CO_2 concentration, which leads to a decrease in blood pH, will result in hemoglobin proteins releasing their load of oxygen. Conversely, a decrease in carbon dioxide provokes an increase in pH, which results in haemoglobin picking up more oxygen. Since carbon dioxide reacts with water to form carbonic acid, an increase in CO_2 results in a decrease in blood pH.

The Bohr effect facilitates oxygen transport as heemoglobin binds to oxygen in the lungs, but then releases it in the tissues, particularly those tissues in most need of oxygen. When a tissue's metabolic rate increases, its carbon dioxide production increases. Carbon dioxide forms bicarbonate through the following reaction:

$CO_2 + H_2O <=> H_2CO_3 <=> H^+ + HCO_3^-$

Although the reaction usually proceeds very slowly, the enzyme family of carbonic anhydrase, which is present in red blood cells, accelerates the formation of bicarbonate and protons. This causes the pH of tissues to decrease, and so, promotes the dissociation of oxygen from haemoglobin to the tissue, allowing the tissue to obtain enough oxygen to meet its demands. Conversely, in the lungs, where oxygen concentration is high, binding of oxygen causes haemoglobin to release protons, which combine with bicarbonate to drive off carbon dioxide in exhalation. Since these two reactions are closely matched, there is little change in blood pH.

The dissociation curve shifts to the right when carbon dioxide or hydrogen ion concentration is increased. This facilitates increased oxygen dumping. This mechanism allows for the body to adapt the problem of supplying more oxygen to tissues that need it the most. When muscles are undergoing strenuous activity, they generate CO_2 and lactic acid as products of cellular respiration and lactic acid fermentation. In fact, muscles generate lactic acid so quickly that pH of the blood passing through the muscles will drop to around 7.2. As lactic acid releases its protons, pH decreases, which causes hemoglobin to release ~10% more oxygen.

https://en.wikipedia.org/wiki/Bohr_effect

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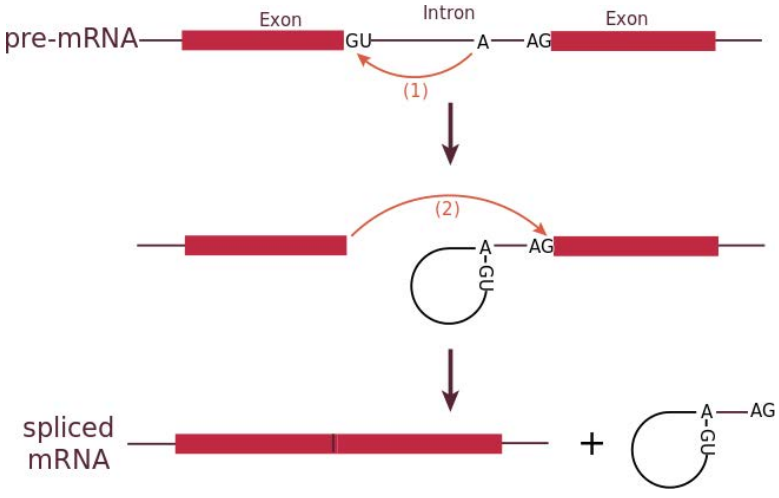
Branch Site

Spliceosomal introns often reside within the sequence of eukaryotic protein-coding genes. Within the intron, a donor site (5' end of the intron), a branch site (near the 3' end of the intron) and an acceptor site (3' end of the intron) are required for splicing. The splice donor site includes an almost invariant sequence GU at the 5' end of the intron, within a larger, less highly conserved region. The splice acceptor site at the 3' end of the intron terminates the intron with an almost invariant AG sequence. Upstream (5'-ward) from the AG there is a region high in pyrimidines (C and U), or polypyrimidine tract. Further upstream from the polypyrimidine tract is the branchpoint, which includes an adenine nucleotide involved in lariat formation. The consensus sequence for an intron (in IUPAC nucleic acid notation) is: G-G-[cut]-G-U-R-A-G-U (donor site) ... intron sequence ... Y-U-R-A-C (branch sequence 20-50 nucleotides upstream of acceptor site) ... Y-rich-N-C-A-G-[cut]-G (acceptor site). However, it is noted that the specific sequence of intronic splicing elements and the number of nucleotides between the branchpoint and the nearest 3’ acceptor site affect splice site selection. Also, point mutations in the underlying DNA or errors during transcription can activate a cryptic splice site in part of the transcript that usually is not spliced. This results in a mature messenger RNA with a missing section of an exon. In this way, a point mutation, which might otherwise only affect a single amino acid, can manifest as a deletion or truncation in the final protein.



https://en.wikipedia.org/wiki/RNA_splicing

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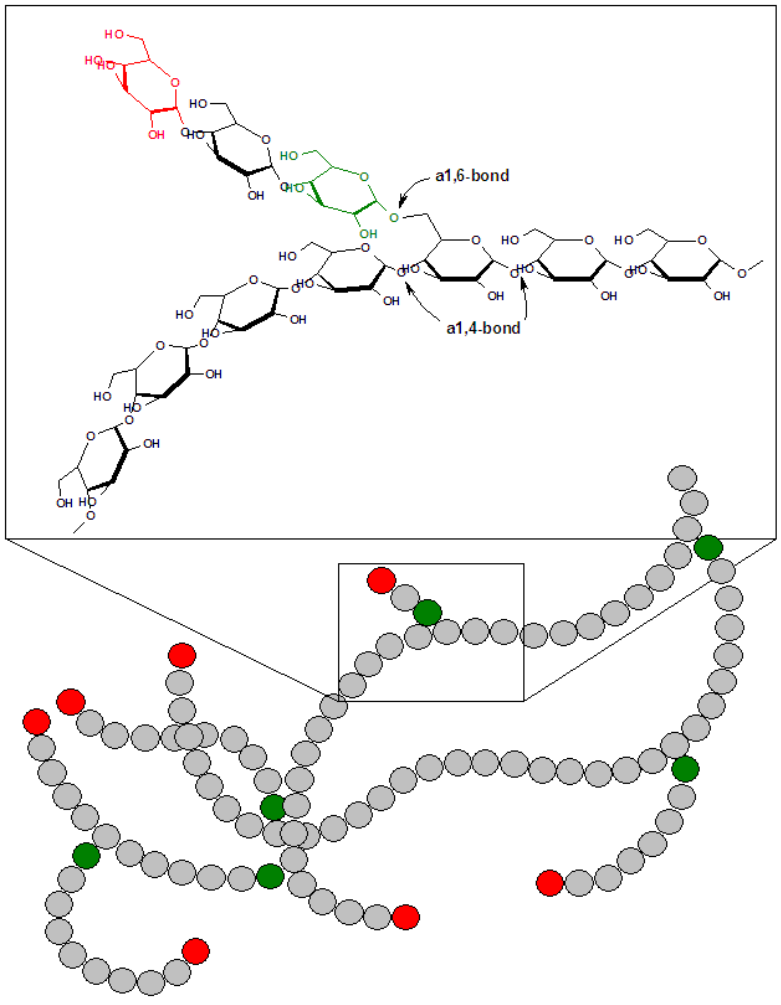
Branching

Glycogen is a biopolymer consisting of linear chains of glucose residues with further chains branching off every 8 to 12 glucoses or so. Glucoses are linked together linearly by α(1→4) glycosidic bonds from one glucose to the next.

Branches are linked to the chains from which they are branching off by α(1→6) glycosidic bonds between the first glucose of the new branch and a glucose on the stem chain.

Branching is an important consideration for glycogen metabolism, since glucose units are excised from glycogen from free ends. More branching = more ends = more glucose quickly released. Branching of glycogen is shown below. Free ends are marked in red. Glucose units involved in branches marked in green.



https://en.wikipedia.org/wiki/Glycogen

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Chapter 2 - Structure & Function: Carbohydrates

Branching Enzyme

Glycogen branching enzyme is an enzyme that adds branches to the growing glycogen molecule during the synthesis of glycogen, a storage form of glucose. More specifically, during glycogen synthesis, a glucose 1-phosphate molecule reacts with uridine triphosphate (UTP) to become UDP-glucose, an activated form of glucose. The activated glucosyl unit of UDP-glucose is then transferred to the hydroxyl group at the C-4 of a terminal residue of glycogen to form an α-1,4-glycosidic linkage, a reaction catalyzed by glycogen synthase.

In glycogen, every 10 to 14 glucose units, a side branch with an additional chain of glucose units occurs. The side chain attaches at carbon atom 6 of a glucose unit, an α-1,6-glycosidic bond. This connection is catalyzed by a branching enzyme, generally given the name α-glucan branching enzyme. A branching enzyme attaches a string of seven glucose units (with some minor variation to this number) to the carbon at the C-6 position on the glucose unit, forming the α-1,6-glycosidic bond. The specific nature of this enzyme means that this chain of 7 carbons is usually attached to a glucose molecule that is in position three from the non-reducing end of another chain. Because the enzyme works with such specificity regarding the number of glucose units transferred and the position to which they are transferred, the enzyme creates the very characteristic, highly-branched glycogen molecule.

https://en.wikipedia.org/wiki/Glycogen_branching_enzyme

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Brevican

Brevican is a proteoglycan localized to the surface of neurons in the brain.

https://en.wikipedia.org/wiki/Brevican

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Chapter 2 - Structure & Function: Carbohydrates

Chapter 9 - Point by Point: Structure and Function

Brown Fat

Brown adipose tissue (BAT) or brown fat is one of two types of fat or adipose tissue (the other being white adipose tissue, or white fat) found in mammals. Importantly, classification of brown fat in humans refers to at least two distinct cell populations with similar functions. The first shares a common embryological origin with muscle cells, found in larger "classic" deposits. The second develops from adrenergically induced adipocytes, found interspersed in white adipose tissue.

It is especially abundant in newborns and in hibernating mammals. Its primary function is to generate body heat in animals or newborns that do not shiver. In contrast to white adipocytes (fat cells), which contain a single lipid droplet, brown adipocytes contain numerous smaller droplets and a much higher number of (iron-containing) mitochondria, which make it brown. Brown fat also contains more capillaries than white fat, since it has a greater need for oxygen than most tissues.

The mitochondria in a eukaryotic cell utilize fuels to produce energy in the form of adenosine triphosphate (ATP). This process involves storing energy as a proton gradient, also known as the proton motive force (PMF), across the mitochondrial inner membrane. This energy is used to synthesize ATP when the protons flow across the membrane (down their concentration gradient) through the ATP synthase enzyme. This is known as chemiosmosis.

In endotherms, body heat is maintained by signaling the mitochondria to allow protons to run back along the gradient without producing ATP (proton leak). This can occur since an alternative return route for the protons exists through an uncoupling protein in the inner membrane. This protein, known as uncoupling protein 1 (thermogenin), facilitates the return of the protons after they have been actively pumped out of the mitochondria by the electron transport chain. This alternative route for protons uncouples oxidative phosphorylation and the energy in the PMF is instead released as heat.

To some degree, all cells of endotherms give off heat, especially when body temperature is below a regulatory threshold. However, brown adipose tissue is highly specialized for this non-shivering thermogenesis. First, each cell has a higher number of mitochondria compared to more typical cells. Second, these mitochondria have a higher-than-normal concentration of thermogenin in the inner membrane.

https://en.wikipedia.org/wiki/Brown_adipose_tissue

Bruce Ames

Bruce Nathan Ames (born December 16, 1928) is an American biochemist. He is a professor of Biochemistry and Molecular Biology Emeritus at the University of California, Berkeley, and a senior scientist at Children's Hospital Oakland Research Institute (CHORI). He is the inventor of the Ames test, a system for easily and cheaply testing the mutagenicity of compounds.

In the 1970s, Bruce Ames developed the Ames test which is a cheap and convenient assay for mutagens and therefore potential carcinogens. Previous carcinogenic testing used live animals, and the procedures are expensive and time-consuming. This made animal testing impractical for use in screening on a wide scale, and reduced the number of compounds that could be tested. The Ames test on the other hand uses the bacteria Salmonella typhimurium to test for mutagens, and is considerably cheaper and faster. The Ames test became widely used as an initial screen for possible carcinogens and has been used to identify potential carcinogens previously used in commercial products. Their identification led to some of those formulations, such as chemicals used in hair dye, being withdrawn from commercial use. The ease with which Ames test allows widely used chemicals to be identified as possible carcinogens made him an early hero of environmentalism.

https://en.wikipedia.org/wiki/Bruce_Ames

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Buffer

A buffer solution (more precisely, pH buffer or hydrogen ion buffer) is an aqueous solution consisting of a mixture of a weak acid and its conjugate base, or vice versa. Its pH changes very little when a small or moderate amount of strong acid or base is added to it and thus it is used to prevent changes in the pH of a solution. Buffer solutions are used as a means of keeping pH at a nearly constant value in a wide variety of chemical applications. Many life forms thrive only in a relatively small pH range so they utilize a buffer solution to maintain a constant pH. In nature, the bicarbonate buffering system is used to regulate the pH of blood.

Buffer solutions achieve their resistance to pH change because of the presence of an equilibrium between the acid HA and its salt A^-.

$$HA \rightleftharpoons H^+ + A^-$$

When some strong acid is added to an equilibrium mixture of the weak acid and its salt, the equilibrium is shifted to the left, in accordance with Le Châtelier's principle. Because of this, the hydrogen ion concentration increases by less than the amount expected for the quantity of strong acid added. Similarly, if strong alkali is added to the mixture the hydrogen ion concentration decreases by less than the amount expected for the quantity of alkali added.

https://en.wikipedia.org/wiki/Buffer_solution

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Buffer Capacity

Buffer capacity is a quantitative measure of the resistance of a buffer soluti
change on addition of protons or hydroxide ions. It may be thought of as th
concentration of the buffer in the solution.

https://en.wikipedia.org/wiki/Buffer_solution#Buffer_capacity

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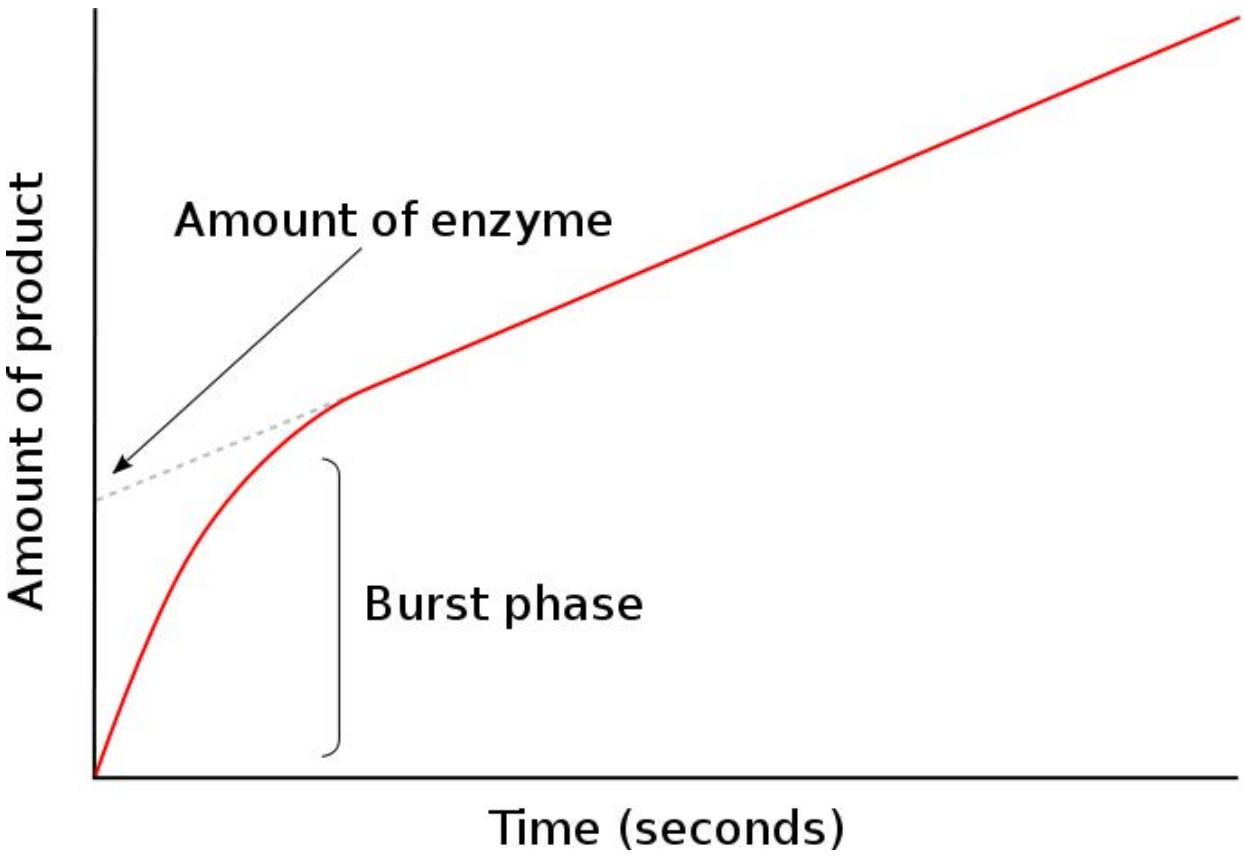
Burst Phase

Burst kinetics is a form of enzyme kinetics that refers to an initial high velocity of enzymatic turnover when adding enzyme to substrate. The initial period of high velocity product formation is referred to as the "Burst Phase". This period is observed as the enzymes become saturated with substrate up until all enzymes are saturated. Once all enzymes are saturated, the Burst Phase gives way to a linear reaction velocity. An example of a burst kinetics is observed in Step 6 of glycolysis involving glyceraldehyde-3-phosphate dehydrogenase (also called GAPDH) and the reduction of NAD^+ to NADH.



https://en.wikipedia.org/wiki/Burst_kinetics

Related Glossary Terms

C-linked Glycosylation

C-linked glycosylation is a rare form of glycosylation where a sugar is adde
bon on a tryptophan side-chain.

In C-linked glycosylation, a mannose sugar is added to the first tryptophan
the sequence W-X-X-W (W indicates tryptophan - X is any amino acid). Th
spondins are one of the most commonly C-modified proteins, although this
cosylation appears elsewhere as well. C-mannosylation is unusual because
linked to a carbon rather than a reactive atom such as nitrogen or oxygen.

https://en.wikipedia.org/wiki/Glycosylation

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C-terminal

The C-terminus (also known as the carboxyl-terminus, carboxy-terminus, C tail, C-terminal end, or COOH-terminus) is the end of an amino acid chain polypeptide), terminated by a free carboxyl group (-COOH).

When a protein is translated from messenger RNA, it is created from N-ter terminus. The convention for writing peptide sequences is to put the C-terr on the right and write the sequence from N- to C-terminus.

https://en.wikipedia.org/wiki/C-terminus

Related Glossary Terms

Drag related terms here

C-terminal Domain

The carboxy-terminal domain of RNA polymerase II typically consists of up to 5
peats of the sequence Tyr-Ser-Pro-Thr-Ser-Pro-Ser. The RNA Polymerase CTD
covered first in the laboratory of C.J.Ingles at the University of Toronto and als
laboratory of J Corden at Johns Hopkins University during the processes of seq
ing the DNA encoding the RPB1 subunit of RNA polymerase from Yeast and Mi
spectively. Other proteins often bind the C-terminal domain of RNA polymeras
der to activate polymerase activity. It is the protein domain that is involved in t
tion of transcription, the capping of the RNA transcript, and attachment to the
some for RNA splicing. In transcription initiation, the C-terminal domain of R
lymerase II gets phosphorylated.

https://en.wikipedia.org/wiki/RNA_polymerase_II

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C_4 Plants

A C_4 plant is a plant that uses C_4 carbon fixation. C_4 carbon fixation is one of three biochemical processes, along with C_3 and CAM photosynthesis, used to fix carbon. It is named for the 4-carbon molecule present in the first product of carbon fixation in the small subset of plants that use that process, in contrast to the 3-carbon molecule products in C_3 plants.

C_4 fixation is an elaboration of the more common C_3 carbon fixation and is believed to have evolved more recently. C_4 and CAM overcome the tendency of the enzyme RuBisCO to wastefully fix oxygen rather than carbon dioxide in the process of photorespiration. This is achieved in a more efficient environment for RubisCo by shuttling CO_2 via malate or aspartate from mesophyll cells to bundle-sheath cells. In these bundle-sheath cells, RuBisCO is isolated from atmospheric oxygen and saturated with the CO_2 released by decarboxylation of the malate.

C_4 plants use PEP Carboxylase to capture more CO_2 in the mesophyll cells. PEP Carboxylase (3 carbons) binds to CO_2 to make oxaloacetic acid (OAA). Then OAA makes malate (4 carbons). Malate enters bundle sheath cells and releases CO_2 inside bundle sheath for rubisco to work more efficiently. These additional steps, however, require more energy in the form of ATP. Because of this extra energy requirement, C_4 plants are able to more efficiently fix carbon in drought, high temperatures, and limitations of nitrogen or CO_2, with the more common C_3 pathway being more efficient in the other conditions.

https://en.wikipedia.org/wiki/C4_carbon_fixation

Related Glossary Terms

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CAAT Box

A CCAAT box (also sometimes abbreviated a CAAT box or CAT box) is a distinct pattern of nucleotides with GGCCAATCT consensus sequence that occur upstream by 60-100 bases to the initial transcription site. The CAAT box signals the binding site for the RNA transcription factor, and is typically accompanied by a conserved consensus sequence. It is an invariant DNA sequence at about minus 70 base pairs from the origin of transcription in many eukaryotic promoters. Genes that have this element seem to require it for the gene to be transcribed in sufficient quantities. It is frequently absent from genes that encode proteins used in virtually all cells. This box along with the GC box is known for binding general transcription factors. Both of these consensus sequences belong to the regulatory promoter. Full gene expression occurs when transcription activator proteins bind to each module within the regulatory promoter. Protein specific binding is required for the CCAAT box activation. These proteins are known as CCAAT box binding proteins/CCAAT box binding factors.

A CCAAT box is a feature frequently found before eukaryote coding regions, but is not found in prokaryotes.

https://en.wikipedia.org/wiki/CAAT_box

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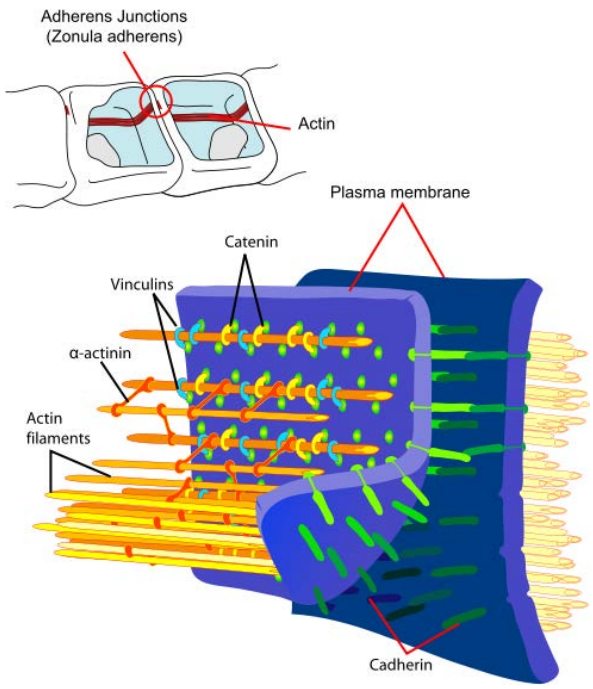
Cadherin

Cadherins (named for "calcium-dependent adhesion") are a class of type-1 transmembrane proteins. They play important roles in cell adhesion, forming adherens junctions to bind cells within tissues together. They are dependent on calcium (Ca^{++}) ions to function, hence their name.

The cadherin superfamily includes cadherins, protocadherins, desmogleins, and desmocollins, and more. In structure, they share cadherin repeats, which are the extracellular Ca^{++}-binding domains. There are multiple classes of cadherin molecule, each designated with a prefix (in general, noting the type of tissue with which it is associated). It has been observed that cells containing a specific cadherin subtype tend to cluster together to the exclusion of other types, both in cell culture and during development. For example, cells containing N-cadherin tend to cluster with other N-cadherin-expressing cells. However, it has been noted that the mixing speed in the cell culture experiments can have an effect on the extent of homotypic specificity. In addition, several groups have observed heterotypic binding affinity (i.e., binding of different types of cadherin together) in various assays. One current model proposes that cells distinguish cadherin subtypes based on kinetic specificity rather than thermodynamic specificity, as different types of cadherin homotypic bonds have different lifetimes.



https://en.wikipedia.org/wiki/Cadherin

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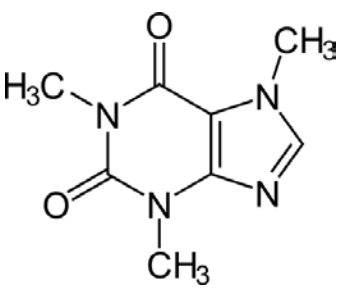
Caffeine

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class. It is the world's most widely consumed psychoactive drug, but — unlike many other psychoactive substances — it is legal and unregulated in nearly all parts of the world. There are several known mechanisms of action to explain the effects of caffeine. The most prominent is that it reversibly blocks the action of adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system.

Caffeine can have both positive and negative health effects. It can be used to treat bronchopulmonary dysplasia of prematurity, and to prevent apnea of prematurity: caffeine citrate was placed on the WHO Model List of Essential Medicines in 2007. It may confer a modest protective effect against some diseases, including Parkinson's disease and certain types of cancer. One meta-analysis concluded that cardiovascular disease such as coronary artery disease and stroke is less likely with 3–5 cups of non-decaffeinated coffee per day but more likely with over 5 cups per day. Some people experience insomnia or sleep disruption if they consume caffeine, especially during the evening hours, but others show little disturbance. Evidence of a risk during pregnancy is equivocal. Some authorities recommend that pregnant women limit consumption to the equivalent of two cups of coffee per day or less. Caffeine can produce a mild form of drug dependence – associated with withdrawal symptoms such as sleepiness, headache, and irritability – when an individual stops using caffeine after repeated daily intake. Tolerance to the autonomic effects of increased blood pressure and heart rate, and increased urine output, develops with chronic use (i.e., these symptoms become less pronounced or do not occur following consistent use).

Caffeine is classified by the Food and Drug Administration as "generally recognized as safe" (GRAS). Toxic doses, over 10 grams per day for an adult, are much higher than typical dose of under 500 milligrams per day. A cup of coffee contains 80–175 mg of caffeine, depending on what "bean" (seed) is used and how it is prepared (e.g. drip, percolation, or espresso). Thus it requires roughly 50–100 ordinary cups of coffee to reach a lethal dose. However pure powdered caffeine, which is available as a dietary supplement, can be lethal in tablespoon-sized amounts.



https://en.wikipedia.org/wiki/Caffeine

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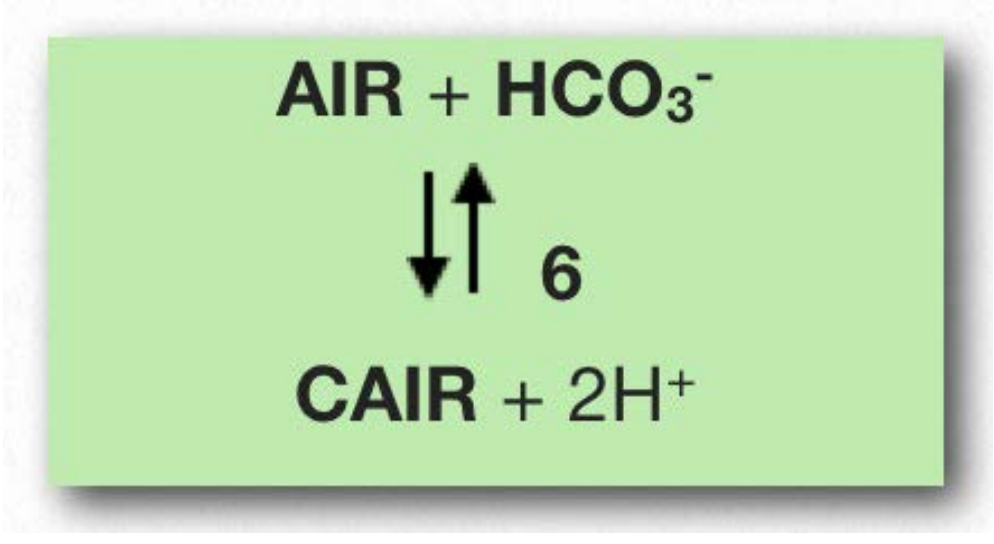
CAIR

5'-Phosphoribosyl-4-carboxy-5-aminoimidazole (CAIR) is an intermediate i
step of the *de novo* biosynthetic pathway of purines by action of phosphorib
imidazole carboxylase (PAIC).



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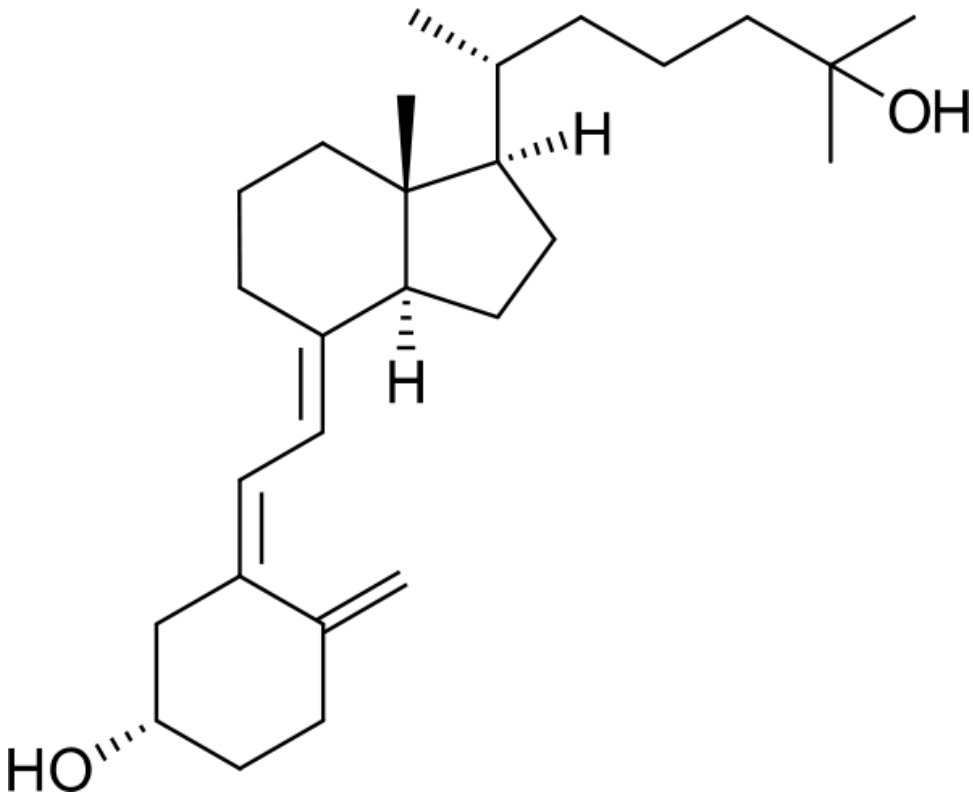
Calcidiol

Calcifediol (INN), also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D (abbreviated 25(OH)D), is a prehormone that is produced in the liver by hydroxylation of vitamin D_3 (cholecalciferol) by the enzyme cholecalciferol 25-hydroxylase which was isolated by Michael F. Holick. Physicians worldwide measure this metabolite to determine a patient's vitamin D status.



https://en.wikipedia.org/wiki/Calcifediol

Related Glossary Terms

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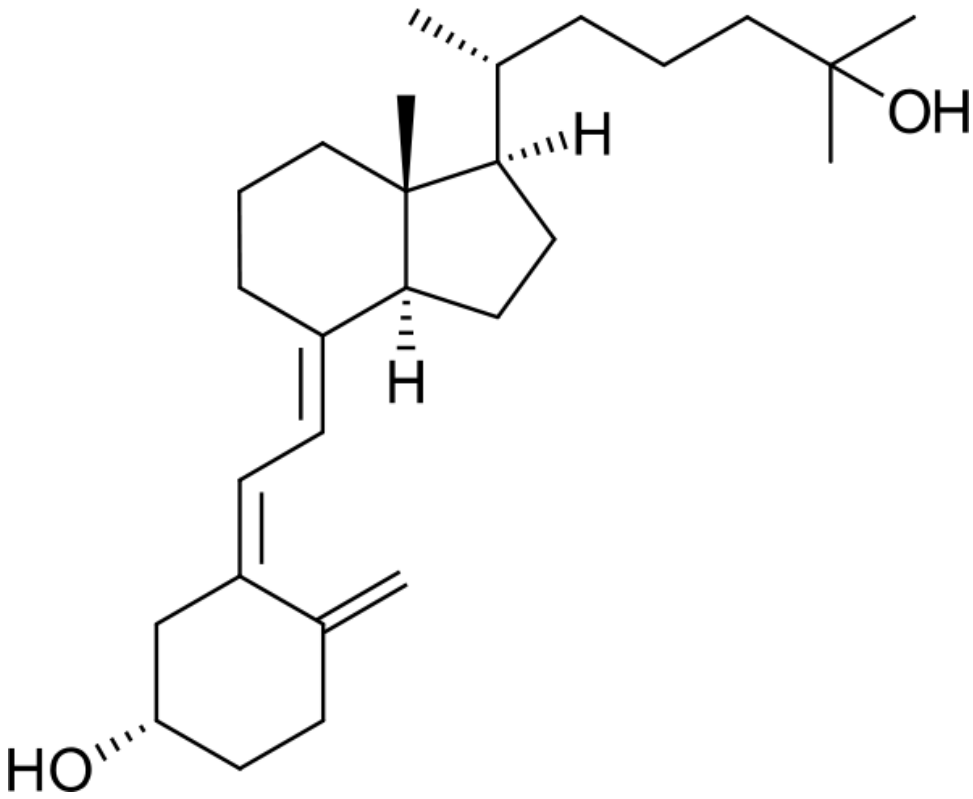

https://en.wikipedia.org/wiki/Calcifediol

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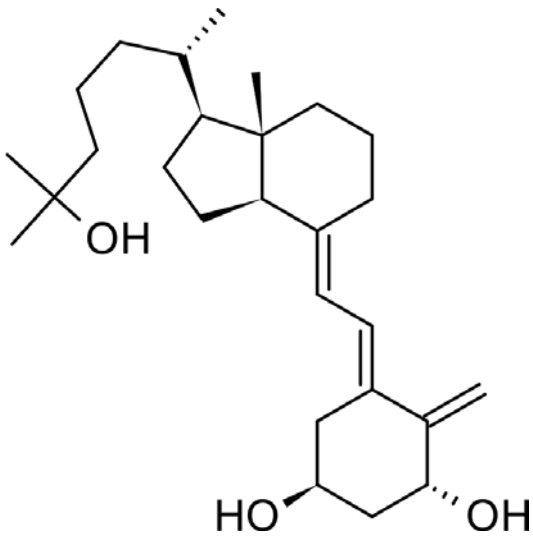
Calcitriol

Calcitriol (INN), also called 1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D_3, is the hormonally active metabolite of vitamin D with three hydroxyl groups (abbreviated 1,25-$(OH)_2D_3$ or simply 1,25$(OH)_2$D).

Calcitriol increases blood calcium levels ([Ca^{++}]) by promoting absorption of dietary calcium from the gastrointestinal tract and increasing renal tubular reabsorption of calcium, thus reducing the loss of calcium in the urine. Calcitriol also stimulates release of calcium from bone by its action on the specific type of bone cells referred to as osteoblasts, causing them to release RANKL, which in turn activates osteoclasts.

Calcitriol acts in concert with parathyroid hormone (PTH) in all three of these roles. For instance, PTH also indirectly stimulates osteoclasts. However, the main effect of PTH is to increase the rate at which the kidneys excrete inorganic phosphate (Pi), the counterion of Ca^{++}. The resulting decrease in serum phosphate causes hydroxyapatite ($Ca_5(PO_4)_3OH$) to dissolve out of bone thus increasing serum calcium. PTH also stimulates the production of calcitriol (see below).

Many of the effects of calcitriol are mediated by its interaction with the calcitriol receptor, also called the vitamin D receptor or VDR. For instance, the unbound inactive form of the calcitriol receptor in intestinal epithelial cells resides in the cytoplasm. When calcitriol binds to the receptor, the ligand-receptor complex translocates to the cell nucleus, where it acts as a transcription factor promoting the expression of a gene encoding a calcium binding protein. The levels of the calcium binding protein increase enabling the cells to actively transport more calcium (Ca^{++}) from the intestine across the intestinal mucosa into the blood.



https://en.wikipedia.org/wiki/Calcitriol

Related Glossary Terms

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Calcium Pump

Calcium pumps are a family of ion transporters found in the cell membrane of all animal cells. They are responsible for the active transport of calcium out of the cell for the maintenance of the steep Ca^{++} electrochemical gradient across the cell membrane. Calcium pumps play a crucial role in proper cell signaling by keeping the intracellular calcium concentration roughly 10,000 times lower than the extracellular concentration. Failure to do so is one cause of muscle cramps. The plasma membrane Ca^{++} ATPase and the sodium-calcium exchanger are together the main regulators of intracellular Ca^{++} concentrations.

Ca^{++} has many important roles as an intracellular messenger. The release of a large amount of free Ca^{++} can trigger a fertilized egg to develop, skeletal muscle cells to contract, secretion by secretory cells and interactions with Ca^{++} -responsive proteins like calmodulin. To maintain low concentrations of free Ca^{++} in the cytosol, cells use membrane pumps like calcium ATPase found in the membranes of sarcoplasmic reticulum of skeletal muscle. These pumps are needed to provide the steep electrochemical gradient that allows Ca^{++} to rush into the cytosol when a stimulus signal opens the Ca^{++} channels in the membrane. The pumps are also necessary to actively pump the Ca^{++} back out of the cytoplasm and return the cell to its pre-signal state.

https://en.wikipedia.org/wiki/Calcium_pump

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Calpain

A calpain (EC 3.4.22.53) is a protein belonging to the family of calcium-dependent, non-lysosomal cysteine proteases (proteolytic enzymes) expressed ubiquitously in mammals and many other organisms. Although the physiological role of calpains is still poorly understood, they have been shown to be active participants in processes such as cell mobility and cell cycle progression, as well as cell-type specific functions such as long-term potentiation in neurons and cell fusion in myoblasts.

Although the physiological role of calpains is still poorly understood, they have been shown to be active participants in processes such as cell mobility and cell cycle progression, as well as cell-type specific functions such as long-term potentiation in neurons and cell fusion in myoblasts. Under these physiological conditions, a transient and localized influx of calcium into the cell activates a small local population of calpains (for example, those close to Ca^{++} channels), which then advance the signal transduction pathway by catalyzing the controlled proteolysis of its target proteins. Other reported roles of calpains are in cell function, helping to regulate clotting and the diameter of blood vessels, and playing a role in memory. Calpains have been implicated in apoptotic cell death, and appear to be an essential component of necrosis.

Enhanced calpain activity, regulated by CAPNS1, significantly contributes to platelet reactivity and thrombosis under hypoxic conditions. In the brain, while μ-calpain is mainly located in the cell body and dendrites of neurons and to a lesser extent in axons and glial cells, m-calpain is found in glia and a small amount in axons. Calpain is also involved in skeletal muscle protein breakdown due to exercise and altered nutritional states.

https://en.wikipedia.org/wiki/Calpain

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Calvin Cycle

The light-independent reactions of photosynthesis are chemical reactions that convert carbon dioxide and other compounds into glucose. These reactions occur in the stroma, the fluid-filled area of a chloroplast outside of the thylakoid membranes. They take the products (ATP and NADPH) of light-dependent reactions and perform further chemical processes on them.

There are three phases to the light-independent reactions, collectively called the Calvin cycle: carbon fixation, reduction reactions, and ribulose 1,5-bisphosphate (RuBP) regeneration.

Despite its name, this process occurs only when light is available. Plants do not carry out the Calvin cycle during nighttime. They instead release sucrose into the phloem from their starch reserves. This process happens when light is available independent of the kind of photosynthesis (C_3 carbon fixation, C_4 carbon fixation, and Crassulacean acid metabolism). CAM plants store malic acid in their vacuoles every night and release it by day in order to make this process work.

The enzymes in the Calvin cycle are functionally equivalent to most enzymes used in other metabolic pathways such as gluconeogenesis and the pentose phosphate pathway, but they are to be found in the chloroplast stroma instead of the cell cytosol, separating the reactions. They are activated in the light (which is why the name "dark reaction" is misleading), and also by products of the light-dependent reaction. These regulatory functions prevent the Calvin cycle from being respired to carbon dioxide. Energy (in the form of ATP) would be wasted in carrying out these reactions that have no net productivity. The sum of reactions in the Calvin cycle is the following:

$3\ CO_2 + 6\ NADPH + 5\ H_2O + 9\ ATP \rightarrow$ Glyceraldehyde-3-phosphate (Glyal-3P) $+ 2\ H^+ + 6\ NADP^+ + 9\ ADP + 8\ P_i$

Hexose (six-carbon) sugars are not a product of the Calvin cycle. Although many texts list a product of photosynthesis as $C_6H_{12}O_6$, this is mainly a convenience to counter the equation of respiration, where six-carbon sugars are oxidized in mitochondria. The carbohydrate products of the Calvin cycle are three-carbon sugar phosphate molecules, or "triose phosphates," namely, Glyal-3P.

https://en.wikipedia.org/wiki/Light-independent_reactions

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Calvin Cycle Duplicate

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https://en.wikipedia.org/wiki/Light-independent_reactions

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cAMP

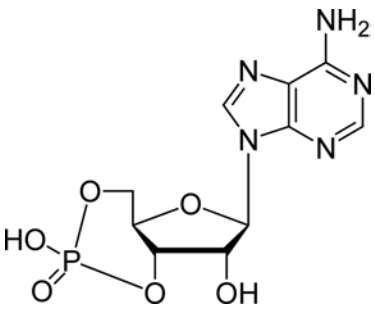
Cyclic adenosine monophosphate (cAMP, cyclic AMP, or 3',5'-cyclic adenosine monophosphate) is a second messenger important in many biological processes. cAMP is a derivative of adenosine triphosphate (ATP) and used for intracellular signal transduction in many different organisms, conveying the cAMP-dependent pathway.

cAMP and its associated kinases function in several biochemical processes, including the regulation of glycogen, sugar, and lipid metabolism. In eukaryotes, cyclic AMP works by activating protein kinase A (PKA, or cAMP-dependent protein kinase). PKA is normally inactive as a tetrameric holoenzyme, consisting of two catalytic and two regulatory units (C_2R_2), with the regulatory units blocking the catalytic centers of the catalytic units.

Cyclic AMP binds to specific locations on the regulatory units of the protein kinase, and causes dissociation between the regulatory and catalytic subunits, thus enabling those catalytic units to phosphorylate substrate proteins.

The active subunits catalyze the transfer of phosphate from ATP to specific serine or threonine residues of protein substrates. The phosphorylated proteins may act directly on the cell's ion channels, or may become activated or inhibited enzymes. Protein kinase A can also phosphorylate specific proteins that bind to promoter regions of DNA, causing increased expression of specific genes. Not all protein kinases respond to cAMP. Several classes of protein kinases, including protein kinase C, are not cAMP-dependent.

Further effects mainly depend on cAMP-dependent protein kinase, which vary based on the type of cell. Still, there are some minor PKA-independent functions of cAMP, e.g., activation of calcium channels, providing a minor pathway by which growth hormone-releasing hormone causes a release of growth hormone.



https://en.wikipedia.org/wiki/Cyclic_adenosine_monophosphate

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cAMP-dependent Protein Kinase

In cell biology, protein kinase A (PKA[N 1]) is a family of enzymes whose act
pendent on cellular levels of cyclic AMP (cAMP). PKA is also known as cAMP
dependent protein kinase (EC 2.7.11.11). Protein kinase A has several functio
cell, including regulation of glycogen, sugar, and lipid metabolism. It should
fused with AMP-activated protein kinase – which, although being of similar
may have opposite effects – nor be confused with cyclin-dependent kinases (
be confused with the acid dissociation constant pK_a.

PKA phosphorylates proteins that have the motif Arginine-Arginine-X-Serin
in turn activating or deactivating the proteins. As protein expression varies f
type to cell type, the proteins that are available for phosphorylation will depe
the cell in which PKA is present. Thus, the effects of PKA activation vary with

https://en.wikipedia.org/wiki/Protein_kinase_A

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Chapter 3 - Membranes: Transport

Cancer

Cancer is a group of diseases involving abnormal cell growth with the poter
vade or spread to other parts of the body. Not all tumors are cancerous. Be
mors do not spread to other parts of the body. Possible signs and symptom
lump, abnormal bleeding, prolonged cough, unexplained weight loss and a
bowel movements. While these symptoms may indicate cancer, they may h
causes. Over 100 cancers affect humans.

https://en.wikipedia.org/wiki/Cancer

Related Glossary Terms

Drag related terms here

Cannabinoid Receptors

Cannabinoid receptors, located throughout the body, are part of the Endocannabinoid system which is involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory.

Cannabinoid receptors are of a class of cell membrane receptors under the G protein-coupled receptor superfamily. As is typical of G protein-coupled receptors, the cannabinoid receptors contain seven transmembrane spanning domains. Cannabinoid receptors are activated by three major groups of ligands: endocannabinoids, produced by the mammillary body; plant cannabinoids (such as cannabidiol, produced by the cannabis plant); and synthetic cannabinoids (such as HU-210). All of the endocannabinoids and plant cannabinoids are lipophilic, such as fat soluble compounds.

There are currently two known subtypes of cannabinoid receptors, termed CB1 and CB2. The CB1 receptor is expressed mainly in the brain (central nervous system or "CNS"), but also in the lungs, liver and kidneys. The CB2 receptor is expressed mainly in the immune system and in hematopoietic cells. Mounting evidence suggests that there are novel cannabinoid receptors that is, non-CB1 and non-CB2, which are expressed in endothelial cells and in the CNS. In 2007, the binding of several cannabinoids to the G protein-coupled receptor GPR55 in the brain was described.

https://en.wikipedia.org/wiki/Cannabinoid_receptor

Related Glossary Terms

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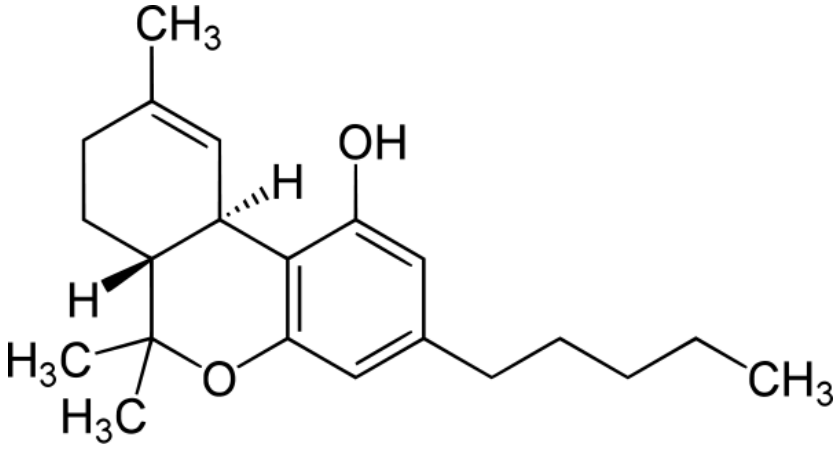
Cannabinoids

Cannabinoids are a class of diverse chemical compounds that act on cannabinoid receptors in cells that repress neurotransmitter release in the brain. Ligands for these receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured artificially).

The most notable cannabinoid is the phytocannabinoid tetrahydrocannabinol (THC - shown below), the primary psychoactive compound in cannabis. Cannabidiol (CBD) is another major constituent of the plant. There are at least 113 different cannabinoids isolated from cannabis, exhibiting varied effects.

Synthetic cannabinoids encompass a variety of distinct chemical classes: the classical cannabinoids structurally related to THC, the nonclassical cannabinoids (cannabimimetics) including the aminoalkylindoles, 1,5-diarylpyrazoles, quinolines, and arylsulfonamides, as well as eicosanoids related to the endocannabinoids.



https://en.wikipedia.org/wiki/Cannabinoid

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CAP

Catabolite Activator Protein (CAP; also known as cAMP receptor protein, CRP) is a transcriptional activator that exists as a homodimer in solution, with each subunit comprising a ligand-binding domain at the N-terminus (CAPN, residues 1-138), which is also responsible for the dimerization of the protein, and a DNA-binding domain at the C-terminus (DBD, residues 139-209). Two cAMP (cyclic AMP) molecules bind dimeric CAP with negative cooperativity and function as allosteric effectors by increasing the protein's affinity for DNA. Cytosolic cAMP levels rise when the amount of glucose transported into the cell is low.

CAP has a characteristic helix-turn-helix structure that allows it to bind to successive major grooves on DNA. The two helices are reinforcing each, causing a 43° turn in the structure, so overall causing a 94° degree turn in the DNA. This opens the DNA molecule up, allowing RNA polymerase to bind and transcribe the genes involved in lactose catabolism. cAMP-CAP is required for transcription of the lac operon.

https://en.wikipedia.org/wiki/Catabolite_activator_protein

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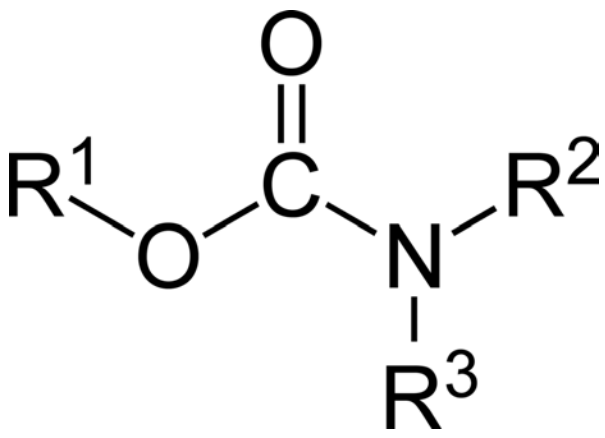
Carbamate

A carbamate is an organic compound derived from carbamic acid (NH_2CO
bamate group, carbamate ester (e.g., ethyl carbamate), and carbamic acids
tional groups that are inter-related structurally and often are interconverte
cally. Carbamate esters are also called urethanes.



https://en.wikipedia.org/wiki/Carbamate

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Chapter 2 - Structure and Function: Proteins

Carbamino

Carbamino refers to a compound created by the addition of carbon dioxide
amino group in an amino acid or a protein, such as hemoglobin forming ca
moglobin.

https://en.wikipedia.org/wiki/Carbamino

Related Glossary Terms

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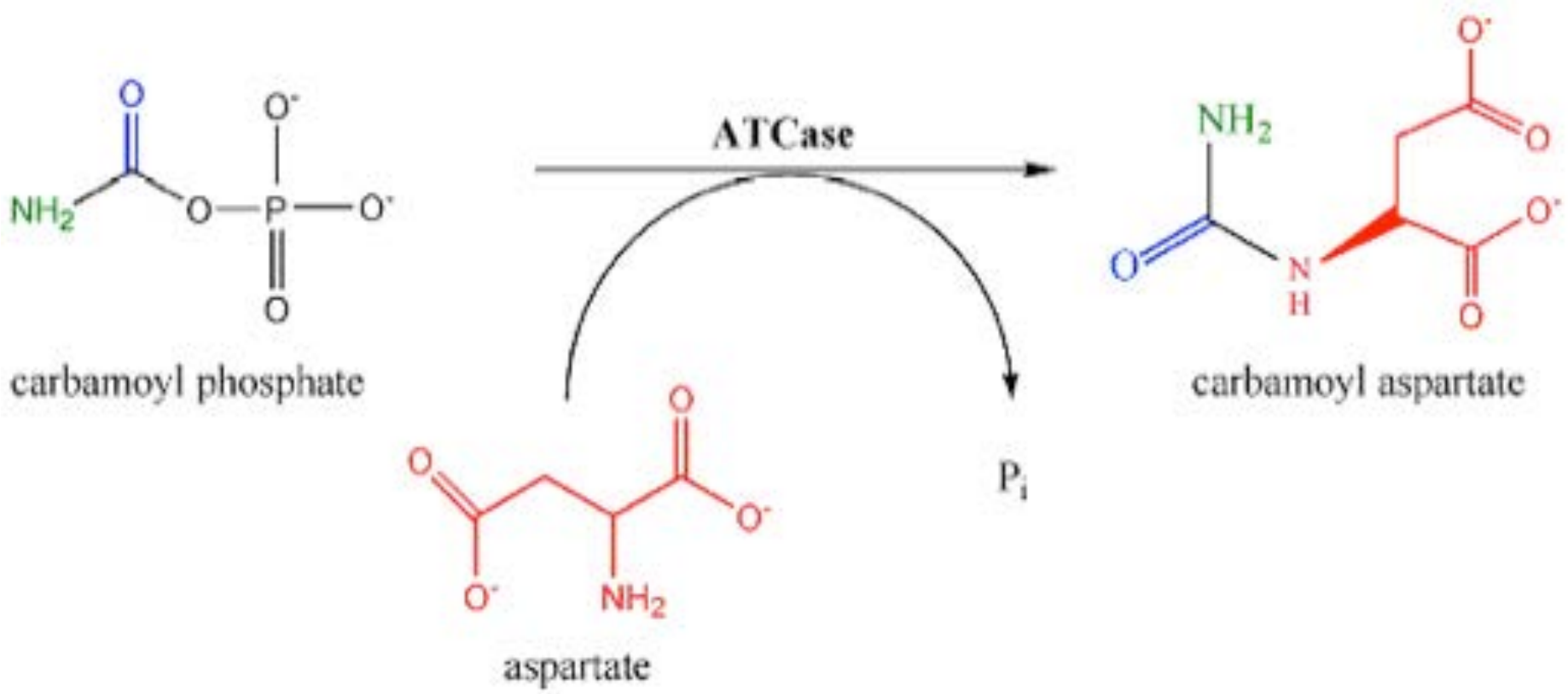
Carbamoyl Aspartate

Carbamoyl aspartate is a product of the second step of the *de novo* synthesi
rimidines, catalyzed by aspartate transcarbamoylase (ATCase).



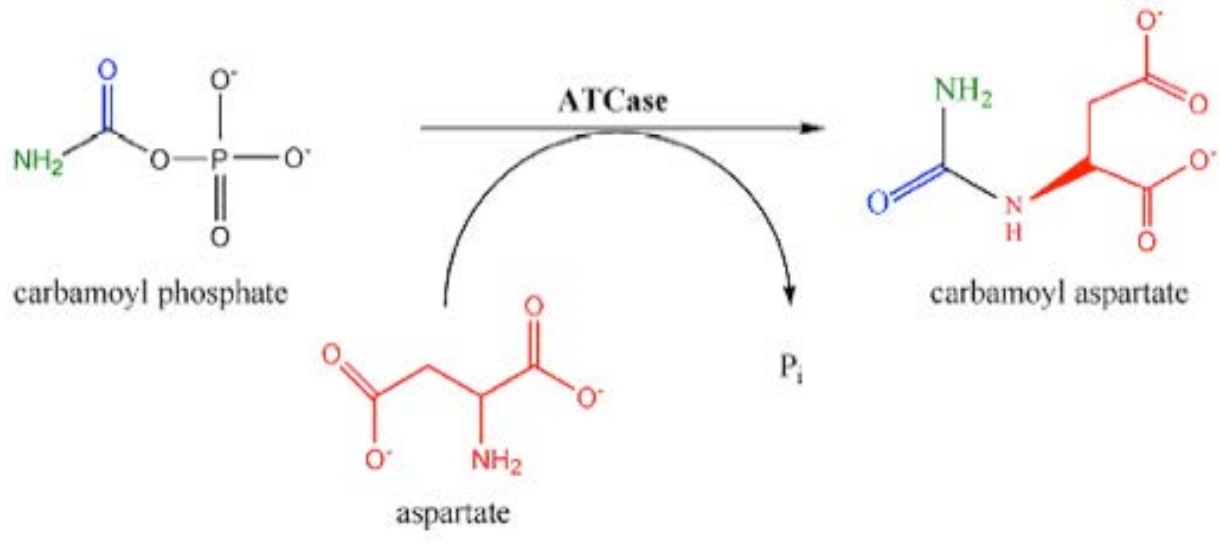
https://en.wikipedia.org/wiki/Aspartate_carbamoyltransferase

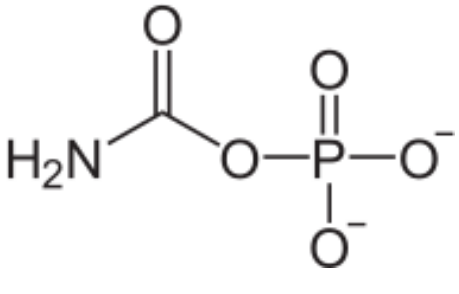
Related Glossary Terms

Drag related terms here

Carbamoyl Phosphate

Carbamoyl phosphate is an anion of biochemical significance. In land-dwelling animals, it is an intermediary metabolite in nitrogen disposal through the urea cycle and in the synthesis of pyrimidines. It is a substrate of the enzyme ATCase, shown below.





https://en.wikipedia.org/wiki/Carbamoyl_phosphate

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Carbamoyl Phosphate Synthetase

Carbamoyl phosphate synthetase catalyzes the ATP-dependent synthesis of carba
phosphate from glutamine (EC 6.3.5.5) or ammonia (EC 6.3.4.16) and bicarbonat
This enzyme catalyzes the reaction of ATP and bicarbonate to produce carboxy ph
phate and ADP. Carboxy phosphate reacts with ammonia to give carbamate. In tu
carbamate reacts with a second ATP to give carbamoyl phosphate plus ADP.

It represents the first committed step in pyrimidine and arginine biosynthesis in p
karyotes and eukaryotes, and in the urea cycle in most terrestrial vertebrates. Mos
karyotes carry one form of CPSase that participates in both arginine and pyrimidi
biosynthesis, however certain bacteria can have separate forms.

https://en.wikipedia.org/wiki/Carbamoyl_phosphate_synthetase

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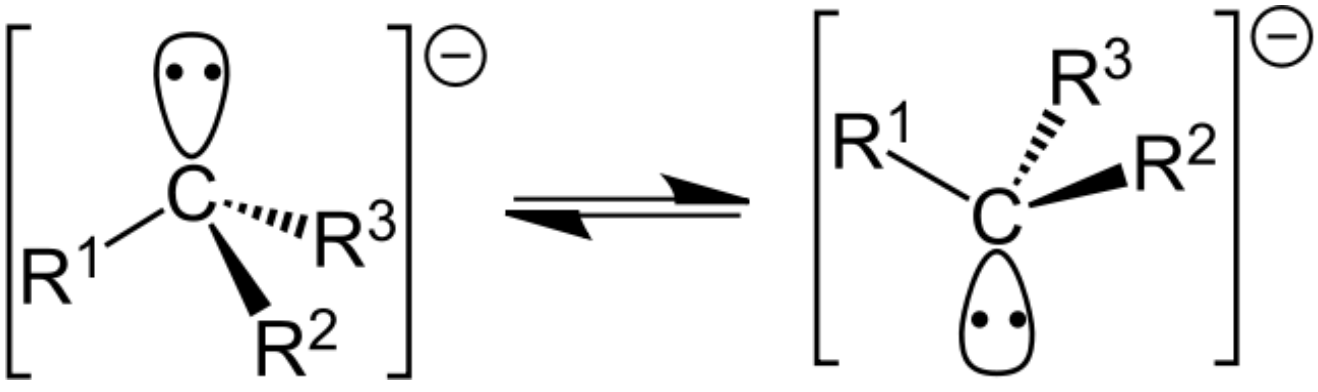
Carbanion

A carbanion is an anion in which carbon has an unshared pair of electrons and
negative charge usually with three substituents for a total of eight valence elect
The carbanion exists in a trigonal pyramidal geometry. Formally, a carbanion is
conjugate base of a carbon acid.



https://en.wikipedia.org/wiki/Carbanion

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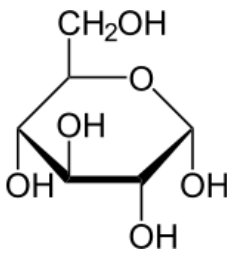
Carbohydrate

A carbohydrate (also called a saccharide) is a biological molecule consisting of carbon (C), hydrogen (H) and oxygen (O) atoms, usually with a hydrogen–oxygen atom ratio of 2:1 (as in water). Some exceptions exist. For example, deoxyribose, a sugar component of DNA, has the empirical formula $C_5H_{10}O_4$. Carbohydrates are technically hydrates of carbon. Structurally it is more accurate to view them as polyhydroxy aldehydes and ketones.

Monosaccharides are the major source of fuel for metabolism, being used both as an energy source (glucose - shown below - being the most important in nature) and in biosynthesis. When monosaccharides are not immediately needed by many cells they are often converted to more space-efficient forms, often polysaccharides. In many animals, including humans, this storage form is glycogen, especially in liver and muscle cells. In plants, starch is used for the same purpose.

The most abundant carbohydrate, cellulose, is a structural component of the cell wall of plants and many forms of algae. Ribose is a component of RNA. Deoxyribose is a component of DNA. Lyxose is a component of lyxoflavin found in the human heart. Ribulose and xylulose occur in the pentose phosphate pathway. Galactose, a component of milk sugar lactose, is found in galactolipids in plant cell membranes and in glycoproteins in many tissues. Mannose occurs in human metabolism, especially in the glycosylation of certain proteins. Fructose, or fruit sugar, is found in many plants and in humans, it is metabolized in the liver, absorbed directly into the intestines during digestion, and found in semen. Trehalose, a major sugar of insects, is rapidly hydrolyzed into two glucose molecules to support continuous flight.



https://en.wikipedia.org/wiki/Carbohydrate

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Carbon

Carbon (from Latin: carbo "coal") is a chemical element with symbol C and
number 6. On the periodic table, it is the first (row 2) of six elements in colu
(group) 14, which have in common the composition of their outer electron s
nonmetallic and tetravalent—making four electrons available to form coval
cal bonds. Three isotopes occur naturally, ^{12}C and ^{13}C being stable while ^{14}C
tive, decaying with a half-life of about 5,730 years.

https://en.wikipedia.org/wiki/Carbon

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Carbon Dioxide

Carbon dioxide (chemical formula CO_2) is a colorless and odorless gas vital to life on Earth. This naturally occurring chemical compound is composed of a carbon atom covalently double-bonded to two oxygen atoms.

Carbon dioxide exists in Earth's atmosphere as a trace gas at a concentration of about 0.04 percent (400 ppm) by volume. Natural sources include volcanoes, hot springs and geysers, and it is freed from carbonate rocks by dissolution in water and acids. Because carbon dioxide is soluble in water, it occurs naturally in groundwater, rivers and lakes, in ice caps and glaciers and also in seawater. It is present in deposits of petroleum and natural gas.

Atmospheric carbon dioxide is the primary source of carbon in life on Earth and its concentration in Earth's pre-industrial atmosphere since late in the Precambrian was regulated by photosynthetic organisms and geological phenomena. As part of the carbon cycle, plants, algae, and cyanobacteria use light energy to photosynthesize carbohydrate from carbon dioxide and water, with oxygen produced as a waste product.

Carbon dioxide (CO_2) is produced by all aerobic organisms when they metabolize carbohydrate and lipids to produce energy by respiration. It is returned to water via the gills of fish and to the air via the lungs of air-breathing land animals, including humans. Carbon dioxide is produced during the processes of decay of organic materials and the fermentation of sugars in bread, beer and winemaking. It is produced by combustion of wood, carbohydrates and fossil fuels such as coal, peat, petroleum and natural gas.

https://en.wikipedia.org/wiki/Carbon_dioxide

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Carbon Monoxide

Carbon monoxide consists of one carbon atom and one oxygen atom, connected by a triple bond that consists of two covalent bonds as well as one dative covalent bond. It is the simplest oxocarbon and is isoelectronic with the cyanide anion, the nitrosonium cation and molecular nitrogen. In coordination complexes the carbon monoxide ligand is called carbonyl.

In biology, carbon monoxide is naturally produced by the action of heme oxygenase 1 and 2 on the heme from hemoglobin breakdown. This process produces a certain amount of carboxyhemoglobin in normal persons, even if they do not breathe any carbon monoxide. Following the first report that carbon monoxide is a normal neurotransmitter in 1993, as well as one of three gases that naturally modulate inflammatory responses in the body (the other two being nitric oxide and hydrogen sulfide), carbon monoxide has received a great deal of clinical attention as a biological regulator. In many tissues, all three gases are known to act as anti-inflammatories, vasodilators, and promoters of neovascular growth. Clinical trials of small amounts of carbon monoxide as a drug are ongoing. Nonetheless, too much carbon monoxide causes carbon monoxide poisoning. Carbon monoxide competes with oxygen for binding on hemoglobin, thus reducing oxygen carrying capacity.

https://en.wikipedia.org/wiki/Carbon_monoxide

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Carbonic Acid

Carbonic acid is a chemical compound with the chemical formula H_2CO_3. It is also a name sometimes given to solutions of carbon dioxide in water (carbonated water), because such solutions contain small amounts of H_2CO_3. In physiology, carbonic acid is described as volatile acid or respiratory acid, because it is the only acid excreted as a gas by the lungs. Carbonic acid, which is a weak acid, forms two kinds of salts, the carbonates and the bicarbonates.

When carbon dioxide dissolves in water it exists in chemical equilibrium producing carbonic acid:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

The hydration equilibrium constant at 25 °C is called K_h, which in the case of carbonic acid is $[H_2CO_3]/[CO_2] \approx 1.7\times10^{-3}$ in pure water and $\approx 1.2\times10^{-3}$ in seawater. Hence, the majority of the carbon dioxide is not converted into carbonic acid, remaining as CO_2 molecules. In the absence of a catalyst, the equilibrium is reached quite slowly.

https://en.wikipedia.org/wiki/Carbonic_acid

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Carbonic Anhydrase

The carbonic anhydrases (or carbonate dehydratases) form a family of enzy
catalyze the rapid interconversion of carbon dioxide and water to bicarbona
tons (or vice versa), shown below, a reversible reaction that occurs relativel
the absence of a catalyst. The active site of most carbonic anhydrases conta
ion. They are therefore classified as metalloenzymes. The primary functio
zyme in animals is to interconvert carbon dioxide and bicarbonate to maint
base balance in blood and other tissues, and to help transport carbon dioxi
sues.

$$CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3$$

https://en.wikipedia.org/wiki/Carbonic_anhydrase

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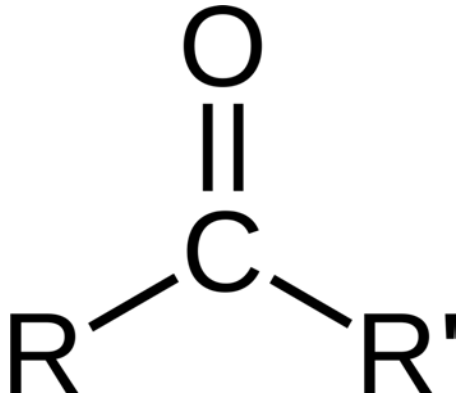
Chapter 4 - Catalysis: Basic Principles

Carbonyl

In organic chemistry, a carbonyl group is a functional group composed of a carbon atom double-bonded to an oxygen atom: C=O. It is common to several classes of organic compounds, as part of many larger functional groups. A compound containing a carbonyl group is often referred to as a carbonyl compound.



https://en.wikipedia.org/wiki/Carbonyl

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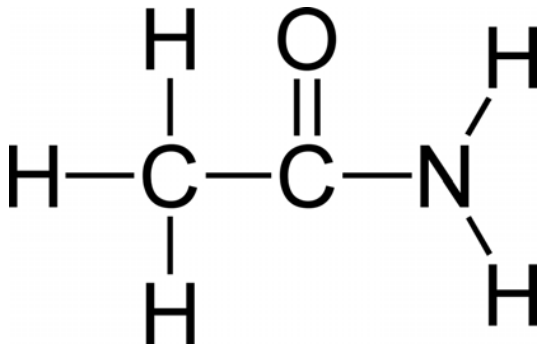
Carboxamide

In organic chemistry carboxamides (or amino carbonyls or carboxyamides)
tional groups with the general R-CO-NR'R'' with R, R', and R'' as organic s
or hydrogen.



https://en.wikipedia.org/wiki/Carboxamide

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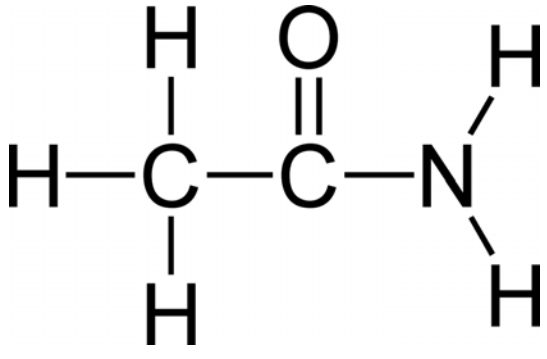
Chapter 2 - Structure & Function: Amino Acids

Carboxyamide

In organic chemistry carboxamides (or amino carbonyls or carboxyamides) tional groups with the general R-CO-NR'R′′ with R, R', and R′′ as organic s or hydrogen.



https://en.wikipedia.org/wiki/Carboxamide

Related Glossary Terms

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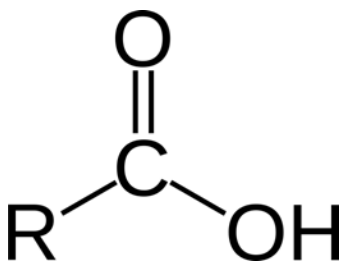
Carboxyl Group

A carboxylic acid is an organic compound that contains a carboxyl group (C(O)OH). The general formula of a carboxylic acid is R–C(O)OH, with R referring to the rest of the (possibly quite large) molecule.



https://en.wikipedia.org/wiki/Carboxylic_acid

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Carboxyl Terminus

The C-terminus (also known as the carboxyl-terminus, carboxy-terminus, C-terminal tail, C-terminal end, or COOH-terminus) is the end of an amino acid chain (protein or polypeptide), terminated by a free carboxyl group (-COOH).

When a protein is translated from messenger RNA, it is created from N-terminus to C-terminus. The convention for writing peptide sequences is to put the C-terminal end on the right and write the sequence from N- to C-terminus.

https://en.wikipedia.org/wiki/C-terminus

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Carboxylated

Carboxylation in chemistry is a chemical reaction in which a carboxylic acid group is introduced in a substrate. The opposite reaction is decarboxylation.

One example of carboxylation in biochemistry is a posttranslational modification of glutamate residues, to γ-carboxyglutamate, in proteins. It occurs primarily in proteins involved in the blood clotting cascade, specifically factors II, VII, IX, and X, protein C, and protein S, and also in some bone proteins. This modification is required for these proteins to function. Carboxylation occurs in the liver and is performed by γ-glutamyl carboxylase.

The carboxylase requires vitamin K as a cofactor and performs the reaction in a processive manner. γ-carboxyglutamate binds calcium, which is essential for its activity. For example, in prothrombin, calcium binding allows the protein to associate with the plasma membrane in platelets, bringing it into close proximity with the proteins that cleave prothrombin to active thrombin after injury.

https://en.wikipedia.org/wiki/Carboxylation

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Carboxypeptidases

A carboxypeptidase (EC number 3.4.16 - 3.4.18) is a protease enzyme that hyd
(cleaves) a peptide bond at the carboxy-terminal (C-terminal) end of a protein
tide. (Contrast with an aminopeptidase, which cleaves peptide bonds at the ot
of the protein.)

The first carboxypeptidases studied were those involved in the digestion of foo
creatic carboxypeptidases A_1, A_2, and B). However, most of the known carboxy
dases are not involved in catabolism. They help to mature proteins (e.g., Post
translational modification) or regulate biological processes. For example, the
thesis of neuroendocrine peptides such as insulin requires a carboxypeptidase
boxypeptidases also function in blood clotting, growth factor production, wou
ing, reproduction, and many other processes.

https://en.wikipedia.org/wiki/Carboxypeptidase

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Carcinogen

A carcinogen is any substance, radionuclide, or radiation that is an agent directly involved in causing cancer. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes. Several radioactive substances are considered carcinogens, but their carcinogenic activity is attributed to the radiation, for example γ rays and α particles, which they emit. Common examples of non-radioactive carcinogens are inhaled asbestos, certain dioxins, and tobacco smoke. Although the public generally associates carcinogenicity with synthetic chemicals, it is equally likely to arise in both natural and synthetic substances. Carcinogens are not necessarily immediately toxic, thus their effect can be insidious.

Cancer is any disease in which normal cells are damaged and do not undergo programmed cell death as fast as they divide via mitosis. Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes, and induces the uncontrolled, malignant division, ultimately leading to the formation of tumors. Usually, severe DNA damage leads to apoptosis, but if the programmed cell death pathway is damaged, then the cell cannot prevent itself from becoming a cancer cell.

There are many natural carcinogens. Aflatoxin B_1, which is produced by the fungus *Aspergillus flavus* growing on stored grains, nuts and peanut butter, is an example of a potent, naturally occurring microbial carcinogen. Certain viruses such as hepatitis B and human papilloma virus have been found to cause cancer in humans. The first one shown to cause cancer in animals is Rous sarcoma virus, discovered in 1910 by Peyton Rous. Other infectious organisms which cause cancer in humans include some bacteria (e.g. *Helicobacter pylori*) and helminths (e.g. *Opisthorchis viverrini* and *Clonorchis sinensis*).

Dioxins and dioxin-like compounds, benzene, kepone, EDB, and asbestos have all been classified as carcinogenic. As far back as the 1930s, industrial smoke and tobacco smoke were identified as sources of dozens of carcinogens, including benzo[a]pyrene, tobacco-specific nitrosamines such as nitrosonornicotine, and reactive aldehydes such as formaldehyde—which is also a hazard in embalming and making plastics. Vinyl chloride, from which PVC is manufactured, is a carcinogen and thus a hazard in PVC production.

https://en.wikipedia.org/wiki/Carcinogen

Cardiac Muscle

Cardiac muscle (heart muscle) is involuntary, striated muscle that is found
and histological foundation of the heart, specifically the myocardium. Card
is one of three major types of muscle, the others being skeletal and smooth
These three types of muscle all form in the process of myogenesis. The cells
tute cardiac muscle, called cardiomyocytes or myocardiocytes, predominan
only one nucleus, although populations with two to four nuclei do exist. Th
dium is the muscle tissue of the heart, and forms a thick middle layer betwe
outer epicardium layer and the inner endocardium layer.

https://en.wikipedia.org/wiki/Cardiac_muscle

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Chapter 1 - Chemistry, Buffers, and Energy

Cardiolipin

Cardiolipin (IUPAC name "1,3-bis(sn-3'-phosphatidyl)-sn-glycerol") is an important component of the inner mitochondrial membrane, where it constitutes about 20% of the total lipid composition. It can also be found in the membranes of most bacteria. The name 'cardiolipin' is derived from the fact that it was first found in animal hearts.

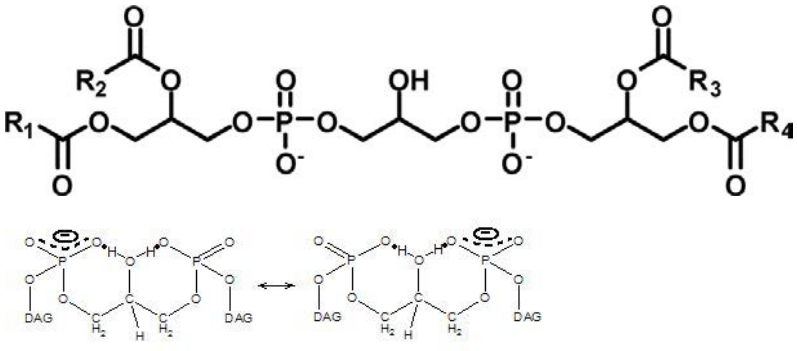
In mammalian cells, but also in plant cells, cardiolipin (CL) is found almost exclusively in the inner mitochondrial membrane where it is essential for the optimal function of numerous enzymes that are involved in mitochondrial energy metabolism.

Because of cardiolipin's unique bicyclic structure, a change in pH and the presence of divalent cations can induce a structural change. CL shows a great variety of forms of aggregates. It is found that in the presence of Ca^{++} or other divalent cations, CL can be induced to have a lamellar-to-hexagonal (La-HII) phase transition. And it is believed to have a close connection with membrane fusion.

The enzyme cytochrome c oxidase or Complex IV is a large transmembrane protein complex found in bacteria and the mitochondrion. It is the last enzyme in the respiratory electron transport chain of mitochondria (or bacteria) located in the mitochondrial (or bacterial) membrane. It receives an electron from each of four cytochrome c molecules, and transfers them to one oxygen molecule, converting molecular oxygen to two molecules of water. Complex IV has been shown to require two associated CL molecules in order to maintain its full enzymatic function. Cytochrome bc_1(Complex III) also needs cardiolipin to maintain its quaternary structure and to maintains its functional role. Complex V of the oxidative phosphorylation machinery also displays high binding affinity for CL, binding four molecules of CL per molecule of complex V.

Cardiolipin distribution to the outer mitochondrial membrane would lead to apoptosis of the cells, as evidenced by cytochrome c (cyt c) release, Caspase-8 activation, MOMP induction and NLRP3 inflammasome activation. During apoptosis, cyt c is released from the intermembrane spaces of mitochondria into the cytosol. Cyt c can then bind to the IP_3 receptor on ER, stimulating calcium release, which then reacts back to cause the release of cyt c. When the calcium concentration reaches a toxic level, this causes cell death. Cytochrome c is thought to play a role in apoptosis via the release of apoptotic factors from the mitochondria. A cardiolipin-specific oxygenase produces CL hydroperoxides which can result in the conformation change of the lipid. The oxidized CL transfers from the inner membrane to the outer membrane, and then helps to form a permeable pore which releases cyt c.

During the oxidative phosphorylation process catalyzed by Complex IV, large quantities of protons are transferred from one side of the membrane to another side causing a large pH change. CL is suggested to function as a proton trap within the mitochondrial membranes, thereby strictly localizing the proton pool and minimizing the changes in pH in the mitochondrial intermembrane space. This function is due to CL's unique structure. As stated above, CL can trap a proton within the bicyclic structure while carrying a negative charge. Thus, this bicyclic structure can serve as an electron buffer pool to release or absorb protons to maintain the pH near the membranes.

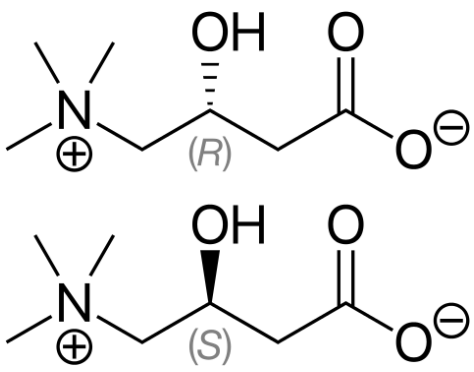


Bicyclic structure of Cardiolipin

https://en.wikipedia.org/wiki/Cardiolipin

Carnitine

Carnitine is an amino acid derivative and nutrient involved in lipid (fat) metabolism in mammals and other eukaryotes. It is in the chemical compound classes of β-hydroxyacids and quaternary ammonium compounds, and because of the hydroxyl-substituent, it exists in two stereoisomers, the biologically active enantiomer L-carnitine, and the essentially biologically inactive D-carnitine. In such eukaryotic cells, it is specifically required for the transport of fatty acids from the intermembraneous space in the mitochondria into the mitochondrial matrix during the catabolism of lipids, in the generation of metabolic energy.



https://en.wikipedia.org/wiki/Carnitine

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Carnitine Acyl Transferase

Carnitine palmitoyltransferase I (CPT1) also known as carnitine acyltransferase I, CPTI, CAT1, CoA:carnitine acyl transferase (CCAT), or palmitoylCoA transferase I, is a mitochondrial enzyme responsible for the formation of acyl carnitines by catalyzing the transfer of the acyl group of a long-chain fatty acyl-CoA from coenzyme A to l-carnitine. The product is often Palmitoylcarnitine (thus the name), but other fatty acids may also be substrates. It is part of a family of enzymes called carnitine acyltransferases. This "preparation" allows for subsequent movement of the acyl carnitine from the cytosol into the intermembrane space of mitochondria.

Three isoforms of CPT1 are currently known: CPT1A, CPT1B, and CPT1C. CPT1 is associated with the outer mitochondrial membrane. This enzyme can be inhibited by malonyl CoA, the first committed intermediate produced during fatty acid synthesis. Its role in fatty acid metabolism makes CPT1 important in many metabolic disorders such as diabetes.

The carnitine palmitoyltransferase system is an essential step in the β-oxidation of long chain fatty acids. This transfer system is necessary because, while fatty acids are activated (in the form of a thioester linkage to coenzyme A) on the outer mitochondrial membrane, the activated fatty acids must be oxidized within the mitochondrial matrix. Long chain fatty acids such as palmitoyl-CoA, cannot freely diffuse through the mitochondrial inner membrane, and require a shuttle system to be transported to the mitochondrial matrix.

Carnitine palmitoyltransferase I is the first component and rate-limiting step of the carnitine palmitoyltransferase system, catalyzing the transfer of the acyl group from coenzyme A to carnitine to form palmitoylcarnitine. A translocase then shuttles the acyl carnitine across the inner mitochondrial membrane where it is converted back into palmitoyl-CoA. By acting as an acyl group acceptor, carnitine may also play the role of regulating the intracellular CoA:acyl-CoA ratio.

CPT1 is inhibited by malonyl-CoA, although the exact mechanism of inhibition remains unknown. The CPT1 skeletal muscle and heart isoform, CPT1B, has been shown to be 30-100-fold more sensitive to malonyl-CoA inhibition than CPT1A. This inhibition is a good target for future attempts to regulate CPT1 for the treatment of metabolic disorders.

Acetyl-CoA carboxylase (ACC), the enzyme that catalyzes the formation of malonyl-CoA from acetyl-CoA, is important in the regulation of fatty acid metabolism. Scientists have demonstrated that ACC2 knockout mice have reduced body fat and weight when compared to wild type mice. This is a result of decreased activity of ACC which causes a subsequent decrease in malonyl-CoA concentrations. These decreased malonyl-CoA levels in turn prevent inhibition of CPT1, causing an ultimate increase in fatty acid oxidation. Since heart and skeletal muscle cells have a low capacity for fatty acid synthesis, ACC may act purely as a regulatory enzyme in these cells.

https://en.wikipedia.org/wiki/Carnitine_palmitoyltransferase_I

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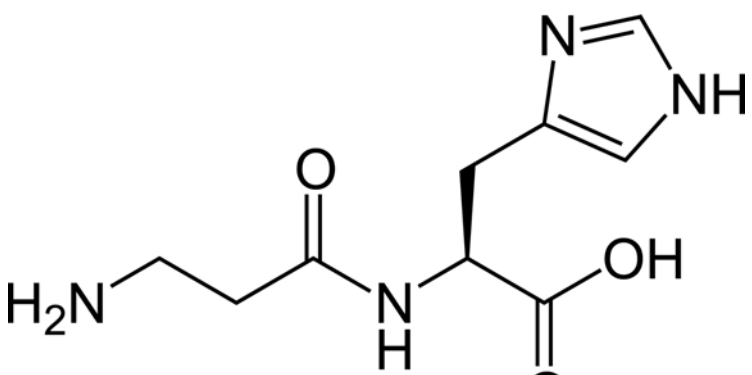
Carnosine

Carnosine (β-alanyl-L-histidine) is a dipeptide of the amino acids β-alanine and histidine. It is highly concentrated in muscle and brain tissues.

Carnosine acts as an antiglycating agent, reducing the rate of formation of advanced glycation end-products (AGEs) (substances that can be a factor in the development or worsening of many degenerative diseases, such as diabetes, atherosclerosis, chronic renal failure, and Alzheimer's disease.), and ultimately reducing development of atherosclerotic plaque build-up. Chronic glycolysis is speculated to accelerate aging.



https://en.wikipedia.org/wiki/Carnosine

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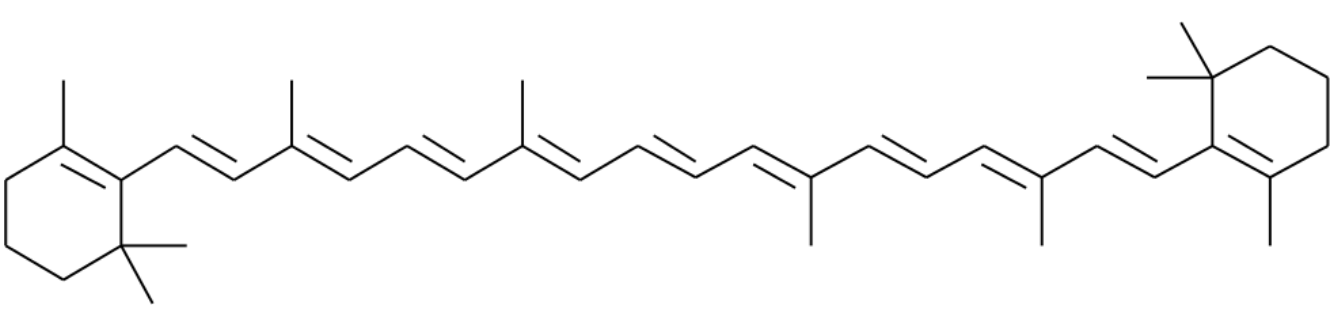
Chapter 6 - Metabolism: Nucleotides

Chapter 9 - Point by Point: Metabolism

Carotenes

The term carotene (also carotin, from the Latin carota, "carrot") is used for many r
lated unsaturated hydrocarbon substances having the formula $C_{40}H_x$, which are sy
sized by plants but in general cannot be made by animals (with the sole known exc
tion of some aphids and spider mites which acquired the synthetic genes from fung
Carotenes are photosynthetic pigments important for photosynthesis. Carotenes co
tain no oxygen atoms. They absorb ultraviolet, violet, and blue light and scatter ora
or red light, and (in low concentrations) yellow light.



https://en.wikipedia.org/wiki/Carotene

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Cartilage

Cartilage is a flexible connective tissues, including the joints between bones cage, the ear, the nose, the bronchial tubes and the intervertebral discs. It is hard and rigid as bone, but it is stiffer and less flexible than muscle. Becaus ity, cartilage often serves the purpose of holding tubes open in the body. Ex clude the rings of the trachea, such as the cricoid cartilage and carina, the t ius at the opening of the pharyngotympanic/auditory tube, the ala of the no the auricle/pinna of the ear.

https://en.wikipedia.org/wiki/Cartilage

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Cas (9)

Cas9 (CRISPR associated protein 9) is an RNA-guided DNA endonuclease enzyme associated with the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) adaptive immunity system in Streptococcus pyogenes, among other bacteria. S. pyogenes utilizes Cas9 to memorize and later interrogate and cleave foreign DNA, such as invading bacteriophage DNA or plasmid DNA. Cas9 performs this interrogation by unwinding foreign DNA and checking whether it is complementary to the 20 basepair spacer region of the guide RNA. If the DNA substrate is complementary to the guide RNA, Cas9 cleaves the invading DNA. In this sense, the CRISPR-Cas9 mechanism has a number of parallels with the RNA interference (RNAi) mechanism in eukaryotes.

Apart from its original function in bacterial immunity, the Cas9 protein has been heavily utilized as a genome engineering tool to induce site-directed double strand breaks in DNA. These breaks can lead to gene inactivation or the introduction of heterologous genes through non-homologous end joining and homologous recombination respectively in many laboratory model organisms. Alongside zinc finger nucleases and TALEN proteins, Cas9 is becoming a prominent tool in the field of genome editing.

Cas9 has gained traction in recent years because it can cleave nearly any sequence complementary to the guide RNA. Because the target specificity of Cas9 stems from the guide RNA:DNA complementarity and not modifications to the protein itself (like TALENs and Zinc-fingers), engineering Cas9 to target new DNA is straightforward. Versions of Cas9 that bind but do not cleave cognate DNA can be used to localize transcriptional activator or repressors to specific DNA sequences in order to control transcriptional activation and repression. While native Cas9 requires a guide RNA composed of two disparate RNAs that associate to make the guide - the CRISPR RNA (crRNA), and the trans-activating RNA (tracrRNA). Cas9 targeting has been simplified through the engineering of a chimeric single guide RNA. Scientists have suggested that Cas9-based gene drives may be capable of editing the genomes of entire populations of organisms. In 2015, scientists used Cas9 to modify the genome of human embryos for the first time. The Heroes of CRISPR are the individuals who have, since its initial discovery in the Mediterranean port of Santa Pola on Spain’s Costa Blanca in 1989, made significant contributions in the elucidation of the Class 2, Type II CRISPR/Cas9 system.

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Cascade

A cascade is a term used to describe a series of enzymatic reactions in whic
enzymes catalyzes a reaction on another set of enzymes to activate them an
vated enzymes catalyze similar activating reactions on other sets of enzyme
fects of cascades is to amplify activation processes quickly and broadly. Sys
cascading effects include blood clotting and glycogen metabolism enzymes.

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Caspases

Caspases (cysteine-aspartic proteases, cysteine aspartases or cysteine-dependent aspartate-directed proteases) are a family of protease enzymes playing essential roles in programmed cell death (including apoptosis, pyroptosis and necroptosis) and inflammation. They are named caspases due to their specific cysteine protease activity - a cysteine in its active site nucleophilically attacks and cleaves a target protein only at the C-terminal of an aspartic acid amino acid.

The role of these enzymes in programmed cell death was first identified in 1993, with their functions in apoptosis well characterized. This is a form of programmed cell death, occurring widely during development, and throughout life to maintain cell homeostasis. Activation of caspases ensure that the cellular components are degraded in a controlled manner, carrying out cell death with minimal effect to surrounding tissues.

Caspases have other identified roles in programmed cell death such as Pyroptosis and Necroptosis. These forms of cell death are important for protecting an organism from stress signals and pathogenic attack. Caspases also have a role in inflammation, whereby it directly processes pro-inflammatory cytokines such as pro-IL1β. These are signaling molecules that allow recruitment of immune cells to an infected cell or tissue. There are other identified roles of caspases such as cell proliferation, tumor suppression, cell differentiation, neural development and axon guidance and aging.

Caspase deficiency has been identified as a cause of tumor development. Tumor growth can occur by a combination of factors, including a mutation in a cell cycle gene which removes the restrains of cell growth, combined with mutations in apoptopic proteins such as caspases that would respond by inducing cell death in abnormal growing cells. On the contrary, over activation of some caspases such as caspase-3 can lead to excessive programmed cell death. This is seen in several neurodegenerative diseases where neural cells are lost, such as Alzheimers disease. Caspases involved with processing inflammatory signals are also implicated in disease. Insufficient activation of these caspases can increase the organisms susceptibility to infection as an appropriate immune response may not be activated. The integral role caspases play in cell death and disease has led to research for using caspases as a drug target. For example, inflammatory caspase-1 has been implicated in causing autoimmune diseases. Drugs blocking the activation of caspase-1 have been used to improve the health of patients. Additionally, scientists have used caspases as cancer therapy to kill unwanted cells in tumors.

https://en.wikipedia.org/wiki/Caspase

Catabolic

Catabolism (from Greek κάτω kato, "downward" and βάλλειν ballein, "to throw") is the set of metabolic pathways that breaks down molecules into smaller units that are either oxidized to release energy, or used in other anabolic reactions. Catabolism breaks down large molecules (such as polysaccharides, lipids, nucleic acids and proteins) into smaller units (such as monosaccharides, fatty acids, nucleotides, and amino acids, respectively).

Cells use the monomers released from breaking down polymers to either construct new polymer molecules, or degrade the monomers further to simple waste products, releasing energy. Cellular wastes include lactic acid, acetic acid, carbon dioxide, ammonia, and urea. The creation of these wastes is usually an oxidation process involving a release of chemical free energy, some of which is lost as heat, but the rest of which is used to drive the synthesis of adenosine triphosphate (ATP). This molecule acts as a way for the cell to transfer the energy released by catabolism to the energy-requiring reactions that make up anabolism. (Catabolism is seen as destructive metabolism and anabolism as constructive metabolism). Catabolism therefore provides the chemical energy necessary for the maintenance and growth of cells. Examples of catabolic processes include glycolysis, the citric acid cycle, the breakdown of muscle protein in order to use amino acids as substrates for gluconeogenesis, the breakdown of fat in adipose tissue to fatty acids, and oxidative deamination of neurotransmitters by monoamine oxidase.

There are many signals that control catabolism. Most of the known signals are hormones and the molecules involved in metabolism itself. Endocrinologists have traditionally classified many of the hormones as anabolic or catabolic, depending on which part of metabolism they stimulate. The so-called classic catabolic hormones known since the early 20th century are cortisol, glucagon, and adrenaline (and other catecholamines). In recent decades, many more hormones with at least some catabolic effects have been discovered, including cytokines, orexin (also known as hypocretin), and melatonin.

https://en.wikipedia.org/wiki/Catabolism

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Catalase

Catalase is a common enzyme found in nearly all living organisms exposed to oxygen (such as bacteria, plants, and animals). It catalyzes the decomposition of hydrogen peroxide to water and oxygen. It is a very important enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS). Likewise, catalase has one of the highest turnover numbers of all enzymes. One catalase molecule can convert approximately 5 million molecules of hydrogen peroxide to water and oxygen each minute.

The reaction of catalase in the decomposition of hydrogen peroxide in living tissue:

$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$

The presence of catalase in a microbial or tissue sample can be tested by adding a volume of hydrogen peroxide and observing the reaction. The formation of bubbles, oxygen, indicates a positive result. This easy assay, which can be seen with the naked eye, without the aid of instruments, is possible because catalase has a very high specific activity, which produces a detectable response. Alternative splicing may result in different protein variants.

Hydrogen peroxide is a harmful byproduct of many normal metabolic processes. To prevent damage to cells and tissues, it must be quickly converted into other, less dangerous substances. To this end, catalase is frequently used by cells to rapidly catalyze the decomposition of hydrogen peroxide into less-reactive gaseous oxygen and water molecules.

The true biological significance of catalase is not always straightforward to assess: Mice genetically engineered to lack catalase are phenotypically normal, indicating this enzyme is dispensable in animals under some conditions. A catalase deficiency may increase the likelihood of developing type 2 diabetes. Some humans have very low levels of catalase (acatalasia), yet show few ill effects. The predominant scavengers of H_2O_2 in normal mammalian cells are likely peroxiredoxins rather than catalase.

https://en.wikipedia.org/wiki/Catalase

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Catalysis

Catalysis is the increase in the rate of a chemical reaction due to the participation of an additional substance called a catalyst. With a catalyst, reactions occur faster and require less activation energy. Because catalysts are not consumed in the catalyzed reaction, they can continue to catalyze the reaction of further quantities of reactant. Often only tiny amounts are required.

In the presence of a catalyst, less free energy is required to reach the transition state, but the total free energy from reactants to products does not change. A catalyst may participate in multiple chemical transformations. The effect of a catalyst may vary due to the presence of other substances known as inhibitors or poisons (which reduce the catalytic activity) or promoters (which increase the activity). The opposite of a catalyst, a substance that reduces the rate of a reaction, is an inhibitor.

Catalyzed reactions have a lower activation energy (rate-limiting free energy of activation) than the corresponding uncatalyzed reaction, resulting in a higher reaction rate at the same temperature and for the same reactant concentrations. However, the detailed mechanics of catalysis is complex. Catalysts may affect the reaction environment favorably, or bind to the reagents to polarize bonds, e.g. acid catalysts for reactions of carbonyl compounds, or form specific intermediates that are not produced naturally, such as osmate esters in osmium tetroxide-catalyzed dihydroxylation of alkenes, or cause dissociation of reagents to reactive forms, such as chemisorbed hydrogen in catalytic hydrogenation.

Kinetically, catalytic reactions are typical chemical reactions; i.e. the reaction rate depends on the frequency of contact of the reactants in the rate-determining step. Usually, the catalyst participates in this slowest step, and rates are limited by amount of catalyst and its "activity". In heterogeneous catalysis, the diffusion of reagents to the surface and diffusion of products from the surface can be rate determining. A nanomaterial-based catalyst is an example of a heterogeneous catalyst. Analogous events associated with substrate binding and product dissociation apply to homogeneous catalysts.

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Catalyst

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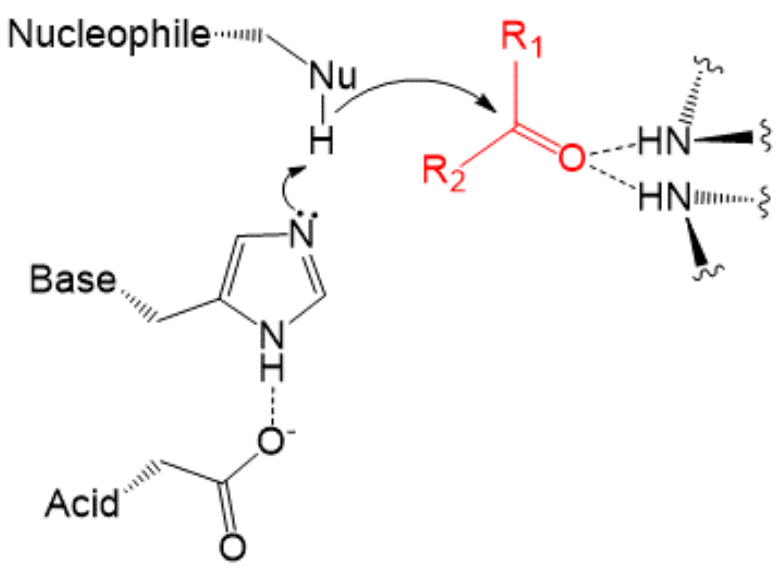
Catalytic Triad

A catalytic triad refers to the three amino acid residues that function together at the center of the active site of some hydrolase and transferase enzymes (e.g. proteases, amidases, esterases, acylases, lipases and β-lactamases). An Acid-Base-Nucleophile triad is a common motif for generating a nucleophilic residue for covalent catalysis. The residues form a charge-relay network to polarise and activate the nucleophile, which attacks the substrate, forming a covalent intermediate which is then hydrolyzed to regenerate free enzyme. The nucleophile is most commonly a serine or cysteine amino acid, but occasionally threonine. Because enzymes fold into complex three-dimensional structures, the residues of a catalytic triad can be far from each other along the amino-acid sequence (primary structure), however, they are brought close together in the final fold.

In serine proteases, the triad consists of the amino acids serine, histidine, and aspartic acid.



https://en.wikipedia.org/wiki/Catalytic_triad

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Cataplerotic

Anaplerotic reactions are chemical reactions that form intermediates of a m
pathway. Examples of such are found in the citric acid cycle (TCA cycle). In
function of this cycle for respiration, concentrations of TCA intermediates r
stant. However, many biosynthetic reactions also use these molecules as a
Removal of pathway intermediates for biosynthesis of other cellular compo
ferred to as a set of cataplerotic reactions.

The TCA cycle is a hub of metabolism, with central importance in both ener
tion and biosynthesis. Therefore, it is crucial for the cell to regulate concent
TCA cycle metabolites in the mitochondria. Anaplerotic flux must balance c
flux in order to retain homeostasis of cellular metabolism.

https://en.wikipedia.org/wiki/Anaplerotic_reactions

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Catecholamines

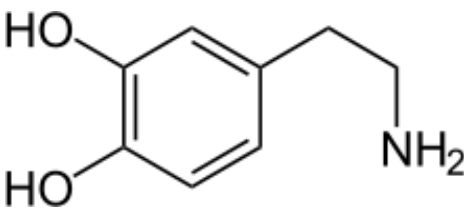
A catecholamine (CA) is a monoamine, an organic compound that has a catechol (benzene with two hydroxyl side groups) and a side-chain amine.

Catecholamines are derived from the amino acid tyrosine. Catecholamines are water-soluble and are 50%-bound to plasma proteins in circulation.

Included among catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine (pictured below), all of which are produced from phenylalanine and tyrosine. Release of the hormones epinephrine and norepinephrine from the adrenal medulla of the adrenal glands is part of the fight-or-flight response.

Tyrosine is created from phenylalanine by hydroxylation by the enzyme phenylalanine hydroxylase. Tyrosine is also ingested directly from dietary protein. Catecholamine-secreting cells use several reactions to convert tyrosine serially to L-DOPA and then to dopamine. Depending on the cell type, dopamine may be further converted to norepinephrine or even further converted to epinephrine.

Various stimulant drugs are catecholamine analogues.



https://en.wikipedia.org/wiki/Catecholamine

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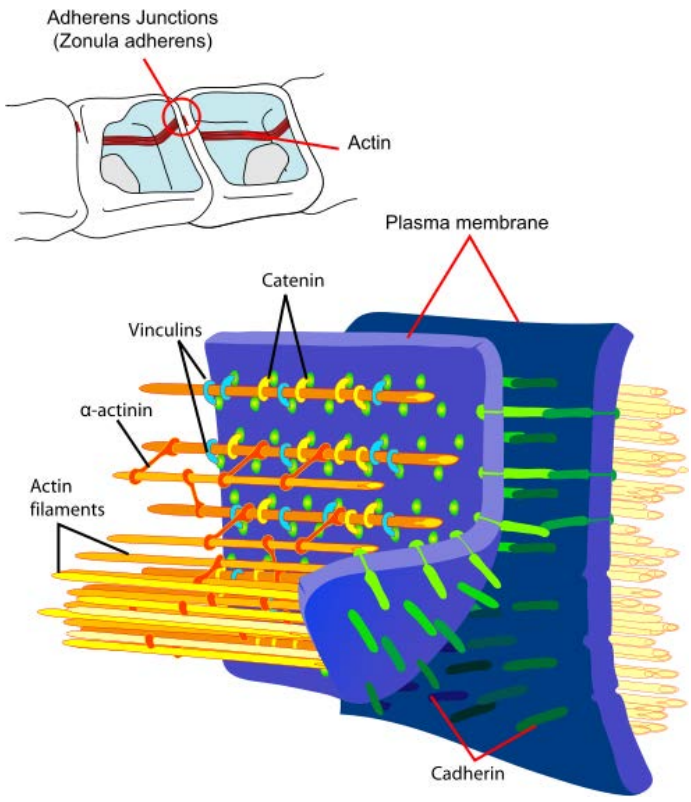
Catenins

Catenins are a family of proteins found in complexes with cadherin cell adhesion molecules of animal cells. The first two catenins that were identified became known as α-catenin and β-catenin. A-catenin can bind to β-catenin and can also bind actin. B-catenin binds the cytoplasmic domain of some cadherins. Additional catenins such as γ-catenin and δ-catenin have been identified. The name "catenin" was originally selected ('catena' means 'chain' in Latin) because it was suspected that catenins might link cadherins to the cytoskeleton.

Cell-cell adhesion complexes are required for simple epithelia in higher organisms to maintain structure, function and polarity. These complexes, which help regulate cell growth in addition to creating and maintaining epithelial layers, are known as adherens junctions and they typically include at least cadherin, β-catenin, and α-catenin. Catenins play roles in cellular organization and polarity long before the development and incorporation of Wnt signaling pathways and cadherins.

The primary mechanical role of catenins is connecting cadherins to actin filaments, specifically in these adhesion junctions of epithelial cells. Most studies investigating catenin actions focus on α-catenin and β-catenin. β-catenin is particularly interesting as it plays a dual role in the cell. First of all, by binding to cadherin receptor intracellular cytoplasmic tail domains, it can act as an integral component of a protein complex in adherens junctions that helps cells maintain epithelial layers. β-catenin acts by anchoring the actin cytoskeleton to the junctions, and may possibly aid in contact inhibition signaling within the cell.



https://en.wikipedia.org/wiki/Catenin

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Cathepsin K

The protein encoded by this gene is a lysosomal cysteine protease involved
modeling and resorption. This protein, which is a member of the peptidase
family, is expressed predominantly in osteoclasts. Cathepsin K is a protease
defined by its high specificity for kinins, that is involved in bone resorption
zyme's ability to catabolize elastin, collagen, and gelatin allow it to break do
and cartilage. This catabolic activity is also partially responsible for the loss
ticity and recoil in emphysema.

Cathepsin K inhibitors, such as odanacatib, show great potential in the trea
teoporosis. Cathepsin K is degraded by Cathepsin S, called Controlled Cath
balism. Cathepsin K expression is stimulated by inflammatory cytokines th
leased after tissue injury.

https://en.wikipedia.org/wiki/Cathepsin_K

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Cation Exchange Chromatography

Ion-exchange chromatography (or ion chromatography) is a chromatograp
that separates ions and polar molecules based on their affinity to the ion ex
works on almost any kind of charged molecule—including large proteins, sr
tides, and amino acids. It is often used in protein purification, water analys
ity control. Cation exchange chromatography is used when the desired mol
separate are cations, and an anion exchange chromatography is to separate
meaning that the beads in the column contain positively charged functiona
attract the anions.

https://en.wikipedia.org/wiki/Ion_chromatography#Weak_and_strong_i
gers

Related Glossary Terms

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Cationic

A cation is an ion with fewer electrons than protons, giving it a positive cha
thing that is cationic is said to me more like a cationic, that is, more positiv

https://en.wikipedia.org/wiki/Ion#Anions_and_cations

Related Glossary Terms

Drag related terms here

Cations

A cation is an ion with fewer electrons than protons, giving it a positive cha
There are additional names used for ions with multiple charges. For examp
with a −2 charge is known as a dianion and an ion with a +2 charge is know
tion. A zwitterion is a neutral molecule with positive and negative charges a
locations within that molecule.

https://en.wikipedia.org/wiki/Ion#Anions_and_cations

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Caveolae-based Endocytosis

In biology, caveolae (Latin for "little caves" - singular, caveola), which are a special type of lipid raft, are small (50–100 nanometer) invaginations of the plasma membrane in many vertebrate cell types, especially in endothelial cells and adipocytes. These flask-shaped structures are rich in proteins as well as lipids such as cholesterol and sphingolipids and have several functions in signal transduction.

Caveolae are one source of clathrin-independent raft-dependent endocytosis. The ability of caveolins to oligomerize due to their oligomerization domains is necessary for formation of caveolar endocytic vesicles. The oligomerization leads to formation of caveolin-rich microdomains in the plasma membrane. Increased levels of cholesterol and insertion of scaffolding domain of caveolins to the plasma membrane then lead to expansion of the caveolar invagination and to formation of endocytic vesicle. Fission of the vesicle from the plasma membrane is then mediated by GTPase dynamin II which is localized at the neck of the budding vesicle. The released caveolar vesicle can fuse with early endosome or caveosome. The caveosome is an endosomal compartment with neutral pH which does not have early endosomal markers, however, contains molecules internalized by the caveolar endocytosis.

This type of endocytosis is used for example for transcytosis of albumin in endothelial cells or for internalization of the insulin receptor in primary adipocytes.

https://en.wikipedia.org/wiki/Caveolae

Related Glossary Terms

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Caveolin

Caveolins are a family of integral membrane proteins that are the principal components of caveolae membranes and involved in receptor-independent endocytosis. Caveolins may act as scaffolding proteins within caveolar membranes by compartmentalizing and concentrating signaling molecules. Various classes of signaling molecules, including G-protein subunits, receptor and non-receptor tyrosine kinases, endothelial nitric oxide synthase (eNOS), and small GTPases, bind Cav-1 through its 'caveolin-scaffolding domain'.

The functions of caveolins are still under intensive investigation. They are best known for their role in the formation of 50-nanometer-size invaginations of the plasma membrane, called caveolae. Oligomers of caveolin form the coat of these domains. Cells that lack caveolins also lack caveolae. Many functions are ascribed to these domains, ranging from endocytosis and transcytosis to signal transduction.

Caveolin-1 has also been shown to play a role in the integrin signaling. The tyrosine phosphorylated form of caveolin-1 colocalizes with focal adhesions, suggesting a role for caveolin-1 in migration. Indeed, downregulation of caveolin-1 leads to less efficient migration *in vitro*.

https://en.wikipedia.org/wiki/Caveolin

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CD36

CD36 (cluster of differentiation 36), also known as FAT (fatty acid translocase), FAT/CD36, (FAT)/CD36, SCARB3, GP88, glycoprotein IV (gpIV), and glycoprotein IIIb (gpIIIb), is an integral membrane protein found on the surface of many cell types in vertebrate animals. CD36 is a member of the class B scavenger receptor family of cell surface proteins. CD36 binds many ligands including collagen, thrombospondin, erythrocytes parasitized with Plasmodium falciparum, oxidized low density lipoprotein, native lipoproteins, oxidized phospholipids, and long-chain fatty acids.

Recent work using genetically modified rodents have identified a clear role for CD36 in fatty acid metabolism, heart disease, taste, and dietary fat processing in the intestine. It may be involved in glucose intolerance, atherosclerosis, arterial hypertension, diabetes, cardiomyopathy and Alzheimer's disease.

CD36's function in long-chain fatty acid uptake and signaling can be irreversibly inhibited by sulfo-N-succinimidyl oleate (SSO), which binds lysine 164 within a hydrophobic pocked shared by several CD36 ligands, e.g. fatty acid and oxLDL.

On binding a ligand the protein and ligand are internalized. This internalization is independent of macropinocytosis and occurs by an actin dependent mechanism requiring the activation Src-family kinases, JNK and Rho-family GTPases. Unlike macropinocytosis this process is not affected by inhibitors of phosphatidylinositol 3-kinase or Na^+/H^+ exchange.

https://en.wikipedia.org/wiki/CD36

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cDNA

Complementary DNA (cDNA) is double-stranded DNA synthesized from a messenger RNA (mRNA) template in a reaction catalyzed by the enzyme reverse transcriptase. cDNA is often used to clone eukaryotic genes in prokaryotes. When scientists want to express a specific protein in a cell that does not normally express that protein (i.e., heterologous expression), they will transfer the cDNA that codes for the protein to the recipient cell.

Although there are several methods for doing so, cDNA is most often synthesized from mature (fully spliced) mRNA using the enzyme reverse transcriptase. This enzyme, which naturally occurs in retroviruses, operates on a single strand of mRNA, generating its complementary DNA based on the pairing of RNA base pairs (A, U, G and C) to their DNA complements (T, A, C and G, respectively).
To obtain eukaryotic cDNA whose introns have been removed:

1 A eukaryotic cell transcribes the DNA (from genes) into RNA (pre-mRNA).
2 The same cell processes the pre-mRNA strands by removing introns, and adding a poly-A tail and 5’ Methyl-Guanine cap (this is known as post-transcriptional modification)
3 This mixture of mature mRNA strands is extracted from the cell. The Poly-A tail of the post-transcription mRNA can be taken advantage of with oligo(dT) beads in an affinity chromatography assay.
4 A poly-T oligonucleotide primer is hybridized onto the poly-A tail of the mature mRNA template, or random hexamer primers can be added which contain every possible 6 base single strand of DNA and can therefore hybridize anywhere on the RNA (Reverse transcriptase requires this double-stranded segment as a primer to start its operation.)
5 Reverse transcriptase is added, along with deoxynucleotide triphosphates (A, T, G, C). This synthesizes one complementary strand of DNA hybridized to the original mRNA strand.
6 To synthesize an additional DNA strand, traditionally one would digest the RNA of the hybrid strand, using an enzyme like RNase H, or through alkali digestion method.
7 After digestion of the RNA, a single stranded DNA (ssDNA) is left and because single stranded nucleic acids are hydrophobic, it tends to loop around itself. It is likely that the ssDNA forms a hairpin loop at the 3' end.
8 From the hairpin loop, a DNA polymerase can then use it as a primer to transcribe a complementary sequence for the ss cDNA.
9 Now, you should be left with a double stranded cDNA with identical sequence as the mRNA of interest.

https://en.wikipedia.org/wiki/Complementary_DNA

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cDNA Library

A cDNA library is a combination of cloned cDNA (complementary DNA) fragm
serted into a collection of host cells, which together constitute some portion of
scriptome of the organism. cDNA is produced from fully transcribed mRNA fo
the nucleus and therefore contains only the expressed genes of an organism. Si
tissue-specific cDNA libraries can be produced. In eukaryotic cells the mature
is already spliced, hence the cDNA produced lacks introns and can be readily e
pressed in a bacterial cell. While information in cDNA libraries is a powerful a
ful tool since gene products are easily identified, the libraries lack information
enhancers, introns, and other regulatory elements found in a genomic DNA lib

https://en.wikipedia.org/wiki/CDNA_library

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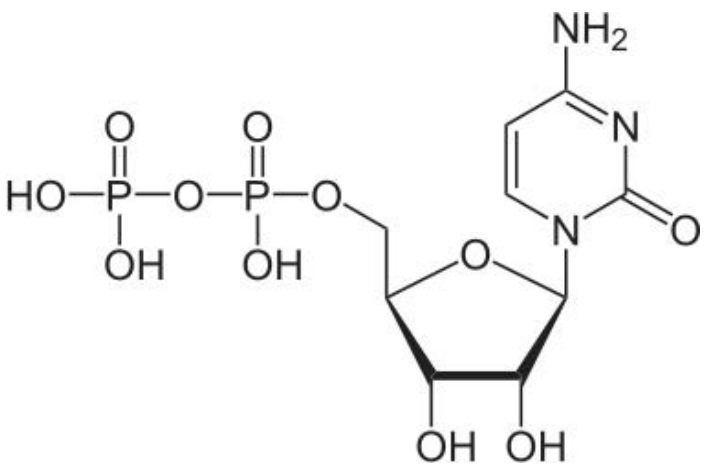
CDP

Cytidine diphosphate, abbreviated CDP, is a nucleoside diphosphate. It is an ester of pyrophosphoric acid with the nucleoside cytidine. CDP consists of the pyrophosphate group, the pentose sugar ribose, and the nucleobase cytosine.



https://en.wikipedia.org/wiki/Cytidine_diphosphate

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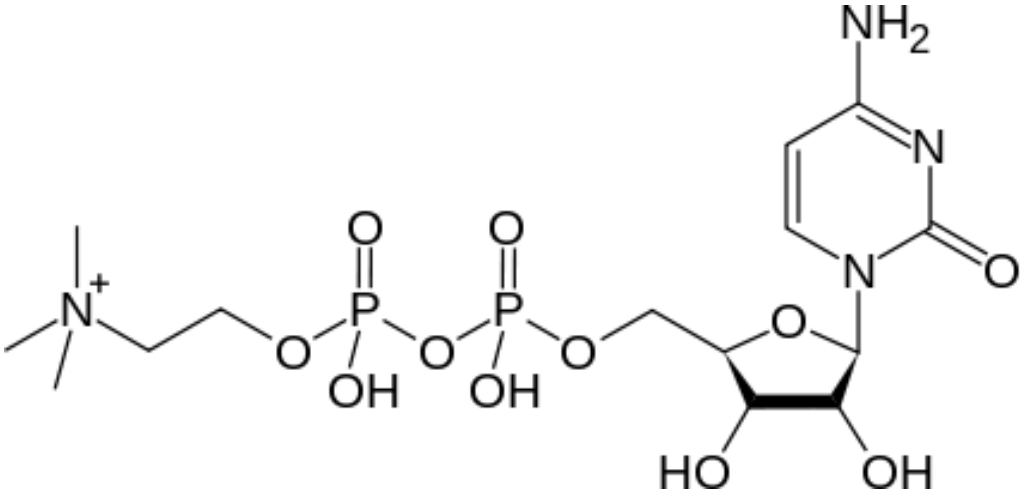
CDP-choline

Citicoline (INN), also known as cytidine diphosphate-choline (CDP-Choline) or cytidine 5'-diphosphocholine is a psychostimulant/nootropic. It is an intermediate in the generation of phosphatidylcholine from choline.

Studies suggest that CDP-choline supplements increase dopamine receptor densities, and suggest that CDP-choline supplementation helps prevent memory impairment resulting from poor environmental conditions. Preliminary research has found that citicoline supplements help improve focus and mental energy and may possibly be useful in the treatment of attention deficit disorder.

Citicoline has also been shown to elevate ACTH independently from CRH levels and to amplify the release of other HPA axis hormones such as LH, FSH, GH and TSH in response to hypothalamic releasing factors. These effects on HPA hormone levels may be beneficial for some individuals but may have undesirable effects in those with medical conditions featuring ACTH or cortisol hypersecretion including PCOS, type II diabetes and major depressive disorder.



https://en.wikipedia.org/wiki/Citicoline

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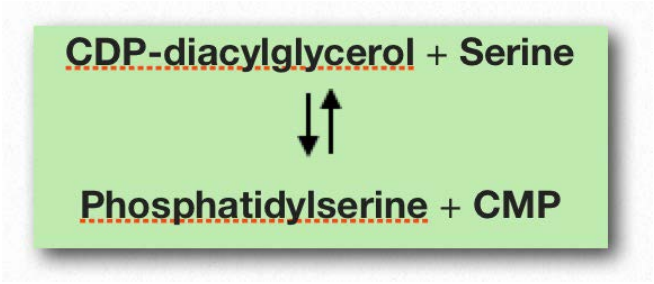
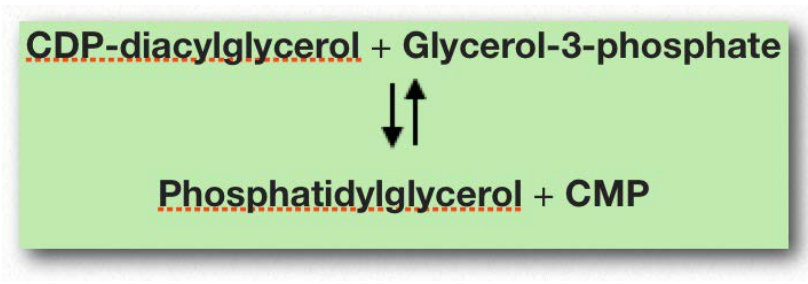
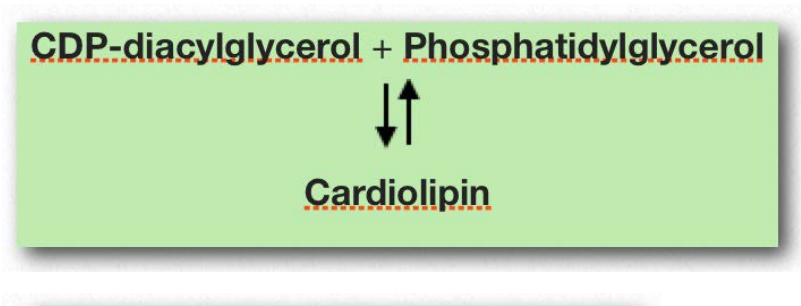
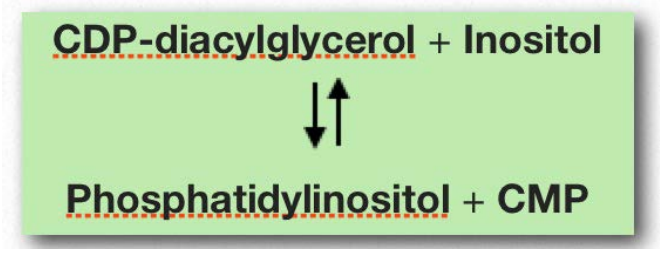
CDP-diacylglycerol

CDP-diacylglycerol is an activated intermediate found in biosynthesis of various glycerophospholipids. The high energy of the bond between the cytidine and the diacylglycerol is used to attach the phosphatidyl part of itself to another molecule, leaving behind a CMP. Several examples are shown below.









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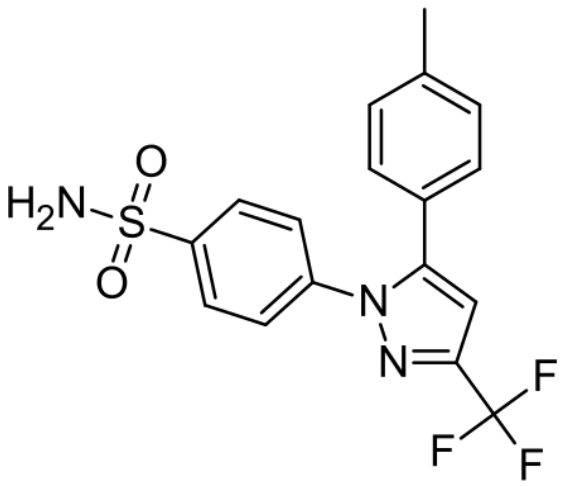
Celebrex

Celecoxib (also known as Celebrex) is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). It is used to treat the pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation, and juvenile rheumatoid arthritis in people two years or older.

Side effects include a 37% increase in incidence of major vascular events, which include nonfatal myocardial infarction, nonfatal stroke, or death from a blood vessel-related cause. Additionally, an 81% increase in incidence of upper gastrointestinal complications occurs, which include perforations, obstructions, or gastrointestinal bleeding as in all NSAIDs.

In July 2015 the FDA strengthened the warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes.



https://en.wikipedia.org/wiki/Celecoxib

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Chapter 6 - Metabolism: Fats and Fatty Acids

Chapter 9 - Point by Point: Metabolism

Cell Cycle

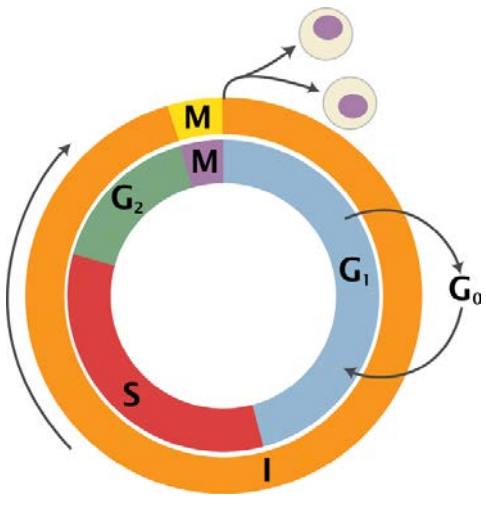
The cell cycle or cell-division cycle is the series of events that take place in a cell leading to its division and duplication of its DNA (DNA replication) to produce two daughter cells.

In bacteria, which lack a cell nucleus, the cell cycle is divided into the B, C, and D periods. The B period extends from the end of cell division to the beginning of DNA replication. DNA replication occurs during the C period. The D period refers to the stage between the end of DNA replication and the splitting of the bacterial cell into two daughter cells.

In cells with a nucleus, as in eukaryotes, the cell cycle is also divided into three periods: interphase, the mitotic (M) phase, and cytokinesis. During interphase, the cell grows, accumulating nutrients needed for mitosis, preparing it for cell division and duplicating its DNA. During the mitotic phase, the cell splits itself into two distinct daughter cells. During the final stage, cytokinesis, the new cell is completely divided. To ensure the proper division of the cell, there are control mechanisms known as cell cycle checkpoints.

The cell-division cycle is a vital process by which a single-celled fertilized egg develops into a mature organism, as well as the process by which hair, skin, blood cells, and some internal organs are renewed. After cell division, each of the daughter cells begin the interphase of a new cycle. Although the various stages of interphase are not usually morphologically distinguishable, each phase of the cell cycle has a distinct set of specialized biochemical processes that prepare the cell for initiation of cell division.

In the figure below, I is interphase and M is mitosis.



https://en.wikipedia.org/wiki/Cell_cycle

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Cell Cycle Regulation

Regulation of the cell cycle involves processes crucial to the survival of a cell, including the detection and repair of genetic damage as well as the prevention of uncontrolled cell division. The molecular events that control the cell cycle are ordered and directional. That is, each process occurs in a sequential fashion and it is impossible to "reverse" the cycle.

Two key classes of regulatory molecules, cyclins and cyclin-dependent kinases (CDKs), determine a cell's progress through the cell cycle. Leland H. Hartwell, R. Timothy Hunt, and Paul M. Nurse won the 2001 Nobel Prize in Physiology or Medicine for their discovery of these central molecules. Many of the genes encoding cyclins and CDKs are conserved among all eukaryotes, but in general more complex organisms have more elaborate cell cycle control systems that incorporate more individual components. Many of the relevant genes were first identified by studying yeast, especially *Saccharomyces cerevisiae*. Genetic nomenclature in yeast dubs many of these genes cdc (for "cell division cycle") followed by an identifying number, e.g. cdc25 or cdc20.

Cyclins form the regulatory subunits and CDKs the catalytic subunits of an activated heterodimer. Cyclins have no catalytic activity and CDKs are inactive in the absence of a partner cyclin. When activated by a bound cyclin, CDKs perform a common biochemical reaction called phosphorylation that activates or inactivates target proteins to orchestrate coordinated entry into the next phase of the cell cycle. Different cyclin-CDK combinations determine the downstream proteins targeted. CDKs are constitutively expressed in cells whereas cyclins are synthesized at specific stages of the cell cycle, in response to various molecular signals.

https://en.wikipedia.org/wiki/Cell_cycle#Regulation_of_eukaryotic_cell_cycle

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Chapter 2 - Structure and Function: Proteins

Cell Division

Cell division is the process by which a parent cell divides into two or more daughter cells. Cell division usually occurs as part of a larger cell cycle. In eukaryotes, there are two distinct types of cell division: a vegetative division, whereby each daughter cell is genetically identical to the parent cell (mitosis), and a reproductive cell division, whereby the number of chromosomes in the daughter cells is reduced by half, to produce haploid gametes (meiosis). Meiosis results in four haploid daughter cells by undergoing one round of DNA replication followed by two divisions: homologous chromosomes are separated in the first division, and sister chromatids are separated in the second division. Both of these cell division cycles are used in sexually reproducing organisms at some point in their life cycle, and both are believed to be present in the last eukaryotic common ancestor. Prokaryotes also undergo a vegetative cell division known as binary fission, where their genetic material is segregated equally into two daughter cells. All cell divisions, regardless of organism, are preceded by a single round of DNA replication.

For simple unicellular organisms, such as the amoeba, one cell division is equivalent to reproduction – an entire new organism is created. On a larger scale, mitotic cell division can create progeny from multicellular organisms, such as plants that grow from cuttings. Cell division also enables sexually reproducing organisms to develop from the one-celled zygote, which itself was produced by cell division from gametes. And after growth, cell division allows for continual construction and repair of the organism. A human being's body experiences about 10 quadrillion cell divisions in a lifetime.

The primary concern of cell division is the maintenance of the original cell's genome. Before division can occur, the genomic information that is stored in chromosomes must be replicated, and the duplicated genome must be separated cleanly between cells. A great deal of cellular infrastructure is involved in keeping genomic information consistent between "generations".

https://en.wikipedia.org/wiki/Cell_division

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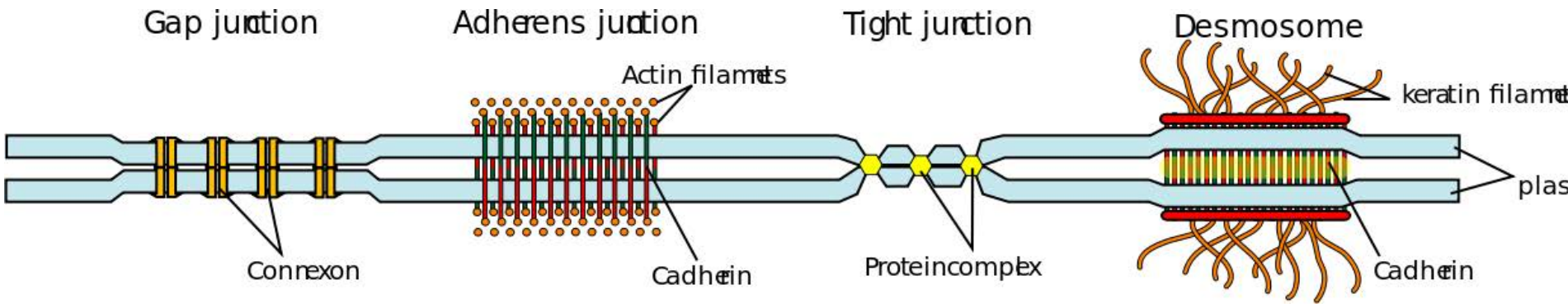
Cell Junctions

A cell junction (or intercellular bridge) is a type of structure that exists within th
sue of some multicellular organisms, such as animals. Cell junctions consist of m
protein complexes that provide contact between neighboring cells or between a
and the extracellular matrix. They also build up the paracellular barrier of epith
and control the paracellular transport. Cell junctions are especially abundant in
lial tissues.



https://en.wikipedia.org/wiki/Cell_junction

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Cell Membrane

The cell membrane (or plasma membrane or plasmalemma) surrounds the cytoplasm of living cells, physically separating the intracellular components from the extracellular environment. Fungi, bacteria and plants also have a cell wall in addition, which provides a mechanical support to the cell and precludes the passage of larger molecules. The cell membrane also plays a role in anchoring the cytoskeleton to provide shape to the cell, and in attaching to the extracellular matrix and other cells to hold them together to form tissues.

The cell membrane is selectively permeable and able to regulate what enters and exits the cell, thus facilitating the transport of materials needed for survival. The movement of substances across the membrane can be either "passive", occurring without the input of cellular energy, or "active", requiring the cell to expend energy in transporting it. The membrane also maintains the cell potential. The cell membrane thus works as a selective filter that allows only certain things to come inside or go outside the cell. The cell employs a number of transport mechanisms that involve biological membranes:

Passive osmosis and diffusion: Some substances (small molecules, ions) such as carbon dioxide (CO_2) and oxygen (O_2), can move across the plasma membrane by diffusion, which is a passive transport process. Because the membrane acts as a barrier for certain molecules and ions, they can occur in different concentrations on the two sides of the membrane. Such a concentration gradient across a semipermeable membrane sets up an osmotic flow for the water.

Transmembrane protein channels and transporters: Nutrients, such as sugars or amino acids, must enter the cell, and certain products of metabolism must leave the cell. Such molecules diffuse passively through protein channels such as aquaporins (in the case of water (H_2O)) in facilitated diffusion or are pumped across the membrane by transmembrane transporters. Protein channel proteins, also called permeases, are usually quite specific, recognizing and transporting only a limited food group of chemical substances, often even only a single substance.

Endocytosis: Endocytosis is the process in which cells absorb molecules by engulfing them. The plasma membrane creates a small deformation inward, called an invagination, in which the substance to be transported is captured. The deformation then pinches off from the membrane on the inside of the cell, creating a vesicle containing the captured substance. Endocytosis is a pathway for internalizing solid particles ("cell eating" or phagocytosis), small molecules and ions ("cell drinking" or pinocytosis), and macromolecules. Endocytosis requires energy and is thus a form of active transport.

Exocytosis: Just as material can be brought into the cell by invagination and formation of a vesicle, the membrane of a vesicle can be fused with the plasma membrane, extruding its contents to the surrounding medium. This is the process of exocytosis. Exocytosis occurs in various cells to remove undigested residues of substances brought in by endocytosis, to secrete substances such as hormones and enzymes, and to transport a substance completely across a cellular barrier. In the process of exocytosis, the undigested waste-containing food vacuole or the secretory vesicle budded from Golgi apparatus, is first moved by cytoskeleton from the interior of the cell to the surface. The vesicle membrane comes in contact with the plasma membrane. The lipid molecules of the two bilayers rearrange themselves and the two membranes are, thus, fused. A passage is formed in the fused membrane and the vesicles discharges its contents outside the cell.

https://en.wikipedia.org/wiki/Cell_membrane

Related Glossary Terms

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Cell Suicide

Apoptosis (from Ancient Greek ἀπόπτωσις "falling off") is a process of programmed cell death that occurs in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation, and global mRNA decay. Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day.

In contrast to necrosis, which is a form of traumatic cell death that results from acute cellular injury, apoptosis is a highly regulated and controlled process that confers advantages during an organism's lifecycle. For example, the separation of fingers and toes in a developing human embryo occurs because cells between the digits undergo apoptosis. Unlike necrosis, apoptosis produces cell fragments called apoptotic bodies that phagocytic cells are able to engulf and quickly remove before the contents of the cell can spill out onto surrounding cells and cause damage.

Because apoptosis cannot stop once it has begun, it is a highly regulated process. Apoptosis can be initiated through one of two pathways. In the intrinsic pathway the cell kills itself because it senses cell stress, while in the extrinsic pathway the cell kills itself because of signals from other cells. Both pathways induce cell death by activating caspases, which are proteases, or enzymes that degrade proteins. The two pathways both activate initiator caspases, which then activate executioner caspases, which then kill the cell by degrading proteins indiscriminately.

Research on apoptosis has increased substantially since the early 1990s. In addition to its importance as a biological phenomenon, defective apoptotic processes have been implicated in a wide variety of diseases. Excessive apoptosis causes atrophy, whereas an insufficient amount results in uncontrolled cell proliferation, such as cancer. Some factors like Fas receptors and caspases promote apoptosis, while some members of the Bcl-2 family of proteins inhibit apoptosis.

https://en.wikipedia.org/wiki/Apoptosis

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Chapter 2 - Structure & Function: Lipids

Cell Wall

A cell wall is a structural layer that surrounds some types of cells, situated outside the cell membrane. It can be tough, flexible, and sometimes rigid. It provides cells with both structural support and protection, and also acts as a filtering mechanism. Cell walls are present in plants, fungi and prokaryotic cells, where a major function is to act as pressure vessels, preventing over-expansion when water enters the cells. Cell walls are absent from mycoplasmas.

The composition of cell walls varies between species and may depend on cell type and developmental stage. The primary cell wall of land plants is composed of the polysaccharides cellulose, hemicellulose and pectin. In bacteria, the cell wall is composed of peptidoglycan. Archaean cell walls have various compositions, and may be formed of glycoprotein S-layers, pseudopeptidoglycan, or polysaccharides. Fungi possess cell walls made of the glucosamine polymer chitin, and algae typically possess walls made of glycoproteins and polysaccharides. Unusually, diatoms have a cell wall composed of biogenic silica. Often, other accessory molecules such as lignin or cutin are found anchored to the cell wall.

https://en.wikipedia.org/wiki/Cell_wall

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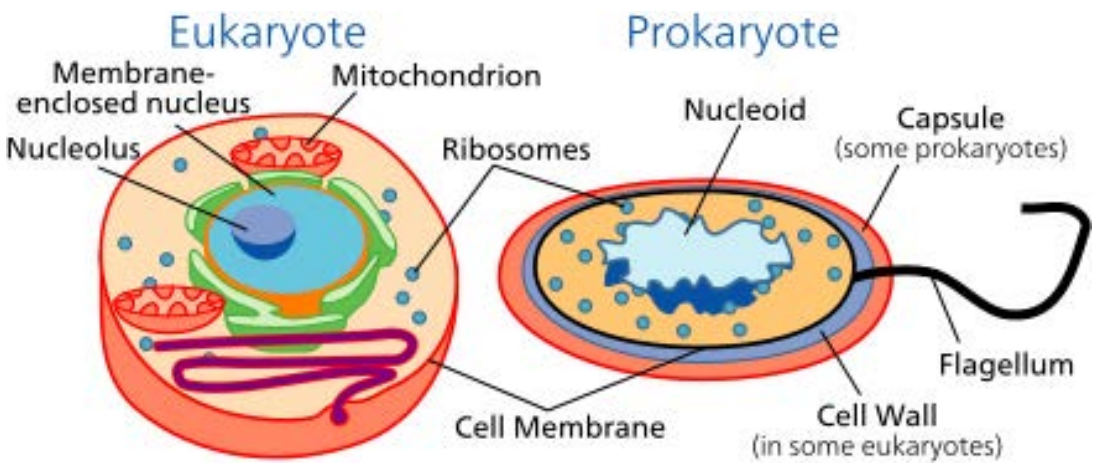
Cells

The cell (from Latin cella, meaning "small room") is the basic structural, functional, and biological unit of all known living organisms. A cell is the smallest unit of life that can replicate independently, and cells are often called the "building blocks of life". The study of cells is called cell biology. Cells consist of cytoplasm enclosed within a membrane, which contains many biomolecules such as proteins and nucleic acids. Organisms can be classified as unicellular (consisting of a single cell, including bacteria) or multicellular (including plants and animals).

Cells consist of cytoplasm enclosed within a membrane, which contains many biomolecules such as proteins and nucleic acids. Organisms can be classified as unicellular (consisting of a single cell; including bacteria) or multicellular (including plants and animals). While the number of cells in plants and animals varies from species to species, humans contain more than 10 trillion (10^{13}) cells. Most plant and animal cells are visible only under the microscope, with dimensions between 1 and 100 µM.



https://en.wikipedia.org/wiki/Cell_(biology)

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Cellular Response

The cellular response is one of two primary responses of the blood clotting system to injury. The other response is known as the molecular response and is the response that makes the blood clot.

The cellular response, by contrast, is the first response to injury. Injury to the epithelial lining of a blood vessel begins the process of coagulation almost instantly. The cellular response has an initial action followed by an amplification step. In the cellular response, the platelets bind directly to collagen using Ia/IIa collagen-binding surface receptors and glycoprotein VI to form a plug. The signal to the platelets to take this action is exposure of the underlying collagen, something that would not happen in the absence of a wound. In this overall process, platelets' integrins get activated and then bind tightly to the extracellular matrix to anchor them to the site of the wound.
The von Willebrand factor assists by forming additional links between the platelets' glycoprotein Ib/IX/V and the fibrils of the collagen.

In the amplification part of the cellular response, the activated platelets release a large number of factors, including platelet factor 4 (a cytokine stimulating inflammation and moderating action of the heparin anticoagulant) and thromboxane A_2, The latter has the effect of increasing the "stickiness" of platelets, favoring their aggregation. In addition, a a Gq-linked protein receptor cascade is activated, resulting in release of calcium in the area. This plays a role in the molecular response.

https://en.wikipedia.org/wiki/Coagulation

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Cellulase

Cellulase is any of several enzymes produced chiefly by fungi, bacteria, and protozoans that catalyze cellulolysis, the decomposition of cellulose and of some related polysaccharides. The name is also used for any naturally occurring mixture or complex of various such enzymes, that act serially or synergistically to decompose cellulosic material. Cellulases break down the cellulose molecule into monosaccharides ("simple sugars") such as β-glucose, or shorter polysaccharides and oligosaccharides. Cellulose breakdown is of considerable economic importance, because it makes a major constituent of plants available for consumption and use in chemical reactions. The specific reaction involved is the hydrolysis of the 1,4-β-D-glycosidic linkages in cellulose, hemicellulose, lichenin, and cereal β-D-glucans. Because cellulose molecules bind strongly to each other, cellulolysis is relatively difficult compared to the breakdown of other polysaccharides such as starch.

Most mammals have only very limited ability to digest dietary fibers such as cellulose by themselves. In many herbivorous animals such as ruminants like cattle and sheep and hindgut fermenters like horses, cellulases are produced by symbiotic bacteria. Cellulases are produced by a few types of animals, such as some termites.

https://en.wikipedia.org/wiki/Cellulase

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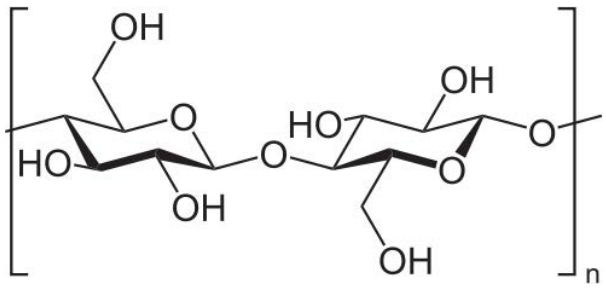
Cellulose

Cellulose is an organic compound with the formula $(C_6H_{10}O_5)n$, a polysaccharide consisting of a linear chain of several hundred to many thousands of β(1→4) linked D-glucose units. Cellulose is an important structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. Some species of bacteria secrete it to form biofilms. Cellulose is the most abundant organic polymer on Earth.

Cellulose is mainly used to produce paperboard and paper. Smaller quantities are converted into a wide variety of derivative products such as cellophane and rayon. Conversion of cellulose from energy crops into biofuels such as cellulosic ethanol is under investigation as an alternative fuel source. Cellulose for industrial use is mainly obtained from wood pulp and cotton.

Some animals, particularly ruminants and termites, can digest cellulose with the help of symbiotic micro-organisms that live in their guts, such as *Trichonympha*. In humans, cellulose acts as a hydrophilic bulking agent for feces and is often referred to as a "dietary fiber".



https://en.wikipedia.org/wiki/Cellulose

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Cellulose Synthase

Cellulose synthase (GDP-forming) (EC 2.4.1.29) is an enzyme that catalyzes the chemical reaction

UDP-glucose + $(1,4\text{-}\beta\text{-D-glucosyl})_n$ <-> UDP + $(1,4\text{-}\beta\text{-D-glucosyl})_{n+1}$

Some forms of the enzyme can use GDP-glucose instead of UDP-glucose.

Cellulose biosynthesis is the process during which separate homogeneous β-1,4-glucan chains, ranging from 2,000 to 25,000 glucose residues in length, are synthesized and then immediately hydrogen bonded with one another to form rigid crystalline arrays, or microfibrils. Microfibrils in the primary cell wall are approximately 36 chains long while those of the secondary cell wall are much larger, containing up to 1200 β-1,4-glucan chains. Uridine diphosphate-glucose (UDP), which is produced by the enzyme sucrose synthase (SuSy) that produces and transports UDP-glucose to the plasma membrane is the substrate used by cellulose synthase to produce the glucan chains. The rate at which glucose residues are synthesized per one glucan chain ranges from 300-1000 glucose residues per minute, the higher rate being more prevalent in secondary wall particles, such as in the xylem.

https://en.wikipedia.org/wiki/Cellulose_synthase_(UDP-forming)

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Central Dogma

The central dogma of molecular biology is an explanation of the flow of genetic information within a biological system.

The central dogma has also been described as "DNA makes RNA and RNA makes protein," a positive statement which was originally termed the sequence hypothesis by Francis Crick. However, this simplification does not make it clear that the central dogma as stated by Crick does not preclude the reverse flow of information from RNA to DNA, only ruling out the flow from protein to RNA or DNA.

The dogma is a framework for understanding the transfer of sequence information between information-carrying biopolymers, in the most common or general case, in living organisms. There are 3 major classes of such biopolymers: DNA and RNA (both nucleic acids), and protein. There are 3×3 = 9 conceivable direct transfers of information that can occur between these. The dogma classes these into 3 groups of 3: 3 general transfers (believed to occur normally in most cells), 3 special transfers (known to occur, but only under specific conditions in case of some viruses or in a laboratory), and 3 unknown transfers (believed never to occur). The general transfers describe the normal flow of biological information: DNA can be copied to DNA (DNA replication), DNA information can be copied into mRNA (transcription), and proteins can be synthesized using the information in mRNA as a template (translation).

Crick's use of the word dogma was unconventional, and has been controversial.

https://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology

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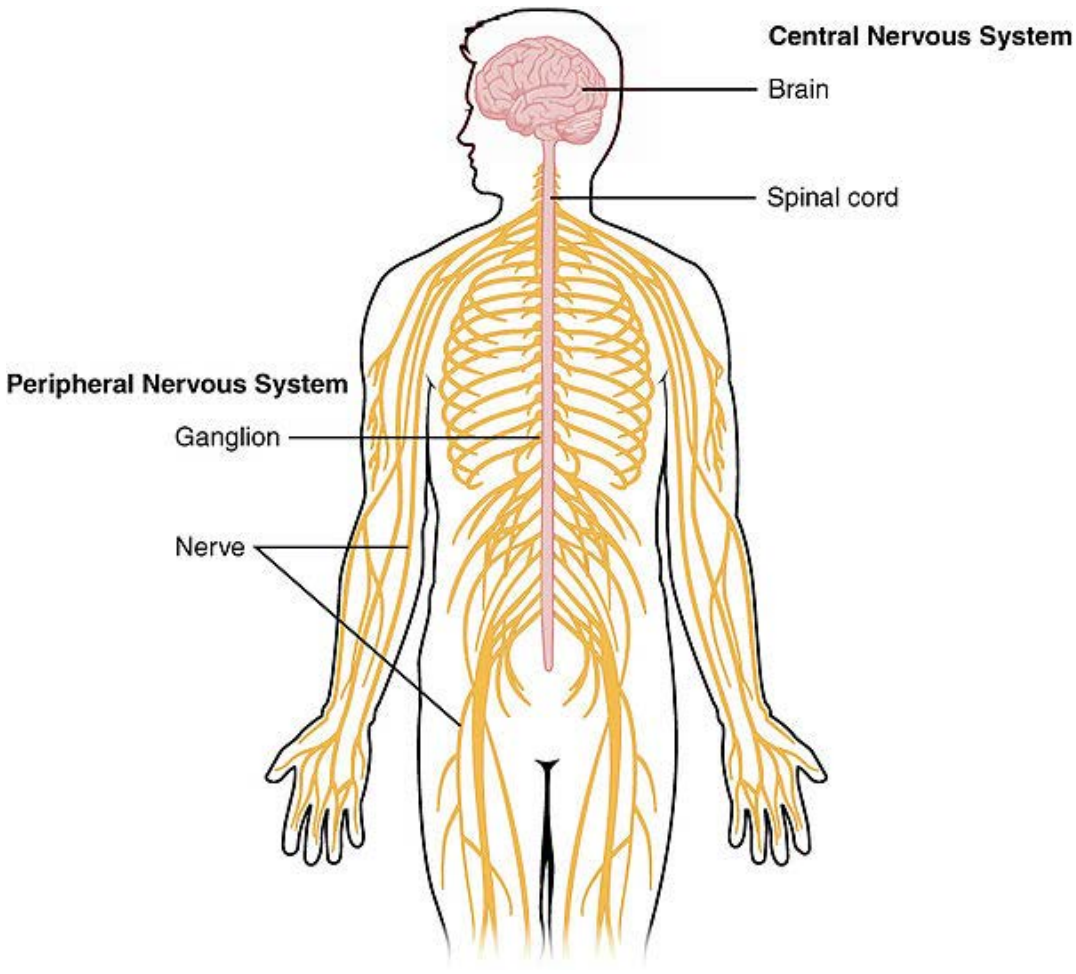
Central Nervous System

The central nervous system (CNS) is the part of the nervous system consisting of the brain and spinal cord. The central nervous system is so named because it integrates information it receives from, and coordinates and influences the activity of, all parts of the bodies of bilaterally symmetric animals—that is, all multicellular animals except sponges and radially symmetric animals such as jellyfish—and it contains the majority of the nervous system.



https://en.wikipedia.org/wiki/Central_nervous_system

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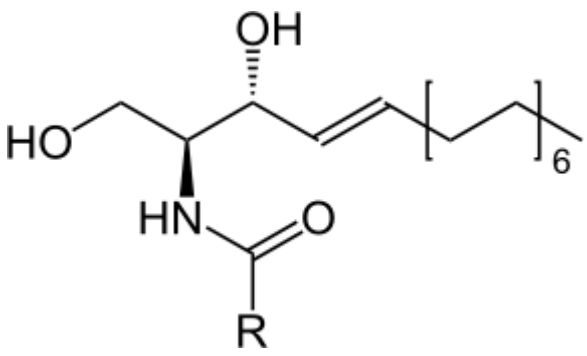
Ceramide

Ceramides are a family of waxy lipid molecules. A ceramide is composed of sphingosine and a fatty acid. Ceramides are found in high concentrations within the cell membrane of cells. They are one of the component lipids that make up sphingomyelin, one of the major lipids in the lipid bilayer.

As a bioactive lipid, ceramide has been implicated in a variety of physiological functions including apoptosis, cell growth arrest, differentiation, cell senescence, cell migration and adhesion. Roles for ceramide and its downstream metabolites have also been suggested in a number of pathological states including cancer, neurodegeneration, diabetes, microbial pathogenesis, obesity, and inflammation.

One of the most studied roles of ceramide pertains to its function as a proapoptotic molecule. Apoptosis, or Type I programmed cell death, is essential for the maintenance of normal cellular homeostasis and is an important physiological response to many forms of cellular stress. Ceramide accumulation has been found following treatment of cells with a number of apoptotic agents including ionizing radiation, UV light, TNF-α, and chemotherapeutic agents. This suggests a role for ceramide in the biological responses of all these agents. Because of its apoptosis-inducing effects in cancer cells, ceramide has been termed the “tumor suppressor lipid” . Several studies have attempted to define further the specific role of ceramide in the events of cell death and some evidence suggests ceramide functions upstream of the mitochondria in inducing apoptosis. However, owing to the conflicting and variable nature of studies into the role of ceramide in apoptosis, the mechanism by which this lipid regulates apoptosis remains elusive. (R below in the figure is the non-polar end of a fatty acid).



https://en.wikipedia.org/wiki/Ceramide

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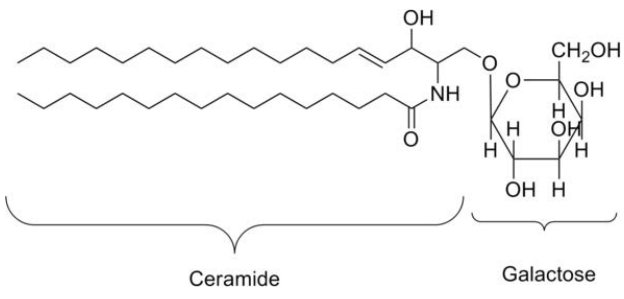
Cerebroside

Cerebrosides is the common name for a group of glycosphingolipids called monoglycosylceramides which are important components in animal muscle and nerve cell membranes. They consist of a ceramide with a single sugar residue at the 1-hydroxyl moiety. The sugar residue can be either glucose or galactose. The two major types are therefore called glucocerebrosides and galactocerebrosides. Galactocerebrosides are typically found in neural tissue, while glucocerebrosides are found in other tissues.

The fundamental structure of a cerebroside is ceramide. Monoglycosyl and oligoglycosylceramides having a mono or polysaccharide bonded glycosidically to the terminal OH group of ceramide are defined as cerebrosides. Sphingosine is the main long-chain base present in ceramide.

Galactosylceramide (shown at bottom) is the principal glycosphingolipid in brain tissue. Galactosylceramides are present in all nervous tissues, and can compose up to 2% dry weight of grey matter and 12% of white matter. They are major constituents of oligodendrocytes. Glucosylceramide is found at low levels in animal cells such as the spleen, erythrocytes, and nervous tissues, especially neurons. Glucosylceramide is a major constituent of skin lipids, where it is essential for lamellar body formation in the stratum corneum and to maintain the water permeability barrier of the skin. Glucosylceramide is the only glycosphingolipid common to plants, fungi and animals. It is usually considered to be the principal glycosphingolipid in plants. It is a major component of the outer layer of the plasma membrane. Galactosylceramides have not been found in plants.

Monogalactosylceramide is the largest single component of the myelin sheath of nerves. Cerebroside synthesis can therefore give a measurement of myelin formation or remyelination. The sugar moiety is linked glycosidically to the C-1 hydroxyl group of ceramide, such as in lactosylceramide. Cerebrosides containing a sulfuric ester (sulfate) group, known as sulfatides, also occur in the myelin sheath of nerves. These compounds are preferably named as sulfates of the parent glycosphingolipid.



https://en.wikipedia.org/wiki/Cerebroside

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CFTR

Cystic fibrosis transmembrane conductance regulator (CFTR) is a membrane protein and chloride channel in vertebrates that is encoded by the CFTR gene.

CFTR is an ABC transporter-class ion channel that codes for a protein that conducts chloride and thiocyanate ions across epithelial cell membranes. Mutations of the CFTR gene affecting chloride ion channel function lead to dysregulation of epithelial fluid transport in the lung, pancreas and other organs, resulting in cystic fibrosis.

The CFTR protein is a channel protein that controls the flow of H_2O and Cl^- ions in and out of cells inside the lungs. When the CFTR protein is working correctly, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterized by the buildup of thick mucus in the lungs.

Complications include thickened mucus in the lungs with frequent respiratory infections, and pancreatic insufficiency giving rise to malnutrition and diabetes. These conditions lead to chronic disability and reduced life expectancy. In male patients, the progressive obstruction and destruction of the developing vas deferens (spermatic cord) and epididymis appear to result from abnormal intraluminal secretions, causing congenital absence of the *vas deferens* and male infertility.

https://en.wikipedia.org/wiki/Cystic_fibrosis_transmembrane_conductance_regulator

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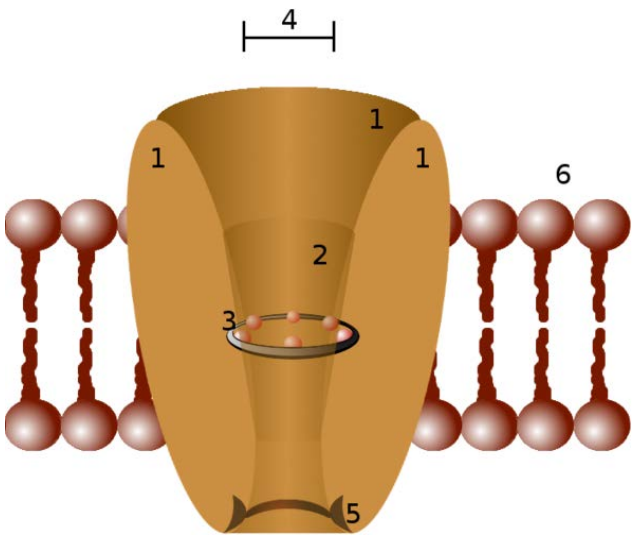
Channels

Ion channels are pore-forming membrane proteins whose functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume. Ion channels are present in the membranes of all cells. Ion channels are considered to be one of the two traditional classes of ionophoric proteins, with the other class known as ion transporters (including the sodium-potassium pump, sodium-calcium exchanger, and sodium-glucose transport proteins, amongst others).

Study of ion channels (channelomics) often includes biophysics, electrophysiology and pharmacology, utilizing techniques including voltage clamp, patch clamp, immunohistochemistry, X-ray crystallography, fluorescence, and RT-PCR.



https://en.wikipedia.org/wiki/Ion_channel

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Chaperonin

Chaperonins are proteins that provide favorable conditions for the correct folding of other proteins, thus preventing aggregation. Newly made proteins usually must fold from a linear chain of amino acids into a three-dimensional form. Chaperonins belong to a large class of molecules that assist protein folding, called molecular chaperones. The energy to fold proteins is supplied by adenosine triphosphate (ATP).

Chaperonins undergo large conformational changes during a folding reaction as a function of the enzymatic hydrolysis of ATP as well as binding of substrate proteins and co-chaperonins, such as GroES. These conformational changes allow the chaperonin to bind an unfolded or misfolded protein, encapsulate that protein within one of the cavities formed by the two rings, and release the protein back into solution. Upon release, the substrate protein will either be folded or will require further rounds of folding, in which case it can again be bound by a chaperonin.

The exact mechanism by which chaperonins facilitate folding of substrate proteins is unknown. According to recent analyses by different experimental techniques, GroEL-bound substrate proteins populate an ensemble of compact and locally expanded states that lack stable tertiary interactions. A number of models of chaperonin action have been proposed, which generally focus on two (not mutually exclusive) roles of chaperonin interior: passive and active. Passive models treat the chaperonin cage as an inert form, exerting influence by reducing the conformational space accessible to a protein substrate or preventing intermolecular interactions e.g. by aggregation prevention. The active chaperonin role is in turn involved with specific chaperonin–substrate interactions that may be coupled to conformational rearrangements of the chaperonin.

Probably the most popular model of the chaperonin active role is the iterative annealing mechanism (IAM), which focus on the effect of iterative, and hydrophobic in nature, binding of the protein substrate to the chaperonin. According to computational simulation studies, the IAM leads to more productive folding by unfolding the substrate from misfolded conformations or by prevention from protein misfolding through changing the folding pathway.

https://en.wikipedia.org/wiki/Chaperonin

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Chaperonins

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https://en.wikipedia.org/wiki/Chaperonin

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Chapter 2 - Structure & Function: Proteins I
Chapter 7 - Information Processing: Translation

Chemerin

Chemerin, also known as retinoic acid receptor responder protein 2 (RARR
tazarotene-induced gene 2 protein (TIG2), or RAR-responsive protein TIG2
tein that in humans is encoded by the RARRES2 gene. Retinoids exert biol
such as potent growth inhibitory and cell differentiation activities and are u
treatment of hyperproliferative dermatological diseases. These effects are m
specific nuclear receptor proteins that are members of the steroid and thyro
mone receptor superfamily of transcriptional regulators.

https://en.wikipedia.org/wiki/Chemerin

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Chapter 6 - Metabolism: Fats and Fatty Acids

Chapter 9 - Point by Point: Metabolism

Chemiosmotic

Chemiosmosis is the movement of ions across a selectively permeable membrane, down their electrochemical gradient. More specifically, it relates to the generation of ATP by the movement of hydrogen ions across a membrane during cellular respiration or photosynthesis.

Hydrogen ions (protons) will diffuse from an area of high proton concentration to an area of lower proton concentration, and an electrochemical concentration gradient of protons across a membrane can be harnessed to make ATP. This process is related to osmosis, the diffusion of water across a membrane, which is why it is called chemiosmosis.

ATP synthase is the enzyme that makes ATP by chemiosmosis. It allows protons to pass through the membrane and uses the kinetic energy to phosphorylate ADP, making ATP. The generation of ATP by chemiosmosis occurs in chloroplasts as well as in most bacteria and archaea.

Peter D. Mitchell proposed the chemiosmotic hypothesis in 1961. The theory suggests essentially that most ATP synthesis in respiring cells comes from the electrochemical gradient across the inner membranes of mitochondria by using the energy of NADH and $FADH_2$ formed from the breaking down of energy-rich molecules such as glucose.

Molecules such as glucose are metabolized to produce acetyl CoA as an energy-rich intermediate. The oxidation of acetyl CoA in the mitochondrial matrix is coupled to the reduction of a carrier molecule such as NAD and FAD. The carriers pass electrons to the electron transport chain (ETC) in the inner mitochondrial membrane, which in turn pass them to other proteins in the ETC. The energy available in the electrons is used to pump protons from the matrix across the inner mitochondrial membrane, storing energy in the form of a transmembrane electrochemical gradient. The protons move back across the inner membrane through the enzyme ATP synthase. The flow of protons back into the matrix of the mitochondrion via ATP synthase provides enough energy for ADP to combine with inorganic phosphate to form ATP. The electrons and protons at the last pump in the ETC are taken up by oxygen to form water.

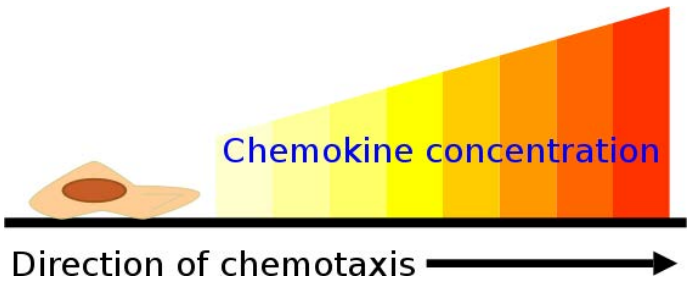
https://en.wikipedia.org/wiki/Chemiosmosis

Chemokine

Chemokines (Greek -kinos, movement) are a family of small cytokines, or signaling proteins secreted by cells. Their name is derived from their ability to induce directed chemotaxis in nearby responsive cells. They are chemotactic cytokines.

The major role of chemokines is to act as a chemoattractant to guide the migration of cells. Cells that are attracted by chemokines follow a signal of increasing chemokine concentration towards the source of the chemokine. Some chemokines control cells of the immune system during processes of immune surveillance, such as directing lymphocytes to the lymph nodes so they can screen for invasion of pathogens by interacting with antigen-presenting cells residing in these tissues. These are known as homeostatic chemokines and are produced and secreted without any need to stimulate their source cell(s).

Some chemokines have roles in development. They promote angiogenesis (the growth of new blood vessels), or guide cells to tissues that provide specific signals critical for cellular maturation. Other chemokines are inflammatory and are released from a wide variety of cells in response to bacterial infection, viruses and agents that cause physical damage such as silica or the urate crystals that occur in gout. Their release is often stimulated by pro-inflammatory cytokines such as interleukin 1. Inflammatory chemokines function mainly as chemoattractants for leukocytes, recruiting monocytes, neutrophils and other effector cells from the blood to sites of infection or tissue damage. Certain inflammatory chemokines activate cells to initiate an immune response or promote wound healing. They are released by many different cell types and serve to guide cells of both innate immune system and adaptive immune system.



https://en.wikipedia.org/wiki/Chemokine

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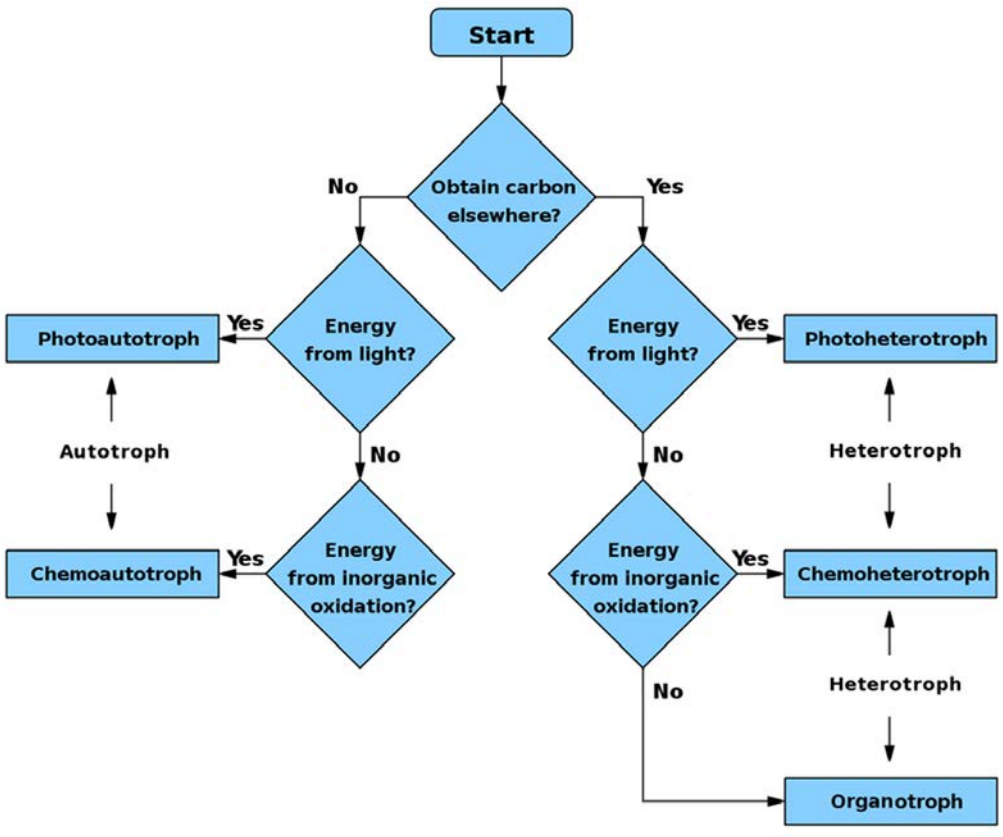
Chemotrophic

Chemotrophs are organisms that obtain energy by the oxidation of electron donors in their environments. These molecules can be organic (chemoorganotrophs) or inorganic (chemolithotrophs). The chemotroph designation is in contrast to phototrophs, which utilize solar energy. Chemotrophs can be either autotrophic or heterotrophic. Chemoautotrophs are commonly found in ocean floors where sunlight cannot reach them because they are not dependent on solar energy. Ocean floors often contain underwater volcanos that can provide heat to substitute sunlight for warmth.

In addition to deriving energy from chemical reactions, chemoautotrphos synthesize all necessary organic compounds from carbon dioxide. Chemoautotrophs use inorganic energy sources, such as hydrogen sulfide, elemental sulfur, ferrous iron, and also molecular hydrogen, and ammonia. Most are bacteria or archaea that live in hostile environments such as deep sea vents and are the primary producers in such ecosystems. Chemoautotrophs generally fall into several groups: methanogens, halophiles, sulfur oxidizers and reducers, nitrifiers, anammox bacteria, and thermoacidophiles. Chemolithotrophic growth could be dramatically fast, such as *Thiomicrospira crunogena* with a doubling time around one hour.



https://en.wikipedia.org/wiki/Chemotroph

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Chapter 1 - Chemistry, Buffers, and Energy

Chapter 1 - Introduction: Basic Chemistry

Chemotrophs

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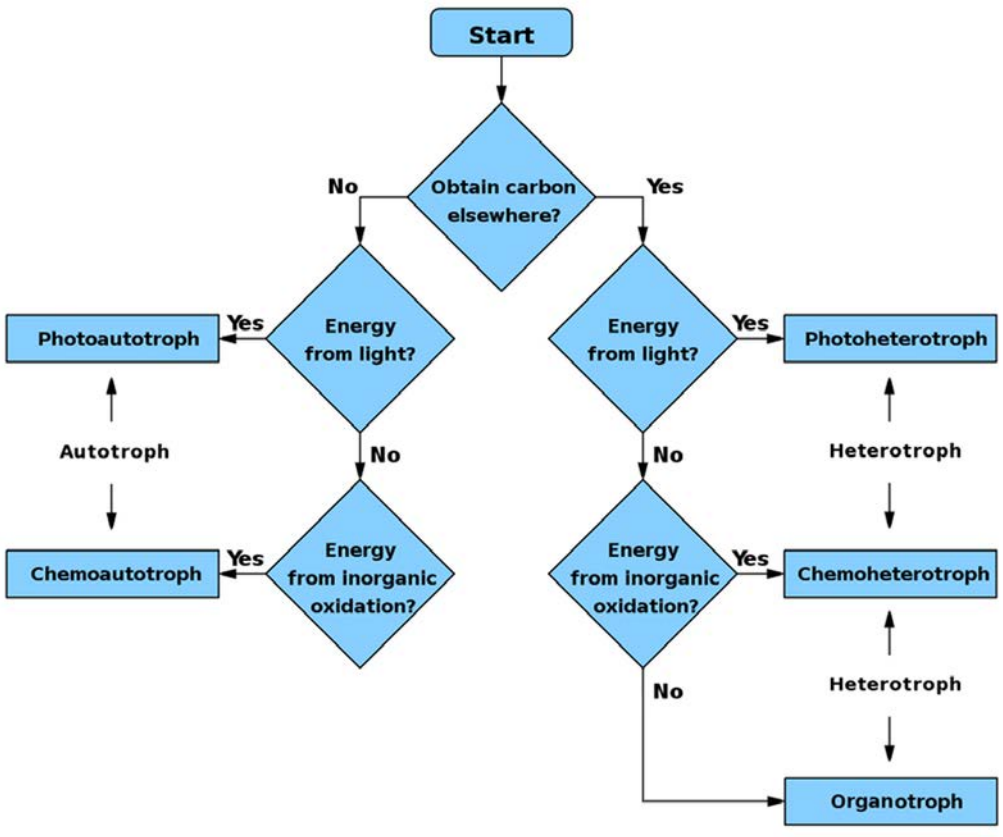

https://en.wikipedia.org/wiki/Chemotroph

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Chapter 9 - Point by Point: In the Beginning

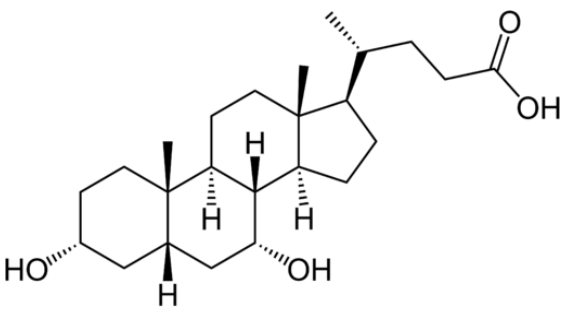
Chenodeoxycholic Acid

Chenodeoxycholic acid (also known as chenodesoxycholic acid, chenocholic acid and 3α,7α-dihydroxy-5β-cholan-24-oic acid) is a bile acid. It occurs as a white crystalline substance insoluble in water but soluble in alcohol and acetic acid, with melting point at 165-167°C. Salts of this carboxylic acid are called chenodeoxycholates. Chenodeoxycholic acid is one of the main bile acids produced by the liver.

Chenodeoxycholic acid and cholic acid are the two primary bile acids in humans. Some other mammals have muricholic acid or deoxycholic acid rather than chenodeoxycholic acid.

Chenodeoxycholic acid is synthesized in the liver from cholesterol by a process which involves several enzymatic steps. Like other bile acids, it can be conjugated in the liver with taurine or glycine, forming taurochenodeoxycholate or glycochenodeoxycholate. Conjugation results in a lower pKa. This means the conjugated bile acids are ionized at the usual pH in the intestine and will stay in the gastrointestinal tract until reaching the ileum where most will be reabsorbed. Bile acids form micelles which facilitate lipid digestion. After absorption, they are taken up by the liver and resecreted, so undergoing an enterohepatic circulation. Unabsorbed chenodeoxycholic acid can be metabolized by bacteria in the colon to form the secondary bile acid known as lithocholic acid.

Choendeoxycholic acid is the most potent natural bile acid at stimulating the nuclear bile acid receptor, farnesoid X receptor (FXR). The transcription of many genes is activated by FXR.



https://en.wikipedia.org/wiki/Chenodeoxycholic_acid

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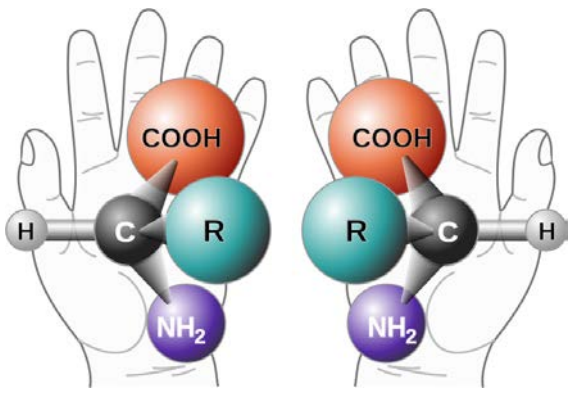
Chirality

Chirality is a property of asymmetry important in several branches of science. The word chirality is derived from the Greek, χειρ (kheir), "hand", a familiar chiral object.

An object or a system is chiral if it is distinguishable from its mirror image. That is, it cannot be superposed onto it. Conversely, a mirror image of an achiral object, such as a sphere, cannot be distinguished from the object. A chiral object and its mirror image are called enantiomorphs (Greek opposite forms) or, when referring to molecules, enantiomers. A non-chiral object is called achiral (sometimes also amphichiral) and can be superposed on its mirror image. If the object is non-chiral and is imagined as being colored blue and its mirror image is imagined as colored yellow, then by a series of rotations and translations the two can be superposed producing green with none of the original colors remaining.

The term was first used by Lord Kelvin in 1893 in the second Robert Boyle Lecture at the Oxford University Junior Scientific Club which was published in 1894:
I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.

Human hands are perhaps the most universally recognized example of chirality: The left hand is a non-superimposable mirror image of the right hand. No matter how the two hands are oriented, it is impossible for all the major features of both hands to coincide across all axes. This difference in symmetry becomes obvious if someone attempts to shake the right hand of a person using their left hand, or if a left-handed glove is placed on a right hand. In mathematics chirality is the property of a figure that is not identical to its mirror image.



https://commons.wikimedia.org/wiki/File:Chirality_with_hands.svg

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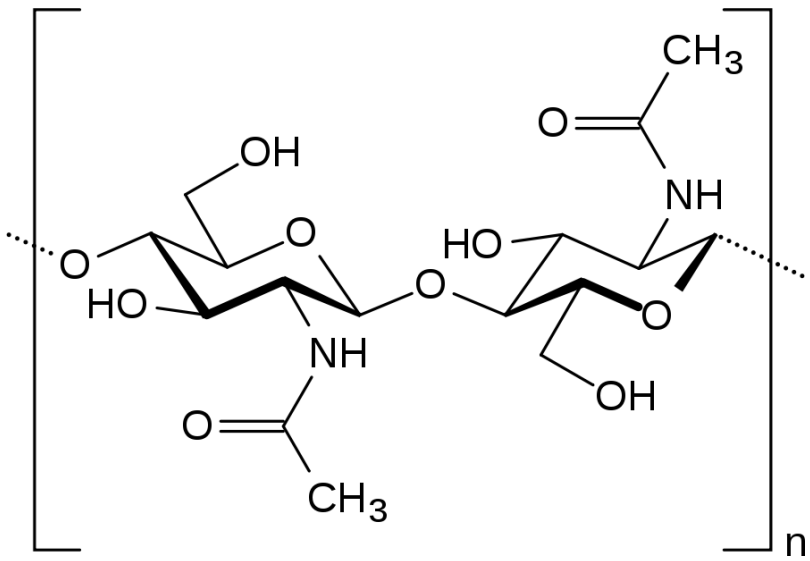
Chitin

Chitin $(C_8H_{13}O_5N)n$ is a long-chain polymer of an N-acetylglucosamine, a derivative of glucose, and is found in many places throughout the natural world. It is a characteristic component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulae of molluscs, and the beaks and internal shells of cephalopods, including squid and octopuses and on the scales and other soft tissues of fish and lissamphibians. The structure of chitin is comparable to the polysaccharide cellulose, forming crystalline nanofibrils or whiskers. In terms of function, it may be compared to the protein keratin.



https://en.wikipedia.org/wiki/Chitin

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Chlorophyll

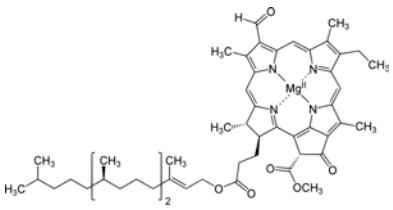
Chlorophyll (also chlorophyl) is a term used for several closely related green pigments found in cyanobacteria and the chloroplasts of algae and plants. Its name is derived from the Greek words χλωρός, chloros ("green") and φύλλον, phyllon ("leaf"). Chlorophyll is an extremely important biomolecule, critical in photosynthesis, which allows plants to absorb energy from light. Chlorophyll absorbs light most strongly in the blue portion of the electromagnetic spectrum, followed by the red portion. Conversely, it is a poor absorber of green and near-green portions of the spectrum which it reflects, hence the green color of chlorophyll-containing tissues.

Chlorophyll molecules are specifically arranged in and around photosystems that are embedded in the thylakoid membranes of chloroplasts. In these complexes, chlorophyll serves two primary functions. The function of the vast majority of chlorophyll (up to several hundred molecules per photosystem) is to absorb light and transfer that light energy by resonance energy transfer to a specific chlorophyll pair in the reaction center of the photosystems. The two currently accepted photosystem units are photosystem II and photosystem I, which have their own distinct reaction centers, named P_{680} and P_{700}, respectively. These centers are named after the wavelength (in nanometers) of their red-peak absorption maximum. The identity, function and spectral properties of the types of chlorophyll in each photosystem are distinct and determined by each other and the protein structure surrounding them. Once extracted from the protein into a solvent (such as acetone or methanol), these chlorophyll pigments can be separated into chlorophyll a and chlorophyll b.

The function of the reaction center of chlorophyll is to absorb light energy and transfer it to other parts of the photosystem. The absorbed energy of the photon is transferred to an electron in a process called charge separation. The removal of the electron from the chlorophyll is an oxidation reaction. The chlorophyll donates the high energy electron to a series of molecular intermediates called an electron transport chain. The charged reaction center of chlorophyll (P_{680}^+) is then reduced back to its ground state by accepting an electron stripped from water. The electron that reduces P_{680}^+ ultimately comes from the oxidation of water into O_2 and H^+ through several intermediates. This reaction is how photosynthetic organisms such as plants produce O_2 gas, and is the source for practically all the O_2 in Earth's atmosphere. Photosystem I typically works in series with Photosystem II. Thus the P_{700}^+ of Photosystem I is usually reduced as it accepts the electron, via many intermediates in the thylakoid membrane, by electrons come, ultimately, from Photosystem II. Electron transfer reactions in the thylakoid membranes are complex, however, and the source of electrons used to reduce P_{700}^+ can vary.

The electron flow produced by the reaction center chlorophyll pigments is used to pump H^+ ions across the thylakoid membrane, setting up a chemiosmotic potential used mainly in the production of ATP (stored chemical energy) or to reduce $NADP^+$ to NADPH. NADPH is a universal agent used to reduce CO_2 into sugars as well as other biosynthetic reactions.

Reaction center chlorophyll–protein complexes are capable of directly absorbing light and performing charge separation events without other the assistance of other chlorophyll pigments, but the probability of that happening under a given light intensity is small. Thus, the other chlorophylls in the photosystem and antenna pigment proteins all cooperatively absorb and funnel light energy to the reaction center. Besides chlorophyll a, there are other pigments, called accessory pigments, which occur in these pigment–protein antenna complexes.



https://en.wikipedia.org/wiki/Chlorophyll

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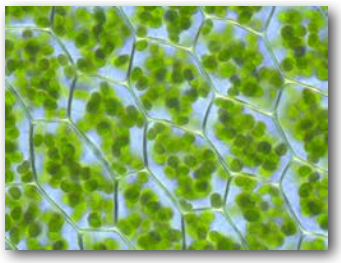
Chloroplasts

Chloroplasts are organelles, specialized subunits, in plant and algal cells. Chloroplasts' main role is to conduct photosynthesis, where the photosynthetic pigment chlorophyll captures the energy from sunlight and converts it and stores it in the energy-storage molecules ATP and NADPH while freeing oxygen from water. They then use the ATP and NADPH to make organic molecules from carbon dioxide in a process known as the Calvin cycle. Chloroplasts carry out a number of other functions, including fatty acid synthesis, much amino acid synthesis, and the immune response in plants.

A chloroplast is one of three types of plastids, characterized by its high concentration of chlorophyll, the other two types, the leucoplast and the chromoplast, contain little chlorophyll and do not carry out photosynthesis.

Chloroplasts are highly dynamic—they circulate and are moved around within plant cells, and occasionally pinch in two to reproduce. Their behavior is strongly influenced by environmental factors like light color and intensity. Chloroplasts, like mitochondria, contain their own DNA, which is thought to be inherited from their ancestor—a photosynthetic cyanobacterium that was engulfed by an early eukaryotic cell. Chloroplasts cannot be made by the plant cell and must be inherited by each daughter cell during cell division.

With one exception (the amoeboid *Paulinella chromatophora*), all chloroplasts can probably be traced back to a single endosymbiotic event, when a cyanobacterium was engulfed by the eukaryote. Despite this, chloroplasts can be found in an extremely wide set of organisms, some not even directly related to each other—a consequence of many secondary and even tertiary endosymbiotic events.



https://en.wikipedia.org/wiki/Chloroplast

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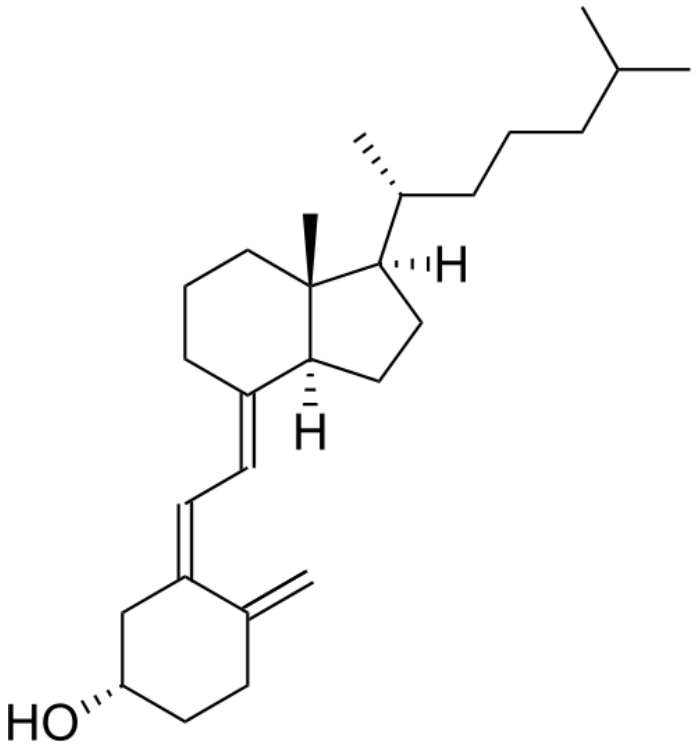
Cholecalciferol

Cholecalciferol (vitamin D_3) is one of the five forms of vitamin D. It is a secosteroid, that is, a steroid molecule with one ring open. Cholecalciferol is inactive: it is converted to its active form by two hydroxylations: the first in the liver, the second in the kidney, to form calcitriol, whose action is mediated by the vitamin D receptor, a nuclear receptor which regulates the synthesis of hundreds of enzymes and is present in virtually every cell in the body.



https://en.wikipedia.org/wiki/Cholecalciferol

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Cholesterol

Cholesterol, from the Ancient Greek chole- (bile) and stereos (solid) followed by the chemical suffix -ol for an alcohol, is an organic molecule. It is a sterol (or modified steroid), a lipid molecule and is biosynthesized by all animal cells because it is an essential structural component of all animal (not plant or bacterial) cell membranes that is required to maintain both membrane structural integrity and fluidity. Cholesterol enables animal cells to dispense with a cell wall to protect membrane integrity and cell viability, thus allowing them to change shape and move about (unlike bacteria and plant cells which are restricted by their cell walls).

In addition to its importance for animal cell structure, cholesterol also serves as a precursor for the biosynthesis of steroid hormones and bile acids. Cholesterol is the principal sterol synthesized by all animals. In vertebrates the hepatic cells typically produce greater amounts than other cells. It is absent among prokaryotes (bacteria and archaea), although there are some exceptions such as Mycoplasma, which require cholesterol for growth.

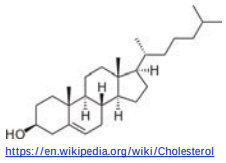
Cholesterol, given that it composes about 30% of all animal cell membranes, is required to build and maintain membranes; and modulates membrane fluidity over the range of physiological temperatures. The hydroxy group on cholesterol interacts with the polar head groups of the membrane phospholipids and sphingolipids, while the bulky steroid and the hydrocarbon chain are embedded in the membrane, alongside the nonpolar fatty-acid chain of the other lipids. Through the interaction with the phospholipid fatty-acid chains, cholesterol increases membrane packing, which both:

(a) alters membrane fluidity and
(b) maintains membrane integrity so that animal cells do not need to build cell walls (like plants and most bacteria)
allowing animal cells to change shape and animals to move. The structure of the tetracyclic ring of cholesterol contributes to the fluidity of the cell membrane as the molecule is in a trans conformation making all but the side chain of cholesterol rigid and planar. In this structural role, cholesterol also reduces the permeability of the plasma membrane to neutral solutes, hydrogen ions, and sodium ions.

Within the cell membrane, cholesterol also functions in intracellular transport, cell signaling and nerve conduction. Cholesterol is essential for the structure and function of invaginated caveolae and clathrin-coated pits, including caveola-dependent and clathrin-dependent endocytosis. The role of cholesterol in such endocytosis can be investigated by using methyl β cyclodextrin (MβCD) to remove cholesterol from the plasma membrane. Recent studies show that cholesterol is also implicated in cell signaling processes, assisting in the formation of lipid rafts in the plasma membrane. Lipid raft formation brings receptor proteins in close proximity with high concentrations of second messenger molecules. Cholesterol & phospholipids, both electrical insulators, in multiple layers, can facilitate speed of transmission of electrical impulses along nerve tissue. For many neuron fibers, a myelin sheath, rich in cholesterol, since it is derived from compacted layers of Schwann cell membrane, provides insulation for more efficient conduction of impulses. Demyelination (loss of some of these schwann cells) is believed to be part of the basis for multiple sclerosis.

Within cells, cholesterol is also a precursor molecule for several biochemical pathways. For example, it is the precursor molecule for the synthesis of vitamin D and all steroid hormones, including the adrenal gland hormones cortisol and aldosterone, as well as the sex hormones progesterone, estrogens, and testosterone, and their derivatives.

The liver excretes cholesterol into biliary fluids, which is then stored in the gallbladder. Bile contains bile salts, which solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins, A, D, E, and K.



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Cholesteryl Esters

Cholesteryl ester, a dietary lipid, is an ester of cholesterol. The ester bond is
tween the carboxylate group of a fatty acid and the hydroxyl group of choles
lesteryl esters have a lower solubility in water due to their increased hydrop
They are hydrolyzed by pancreatic enzymes, cholesterol esterase, to produc
terol and free fatty acids. They are associated with atherosclerosis.

https://en.wikipedia.org/wiki/Cholesteryl_ester

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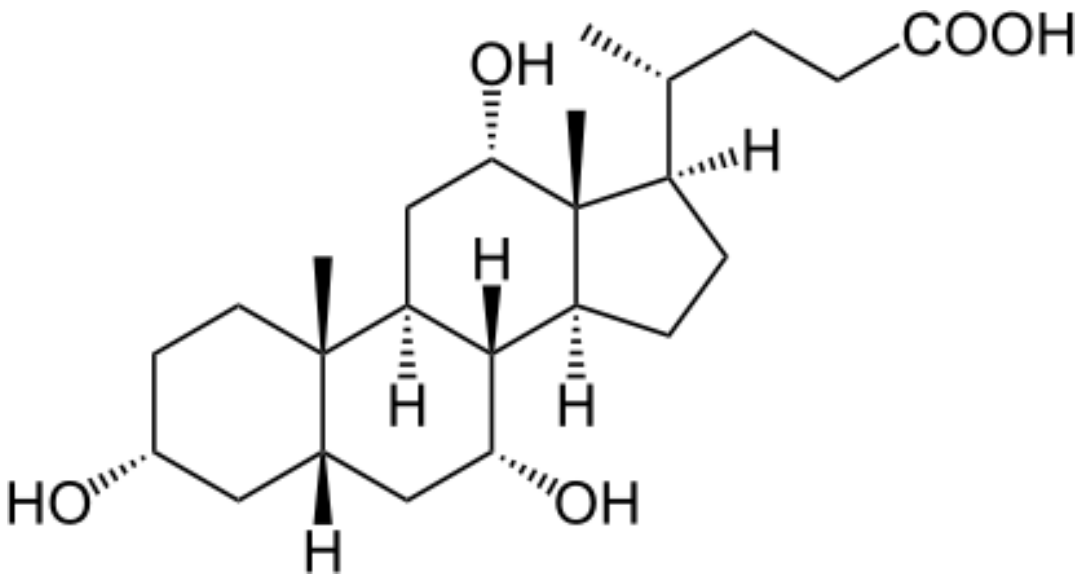
Cholic Acid

Cholic acid, also known as 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid is a primary bile acid that is insoluble in water (soluble in alcohol and acetic acid), it is a white crystalline substance. Salts of cholic acid are called cholates. Cholic acid, along with chenodeoxycholic acid, is one of the two major bile acids produced by the liver, where it is synthesized from cholesterol. These two major bile acids are roughly equal in concentration in humans. Derivatives are made from cholyl-CoA, which exchanges its CoA with either glycine, or taurine, yielding glycocholic and taurocholic acid, respectively.

Cholic acid downregulates cholesterol-7-α-hydroxylase (rate-limiting step in bile acid synthesis), and cholesterol does the opposite. This is why chenodeoxycholic acid, and not cholic acid, can be used to treat gallstones (because decreasing bile acid synthesis would supersaturate the stones even more).



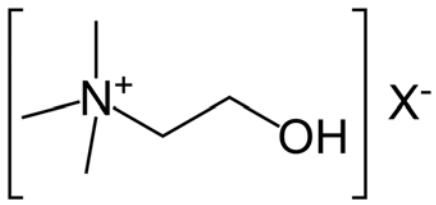
https://en.wikipedia.org/wiki/Cholic_acid

Choline

Choline is a water-soluble nutrient. It is usually grouped within the B-complex vitamins. Choline generally refers to the various quaternary ammonium salts containing the N,N,N-trimethylethanolammonium cation. (X– on the right denotes an undefined counteranion.) The cation appears in the head groups of phosphatidylcholine and sphingomyelin, two classes of phospholipid that are abundant in cell membranes. Choline is the precursor molecule for the neurotransmitter acetylcholine, which is involved in many functions including memory and muscle control.

Some animals must consume choline through their diet to remain healthy. To humans, choline is an essential nutrient, as its role in reducing the risk of neural tube defects, fatty liver disease, and other pathologies has been documented. Furthermore, while methionine and folate are known to interact with choline in the methylation of homocysteine to produce methionine, recent studies have shown that choline deficiency may have adverse effects, even when sufficient amounts of methionine and folate are present. It is used in the synthesis of components in cell membranes. The 2005 National Health and Nutrition Examination Survey stated that only 2% of postmenopausal women consume the recommended intake for choline.

Choline and its metabolites are needed for three main physiological purposes: structural integrity and signaling roles for cell membranes, cholinergic neurotransmission (acetylcholine synthesis), and a major source for methyl groups via its metabolite, trimethylglycine (betaine), which participates in the S-adenosylmethionine (SAMe) synthesis pathways.



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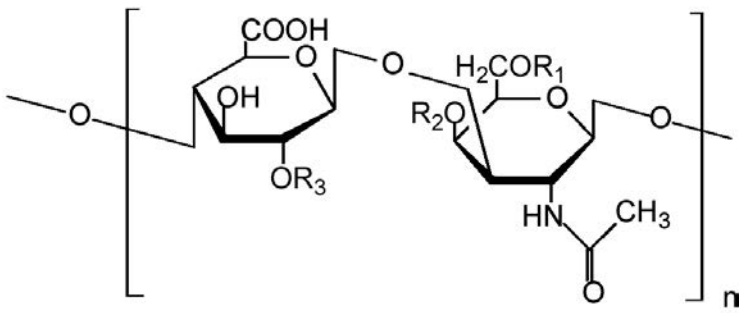
Chondroitin Sulfate

Chondroitin sulfate is a sulfated glycosaminoglycan (GAG) composed of a chain of alternating sugars (N-acetylgalactosamine and glucuronic acid). It is usually found attached to proteins as part of a proteoglycan. A chondroitin chain can have over 100 individual sugars, each of which can be sulfated in variable positions and quantities. Chondroitin sulfate is an important structural component of cartilage and provides much of its resistance to compression. Along with glucosamine, chondroitin sulfate has become a widely used dietary supplement for treatment of osteoarthritis.

The effect of chondroitin sulfate in patients with osteoarthritis is likely the result of a number of reactions including its anti-inflammatory activity, the stimulation of the synthesis of proteoglycans and hyaluronic acid, and the decrease in catabolic activity of chondrocytes inhibiting the synthesis of proteolytic enzymes, nitric oxide, and other substances that contribute to damage cartilage matrix and cause death of articular chondrocytes. A recent review summarizes data from relevant reports describing the biochemical basis of the effect of chondroitin sulfate on osteoarthritis articular tissues. The rationale behind the use of chondroitin sulfate is based on the belief that osteoarthritis is associated with a local deficiency or degradation of natural substances, including internal chondroitin sulfate.

Recently, new mechanisms of action have been described for chondroitin sulfate. In an *in vitro* study, chondroitin sulfate reduced the IL-1β-induced nuclear factor-kB (NF-κB) translocation in chondrocytes. In addition, chondroitin sulfate has recently shown a positive effect on osteoarthritic structural changes occurred in the subchondral bone.



https://en.wikipedia.org/wiki/Chondroitin_sulfate

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Chorismate Mutase

Chorismate mutase (EC 5.4.99.5) is an enzyme that catalyzes the chemical
the conversion of chorismate to prephenate in the pathway to the productio
ylalanine and tyrosine, also known as the shikimate pathway.

Chorismate mutase is found at a branch point in the pathway. The enzyme
the substrate, chorismate to the biosynthesis of tyrosine and phenylalanine
from tryptophan. Its role in maintaining the balance of these aromatic ami
the cell is vital. This is the single known example of a naturally occurring en
lyzing a pericyclic reaction. Chorismate mutase is only found in fungi, bacte
higher plants. This protein may use the morpheein model of allosteric regu

https://en.wikipedia.org/wiki/Chorismate_mutase

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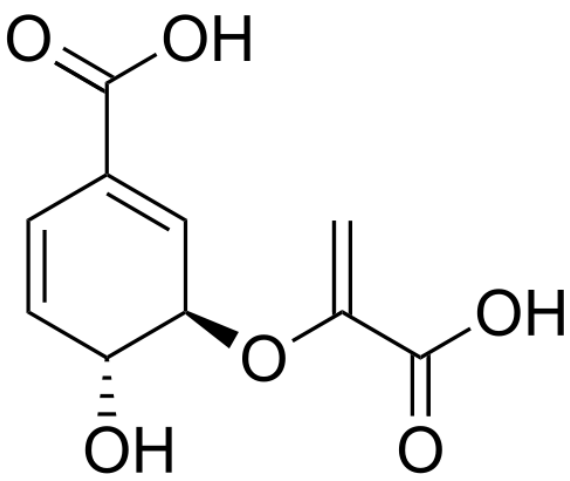
Chorismic Acid

Chorismic acid, more commonly known as its anionic form chorismate, is an important biochemical intermediate in plants and microorganisms. The name chorismic acid derives from a classical Greek word, χωρίζω meaning "to separate", because the compound plays a role as a branch-point in aromatic amino acid biosynthesis. It is a precursor for:

- The aromatic amino acids phenylalanine, tryptophan, and tyrosine
- Indole, indole derivatives and tryptophan
- 2,3-Dihydroxybenzoic acid (DHB) used for enterobactin biosynthesis
- The plant hormone salicylic acid
- Many alkaloids and other aromatic metabolites.
- The folate precursor para-aminobenzoate (pABA)
- The biosynthesis of Vitamin K and folate in plants and microorganisms.



https://en.wikipedia.org/wiki/Chorismic_acid

Related Glossary Terms

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Christian Bohr

Christian Harald Lauritz Peter Emil Bohr (1855–1911) was a Danish physic
of the physicist and Nobel laureate Niels Bohr, as well as the mathematician
ball player Harald Bohr and grandfather of another physicist and Nobel lau
Bohr. He married Ellen Adler in 1881.

In 1891, he was the first to characterize dead space. In 1903, Christian Boh
the phenomenon, now called the Bohr effect, whereby hydrogen ions and ca
ide heterotopically decrease hemoglobin's oxygen-binding affinity. This reg
creases the efficiency of oxygen release by hemoglobin in tissues, like active
sue, where rapid metabolization has produced relatively high concentration
gen ions and carbon dioxide.

https://en.wikipedia.org/wiki/Christian_Bohr

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Chapter 2 - Structure and Function: Proteins

Chromatin

Chromatin is a complex of macromolecules found in cells, consisting of DNA, protein, and RNA. The primary functions of chromatin are 1) to package DNA into a smaller volume to fit in the cell, 2) to reinforce the DNA macromolecule to allow mitosis, 3) to prevent DNA damage, and 4) to control gene expression and DNA replication. The primary protein components of chromatin are histones that compact the DNA. Chromatin is only found in eukaryotic cells (cells with defined nuclei). Prokaryotic cells have a different organization of their DNA (the prokaryotic chromosome equivalent is called genophore and is localized within the nucleoid region).

The structure of chromatin depends on several factors. The overall structure depends on the stage of the cell cycle. During interphase, the chromatin is structurally loose to allow access to RNA and DNA polymerases that transcribe and replicate the DNA. The local structure of chromatin during interphase depends on the genes present on the DNA: DNA coding genes that are actively transcribed ("turned on") are more loosely packaged and are found associated with RNA polymerases (referred to as euchromatin) while DNA coding inactive genes ("turned off") are found associated with structural proteins and are more tightly packaged (heterochromatin). Epigenetic chemical modification of the structural proteins in chromatin also alters the local chromatin structure, in particular chemical modifications of histone proteins by methylation and acetylation. As the cell prepares to divide, i.e. enters mitosis or meiosis, the chromatin packages more tightly to facilitate segregation of the chromosomes during anaphase. During this stage of the cell cycle this makes the individual chromosomes in many cells visible by optical microscope.

In general terms, there are three levels of chromatin organization:
1 - DNA wraps around histone proteins forming nucleosomes - the "beads on a string" structure (euchromatin).
2 - Multiple histones wrap into a 30 nm fiber consisting of nucleosome arrays in their most compact form (heterochromatin). (Definitively established to exist *in vitro*, the 30-nanometer fiber was not seen in recent X-ray studies of human mitotic chromosomes.)
3 - Higher-level DNA packaging of the 30 nm fiber into the metaphase chromosome (during mitosis and meiosis).

https://en.wikipedia.org/wiki/Chromatin

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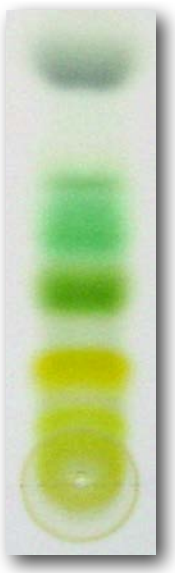
Chromatography

Chromatography (from Greek χρῶμα chroma which means "color" and γράφειν graphein "to write") is the collective term for a set of laboratory techniques for the separation of mixtures. The mixture is dissolved in a fluid called the mobile phase, which carries it through a structure holding another material called the stationary phase. The various constituents of the mixture travel at different speeds, causing them to separate. The separation is based on differential partitioning between the mobile and stationary phases. Subtle differences in a compound's partition coefficient result in differential retention on the stationary phase and thus changing the separation.

Chromatography was first employed in Russia by the Italian-born scientist Mikhail Tsvet in 1900. He continued to work with chromatography in the first decade of the 20th century, primarily for the separation of plant pigments such as chlorophyll, carotenes, and xanthophylls. Since these components have different colors (green, orange, and yellow, respectively) they gave the technique its name. New types of chromatography developed during the 1930s and 1940s made the technique useful for many separation processes.

Chromatography technique developed substantially as a result of the work of Archer John Porter Martin and Richard Laurence Millington Synge during the 1940s and 1950s. They established the principles and basic techniques of partition chromatography, and their work encouraged the rapid development of several chromatographic methods: paper chromatography, gas chromatography, and what would become known as high performance liquid chromatography. Since then, the technology has advanced rapidly. Researchers found that the main principles of Tsvet's chromatography could be applied in many different ways, resulting in the different varieties of chromatography described below. Advances are continually improving the technical performance of chromatography, allowing the separation of increasingly similar molecules.

Shown below - separation by thin layer chromatography.



https://en.wikipedia.org/wiki/Chromatography

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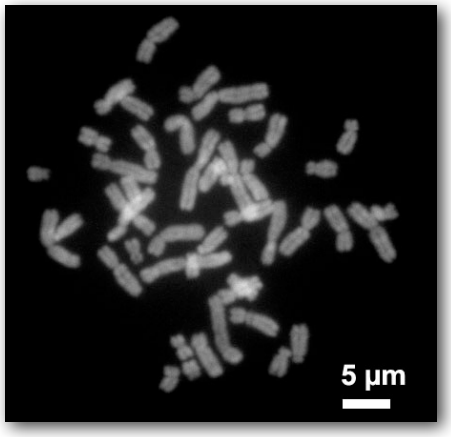
Chromosome

A chromosome (from Greek: χρῶμα color and σῶμα body) is a packaged and organized structure containing most of the DNA of a living organism. It is not usually found on its own, but rather is structured by being wrapped around protein complexes called nucleosomes, which consist of proteins called histones. The DNA in chromosomes is also associated with transcription (copying of genetic sequences) factors and several other macromolecules. During most of the duration of the cell cycle, a chromosome consists of one long double-stranded DNA molecule (with associated proteins).

Chromosomes in humans can be divided into two types: autosomes (body chromosome(s)) and allosome (sex chromosome(s)). Certain genetic traits are linked to a person's sex and are passed on through the sex chromosomes. The autosomes contain the rest of the genetic hereditary information. All act in the same way during cell division. Human cells have 23 pairs of chromosomes (22 pairs of autosomes and one pair of sex chromosomes), giving a total of 46 per cell. In addition to these, human cells have many hundreds of copies of the mitochondrial genome. Sequencing of the human genome has provided a great deal of information about each of the chromosomes.

Shown below - human chromosomes in metaphase.



https://en.wikipedia.org/wiki/Chromosome

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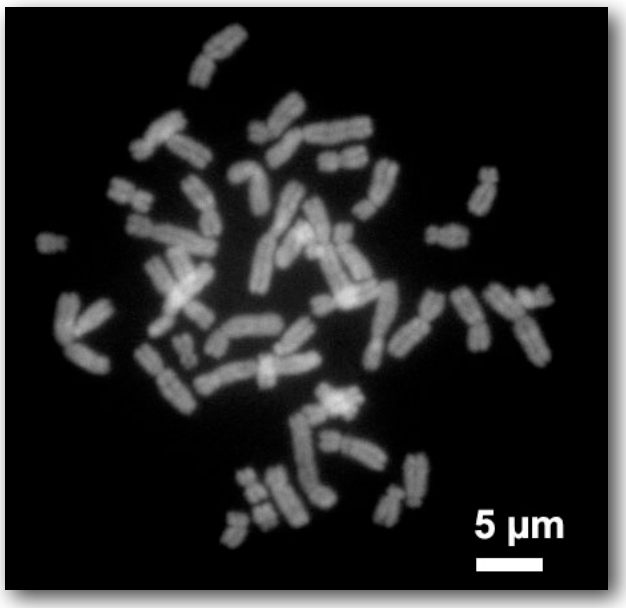

https://en.wikipedia.org/wiki/Chromosome

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Chylomicron Remnant

Chylomicrons transport lipids absorbed from the intestine to adipose, card
skeletal muscle tissue, where their triglyceride components are hydrolyzed
ity of the lipoprotein lipase, allowing the released free fatty acids to be abso
tissues. When a large portion of the triacylglycerol core has been hydrolyze
cron remnants are formed and are taken up by the liver, hereby transferrin
also to the liver.

https://en.wikipedia.org/wiki/Chylomicron

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Chylomicrons

Chylomicrons (from the Greek chylo, meaning juice or milky fluid, and micron, ing small particle) are lipoprotein particles that consist of triglycerides (85–92% pholipids (6–12%), cholesterol (1–3%), and proteins (1–2%). They transport die ids from the intestines to other locations in the body. Chylomicrons are one of th major groups of lipoproteins that enable fats and cholesterol to move within the based solution of the bloodstream.

https://en.wikipedia.org/wiki/Chylomicron

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Chymotrypsin

Chymotrypsin is a digestive enzyme component of pancreatic juice acting in the duodenum where it performs proteolysis, the breakdown of proteins and polypeptides. Chymotrypsin preferentially cleaves peptide amide bonds where the carboxyl side of the amide bond (the P1 position) is a large hydrophobic amino acid (tyrosine, tryptophan, and phenylalanine).

In Vivo, chymotrypsin is a proteolytic enzyme (Serine protease) acting in the digestive systems of many organisms. It facilitates the cleavage of peptide bonds by a hydrolysis reaction, which despite being thermodynamically favorable occurs extremely slowly in the absence of a catalyst. The main substrates of chymotrypsin include tryptophan, tyrosine, phenylalanine, and leucine residues in proteins. The enzyme cleaves at the carboxyl end of each of these in a substrate protein. Like many proteases, chymotrypsin will also hydrolyze amide bonds *in vitro*, a virtue that enabled the use of substrate analogs such as N-acetyl-L-phenylalanine p-nitrophenyl amide for enzyme assays.

Chymotrypsin cleaves peptide bonds by attacking the unreactive carbonyl group with a powerful nucleophile, the serine 195 residue located in the active site of the enzyme, which briefly becomes covalently bonded to the substrate, forming an enzyme-substrate intermediate. Along with histidine 57 and aspartic acid 102, this serine residue constitutes the catalytic triad of the active site.

https://en.wikipedia.org/wiki/Chymotrypsin

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Chymotrypsinogen

Chymotrypsinogen is a proteolytic enzyme and a precursor (zymogen) of the digestive enzyme chymotrypsin. It is a single polypetide chain consisting of 245 amino acid residues. It is synthesized in the acinar cells of the pancreas and stored inside membrane-bounded granules at the apex of the acinar cell. The cell is then stimulated by either a hormonal signal or a nerve impulse and the contents of the granules spill into a duct leading into the duodenum.

Chymotrypsinogen must be inactive until it gets to the digestive tract. This prevents damage to the pancreas or any other organs. It is activated into its active form by another enzyme called trypsin. This active form is called π-Chymotrypsin and is used to create α-Chymotrypsin. Trypsin cleaves the peptide bond in chymotrypsinogen between arginine-15 and isoleucine-16. This creates two peptides within π-chymotrypsin molecule held together by a disulfide bond. One of the π-chymotrypsin acts on another by breaking a leucine and serine peptide bond. The activated π-chymotrypsin reacts with other π-chymotrypsin molecules to cleave out two dipeptides, which are, Serine-14–Arginine-15 and Threonine-147–Asparagine-148. This reaction yields the α-chymotrypsin.

https://en.wikipedia.org/wiki/Chymotrypsinogen

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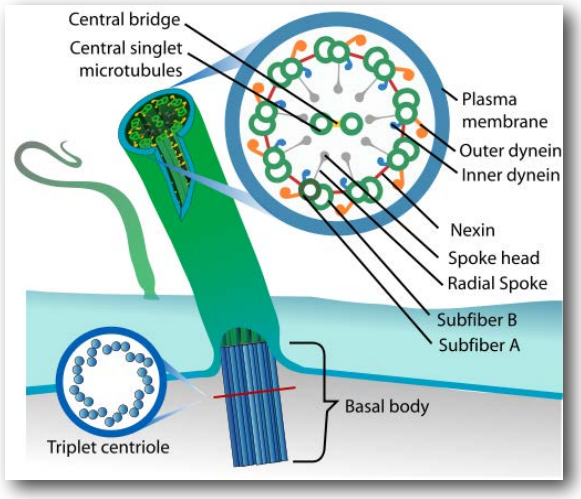
Cilia

A cilium (Latin for eyelash; the plural is cilia) is an organelle found in eukaryotic cells. Cilia are thick protuberances that project from the much larger cell body. There are two types of cilia: motile cilia and nonmotile, or primary cilia, which typically serve as sensory organelles. In eukaryotes, motile cilia and flagella together make up a group of organelles known as undulipodia. Eukaryotic cilia are structurally identical to eukaryotic flagella, although distinctions are sometimes made according to function and/or length. Biologists have various ideas about how the various flagella may have evolved.

Inside cilia and flagella is a microtubule-based cytoskeleton called the axoneme. The axoneme of primary cilia typically has a ring of nine outer microtubule doublets (called a 9+0 axoneme), and the axoneme of a motile cilium has two central microtubule singlets in addition to the nine outer doublets (called a 9+2 axoneme). The axonemal cytoskeleton acts as a scaffolding for various protein complexes and provides binding sites for molecular motor proteins such as kinesin II, that help carry proteins up and down the microtubules.

The dynein in the axoneme forms bridges between neighboring microtubule doublets. When ATP activates the motor domain of dynein, it attempts to walk along the adjoining microtubule doublet. This would force the adjacent doublets to slide over one another if not for the presence of Nexin between the microtubule doublets. And thus the force generated by dyenin is instead converted into a bending motion.

Cilia are formed through the process of ciliogenesis. The building blocks of the cilia such as tubulins and other partially assembled axonemal proteins are added to the ciliary tips which point away from the cell body. In most species bi-directional motility called intraflagellar transport (IFT) plays an essential role to move these building materials from the cell body to the assembly site. IFT also carries the disassembled material to be recycled from the ciliary tip back to the cell body. By regulating the equilibrium between these two IFT processes, the length of cilia can be maintained dynamically. Disassembly of cilia requires the action of the Aurora A kinase.



https://en.wikipedia.org/wiki/Cilium

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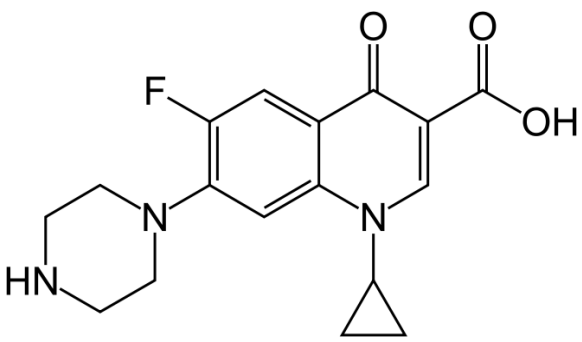
Ciprofloxacin

Ciprofloxacin is an antibiotic used to treat a number of bacterial infections. This includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others. For some infections it is used in addition to other antibiotics. It can be taken by mouth or used intravenously.

Ciprofloxacin is used to treat a wide variety of infections, including infections of bones and joints, endocarditis, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, and chancroid.

Ciprofloxacin only treats bacterial infections. It does not treat viral infections such as the common cold. For certain uses including acute sinusitis, lower respiratory tract infections and uncomplicated gonorrhea, ciprofloxacin is not considered a first-line agent.

Ciprofloxacin occupies an important role in treatment guidelines issued by major medical societies for the treatment of serious infections, especially those likely to be caused by Gram-negative bacteria, including Pseudomonas aeruginosa. For example, ciprofloxacin in combination with metronidazole is one of several first-line antibiotic regimens recommended by the Infectious Diseases Society of America for the treatment of community-acquired abdominal infections in adults. It also features prominently in treatment guidelines for acute pyelonephritis, complicated or hospital-acquired urinary tract infection, acute or chronic prostatitis, certain types of endocarditis, certain skin infections, and prosthetic joint infections.



https://en.wikipedia.org/wiki/Ciprofloxacin

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Circular Dichroism

Circular dichroism (CD) is dichroism involving circularly polarized light, i.e., the differential absorption of left- and right-handed light. Left-hand circular (LHC) and right-hand circular (RHC) polarized light represent two possible spin angular momentum states for a photon, and so circular dichroism is also referred to as dichroism for spin angular momentum.

In general, this phenomenon will be exhibited in absorption bands of any optically active molecule. As a consequence, circular dichroism is exhibited by biological molecules, because of their dextrorotary and levorotary components. Even more important is that a secondary structure will also impart a distinct CD to its respective molecules. Therefore, the α helix of proteins and the double helix of nucleic acids have CD spectral signatures representative of their structures. The capacity of CD to give a representative structural signature makes it a powerful tool in modern biochemistry with applications that can be found in virtually every field of study.

CD is closely related to the optical rotatory dispersion (ORD) technique, and is generally considered to be more advanced. CD is measured in or near the absorption bands of the molecule of interest, while ORD can be measured far from these bands. CD's advantage is apparent in the data analysis. Structural elements are more clearly distinguished since their recorded bands do not overlap extensively at particular wavelengths as they do in ORD. In principle these two spectral measurements can be interconverted through an integral transform (Kramers–Kronig relation), if all the absorptions are included in the measurements.

https://en.wikipedia.org/wiki/Circular_dichroism

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Circular DNA

Circular DNA is DNA that forms a closed loop and therefore has no free en
rial chromosomes, mitochondrial chromosomes, many viruses, and most p
plasmids exist as circles.

https://en.wikipedia.org/wiki/Circular_DNA

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Chapter 2 - Structure and Function: Nucleic Acids

Citrate

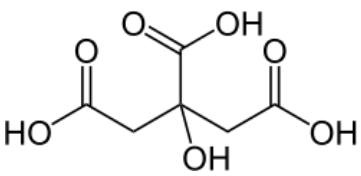
Citric acid is a weak organic tribasic acid. It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms.

Citrate is an intermediate in the citric acid cycle, a central metabolic pathway for animals, plants and bacteria. Citrate synthase catalyzes the condensation of oxaloacetate with acetyl CoA to form citrate. Citrate then acts as the substrate for aconitase and is converted into aconitic acid. The cycle ends with regeneration of oxaloacetate. This series of chemical reactions is the source of two-thirds of the food-derived energy in higher organisms. Hans Adolf Krebs received the 1953 Nobel Prize in Physiology or Medicine for the discovery.

Some bacteria, notably *E. coli*, can produce and consume citrate internally as part of their citric acid cycle, but are unable to use it as food because they lack the enzymes required to import it into the cell. The acquisition by these bacteria, after tens of thousands of generations, of the ability to use citrate as food was studied by Lenski *et al,* to explore mechanisms of evolution under selective pressure (in this case, a citrate-containing culture medium with limited amounts of other foods). They found evidence that in this case the innovation occurred via an accumulation of several somewhat rare mutations, none of which by itself would confer the selective advantage, rather than by a single extremely rare mutation.

Citrate can be transported out of the mitochondria and into the cytoplasm, then broken down into acetyl-CoA for fatty acid synthesis and into oxaloacetate. Citrate is a positive modulator of this conversion, and allosterically regulates the enzyme acetyl-CoA carboxylase, which is the regulating enzyme in the conversion of acetyl-CoA into malonyl-CoA (the commitment step in fatty acid synthesis). In short, citrate is transported to the cytoplasm, converted to acetyl CoA, which is converted into malonyl CoA by the acetyl CoA carboxylase, which is allosterically modulated by citrate.

High concentrations of cytosolic citrate can inhibit phosphofructokinase, the catalyst of one of the rate-limiting steps of glycolysis. This effect is advantageous: high concentrations of citrate indicate that there is a large supply of biosynthetic precursor molecules, so there is no need for phosphofructokinase to continue to send molecules of its substrate, fructose 6-phosphate, into glycolysis. Citrate acts by augmenting the inhibitory effect of high concentrations of ATP, another sign that there is no need to carry out glycolysis.



https://en.wikipedia.org/wiki/Citric_acid

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Citrate Lyase

In the presence of ATP and Coenzyme A, citrate lyase (also called ATP citrate lyase) catalyzes the cleavage of citrate to yield acetyl CoA, oxaloacetate, ADP, and orthophosphate:

Citrate + ATP + CoA + H_2O <=> Oxaloacetate + Acetyl-CoA + ADP + P_i

ATP citrate lyase is the primary enzyme responsible for the synthesis of cytosolic acetyl-CoA in many tissues. The enzyme is a tetramer of apparently identical subunits. The product, acetyl-CoA, in animals serves several important biosynthetic pathways, including lipogenesis and cholesterogenesis. It is activated by insulin signaling. In plants, ATP citrate lyase generates the acetyl-CoA for cytosolically-synthesized metabolites. (Acetyl-CoA is not transported across subcellular membranes of plants.) These include: elongated fatty acids (used in seed oils, membrane phospholipids, the ceramide moiety of sphingolipids, cuticle, cutin, and suberin); flavonoids; malonic acid; acetylated phenolics, alkaloids, isoprenoids, anthocyanins, and sugars; and, mevalonate-derived isoprenoids (e.g., sesquiterpenes, sterols, brassinosteroids); malonyl and acyl-derivatives (d-amino acids, malonylated flavonoids, acylated, prenylated and malonated proteins). *De novo* fatty acid biosynthesis in plants is plastidic, thus ATP citrate lyase is not important for this pathway.

https://en.wikipedia.org/wiki/ATP_citrate_lyase

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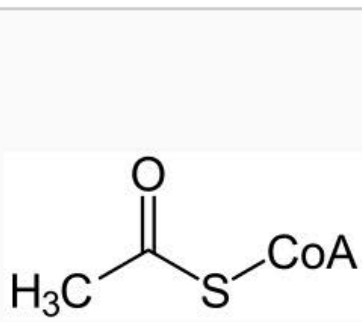
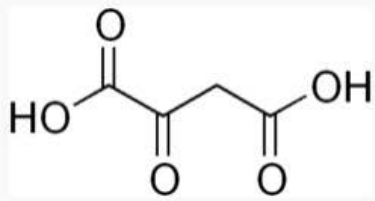
Citrate Synthase

Citrate synthase is localized within eukaryotic cells in the mitochondrial matrix, but is encoded by nuclear DNA rather than mitochondrial. It is synthesized using cytoplasmic ribosomes, then transported into the mitochondrial matrix. Citrate synthase is commonly used as a quantitative enzyme marker for the presence of intact mitochondria. Citrate synthase catalyzes the condensation reaction of the two-carbon acetate residue from acetyl coenzyme A and a molecule of four-carbon oxaloacetate to form the six-carbon citrate.

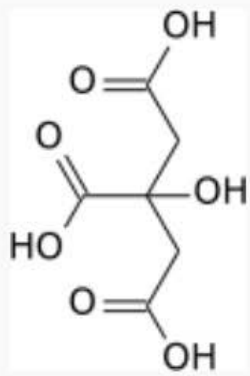
- acetyl-CoA + oxaloacetate + H_2O → citrate + CoA-SH



acetyl-CoA



Oxaloacetic acid



Citric acid

https://en.wikipedia.org/wiki/Citrate_synthase

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Citric Acid Cycle

The citric acid cycle – also known as the tricarboxylic acid (TCA) cycle or the Krebs cycle – is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidation of acetyl-CoA derived from carbohydrates, fats and proteins into carbon dioxide and chemical energy in the form of guanosine triphosphate (GTP). In addition, the cycle provides precursors of certain amino acids as well as the reducing agent NADH that is used in numerous other biochemical reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest established components of cellular metabolism and may have originated abiogenically.

The citric acid cycle is a key metabolic pathway that unifies carbohydrate, fat, and protein metabolism. The reactions of the cycle are carried out by 8 enzymes that completely oxidize acetate, in the form of acetyl-CoA, into two molecules each of carbon dioxide and water. Through catabolism of sugars, fats, and proteins, a two-carbon organic product acetate in the form of acetyl-CoA is produced which enters the citric acid cycle.

The reactions of the cycle also convert three equivalents of nicotinamide adenine dinucleotide (NAD^+) into three equivalents of reduced NAD^+ (NADH), one equivalent of flavin adenine dinucleotide (FAD) into one equivalent of $FADH_2$, and one equivalent each of guanosine diphosphate (GDP) and inorganic phosphate (P_i) into one equivalent of guanosine triphosphate (GTP). The NADH and $FADH_2$ generated by the citric acid cycle are in turn used by the oxidative phosphorylation pathway to generate energy-rich adenosine triphosphate (ATP).

One of the primary sources of acetyl-CoA is from the breakdown of sugars by glycolysis which yield pyruvate that in turn is decarboxylated by the enzyme pyruvate dehydrogenase generating acetyl-CoA according to the following reaction scheme:

Pyruvate + CoASH + NAD^+ → Acetyl-CoA + NADH + CO_2

The product of this reaction, acetyl-CoA, is the starting point for the citric acid cycle. Acetyl-CoA may also be obtained from the oxidation of fatty acids. Below is a schematic outline of the cycle:

- The citric acid cycle begins with the transfer of a two-carbon acetyl group from acetyl-CoA to the four-carbon acceptor compound (oxaloacetate) to form a six-carbon compound (citrate).
- The citrate then goes through a series of chemical transformations, losing two carboxyl groups as CO_2. The carbons lost as CO_2 originate from what was oxaloacetate, not directly from acetyl-CoA. The carbons donated by acetyl-CoA become part of the oxaloacetate carbon backbone after the first turn of the citric acid cycle. Loss of the acetyl-CoA-donated carbons as CO_2 requires several turns of the citric acid cycle. However, because of the role of the citric acid cycle in anabolism, they might not be lost, since many TCA cycle intermediates are also used as precursors for the biosynthesis of other molecules.
- Most of the energy made available by the oxidative steps of the cycle is transferred as energy-rich electrons to NAD^+, forming NADH. For each acetyl group that enters the citric acid cycle, three molecules of NADH are produced.
- Electrons are also transferred to the electron acceptor Q, forming QH_2.
- At the end of each cycle, the four-carbon oxaloacetate has been regenerated, and the cycle continues.

https://en.wikipedia.org/wiki/Citric_acid_cycle

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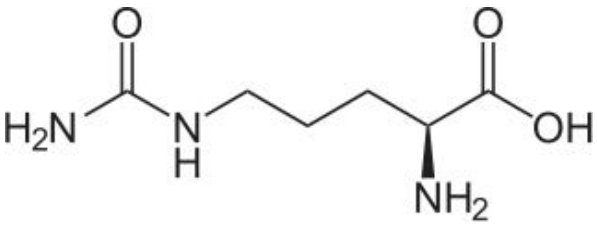
Citrulline

The organic compound citrulline is an α-amino acid. It is a key intermediate in the urea cycle, the pathway by which mammals excrete ammonia. In the body, citrulline is produced as a byproduct of the enzymatic production of nitric oxide from the amino acid arginine, catalyzed by nitric oxide synthase. This is an essential reaction in the body because nitric oxide is an important vasodilator required for regulating blood pressure.

Several proteins contain citrulline as a result of a posttranslational modification. These citrulline residues are generated by a family of enzymes called peptidylarginine deiminases (PADs), which convert arginine into citrulline in a process called citrullination or deimination. Proteins that normally contain citrulline residues include myelin basic protein (MBP), filaggrin, and several histone proteins, whereas other proteins, such as fibrin and vimentin are susceptible to citrullination during cell death and tissue inflammation.

Patients with rheumatoid arthritis often have detectable antibodies against proteins containing citrulline. Although the origin of this immune response is not known, detection of antibodies reactive with citrulline (anti-citrullinated protein antibodies) containing proteins or peptides is now becoming an important help in the diagnosis of rheumatoid arthritis.

Circulating citrulline concentration is, in humans, a biomarker of intestinal functionality.



https://en.wikipedia.org/wiki/Citrulline

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Clamp Loader

Sliding clamps for DNA polymerases are loaded onto their associated DNA te
strands by specialized proteins known as "sliding clamp loaders", which also c
ble the clamps after replication has completed. The binding sites for these init
teins overlap with the binding sites for the DNA polymerase, so the clamp can
taneously associate with a clamp loader and with a polymerase. Thus the clam
not be actively disassembled while the polymerase remains bound. DNA clam
associate with other factors involved in DNA and genome homeostasis, such a
some assembly factors, Okazaki fragment ligases, and DNA repair proteins. A
proteins also share a binding site on the DNA clamp that overlaps with the cla
loader site, ensuring that the clamp will not be removed while any enzyme is s
ing on the DNA. The activity of the clamp loader requires ATP hydrolysis to "c
clamp around the DNA.

https://en.wikipedia.org/wiki/DNA_clamp#Assembly

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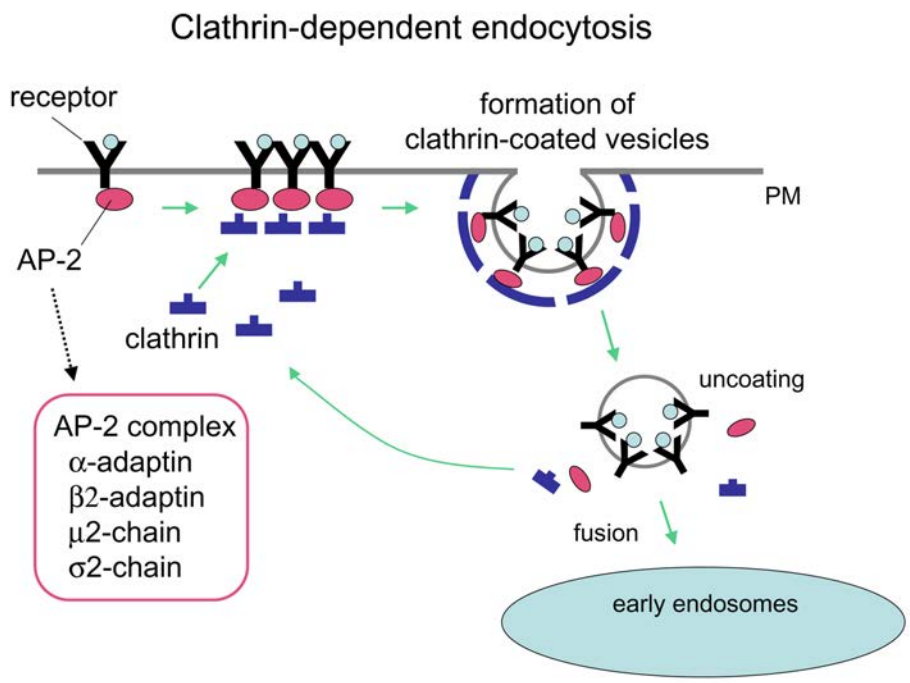
Clathrin

Clathrin is a protein that plays a major role in the formation of coated vesicles. Clathrin was first isolated and named by Barbara Pearse in 1975. It forms a triskelion shape composed of three clathrin heavy chains and three light chains. When the triskelia interact they form a polyhedral lattice that surrounds the vesicle. This is how clathrin gets its name, from the Latin clatratus meaning like a lattice. Coat-proteins, like clathrin, are used to build small vesicles in order to transport molecules within cells. The endocytosis and exocytosis of vesicles allows cells to communicate, to transfer nutrients, to import signaling receptors, to mediate an immune response after sampling the extracellular world, and to clean up the cell debris left by tissue inflammation. The endocytic pathway can be hijacked by viruses and other pathogens in order to gain entry to the cell during infection.



https://en.wikipedia.org/wiki/Clathrin

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Clot Formation

Coagulation (also known as blood clotting) is the process by which blood changes from a liquid to a gel, forming a clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin. Disorders of coagulation are disease states which can result in bleeding (hemorrhage or bruising) or obstructive clotting (thrombosis).

Coagulation is highly conserved throughout biology. In all mammals, coagulation involves both a cellular (platelet) and a protein (coagulation factor) component. The system in humans has been the most extensively researched and is the best understood.

Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining the vessel. Exposure of blood to the space under the endothelium initiates two processes: changes in platelets, and the exposure of subendothilial tissue factor to plasma Factor VII, which ultimately leads to fibrin formation. Platelets immediately form a plug at the site of injury. This is called primary hemostasis. Secondary hemostasis occurs simultaneously: Additional coagulation factors or clotting factors beyond Factor VII respond in a complex cascade to form fibrin strands, which strengthen the platelet plug.

https://en.wikipedia.org/wiki/Coagulation

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Chapter 2 - Structure & Function: Lipids

Clotting of Blood

Coagulation (also known as blood clotting) is the process by which blood changes from a liquid to a gel, forming a clot. It potentially results in hemostasis, the cessation of blood loss from a damaged vessel, followed by repair. The mechanism of coagulation involves activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin. Disorders of coagulation are disease states which can result in bleeding (hemorrhage or bruising) or obstructive clotting (thrombosis).

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https://en.wikipedia.org/wiki/Coagulation

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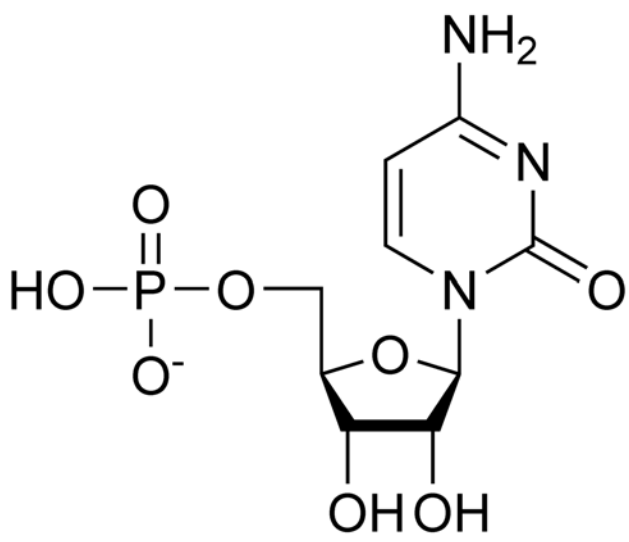
CMP

Cytidine monophosphate, also known as 5'-cytidylic acid or simply cytidylate, and abbreviated CMP, is a nucleotide that is used as a monomer in RNA. It is an ester of phosphoric acid with the nucleoside cytidine. CMP consists of the phosphate group, the pentose sugar ribose, and the nucleobase cytosine. Hence, a ribonucleoside monophosphate. As a substituent it takes the form of the prefix cytidylyl-.

CMP can be phosphorylated to cytidine diphosphate by the enzyme CMP kinase, with adenosine triphosphate or guanosine triphosphate donating the phosphate group. Since cytidine triphosphate is generated by amination of uridine triphosphate, the main source of CMP is from RNA being decomposed by RNAse.



https://en.wikipedia.org/wiki/Cytidine_monophosphate

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CMP Kinase

Cytidylate kinase (EC 2.7.4.14 - also called UMP/CMP kinase) is an enzyme t
lyzes the chemical reaction

ATP + (d)CMP ⇔ ADP + (d)CDP

This enzyme belongs to the family of transferases, specifically those transferr
phosphorus-containing groups (phosphotransferases) with a phosphate grou
tor. The systematic name of this enzyme class is ATP:CMP phosphotransfera
names in common use include: deoxycytidylate kinase, deoxycytidylate kinas
kinase, CTP:CMP phosphotransferase, dCMP kinase, deoxycytidine monoph
nase, UMP-CMP kinase, ATP:UMP-CMP phosphotransferase, and pyrimidin
side monophosphate kinase. This enzyme participates in pyrimidine metabo

https://en.wikipedia.org/wiki/Cytidylate_kinase

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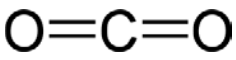
CO_2

Carbon dioxide (chemical formula CO_2) is a colorless and odorless gas vital to life on Earth. This naturally occurring chemical compound is composed of a carbon atom covalently double-bonded to two oxygen atoms.

Carbon dioxide exists in Earth's atmosphere as a trace gas at a concentration of about 0.04 percent (400 ppm) by volume. Natural sources include volcanoes, hot springs and geysers, and it is freed from carbonate rocks by dissolution in water and acids. Because carbon dioxide is soluble in water, it occurs naturally in groundwater, rivers and lakes, in ice caps and glaciers and also in seawater. It is present in deposits of petroleum and natural gas.

Atmospheric carbon dioxide is the primary source of carbon in life on Earth and its concentration in Earth's pre-industrial atmosphere since late in the Precambrian was regulated by photosynthetic organisms and geological phenomena. As part of the carbon cycle, plants, algae, and cyanobacteria use light energy to photosynthesize carbohydrate from carbon dioxide and water, with oxygen produced as a waste product.

Carbon dioxide (CO_2) is produced by all aerobic organisms when they metabolize carbohydrate and lipids to produce energy by respiration. It is returned to water via the gills of fish and to the air via the lungs of air-breathing land animals, including humans. Carbon dioxide is produced during the processes of decay of organic materials and the fermentation of sugars in bread, beer and winemaking. It is produced by combustion of wood, carbohydrates and fossil fuels such as coal, peat, petroleum and natural gas.



https://en.wikipedia.org/wiki/Carbon_dioxide

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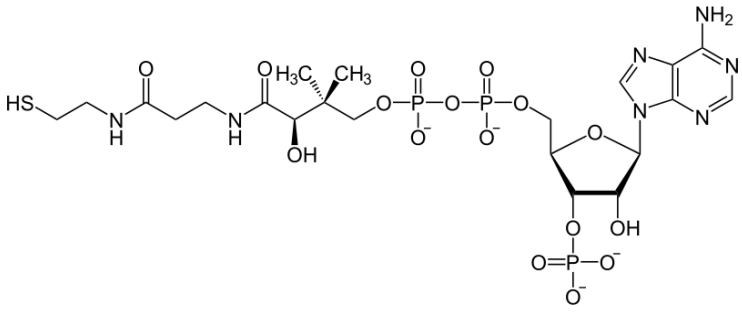
CoA-SH

Coenzyme A (CoA, CoASH, or HSCoA) is a coenzyme, notable for its role in the synthesis and oxidation of fatty acids, and the oxidation of pyruvate in the citric acid cycle. All genomes sequenced to date encode enzymes that use coenzyme A as a substrate, and around 4% of cellular enzymes use it (or a thioester, such as acetyl-CoA) as a substrate. In humans, CoA biosynthesis requires cysteine, pantothenate, and adenosine triphosphate (ATP).

Since coenzyme A is, in chemical terms, a thiol, it can react with carboxylic acids to form thioesters, thus functioning as an acyl group carrier. It assists in transferring fatty acids from the cytoplasm to mitochondria. A molecule of coenzyme A carrying an acetyl group is also referred to as acetyl-CoA. When it is not attached to an acyl group, it is usually referred to as 'CoASH' or 'HSCoA'.

Coenzyme A is also the source of the phosphopantetheine group that is added as a prosthetic group to proteins such as acyl carrier protein and formyltetrahydrofolate dehydrogenase.



https://en.wikipedia.org/wiki/Coenzyme_A

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Coated Pits

Caveolae (also called coated pits are a special type of lipid raft. They are small (50–100 nanometer) invaginations of the plasma membrane in many vertebrate cell types, especially in endothelial cells and adipocytes.

These flask-shaped structures are rich in proteins as well as lipids such as cholesterol and sphingolipids and have several functions in signal transduction. They are also believed to play a role in endocytosis, oncogenesis, and the uptake of pathogenic bacteria and certain viruses.

Formation and maintenance of caveolae is primarily due to the protein caveolin, a 21 kD protein. There are three homologous genes of caveolin expressed in mammalian cells: Cav1, Cav2 and Cav3. These proteins have a common topology: cytoplasmic N-terminus with scaffolding domain, long hairpin transmembrane domain and cytoplasmic C-terminus. Caveolins are synthesized as monomers and transported to the Golgi apparatus. During their subsequent transport through the secretory pathway, caveolins associate with lipid rafts and form oligomers (14-16 molecules). These oligomerized caveolins form the caveolae. The presence of caveolin leads to a local change in morphology of the membrane.

Caveolae are one source of clathrin-independent raft-dependent endocytosis. The ability of caveolins to oligomerize due to their oligomerization domains is necessary for formation of caveolar endocytic vesicles. The oligomerization leads to formation of caveolin-rich microdomains in the plasma membrane. Increased levels of cholesterol and insertion of scaffolding domain of caveolins to the plasma membrane then lead to expansion of the caveolar invagination and to formation of endocytic vesicle. Fission of the vesicle from the plasma membrane is then mediated by GTPase dynamin II which is localized at the neck of the budding vesicle. The released caveolar vesicle can fuse with early endosome or caveosome. The caveosome is an endosomal compartment with neutral pH which does not have early endosomal markers, however, contains molecules internalized by the caveolar endocytosis.

https://en.wikipedia.org/wiki/Caveolae

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Chapter 3 - Membranes: Other Considerations

Chapter 9 - Point by Point: Membranes

Coated Vesicles

Clathrin represents a perfect case of form following function. It performs c
in shaping rounded vesicles in the cytoplasm for intracellular trafficking. C
coated vesicles (CCV) selectively sort cargo at the cell membrane, *trans*-Go
and endosomal compartments for multiple membrane traffic pathways. Aft
buds into the cytoplasm, the coat rapidly disassembles, allowing the clathri
while the vesicle gets transported to a variety of locations.

https://en.wikipedia.org/wiki/Clathrin

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Coding Regions

The coding region of a gene, also known as the coding sequence or CDS (fro
DNA sequence), is that portion of a gene's DNA or RNA, composed of exons
for protein. The region is bounded nearer the 5' end by a start codon and ne
end with a stop codon. The coding region in mRNA is bounded by the five p
translated region (5'-UTR) and the three prime untranslated region (3'-UTR
are also parts of the exons. The CDS is that portion of an mRNA transcript t
lated by a ribosome. The coding region of an organism is the sum total of th
ism's genome that is composed of gene coding regions.

https://en.wikipedia.org/wiki/Coding_region

Related Glossary Terms

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Codon

The genome of an organism is inscribed in DNA, or, in the case of some viruses, RNA. The portion of the genome that codes for a protein or an RNA is called a gene. Those genes that code for proteins are composed of tri-nucleotide units called codons, each coding for a single amino acid.

A codon is defined by the initial nucleotide from which translation starts. For example, the string GGGAAACCC, if read from the first position, contains the codons GGG, AAA, and CCC. If read from the second position, it contains the codons GGA and AAC. If read starting from the third position, GAA and ACC. Every sequence can, thus, be read in its 5' → 3' direction in three reading frames, each of which will produce a different amino acid sequence (in the given example, Gly-Lys-Pro, Gly-Asn, or Glu-Thr, respectively). With double-stranded DNA, there are six possible reading frames, three in the forward orientation on one strand and three reverse on the opposite strand. The actual frame from which a protein sequence is translated is defined by a start codon, usually the first AUG codon in the mRNA sequence.

Translation starts with a chain initiation codon or start codon. Unlike stop codons, the codon alone is not sufficient to begin the process. Nearby sequences such as the Shine-Dalgarno sequence in *E. coli* and initiation factors are also required to start translation. The most common start codon is AUG, which is read as methionine or, in bacteria, as formylmethionine. Alternative start codons depending on the organism include "GUG" or "UUG". These codons normally represent valine and leucine, respectively, but as start codons they are translated as methionine or formylmethionine.

The three stop codons have been given names: UAG is amber, UGA is opal (sometimes also called umber), and UAA is ochre. "Amber" was named by discoverers Richard Epstein and Charles Steinberg after their friend Harris Bernstein, whose last name means "amber" in German. The other two stop codons were named "ochre" and "opal" in order to keep the "color names" theme. Stop codons are also called "termination" or "nonsense" codons. They signal release of the nascent polypeptide from the ribosome because there is no cognate tRNA that has anticodons complementary to these stop signals, and so a release factor binds to the ribosome instead.

Standard genetic code

1st base	2nd base								3rd base
	U		C		A		G		
U	UUU	(Phe/F) Phenylalanine	UCU	(Ser/S) Serine	UAU	(Tyr/Y) Tyrosine	UGU	(Cys/C) Cysteine	U
	UUC		UCC		UAC		UGC		C
	UUA	(Leu/L) Leucine	UCA		UAA	Stop (*Ochre*)	UGA	Stop (*Opal*)	A
	UUG		UCG		UAG	Stop (*Amber*)	UGG	(Trp/W) Tryptophan	G
C	CUU		CCU	(Pro/P) Proline	CAU	(His/H) Histidine	CGU	(Arg/R) Arginine	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	(Gln/Q) Glutamine	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	(Ile/I) Isoleucine	ACU	(Thr/T) Threonine	AAU	(Asn/N) Asparagine	AGU	(Ser/S) Serine	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	(Lys/K) Lysine	AGA	(Arg/R) Arginine	A
	AUG[A]	(Met/M) Methionine	ACG		AAG		AGG		G
G	GUU	(Val/V) Valine	GCU	(Ala/A) Alanine	GAU	(Asp/D) Aspartic acid	GGU	(Gly/G) Glycine	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	(Glu/E) Glutamic acid	GGA		A
	GUG		GCG		GAG		GGG		G

https://en.wikipedia.org/wiki/Genetic_code#Transfer_of_information_via_the_genetic_code

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Codons

The genome of an organism is inscribed in DNA, or, in the case of some viruses, RNA. The portion of the genome that codes for a protein or an RNA is called a gene. Those genes that code for proteins are composed of tri-nucleotide units called codons, each coding for a single amino acid.

A codon is defined by the initial nucleotide from which translation starts. For example, the string GGGAAACCC, if read from the first position, contains the codons GGG, AAA, and CCC; and, if read from the second position, it contains the codons GGA and AAC. If read starting from the third position, GAA and ACC. Every sequence can, thus, be read in its 5' → 3' direction in three reading frames, each of which will produce a different amino acid sequence (in the given example, Gly-Lys-Pro, Gly-Asn, or Glu-Thr, respectively). With double-stranded DNA, there are six possible reading frames, three in the forward orientation on one strand and three reverse on the opposite strand. The actual frame from which a protein sequence is translated is defined by a start codon, usually the first AUG codon in the mRNA sequence.

Translation starts with a chain initiation codon or start codon. Unlike stop codons, the codon alone is not sufficient to begin the process. Nearby sequences such as the Shine-Dalgarno sequence in *E. coli* and initiation factors are also required to start translation. The most common start codon is AUG, which is read as methionine or, in bacteria, as formylmethionine. Alternative start codons depending on the organism include "GUG" or "UUG"; these codons normally represent valine and leucine, respectively, but as start codons they are translated as methionine or formylmethionine.

The three stop codons have been given names: UAG is amber, UGA is opal (sometimes also called umber), and UAA is ochre. "Amber" was named by discoverers Richard Epstein and Charles Steinberg after their friend Harris Bernstein, whose last name means "amber" in German. The other two stop codons were named "ochre" and "opal" in order to keep the "color names" theme. Stop codons are also called "termination" or "nonsense" codons. They signal release of the nascent polypeptide from the ribosome because there is no cognate tRNA that has anticodons complementary to these stop signals, and so a release factor binds to the ribosome instead.

Standard genetic code

1st base	2nd base								3rd base
	U		C		A		G		
U	UUU	(Phe/F) Phenylalanine	UCU	(Ser/S) Serine	UAU	(Tyr/Y) Tyrosine	UGU	(Cys/C) Cysteine	U
	UUC		UCC		UAC		UGC		C
	UUA	(Leu/L) Leucine	UCA		UAA	Stop (*Ochre*)	UGA	Stop (*Opal*)	A
	UUG		UCG		UAG	Stop (*Amber*)	UGG	(Trp/W) Tryptophan	G
C	CUU		CCU	(Pro/P) Proline	CAU	(His/H) Histidine	CGU	(Arg/R) Arginine	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	(Gln/Q) Glutamine	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	(Ile/I) Isoleucine	ACU	(Thr/T) Threonine	AAU	(Asn/N) Asparagine	AGU	(Ser/S) Serine	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	(Lys/K) Lysine	AGA	(Arg/R) Arginine	A
	AUG[A]	(Met/M) Methionine	ACG		AAG		AGG		G
G	GUU	(Val/V) Valine	GCU	(Ala/A) Alanine	GAU	(Asp/D) Aspartic acid	GGU	(Gly/G) Glycine	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	(Glu/E) Glutamic acid	GGA		A
	GUG		GCG		GAG		GGG		G

https://en.wikipedia.org/wiki/Genetic_code#Transfer_of_information_via_the_genetic_code

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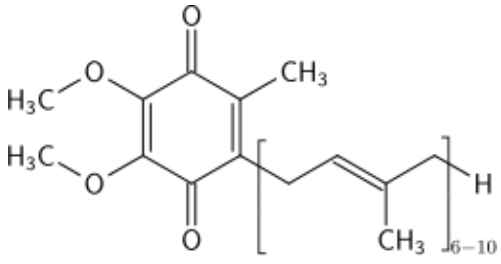
Coenzyme Q

Coenzyme Q_{10}, also known as ubiquinone, ubidecarenone, coenzyme Q, and abbreviated at times to CoQ_{10}, CoQ, or Q_{10} is a coenzyme that is ubiquitous in the bodies of most animals. It is a 1,4-benzoquinone, where Q refers to the quinone chemical group and 10 refers to the number of isoprenyl chemical subunits in its tail. This fat-soluble substance, which resembles a vitamin, is present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, which generates energy in the form of ATP.

There are three redox states of CoQ_{10}: fully oxidized (ubiquinone), semiquinone (ubisemiquinone), and fully reduced (ubiquinol). The capacity of this molecule to act as a 2 electron carrier (moving between the quinone and quinol form) and 1 electron carrier (moving between the semiquinone and one of these other forms) is central to its role in the electron transport chain, and as radical-scavenging antioxidant.



https://en.wikipedia.org/wiki/Coenzyme_Q10

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Coenzymes

A cofactor is a non-protein chemical compound that is required for the protein's biological activity to happen. These proteins are commonly enzymes, and cofactors can be considered "helper molecules" that assist in biochemical transformations. Cofactors can be subdivided into either one or more inorganic ions, or a complex organic or metalloorganic molecule called a coenzyme, most of which are derived from vitamins and from required organic nutrients in small amounts.

Organic cofactors are often vitamins or are made from vitamins. Many contain the nucleotide adenosine monophosphate (AMP) as part of their structures, such as ATP, coenzyme A, FAD, and NAD^+. This common structure may reflect a common evolutionary origin as part of ribozymes in an ancient RNA world. It has been suggested that the AMP part of the molecule can be considered to be a kind of "handle" by which the enzyme can "grasp" the coenzyme to switch it between different catalytic centers.

https://en.wikipedia.org/wiki/Cofactor_(biochemistry)

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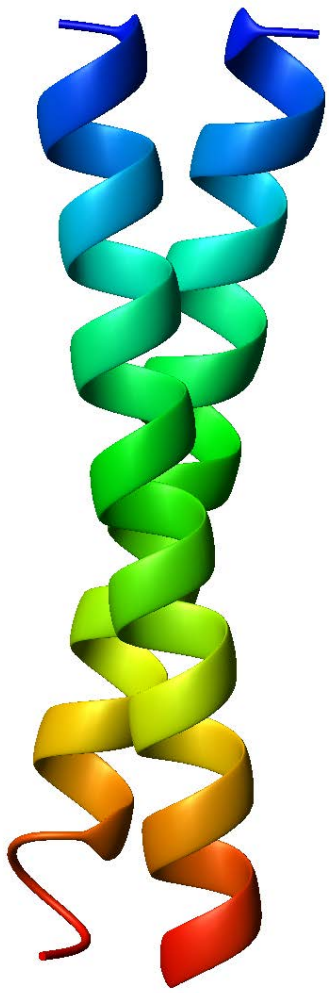
Coiled Coil

A coiled coil is a structural motif in proteins in which 2-7 α-helices are coiled together like the strands of a rope (dimers and trimers are the most common types). Many coiled coil-type proteins are involved in important biological functions such as the regulation of gene expression, e.g. transcription factors. Notable examples are the oncoproteins c-Fos and c-jun, as well as the muscle protein tropomyosin.



https://en.wikipedia.org/wiki/Coiled_coil

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Collagen

Collagen is the main structural protein in the extracellular space in the various connective tissues in animal bodies. As the main component of connective tissue, it is the most abundant protein in mammals, making up from 25% to 35% of the whole-body protein content. Depending upon the degree of mineralization, collagen tissues may be rigid (bone), compliant (tendon), or have a gradient from rigid to compliant (cartilage). Collagen, in the form of elongated fibrils, is mostly found in fibrous tissues such as tendons, ligaments and skin. It is also abundant in corneas, cartilage, bones, blood vessels, the gut, intervertebral discs and the dentin in teeth. In muscle tissue, it serves as a major component of the endomysium. Collagen constitutes one to two percent of muscle tissue, and accounts for 6% of the weight of strong, tendinous muscles. The fibroblast is the most common cell that creates collagen.

A single collagen molecule, tropocollagen, is used to make up larger collagen aggregates, such as fibrils. It is approximately 300 nm long and 1.5 nm in diameter, and it is made up of three polypeptide strands (called α peptides, see step 2), each of which has the conformation of a left-handed helix – this should not be confused with the right-handed α helix. These three left-handed helices are twisted together into a right-handed triple helix or "super helix", a cooperative quaternary structure stabilized by many hydrogen bonds. With type I collagen and possibly all fibrillar collagens, if not all collagens, each triple-helix associates into a right-handed super-super-coil referred to as the collagen microfibril. Each microfibril is interdigitated with its neighboring microfibrils to a degree that might suggest they are individually unstable, although within collagen fibrils, they are so well ordered as to be crystalline.

Three polypeptides coil to form tropocollagen. Many tropocollagens then bind together to form a fibril, and many of these then form a fiber. A distinctive feature of collagen is the regular arrangement of amino acids in each of the three chains of these collagen subunits. The sequence often follows the pattern Gly-Pro-X or Gly-X-Hyp, where X may be any of various other amino acid residues. Proline or hydroxyproline constitute about 1/6 of the total sequence. With glycine accounting for the 1/3 of the sequence, this means approximately half of the collagen sequence is not glycine, proline or hydroxyproline, a fact often missed due to the distraction of the unusual GX1X2 character of collagen α-peptides. The high glycine content of collagen is important with respect to stabilization of the collagen helix as this allows the very close association of the collagen fibers within the molecule, facilitating hydrogen bonding and the formation of intermolecular cross-links. This kind of regular repetition and high glycine content is found in only a few other fibrous proteins, such as silk fibroin.

https://en.wikipedia.org/wiki/Collagen

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Collagenases

Collagenases are enzymes that break the peptide bonds in collagen. They ass
stroying extracellular structures in the pathogenesis of bacteria such as Clost
They are considered a virulence factor, facilitating the spread of gas gangren
normally target the connective tissue in muscle cells and other body organs.

Collagen, a key component of the animal extracellular matrix, is made throu
age of pro-collagen by collagenase once it has been secreted from the cell. Th
large structures from forming inside the cell itself.

In addition to being produced by some bacteria, collagenase can be made by
as part of its normal immune response. This production is induced by cytoki
stimulate cells such as fibroblasts and osteoblasts, and can cause indirect tiss
age.

https://en.wikipedia.org/wiki/Collagenase

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Competitive Inhibition

Competitive inhibition is a form of enzyme inhibition where binding of the inhibitor to the active site on the enzyme prevents binding of the substrate and vice versa. Most competitive inhibitors function by binding reversibly to the active site of the enzyme. As a result, many sources state that this is the defining feature of competitive inhibitors. This, however, is a misleading oversimplification, as there are many possible mechanisms by which an enzyme may bind either the inhibitor or the substrate but never both at the same time. For example, allosteric inhibitors may display competitive, non-competitive, or uncompetitive inhibition.

In competitive inhibition, at any given moment, the enzyme may be bound to the inhibitor, the substrate, or neither, but it cannot bind both at the same time.
In virtually every case, competitive inhibitors bind in the same binding site as the substrate, but same-site binding is not a requirement. A competitive inhibitor could bind to an allosteric site of the free enzyme and prevent substrate binding, as long as it does not bind to the allosteric site when the substrate is bound. For example, strychnine acts as an allosteric inhibitor of the glycine receptor in the mammalian spinal cord and brain stem. Glycine is a major post-synaptic inhibitory neurotransmitter with a specific receptor site. Strychnine binds to an alternate site that reduces the affinity of the glycine receptor for glycine, resulting in convulsions due to lessened inhibition by the glycine.

In competitive inhibition, the maximum velocity (V_{max}) of the reaction is unchanged, while the apparent affinity of the substrate to the binding site is decreased (K_m increases). Any given competitive inhibitor concentration can be overcome by increasing the substrate concentration sufficiently.

https://en.wikipedia.org/wiki/Competitive_inhibition

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https://en.wikipedia.org/wiki/Competitive_inhibition

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Complex I

Complex I (EC 1.6.5.3) (also referred to as NADH:ubiquinone oxidoreductase or, especially in the context of the human protein, NADH dehydrogenase (ubiquinone)) is an enzyme of the respiratory chains of myriad organisms from bacteria to humans. It catalyzes the transfer of electrons from NADH to coenzyme Q_{10} (CoQ_{10}) and, in eukaryotes, it is located in the inner mitochondrial membrane. It is one of the "entry enzymes" of cellular respiration or oxidative phosphorylation in the mitochondria.

Complex I is the first enzyme of the mitochondrial electron transport chain. There are three energy-transducing enzymes in the electron transport chain - NADH:ubiquinone oxidoreductase (complex I), Coenzyme Q – cytochrome c reductase (complex III), and cytochrome c oxidase (complex IV). Complex I is the largest and most complicated enzyme of the electron transport chain.

The reaction catalyzed by complex I is:

$NADH + H^+ + CoQ + 4\ H^+in \rightarrow NAD^+ + CoQH_2 + 4\ H^+out$

In this process, the complex translocates four protons across the inner membrane per molecule of oxidized NADH, helping to build the electrochemical potential difference used to produce ATP.

The reaction can be reversed - referred to as aerobic succinate-supported NAD^+ reduction - in the presence of a high membrane potential, but the exact catalytic mechanism remains unknown.

Complex I may have a role in triggering apoptosis. In fact, there has been shown to be a correlation between mitochondrial activities and programmed cell death (PCD) during somatic embryo development.

The best-known inhibitor of complex I is rotenone (commonly used as an organic pesticide). Rotenone and rotenoids are isoflavonoids occurring in several genera of tropical plants such as Antonia (*Loganiaceae*), Derris and Lonchocarpus (*Faboideae*, *Fabaceae*). There have been reports of the indigenous people of French Guiana using rotenone-containing plants to fish - due to its ichthyotoxic effect - as early as the 17th century. Rotenone binds to the ubiquinone binding site of complex I as well as piericidin A, another potent inhibitor with a close structural homologue to ubiquinone.

https://en.wikipedia.org/wiki/NADH:ubiquinone_reductase_(H%2B-translocating)

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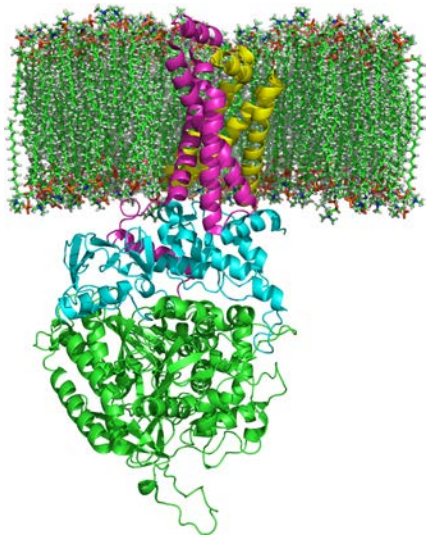
Complex II

Succinate dehydrogenase or succinate-coenzyme Q reductase (SQR) or respiratory Complex II is an enzyme complex, bound to the inner mitochondrial membrane of mammalian mitochondria and many bacterial cells. It is the only enzyme that participates in both the citric acid cycle and the electron transport chain. In step 6 of the citric acid cycle, SQR catalyzes the oxidation of succinate to fumarate with the reduction of ubiquinone to ubiquinol. This occurs in the inner mitochondrial membrane by coupling the two reactions together.

The fundamental role of succinate-coenzyme Q reductase in the electron transfer chain of mitochondria makes it vital in most multicellular organisms, removal of this enzyme from the genome has also been shown to be lethal at the embryonic stage in mice.
• SdhA mutations can lead to Leigh syndrome, mitochondrial encephalopathy, and optic atrophy.
• SdhB mutations can lead to tumorogenesis in chromaffin cells, causing hereditary paraganglioma and hereditary pheochromocytoma. Tumors tend to be malignant. It can also lead to decreased life-span and increased production of superoxide ions.
• SdhC mutations can lead to decreased life-span, increased production of superoxide ions, hereditary paraganglioma and hereditary pheochromocytoma. Tumors tend to be benign. These mutations are uncommon.
• SdhD mutations can lead to hereditary paraganglioma and hereditary pheochromocytoma. Tumors tend to be benign, and occur often in the head and neck regions. These mutations can also decrease life-span and increase production of superoxide ions.
Mammalian succinate dehydrogenase functions not only in mitochondrial energy generation, but also has a role in oxygen sensing and tumor suppression and, therefore, is the object of ongoing research.



https://en.wikipedia.org/wiki/Succinate_dehydrogenase

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Complex III

The coenzyme Q : cytochrome c — oxidoreductase, sometimes called the cytochrome bc1 complex, and at other times complex III, is the third complex in the electron transport chain (EC 1.10.2.2), playing a critical role in biochemical generation of ATP (oxidative phosphorylation). Complex III is a multisubunit transmembrane protein encoded by both the mitochondrial (cytochrome b) and the nuclear genomes (all other subunits). Complex III is present in the mitochondria of all animals and all aerobic eukaryotes and the inner membranes of most eubacteria. Mutations in Complex III cause exercise intolerance as well as multisystem disorders.

The reaction proceeds according to the following steps:

Round 1:
1 - Cytochrome b binds a ubiquinol and a ubiquinone.
2 - The 2Fe/2S center and BL heme each pull an electron off the bound ubiquinol, releasing two hydrogens into the intermembrane space.
3 - One electron is transferred to cytochrome c1 from the 2Fe/2S centre, whilst another is transferred from the BL heme to the BH Heme.
4 - Cytochrome c1 transfers its electron to cytochrome c (not to be confused with cytochrome c1), and the BH Heme transfers its electron to a nearby ubiquinone, resulting in the formation of a ubisemiquinone.
5 - Cytochrome c diffuses. The first ubiquinol (now oxidized to ubiquinone) is released, whilst the semiquinone remains bound.

Round 2:
1 - A second ubiquinol is bound by cytochrome b.
2 - The 2Fe/2S center and BL heme each pull an electron off the bound ubiquinol, releasing two hydrogens into the intermembrane space.
3 - One electron is transferred to cytochrome c1 from the 2Fe/2S centre, whilst another is transferred from the BL heme to the BH Heme.
4 - Cytocrome c1 then transfers its electron to cytochrome c, whilst the nearby semiquinone picks up a second electron from the BH heme, along with two protons from the matrix.
5 - The second ubiquinol (now oxidized to ubiquinone), along with the newly formed ubiquinol are released.

Complex III inhibitors include
• Antimycin A binds to the Q_i site and inhibits the transfer of electrons in Complex III from heme bH to oxidized Q (Q_i site inhibitor).
• Myxothiazol and stigmatellin binds to the Q_o site and inhibits the transfer of electrons from reduced QH_2 to the Rieske Iron sulfur protein. Myxothiazol and stigmatellin bind to distinct but overlapping pockets within the Q_o site.
• Myxothiazol binds nearer to cytochrome bL (hence termed a "proximal" inhibitor).
• Stigmatellin binds farther from heme bL and nearer the Rieske Iron sulfur protein, with which it strongly interacts.

https://en.wikipedia.org/wiki/Coenzyme_Q_%E2%80%93_cytochrome_c_reductase

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Related Glossary Terms

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Complex IV

The enzyme cytochrome c oxidase or Complex IV, EC 1.9.3.1 is a large transmembrane protein complex found in bacteria and the mitochondrion of eukaryotes. It is the last enzyme in the respiratory electron transport chain of mitochondria (or bacteria) located in the mitochondrial (or bacterial) membrane. Complex IV receives an electron from each of four cytochrome c molecules, and transfers them to one oxygen molecule, converting molecular oxygen to two molecules of water. In the process, it binds four protons from the inner aqueous phase to make water, and in addition translocates four protons across the membrane, helping to establish a transmembrane difference of proton electrochemical potential that the ATP synthase then uses to synthesize ATP.

Summary reaction:

$4\ Fe^{++}$-cytochrome c + $8\ H^{+}in + O_2 \rightarrow 4\ Fe^{+++}$-cytochrome c + $2\ H_2O + 4\ H^{+}out$

Two electrons are passed from two cytochrome c's, through the CuA and cytochrome a sites to the cytochrome a3- CuB binuclear center, reducing the metals to the Fe^{++} form and Cu^{+}. The hydroxide ligand is protonated and lost as water, creating a void between the metals that is filled by O_2. The oxygen is rapidly reduced, with two electrons coming from the Fe^{++}cytochrome a_3, which is converted to the ferryl oxo form (Fe^{++++}=O).

The oxygen atom close to CuB picks up one electron from Cu^{+}, and a second electron and a proton from the hydroxyl of Tyr(244), which becomes a tyrosyl radical: The second oxygen is converted to a hydroxide ion by picking up two electrons and a proton. A third electron arising from another cytochrome c is passed through the first two electron carriers to the cytochrome a_3- CuB binuclear center, and this electron and two protons convert the tyrosyl radical back to Tyr, and the hydroxide bound to CuB^{++} to a water molecule. The fourth electron from another cytochrome c flows through CuA and cytochrome a to the cytochrome a_3- CuB binuclear center, reducing the Fe^{++++}=O to Fe^{+++}, with the oxygen atom picking up a proton simultaneously, regenerating this oxygen as a hydroxide ion coordinated in the middle of the cytochrome a_3- CuB center as it was at the start of this cycle. The net process is that four reduced cytochrome c molecules are used, along with 4 protons, to reduce O_2 to two water molecules.

https://en.wikipedia.org/wiki/Cytochrome_c_oxidase

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Complex V

ATP synthase (EC 3.6.3.14) is an important enzyme that creates the energy currency molecule adenosine triphosphate (ATP). ATP is the most commonly used "energy currency" of cells from most organisms. It is formed from adenosine diphosphate (ADP) and inorganic phosphate (P_i), and needs energy for its formation.

The overall reaction sequence is:

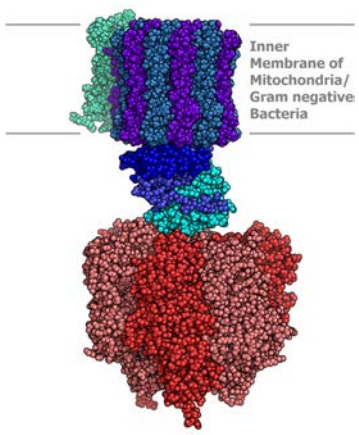
$ADP + P_i + Energy \rightarrow ATP$

where ADP and Pi are joined together by ATP synthase.

Energy used is available in the form of hydrogen ions (H^+), moving down an electrochemical gradient, such as from the thylakoid lumen through the thylakoid membrane and into the chloroplast stroma (of plants) or from the inter-membrane space and into the matrix in mitochondria.

ATP synthase consists of two regions
• the F_0 portion embedded within the membrane.
the F_1 portion of the ATP synthase is outside the membrane, but inside the matrix of the mitochondria.

In plants, ATP synthase is also present in chloroplasts ($CF1F_O$-ATP synthase). The enzyme is integrated into thylakoid membrane. The CF_1-part sticks into stroma, where dark reactions of photosynthesis (also called the light-independent reactions or the Calvin cycle) and ATP synthesis take place. The overall structure and the catalytic mechanism of the chloroplast ATP synthase are almost the same as those of the mitochondrial enzyme. However, in chloroplasts, the proton motive force is generated not by respiratory electron transport chain but by primary photosynthetic proteins.



https://commons.wikimedia.org/wiki/File:Atp_synthase.PNG

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Concentration Gradient

Whenever there is a difference in concentration of molecules across a mem
is said to be a concentration gradient across it.

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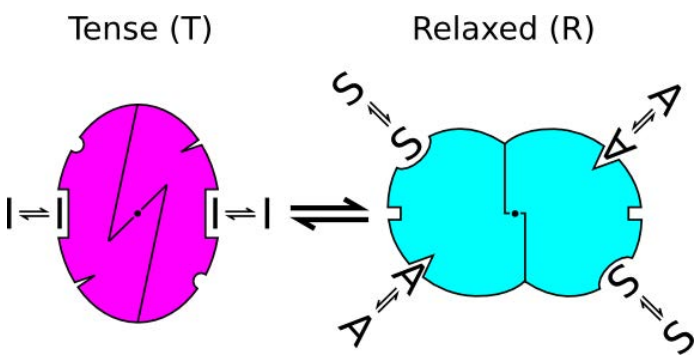
Concerted Model

In biochemistry, the Monod-Wyman-Changeux model (MWC model, also known as the concerted model or symmetry model) describes allosteric transitions of proteins made up of identical subunits. It was proposed by Jean-Pierre Changeux based on his PhD experiments, and described by Jacques Monod, Jeffries Wyman, and Jean-Pierre Changeux. It stands in opposition to the sequential model.

The concept of two distinct symmetric states is the central postulate of the MWC model.The main idea of the model is that regulated proteins, such as many enzymes and receptors, exist in different interconvertible states in the absence of any regulator. The ratio of the different conformational states is determined by thermal equilibrium. The ratio of the different conformational states is determined by thermal equilibrium. This model, alternatively termed the MWC model, is defined by the following rules:

1 - An allosteric protein is an oligomer of protomers that are symmetrically related (for hemoglobin, we shall assume, for the sake of algebraic simplicity, that all four subunits are functionally identical).
2 - Each protomer can exist in (at least) two conformational states, designated T and R. These states are in equilibrium whether or not ligand is bound to the oligomer.
3 - The ligand can bind to a protomer in either conformation. Only the conformational change alters the affinity of a protomer for the ligand. The regulators merely shift the equilibrium toward one state or another. For instance, an agonist will stabilize the active form of a pharmacological receptor. Phenomenologically, it looks as if the agonist provokes the conformational transition.

One crucial feature of the model is the dissociation between the binding function (the fraction of protein bound to the regulator), and the state function (the fraction of protein under the activated state). In the models said of "induced-fit", those functions are identical.



https://en.wikipedia.org/wiki/Monod-Wyman-Changeux_model

Connective Tissue

Connective tissue (CT) is one of the four types of biological tissue that support, connect, or separate different types of tissues and organs in the body. It develops from the mesoderm. The other three types are epithelial, muscle, and nervous tissue. Connective tissue is found in between other tissues everywhere in the body, including the nervous system. In the central nervous system, the three outer membranes (the meninges) that envelop the brain and spinal cord are composed of connective tissue. All connective tissue apart from blood and lymph consists of three main components: fibers (elastic and collagenous fibers), ground substance and cells. (Not all authorities include blood or lymph as connective tissue.) Blood and lymph lack the fiber component. All are immersed in the body water. The cells of connective tissue include fibroblasts, adipocytes, macrophages, mast cells and leucocytes.

Connective tissue has a wide variety of functions that depend on the types of cells and the different classes of fibers involved. Loose and dense irregular connective tissue, formed mainly by fibroblasts and collagen fibers, have an important role in providing a medium for oxygen and nutrients to diffuse from capillaries to cells, and carbon dioxide and waste substances to diffuse from cells back into circulation. They also allow organs to resist stretching and tearing forces. Dense regular connective tissue, which forms organized structures, is a major functional component of tendons, ligaments and aponeuroses, and is also found in highly specialized organs such as the cornea. Elastic fibers, made from elastin and fibrillin, also provide resistance to stretch forces. They are found in the walls of large blood vessels and in certain ligaments, particularly in the ligamenta flava.

https://en.wikipedia.org/wiki/Connective_tissue

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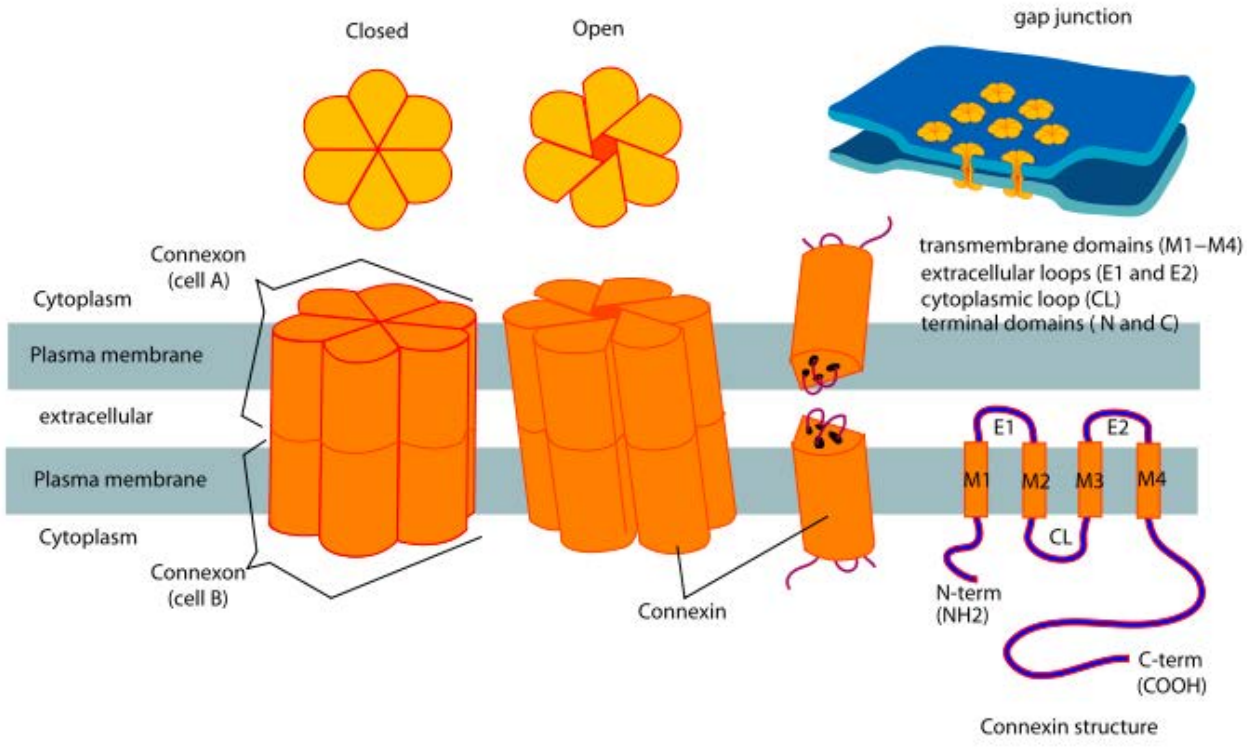
Connexons

In biology, a connexon, also known as a connexin hemichannel or a pannexin channel, is an assembly of six proteins called connexins that form the pore for a gap junction between the cytoplasm of two adjacent cells. This channel allows for bidirectional flow of ions and signaling molecules. The connexon is the hemichannel supplied by a cell on one side of the junction. Two connexons from opposing cells normally come together to form the complete intercellular gap junction channel. However, in some cells, the hemichannel itself is active as a conduit between the cytoplasm and the extracellular space, allowing the transference of ions and small molecules lower than 1-2 KDa. Little is known about this function of connexons besides the new evidence suggesting their key role in intracellular signaling. Connexons made of the same type of connexins are considered homomeric, while connexons made of differing types of connexins are heteromeric.



https://en.wikipedia.org/wiki/Connexon

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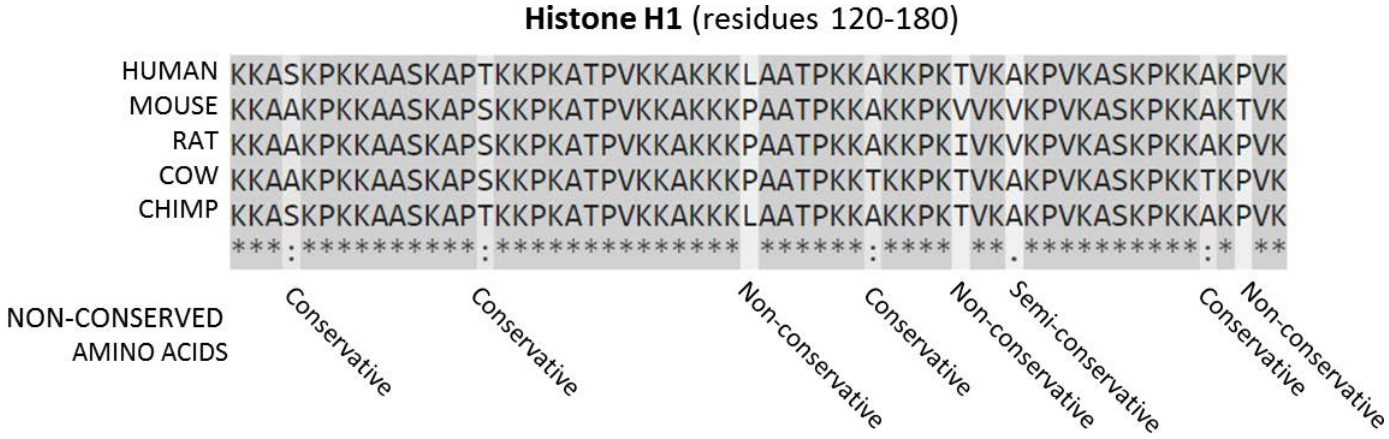
Chapter 3 - Membranes: Other Considerations

Chapter 9 - Point by Point: Membranes

Conserved

In biology, conserved sequences are similar or identical sequences that occur within nucleic acid sequences (such as RNA and DNA sequences), protein sequences, protein structures or polymeric carbohydrates across species (orthologous sequences) or within different molecules produced by the same organism (paralogous sequences). In the case of cross species conservation, this indicates that a particular sequence may have been maintained by evolution despite speciation. The further back up the phylogenetic tree a particular conserved sequence may occur the more highly conserved it is said to be. Since sequence information is normally transmitted from parents to progeny by genes, a conserved sequence implies that there is a conserved gene. It is widely believed that mutation in a "highly conserved" region leads to a non-viable life form, or a form that is eliminated through natural selection. What determines conserved and non-conserved is the environment. If for example, a microorganism with antibiotic resistance genes is in the presence of antibiotic, the antibiotic resistance genes will be highly conserved. If not in the presence of antibiotics, the genes will become non-conserved.



https://en.wikipedia.org/wiki/Conserved_sequence

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Chapter 2 - Structure and Function: Proteins

Constitutive

In cell biology, a constitutively active protein is a protein which is constantl
When used in conjunction with gene expression, it refers to expression that
active or ongoing.

https://en.wikipedia.org/wiki/Constitutive

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Chapter 6 - Metabolism: Fats and Fatty Acids

Convergent Evolution

Convergent evolution is the independent evolution of similar features in species of different lineages. Convergent evolution creates analogous structures that have similar form or function but were not present in the last common ancestor of those groups. The cladistic term for the same phenomenon is homoplasy, from Greek for same form. The recurrent evolution of flight is a classic example of convergent evolution. Flying insects, birds, and bats have all evolved the capacity of flight independently. They have "converged" on this useful trait.

Functionally similar features arising through convergent evolution are termed analogous, in contrast to homologous structures or traits, which have a common origin but not necessarily a similar function. The British anatomist Richard Owen was the first scientist to recognize the fundamental difference between analogies and homologies. Bat and pterosaur wings constitute an example of analogous structures, while the bat wing is homologous to human and other mammal forearms, sharing an ancestral state despite serving different functions. The opposite of convergent evolution is divergent evolution in which related species evolve different traits. On a molecular level, that can happen from random mutation unrelated to adaptive changes.

Convergent evolution is similar to but different from parallel evolution. Parallel evolution occurs when two independent but similar species evolve in the same direction and thus independently acquire similar characteristic. For instance, gliding frogs have evolved in parallel from multiple types of tree frog.

https://en.wikipedia.org/wiki/Convergent_evolution

Related Glossary Terms

Cooperative Binding

Molecular binding is an interaction between molecules that results in a stable physical association between those molecules. Cooperative binding occurs in binding systems containing more than one type, or species, of molecule and in which one of the partners is not mono-valent and can bind more than one molecule of the other species.

In 1904, Christian Bohr studied hemoglobin binding to oxygen under different conditions. When plotting hemoglobin saturation with oxygen as a function of the partial pressure of oxygen, he obtained a sigmoidal (or "S-shaped") curve. This indicates that the more oxygen is bound to hemoglobin, the easier it is for more oxygen to bind - until all binding sites are saturated. In addition, Bohr noticed that increasing CO_2 pressure shifted this curve to the right - i.e. higher concentrations of CO_2 make it more difficult for hemoglobin to bind oxygen. This latter phenomenon, together with the observation that hemoglobin's affinity for oxygen increases with increasing pH, is known as the Bohr effect.

A receptor molecule is said to exhibit cooperative binding if its binding to ligand scales non-linearly with ligand concentration. Cooperativity can be positive (if binding of a ligand molecule increases the receptor's apparent affinity, and hence increases the chance of another ligand molecule binding) or negative (if binding of a ligand molecule decreases affinity and hence makes binding of other ligand molecules less likely).

The concept of cooperative binding only applies to molecules or complexes with more than one ligand binding sites. If several ligand binding sites exist, but ligand binding to any one site does not affect the others, the receptor is said to be non-cooperative. Cooperativity can be homotropic, if a ligand influences the binding of ligands of the same kind, or heterotropic, if it influences binding of other kinds of ligands. In the case of hemoglobin, Bohr observed homotropic positive cooperativity (binding of oxygen facilitates binding of more oxygen) and heterotropic negative cooperativity (binding of CO_2 reduces hemoglobin's facility to bind oxygen.)

https://en.wikipedia.org/wiki/Cooperative_binding

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Chapter 2 - Structure and Function: Proteins
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Chapter 9 - Point by Point: Catalysis

Cooperativity

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https://en.wikipedia.org/wiki/Cooperative_binding

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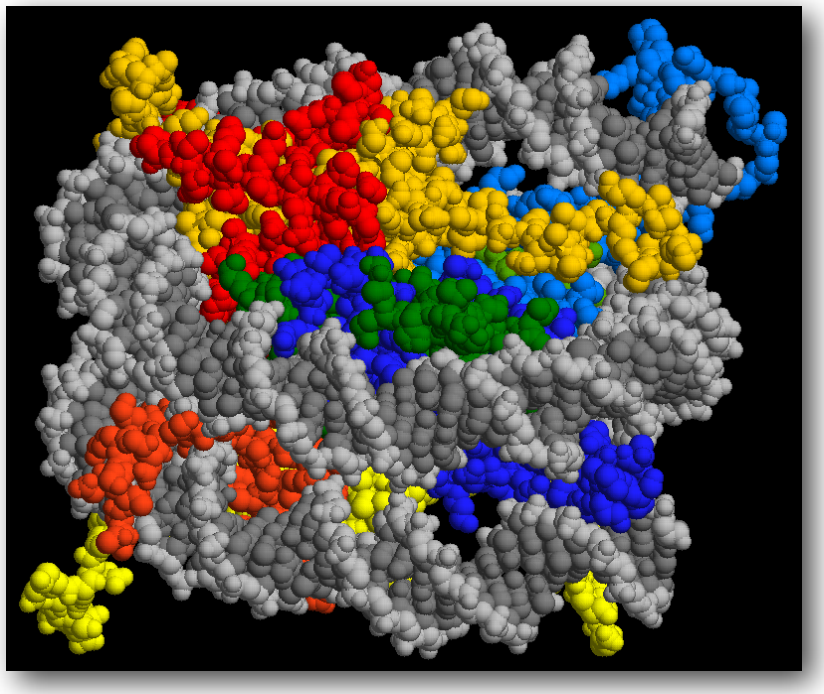
Core Particle

The nucleosome core particle consists of approximately 147 base pairs of DNA wrapped in 1.67 left-handed superhelical turns around a histone octamer consisting of 2 copies each of the core histones H2A, H2B, H3, and H4. Core particles are connected by stretches of "linker DNA", which can be up to about 80 bp long. Technically, a nucleosome is defined as the core particle plus one of these linker regions. However the word is often synonymous with the core particle. Genome-wide nucleosome positioning maps are now available for many model organisms including mouse liver and brain.

A core particle is depicted below. Histones H2A, H2B, H3 and H4 are colored, DNA is gray.



https://en.wikipedia.org/wiki/Nucleosome

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Cori Cycle

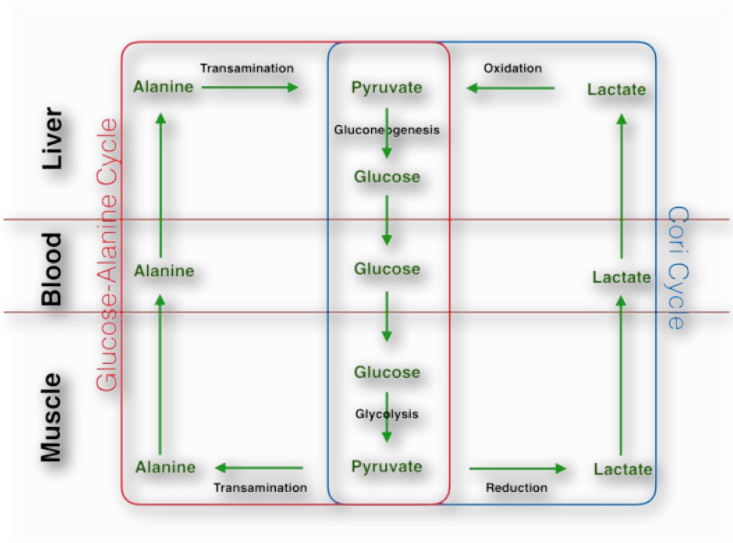
The Cori cycle (also known as the lactic acid cycle), named after its discoverers, Carl Ferdinand Cori and Gerty Cori, refers to the metabolic pathway in which lactate produced by anaerobic glycolysis in the muscles moves to the liver and is converted to glucose, which then returns to the muscles and is metabolized back to lactate.

Muscular activity requires ATP, which is provided by the breakdown of glycogen in the skeletal muscles. The breakdown of glycogen, a process known as glycogenolysis, releases glucose in the form of glucose-1-phosphate (G-1-P). The G-1-P is converted to G-6-P by the enzyme phosphoglucomutase. G-6-P is readily fed into glycolysis, (or can go into the pentose phosphate pathway if G-6-P concentration is high) a process that provides ATP to the muscle cells as an energy source. During muscular activity, the store of ATP needs to be constantly replenished. When the supply of oxygen is sufficient, this energy comes from feeding pyruvate, one product of glycolysis, into the citric acid cycle.

When oxygen supply is insufficient, typically during intense muscular activity, energy must be released through anaerobic metabolism. Lactic acid fermentation converts pyruvate to lactate by lactate dehydrogenase. Most important, fermentation regenerates NAD^+, maintaining the NAD^+ concentration so that additional glycolysis reactions can occur. The fermentation step oxidizes the NADH produced by glycolysis back to NAD^+, transferring two electrons from NADH to reduce pyruvate into lactate. Refer to the main articles on glycolysis and fermentation for the details.

Instead of accumulating inside the muscle cells, lactate produced by anaerobic fermentation is taken up by the liver. This initiates the other half of the Cori cycle. In the liver, gluconeogenesis occurs. From an intuitive perspective, gluconeogenesis reverses both glycolysis and fermentation by converting lactate first into pyruvate, and finally back to glucose. The glucose is then supplied to the muscles through the bloodstream. It is ready to be fed into further glycolysis reactions. If muscle activity has stopped, the glucose is used to replenish the supplies of glycogen through glycogenesis.

Overall, the glycolysis part of the cycle produces 2 ATP molecules at a cost of 6 ATP molecules consumed in the gluconeogenesis part. Each iteration of the cycle must be maintained by a net consumption of 4 ATP molecules. As a result, the cycle cannot be sustained indefinitely. The intensive consumption of ATP molecules indicates that the Cori cycle shifts the metabolic burden from the muscles to the liver.



https://en.wikipedia.org/wiki/Cori_cycle

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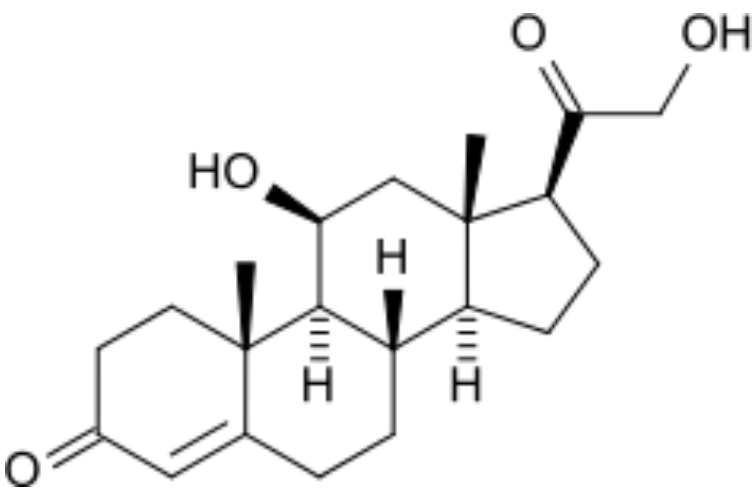
Corticosteroid

Corticosteroids are a class of steroid hormones that are produced in the adrenal corte
of vertebrates, as well as the synthetic analogues of these hormones. Corticosteroids
are involved in a wide range of physiological processes, including stress response, im-
mune response, and regulation of inflammation, carbohydrate metabolism, protein ca
tabolism, blood electrolyte levels, and behavior.
Some common natural hormones are corticosterone ($C_{21}H_{30}O_4$), cortisone ($C_{21}H_{28}O_5$,
17-hydroxy-11-dehydrocorticosterone) and aldosterone.

Shown below is corticosterone.



https://en.wikipedia.org/wiki/Corticosteroid

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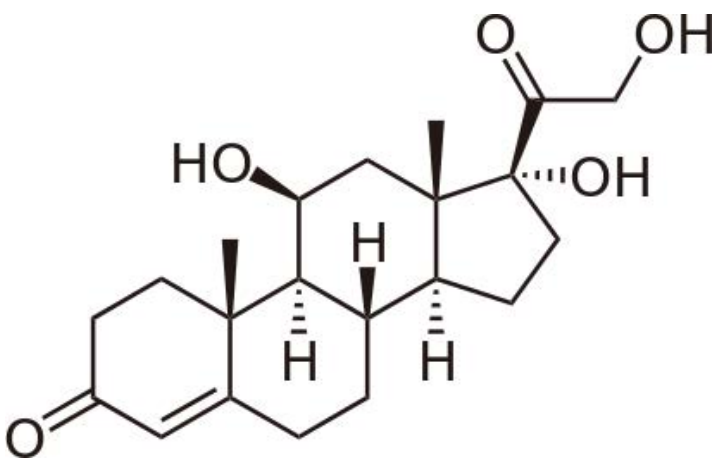
Cortisol

Cortisol is a steroid hormone, in the glucocorticoid class of hormones, and is pro
in humans by the zona fasciculata of the adrenal cortex within the adrenal gland
released in response to stress and low blood-glucose concentration. It functions
crease blood sugar through gluconeogenesis, to suppress the immune system, an
aid in the metabolism of fat, protein, and carbohydrates. It also decreases bone f
tion.



https://en.wikipedia.org/wiki/Cortisol

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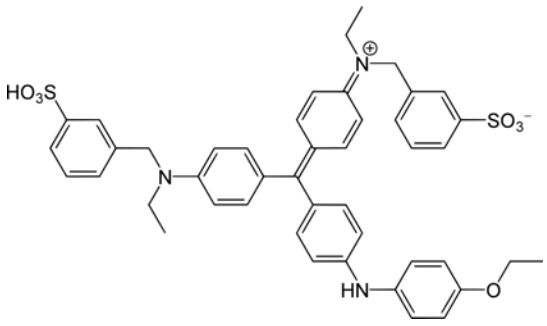
Coumassie Brilliant Blue

Coomassie Brilliant Blue is the name of two similar triphenylmethane dyes that were developed for use in the textile industry but are now commonly used for staining proteins in analytical biochemistry.

Coomassie Brilliant Blue R-250 was first used to visualize proteins in 1964 by Fazekas de St. Groth and colleagues. Protein samples were separated electrophoretically on a cellulose acetate sheet. The sheet was then soaked in sulfosalicylic acid to fix the protein bands and then transferred to a solution of the dye.

Two years later in 1965 Meyer and Lambert used Coomassie Brilliant Blue R-250 to stain protein samples after electrophoretic separation in a polyacrylamide gel. They soaked the gel in a dye solution containing methanol, acetic acid and water. As the dye stained the polyacrylamide gel as well as the protein, to visualize the protein bands they needed to destain the gel which they did electrophoretically.Subsequent publications reported that polyacrylamide gels could be successfully destained using an acetic acid solution.

The Bradford assay uses the spectral properties of Coomassie Brilliant Blue G-250 to estimate the amount of protein in a solution. A protein sample is added to a solution of the dye in phosphoric acid and ethanol. Under the acid conditions the dye is normally a brownish color but on binding to the protein the blue form of the dye is produced. The optical absorbance of the solution is measured at a wavelength of 595 nm. On binding to a protein the negatively charged Coomassie Brilliant Blue G-250 dye molecule will give an overall negative charge to the protein. This property can be used to separate proteins or protein complexes using polyacrylamide gel electrophoresis under non-denaturing conditions in a technique called Blue Native PAGE. The mobility of the complex in the polyacrylamide gel will depend on both the size of the protein complex (i.e. the molecular weight) and on the amount of dye bound to the protein.



https://en.wikipedia.org/wiki/Coomassie_Brilliant_Blue

Covalent Bond

A covalent bond, also called a molecular bond, is a chemical bond that involves the sharing of electron pairs between atoms. These electron pairs are known as shared pairs or bonding pairs, and the stable balance of attractive and repulsive forces between atoms, when they share electrons, is known as covalent bonding.

https://en.wikipedia.org/wiki/Covalent_bond

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Covalent Modification

Post-translational modification (PTM) refers to the covalent and generally enzymatic modification of proteins during or after protein biosynthesis. Proteins are synthesized by ribosomes translating mRNA into polypeptide chains, which may then undergo PTM to form the mature protein product. PTMs are important components in cell signaling.

Post-translational modifications can occur on the amino acid side chains or at the protein's C- or N- termini. They can extend the chemical repertoire of the 20 standard amino acids by introducing new functional groups such as phosphate, acetate, amide groups, or methyl groups. Phosphorylation is a very common mechanism for regulating the activity of enzymes and is the most common post-translational modification. Many eukaryotic proteins also have carbohydrate molecules attached to them in a process called glycosylation, which can promote protein folding and improve stability as well as serving regulatory functions. Attachment of lipid molecules, known as lipidation, often targets a protein or part of a protein to the cell membrane.

Other forms of post-translational modification consist of cleaving peptide bonds, as in processing a propeptide to a mature form or removing the initiator methionine residue. The formation of disulfide bonds from cysteine residues may also be referred to as a post-translational modification. For instance, the peptide hormone insulin is cut twice after disulfide bonds are formed, and a propeptide is removed from the middle of the chain. The resulting protein consists of two polypeptide chains connected by disulfide bonds.

Some types of post-translational modification are consequences of oxidative stress. Carbonylation is one example that targets the modified protein for degradation and can result in the formation of protein aggregates. Specific amino acid modifications can be used as biomarkers indicating oxidative damage.

https://en.wikipedia.org/wiki/Post-translational_modification

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COX-1

Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme (EC 1.14.99.1) that is responsible for formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin.
The abbreviation "COX" is more often encountered in medicine. In genetics, the "PTGS" symbol is officially used for the prostaglandin-endoperoxide synthase (cyclooxygenase) family of genes and proteins, because the stem "COX" was already used for the cytochrome c oxidase family of genes and proteins.

Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain. Non-steroidal anti-inflammatory drugs (NSAID), such as aspirin and ibuprofen, exert their effects through inhibition of COX. The names "prostaglandin synthase (PHS)" and "prostaglandin endoperoxide synthetase (PES)" are still used to refer to COX.

In terms of their molecular biology, COX-1 and COX-2 are of similar molecular weight, approximately 70 and 72 kDa, respectively, and having 65% amino acid sequence homology and near-identical catalytic sites. COX-3 has been reported as a splice variant of COX-1, but information about it is unclear. The most significant difference between the isoenzymes, which allows for selective inhibition, is the substitution of isoleucine at position 523 in COX-1 with valine in COX-2. The smaller Val523 residue in COX-2 allows access to a hydrophobic side-pocket in the enzyme (which Ile523 sterically hinders). Drug molecules, such as DuP-697 and the coxibs derived from it, bind to this alternative site and are considered to be selective inhibitors of COX-2.

https://en.wikipedia.org/wiki/Cyclooxygenase

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COX-2

Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme (EC 1.14.99.1) that is responsible for formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin.
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https://en.wikipedia.org/wiki/Cyclooxygenase

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COX-3

Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme (EC 1.14.99.1) that is responsible for formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin.
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https://en.wikipedia.org/wiki/Cyclooxygenase

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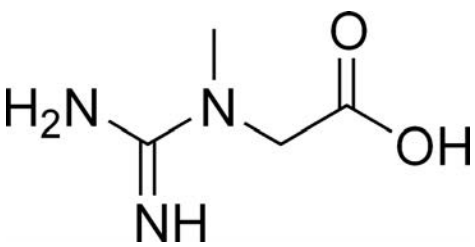
Chapter 6 - Metabolism: Fats and Fatty Acids

Creatine

Creatine is a nitrogenous organic acid that occurs naturally in vertebrates and helps to supply energy to all cells in the body, primarily muscle. This is achieved by increasing the formation of adenosine triphosphate (ATP).

Creatine is not an essential nutrient as it is naturally produced in the human body from the amino acids glycine and arginine. In the first step of the biosynthesis these two amino acids are combined by the enzyme arginine:glycine amidinotransferase (AGAT, EC:2.1.4.1) to form guanidinoacetate, this is then methylated by guanidinoacetate N-methyltransferase (GAMT,EC:2.1.1.2), using S-adenosyl methionine as the methyl donor. Creatine itself can be phosphorylated by creatine kinase to form phosphocreatine, which is used as an energy reserve (energy battery) in skeletal muscles and the brain.

Creatine, synthesized in the liver and kidney, is transported through the blood and taken up by tissues with high energy demands, such as the brain and skeletal muscle, through an active transport system. The concentration of ATP in skeletal muscle is usually 2-5 mM, which would result in a muscle contraction of only a few seconds. Fortunately, during times of increased energy demands, the phosphagen (or ATP/PCr) system rapidly resynthesizes ATP from ADP with the use of phosphocreatine (PCr) through a reversible reaction with the enzyme creatine kinase (CK). In skeletal muscle, PCr concentrations may reach 20-35 mM or more. Additionally, in most muscles, the ATP regeneration capacity of CK is very high and is therefore not a limiting factor. Although the cellular concentrations of ATP are small, changes are difficult to detect because ATP is continuously and efficiently replenished from the large pools of PCr and CK. Creatine has the ability to increase muscle stores of PCr, potentially increasing the muscle's ability to resynthesize ATP from ADP to meet increased energy demands.



https://en.wikipedia.org/wiki/Creatine

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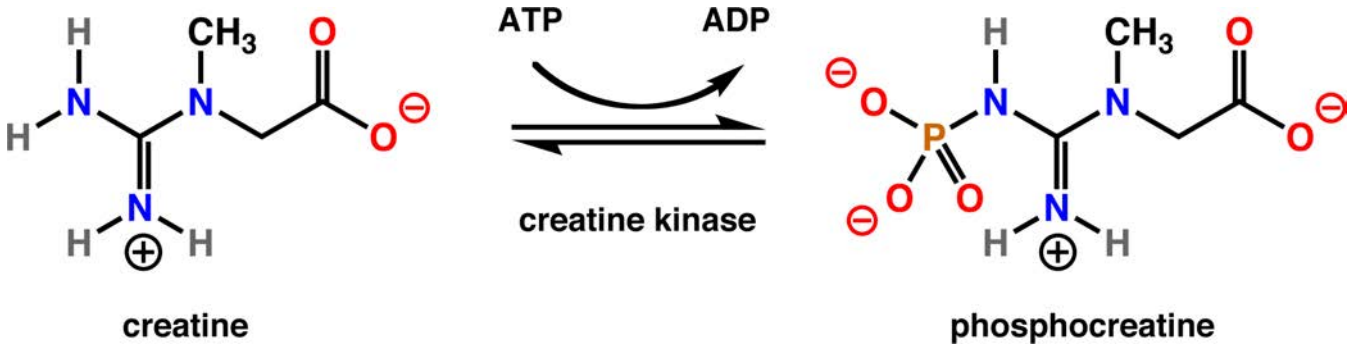
Creatine Kinase

Creatine kinase (CK) — also known as creatine phosphokinase (CPK) or phosphocreatine kinase — is an enzyme (EC 2.7.3.2) expressed by various tissues and cell types. CK catalyzes the conversion of creatine and utilizes adenosine triphosphate (ATP) to create phosphocreatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible and thus ATP can be generated from PCr and ADP.



In tissues and cells that consume ATP rapidly, especially skeletal muscle, but also brain, photoreceptor cells of the retina, hair cells of the inner ear, spermatozoa and smooth muscle, PCr serves as an energy reservoir for the rapid buffering and regeneration of ATP in situ, as well as for intracellular energy transport by the PCr shuttle or circuit. Thus creatine kinase is an important enzyme in such tissues.

Clinically, creatine kinase is assayed in blood tests as a marker of damage of CK-rich tissue such as in myocardial infarction (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy, the autoimmune myositides and in acute renal failure.

https://en.wikipedia.org/wiki/Creatine_kinase

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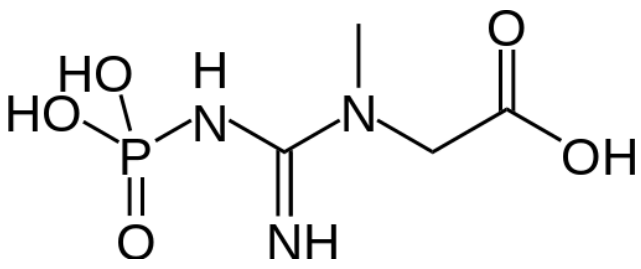
Creatine Phosphate

Phosphocreatine, also known as creatine phosphate (CP) or PCr, is a phosphorylated creatine molecule that serves as a rapidly mobilizable reserve of high-energy phosphates in skeletal muscle and the brain.

Phosphocreatine can anaerobically donate a phosphate group to ADP to form ATP during the first 2 to 7 seconds following an intense muscular or neuronal effort. Conversely, excess ATP can be used during a period of low effort to convert creatine to phosphocreatine. The reversible phosphorylation of creatine (i.e., both the forward and backward reaction) is catalyzed by several creatine kinases. The presence of creatine kinase (CK-MB, MB for muscle/brain) in blood plasma is indicative of tissue damage and is used in the diagnosis of myocardial infarction. The cell's ability to generate phosphocreatine from excess ATP during rest, as well as its use of phosphocreatine for quick regeneration of ATP during intense activity, provides a spatial and temporal buffer of ATP concentration. In other words, phosphocreatine acts as high-energy reserve in a coupled reaction. The energy given off from donating the phosphate group is used to regenerate the other compound - in this case, ATP. Phosphocreatine plays a particularly important role in tissues that have high, fluctuating energy demands such as muscle and brain.

https://en.wikipedia.org/wiki/Phosphocreatine



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CREB

CREB (cAMP response element-binding protein) is a cellular transcription factor. It binds to certain DNA sequences called cAMP response elements (CRE), thereby increasing or decreasing the transcription of the downstream genes.

CREB has a well-documented role in neuronal plasticity and long-term memory formation in the brain and has been shown to be integral in the formation of spatial memory. CREB downregulation is implicated in the pathology of Alzheimer's disease and increasing the expression of CREB is being considered as a possible therapeutic target for Alzheimers disease. CREB also has a role in photoentrainment in mammals.

CREB has many functions in many different organs, and some of its functions have been studied in relation to the brain. CREB proteins in neurons are thought to be involved in the formation of long-term memories. This has been shown in the marine snail Aplysia, the fruit fly Drosophila melanogaster, in rats and in mice (see CREB in Molecular and Cellular Cognition). CREB is necessary for the late stage of long-term potentiation. CREB also has an important role in the development of drug addiction and even more so in psychological dependence. There are activator and repressor forms of CREB. Flies genetically engineered to overexpress the inactive form of CREB lose their ability to retain long-term memory. CREB is also important for the survival of neurons, as shown in genetically engineered mice, where CREB and CREM were deleted in the brain. If CREB is lost in the whole developing mouse embryo, the mice die immediately after birth, again highlighting the critical role of CREB in promoting survival.

https://en.wikipedia.org/wiki/CREB

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Chapter 2 - Structure and Function: Proteins

Creutzfeld-Jacob

Creutzfeldt–Jakob disease or CJD is a degenerative neurological disease that is incurable and invariably fatal. CJD is at times called a human form of mad cow disease (bovine spongiform encephalopathy or BSE). However, given that BSE is believed to be the cause of variant Creutzfeldt–Jakob (vCJD) disease in humans, the two are often confused. CJD is caused by an infectious agent called a prion. Prions are misfolded proteins that replicate by converting their properly folded counterparts, in their host, to the same misfolded structure they possess. CJD causes the brain tissue to degenerate rapidly, and as the disease destroys the brain, the brain develops holes and the texture changes to resemble that of a kitchen sponge.

Transmissible spongiform encephalopathy diseases are caused by prions. Prions are proteins that occur normally in neurons of the central nervous system (CNS). As of 2007, these proteins were thought to affect signaling processes, damaging neurons and resulting in degeneration that causes the spongiform appearance in the affected brain. The CJD prion is dangerous because it promotes refolding of native proteins into the diseased state. The number of misfolded protein molecules will increase exponentially and the process leads to a large quantity of insoluble protein in affected cells. This mass of misfolded proteins disrupts neuronal cell function and causes cell death. Mutations in the gene for the prion protein can cause a misfolding of the dominantly α helical regions into β pleated sheets. This change in conformation disables the ability of the protein to undergo digestion. Once the prion is transmitted, the defective proteins invade the brain and are produced in a self-sustaining feedback loop.These neurodegenerative diseases are commonly called prion diseases.

People can also acquire CJD genetically through a mutation of the gene that codes for the prion protein (PRNP). This occurs in only 5-10% of all CJD cases. An EU study determined that "87% of cases were sporadic, 8% genetic, and 5% iatrogenic."

https://en.wikipedia.org/wiki/Creutzfeldt%E2%80%93Jakob_disease

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Chapter 9 - Point by Point: Structure and Function

Creutzfeld-Jacob Disease

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https://en.wikipedia.org/wiki/Creutzfeldt%E2%80%93Jakob_disease

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CRISPR/Cas9

Clustered regularly interspaced short palindromic repeats (CRISPR, pronounced crisper) are segments of prokaryotic DNA containing short repetitions of base sequences. Each repetition is followed by short segments of "spacer DNA" from previous exposures to a bacteriophage virus or plasmid.

The CRISPR/Cas system is a prokaryotic immune system that confers resistance to foreign genetic elements such as those present within plasmids and phages, and provides a form of acquired immunity. CRISPR spacers recognize and cut these exogenous genetic elements in a manner analogous to RNA interference in eukaryotic organisms. CRISPRs are found in approximately 40% of sequenced bacterial genomes and 90% of sequenced *archaea*.

By delivering the Cas9 nuclease and appropriate guide RNAs into a cell, the cell's genome can be cut at a desired location, allowing existing genes to be removed and/or new ones added. CRISPRs have been used in concert with specific endonuclease enzymes for genome editing and gene regulation in species throughout the tree of life.

Cas9 was the first nuclease discovered, followed by Cpf1, which was discovered in the CRISPR/Cpf1 system of Francisella novicida. Other such systems are thought to exist.

CRISPR/C2c2 from the bacterium *Leptotrichia shahii* is RNA-guided CRISPR system that targets RNA rather than DNA, and can either cleave single-stranded RNA targets or knock them down.

The CRISPR interference technique has many potential applications, including altering the germline of humans, animals, and food crops. The use of CRISPR for genome editing was the AAAS's choice for breakthrough of the year in 2015.

https://en.wikipedia.org/wiki/CRISPR

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CTP

Cytidine triphosphate is a pyrimidine nucleoside triphosphate. CTP is a substrate in the synthesis of RNA. CTP is a high-energy molecule similar to ATP, but its role as an energy coupler is limited to a much smaller subset of metabolic reactions. CTP is a co-enzyme in metabolic reactions like the synthesis of glycerophospholipids and glycosylation of proteins. CTP acts as an inhibitor of the enzyme Aspartate carbamoyltransferase, which is used in pyrimidine biosynthesis.

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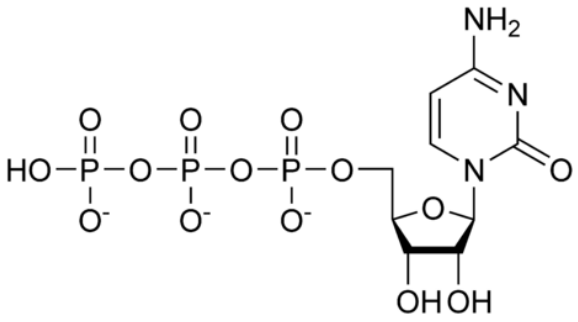

https://en.wikipedia.org/wiki/Cytidine_triphosphate

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CTP Synthetase

CTP synthetase is an enzyme involved in pyrimidine biosynthesis that interconverts UTP and CTP. Active CTP synthase exists as a homotetrameric enzyme. At low enzyme concentrations and in the absence of ATP and UTP, CTP synthase exists as inactive monomer. As enzyme concentration increases, it polymerizes first to a dimer (such as the form shown to the left) and, in the presence of ATP and UTP, forms a tetramer.

The enzyme contains two major domains, responsible for the aminotransferase and synthase activity, respectively. The amidotransferase domains are located away from the tetramer interfaces and are not affected by the oligomeric state. The ATP-binding site and CTP-binding site in the synthase domain are located at the tetramer interface. It is for this reason that ATP and UTP are required for tetramerization.

CTP synthase is precisely regulated by the intracellular concentrations of CTP and UTP, and both hCTPS1 and hCTPS2 have been seen to be maximally active at physiological concentrations of ATP, GTP, and glutamine.

The activity of human CTPS1 isozyme has been demonstrated to be inhibited by phosphorylation. One major example of this is phosphorylation of the Ser-571 residue by glycogen synthase kinase 3 (GSK3) in response to low serum conditions. Additionally, Ser568 has been seen to be phosphorylated by casein kinase 1, inhibiting CTP synthase activity.

CTP is also subject to various forms of allosteric regulation. GTP acts as an allosteric activator that strongly promotes the hydrolysis of glutamine, but is also inhibiting to glutamine-dependent CTP formation at high concentrations. This acts to balance the relative amounts of purine and pyrimidine nucleotides. The reaction product CTP also serves as an allosteric inhibitor. The triphosphate binding site overlaps with that of UTP, but the nucleoside moiety of CTP binds in an alternative pocket opposite the binding site for UTP.

The glutamine analog DON has also been seen to act as an irreversible inhibitor, and has been used as an anti-cancer agent.

https://en.wikipedia.org/wiki/CTP_synthetase

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Cu_A

Complex IV of the electron transport system is a large integral membrane p
posed of several metal prosthetic sites and 14 protein subunits in mammals
mals, eleven subunits are nuclear in origin, and three are synthesized in the
dria. The complex contains two hemes, a cytochrome a and cytochrome a_3,
per centers, the Cu_A and Cu_B centers. In fact, the cytochrome a_3 and Cu_B for
clear center that is the site of oxygen reduction. Cytochrome c, which is red
preceding component of the respiratory chain (cytochrome bc1 complex, co
docks near the Cu_A binuclear center and passes an electron to it, being oxid
cytochrome c containing Fe^{+++}. The reduced Cu_A binuclear center now pass
tron on to cytochrome a, which in turn passes an electron on to the cytochr
binuclear center. The two metal ions in this binuclear center are 4.5 Å apar
nate a hydroxide ion in the fully oxidized state.

https://en.wikipedia.org/wiki/Cytochrome_c_oxidase

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https://en.wikipedia.org/wiki/Cytochrome_c_oxidase

Related Glossary Terms

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Cyanide

A cyanide is any chemical compound that contains monovalent combining group CN. This group, known as the cyano group, consists of a carbon atom triple-bonded to a nitrogen atom. In inorganic cyanides, such as sodium cyanide and potassium cyanide this group is present as the negatively charged polyatomic cyanide ion (CN^-). These compounds, which are regarded as salts of hydrocyanic acid, are highly toxic. The cyanide ion is isoelectronic with carbon monoxide and with molecular nitrogen. Organic cyanides are usually called nitriles. In these, the CN group is linked by a covalent bond to a carbon-containing group, such as methyl (CH_3) in methyl cyanide (acetonitrile).

Many cyanides are highly toxic. The cyanide anion is an inhibitor of the enzyme cytochrome c oxidase (also known as aa_3) in the fourth complex of the electron transport chain (found in the membrane of the mitochondria of eukaryotic cells). It attaches to the iron within this protein. The binding of cyanide to this enzyme prevents transport of electrons from cytochrome c to oxygen. As a result, the electron transport chain is disrupted, meaning that the cell can no longer aerobically produce ATP for energy.

Tissues that depend highly on aerobic respiration, such as the central nervous system and the heart, are particularly affected. This is an example of histotoxic hypoxia.
The most hazardous compound is hydrogen cyanide, which is a gas at ambient temperatures and pressure and can therefore be inhaled. For this reason, an air respirator supplied by an external oxygen source must be worn when working with hydrogen cyanide. Hydrogen cyanide is produced when a solution containing a labile cyanide is made acidic, because HCN is a weak acid. Alkaline solutions are safer to use because they do not evolve hydrogen cyanide gas. Hydrogen cyanide may be produced in the combustion of polyurethanes. For this reason, polyurethanes are not recommended for use in domestic and aircraft furniture. Oral ingestion of a small quantity of solid cyanide or a cyanide solution as little as 200 mg, or to airborne cyanide of 270 ppm is sufficient to cause death within minutes.

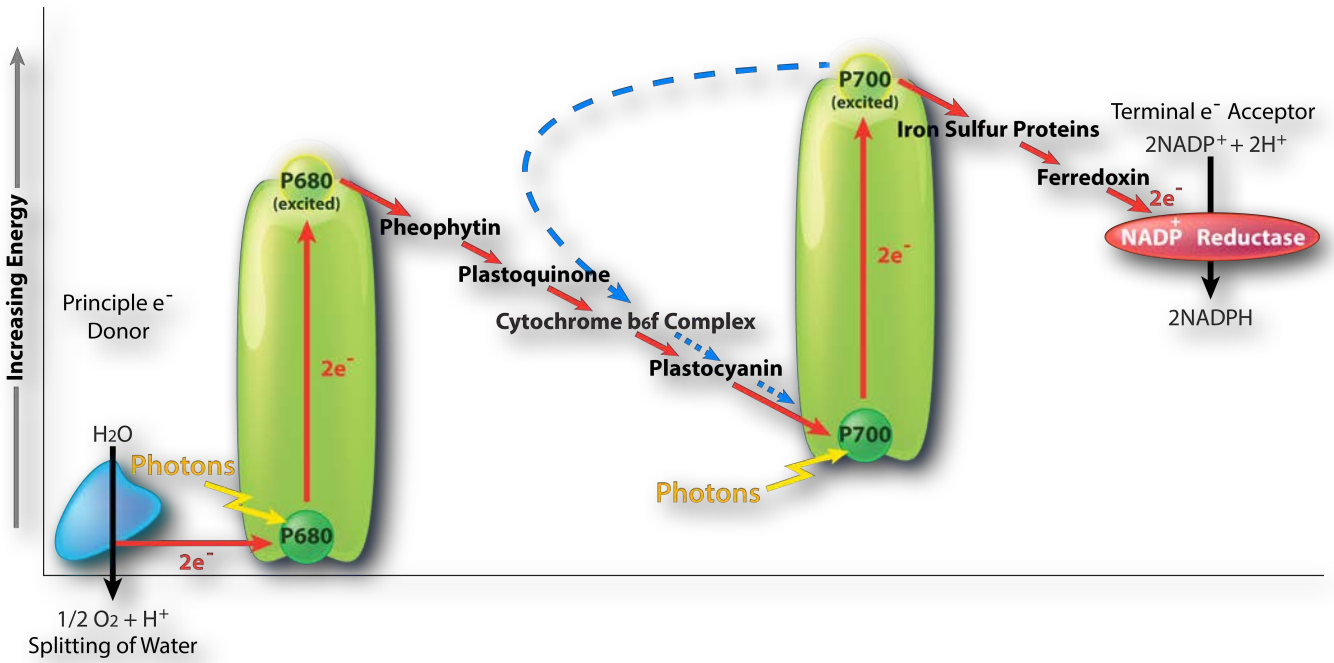
https://en.wikipedia.org/wiki/Cyanide

Cyclic Photophosphorylation

This form of photophosphorylation occurs on the thylakoid membrane. In cyclic electron flow, the electron begins in a pigment complex called photosystem I, passes from the primary acceptor to ferredoxin, then to cytochrome b_6f (a similar complex to that found in mitochondria), and then to plastocyanin before returning to chlorophyll. This transport chain produces a proton-motive force, pumping H^+ ions across the membrane. This produces a concentration gradient that can be used to power ATP synthase during chemiosmosis. This pathway is known as cyclic photophosphorylation, and it produces neither O_2 nor NADPH. Unlike non-cyclic photophosphorylation, $NADP^+$ does not accept the electrons. They are instead sent back to cytochrome b_6f complex.

In bacterial photosynthesis, a single photosystem is used, and therefore is involved in cyclic photophosphorylation. It is favored in anaerobic conditions and conditions of high irradiance and CO_2 compensation points.

In the figure below, cyclic photophosphorylation is shown by the blue dashed line.



https://en.wikipedia.org/wiki/Photophosphorylation#Cyclic_photophosphorylation

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Chapter 5 - Energy: Photophosphorylation

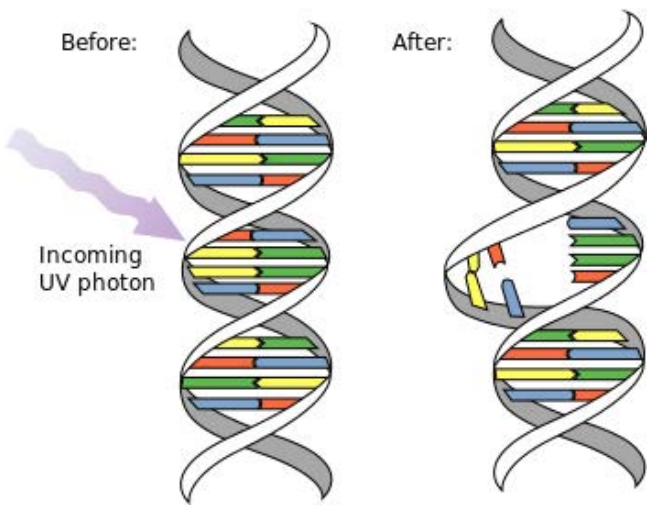
Chapter 9 - Short & Sweet: Energy

Cyclobutane Pyrimidine Dimers

Pyrimidine dimers are molecular lesions formed from thymine or cytosine bases in DNA via photochemical reactions. Ultraviolet light induces the formation of covalent linkages by reactions localized on the C=C double bonds. In dsRNA (double-stranded RNA), uracil dimers may also accumulate as a result of UV radiation. Two common UV products are cyclobutane pyrimidine dimers (CPDs, including thymine dimers) and 6,4 photoproducts. These premutagenic lesions alter the structure of DNA and consequently inhibit polymerases and arrest replication. Dimers may be repaired by photoreactivation or nucleotide excision repair, but unrepaired dimers are mutagenic. Pyrimidine dimers are the primary cause of melanomas in humans.

A cyclobutane pyrimidine dimer (CPD) contains a four membered ring arising from the coupling of the C=C double bonds of pyrimidines. Such dimers interfere with base pairing during DNA replication, leading to mutations.

6,4-photoproducts, or 6,4 pyrimidine-pyrimidones, occur at one third the frequency of CPDs but are more mutagenic. Spore photoproduct lyase provides another enzymatic pathway for repair of thymine photodimers.



https://en.wikipedia.org/wiki/Pyrimidine_dimer

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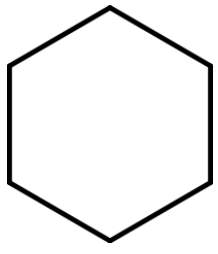
Cyclohexane

Cyclohexane is a cycloalkane with the molecular formula C_6H_{12}. Cyclohexar
used for the industrial production of adipic acid and caprolactam, which ar
to nylon. Cyclohexane is a colorless, flammable liquid with a distinctive det
odor, reminiscent of cleaning products (in which it is sometimes used).



https://en.wikipedia.org/wiki/Cyclohexane

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Chapter 2 - Structure & Function: Lipids

Cyclooxygenase

Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme (EC 1.14.99.1) that is responsible for formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin.
The abbreviation "COX" is more often encountered in medicine. In genetics, the "PTGS" symbol is officially used for the prostaglandin-endoperoxide synthase (cyclooxygenase) family of genes and proteins, because the stem "COX" was already used for the cytochrome c oxidase family of genes and proteins.

Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain. Non-steroidal anti-inflammatory drugs (NSAID), such as aspirin and ibuprofen, exert their effects through inhibition of COX. The names "prostaglandin synthase (PHS)" and "prostaglandin endoperoxide synthetase (PES)" are still used to refer to COX.

In terms of their molecular biology, COX-1 and COX-2 are of similar molecular weight, approximately 70 and 72 kDa, respectively, and having 65% amino acid sequence homology and near-identical catalytic sites. COX-3 has been reported as a splice variant of COX-1, but information about it is unclear. The most significant difference between the isoenzymes, which allows for selective inhibition, is the substitution of isoleucine at position 523 in COX-1 with valine in COX-2. The smaller Val523 residue in COX-2 allows access to a hydrophobic side-pocket in the enzyme (which Ile523 sterically hinders). Drug molecules, such as DuP-697 and the coxibs derived from it, bind to this alternative site and are considered to be selective inhibitors of COX-2.

https://en.wikipedia.org/wiki/Cyclooxygenase

Related Glossary Terms

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CYP3A4

Cytochrome P450 3A4 (abbreviated CYP3A4) (EC 1.14.13.97), is an important enzym in the body, mainly found in the liver and in the intestine. Its purpose is to oxidize small foreign organic molecules (xenobiotics), such as toxins or drugs, so that they ca be removed from the body.

CYP3A4 is a member of the cytochrome P450 family of oxidizing enzymes. Several other members of this family are also involved in drug metabolism, but CYP3A4 is th most common and the most versatile one. Like all members of this family, it is a hem protein, i.e. a protein containing a heme group with an iron atom. In humans, the CYP3A4 protein is encoded by the CYP3A4 gene. This gene is part of a cluster of cyto chrome P450 genes on chromosome 7q21.1.

While many drugs are deactivated by CYP3A4, there are also some drugs which are a vated by the enzyme. Some substances, such as grapefruit juice and some drugs, inte fere with the action of CYP3A4. These substances will therefore either amplify or weaken the action of those drugs that are modified by CYP3A4.

https://en.wikipedia.org/wiki/CYP3A4

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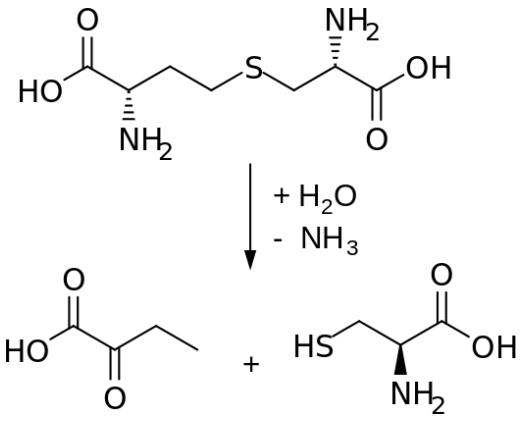
Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Cystathionase

Cystathionine γ-lyase (CTH or CSE) (also known as cystathionase) is an enzyme which breaks down cystathionine into cysteine, α-ketobutyrate, and ammonia. Pyridoxal phosphate is a prosthetic group of this enzyme.



Cystathionine γ-lyase also catalyzes the following elimination reactions:

- L-homoserine to form H_2O, NH_3 and 2-oxobutanoate
- L-cystine, producing thiocysteine, pyruvate and NH_3

• L-cysteine producing pyruvate, NH_3 and H_2S

In some bacteria and mammals, including humans, this enzyme takes part in generating hydrogen sulfide. Hydrogen sulfide is one of a few gases that was recently discovered to have a role in cell signaling in the body.

Cysteine is the rate-limiting substrate in the synthetic pathway for glutathione in the eye. Glutathione is an antioxidant that protects crystallins in the eye from reactive oxygen species. Denatured crystallins can lead to cataracts. Cystathionase is also a target for reactive oxygen species. Thus as cystathionase is oxidized, its activity decreases, causing a decrease in cysteine and, in turn, glutathione in the eye, leading to a decrease in antioxidant availability, causing a further decrease in cystathionase activity. Deficiencies in cystathionase activity have also been shown to contribute to glutathione depletion in patients with cancer and AIDS.

https://en.wikipedia.org/wiki/Cystathionine_gamma-lyase

Related Glossary Terms

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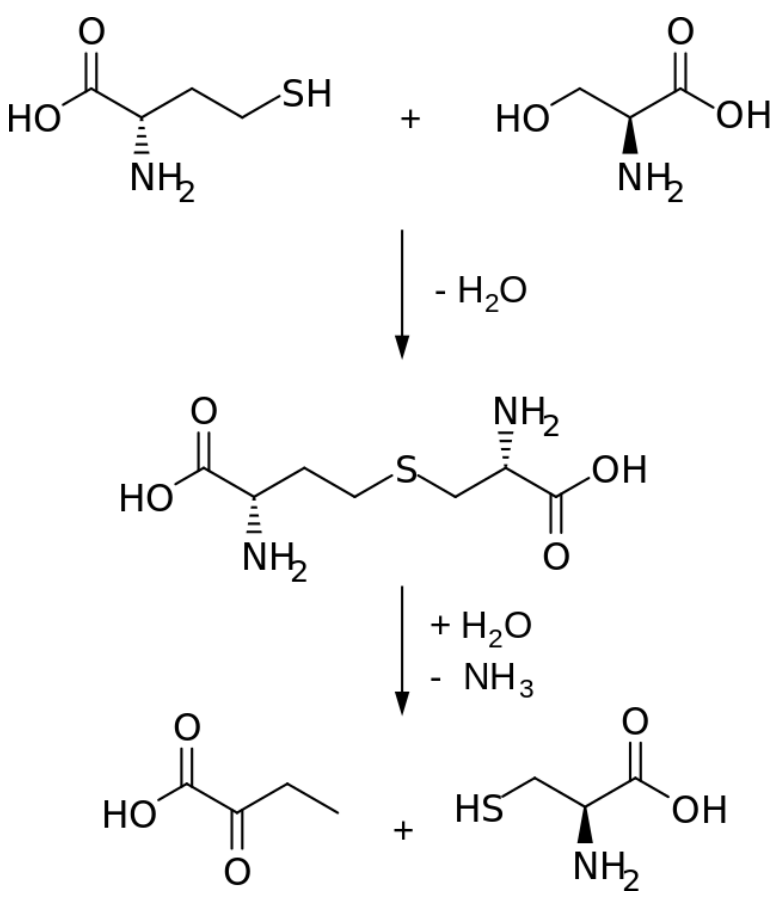
Cystathionine

Cystathionine is an intermediate in the synthesis of cysteine. An excess in the urine is called cystathioninuria. Biosynthetically, cystathionineis generated from homocysteine and serine by cystathionine β synthase (upper reaction in the diagram below). It is then cleaved into cysteine and α-ketobutyrate by cystathionine γ-lyase (lower reaction).



https://en.wikipedia.org/wiki/Cystathionine

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Cystathionine β-synthase

Cystathionine-β-synthase, also known as CBS, is an enzyme (EC 4.2.1.22) t
mans is encoded by the CBS gene. It catalyzes the first step of the transsulfu
way, from homocysteine to cystathionine:

L-serine + L-homocysteine <-> L-cystathionine + H_2O

CBS uses the cofactor pyridoxal-phosphate (PLP) and can be allosterically r
effectors such as the ubiquitous cofactor S-adenosyl-L-methionine (adoMe

https://en.wikipedia.org/wiki/Cystathionine_beta_synthase

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Cystathionine-β-lyase

Cystathionine β-lyase (EC 4.4.1.8) is an enzyme that catalyzes the chemical rea

L-cystathionine + H_2O <-> L-homocysteine + NH_3 + Pyruvate

This enzyme belongs to the family of lyases, specifically the class of carbon-sulf
ases. The systematic name of this enzyme class is L-cystathionine L-homocyste
lyase (deaminating; pyruvate-forming). Other names in common use include β-
cystathionase, cystine lyase, cystathionine L-homocysteine-lyase (deaminating)
cystathionine L-homocysteine-lyase (deaminating).

This enzyme participates in 5 metabolic pathways: methionine metabolism, cys
metabolism, selenoamino acid metabolism, nitrogen metabolism, and sulfur m
lism. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Cystathionine_beta-lyase

Related Glossary Terms

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Cystathionine-γ-synthase

Cystathionine γ-synthase (EC 2.5.1.48) is an enzyme that catalyzes the chemical reaction

O_4-succinyl-L-homoserine + L-cysteine <-> L-cystathionine + Succinate

This enzyme belongs to the family of transferases, specifically those transferring aryl or alkyl groups other than methyl groups. The systematic name of this enzyme class is O4-succinyl-L-homoserine:L-cysteine S-(3-amino-3-carboxypropyl)transferase. Other names in common use include O-succinyl-L-homoserine succinate-lyase (adding cysteine), O-succinylhomoserine (thiol)-lyase, homoserine O-transsuccinylase, O-succinylhomoserine synthase, O-succinylhomoserine synthetase, cystathionine synthase, cystathionine synthetase, homoserine transsuccinylase, 4-O-succinyl-L-homoserine:L-cysteine, and S-(3-amino-3-carboxypropyl)transferase.

This enzyme participates in 4 metabolic pathways: methionine metabolism, cysteine metabolism, selenoamino acid metabolism, and sulfur metabolism. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Cystathionine_gamma-synthase

Related Glossary Terms

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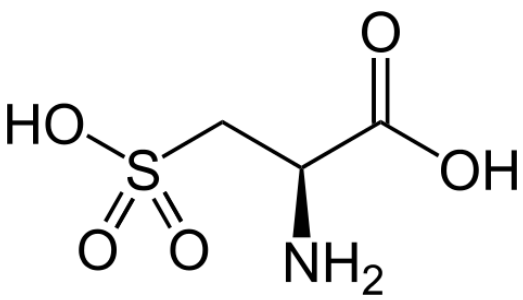
Cysteic Acid

Cysteic acid is an intermediate in cysteine metabolism.

L-cysteic Acid + **H_2S**

⇅

L-cysteine + Sulfite



https://en.wikipedia.org/wiki/Cysteic_acid

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Cysteine

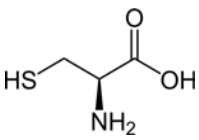
Cysteine (abbreviated as Cys or C) is a semi-essential proteinogenic amino acid with the formula $HO_2CCH(NH_2)CH_2SH$>. It is encoded by the codons UGU and UGC. The thiol side chain in cysteine often participates in enzymatic reactions, as a nucleophile. The thiol is susceptible to oxidization to give the disulfide derivative cystine, which serves an important structural role in many proteins.

The cysteine thiol group is nucleophilic and easily oxidized. The reactivity is enhanced when the thiol is ionized, and cysteine residues in proteins have pKa values close to neutrality, so are often in their reactive thiolate form in the cell. Because of its high reactivity, the thiol group of cysteine has numerous biological functions.

Cysteine has antioxidant properties. Cysteine's antioxidant properties are typically expressed in the tripeptide glutathione, which occurs in humans as well as other organisms. The systemic availability of oral glutathione (GSH) is negligible; so it must be biosynthesized from its constituent amino acids, cysteine, glycine, and glutamic acid. Glutamic acid and glycine are readily available in most Western diets, but the availability of cysteine can be the limiting substrate.

Cysteine is an important source of sulfide in human metabolism. The sulfide in iron-sulfur clusters and in nitrogenase is extracted from cysteine, which is converted to alanine in the process.

Beyond the iron-sulfur proteins, many other metal cofactors in enzymes are bound to the thiolate substituent of cysteinyl residues. Examples include zinc in zinc fingers and alcohol dehydrogenase, copper in the blue copper proteins, iron in cytochrome P450, and nickel in the [NiFe]-hydrogenases. The thiol group also has a high affinity for heavy metals, so that proteins containing cysteine, such as metallothionein, will bind metals such as mercury, lead, and cadmium tightly.



https://en.wikipedia.org/wiki/Cysteine

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Cysteine Lyase

Cysteine lyase (EC 4.4.1.10) is an enzyme that catalyzes the chemical reacti

L-cysteine + Sulfite <-> L-cysteate + H_2S

This enzyme belongs to the family of lyases, specifically the class of carbon-
ases. The systematic name of this enzyme class is L-cysteine hydrogen-sulfi
(adding sulfite L-cysteate-forming). Other names in common use include cy
fite) lyase, and L-cysteine hydrogen-sulfide-lyase (adding sulfite).

This enzyme participates in cysteine metabolism and taurine and hypotaur
lism. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Cysteine_lyase

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Cysteine Proteases

Cysteine proteases, also known as thiol proteases, are enzymes that degrade proteins. These proteases share a common catalytic mechanism that involves a nucleophilic cysteine thiol in a catalytic triad or dyad.

Cysteine proteases are commonly encountered in fruits including the papaya, pineapple, fig and kiwifruit. The proportion of protease tends to be higher when the fruit is unripe. In fact, dozens of latices of different plant families are known to contain cysteine proteases. Cysteine proteases are used as an ingredient in meat tenderizers.

The first step in the reaction mechanism by which cysteine proteases catalyze the hydrolysis of peptide bonds is deprotonation of a thiol in the enzyme's active site by an adjacent amino acid with a basic side chain, usually a histidine residue. The next step is nucleophilic attack by the deprotonated cysteine's anionic sulfur on the substrate carbonyl carbon. In this step, a fragment of the substrate is released with an amine terminus, the histidine residue in the protease is restored to its deprotonated form, and a thioester intermediate linking the new carboxy-terminus of the substrate to the cysteine thiol is formed. Therefore they are also sometimes referred to as thiol proteases. The thioester bond is subsequently hydrolyzed to generate a carboxylic acid moiety on the remaining substrate fragment, while regenerating the free enzyme.

Cysteine proteases play multi-faceted roles, virtually in every aspect of physiology and development. In plants they are important in growth and development and in accumulation and mobilization of storage proteins such as in seeds. In addition, they are involved in signaling pathways and in the response to biotic and abiotic stresses. In humans and other animals, they are responsible for senescence and apoptosis (programmed cell death), MHC class II immune responses, prohormone processing, and extracellular matrix remodeling important to bone development. The ability of macrophages and other cells to mobilize elastolytic cysteine proteases to their surfaces under specialized conditions may also lead to accelerated collagen and elastin degradation at sites of inflammation in diseases such as atherosclerosis and emphysema. Several viruses (e.g. polio, hepatitis C) express their entire genome as a singe massive polyprotein and use a protease to cleave it into functional units (e.g. Tobacco Etch Virus protease).

https://en.wikipedia.org/wiki/Cysteine_protease

Cysteine Synthase

Cysteine synthase (EC 2.5.1.47) is an enzyme that catalyzes the chemical reaction

O_3-acetyl-L-serine + H_2S <-> L-cysteine + Acetate

This enzyme belongs to the family of transferases, specifically those transferring aryl or alkyl groups other than methyl groups. The systematic name of this enzyme class is O3-acetyl-L-serine:hydrogen-sulfide 2-amino-2-carboxyethyltransferase. Other names in common use include O-acetyl-L-serine sulfhydrylase, O-acetyl-L-serine sulfohydrolase, O-acetylserine (thiol)-lyase, O-acetylserine (thiol)-lyase A, O-acetylserine sulfhydrylase, O3-acetyl-L-serine acetate-lyase (adding hydrogen-sulfide), acetylserine sulfhydrylase, cysteine synthetase, S-sulfocysteine synthase, 3-O-acetyl-L-serine:hydrogen-sulfide, and 2-amino-2-carboxyethyltransferase.

This enzyme participates in 3 metabolic pathways: cysteine metabolism, selenoamino acid metabolism, and sulfur metabolism. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Cysteine_synthase

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Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disorder that affects mostly the lungs but also the pancreas, liver, kidneys, and intestine. Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections. Other signs and symptoms include sinus infections, poor growth, fatty stool, clubbing of the fingers and toes, and infertility in males, among others. Different people may have different degrees of symptoms. CF is inherited in an autosomal recessive manner. It is caused by the presence of mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Those with a single working copy are carriers and otherwise mostly normal.

CF is most common among people of Northern European ancestry and affects about one out of every 3,000 newborns. About one in 25 people are carriers. It is least common in Africans and Asians. It was first recognized as a specific disease by Dorothy Andersen in 1938, with descriptions that fit the condition occurring at least as far back as 1595. The name cystic fibrosis refers to the characteristic fibrosis and cysts that form within the pancreas.

https://en.wikipedia.org/wiki/Cystic_fibrosis

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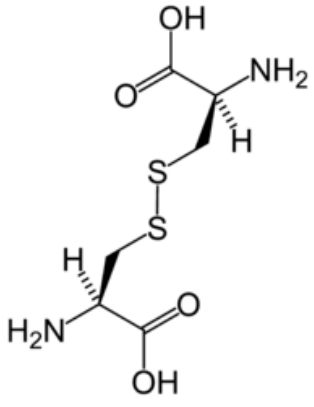
Cystine

Cystine is the oxidized dimer form of the amino acid cysteine and has formula $(SCH_2CH(NH_2)CO_2H)_2$. It is a white solid that is slightly soluble in water. It serves two biological functions, a site of redox reactions and a mechanical linkage that allows proteins to retain their 3-dimensional structure.

Cystine is formed from the oxidation of two cysteine molecules, via the formation of a disulfide bond. In cell biology, cystine (found in proteins) can only exist in non-reductive (oxidative) organelles, such as the secretory pathway (ER, Golgi, Lysosomes, Vesicles and ECM). Meaning that in reductive conditions (Cytoplasm, Nucleus, etc.) cysteine is favorably found. The disulfide link is readily reduced to give the corresponding thiol cysteine. Typical thiols for this reaction are mercaptoethanol and dithiothreitol:

$$(SCH_2CH(NH_2)CO_2H)_2 + 2\ RSH \rightarrow 2\ HSCH_2CH(NH_2)CO_2H + RSSR$$

Because of the facility of the thiol-disulfide exchange, the nutritional benefits and sources of cystine are identical to those for the more-common cysteine. Disulfide bonds cleave more rapidly at higher temperatures.



https://en.wikipedia.org/wiki/Cystine

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Cystine Reductase

Cystine reductase (EC 1.8.1.6) is an enzyme that catalyzes the chemical reac

2 L-cysteine + NAD^+ <-> L-cystine + NADH + H^+

This enzyme belongs to the family of oxidoreductases, specifically those act
fur group of donors with NAD^+ or $NADP^+$ as acceptor. The systematic name
zyme class is L-cysteine:NAD^+ oxidoreductase. Other names in common us
cystine reductase (NADH), NADH-dependent cystine reductase, cystine red
(NADH), and NADH:L-cystine oxidoreductase.

This enzyme participates in cysteine metabolism and is named for the reve

https://en.wikipedia.org/wiki/Cystine_reductase

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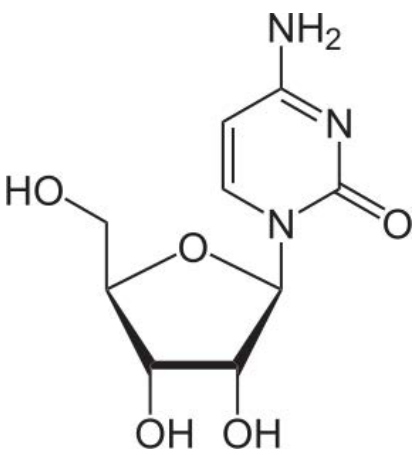
Cytidine

Cytidine is a nucleoside molecule that is formed when cytosine is attached to a ribose ring (also known as a ribofuranose) via a β-N1-glycosidic bond. Cytidine is a component of RNA.

If cytosine is attached to a deoxyribose ring, it is known as a deoxycytidine.

In addition to its role as a pyrimidine component of RNA, cytidine has been found to control neuronal-glial glutamate cycling, with supplementation decreasing midfrontal/cerebral glutamate/glutamine levels. As such, cytidine has generated interest as a potential glutamatergic antidepressant drug.



https://en.wikipedia.org/wiki/Cytidine

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Cytidine Deaminase

Cytidine deaminase is an enzyme that in humans is encoded by the CDA ge
gene encodes an enzyme involved in pyrimidine salvaging. The encoded pr
a homotetramer that catalyzes the irreversible hydrolytic deamination of cy
deoxycytidine to uridine and deoxyuridine, respectively. It is one of several
responsible for maintaining the cellular pyrimidine pool. Mutations in this
sociated with decreased sensitivity to the cytosine nucleoside analogue cyto
noside used in the treatment of certain childhood leukemias.

A related activation-induced (cytidine) deaminase (AID) regulates antibody
tion, especially the process of somatic hypermutation.

https://en.wikipedia.org/wiki/Cytidine_deaminase

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Cytochrome a

Cytochrome a is a cytochrome found in Complex IV of the electron transpo
In the movement of electrons through the complex, cytochrome a accepts a
from the Cu_A binuclear center of Complex IV and passes it off to the cytoch
binuclear center.

https://en.wikipedia.org/wiki/Cytochrome_c_oxidase

Related Glossary Terms

Drag related terms here

Cytochrome a_3

Complex IV of the electron transport system is a large integral membrane pro
posed of several metal prosthetic sites and 14 protein subunits in mammals. I
mals, eleven subunits are nuclear in origin, and three are synthesized in the m
dria. The complex contains two hemes, a cytochrome a and cytochrome a_3, ar
per centers, the Cu_A and Cu_B centers. In fact, the cytochrome a_3 and Cu_B form
clear center that is the site of oxygen reduction. Cytochrome c, which is reduc
preceding component of the respiratory chain (cytochrome bc1 complex, com
docks near the Cu_A binuclear center and passes an electron to it, being oxidize
cytochrome c containing Fe^{+++}. The reduced Cu_A binuclear center now passes
tron on to cytochrome a, which in turn passes an electron on to the cytochrom
binuclear center. The two metal ions in this binuclear center are 4.5 Å apart a
nate a hydroxide ion in the fully oxidized state.

https://en.wikipedia.org/wiki/Cytochrome_c_oxidase

Related Glossary Terms

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Cytochrome b

Cytochrome b is a protein found in the mitochondria of eukaryotic cells. It fu
part of the electron transport chain and is the main subunit of transmembran
chrome bc1 and b6f complexes. In the mitochondrion of eukaryotes and in ae
karyotes, cytochrome b is a component of respiratory chain complex III (EC 1
also known as the bc_1 complex or ubiquinol-cytochrome c reductase.

In plant chloroplasts and cyanobacteria, there is an analogous protein, cytoch
a component of the plastoquinone-plastocyanin reductase (EC 1.10.99.1), also
as the b_6f complex. These complexes are involved in electron transport, pump
protons to the create a PMF. The proton gradient is finally used for the genera
ATP. Concluding, the complexes play a vital role in cells.

https://en.wikipedia.org/wiki/Cytochrome_b

Related Glossary Terms

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Cytochrome b_5

Cytochromes b_5 are ubiquitous electron transport hemoproteins found in ani
plants, fungi and purple phototrophic bacteria. The microsomal and mitocho
variants are membrane-bound, while bacterial and those from erythrocytes a
animal tissues are water-soluble.

The family of cytochrome b_5-like proteins includes (besides cytochrome b_5 its
protein domains covalently associated with other redox domains in flavocyto
cytochrome b_2 (L-lactate dehydrogenase; EC 1.1.2.3), sulfite oxidase (EC 1.8.3
and fungal nitrate reductases (EC 1.7.1.1, EC 1.7.1.2, EC 1.7.1.3), and plant and
cytochrome b5/acyl lipid desaturase fusion proteins.

https://en.wikipedia.org/wiki/Cytochrome_b5

Related Glossary Terms

Drag related terms here

Cytochrome b_6f Complex

The cytochrome b_6f complex (plastoquinol—plastocyanin reductase; EC 1.10.99.1) is an enzyme found in the thylakoid membrane in chloroplasts of plants, cyanobacteria, and green algae that catalyzes the transfer of electrons from plastoquinol to plastocyanin.

The reaction is analogous to the reaction catalyzed by cytochrome bc_1 (Complex III) of the mitochondrial electron transport chain. During photosynthesis, the cytochrome b_6f complex transfers electrons from Photosystem II to Photosystem I, whereby pumping protons into the thylakoid space and creating an electrochemical (energy) gradient where it is later used to create adenosine triphosphate (ATP).

In photosynthesis, the cytochrome b_6f complex functions to mediate the transfer of electrons between the two photosynthetic reaction center complexes, from Photosystem II to Photosystem I, while transferring protons from the chloroplast stroma across the thylakoid membrane into the lumen. Electron transport via cytochrome b_6f is responsible for creating the proton gradient that drives the synthesis of ATP in chloroplasts.
In a separate reaction, the cytochrome b_6f complex plays a central role in cyclic photophosphorylation, when $NADP^+$ is not available to accept electrons from reduced ferredoxin. This cycle results in the creation of a proton gradient by cytochrome b6f, which can be used to drive ATP synthesis. It has also been shown that this cycle is essential for photosynthesis, in which it is proposed to help maintain the proper ratio of ATP/NADPH production for carbon fixation.

The p-side quinol deprotonation-oxidation reactions within the cytochrome b_6f complex have been implicated in the generation of reactive oxygen species. An integral chlorophyll molecule located within the quinol oxidation site has been suggested to perform a structural, non-photochemical function in enhancing the rate of formation of the reactive oxygen species, possibly to provide a redox-pathway for intra-cellular communication.

https://en.wikipedia.org/wiki/Cytochrome_b6f_complex

Related Glossary Terms

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Cytochrome c

The cytochrome complex, or cyt c is a small hemeprotein found loosely associated with the inner membrane of the mitochondrion. It belongs to the cytochrome c family of proteins. Cytochrome c is highly water-soluble, unlike other cytochromes, and is an essential component of the electron transport chain, where it carries one electron. It is capable of undergoing oxidation and reduction, but does not bind oxygen. It transfers electrons between Complexes III (Coenzyme Q – Cyt C reductase) and IV (Cyt C oxidase). In humans, cytochrome c is encoded by the CYCS gene.

Cytochrome c is a component of the electron transport chain in mitochondria. The heme group of cytochrome c accepts electrons from the bc1 complex and transfers electrons to the complex IV. Cytochrome c is also involved in initiation of apoptosis. Upon release of cytochrome c to the cytoplasm, the protein binds apoptotic protease activating factor-1 (Apaf-1).

Cytochrome c is also an intermediate in apoptosis, a controlled form of cell death used to kill cells in the process of development or in response to infection or DNA damage. Cytochrome c binds to cardiolipin in the inner mitochondrial membrane, thus anchoring its presence and keeping it from releasing out of the mitochondria and initiating apoptosis. While the initial attraction between cardiolipin and cytochrome c is electrostatic due to the extreme positive charge on cytochrome c, the final interaction is hydrophobic, where a hydrophobic tail from cardiolipin inserts itself into the hydrophobic portion of cytochrome c.

During the early phase of apoptosis, mitochondrial ROS production is stimulated, and cardiolipin is oxidized by a peroxidase function of the cardiolipin–cytochrome c complex. The hemoprotein is then detached from the mitochondrial inner membrane and can be extruded into the soluble cytoplasm through pores in the outer membrane. The sustained elevation in calcium levels precedes cyt c release from the mitochondria. The release of small amounts of cyt c leads to an interaction with the IP3 receptor (IP3R) on the endoplasmic reticulum (ER), causing ER calcium release. The overall increase in calcium triggers a massive release of cyt c, which then acts in the positive feedback loop to maintain ER calcium release through the IP3Rs. This explains how the ER calcium release can reach cytotoxic levels. This release of cytochrome c in turn activates caspase 9, a cysteine protease. Caspase 9 can then go on to activate caspase 3 and caspase 7, which are responsible for destroying the cell from within.

One of the ways cell apoptosis is activated is by release of cytochrome c from the mitochondria into cytosol. A study has shown that cells are able to protect themselves from apoptosis by block the release of cytochrome c using Bcl-xL. Another way that cells can control apoptosis is by phosphorylation of Tyr48 which would turn cytochrome c into an anti-apoptotic switch.

Cytochrome c is known to play a role in the electron transport chain and cell apoptosis. However, a recent study has shown that it can also act as an antioxidative enzyme in the mitochondria. It does so by removing superoxide (O_2^-) and hydrogen peroxide (H_2O_2) from mitochondria. Therefore, not only is cytochrome c required in the mitochondria for cell respiration, but it is also needed in the mitochondria to limit the production of $O2^-$ and H_2O_2.

https://en.wikipedia.org/wiki/Cytochrome_c

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Cytochrome C

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https://en.wikipedia.org/wiki/Cytochrome_c

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Cytochrome c_1

Cytochrome c_1 is formed in the cytosol and targeted to the mitochondrial intermembrane space. It is one of the constituents of complex III, which forms the third proton pump in the mitochondrial electron transport chain. Cytochrome c_1 is a subunit of th electron transport chain protein Ubiquinol Cytochrome c Reductase (UQCR, Complex III or Cytochrome bc_1 complex).

Ubiquinol:ferricytochrome c oxidoreductase is found in mitochondria, photosynthetic bacteria and other prokaryotes. The general function of the complex is electron transfer between two mobile redox carriers, ubiquinol and cytochrome c. The electron transfer is coupled with proton translocation across the membrane, thus generating proton motive force in the form of an electrochemical potential difference that can drive ATP synthesis. In its structure and functions, the cytochrome bc_1 complex bears extensive analogy to the cytochrome b_6f complex of chloroplasts and cyanobacteria. Cyt c_1 plays an analogous role to cytochrome f, in spite of their different structures.

https://en.wikipedia.org/wiki/Cytochrome_C1

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Cytochrome P_{450}

Cytochromes P_{450} (CYPs) belong to the superfamily of proteins containing a heme co-factor and, therefore, are hemoproteins. CYPs use a variety of small and large molecules as substrates in enzymatic reactions. They are, in general, the terminal oxidase enzymes in electron transfer chains, broadly categorized as P450-containing systems. The term P450 is derived from the spectrophotometric peak at the wavelength of the absorption maximum of the enzyme (450 nm) when it is in the reduced state and complexed with CO.

CYP enzymes have been identified in all domains of life - animals, plants, fungi, protists, bacteria, archaea, and even in viruses. However, the enzymes have not been found in *E. coli*. Most CYPs require a protein partner to deliver one or more electrons to reduce the iron (and eventually molecular oxygen). Based on the nature of the electron transfer proteins, CYPs can be classified into several groups:

- Microsomal P_{450} systems in which electrons are transferred from NADPH via cytochrome P_{450} reductase (variously CPR, POR, or CYPOR). Cytochrome b5 (cyb5) can also contribute reducing power to this system after being reduced by cytochrome b5 reductase (CYB5R).
- Mitochondrial P_{450} systems, that employ adrenodoxin reductase and adrenodoxin to transfer electrons from NADPH to P450.
- Bacterial P450 systems, that employ a ferredoxin reductase and a ferredoxin to transfer electrons to P_{450}.
- CYB5R/cyb5/P_{450} systems in which both electrons required by the CYP come from cytochrome b5.
- FMN/Fd/P_{450} systems originally found in Rhodococcus sp. in which a FMN-domain-containing reductase is fused to the CYP.
- P_{450} only systems, which do not require external reducing power. Notable ones include thromboxane synthase (CYP5), prostacyclin synthase (CYP8), and CYP74A (allene oxide synthase).

The most common reaction catalyzed by cytochromes P_{450} is a monooxygenase reaction, e.g., insertion of one atom of oxygen into the aliphatic position of an organic substrate (RH) while the other oxygen atom is reduced to water:

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$$

The Human Genome Project has identified 57 human genes coding for the various cytochrome P_{450} enzymes. Human CYPs are primarily membrane-associated proteins located either in the inner membrane of mitochondria or in the endoplasmic reticulum of cells. CYPs metabolize thousands of endogenous and exogenous chemicals. Some CYPs metabolize only one (or a very few) substrates, such as CYP19 (aromatase), while others may metabolize multiple substrates. Both of these characteristics account for their central importance in medicine. Cytochrome P_{450} enzymes are present in most tissues of the body, and play important roles in hormone synthesis and breakdown (including estrogen and testosterone synthesis and metabolism), cholesterol synthesis, and vitamin D metabolism. Cytochrome P_{450} enzymes also function to metabolize potentially toxic compounds, including drugs and products of endogenous metabolism such as bilirubin, principally in the liver.

https://en.wikipedia.org/wiki/Cytochrome_P450

Related Glossary Terms

Cytochromes

Cytochromes are iron containing hemeproteins central to which are heme groups that are primarily responsible for the generation of ATP via electron transport. They are found either as monomeric proteins (e.g., cytochrome c) or as subunits of larger enzymatic complexes that catalyze redox reactions.

The heme group is a highly conjugated ring system (which allows its electrons to be very mobile) surrounding a metal ion, which readily interconverts between the oxidation states. For many cytochromes, the metal ion present is that of iron, which interconverts between Fe^{++} (reduced) and Fe^{+++} (oxidized) states (electron-transfer processes) or between Fe^{++} (reduced) and Fe^{+++} (formal, oxidized) states (oxidative processes). Cytochromes are, thus, capable of performing oxidation and reduction. Because the cytochromes (as well as other complexes) are held within membranes in an organized way, the redox reactions are carried out in the proper sequence for maximum efficiency.

In the process of oxidative phosphorylation, which is the principal energy-generating process undertaken by organisms, other membrane-bound and -soluble complexes and cofactors are involved in the chain of redox reactions, with the additional net effect that protons (H^+) are transported across the mitochondrial inner membrane. The resulting transmembrane proton gradient (protonmotive force) is used to generate ATP, which is the universal chemical energy currency of life. ATP is consumed to drive cellular processes that require energy (such as synthesis of macromolecules, active transport of molecules across the membrane, and assembly of flagella).

https://en.wikipedia.org/wiki/Cytochrome

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Cytoglobin

Cytoglobin is the protein product of CYGB, a human and mammalian gene. is a globin molecule ubiquitously expressed in all tissues and most notably marine mammals. It was discovered in 2001 and named cytoglobin in 2002 thought to protect against hypoxia. The predicted function of cytoglobin is of oxygen from arterial blood to the brain. Cytoglobin is a ubiquitously exp coordinate hemoglobin that may facilitate diffusion of oxygen through tissu enge nitric oxide or reactive oxygen species, or serve a protective function c tive stress.

https://en.wikipedia.org/wiki/Cytoglobin

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Cytokine

Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling. They are released by cells and affect the behavior of other cells. Cytokines can also be involved in autocrine signaling. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells. A given cytokine may be produced by more than one type of cell.

Each cytokine has a matching cell-surface receptor. Subsequent cascades of intracellular signaling then alter cell functions. This may include the upregulation and/or downregulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition.

The effect of a particular cytokine on a given cell depends on the cytokine, its extracellular abundance, the presence and abundance of the complementary receptor on the cell surface, and downstream signals activated by receptor binding. These last two factors can vary by cell type. Cytokines are characterized by considerable "redundancy", in that many cytokines appear to share similar functions.

Cytokines are often involved in several developmental processes during embryogenesis. Cytokines are crucial for fighting off infections and in other immune responses. However, they can become dysregulated and pathological in inflammation, trauma, and sepsis. Adverse effects of cytokines have been linked to many disease states and conditions ranging from schizophrenia, major depression and Alzheimer's disease to cancer. Normal tissue integrity is preserved by feedback interactions between diverse cell types mediated by adhesion molecules and secreted cytokines. Disruption of normal feedback mechanisms in cancer, threatens tissue integrity. Over-secretion of cytokines can trigger a dangerous syndrome known as a cytokine storm. This may have been the cause of severe adverse events during a clinical trial of TGN1412. Cytokine storms also were the main cause of death in the 1918 "Spanish Flu" pandemic. Deaths were weighted more heavily towards people with healthy immune systems, due to its ability to produce stronger immune responses, likely increasing cytokine levels. Another important example of cytokine storm is seen in acute pancreatitis. Cytokines are integral and implicated in all angles of the cascade resulting in the systemic inflammatory response syndrome and multi organ failure associated with this intra-abdominal catastrophe.

https://en.wikipedia.org/wiki/Cytokine

Cytokinesis

Cytokinesis (from the Greek κύτος, "container" and κίνησις, "motion") is the process during cell division in which the cytoplasm of a single eukaryotic cell is divided to form two daughter cells. It usually initiates during the late stages of mitosis, and sometimes meiosis, splitting a mitotic cell in two, to ensure that chromosome number is maintained from one generation to the next. After cytokinesis two (daughter) cells will be formed that are exact copies of the (parent) original cell. It is formed after cytokinesis, each daughter cell is in the interphase portion of the cell cycle.

https://en.wikipedia.org/wiki/Cytokinesis

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Cytokinins

Cytokinins (CK) are a class of plant growth substances (phytohormones) that promote cell division, or cytokinesis, in plant roots and shoots. They are involved primarily in cell growth and differentiation, but also affect apical dominance, axillary bud growth, and leaf senescence.

There are two types of cytokinins: adenine-type cytokinins represented by kinetin, zeatin, and 6-benzylaminopurine, and phenylurea-type cytokinins like diphenylurea and thidiazuron (TDZ). Most adenine-type cytokinins are synthesized in roots. Cambium and other actively dividing tissues also synthesize cytokinins. No phenylurea cytokinins have been found in plants. Cytokinins participate in local and long-distance signaling, with the same transport mechanism as purines and nucleosides. Typically, cytokinins are transported in the xylem.

Cytokinins act in concert with auxin, another plant growth hormone. The two are complementary, having generally opposite effects. The ratio of auxin to cytokinin plays an important role in the effect of cytokinin on plant growth. Cytokinin alone has no effect on parenchyma cells. When cultured with auxin but no cytokinin, they grow large but do not divide. When cytokinin is added, the cells expand and differentiate. When cytokinin and auxin are present in equal levels, the parenchyma cells form an undifferentiated callus. More cytokinin induces growth of shoot buds, while more auxin induces root formation.

Cytokinins are involved in many plant processes, including cell division and shoot and root morphogenesis. They are known to regulate axillary bud growth and apical dominance. The "direct inhibition hypothesis" posits that these effects result from the cytokinin to auxin ratio. This theory states that auxin from apical buds travels down shoots to inhibit axiliary bud growth. This promotes shoot growth, and restricts lateral branching. Cytokinin moves from the roots into the shoots, eventually signaling lateral bud growth. Simple experiments support this theory. When the apical bud is removed, the axillary buds are uninhibited, lateral growth increases, and plants become bushier. Applying auxin to the cut stem again inhibits lateral dominance.

https://en.wikipedia.org/wiki/Cytokinin

Related Glossary Terms

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Cytoplasm

The cytoplasm comprises cytosol (the gel-like substance enclosed within the cell membrane) and the organelles – the cell's internal sub-structures. All of the contents of the cells of prokaryote organisms (such as bacteria, which lack a cell nucleus) are contained within the cytoplasm. Within the cells of eukaryote organisms the contents of the cell nucleus are separated from the cytoplasm, and are then called the nucleoplasm. The cytoplasm is about 80% water and usually colorless. It is within the cytoplasm that most cellular activities occur, such as many metabolic pathways including glycolysis, and processes such as cell division. The concentrated inner area is called the endoplasm and the outer layer is called the cell cortex or the ectoplasm. Movement of calcium ions in and out of the cytoplasm is a signaling activity for metabolic processes.

https://en.wikipedia.org/wiki/Cytoplasm

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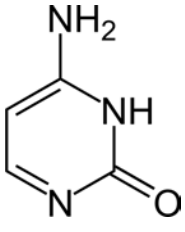
Cytosine

Cytosine is one of the four main bases found in DNA and RNA, along with adenine, guanine, and thymine (uracil in RNA). It is a pyrimidine derivative, with a heterocyclic aromatic ring and two substituents attached (an amine group at position 4 and a keto group at position 2). The nucleoside of cytosine is cytidine. In Watson-Crick base pairing, it forms three hydrogen bonds with guanine.

Cytosine can be found as part of DNA, as part of RNA, or as a part of a nucleotide. As cytidine triphosphate (CTP), it can act as a co-factor to enzymes, and can transfer a phosphate to convert adenosine diphosphate (ADP) to adenosine triphosphate (ATP). In DNA and RNA, cytosine is paired with guanine. However, it is inherently unstable, and can change into uracil (spontaneous deamination). This can lead to a point mutation if not repaired by the DNA repair enzymes such as uracil glycosylase, which cleaves a uracil in DNA.

When found third in a codon of RNA, cytosine is synonymous with uracil, as they are interchangeable as the third base. When found as the second base in a codon, the third is always interchangeable. For example, UCU, UCC, UCA and UCG are all serine, regardless of the third base.

Cytosine can also be methylated into 5-methylcytosine by an enzyme called DNA methyltransferase or be methylated and hydroxylated to make 5-hydroxymethylcytosine. Active enzymatic deamination of cytosine or 5-methylcytosine by the APOBEC family of cytosine deaminases could have both beneficial and detrimental implications on various cellular processes as well as on organismal evolution. The implications of deamination on 5-hydroxymethylcytosine, on the other hand, remains less understood.



https://en.wikipedia.org/wiki/Cytosine

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Cytoskeleton

In all cells of all domains of life (archaea, bacteria, eukaryotes) a cytoskeleton is found (notably in all eukaryotic cells, which include human, animal, fungal and plant cells). The cytoskeleton can be referred to as a complex network of interlinking filaments and tubules that extend throughout the cytoplasm, from the nucleus to the plasma membrane. The cytoskeletal systems of different organisms are composed of similar proteins. In eukaryotes, the cytoskeletal matrix is a dynamic structure composed of three main proteins, which are capable of rapid growth or disassembly dependent on the cell's requirements at a certain period of time.

However, the structure, function and dynamic behavior of the cytoskeleton can be very different, depending on organism and cell type. Similarly, within the same cell type the structure, dynamic behavior, and function of the cytoskeleton can change through association with other proteins and the previous history of the network.

There is a multitude of functions that the cytoskeleton can perform. Primarily, it gives the cell shape and mechanical resistance to deformation, so that through association with extracellular connective tissue and other cells it stabilizes entire tissues. The cytoskeleton can also actively contract, thereby deforming the cell and the cell's environment and allowing cells to migrate. Moreover, it is involved in many cell signaling pathways, in the uptake of extracellular material (endocytosis), segregates chromosomes during cellular division, is involved in cytokinesis (the division of a mother cell into two daughter cells), provides a scaffold to organize the contents of the cell in space and for intracellular transport (for example, the movement of vesicles and organelles within the cell); and can be a template for the construction of a cell wall. Furthermore, it forms specialized structures, such as flagella, cilia, lamellipodia and podosomes.

A large-scale example of an action performed by the cytoskeleton is muscle contraction. During contraction of a muscle, within each muscle cell, myosin molecular motors collectively exert forces on parallel actin filaments. This action contracts the muscle cell, and through the synchronous process in many muscle cells, the entire muscle.

https://en.wikipedia.org/wiki/Cytoskeleton

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Cytotoxic

Cytotoxicity is the quality of being toxic to cells. Examples of toxic agents are an immune cell or some types of venom, e.g. from the puff adder (*Bitis arietans*) or brown recluse spider (*Loxosceles reclusa*).

Treating cells with the cytotoxic compound can result in a variety of cell fates. The cells may undergo necrosis, in which they lose membrane integrity and die rapidly as a result of cell lysis. The cells can stop actively growing and dividing (a decrease in cell viability), or the cells can activate a genetic program of controlled cell death (apoptosis).

Cells undergoing necrosis typically exhibit rapid swelling, lose membrane integrity, shut down metabolism and release their contents into the environment. Cells that undergo rapid necrosis *in vitro* do not have sufficient time or energy to activate apoptotic machinery and will not express apoptotic markers. Apoptosis is characterized by well defined cytological and molecular events including a change in the refractive index of the cell, cytoplasmic shrinkage, nuclear condensation and cleavage of DNA into regularly sized fragments. Cells in culture that are undergoing apoptosis eventually undergo secondary necrosis. They will shut down metabolism, lose membrane integrity and lyse.

https://en.wikipedia.org/wiki/Cytotoxicity

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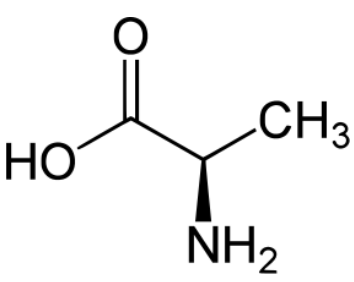
Chapter 4 - Catalysis: Basic Principles

D-alanine

The amino acid L-alanine is one of the most abundant ones in proteins. The right-handed form, D-alanine occurs in the peptidoglycan bacterial cell walls and in some peptide antibiotics.

The peptidoglycan layer in the bacterial cell wall is a crystal lattice structure formed from linear chains of two alternating amino sugars, namely N-acetylglucosamine (GlcNAc or NAG) and N-acetylmuramic acid (MurNAc or NAM). The alternating sugars are connected by a β-(1,4)-glycosidic bond. Each MurNAc is attached to a short (4- to 5-residue) amino acid chain, containing L-alanine, D-glutamic acid, meso-diaminopimelic acid, and D-alanine in the case of *Escherichia coli* (a Gram-negative bacterium) or L-alanine, D-glutamine, L-lysine, and D-alanine with a 5-glycine inter-bridge between tetrapeptides in the case of Staphylococcus aureus (a Gram-positive bacterium).



https://en.wikipedia.org/wiki/Alanine

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D-galactose

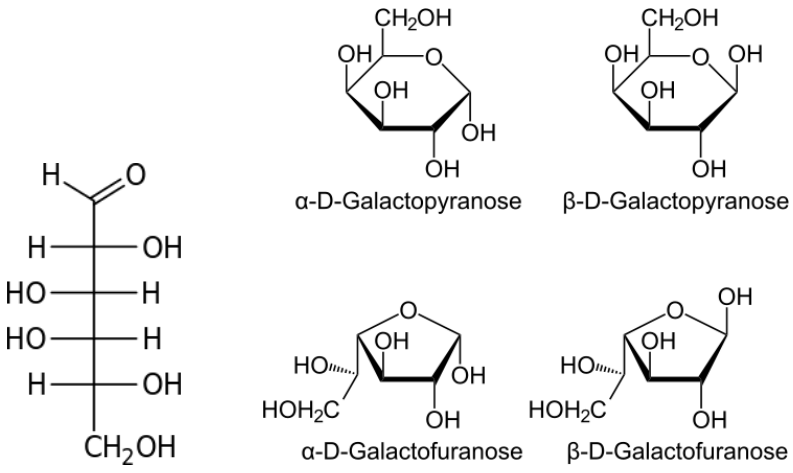
Galactose (galacto- + -ose, "milk sugar"), sometimes abbreviated Gal, is a monosaccharide sugar that is less sweet than glucose and fructose. It is a C-4 epimer of glucose. Galactan is a polymeric form of galactose found in hemicellulose. Galactan can be converted to galactose by hydrolysis.

Galactose is a monosaccharide. When combined with glucose (monosaccharide), through a condensation reaction, the result is the disaccharide lactose. The hydrolysis of lactose to glucose and galactose is catalyzed by the enzymes lactase and β-galactosidase. The latter is produced by the lac operon in *Escherichia coli*.

In nature, lactose is found primarily in milk and milk products. Consequently, various food products made with dairy-derived ingredients, e.g. breads and cereals, can contain lactose. Galactose metabolism, which converts galactose into glucose, is carried out by the three principal enzymes in a mechanism known as the Leloir pathway. The enzymes are listed in the order of the metabolic pathway: galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), and UDP-galactose-4'-epimerase (GALE).

In the human body, glucose is changed into galactose via hexoneogenesis to enable the mammary glands to secrete lactose. However, most lactose in breast milk is synthesized from galactose taken up from the blood, and only 35±6% is made from galactose from *de novo* synthesis. Glycerol also contributes some to the mammary galactose production.

Depicted below are the linear form of D-galactose and four different cyclic forms of D-galactose.



https://en.wikipedia.org/wiki/Galactose

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Chapter 2 - Structure & Function: Carbohydrates

D-glucose

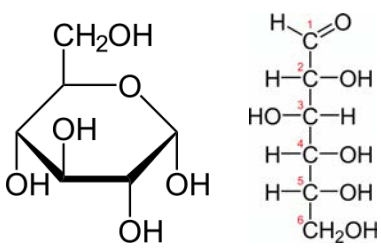
Glucose is a sugar with the molecular formula C6H12O6. The name "glucose" comes from the Greek word γλυκός, meaning "sweet wine, must". The suffix "-ose" is a chemical classifier, denoting a carbohydrate. It is also known as grape sugar. With 6 carbon atoms, it is classed as a hexose, a sub-category of monosaccharides. D-glucose is one of the 16 aldohexose stereoisomers. The D-isomer (D-glucose), also known as dextrose, occurs widely in nature, but the L-isomer (L-glucose) does not. Glucose is made during photosynthesis from water and carbon dioxide, using energy from sunlight. The reverse of the photosynthesis reaction, which releases this energy, is a very important source of power for cellular respiration. Glucose is stored as a polymer, in plants as starch and in animals as glycogen, for times when the organism will need it. Glucose circulates in the blood of animals as blood sugar. Glucose can be obtained by hydrolysis of carbohydrates such as milk, cane sugar, maltose, cellulose, glycogen etc. It is however, manufactured by hydrolysis of cornstarch by steaming and diluting acid.

Glucose is the most widely used aldohexose in living organisms. One possible explanation for this is that glucose has a lower tendency than other aldohexoses to react non-specifically with the amine groups of proteins. This reaction – glycation – impairs or destroys the function of many proteins. Glucose's low rate of glycation can be attributed to it having a more stable cyclic form compared to other aldohexoses, which means it spends less time than they do in its reactive open-chain form. The reason for glucose having the most stable cyclic form of all the aldohexoses is that its hydroxy groups (with the exception of the hydroxy group on the anomeric carbon of D-glucose) are in the equatorial position. Many of the long-term complications of diabetes (e.g., blindness, renal failure, and peripheral neuropathy) are probably due to the glycation of proteins or lipids. In contrast, enzyme-regulated addition of sugars to protein is called glycosylation and is essential for the function of many proteins.

Use of glucose as an energy source in cells is by either aerobic respiration, anaerobic respiration, or fermentation. All of these processes follow from an earlier metabolic pathway known as glycolysis. The first step of glycolysis is the phosphorylation of glucose by a hexokinase to form glucose 6-phosphate. The main reason for the immediate phosphorylation of glucose is to prevent its diffusion out of the cell as the charged phosphate group prevents glucose 6-phosphate from easily crossing the cell membrane. Furthermore, addition of the high-energy phosphate group activates glucose for subsequent breakdown in later steps of glycolysis. At physiological conditions this initial reaction is irreversible.

In anaerobic respiration, one glucose molecule produces a net gain of two ATP molecules (four ATP molecules are produced during glycolysis, but two are required by enzymes used during the process). In aerobic respiration, a molecule of glucose is much more profitable in that a maximum net production of 30 or 32 ATP molecules (depending on the organism) is generated.

Shown below are the cyclic and linear forms of glucose.



https://en.wikipedia.org/wiki/Glucose

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D-Glutamic Acid

Glutamic acid (abbreviated as Glu or E; encoded by the codons GAA or GAG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain carboxylic acid, classifying it as a polar negatively charged (at physiological pH), aliphatic amino acid. It is non-essential in humans, meaning the body can synthesize it.

Glutamate is a key compound in cellular metabolism. In humans, dietary proteins are broken down by digestion into amino acids, which serve as metabolic fuel for other functional roles in the body. A key process in amino acid degradation is transamination, in which the amino group of an amino acid is transferred to an α-ketoacid, typically catalyzed by a transaminase. The reaction can be generalized as such:

R_1-amino acid + R_2-α-ketoacid ⇌ R_1-α-ketoacid + R_2-amino acid

A very common α-keto acid is α-ketoglutarate, an intermediate in the citric acid cycle. Transamination of α-ketoglutarate gives glutamate. The resulting α-ketoacid product is often a useful one as well, which can contribute as fuel or as a substrate for further metabolism processes. Examples are as follows:

Alanine + α-ketoglutarate ⇌ Pyruvate + Glutamate

Aspartate + α-ketoglutarate ⇌ Oxaloacetate + Glutamate

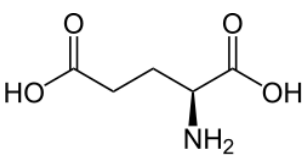
Both pyruvate and oxaloacetate are key components of cellular metabolism, contributing as substrates or intermediates in fundamental processes such as glycolysis, gluconeogenesis, and the citric acid cycle.

Glutamate also plays an important role in the body's disposal of excess or waste nitrogen. Glutamate undergoes deamination, an oxidative reaction catalyzed by glutamate dehydrogenase, as follows:

Glutamate + H_2O + $NADP^+$ → α-ketoglutarate + NADPH + NH_3 + H^+

Ammonia (as ammonium) is then excreted predominantly as urea, synthesized in the liver. Transamination can thus be linked to deamination, effectively allowing nitrogen from the amine groups of amino acids to be removed, via glutamate as an intermediate, and finally excreted from the body in the form of urea.

Glutamate is also a neurotransmitter, which makes it one of the most abundant molecules in the brain. Malignant brain tumors known as glioma or glioblastoma exploit this phenomenon by using glutamate as an energy source, especially when these mutations become more dependent on glutamate due to mutations in the gene IDH1.



https://en.wikipedia.org/wiki/Glutamic_acid

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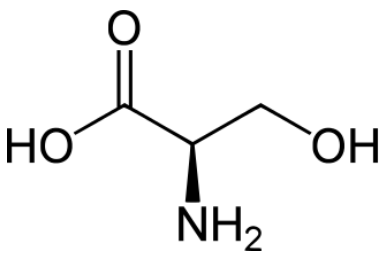
D-serine

Serine (abbreviated as Ser or S) encoded by the codons UCU, UCC, UCA, UCG, AGU and AGC is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), a carboxyl group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain hydroxyl group, classifying it as a polar amino acid. It is non-essential in humans, meaning the body can synthesize it.

D-Serine, synthesized in the brain by serine racemase from L-serine (its enantiomer), serves as a neuromodulator by coactivating NMDA receptors, making them able to open if they then also bind glutamate. D-serine is a potent agonist at the glycine site of the NMDA-type glutamate receptor (NMDAR). For the receptor to open, glutamate and either glycine or D-serine must bind to it. In fact, D-serine is a more potent agonist at the glycine site on the NMDAR than glycine itself. D-serine was only thought to exist in bacteria until relatively recently. It was the second D amino acid discovered to naturally exist in humans, present as a signaling molecule in the brain, soon after the discovery of D-aspartate. Had D amino acids been discovered in humans sooner, the glycine site on the NMDA receptor might instead be named the D-serine site. Apart from central nervous system, D-serine plays a signaling role in peripheral tissues and organs such as cartilage, kidney and corpus cavernosum.



https://en.wikipedia.org/wiki/Serine

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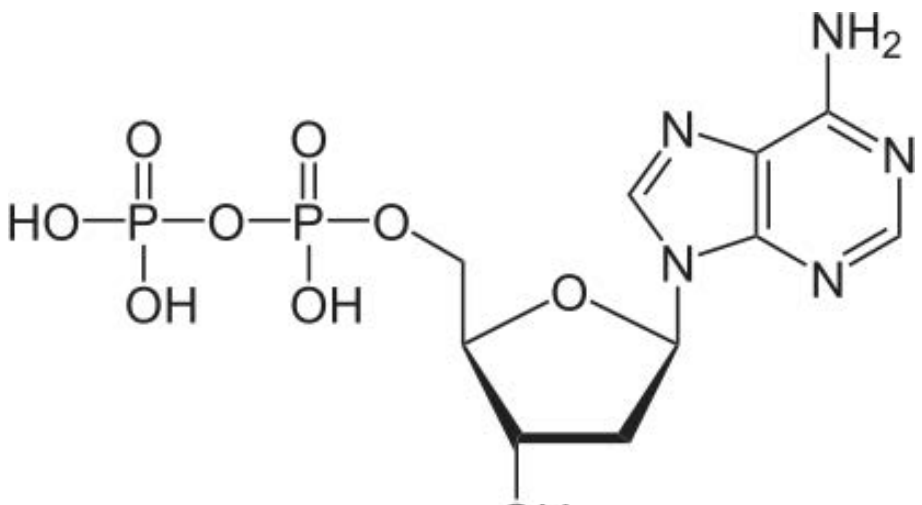
dADP

Deoxyadenosine diphosphate (dADP) is a nucleoside diphosphate. It is related to
common nucleic acid ATP, or adenosine triphosphate, with the -OH (hydroxyl) g
on the 2' carbon on the nucleotide's pentose removed (hence the deoxy- part of th
name), and with one fewer phosphoryl group than ATP. Deoxyadenosine diphosp
is abbreviated dADP.



https://en.wikipedia.org/wiki/Deoxyadenosine_diphosphate

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Chapter 6 - Metabolism: Nucleotides

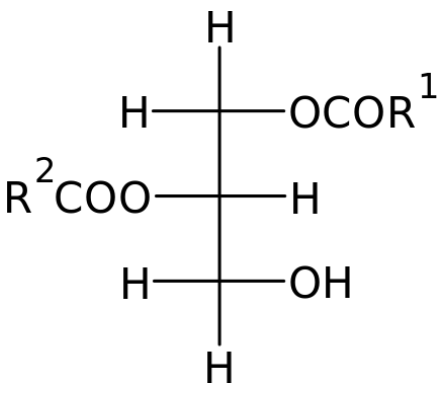
DAG

A diglyceride, or diacylglycerol (DAG), is a glyceride consisting of two fatty acid chains covalently bonded to a glycerol molecule through ester linkages. One example, shown on the right, is 1-palmitoyl-2-oleoyl-glycerol, which contains side-chains derived from palmitic acid and oleic acid. Diacylglycerols can also have many other combinations of fatty acids attached at either the C-1 and C-2 positions or the C-1 and C-3 positions. 1,2 disubstituted glycerols are always chiral, 1,3 disubstituted glycerols are chiral if the substituents are different from each other.

In biochemical signaling, diacylglycerol functions as a second messenger signaling lipid, and is a product of the hydrolysis of the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) by the enzyme phospholipase C (PLC) (a membrane-bound enzyme) that, through the same reaction, produces inositol trisphosphate (IP_3). Although inositol trisphosphate diffuses into the cytosol, diacylglycerol remains within the plasma membrane, due to its hydrophobic properties. IP_3 stimulates the release of calcium ions from the smooth endoplasmic reticulum, whereas DAG is a physiological activator of protein kinase C (PKC). The production of DAG in the membrane facilitates translocation of PKC from the cytosol to the plasma membrane.

In addition to activating PKC, diacylglycerol has a number of other functions in the cell:

- a source for prostaglandins
- a precursor of the endocannabinoid 2-arachidonoylglycerol
- an activator of a subfamily of transient receptor potential canonical (TRPC) cation channels, TRPC3/6/7.
-



https://en.wikipedia.org/wiki/Diglyceride

DAM Methylase

DAM methylase, an abbreviation for deoxyadenosine methylase, is an enzyme that adds a methyl group to the adenine of the sequence 5'-GATC-3' in newly synthesized DNA. Immediately after DNA synthesis, the daughter strand remains unmethylated a short time.

When DNA polymerase makes an error resulting in a mismatched base-pair or a sma insertion or deletion during DNA synthesis, the cell will repair the DNA by a pathway called mismatch repair. However, the cell must be able to differentiate between the template strand and the newly synthesized strand. In bacteria, DNA strands are meth lated by Dam methylase, and therefore, immediately after replication, the DNA will b hemimethylated. A repair enzyme, MutS, binds to mismatches in DNA and recruits MutL, which subsequently activates the endonuclease MutH. MutH binds hemimeth lated GATC sites and when activated will selectively cleave the unmethylated daught strand, allowing helicase and exonucleases to excise the nascent strand in the region surrounding the mismatch. The strand is then re-synthesized by DNA polymerase II

https://en.wikipedia.org/wiki/Dam_methylase

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Dark Cycle

The so-called dark cycle of photosynthesis (also known as the Calvin Cycle) is better called the light-independent cycle, because it is not require light, but actually occurs in the light. The Calvin cycle, reductive pentose phosphate cycle or C_3 cycle is a series of biochemical redox reactions that take place in the stroma of chloroplast in photosynthetic organisms. It is also known as the light-independent reactions.

Photosynthesis occurs in two stages in a cell. In the first stage, light-dependent reactions capture the energy of light and use it to make the energy-storage and transport molecules ATP and NADPH. The light-independent Calvin cycle uses the energy from short-lived electronically excited carriers to convert carbon dioxide and water into organic compounds that can be used by the organism (and by animals that feed on it). This set of reactions is also called carbon fixation. The key enzyme of the cycle is called RuBisCO. In the following biochemical equations, the chemical species (phosphates and carboxylic acids) exist in equilibria among their various ionized states as governed by the pH.

The enzymes in the Calvin cycle are functionally equivalent to most enzymes used in other metabolic pathways such as gluconeogenesis and the pentose phosphate pathway, but they are to be found in the chloroplast stroma instead of the cell cytosol, separating the reactions. They are activated in the light (which is why the name "dark reaction" is misleading), and also by products of the light-dependent reaction. These regulatory functions prevent the Calvin cycle from being respired to carbon dioxide. Energy (in the form of ATP) would be wasted in carrying out these reactions that have no net productivity.

The sum of reactions in the Calvin cycle is the following:

$3\ CO_2 + 6\ NADPH + 5\ H_2O + 9\ ATP \rightarrow \text{Glyceraldehyde-3-phosphate} + 2\ H^+ + 6\ NADP^+ + 9\ ADP + 8\ P_i$

Hexose (six-carbon) sugars are not a product of the Calvin cycle. Although many texts list a product of photosynthesis as $C_6H_{12}O_6$, this is mainly a convenience to counter the equation of respiration, where six-carbon sugars are oxidized in mitochondria. The carbohydrate products of the Calvin cycle are three-carbon sugar phosphate molecules, or "triose phosphates," namely, glyceraldehyde-3-phosphate.

https://en.wikipedia.org/wiki/Light-independent_reactions#Calvin_Cycle

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Related Glossary Terms

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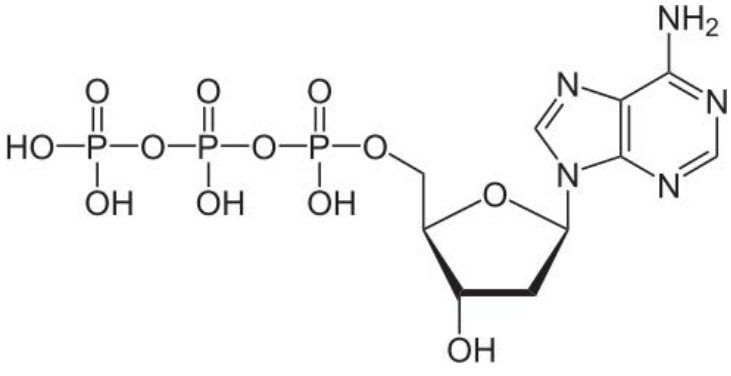
dATP

Deoxyadenosine triphosphate (dATP) is a nucleoside triphosphate used in cells for DNA synthesis (or replication), as a substrate of DNA polymerase. It is also an allosteric inhibitor of the enzyme ribonucleotide reductase.



https://en.wikipedia.org/wiki/Deoxyadenosine_triphosphate

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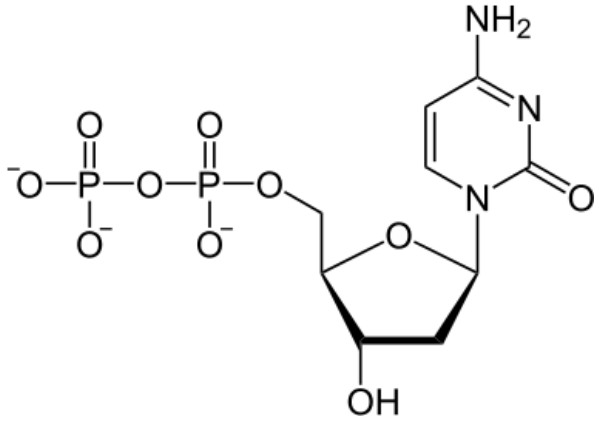
dCDP

Deoxycytidine diphosphate (dCDP) is a nucleoside diphosphate. It is related to the common nucleic acid CTP, or cytidine triphosphate, with the -OH (hydroxyl) group on the 2' carbon on the nucleotide's pentose removed (hence the deoxy- part of the name), and with one fewer phosphoryl group than CTP. 2'-deoxycytidine diphosphate is abbreviated as dCDP. dCDP is a product of action of the enzyme ribonucleotide reductase, which makes it from CDP.



https://en.wikipedia.org/wiki/Deoxycytidine_diphosphate

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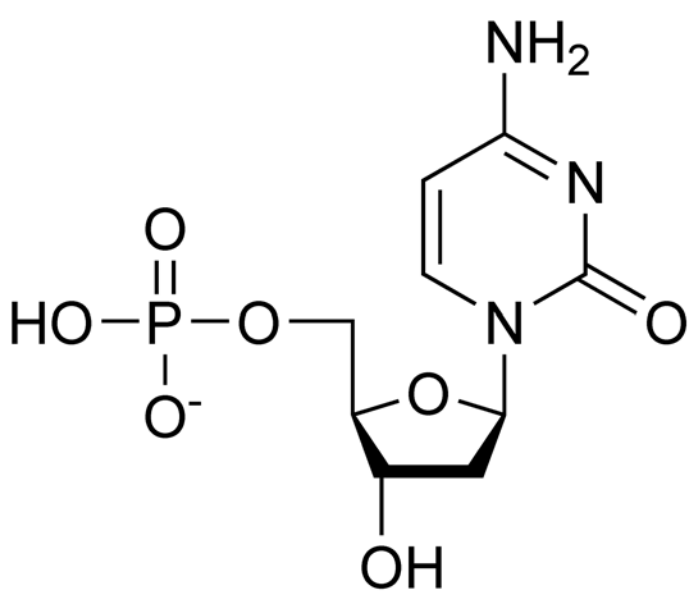
dCMP

Deoxycytidine monophosphate (dCMP), also known as deoxycytidylic acid or deo
dylate in its conjugate acid and conjugate base forms, respectively, is a deoxynucl
tide, and one of the four monomers that make up DNA. In a DNA double helix, it
base pair with deoxyguanosine monophosphate.



https://en.wikipedia.org/wiki/Deoxycytidine_monophosphate

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Chapter 6 - Metabolism: Nucleotides

Chapter 9 - Point by Point: Metabolism

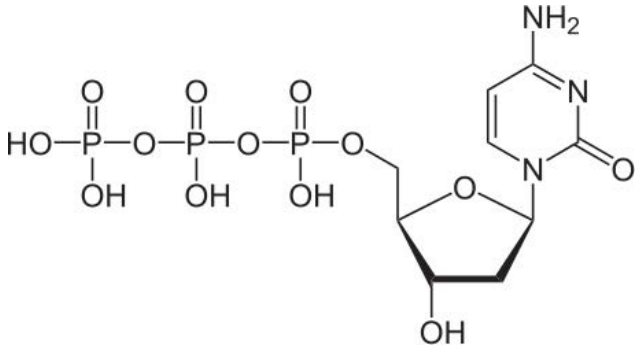
dCTP

Deoxycytidine triphosphate (dCTP) is a nucleoside triphosphate that contains the pyrimidine base cytosine. The triphosphate group contains high-energy phosphoanhydride bonds, which liberate energy when hydrolized.

DNA polymerase enzymes use this energy to incorporate deoxycytidine into a newly synthesized strand of DNA. A chemical equation can be written that represents the process:

$(DNA)n + dCTP \leftrightarrow (DNA)n\text{-}C + PP_i$

That is, dCTP has the PP_i (pyrophosphate) cleaved off and the dCMP is incorporated into the DNA strand at the 3' end. Subsequent hydrolysis of the PP_i drives the equilibrium of the reaction toward the right side, i.e. incorporation of the deoxyribonucleotide in the growing DNA chain.



https://en.wikipedia.org/wiki/Deoxycytidine_triphosphate

Related Glossary Terms

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DD Transpeptidase

The bacterial peptidoglycan cell wall network is built in a multi-step process.
The enzyme catalyzing the addition of the N-acetylmuramic acid-N-acetylglucosamine-decapeptide to the network in the last step of the construction is DD-transpeptidase.
β-Lactam antibiotics inhibit the formation of peptidoglycan cross-links in the bacterial cell wall by binding of the four-membered β-lactam ring of penicillin to the enzyme DD-transpeptidase. As a consequence, DD-transpeptidase cannot catalyze formation of these cross-links, and an imbalance between cell wall production and degradation develops, causing the cell to rapidly die.

Bacteria constantly remodel their peptidoglycan cell walls, simultaneously building and breaking down portions of the cell wall as they grow and divide. The enzymes that hydrolyze the peptidoglycan cross-links continue to function in the presence of penicillin, even while those that form such cross-links do not. This weakens the cell wall of the bacterium, and osmotic pressure becomes increasingly uncompensated—eventually causing cell death (cytolysis). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the cell wall's peptidoglycans. The small size of the penicillins increases their potency, by allowing them to penetrate the entire depth of the cell wall. This is in contrast to the glycopeptide antibiotics vancomycin and teicoplanin, which are both much larger than the penicillins.

https://en.wikipedia.org/wiki/Penicillin

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De novo pathways

De novo is a Latin phrase, literally translating to "from the new," but imply
"from scratch," or "from the beginning." *De novo* synthesis refers to the sy
complex molecules from simple molecules such as sugars or amino acids, a
to recycling after partial degradation. For example, nucleotides are not nee
diet as they can be constructed from small precursor molecules such as for
partate. Methionine, on the other hand, is needed in the diet because while
graded to and then regenerated from homocysteine, it cannot be synthesize

https://en.wikipedia.org/wiki/De_novo_synthesis

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Chapter 6 - Metabolism: Nucleotides

Chapter 9 - Point by Point: Metabolism

Chapter 9 - Point by Point: Metabolism

Chapter 9 - Point by Point: Metabolism

Deaminate

Deamination is the removal of an amine group from a molecule. Enzymes that catalyze this reaction are called deaminases.

Deamination is the removal of an amine group from a molecule. Enzymes that catalyze this reaction are called deaminases. In the human body, deamination takes place primarily in the liver, however glutamate is also deaminated in the kidneys. Deamination is the process by which amino acids are broken down if there is an excess of protein intake. The amino group is removed from the amino acid and converted to ammonia. The rest of the amino acid is made up of mostly carbon and hydrogen, and is recycled or oxidized for energy. Ammonia is toxic to the human system, and enzymes convert it to urea or uric acid by addition of carbon dioxide molecules (which is not considered a deamination process) in the urea cycle, which also takes place in the liver. Urea and uric acid can safely diffuse into the blood and then be excreted in urine.

Spontaneous deamination is the hydrolysis reaction of cytosine into uracil, releasing ammonia in the process. This can occur *in vitro* through the use of bisulfite, which converts cytosine, but not 5-methylcytosine. This property has allowed researchers to sequence methylated DNA to distinguish non-methylated cytosine (shown up as uracil) and methylated cytosine (unaltered).

In DNA, this spontaneous deamination is corrected for by the removal of uracil (product of cytosine deamination and not part of DNA) by uracil-DNA glycosylase, generating an abasic (AP) site. The resulting abasic site is then recognized by enzymes (AP endonucleases) that break a phosphodiester bond in the DNA, permitting the repair of the resulting lesion by replacement with another cytosine. A DNA Polymerase may perform this replacement via nick translation, a terminal excision reaction by its 5'-->3' exonuclease activity, followed by a fill-in reaction by its polymerase activity. DNA ligase then forms a phosphodiester bond to seal the resulting nicked duplex product, which now includes a new, correct cytosine.

Spontaneous deamination of 5-methylcytosine results in thymine and ammonia. This is the most common single nucleotide mutation. In DNA, this reaction, if detected prior to passage of the replication fork, can be corrected by the enzyme thymine-DNA glycosylase, which removes the thymine base in a G/T mismatch. This leaves abasic site that is repaired by AP endonucleases and polymerase, like with uracil-DNA glycosylase.

https://en.wikipedia.org/wiki/Deamination

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https://en.wikipedia.org/wiki/Deamination

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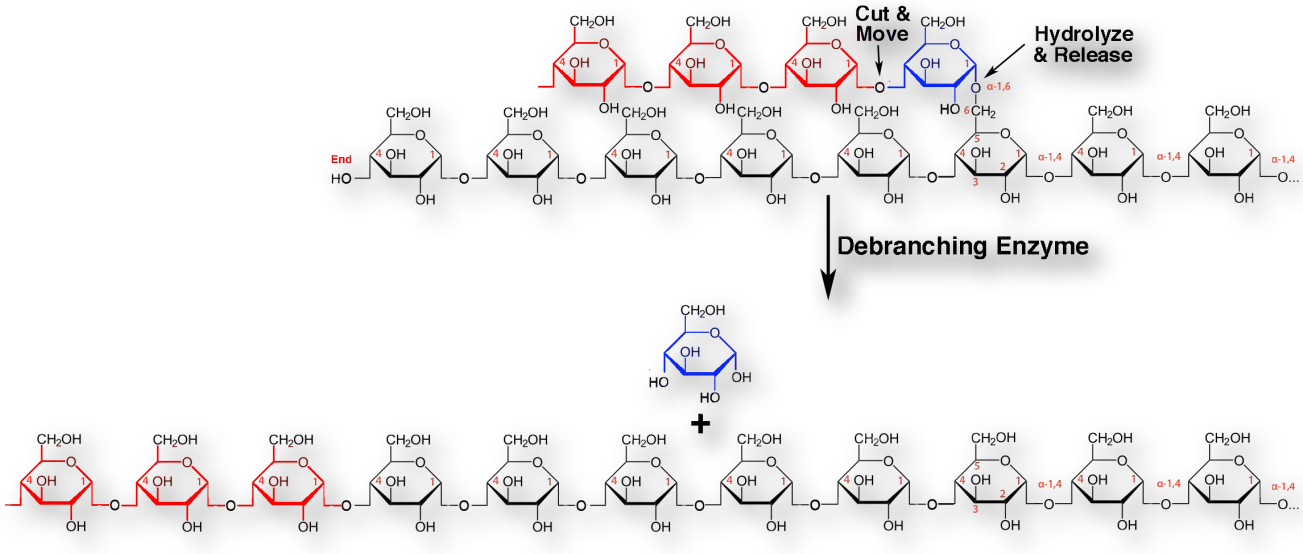
Debranching Enzyme

A debranching enzyme is a molecule that helps facilitate the breakdown of glycogen, which serves as a store of glucose in the body, through glucosyltransferase and glucosidase activity. Together with phosphorylases, debranching enzymes mobilize glucose reserves from glycogen deposits in the muscles and liver. This constitutes a major source of energy reserves in most organisms. Glycogen breakdown is highly regulated in the body, especially in the liver, by various hormones including insulin and glucagon, to maintain a homeostatic balance of blood-glucose levels.

When glycogen breakdown is compromised by mutations in the glycogen debranching enzyme, metabolic diseases such as Glycogen storage disease type III can result. Glucosyltransferase and glucosidase are performed by a single enzyme in mammals, yeast, and some bacteria, but by two distinct enzymes in *E. coli* and other bacteria, complicating nomenclature. Proteins that catalyze both functions are referred to as glycogen debranching enzymes (GDEs). When glucosyltransferase and glucosidase are catalyzed by distinct enzymes, "glycogen debranching enzyme" usually refers to the glucosidase enzyme. In some literature, an enzyme capable only of glucosidase is referred to as a "debranching enzyme".



https://en.wikipedia.org/wiki/Glycogen_debranching_enzyme

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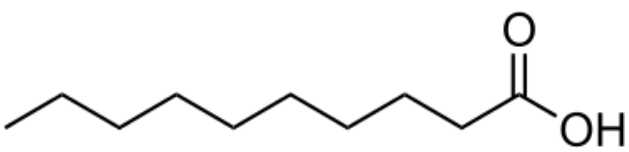
Decanoic Acid

Decanoic acid (capric acid) is a saturated fatty acid. Its formula is $CH_3(CH_2)_8COOH$. Salts and esters of decanoic acid are called decanoates or "caprates". The term capric acid is derived from the Latin "caper / capra" (goat) because the sweaty, unpleasant smell of the compound is reminiscent of goats.

Decanoic acid acts as a non-competitive AMPA receptor antagonist at therapeutically relevant concentrations, in a voltage- and subunit-dependent manner, and this is sufficient to explain its antiseizure effects. This direct inhibition of excitatory neurotransmission by decanoic acid in the brain contributes to the anticonvulsant effect of the MCT ketogenic diet. Decanoic acid and the AMPAr antagonist drug perampanel act at separate sites on the AMPA receptor, and so it is possible that they have a cooperative effect at the AMPA receptor, suggesting that permapanel and the ketogenic diet could be synergistic.

Decanoic acid may mimic the mitochondrial proliferation associated with the ketogenic diet, and that this may occur via PPARγ receptor agonism and its target genes involved in mitochondrial biogenesis.

It should however be noted that orally ingested medium chain fatty acids would be very rapidly degraded by first-pass metabolism by being taken up in the liver via the portal vein, and are quickly metabolized via coenzyme A intermediates through β-oxidation and the citric acid cycle to produce carbon dioxide, acetate and ketone bodies. It is unclear whether the ketones β-hydroxybutryate and acetone have direct antiseizure activity.



https://en.wikipedia.org/wiki/Decanoic_acid

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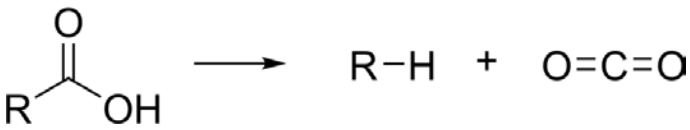
Decarboxylation

Decarboxylation is a chemical reaction that removes a carboxyl group and releases carbon dioxide (CO_2). Usually, decarboxylation refers to a reaction of carboxylic acids, removing a carbon atom from a carbon chain. The reverse process, which is the first chemical step in photosynthesis, is called carboxylation, the addition of CO_2 to a compound. Enzymes that catalyze decarboxylations are called decarboxylases or, the more formal term, carboxy-lyases (EC number 4.1.1).



https://en.wikipedia.org/wiki/Decarboxylation

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Defensins

Defensins are small cysteine-rich cationic proteins found in both vertebrate
tebrates. They have also been reported in plants. They are, and function as,
fense peptides. They are active against bacteria, fungi and many enveloped
veloped viruses. They consist of 18-45 amino acids including six (in vertebr
eight conserved cysteine residues. Cells of the immune system contain thes
to assist in killing phagocytosed bacteria, for example in neutrophil granulo
almost all epithelial cells. Most defensins function by binding to the microb
membrane, and, once embedded, forming pore-like membrane defects that
flux of essential ions and nutrients.

https://en.wikipedia.org/wiki/Defensin

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Dehydration

In chemistry and the biological sciences, a dehydration reaction is usually c
chemical reaction that involves the loss of a water molecule from the reacti
cule. Dehydration reactions are a subset of condensation reactions. Because
droxyl group (–OH) is a poor leaving group, having a Brønsted acid catalys
helps by protonating the hydroxyl group to give the better leaving group, –
reverse of a dehydration reaction is a hydration reaction. Common dehydra
used in organic synthesis include concentrated sulfuric acid, concentrated p
acid, hot aluminium oxide and hot ceramic.

https://en.wikipedia.org/wiki/Dehydration_reaction

Related Glossary Terms

Drag related terms here

Dehydrogenation

Dehydrogenation is a chemical reaction that involves the removal of hydrog
molecule. It is the reverse process of hydrogenation. Dehydrogenation reac
conducted both on industrial and laboratory scales. Dehydrogenation conv
rated fats to unsaturated fats. Enzymes that catalyze dehydrogenation are c
drogenases. Dehydrogenation processes are used extensively to produce sty
fine chemicals, oleochemicals, petrochemicals, and detergents industries.

https://en.wikipedia.org/wiki/Dehydrogenation

Related Glossary Terms

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Delta G

In thermodynamics, the change in the Gibbs free energy is a thermodynamic potential that measures the maximum or reversible work that may be performed by a thermodynamic system at a constant temperature and pressure (isothermal, isobaric).

The Gibbs free energy (kJ in SI units) is the maximum amount of non-expansion work that can be extracted from a thermodynamically closed system (one that can exchange heat and work with its surroundings, but not matter); this maximum can be attained only in a completely reversible process. When a system changes from a well-defined initial state to a well-defined final state, the Gibbs free energy change ΔG equals the work exchanged by the system with its surroundings, minus the work of the pressure forces, during a reversible transformation of the system from the initial state to the final state.

The Gibbs energy (also referred to as G) is also the thermodynamic potential that is minimized when a system reaches chemical equilibrium at constant pressure and temperature. Its derivative with respect to the reaction coordinate of the system vanishes at the equilibrium point. As such, a reduction in G is a necessary condition for the spontaneity of processes at constant pressure and temperature.

https://en.wikipedia.org/wiki/Gibbs_free_energy

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Delta G°’

The change in the standard Gibbs free energy of formation of a compound (ΔG°) is the change of Gibbs free energy that accompanies the formation of 1 mole of a substance in its standard state from its constituent elements in their standard states (the most stable form of the element at 1 bar of pressure and the specified temperature, usually 298.15 K or 25 °C). In biological systems, a slightly modified ΔG° is employed. It is known as ΔG°’ since it substitutes a solution of pH of 7 instead of having protons at 1M, a concentration living systems do not function at.

https://en.wikipedia.org/wiki/Standard_Gibbs_free_energy_of_formation

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Delta H

Enthalpy is a measurement of energy in a thermodynamic system. It include
nal energy, which is the energy required to create a system, and the amount
required to make room for it by displacing its environment and establishing
and pressure.

The ΔH is a positive change in endothermic reactions, and negative in heat-r
exothermic processes.

The change in enthalpy, ΔH, for a reaction, is a factor in the change in Gibbs
ergy for that reaction. Specifically,

$\Delta G = \Delta H - T \Delta S$

https://en.wikipedia.org/wiki/Enthalpy

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Delta S

In thermodynamics, entropy (S) is a measure of the number of microscopic c
tions that correspond to a thermodynamic system in a state specified by cert
scopic variables.

Entropy can be understood as a measure of molecular disorder within a mac
system. The second law of thermodynamics states that an isolated system's e
never decreases.

The change in entropy, ΔS, for a reaction, is a factor in the change in Gibbs f
for that reaction. Specifically,

$\Delta G = \Delta H - T \Delta S$

https://en.wikipedia.org/wiki/Entropy

Related Glossary Terms

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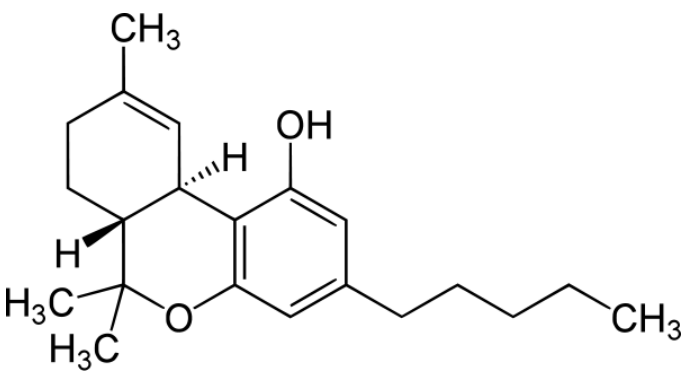
Delta-9-tetrahydrocannabinol

Tetrahydrocannabinol (THC, dronabinol by INN), or more precisely its main isomer (−)-*trans*-Δ9-tetrahydrocannabinol, is the principal psychoactive constituent (or cannabinoid) of cannabis. It can be an amber or gold colored glassy solid when cold, which becomes viscous and sticky if warmed.

Like most pharmacologically-active secondary metabolites of plants, THC in *Cannabis* is assumed to be involved in self-defense, perhaps against herbivores. THC also possesses high UV-B (280–315 nm) absorption properties, which, it has been speculated, could protect the plant from harmful UV radiation exposure.

THC, along with its double bond isomers and their stereoisomers, is one of only three cannabinoids scheduled by the UN Convention on Psychotropic Substances (the other two are dimethylheptylpyran and parahexyl). It was listed under Schedule I in 1971, but reclassified to Schedule II in 1991 following a recommendation from the WHO. Based on subsequent studies, the WHO has recommended the reclassification to the less-stringent Schedule III. Cannabis as a plant is scheduled by the Single Convention on Narcotic Drugs (Schedule I and IV).

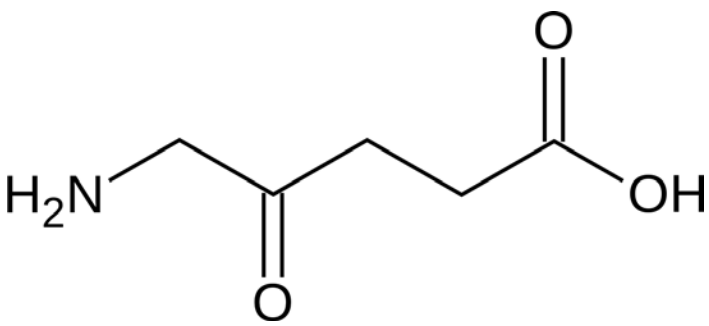


https://en.wikipedia.org/wiki/Tetrahydrocannabinol

Delta-aminolevulinic Acid

δ-Aminolevulinic acid (dALA or δ-ALA or 5ala or 5-aminolevulinic acid) is the first compound in the porphyrin synthesis pathway, the pathway that leads to heme in mammals and chlorophyll in plants.

In plants, production of δ-ALA is the step on which the speed of synthesis of chlorophyll is regulated. Plants that are fed by external δ-ALA accumulate toxic amounts of chlorophyll precursor, protochlorophyllide, indicating that the synthesis of this intermediate is not suppressed anywhere downwards in the chain of reaction. Protochlorophyllide is a strong photosensitizer in plants.



https://en.wikipedia.org/wiki/Aminolevulinic_acid

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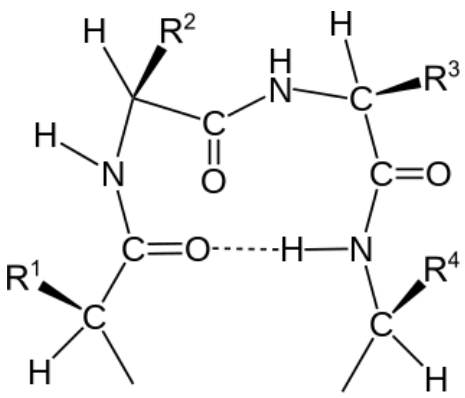
Delta-turns

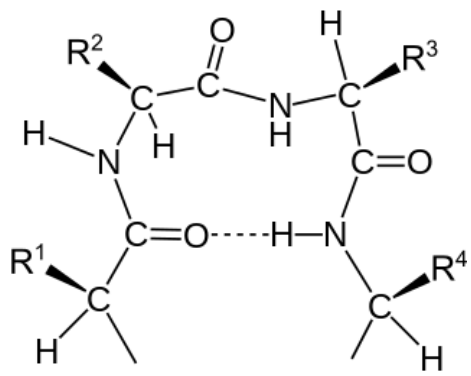
A turn is an element of secondary structure in proteins where the polypeptide chain reverses its overall direction.

Turns are classified according to the separation between the two end residues:
In an α-turn the end residues are separated by four peptide bonds
(i --> i +/- 4).
•In a δ-turn, by one bond
(i --> i +/- 1).

Shown below is a β turn



ß turn: Type I



ß turn: Type II

https://en.wikipedia.org/wiki/Turn_(biochemistry)

Related Glossary Terms

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Dementia

Dementia, also known as senility, is a broad category of brain diseases that
long term and often gradual decrease in the ability to think and remember
enough to affect a person's daily functioning. Other common symptoms inc
tional problems, problems with language, and a decrease in motivation. A p
sciousness is usually not affected. A dementia diagnosis requires a change f
son's usual mental functioning and a greater decline than one would expect
ing. These diseases also have a significant effect on a person's caregivers.

https://en.wikipedia.org/wiki/Dementia

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Chapter 2 - Structure & Function: Proteins I

Denaturation

Denaturation is a process in which proteins or nucleic acids lose the quaternary structure, tertiary structure and secondary structure which is present in their native state, by application of some external stress or compound such as a strong acid or base, a concentrated inorganic salt, an organic solvent (e.g., alcohol or chloroform), radiation or heat. If proteins in a living cell are denatured, this results in disruption of cell activity and possibly cell death. Denatured proteins can exhibit a wide range of characteristics, from conformational change and loss of solubility to aggregation due to the exposure of hydrophobic groups.

Protein folding is key to whether a globular protein or a membrane protein can do its job correctly. It must be folded into the right shape to function. But hydrogen bonds, which play a big part in folding, are rather weak, and it doesn't take much heat, acidity, or other stress to break some and form others, denaturing the protein. This is one reason why tight homeostasis is physiologically necessary in many life forms.

This concept is unrelated to denatured alcohol, which is alcohol that has been mixed with additives to make it unsuitable for human consumption.

https://en.wikipedia.org/wiki/Denaturation_(biochemistry)

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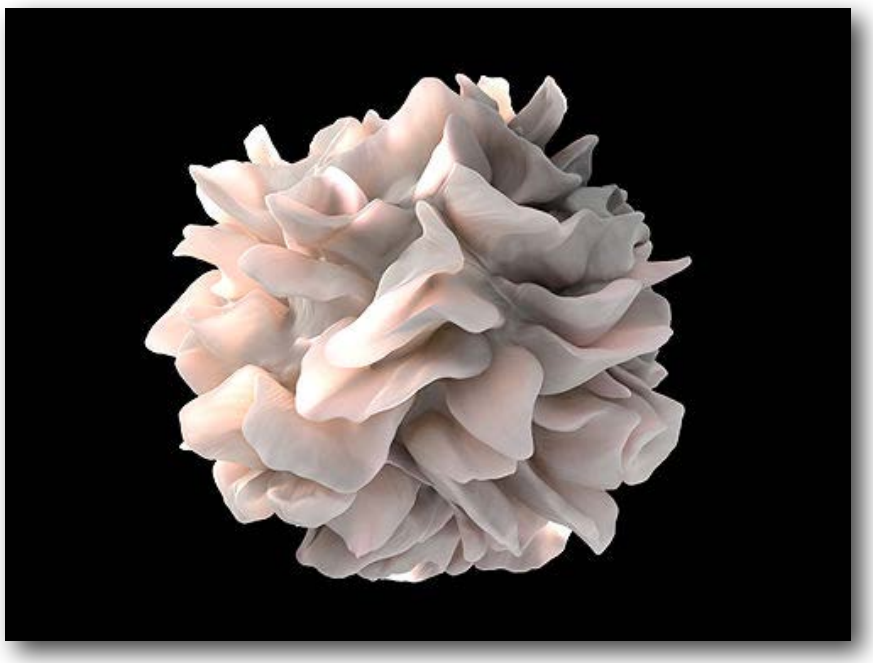
Dendritic cells

Dendritic cells (DCs) are antigen-presenting cells (also known as accessory cells) of the mammalian immune system. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system. They act as messengers between the innate and the adaptive immune systems.

Dendritic cells are present in those tissues that are in contact with the external environment, such as the skin (where there is a specialized dendritic cell type called the Langerhans cell) and the inner lining of the nose, lungs, stomach and intestines. They can also be found in an immature state in the blood. Once activated, they migrate to the lymph nodes where they interact with T cells and B cells to initiate and shape the adaptive immune response. At certain development stages they grow branched projections, the dendrites that give the cell its name (δένδρον or déndron being Greek for "tree"). While similar in appearance, these are structures distinct from the dendrites of neurons. Immature dendritic cells are also called veiled cells, as they possess large cytoplasmic 'veils' rather than dendrites.

Below - an artist's rendering of a dendritic cell.



https://en.wikipedia.org/wiki/Dendritic_cell

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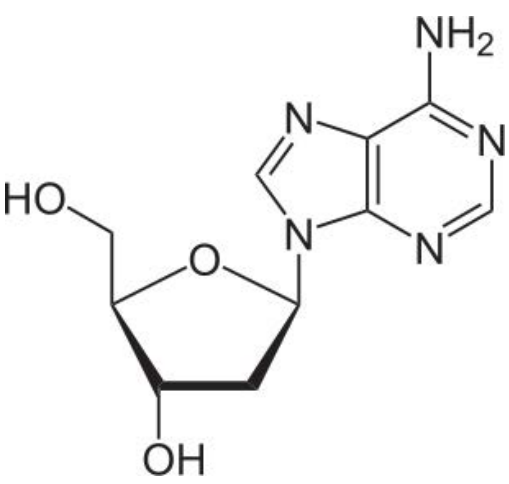
Chapter 2 - Structure & Function: Carbohydrates

Deoxyadenosine

Deoxyadenosine (symbol dA or dAdo) is a deoxyribonucleoside. It is a derivative of the nucleoside adenosine, differing from the latter by the replacement of a hydroxyl group (-OH) by hydrogen (-H) at the 2' position of its ribose sugar moiety. Deoxyadenosine is the DNA nucleoside A, which pairs with deoxythymidine (T) in double-stranded DNA.

In absence of adenosine deaminase (ADA) it accumulates in T lymphocytes and kills these cells resulting in a genetic disorder known as adenosine deaminase severe combined immunodeficiency disease (ADA-SCID).



https://en.wikipedia.org/wiki/Deoxyadenosine

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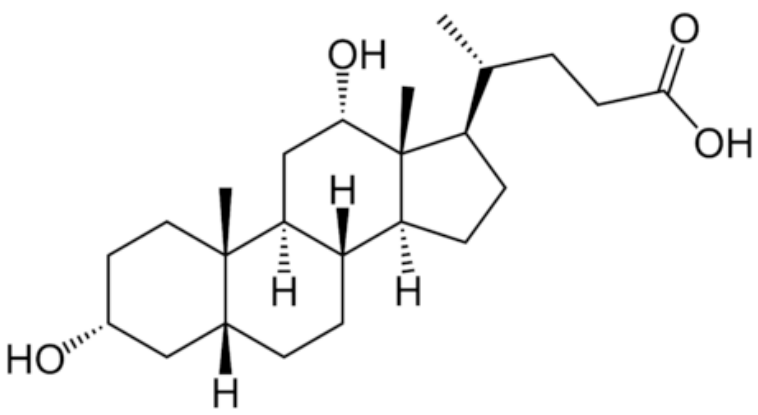
Chapter 2 - Structure and Function: Nucleic Acids

Deoxycholic Acid

Deoxycholic acid (conjugate base deoxycholate), also known as cholanoic acid and 3α, 12α-dihydroxy-5β-cholan-24-oic acid, is a bile acid. Deoxycholic acid is one of the secondary bile acids, which are metabolic byproducts of intestinal bacteria. The two primary bile acids secreted by the liver are cholic acid and chenodeoxycholic acid. Bacteria metabolize chenodeoxycholic acid into the secondary bile acid lithocholic acid, and they metabolize cholic acid into deoxycholic acid. There are additional secondary bile acids, such as ursodeoxycholic acid. Deoxycholic acid is soluble in alcohol and acetic acid. When pure, it comes in a white to off-white crystalline powder form.

A number of factors, including diet, obesity, and exercise, affect the level of deoxycholate in the human colon. When humans were switched from their usual diet to a meat, egg and cheese based diet for five days, deoxycholate in their feces increased by factors of 2 to 10 fold. Rats, fed diets with either 30% beef tallow (high fat) or 5% beef tallow (low fat) had almost 2-fold more deoxycholate in their feces on the high fat compared to the low fat diet. In this study, adding the further dietary elements of curcumin or caffeic acid to the rats' high fat (30% beef tallow) diet reduced the deoxycholate in their feces to levels comparable to levels seen in the rats on a low fat diet. Curcumin is a component of the spice turmeric, and caffeic acid is a component high in some fruits and spices. Caffeic acid is also a digestive break-down product of chlorogenic acid, high in coffee and some fruits and vegetables.



https://en.wikipedia.org/wiki/Deoxycholic_acid

Related Glossary Terms

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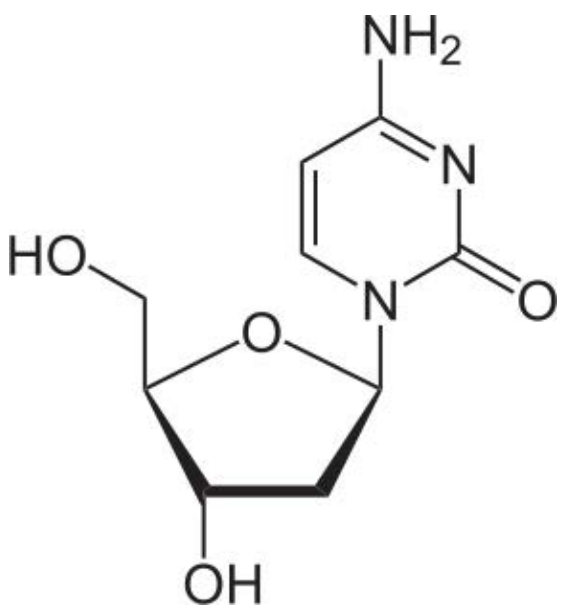
Deoxycytidine

Deoxycytidine is a deoxyribonucleoside, a component of deoxyribonucleic acid
similar to the ribonucleoside cytidine, but with one hydroxyl group removed fr
2' position. Deoxycytidine can be phosphorylated by deoxycytidine kinase (DC



https://en.wikipedia.org/wiki/Deoxycytidine

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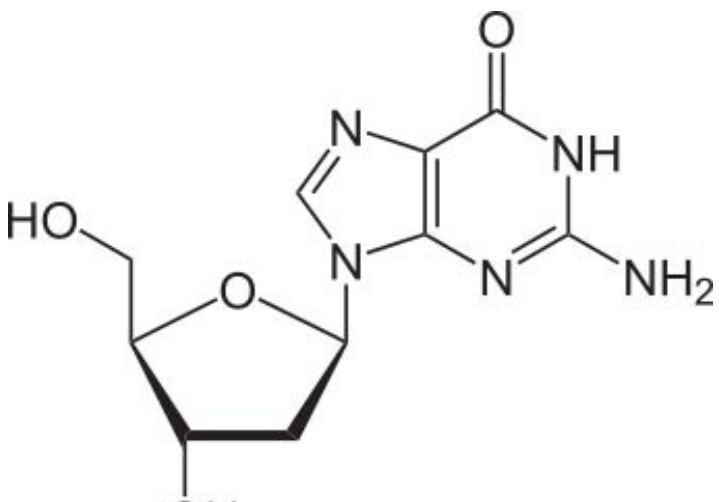
Deoxyguanosine

Deoxyguanosine is composed of the purine nucleobase guanine linked by its N_9 n
gen to the C_1 carbon of deoxyribose. It is similar to guanosine, but with one hydro
group removed from the 2' position of the ribose sugar (making it deoxyribose). I
phosphate group is attached at the 5' position, it becomes deoxyguanosine monop
phate.



https://en.wikipedia.org/wiki/Deoxyguanosine

Related Glossary Terms

Drag related terms here

Deoxynucleotides

A deoxyribonucleotide (deoxynucleotide) is the monomer, or single unit, of
oxyribonucleic acid. Each deoxyribonucleotide comprises three parts: a nitr
base, a deoxyribose sugar, and one phosphate group. The nitrogenous base
bonded to the 1' carbon of the deoxyribose, which is distinguished from ribo
presence of a proton on the 2' carbon rather than an -OH group. The phosp
bind to the 5' carbon of the sugar. When deoxyribonucleotides polymerize t
DNA, the phosphate group from one nucleotide will bond to the 3' carbon o
nucleotide, forming a phosphodiester bond via dehydration synthesis. New
are always added to the 3' carbon of the last nucleotide, so synthesis always
from 5' to 3'.

https://en.wikipedia.org/wiki/Deoxyribonucleotide

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Deoxyribonucleoside Diphosphates

Deoxyribonucleoside diphosphates are the products of action of ribonucleo
tase acting on ribonucleoside disphosphates in the nucleotide synthesis pat
oxyribonucleotides. Specifically they include dADP, dCDP, dUDP, and dGD
not produced by ribonucleotide reductase and instead is made by action of
cleoside monophosphate kinase acting on dTMP. All of the deoxyribonucle
phosphates are substrates for the enzyme NDPK in the synthesis of deoxyri
side triphosphates.

Related Glossary Terms

Drag related terms here

Deoxyribonucleoside Triphosphates

Deoxyribonucleoside triphosphates are the products of action of the enzym
ing on deoxyribonucleoside triphosphates in the nucleotide synthesis pathw
oxyribonucleotides. Specifically they include dATP, dCTP, dUTP, dTTP and
dUTP is rapidly degraded to dUMP by the enzyme dUMPase. All of the deo
cleoside triphosphates are substrates for DNA polymerases and are thus the
blocks of DNA.

Related Glossary Terms

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Deoxyribonucleosides

A deoxyribonucleoside is a type of nucleoside containing deoxyribose as a c

https://en.wikipedia.org/wiki/Deoxyribonucleoside

Related Glossary Terms

Drag related terms here

Deoxyribonucleotides

A deoxyribonucleotide is the monomer, or single unit, of DNA, or deoxyribonucleic acid. Each deoxyribonucleotide comprises three parts: a nitrogenous base, a deoxyribose sugar, and one phosphate group. The nitrogenous base is always bonded to the 1' carbon of the deoxyribose, which is distinguished from ribose by the presence of a proton on the 2' carbon rather than an -OH group. The phosphate groups bind to the 5' carbon of the sugar.

When deoxyribonucleotides polymerize to form DNA, the phosphate group from one nucleotide will bond to the 3' carbon on another nucleotide, forming a phosphodiester bond via dehydration synthesis. New nucleotides are always added to the 3' carbon of the last nucleotide, so synthesis always proceeds from 5' to 3'.

https://en.wikipedia.org/wiki/Deoxyribonucleotide

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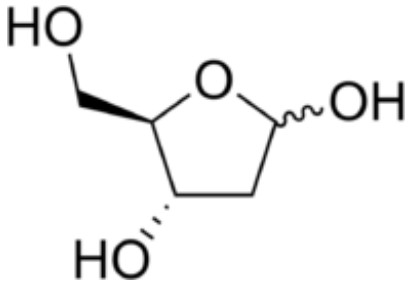
Deoxyribose

Deoxyribose, or more precisely 2-deoxyribose, is a monosaccharide with idealized formula H−(C=O)−(CH_2)−($CHOH)_3$−H. Its name indicates that it is a deoxy sugar, meaning that it is derived from the sugar ribose by loss of an oxygen atom. Since the pentose sugars arabinose and ribose only differ by the stereochemistry at C_2', 2-deoxyribose and 2-deoxyarabinose are equivalent, although the latter term is rarely used because ribose, not arabinose, is the precursor to deoxyribose.



https://en.wikipedia.org/wiki/Deoxyribose

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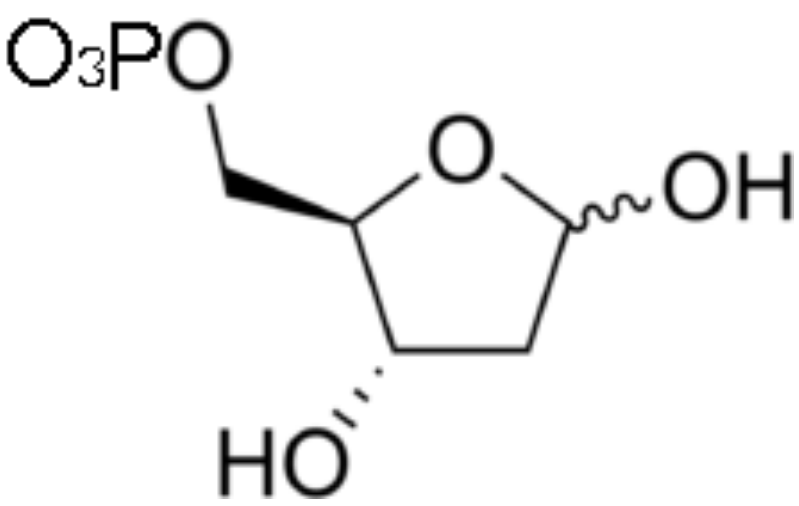
Deoxyribose-5-phosphate

Deoxyribose-5-phosphate is a a molecule that is a breakdown product of a c
cleotide. It is further broken down in the following reaction

2-deoxy-D-ribose 5-phosphate <=> D-glyceraldehyde 3-phosphate + Aceta

by the enzyme deoxyribose-phosphate aldolase



https://en.wikipedia.org/wiki/Deoxyribose-phosphate_aldolase

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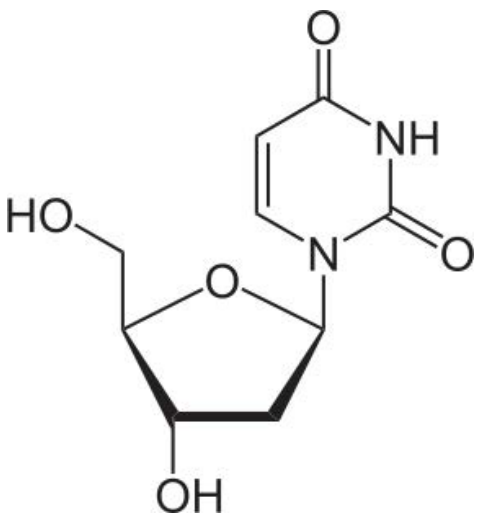
Chapter 6 - Metabolism: Nucleotides

Chapter 9 - Point by Point: Metabolism

Deoxyuridine

Deoxyuridine (dU) is a compound and a nucleoside. It is similar in chemical stru
to uridine, but without the 2'-hydroxyl group. Idoxuridine and Trifluridine are v
of deoxyuridine used as antiviral drugs. They are similar enough to be incorpora
part of DNA replication, but they possess side groups on the uracil component (a
dine and a CF3 group, respectively), that prevent base pairing.



https://en.wikipedia.org/wiki/Deoxyuridine

Related Glossary Terms

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Dephosphorylation

Dephosphorylation is the removal of a phosphate (PO_4^{3-}) group from an organic compound by hydrolysis. It is a reversible post-translational modification. Dephosphorylation and its counterpart, phosphorylation, activate and deactivate enzymes by detaching or attaching phosphoric esters and anhydrides. A notable occurrence of dephosphorylation is the conversion of ATP to ADP and inorganic phosphate.

Dephosphorylation employs a type of hydrolytic enzyme, or hydrolase, which cleave ester bonds. The prominent hydrolase subclass used in dephosphorylation is phosphatase. Phosphatase removes phosphate groups by hydrolyzing phosphoric acid monoesters into a phosphate ion and a molecule with a free hydroxyl (-OH) group. The reversible phosphorylation-dephosphorylation reaction occurs in every physiological process, making proper function of protein phosphatases necessary for organism viability. Because protein dephosphorylation is a key process involved in cell signaling, protein phosphatases are implicated in conditions such as cardiac disease, diabetes, and Alzheimer's disease.

https://en.wikipedia.org/wiki/Dephosphorylation

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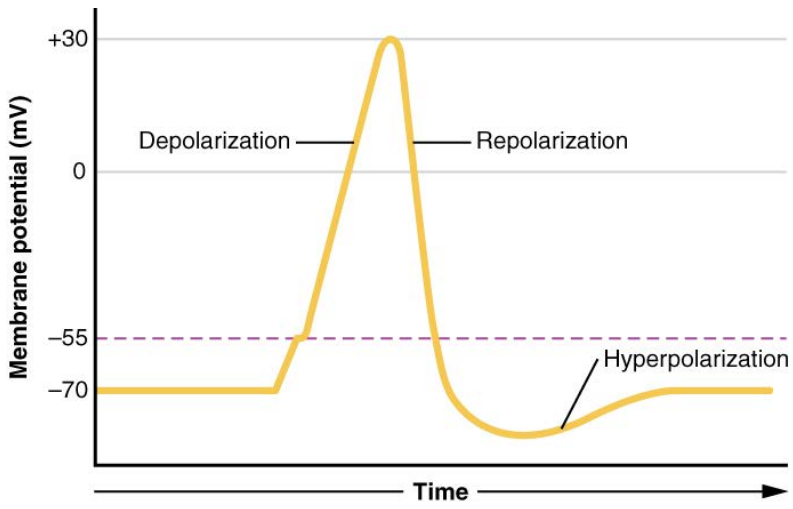
Depolarization

Depolarization, in biology, refers to a sudden change within a cell, during which the cell undergoes a dramatic electrical change. Most cells, especially those that compose the tissues of highly organized animals, typically maintain an internal environment that is negatively charged compared to the cell's surrounding environment. This difference in charge is called the cell's membrane potential. In the process of depolarization, the negative internal charge of the cell becomes positive for a very brief time. This shift from a negative to a positive internal cellular environment allows for the transmission of electrical impulses both within a cell and, in certain instances, between cells. This communicative function of depolarization is essential to the function of many cells, communication between cells, and the overall function of an organism.

The process of depolarization is entirely dependent upon the intrinsic electrical nature of most cells. When a cell is at rest, the cell maintains what is known as a resting potential. The resting potential generated by nearly all cells results in the interior of the cell having a negative charge compared to the exterior of the cell. To maintain this electrical imbalance, microscopic positively and negatively charged particles called ions are transported across the cell's plasma membrane. The transport of the ions across the plasma membrane is accomplished through several different types of transmembrane proteins embedded in the cell's plasma membrane that function as pathways for ions both into and out of the cell, such as ion channels, sodium potassium pumps, and voltage gated ion channels.



https://en.wikipedia.org/wiki/Depolarization

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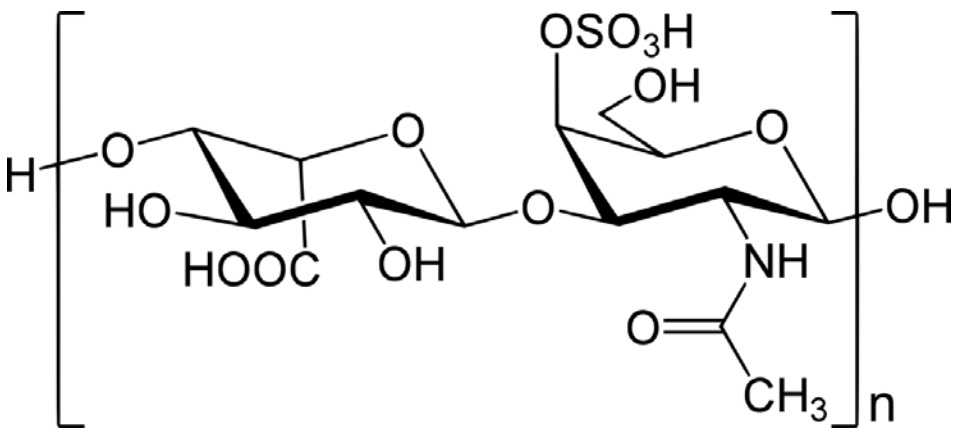
Dermatan Sulfate

Dermatan sulfate is a glycosaminoglycan (formerly called a mucopolysaccharide found mostly in skin, but also in blood vessels, heart valves, tendons, and lungs. also referred to as chondroitin sulfate B, although it is no longer classified as a fo chondroitin sulfate by most sources. The formula is $C_{14}H_{21}NO_{15}S$.

The image below shows the repeating unit of dermatan sulfate.



https://en.wikipedia.org/wiki/Dermatan_sulfate

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Chapter 2 - Structure & Function: Carbohydrates

Chapter 9 - Point by Point: Structure and Function

Desaturase

A fatty acid desaturase is an enzyme that removes two hydrogen atoms from a fatty acid, creating a carbon/carbon double bond. These desaturases are classified as

Δ - indicating that the double bond is created at a fixed position from the carboxyl group of a fatty acid (for example, Δ^9desaturase creates a double bond at the 9th position from the carboxyl end).

ω (e.g. ω^3desaturase) - indicating the double bond is created between the third and fourth carbon from the methyl end of the fatty acid.

In the biosynthesis of essential fatty acids, an elongase alternates with different desaturases (for example, Δ^6desaturase) repeatedly inserting an ethyl group, then forming a double bond.

Four desaturases occur in humans: Δ^9desaturase, Δ^6desaturase, Δ^5desaturase, and Δ^4desaturase. Δ^9desaturase, also known as stearoyl-CoA desaturase-1, is used to synthesize oleic acid, a monounsaturated, ubiquitous component of all cells in the human body. Δ^9desaturase produces oleic acid by desaturating stearic acid, a saturated fatty acid either synthesized in the body from palmitic acid or ingested directly.

Δ^6 and Δ^5 desaturases are required for the synthesis of highly unsaturated fatty acids such as eicosopentaenoic and docosahexaenoic acids (synthesized from α-linolenic acid), and arachidonic acid (synthesized from linoleic acid). This is a multi-stage process requiring successive actions by elongase and desaturase enzymes. The genes coding for Δ^6 and Δ^5desaturase production have been located on human chromosome 11.

https://en.wikipedia.org/wiki/Fatty_acid_desaturase

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Desaturation

In organic chemistry, a saturated compound is a chemical compound that h
of carbon atoms all linked together by single bonds. Alkanes are saturated h
bons. An unsaturated compound is a chemical compound that contains car
double bonds or triple bonds, such as those found in alkenes or alkynes, res
Saturated and unsaturated compounds need not consist only of a carbon at

They can form straight chain, branched chain, or ring arrangements. They c
functional groups, as well. It is in this sense that fatty acids are classified as
or unsaturated. The amount of unsaturation of a fatty acid can be determin
ing its iodine number.

https://en.wikipedia.org/wiki/Saturated_and_unsaturated_compounds

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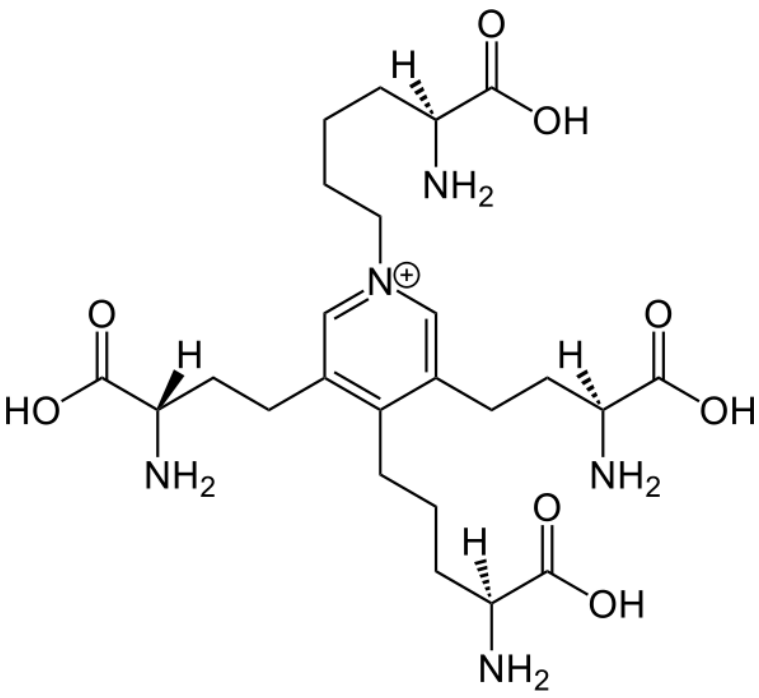
Desmosine

A desmosine cross-link is formed from three allysyl side chains plus one unaltered lysyl side chain from the same or neighboring polypeptides. Detection of desmosine in urine, plasma or sputum samples can be a marker for elastin breakdown due to high elastase activity related to certain diseases.

Desmosine causes a yellow color in elastin and is responsible for its rubbery properties.



https://en.wikipedia.org/wiki/Desmosine

Related Glossary Terms

Dexamethasone

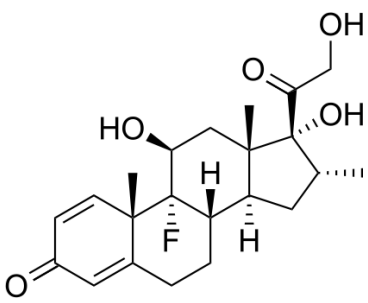
Dexamethasone is a type of steroid medication. It is used in the treatment of rheumatic problems, a number of skin diseases, severe allergies, asthma, chronic obstructive lung disease, croup, brain swelling, and along with antibiotics in tuberculosis, among others. In adrenocortical insufficiency it should be used together with a medication that has greater mineralocorticoid effects such as fludrocortisone. In preterm labor, it may be used to improve outcomes in the baby. It may be taken by mouth, as an injection into a muscle, or intravenously. The effects of dexamethasone are frequently seen within a day and last for about three days.

Dexamethasone is used to treat many inflammatory and autoimmune conditions, such as rheumatoid arthritis and bronchospasm. Idiopathic thrombocytopenic purpura, a decrease in numbers of platelets due to an immune problem, responds to 40 mg daily for four days. It may be administered in 14-day cycles. It is unclear whether dexamethasone in this condition is significantly better than other glucocorticoids.

It is also given in small amounts before and/or after some forms of dental surgery, such as the extraction of the wisdom teeth, an operation which often leaves the patient with puffy, swollen cheeks.

Dexamethasone is injected into the heel when treating plantar fasciitis, sometimes in conjunction with triamcinolone acetonide. It is useful to counteract allergic anaphylactic shock, if given in high doses.

Dexamethasone is present in certain eye drops – particularly after eye surgery – and as a nasal spray (trade name Dexacort), and certain ear drops (Sofradex, when combined with an antibiotic and an antifungal). Dexamethasone intravitreal steroid implants (trade name Ozurdex) have been approved by the FDA to treat ocular conditions such as diabetic macular edema, central retinal vein occlusion, and uveitis.



https://en.wikipedia.org/wiki/Dexamethasone

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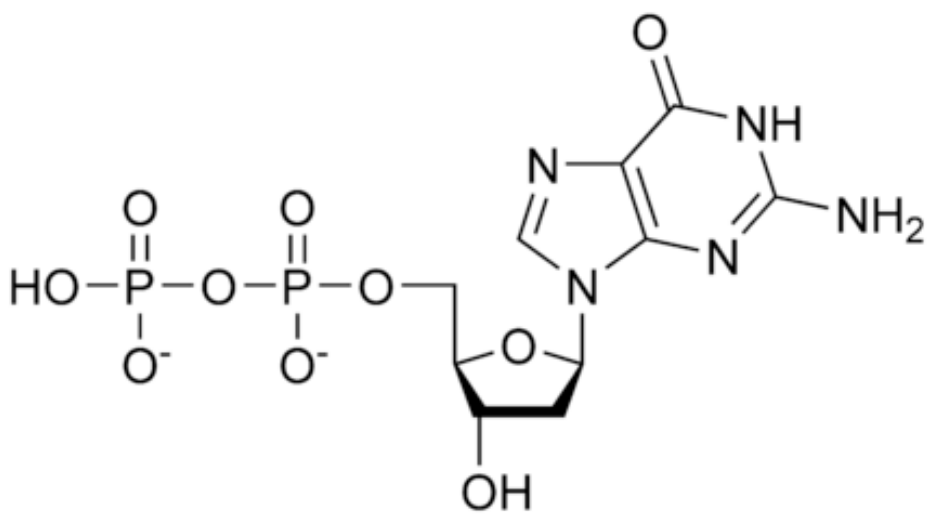
Chapter 2 - Structure & Function: Lipids

dGDP

Deoxyguanosine diphosphate (dGDP) is a nucleoside diphosphate. It is related to
common nucleic acid guanosine triphosphate (GTP), with the -OH group on the 2
bon on the nucleotide's pentose removed (hence the deoxy- part of the name), and
one fewer phosphoryl group than GTP. dGDP is a product of action of ribonucleo
reductase, which uses GDP as a substrate.



https://en.wikipedia.org/wiki/Deoxyguanosine_diphosphate

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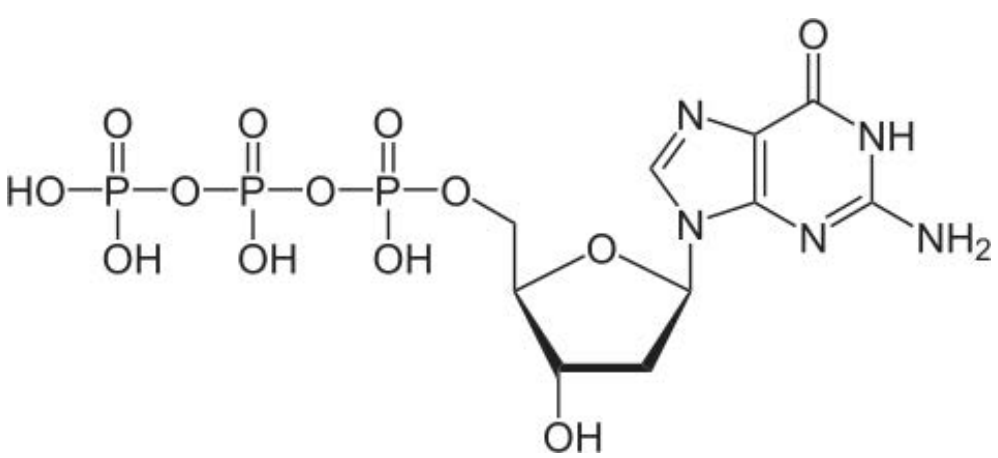
Chapter 6 - Metabolism: Nucleotides

dGTP

Deoxyguanosine triphosphate (dGTP) is a nucleoside triphosphate, and a n
precursor used in cells for DNA synthesis. The substance is used in the poly
chain reaction technique, in sequencing, and in cloning. It is also the compo
hibition onset by acyclovir in the treatment of HSV virus.



https://en.wikipedia.org/wiki/Deoxyguanosine_triphosphate

Related Glossary Terms

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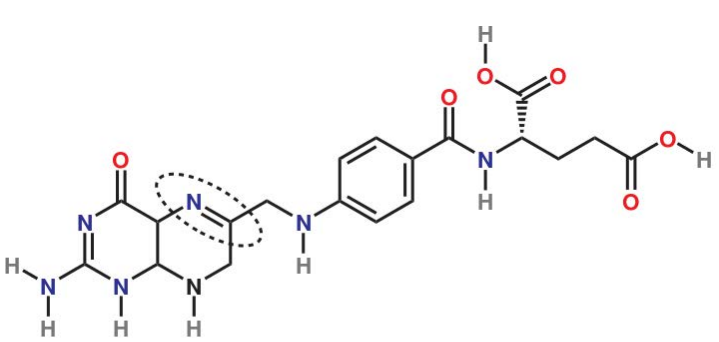
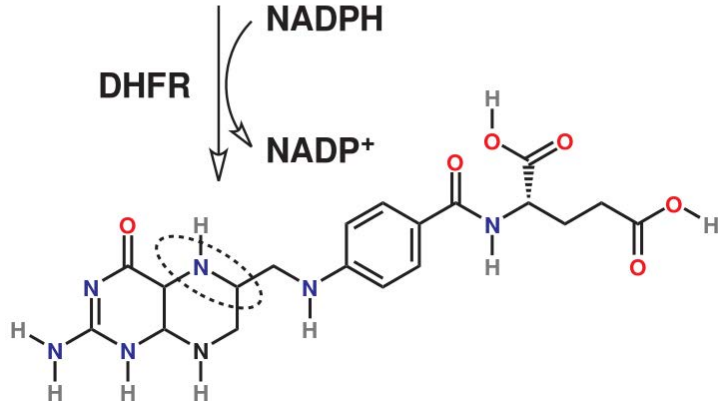
DHFR

Dihydrofolate reductase, or DHFR, is an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid, using NADPH as electron donor, which can be converted to the kinds of tetrahydrofolate cofactors used in 1-carbon transfer chemistry.

Dihydrofolate reductase converts dihydrofolate into tetrahydrofolate, a methyl group shuttle required for the *de novo* synthesis of purines, thymidylic acid, and certain amino acids. While the functional dihydrofolate reductase gene has been mapped to chromosome 5, multiple intronless processed pseudogenes or dihydrofolate reductase-like genes have been identified on separate chromosomes.

The reaction catalyzed by DHFR is shown below.





https://en.wikipedia.org/wiki/Dihydrofolate_reductase

Related Glossary Terms

Drag related terms here

Diabetes

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of me
eases in which there are high blood sugar levels over a prolonged period. Sy
high blood sugar include frequent urination, increased thirst, and increased
left untreated, diabetes can cause many complications. Acute complications
betic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term co
tions include cardiovascular disease, stroke, chronic kidney failure, foot ulc
damage to the eyes. Diabetes is due to either the pancreas not producing en
lin (type I) or the cells of the body not responding properly to the insulin pr
(type II).

https://en.wikipedia.org/wiki/Diabetes_mellitus

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Diacylglyceride Lipase

Diacylglycerol lipase, also known as DAG lipase, diacylglyceride lipase, DA
is a key enzyme in the biosynthesis of the endocannabinoid 2-arachidonoyl
catalyzes the hydrolysis of diacylglycerol, releasing a free fatty acid and mo
erol.

Two separate genes encoding DGL enzymes have been cloned, termed DGL
and DGLβ (DAGLB), that share 33% sequence identity.

https://en.wikipedia.org/wiki/Diacylglycerol_lipase

Related Glossary Terms

Drag related terms here

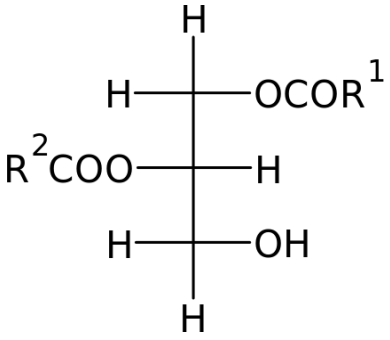
Diacylglycerol

A diglyceride, or diacylglycerol (DAG), is a glyceride consisting of two fatty acid chains covalently bonded to a glycerol molecule through ester linkages. One example, shown on the right, is 1-palmitoyl-2-oleoyl-glycerol, which contains side-chains derived from palmitic acid and oleic acid. Diacylglycerols can also have many other combinations of fatty acids attached at either the C-1 and C-2 positions or the C-1 and C-3 positions. 1,2 disubstituted glycerols are always chiral, 1,3 disubstituted glycerols are chiral if the substituents are different from each other.

In biochemical signaling, diacylglycerol functions as a second messenger signaling lipid, and is a product of the hydrolysis of the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) by the enzyme phospholipase C (PLC) (a membrane-bound enzyme) that, through the same reaction, produces inositol trisphosphate (IP_3). Although inositol trisphosphate diffuses into the cytosol, diacylglycerol remains within the plasma membrane, due to its hydrophobic properties. IP_3 stimulates the release of calcium ions from the smooth endoplasmic reticulum, whereas DAG is a physiological activator of protein kinase C (PKC). The production of DAG in the membrane facilitates translocation of PKC from the cytosol to the plasma membrane.

In addition to activating PKC, diacylglycerol has a number of other functions in the cell:

- a source for prostaglandins
- a precursor of the endocannabinoid 2-arachidonoylglycerol
- an activator of a subfamily of transient receptor potential canonical (TRPC) cation channels, TRPC3/6/7.
-



https://en.wikipedia.org/wiki/Diglyceride

Related Glossary Terms

Drag related terms here

Diaminopimelate Decarboxylase

Diaminopimelate decarboxylase (EC 4.1.1.20) is an enzyme that catalyzes the chem reaction

Meso-2,6-diaminoheptanedioate <-> L-lysine + CO_2

Hence, this enzyme has one substrate, meso-2,6-diaminoheptanedioate, and two p ucts, L-lysine and CO_2. This enzyme belongs to the family of lyases, specifically th carboxy-lyases, which cleave carbon-carbon bonds. The systematic name of this en zyme class is meso-2,6-diaminoheptanedioate carboxy-lyase (L-lysine-forming). C names in common use include diaminopimelic acid decarboxylase, meso-diaminopimelate decarboxylase, DAP-decarboxylase, and meso-2,6-diaminoheptanedioate carboxy-lyase.

This enzyme participates in lysine biosynthesis. It employs one cofactor, pyridoxa phosphate.

https://en.wikipedia.org/wiki/Diaminopimelate_decarboxylase

Related Glossary Terms

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Diaminopimelate Epimerase

Diaminopimelate epimerase (EC 5.1.1.7) is an enzyme that catalyzes the chemical rea
tion

LL-2,6-diaminoheptanedioate <-> Meso-diaminoheptanedioate

The enzyme, which catalyzes the isomerization of L,L-dimaminopimelate to meso-D
in the biosynthetic pathway leading from aspartate to lysine, is a member of the
broader family of PLP-independent amino acid racemases. Diaminopimelate epime-
rase is a monomeric protein of about 30 kDa consisting of two domains which are si
lar in structure though they share little Sequence alignment. Each domain consists o
mixed β-sheets which fold into a barrel around the central helix. The active site cleft
formed from both domains and contains two conserved cysteines thought to functio
as the acid and base in the catalysis. Other PLP-independent racemases such as gluta
mate racemase have been shown to share a similar structure and mechanism of catal
sis.

https://en.wikipedia.org/wiki/Diaminopimelate_epimerase

Related Glossary Terms

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Diastereomers

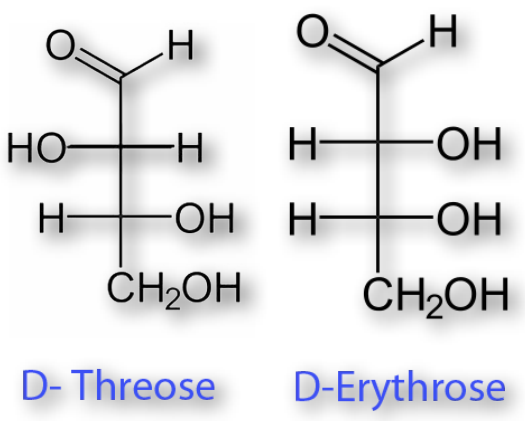
Diastereomers (sometimes called diastereoisomers) are a type of a stereoisomer. Diastereomerism occurs when two or more stereoisomers of a compound have different configurations at one or more (but not all) of the equivalent (related) stereocenters and are not mirror images of each other. When two diastereoisomers differ from each other at only one stereocenter they are epimers. Each stereocenter gives rise to two different configurations and thus increases the number of stereoisomers by a factor of two.

Diastereomers differ from enantiomers in that the latter are pairs of stereoisomers that differ in all stereocenters and are therefore mirror images of one another. Enantiomers of a compound with more than one stereocenter are also diastereomers of the other stereoisomers of that compound that are not their mirror image. Diastereomers have different physical properties (unlike enantiomers) and different chemical reactivity. Diastereoselectivity is the preference for the formation of one or more than one diastereomer over the other in an organic reaction.

If a molecule contains two asymmetric carbons, there are up to 4 possible configurations, and they cannot all be non-superimposable mirror images of each other. The possibilities continue to multiply as there are more asymmetric centers in a molecule. In general, the number of configurational isomers of a molecule can be determined by calculating 2n, where n = the number of chiral centers in the molecule. This holds true except in cases where the molecule has meso forms.

For n = 3, there are eight stereoisomers. There are four pairs of enantiomers: R,R,R and S,S,S; R,R,S and S,S,R; R,S,S and S,R,R; and R,S,R and S,R,S. There are four diastereomers, because each of the pairs of enantiomers is a diastereomer with respect to the other three. For n = 4, there are sixteen stereoisomers, or eight pairs of enantiomers. The four aldopentoses and the eight aldohexoses (subsets of the five- and six-carbon sugars) are examples of sets of compounds that differ in this way.

Pictured below are two diastereomers.



https://en.wikipedia.org/wiki/Diastereomer

Related Glossary Terms

Dicer

Dicer, also known as endoribonuclease Dicer or helicase with RNase motif, is an enzyme that in humans is encoded by the DICER1 gene. Being part of the RNase III family, Dicer cleaves double-stranded RNA (dsRNA) and pre-microRNA (pre-miRNA) into short double-stranded RNA fragments called small interfering RNA and microRNA, respectively. These fragments are approximately 20-25 base pairs long with a two-base overhang on the 3' end. Dicer facilitates the activation of the RNA-induced silencing complex (RISC), which is essential for RNA interference. RISC has a catalytic component argonaute, which is an endonuclease capable of degrading messenger RNA (mRNA).

RNA interference is a process where the breakdown of RNA molecules into miRNA inhibits gene expression of specific host mRNA sequences. miRNA is produced within the cell starting from primary miRNA (pri-miRNA) in the nucleus. These long sequences are cleaved into smaller precursor miRNA (pre-miRNA), which are usually 70 nucleotides with a hairpin structure. Pri-miRNA are identified by DGCR8 and cleaved by Drosha to form the pre-miRNA. These pre-miRNA are then cleaved by Dicer to form mature miRNA.

Small interfering RNA (siRNA) are produced and function in a similar manner to miRNA by cleaving double-stranded RNA with Dicer into smaller fragments 21 to 23 nucleotides in length. Both miRNAs and siRNAs activate the RNA-induced silencing complex (RISC), which finds the complementary target mRNA sequence and cleaves the RNA using RNase. This in turn silences the particular gene by RNA interference. siRNAs and miRNAs differ in the fact that siRNAs are typically specific to the mRNA sequence while miRNAs aren’t completely complementary to the mRNA sequence. MiRNAs can interact with targets that have similar sequences, which inhibits translation of different genes. In general, RNA interference is an essential part of normal processes within organisms such as humans, and it is an area being researched as a diagnostic and therapeutic tool for cancer targets.

Related Glossary Terms

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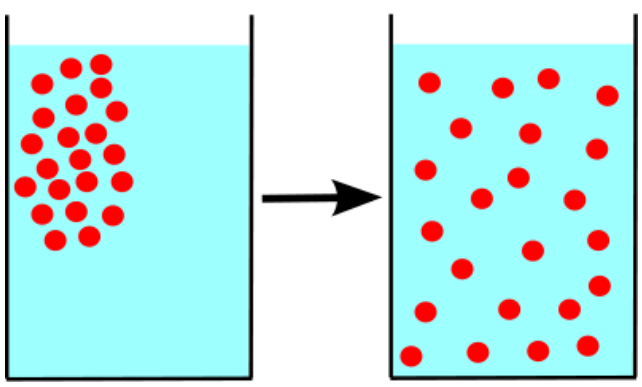
Diffusion

Diffusion is the net movement of molecules or atoms from a region of high concentration (or high chemical potential) to a region of low concentration (or low chemical potential). This is also referred to as the movement of a substance down a concentration gradient. A gradient is the change in the value of a quantity (e.g., concentration, pressure, temperature) with the change in another variable (usually distance). For example, a change in concentration over a distance is called a concentration gradient, a change in pressure over a distance is called a pressure gradient, and a change in temperature over a distance is a called a temperature gradient.



https://en.wikipedia.org/wiki/Diffusion

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Digitalis

A group of medicines extracted from digitalis plants are called digitalin. The use of *D. purpurea* extract containing cardiac glycosides for the treatment of heart conditions was first described in the English-speaking medical literature by William Withering, in 1785, which is considered the beginning of modern therapeutics. It is used to increase cardiac contractility (it is a positive inotrope) and as an antiarrhythmic agent to control the heart rate, particularly in the irregular (and often fast) atrial fibrillation. Digitalis is hence often prescribed for patients in atrial fibrillation, especially if they have been diagnosed with congestive heart failure.

Digoxin was approved for heart failure in 1998 under current regulations by the Food and Drug Administration on the basis of prospective, randomized study and clinical trials. It was also approved for the control of ventricular response rate for patients with atrial fibrillation. American College of Cardiology/American Heart Association guidelines recommend digoxin for symptomatic chronic heart failure for patients with reduced systolic function, preservation of systolic function, and/or rate control for atrial fibrillation with a rapid ventricular response. Heart Failure Society of America guidelines for heart failure provide similar recommendations. Despite its relatively recent approval by the Food and Drug Administration and the guideline recommendations, the therapeutic use of digoxin is declining in patients with heart failure—likely the result of several factors. Safety concerns regarding a proposed link between digoxin therapy and increased mortality in women may be contributing to the decline in therapeutic use of digoxin.

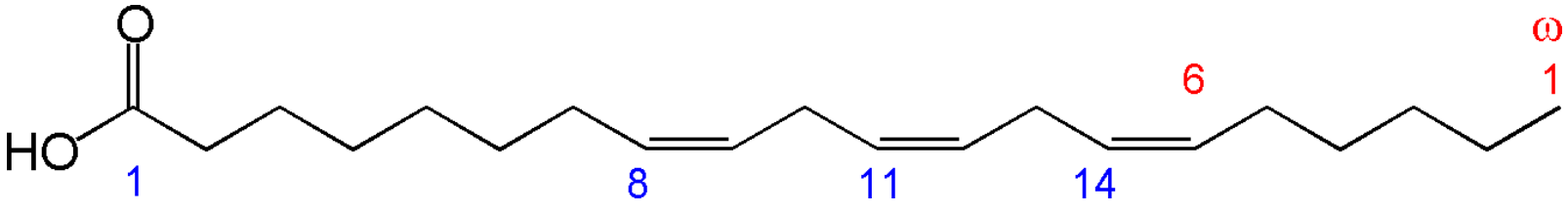
https://en.wikipedia.org/wiki/Digoxin

Related Glossary Terms

Drag related terms here

Dihomo-γ-linolenic acid

Dihomo-γ-linolenic acid (DGLA) is a 20-carbon ω–6 fatty acid. In physiologica
ture, it is given the name 20:3 (ω–6). DGLA is a carboxylic acid with a 20-carb
and three *cis* double bonds. The first double bond is located at the sixth carbo
the ω end. DGLA is the elongation product of γ-linolenic acid (GLA - 18:3, ω–6
in turn, is a desaturation product of linoleic acid (18:2, ω–6). DGLA is made in
body by the elongation of GLA, by an efficient enzyme which does not appear t
any form of (dietary) inhibition. DGLA is an extremely uncommon fatty acid, f
only in trace amounts in animal products.



https://en.wikipedia.org/wiki/Dihomo-%CE%B3-linolenic_acid

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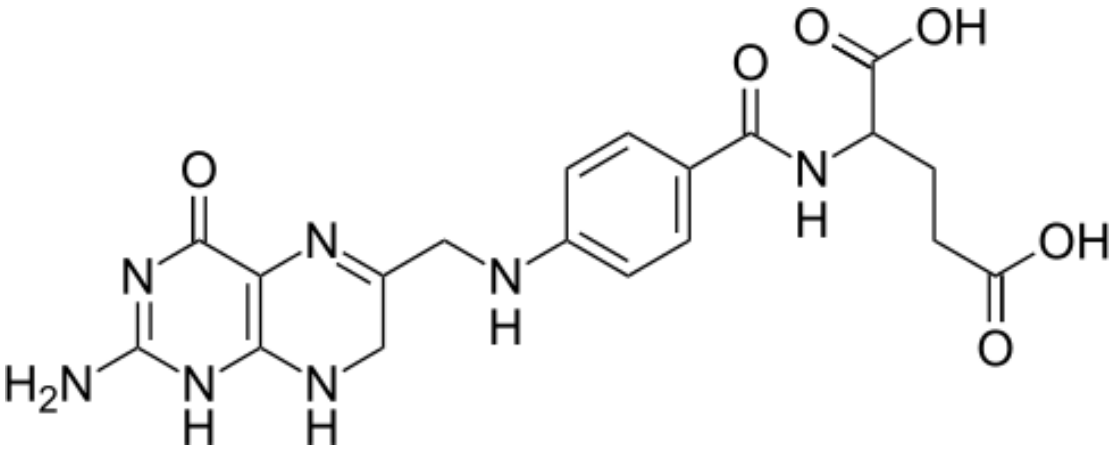
Chapter 9 - Point by Point: Structure and Function

Dihydrofolate

Dihydrofolic acid (conjugate base dihydrofolate) (DHF) is a folic acid (vitam
rivative which is converted to tetrahydrofolic acid by dihydrofolate reductas
rahydrofolate is needed to make both purines and pyrimidines, which are bu
blocks of DNA and RNA, dihydrofolate reductase is targeted by various drug
vent nucleic acid synthesis.



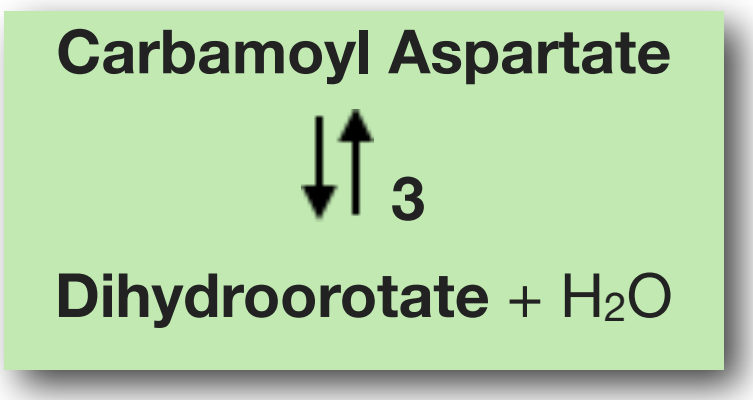
https://en.wikipedia.org/wiki/Dihydrofolic_acid

Related Glossary Terms

Drag related terms here

Dihydroorotase

Dihydroorotase (EC 3.5.2.3, carbamoylaspartic dehydrase, dihydroorotate h
is an enzyme which converts carbamoyl aspartic acid into 4,5-dihydrooroti
biosynthesis of pyrimidines. It forms a multifunctional enzyme with carbar
phate synthetase and aspartate transcarboymalase.



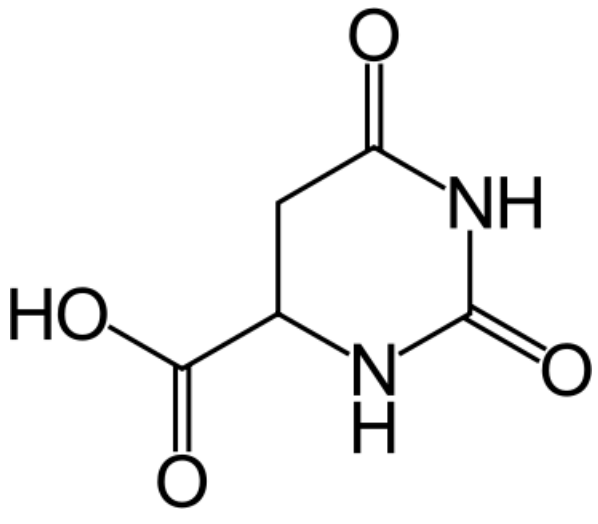
https://en.wikipedia.org/wiki/Dihydroorotase

Related Glossary Terms

Drag related terms here

Dihydroorotate

4,5-dihydroorotic acid is a derivative of orotic acid which serves as an interme
pyrimidine biosynthesis.



https://en.wikipedia.org/wiki/4,5-Dihydroorotic_acid

Related Glossary Terms

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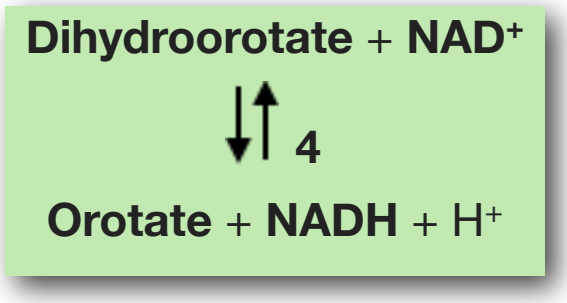
Dihydroorotate Dehydrogenase

Dihydroorotate dehydrogenase (DHODH) is an enzyme that in humans is encoded by the DHODH gene on chromosome 16. The protein encoded by this gene catalyzes the fourth enzymatic step, the ubiquinone-mediated oxidation of dihydroorotate to orotate, in *de novo* pyrimidine biosynthesis. This protein is a mitochondrial protein located on the outer surface of the inner mitochondrial membrane (IMM). Inhibitors of this enzyme are used to treat autoimmune diseases such as rheumatoid arthritis.

In mammalian species, DHODH catalyzes the fourth step in *de novo* pyrimidine biosynthesis, which involves the ubiquinone-mediated oxidation of dihydroorotate to orotate and the reduction of FMN to dihydroflavin mononucleotide ($FMNH_2$)

Human DHODH is a ubiquitous FMN flavoprotein. In bacteria (gene pyrD), it is located on the inner side of the cytosolic membrane. In some yeasts, such as in *Saccharomyces cerevisiae* (gene URA1), it is a cytosolic protein, whereas, in other eukaryotes, it is found in the mitochondria. It is also the only enzyme in the pyrimidine biosynthesis pathway located in the mitochondria rather than the cytosol.



https://en.wikipedia.org/wiki/Dihydroorotate_dehydrogenase

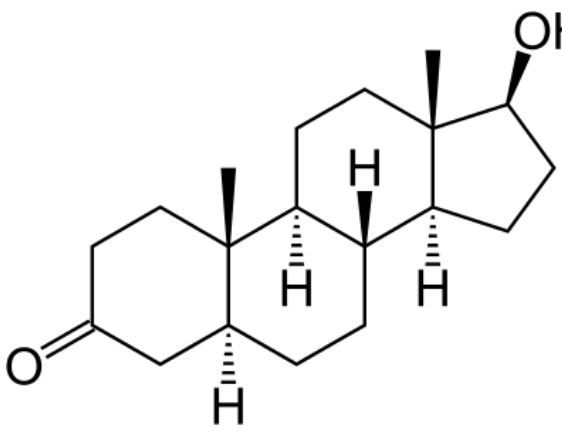
Related Glossary Terms

Drag related terms here

Dihydrotestosterone

Dihydrotestosterone (commonly abbreviated to DHT), or 5α-dihydrotestosterone (5α-DHT), also known as 5α-androstan-17β-ol-3-one, is a sex steroid and androgen hormone. The enzyme 5α-reductase synthesizes DHT from testosterone in the prostate, testes, hair follicles, and adrenal glands. This enzyme reduces the 4,5 double-bond of the testosterone. Relative to testosterone, DHT is much more potent as an agonist of the androgen receptor.

DHT is also known as androstanolone (INN) and stanolone (BAN), and under brand names including Anabolex, Anaprotin, Andractim, Androlone, Gelovit, Neoprol, Pesomax, and Stanaprol, is used clinically as an androgen and anabolic steroid. Unlike testosterone and some anabolic steroids, DHT cannot be aromatized, and hence, has no risk of producing estrogenic effects such as gynecomastia.



https://en.wikipedia.org/wiki/Dihydrotestosterone

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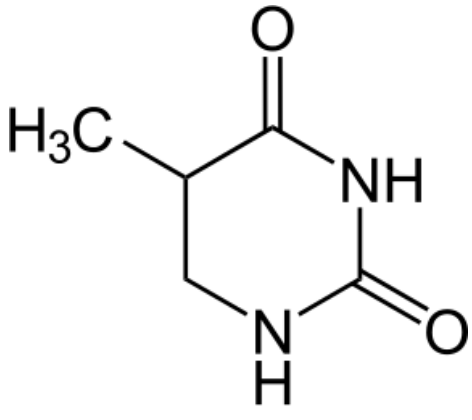
Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

Dihydrothymine

Dihydrothymine is an intermediate in the reductive pathway of pyrimidine
It is produced by reduction of thymine by NADPH.



https://en.wikipedia.org/wiki/Dihydrothymine

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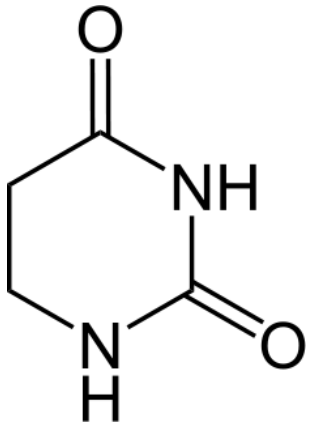
Chapter 6 - Metabolism: Nucleotides

Chapter 9 - Point by Point: Metabolism

Dihydrouracil

Dihydrouracil is an intermediate in the reductive pathway of pyrimidine ca
is produced by reduction of uracil by NADPH.



https://en.wikipedia.org/wiki/Dihydrouracil

Related Glossary Terms

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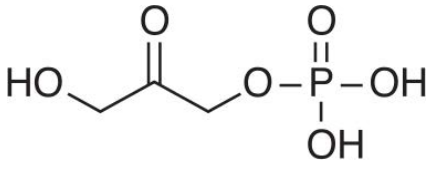
Dihydroxyacetone Phosphate

Dihydroxyacetone phosphate (DHAP) is an intermediate in the glycolysis metabolic pathway, and is one of the two products of breakdown of fructose 1,6-bisphosphate, along with glyceraldehyde 3-phosphate. It is rapidly and reversibly isomerized to glyceraldehyde 3-phosphate.

In the Calvin cycle, DHAP is one of the products of the sixfold reduction of 1,3-bisphosphoglycerate by NADPH. It is also used in the synthesis of sedoheptulose 1,7-bisphosphate and fructose 1,6-bisphosphate, both of which are used to reform ribulose 5-phosphate, the 'key' carbohydrate of the Calvin cycle.

DHAP is also the product of the dehydrogenation of L-glycerol-3-phosphate, which is part of the entry of glycerol (sourced from triglycerides) into the glycolytic pathway. Conversely, reduction of glycolysis-derived DHAP to L-glycerol-3-phosphate provides adipose cells with the activated glycerol backbone they require to synthesize new triglycerides. Both reactions are catalyzed by the enzyme glycerol 3-phosphate dehydrogenase with NAD^+/NADH as cofactor.

DHAP also has a role in the ether-lipid biosynthesis process in the protozoan parasite *Leishmania mexicana*.



https://en.wikipedia.org/wiki/Dihydroxyacetone_phosphate

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Dihydroxyacetone Phosphate duplicate

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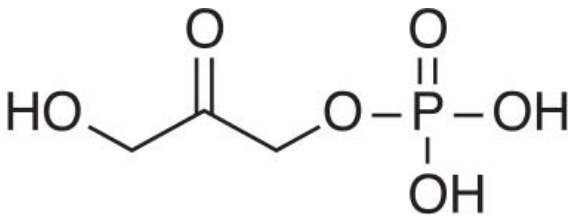

https://en.wikipedia.org/wiki/Dihydroxyacetone_phosphate

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Dihydroxyacid Dehydratase

Dihydroxy-acid dehydratase (EC 4.2.1.9) is an enzyme that catalyzes the chemical reaction

2,3-dihydroxy-3-methylbutanoate <-> 3-methyl-2-oxobutanoate + H_2O

Hence, this enzyme has one substrate, 2,3-dihydroxy-3-methylbutanoate, and two products, 3-methyl-2-oxobutanoate (α-ketoisovaleric acid) and H_2O. This enzyme participates in valine, leucine and isoleucine biosynthesis and pantothenate and coenzyme A (CoA) biosynthesis.

This enzyme belongs to the family of lyases, specifically the hydro-lyases, which cleave carbon-oxygen bonds. The systematic name of this enzyme class is 2,3-dihydroxy-3-methylbutanoate hydro-lyase (3-methyl-2-oxobutanoate-forming). Other names in common use include

- acetohydroxyacid dehydratase,
- α,β-dihydroxyacid dehydratase,
- 2,3-dihydroxyisovalerate dehydratase,
- α,β-dihydroxyisovalerate dehydratase,
- dihydroxy acid dehydrase,
- DHAD,
- and 2,3-dihydroxy-acid hydro-lyase.

https://en.wikipedia.org/wiki/Dihydroxy-acid_dehydratase

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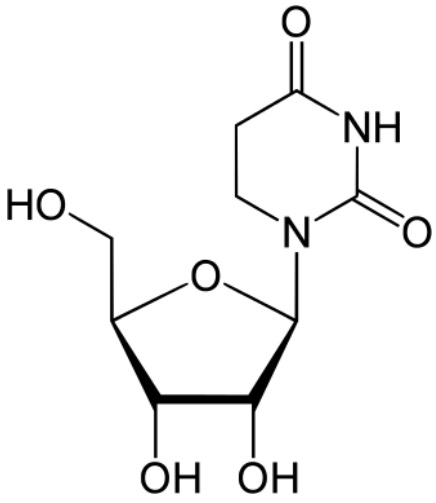
Dihyrouridine

Dihydrouridine (abbreviated as D, DHU, or UH2) is a pyrimidine which is the result of adding two hydrogen atoms to a uridine, making it a fully saturated pyrimidine ring with no remaining double bonds. D is found in tRNA and rRNA molecules as a nucleoside. The corresponding nucleobase is 5,6-dihydrouracil.

Because it is non-planar, D disturbs the stacking interactions in helices and destabilizes the RNA structure. D also stabilizes the C2'-endo sugar conformation, which is more flexible than the C3'-endo conformation, and this effect is propagated to the 5'-neighboring residue. Thus, while pseudouridine and 2'-O-methylations stabilize the local RNA structure, D does the opposite.

tRNA of organisms that grow at low temperatures (psychrophiles) have high 5,6-dihydrouridine levels (40-70% more on average) which provides the necessary, local, flexibility of the tRNA at or below the freezing point.



https://en.wikipedia.org/wiki/Dihydrouridine#/media/File:Dihydrouridine.svg

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Dimerization

In biochemistry, a dimer is a macromolecular complex formed by two, usually non-covalently bound, macromolecules such as proteins or nucleic acids. (The word dimer has roots meaning "two parts", di- + -mer.) It is a quaternary structure of a protein. A homodimer is formed by two identical molecules (a process called homodimerization). A heterodimer is formed by two different macromolecules (called heterodimerization).

https://en.wikipedia.org/wiki/Protein_dimer

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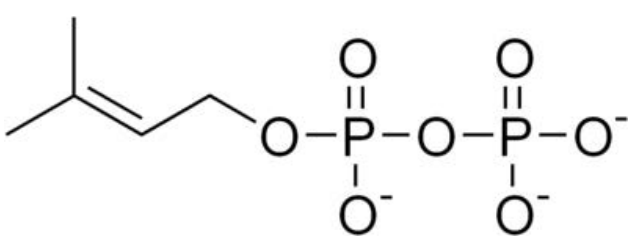
Dimethylallyl Pyrophosphate

Dimethylallyl pyrophosphate (DMAPP) is an intermediate product of both mevalonic acid (MVA) pathway and DOXP/MEP pathway. It is an isomer of isopentenyl pyrophosphate (IPP) and exists in virtually all life forms. The enzyme isopentenyl pyrophosphate isomerase catalyzes the isomerization of DMAPP from IPP. Precursor of DMAPP in the MVA pathway is mevalonic acid, and HMBPP in the MEP/DOXP pathway.

The precursor of DMAPP in the MVA pathway is mevalonic acid, and HMBPP in the MEP/DOXP pathway. At present, it is believed that there is crossover between the two pathways in organisms that use both pathways to create terpenes and terpenoids, such as in plants, and that DMAPP is the crossover product.



https://en.wikipedia.org/wiki/Dimethylallyl_pyrophosphate

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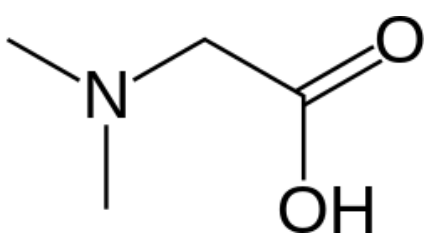
Dimethylglycine

Dimethylglycine is a derivative of the amino acid glycine with the structural
$(CH_3)_2NCH_2COOH$. It can be found in beans and liver. It can be formed fron
ylglycine upon the loss of one of its methyl groups. It is also a byproduct of t
lism of choline. When DMG was first discovered, it was referred to as Vitam
unlike true B vitamins, deficiency of DMG in the diet does not lead to any ill
and it is synthesized by the human body in the citric acid cycle meaning it do
meet the definition of a vitamin.



https://en.wikipedia.org/wiki/Dimethylglycine

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Dioxygenase

Dioxygenases (EC 1.13.11) are oxidoreductase enzymes. Aerobic life, from simple single-celled bacteria species to complex eukaryotic organisms, has evolved to depend on the oxidizing power of dioxygen in various metabolic pathways. From energetic adenosine triphosphate (ATP) generation to xenobiotic degradation, the use of dioxygen as a biological oxidant is widespread and varied in the exact mechanism of its use. Enzymes employ many different schemes to use dioxygen, and this largely depends on the substrate and reaction at hand.

In the monooxygenases, only a single atom of dioxygen is incorporated into a substrate with the other being reduced to a water molecule. The dioxygenases catalyze the oxidation of a substrate without the reduction of one oxygen atom from dioxygen into a water molecule. However, this definition is ambiguous because it does not take into account how many substrates are involved in the reaction. The majority of dioxygenases fully incorporate dioxygen into a single substrate, and a variety of cofactor schemes are utilized to achieve this. For example, in the α-ketoglutarate-dependent enzymes, one atom of dioxygen is incorporated into two substrates, with one always being α-ketoglutarate, and this reaction is brought about by a mononuclear iron center.

https://en.wikipedia.org/wiki/Dioxygenase

Related Glossary Terms

Drag related terms here

Dipole

The difference in electronegativities between hydrogen and the molecule to
covalently bound give rise to partial charges. These tiny charges (δ^+ and δ^-)
mation of hydrogen bonds, which occur when the partial positive charge of
atom is attracted to the partial negative of another molecule. In water, that
hydrogen of one water molecule is attracted to the oxygen of another. Since
asymmetrical molecule, it means also that the charges are asymmetrical. Su
even distribution is what makes a dipole.

https://en.wikipedia.org/wiki/Dipole

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Disaccharide

A disaccharide (also called a double sugar or biose) is the sugar formed when two monosaccharides (simple sugars) are joined. Like monosaccharides, disaccharides are soluble in water. Three common examples are sucrose, lactose, and maltose.

The joining of simple sugars into a double sugar happens by a condensation reaction, which involves the elimination of a water molecule from the functional groups only. Breaking apart a double sugar into its two simple sugars is accomplished by hydrolysis with the help of a type of enzyme called a disaccharidase. As building the larger sugar ejects a water molecule, breaking it down consumes a water molecule. These reactions are vital in metabolism. Each disaccharide is broken down with the help of a corresponding disaccharidase (sucrase, lactase, and maltase).

The formation of a disaccharide molecule from two monosaccharide molecules proceeds by displacing a hydroxyl radical from one molecule and a hydrogen nucleus (a proton) from the other, so that the now vacant bonds on the monosaccharides join the two monomers together. The vacant bonds on the hydroxyl radical and the proton unite in their turn, forming a molecule of water, that then goes free. Because of the removal of the water molecule from the product, the term of convenience for such a process is "dehydration reaction" (also "condensation reaction" or "dehydration synthesis"). For example, milk sugar (lactose) is a disaccharide made by condensation of one molecule of each of the monosaccharides glucose and galactose, whereas the disaccharide sucrose in sugar cane and sugar beet, is a condensation product of glucose and fructose. Maltose, another common disaccharide, is condensed from two glucose molecules.

The dehydration reaction that bonds monosaccharides into disaccharides (and also bonds monosaccharides into more complex polysaccharides) forms what are called glycosidic bonds.

https://en.wikipedia.org/wiki/Disaccharide

Related Glossary Terms

Drag related terms here

Dissociation

Dissociation in chemistry and biochemistry is a general process in which m
ionic compounds such as salts, or complexes) separate or split into smaller
such as atoms, ions or radicals. For instance, when an acid dissolves in wat
lent bond between an electronegative atom and a hydrogen atom is broken
lytic fission, which gives a proton (H^+) and a negative ion. Dissociation is th
of recombination.

https://en.wikipedia.org/wiki/Dissociation_(chemistry)

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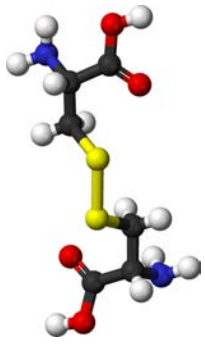
Disulfide

In chemistry and biology a disulfide refers to a functional group with the general structure R–S–S–R. The linkage is also called an SS-bond or a disulfide bridge and is usually derived by the coupling of two thiol groups. In formal terms, the connection is a persulfide, in analogy to its congener, peroxide (R–O–O–R), but this terminology is rarely used, except in reference to hydrodisulfides (R–S–S–H or H–S–S–H compounds).

The disulfide bone of cystine below is shown in yellow.



https://en.wikipedia.org/wiki/Disulfide

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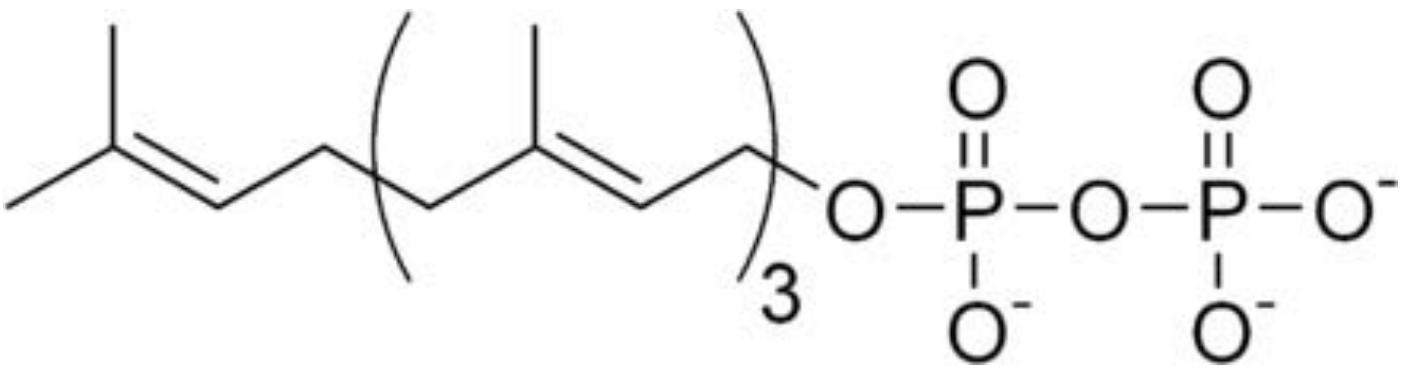
Diterpenes

Diterpenes are a class of chemical compounds composed of two terpene units with th
molecular formula $C_{20}H_{32}$. They may also be thought of as consisting of four isoprene
units. They are biosynthesized by plants, animals and fungi via the HMG-CoA reduc-
tase pathway, with geranylgeranyl pyrophosphate being a primary intermediate. Dite
penes form the basis for biologically important compounds such as retinol, retinal, an
phytol. Diterpenes are known to be antimicrobial and antiinflammatory.

Starting material for diterpene synthesis, geranylpyrophosphate, is shown below.



https://en.wikipedia.org/wiki/Diterpene

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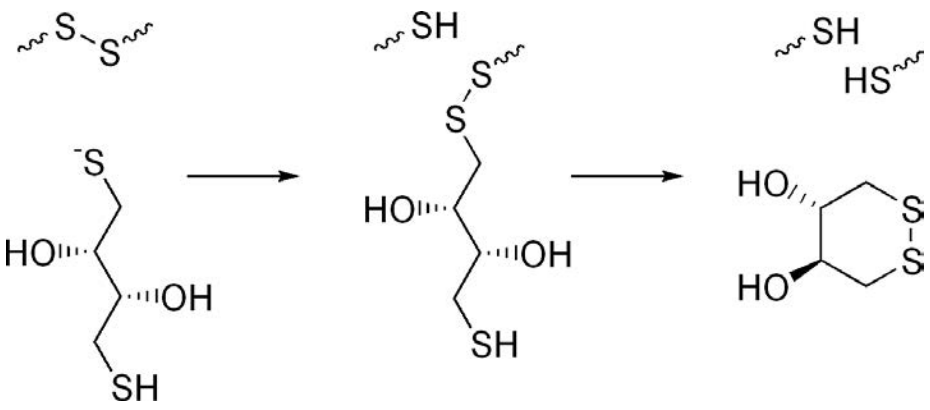
Dithiothreitol

Dithiothreitol (DTT) is the common name for a small-molecule redox reagent also known as Cleland's reagent. DTT's formula is $C_4H_{10}O_2S_2$ and the chemical structure of one of its enantiomers in its reduced form is shown at the right. Its oxidized form is a disulfide bonded 6-membered ring (shown below). The reagent is commonly used in its racemic form, as both enantiomers are reactive. Its name derives from the four-carbon sugar, threose. DTT has an epimeric ('sister') compound, dithioerythritol (DTE).

DTT is a reducing agent. Once oxidized, it forms a stable six-membered ring with an internal disulfide bond. It has a redox potential of -0.33 V at pH 7. The reduction of a typical disulfide bond proceeds by two sequential thiol-disulfide exchange reactions and is illustrated below. The reduction usually does not stop at the mixed-disulfide species because the second thiol of DTT has a high propensity to close the ring, forming oxidized DTT and leaving behind a reduced disulfide bond. The reducing power of DTT is limited to pH values above 7, since only the negatively charged thiolate form -S– is reactive (the protonated thiol form -SH is not). The pK_a of the thiol groups is 9.2 and 10.1.

Reduction of a disulfide bond by DTT is shown below.



https://en.wikipedia.org/wiki/Dithiothreitol

Related Glossary Terms

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DNA

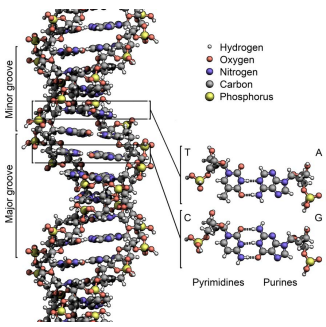
Deoxyribonucleic acid (DNA) is a molecule that carries most of the genetic instructions used in the growth, development, functioning and reproduction of all known living organisms and many viruses. DNA and RNA are nucleic acids; alongside proteins and complex carbohydrates, they comprise the three major types of macromolecule that are essential for all known forms of life. Most DNA molecules consist of two biopolymer strands coiled around each other to form a double helix. The two DNA strands are known as polynucleotides since they are composed of simpler units called nucleotides.

DNA stores biological information. The DNA backbone is resistant to cleavage, and both strands of the double-stranded structure store the same biological information. Biological information is replicated as the two strands are separated. A significant portion of DNA (more than 98% for humans) is non-coding, meaning that these sections do not serve as patterns for protein sequences.

The two strands of DNA run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of nucleobases (informally, bases). It is the sequence of these four nucleobases along the backbone that encodes biological information. Under the genetic code, RNA strands are translated to specify the sequence of amino acids within proteins. These RNA strands are initially created using DNA strands as a template in a process called transcription.

Within cells, DNA is organized into long structures called chromosomes. During cell division these chromosomes are duplicated in the process of DNA replication, providing each cell its own complete set of chromosomes. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in organelles, such as mitochondria or chloroplasts. In contrast, prokaryotes (bacteria and archaea) store their DNA only in the cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

DNA was first isolated by Friedrich Miescher in 1869. Its molecular structure was identified by James Watson and Francis Crick in 1953, whose model-building efforts were guided by X-ray diffraction data acquired by Rosalind Franklin. DNA is used by researchers as a molecular tool to explore physical laws and theories, such as the ergodic theorem and the theory of elasticity. The unique material properties of DNA have made it an attractive molecule for material scientists and engineers interested in micro- and nano-fabrication. Among notable advances in this field are DNA origami and DNA-based hybrid materials.



https://en.wikipedia.org/wiki/DNA

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DNA Adducts

A DNA adduct is a segment of DNA bound to a cancer-causing chemical. This process could be the start of a cancerous cell, or carcinogenesis. DNA adducts in scientific experiments are used as biomarkers of exposure and as such are themselves measured to reflect quantitatively, for comparison, the amount of carcinogen exposure to the subject organism, for example rats or other living animals. Under experimental conditions for study, such DNA adducts are induced by known carcinogens, of which commonly used is DMBA (7,12-dimethylbenz(a)anthracene). For example, the term "DMBA-DNA adduct" in a scientific journal refers to a piece of DNA that has DMBA attached to it. The presence of such an adduct indicates prior exposure to a potential carcinogen, but does not by itself indicate the presence of cancer in the subject animal.

When a chemical binds to DNA, the DNA becomes damaged, and proper and complete replication cannot occur to make the normal intended cell. This could be the start of a mutation, or mutagenesis. Without effective DNA repair, which happens naturally under normal circumstances, this can lead to carcinogenesis, the beginnings of cancer.

Chemicals that form DNA adducts include:
- acetaldehyde, a significant constituent of tobacco smoke
- cisplatin, which binds to DNA and causes crosslinking, leading to death of the cell
- DMBA (7,12-dimethylbenz(a)anthracene)
- malondialdehyde, a naturally occurring product of lipid peroxidation

DNA adducts include:
- etheno-DNA adducts: 1,N(6)-etheno-2'-deoxyadenosine (epsilondA) and 3,N(4)-etheno-2'-deoxycytidine (epsilondC)

https://en.wikipedia.org/wiki/DNA_adduct

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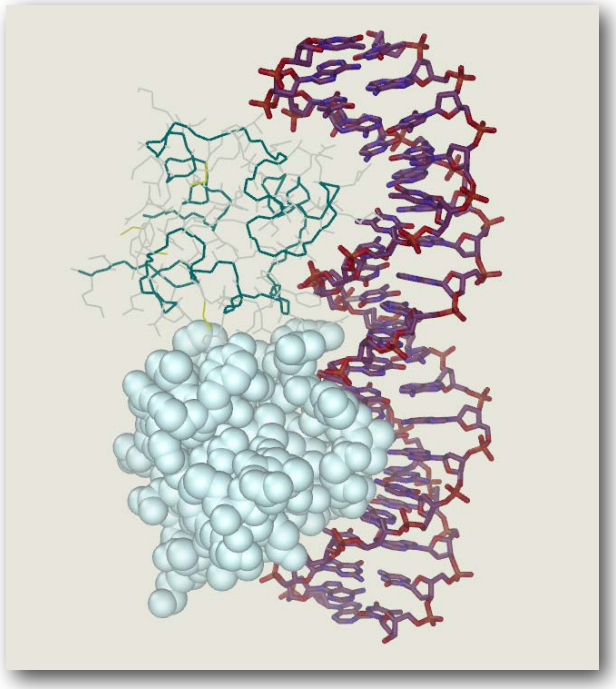
DNA Binding

DNA-binding proteins are proteins that contain DNA-binding domains and thus have a specific or general affinity for either single or double stranded DNA.

Sequence-specific DNA-binding proteins generally interact with the major groove of B-DNA, because it exposes more functional groups that identify a base pair.

DNA-binding proteins include transcription factors which modulate the process of transcription, various polymerases, nucleases which cleave DNA molecules, and histones which are involved in chromosome packaging and transcription in the cell nucleus. DNA-binding proteins can incorporate such domains as the zinc finger, the helix-turn-helix, and the leucine zipper (among many others) that facilitate binding to nucleic acid. There are also more unusual examples such as transcription activator like effectors.

Below - binding of DNA by Cro protein



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DNA damage

DNA damage, due to environmental factors and normal metabolic processes inside the cell, occurs at a rate of 10,000 to 1,000,000 molecular lesions per cell per day. While this constitutes only 0.000165% of the human genome's approximately 6 billion bases (3 billion base pairs), unrepaired lesions in critical genes (such as tumor suppressor genes) can impede a cell's ability to carry out its function and appreciably increase the likelihood of tumor formation and contribute to tumor heterogeneity.

The vast majority of DNA damage affects the primary structure of the double helix. That is, the bases themselves are chemically modified. These modifications can in turn disrupt the molecules' regular helical structure by introducing non-native chemical bonds or bulky adducts that do not fit in the standard double helix. Unlike proteins and RNA, DNA usually lacks tertiary structure and therefore damage or disturbance does not occur at that level. DNA is, however, supercoiled and wound around "packaging" proteins called histones (in eukaryotes), and both superstructures are vulnerable to the effects of DNA damage.

DNA damage can be subdivided into two main types:

1 endogenous damage such as attack by reactive oxygen species produced from normal metabolic byproducts (spontaneous mutation), especially the process of oxidative deamination
    1 also includes replication errors
2 exogenous damage caused by external agents such as
    1 ultraviolet [UV 200-400 nm] radiation from the sun
    2 other radiation frequencies, including x-rays and γ rays
    3 hydrolysis or thermal disruption
    4 certain plant toxins
    5 human-made mutagenic chemicals, especially aromatic compounds that act as DNA intercalating agents
    6 viruses

The replication of damaged DNA before cell division can lead to the incorporation of wrong bases opposite damaged ones. Daughter cells that inherit these wrong bases carry mutations from which the original DNA sequence is unrecoverable (except in the rare case of a back mutation, for example, through gene conversion).

https://en.wikipedia.org/wiki/DNA_damage_(naturally_occurring)

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https://en.wikipedia.org/wiki/DNA_damage_(naturally_occurring)

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DNA Glycosylase

DNA glycosylases are a family of enzymes involved in base excision repair, classified under EC number EC 3.2.2. Base excision repair is the mechanism by which damaged bases in DNA are removed and replaced. DNA glycosylases catalyze the first step of this process. They remove the damaged nitrogenous base while leaving the sugar-phosphate backbone intact, creating an apurinic/apyrimidinic site, commonly referred to as an AP site. This is accomplished by flipping the damaged base out of the double helix followed by cleavage of the N-glycosidic bond.

Glycosylases were first discovered in bacteria, and have since been found in all kingdoms of life. In addition to their role in base excision repair DNA glycosylase enzymes have been implicated in the repression of gene silencing in *A. thaliana*, *N. tabacum* and other plants by active demethylation. 5-methylcytosine residues are excised and replaced with unmethylated cytosines allowing access to the chromatin structure of the enzymes and proteins necessary for transcription and subsequent translation.

Uracil-DNA glycosylase (UDG) is an enzyme that reverts mutations in DNA. The most common mutation is the deamination of cytosine to uracil. UDG repairs these mutations. UDG is crucial in DNA repair, without it these mutations may lead to cancer.

This entry represents various uracil-DNA glycosylases and related DNA glycosylases (EC), such as uracil-DNA glycosylase, thermophilic uracil-DNA glycosylase, G:T/U mismatch-specific DNA glycosylase (Mug), and single-strand selective monofunctional uracil-DNA glycosylase (SMUG1).

Uracil DNA glycosylases remove uracil from DNA, which can arise either by spontaneous deamination of cytosine or by the misincorporation of dU opposite dA during DNA replication. The prototypical member of this family is *E. coli* UDG, which was among the first glycosylases discovered. Four different uracil-DNA glycosylase activities have been identified in mammalian cells, including UNG, SMUG1, TDG, and MBD4. They vary in substrate specificity and subcellular localization. SMUG1 prefers single-stranded DNA as substrate, but also removes U from double-stranded DNA. In addition to unmodified uracil, SMUG1 can excise 5-hydroxyuracil, 5-hydroxymethyluracil and 5-formyluracil bearing an oxidized group at ring C_5. TDG and MBD4 are strictly specific for double-stranded DNA.

TDG can remove thymine glycol when present opposite guanine, as well as derivatives of U with modifications at carbon 5. Current evidence suggests that, in human cells, TDG and SMUG1 are the major enzymes responsible for the repair of the U:G mispairs caused by spontaneous cytosine deamination, whereas uracil arising in DNA through dU misincorporation is mainly dealt with by UNG. MBD4 is thought to correct T:G mismatches that arise from deamination of 5-methylcytosine to thymine in CpG sites. MBD4 mutant mice develop normally and do not show increased cancer susceptibility or reduced survival. But they acquire more C T mutations at CpG sequences in epithelial cells of the small intestine.

The structure of human UNG in complex with DNA revealed that, like other glycosylases, it flips the target nucleotide out of the double helix and into the active site pocket. UDG undergoes a conformational change from an ‘‘open’’ unbound state to a ‘‘closed’’ DNA-bound state.

https://en.wikipedia.org/wiki/DNA_glycosylase

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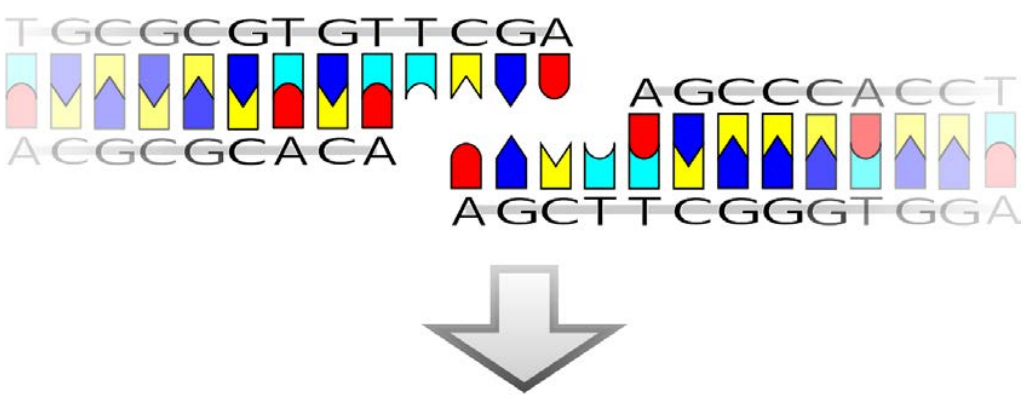
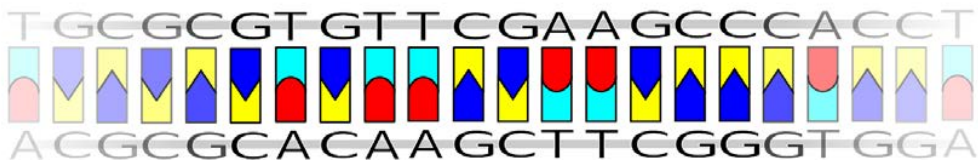
DNA ligase

In molecular biology, DNA ligase is a specific type of enzyme, a ligase, (EC 6.5.1.1) that facilitates the joining of DNA strands together by catalyzing the formation of a phosphodiester bond. It plays a role in repairing single-strand breaks in duplex DNA in living organisms, but some forms (such as DNA ligase IV) may specifically repair double-strand breaks (i.e. a break in both complementary strands of DNA). Single-strand breaks are repaired by DNA ligase using the complementary strand of the double helix as a template, with DNA ligase creating the final phosphodiester bond to fully repair the DNA.

DNA ligase is used in both DNA repair and DNA replication. In addition, DNA ligase has extensive use in molecular biology laboratories for recombinant DNA experiments. Purified DNA ligase is used in gene cloning to join DNA molecules together to form recombinant DNA.





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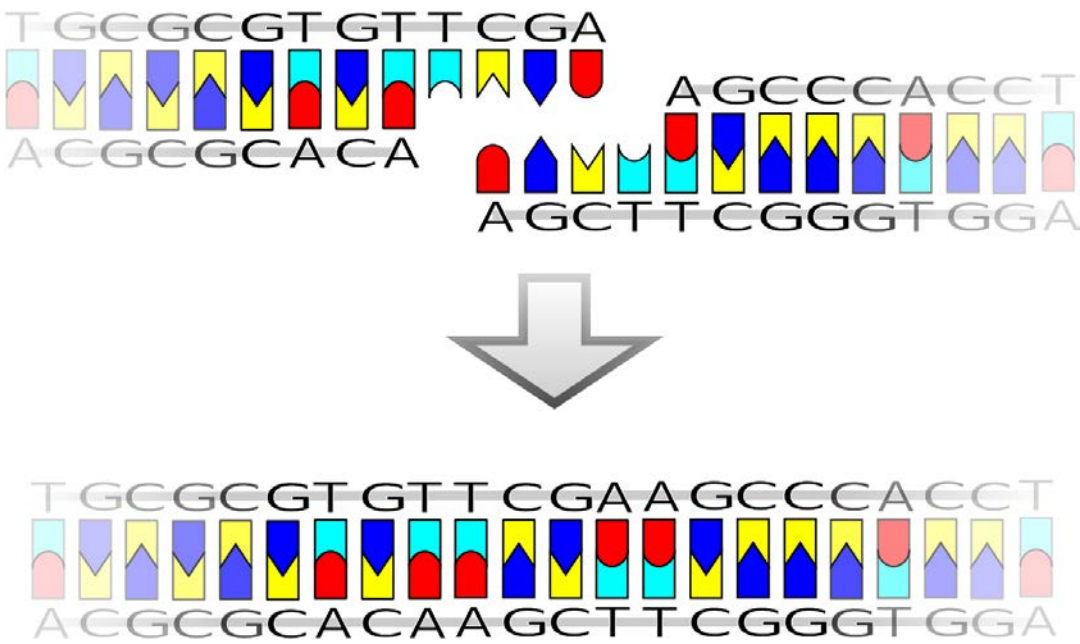

https://en.wikipedia.org/wiki/DNA_ligase

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DNA Methyltransferases

The DNA methyltransferase (DNA MTase) family of enzymes catalyzes the transfer of a methyl group to DNA. DNA methylation serves a wide variety of biological functions. All the known DNA methyltransferases use S-adenosyl methionine (SAM) as the methyl donor.

MTases can be divided into three different groups on the basis of the chemical reactions they catalyze:

- m^6A - those that generate N6-methyladenine EC 2.1.1.72
- m^4C - those that generate N4-methylcytosine EC 2.1.1.113
- m^5C - those that generate C5-methylcytosine EC 2.1.1.37

m^6A and m^4C methyltransferases are found primarily in prokaryotes. m^5C methyltransfereases are found in some lower eukaryotes, in most higher plants, and in animals beginning with the echinoderms. The m^6A methyltransferases (N-6 adenine-specific DNA methylase) (A-Mtase) are enzymes that specifically methylate the amino group at the C-6 position of adenines in DNA. They are found in the three existing types of bacterial restriction-modification systems (in type I system the A-Mtase is the product of the hsdM gene, and in type III it is the product of the mod gene). These enzymes are responsible for the methylation of specific DNA sequences in order to prevent the host from digesting its own genome via its restriction enzymes.

https://en.wikipedia.org/wiki/DNA_methyltransferase

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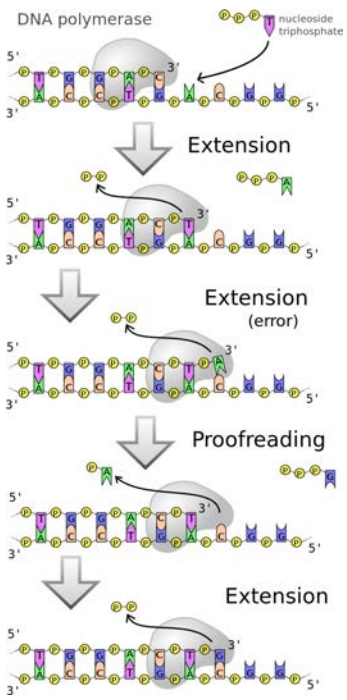
DNA Polymerase

DNA polymerases are enzymes that synthesize DNA molecules from deoxyribonucleotides, the building blocks of DNA. These enzymes are essential to DNA replication and usually work in pairs to create two identical DNA strands from a single original DNA molecule. During this process, DNA polymerase “reads” the existing DNA strands to create two new strands that match the existing ones. It catalyzes DNA-template-directed extension of the 3'- end of a DNA strand by one nucleotide at a time.

These enzymes catalyze the following chemical reaction
Deoxynucleoside triphosphate + DNA_n <+> PP_i + DNA_{n+1}

Every time a cell divides, DNA polymerases are required to help duplicate the cell’s DNA, so that a copy of the original DNA molecule can be passed to each daughter cell. In this way, genetic information is passed down from generation to generation. Before replication can take place, an enzyme called helicase unwinds the DNA molecule from its tightly woven form. This opens up or “unzips” the double-stranded DNA to give two single strands of DNA that can be used as templates for replication.



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DNA Polymerase ∂

Eukaryotic DNA polymerases Pol α (alpha), Pol δ (delta), and Pol ε (epsilon) are members of Family B Polymerases and are the main polymerases involved with nuclear DNA replication. Pol α complex (pol α-DNA primase complex) consists of four subunits: the catalytic subunit POLA1, the regulatory subunit POLA2, and the small and the large primase subunits PRIM1 and PRIM2 respectively. Once primase has created the RNA primer, Pol α starts replication elongating the primer with ~20 nucleotides.

Due to its high processivity, Pol δ takes over the leading and lagging strand synthesis from Pol α. Pol δ is expressed by genes POLD1, creating the catalytic subunit, POLD2, POLD3, and POLD4 creating the other subunits that interact with Proliferating Cell Nuclear Antigen (PCNA), which is a DNA clamp that allows Pol δ to possess processivity.

Pol ε is encoded by the POLE1, the catalytic subunit, POLE2, and POLE3 gene. It has been reported that the function of Pol ε is to extend the leading strand during replication, while Pol δ primarily replicates the lagging strand. However, recent evidence suggested that Pol δ might have a role in replicating the leading of DNA as well. Pol ε's C-terminus region is thought to be essential to cell vitality as well. The C-terminus region is thought to provide a checkpoint before entering anaphase, provide stability to the holoenzyme, and add proteins to the holoenzyme necessary for initiation of replication.

https://en.wikipedia.org/wiki/DNA_polymerase

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DNA Polymerase α

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https://en.wikipedia.org/wiki/DNA_polymerase

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DNA Polymerase ε

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https://en.wikipedia.org/wiki/DNA_polymerase

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DNA Polymerase I

DNA Polymerase I (or Pol I) is an enzyme that participates in the process of DNA replication. Discovered by Arthur Kornberg in 1956, it was the first known DNA polymerase (and, indeed, the first known of any kind of polymerase). It was initially characterized in *E. coli* and is ubiquitous in prokaryotes. In *E. coli* and many other bacteria, the gene that encodes Pol I is known as polA. The *E. coli* form of the enzyme is composed of 928 amino acids, and is an example of a processive enzyme—it can sequentially catalyze multiple polymerizations.

Pol I possesses four enzymatic activities:

1 A 5'→3' (forward) DNA-Dependent DNA polymerase activity, requiring a 3' primer site and a template strand
2 A 3'→5' (reverse) exonuclease activity that mediates proofreading
3 A 5'→3' (forward) exonuclease activity mediating nick translation during DNA repair.
4 A 5'→3' (forward) RNA-Dependent DNA polymerase activity. Pol I operates on RNA templates with considerably lower efficiency (0.1–0.4%) than it does DNA templates, and this activity is probably of only limited biological significance.

In the replication process, RNase H removes the RNA primer (created by Primase) from the lagging strand and then Polymerase I fills in the necessary nucleotides between the Okazaki fragments (see DNA replication) in a 5'→3' direction, proofreading for mistakes as it goes. It is a template-dependent enzyme—it only adds nucleotides that correctly base pair with an existing DNA strand acting as a template. DNA ligase then joins the various fragments together into a continuous strand of DNA.

https://en.wikipedia.org/wiki/DNA_polymerase_I

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DNA Polymerase II

DNA polymerase II (also known as DNA Pol II or Pol II) is a prokaryotic DNA-Dependent DNA polymerase encoded by the PolB gene. DNA Polymerase II is an 89.9-kDa protein and is a member of the B family of DNA polymerases. It was originally isolated by Thomas Kornberg in 1970, and characterized over the next few years.

The *in vivo* functionality of Pol II is under debate, yet consensus shows that Pol II is primarily involved as a backup enzyme in prokaryotic DNA replication. The enzyme has 5' → 3' DNA synthesis capability as well as 3' → 5' exonuclease proofreading activity. DNA Pol II interacts with multiple binding partners common with DNA Pol III in order to enhance its fidelity and processivity.

DNA Polymerase II is a member of the polymerase B family and supports Polymerase III in DNA replication moving from the 3' end to the 5' end. In the case when Polymerase III stalls during a replication error, Polymerase II can interrupt and excise the mismatched bases. Polymerase II has a much higher fidelity factor than Polymerase III, meaning that it is much less likely to create mispairings. Without Polymerase II's proofreading step, Polymerase III would extend the mispairings and thus create a mutation.

In addition to protecting from mutations that could be caused by Polymerase III, Polymerase II functions to protect against mutations caused by Polymerase IV. Polymerase IV is much more error prone than Polymerase II but also functions to repair mismatched base pairings starting from the 3' end. Polymerase II protects the 3' end from Polymerase IV and blocks it from acting. This protection will prevent the formation of mutations while the Polymerase II is functioning normally. If the Polymerase II is knocked out by a mutation or disabled by other factors, Polymerase IV will take its place to fix the mispaired bases.

https://en.wikipedia.org/wiki/DNA_polymerase_II

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DNA Polymerase III

DNA polymerase III holoenzyme is the primary enzyme complex involved in prokaryotic DNA replication. It was discovered by Thomas Kornberg (son of Arthur Kornberg) and Malcolm Gefter in 1970. The complex has high processivity (i.e. the number of nucleotides added per binding event) and, specifically referring to the replication of the E.coli genome, works in conjunction with four other DNA polymerases (Pol I, Pol II, Pol IV, and Pol V). Being the primary holoenzyme involved in replication activity, the DNA Pol III holoenzyme also has proofreading capabilities that correct replication mistakes by means of exonuclease activity working 3'→5'. DNA Pol III is a component of the replisome, which is located at the replication fork.

DNA polymerase III synthesizes base pairs at a rate of around 1000 nucleotides per second. DNA Pol III activity begins after strand separation at the origin of replication. Because DNA synthesis cannot start *de novo*, an RNA primer, complementary to part of the single-stranded DNA, is synthesized by primase (an RNA polymerase). After replication of the desired region, the RNA primer is removed by DNA polymerase I via the process of nick translation. The removal of the RNA primer allows DNA ligase to ligate the DNA-DNA nick between the new fragment and the previous strand. DNA polymerase I & III, along with many other enzymes are all required for the high fidelity, high-processivity of DNA replication.

https://en.wikipedia.org/wiki/DNA_polymerase_III_holoenzyme

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DNA Polymerase IV

DNA polymerase IV is a prokaryotic polymerase that is involved in mutage
hibits no 3'-5' exonuclease (proofreading) activity and hence is error prone.
DNA polymerase IV (Pol 4) is involved in non-targeted mutagenesis. Pol IV
Y polymerase expressed by the dinB gene that is switched on via SOS induc
by stalled polymerases at the replication fork. During SOS induction, Pol IV
tion is increased tenfold and one of the functions during this time is to inte
Pol III holoenzyme processivity. This creates a checkpoint, stops replicatio
lows time to repair DNA lesions via the appropriate repair pathway. Anothe
of Pol IV is to perform translesion synthesis at the stalled replication fork li
ample, bypassing N2-deoxyguanine adducts at a faster rate than transversi
aged DNA. Cells lacking dinB gene have a higher rate of mutagenesis cause
damaging agents.

https://en.wikipedia.org/wiki/DNA_polymerase_IV

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DNA Polymerase V

DNA Polymerase V (Pol V) is a polymerase enzyme involved in DNA repair mechanisms in the bacteria *Escherichia coli*. It is composed of a UmuD' homodimer and a UmuC monomer, forming the UmuD'2C protein complex. It is part of the Y-family of DNA Polymerases, which are capable of performing DNA translesion synthesis (TLS). Translesion polymerases bypass DNA damage lesions during DNA replication, if a lesion is not repaired or bypassed the replication fork can stall and lead to cell death. However, Y polymerases have low sequence fidelity during replication (prone to add wrong nucleotides). When the UmuC and UmuD' proteins were initially discovered in *E. coli*, they were thought to be agents that inhibit faithful DNA replication and caused DNA synthesis to have high mutation rates after exposure to UV-light. The polymerase function of Pol V was not discovered until the late 1990s when UmuC was successfully extracted, consequent experiments unequivocally proved UmuD'2C is a polymerase. This finding lead to the detection of many Pol V orthologs and the discovery of the Y-family of polymerases.

Pol V functions as a TLS polymerase in *E. coli* as part of the SOS response to DNA damage. When DNA is damaged regular DNA synthesis polymerases are unable to add dNTPs onto the newly synthesized strand. DNA Polymerase III (Pol III) is the regular DNA polymerase in *E. coli*. As Pol III stalls unable to add nucleotides to the nascent DNA strand, the cell becomes at risk of having the replication fork collapse and apoptosis to take place. Pol V TLS function depends on association with other elements of the SOS response, most importantly Pol V translesion activity is tightly dependent on the formation of RecA nucleoprotein filaments. Pol V can use TLS on lesions that block replication or miscoding lesions, which modify bases and lead to wrong base pairing. However, it is unable to translate through 5' → 3' backbone nick errors. Pol V also lacks exonuclease activity, thus rendering unable to proofread synthesis causing it to be error prone.

https://en.wikipedia.org/wiki/DNA_polymerase_V

DNA Repair

DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day. Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis. As a consequence, the DNA repair process is constantly active as it responds to damage in the DNA structure. When normal repair processes fail, and when cellular apoptosis does not occur, irreparable DNA damage may occur, including double-strand breaks and DNA crosslinkages (interstrand crosslinks or ICLs).

The rate of DNA repair is dependent on many factors, including the cell type, the age of the cell, and the extracellular environment. A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repairs damage incurred to its DNA, can enter one of three possible states:
1 an irreversible state of dormancy, known as senescence
2 cell suicide, also known as apoptosis or programmed cell death
3 unregulated cell division, which can lead to the formation of a tumor that is cancerous

When only one of the two strands of a double helix has a defect, the other strand can be used as a template to guide the correction of the damaged strand. In order to repair damage to one of the two paired molecules of DNA, there exist a number of excision repair mechanisms that remove the damaged nucleotide and replace it with an undamaged nucleotide complementary to that found in the undamaged DNA strand.

1 Base excision repair (BER) repairs damage to a single nitrogenous base by deploying enzymes called glycosylases. These enzymes remove a single nitrogenous base to create an apurinic or apyrimidinic site (AP site). Enzymes called AP endonucleases nick the damaged DNA backbone at the AP site. DNA polymerase then removes the damaged region using its 5' to 3' exonuclease activity and correctly synthesizes the new strand using the complementary strand as a template.

2 Nucleotide excision repair (NER) repairs damaged DNA which commonly consists of bulky, helix-distorting damage, such as pyrimidine dimerization caused by UV light. Damaged regions are removed in 12-24 nucleotide-long strands in a three-step process which consists of recognition of damage, excision of damaged DNA both upstream and downstream of damage by endonucleases, and resynthesis of removed DNA region. NER is a highly evolutionarily conserved repair mechanism and is used in nearly all eukaryotic and prokaryotic cells. In prokaryotes, NER is mediated by Uvr proteins. In eukaryotes, many more proteins are involved, although the general strategy is the same.

3 Mismatch repair systems are present in essentially all cells to correct errors that are not corrected by proofreading. These systems consist of at least two proteins. One detects the mismatch, and the other recruits an endonuclease that cleaves the newly synthesized DNA strand close to the region of damage. In *E. coli*, the proteins involved are the Mut class proteins. This is followed by removal of damaged region by an exonuclease, resynthesis by DNA polymerase, and nick sealing by DNA ligase.

https://en.wikipedia.org/wiki/DNA_repair

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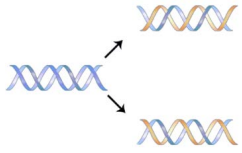
DNA Replication

In molecular biology, DNA replication is the biological process of producing two identical replicas of DNA from one original DNA molecule. This process occurs in all living organisms and is the basis for biological inheritance. DNA is made up of a double helix of two strands, and each strand of the original DNA molecule serves as a template for the production of the complementary strand, a process referred to as semiconservative replication. Cellular proofreading and error-checking mechanisms ensure near perfect fidelity for DNA replication.



In a cell, DNA replication begins at specific locations, or origins of replication, in the genome. Unwinding of DNA at the origin and synthesis of new strands results in replication forks growing bidirectional from the origin. A number of proteins are associated with the replication fork which helps in terms of the initiation and continuation of DNA synthesis. Most prominently, DNA polymerase synthesizes the new DNA by adding complementary nucleotides to the template strand.

DNA replication can also be performed *in vitro* (artificially, outside a cell). DNA polymerases isolated from cells and artificial DNA primers can be used to initiate DNA synthesis at known sequences in a template DNA molecule. The polymerase chain reaction (PCR), a common laboratory technique, cyclically applies such artificial synthesis to amplify a specific target DNA fragment from a pool of DNA.

DNA polymerase adds a new strand of DNA by extending the 3' end of an existing nucleotide chain, adding new nucleotides matched to the template strand one at a time via the creation of phosphodiester bonds. The energy for this process of DNA polymerization comes from hydrolysis of the high-energy phosphate (phosphoanhydride) bonds between the three phosphates attached to each unincorporated base. (Free bases with their attached phosphate groups are called nucleotides. In particular, bases with three attached phosphate groups are called nucleoside triphosphates.) When a nucleotide is being added to a growing DNA strand, the formation of a phosphodiester bond between the proximal phosphate of the nucleotide to the growing chain is accompanied by hydrolysis of a high-energy phosphate bond with release of the two distal phosphates as a pyrophosphate. Enzymatic hydrolysis of the resulting pyrophosphate into inorganic phosphate consumes a second high-energy phosphate bond and renders the reaction effectively irreversible.

In general, DNA polymerases are highly accurate, with an intrinsic error rate of less than one mistake for every 10^7 nucleotides added. In addition, some DNA polymerases also have proofreading ability. They can remove nucleotides from the end of a growing strand in order to correct mismatched bases. Finally, post-replication mismatch repair mechanisms monitor the DNA for errors, being capable of distinguishing mismatches in the newly synthesized DNA strand from the original strand sequence. Together, these three discrimination steps enable replication fidelity of less than one mistake for every 10_9 nucleotides added.

https://en.wikipedia.org/wiki/DNA_replication

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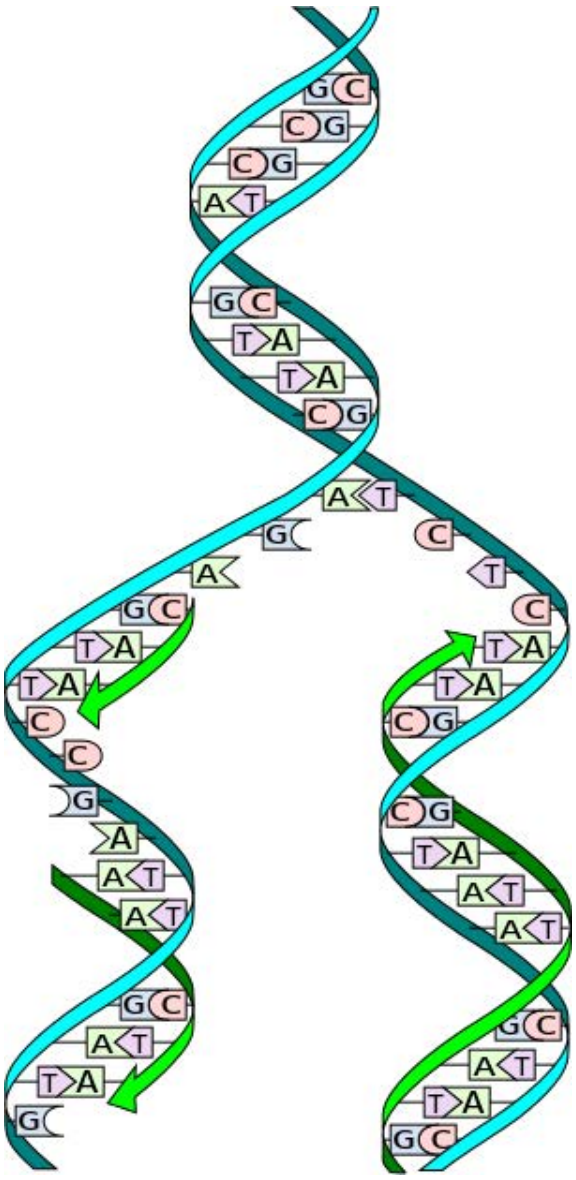
DNA Synthesis

DNA synthesis is the natural or artificial creation of deoxyribonucleic acid (DNA) molecules. The term DNA synthesis can refer to any of the following in various contexts:

- DNA replication - DNA biosynthesis (*in vivo* DNA amplification)
- Polymerase chain reaction - enzymatic DNA synthesis (*in vitro* DNA amplification)
- Gene synthesis - physically creating artificial gene sequences



https://en.wikipedia.org/wiki/DNA_synthesis

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Chapter 6 - Metabolism: Nucleotides

DNA-protein Complexes

Biomolecular complexes, also called macromolecular complexes or biomacromolecular complexes, refer to any biological complexes made of more than one molecule of protein, RNA, DNA, lipids, or carbohydrates. The interactions between these biomolecules are non-covalent.

Examples:
Protein complexes: proteasome, DNA polymerase III holoenzyme, RNA polymerase II holoenzyme, symmetric viral capsids, complex of GroEL and GroES, photosystem I, ATP synthase

RNA-protein complexes: ribosome, spliceosome, vault, SnRNP. Such complexes in cell nucleus are called ribonucleoproteins (RNPs).

DNA-protein complexes: nucleosome

Protein-lipid complexes: lipoproteins

https://en.wikipedia.org/wiki/Biomolecular_complex

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dNTPs

The nucleoside triphosphates containing deoxyribose are called dNTPs, and
prefix deoxy- in their names and small d- in their abbreviations: deoxyaden
phosphate (dATP), deoxyguanosine triphosphate (dGTP), deoxycytidine tri
(dCTP), deoxythymidine triphosphate (dTTP) and deoxyuridine triphospha
The dNTPs are the building blocks for DNA (they lose two of the phosphate
the process of incorporation).

https://en.wikipedia.org/wiki/Nucleoside_triphosphate

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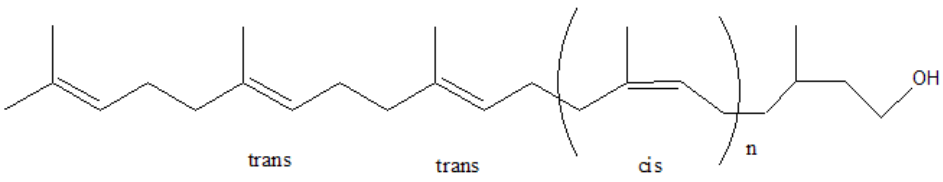
Dolichol

Dolichols play a role in the co-translational modification of proteins known as N-glycosylation in the form of dolichol phosphate. Dolichols function as a membrane anchor for the formation of the oligosaccharide Glc3-Man9-GlcNAc2 (where Glc is glucose, Man is mannose, and GlcNAc is N-acetylglucosamine). This oligosaccharide is transferred from the dolichol donor onto certain asparagine residues (onto a specific sequence that is "Asn-X-Ser/Thr") of newly forming polypeptide chains. Dolichol is also involved in transfer of the monosaccharides to the forming Glc3-Man9-GlcNAc2-Dolichol carrier.

In addition, dolichols can be adducted to proteins as a posttranslational modification, a process in which branched carbohydrate trees are formed on a dolichol moiety and then transferred to an assembly of proteins to form a large glycoprotein in the rough endoplasmic reticulum.

Dolichols are the major lipid component (14% by mass) of human substantia nigra (SN) neuromelanin. Dolichol phosphate was discovered at the University of Liverpool in the 1960s, although researchers did not know its function at the time of discovery.

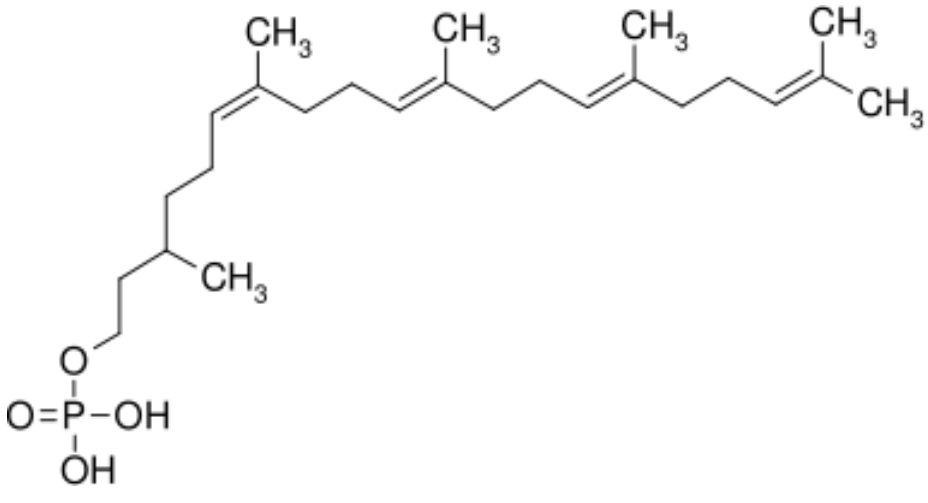
Dolichol has been suggested to be used as a biomarker for aging. During aging, the human brain shows a progressive increase in levels of dolichol, a reduction in levels of ubiquinone, but relatively unchanged concentrations of cholesterol and dolichyl phosphate. In the neurodegenerative disease Alzheimer's disease, the situation is reversed, with decreased levels of dolichol and increased levels of ubiquinone. The concentrations of dolichyl phosphate are also increased, while cholesterol remains unchanged. This study shows that the isoprenoid changes in Alzheimer's disease differ from those occurring during normal aging, and, therefore, this disease cannot be regarded as a result of premature aging. The increase in the sugar carrier dolichyl phosphate may reflect an increased rate of glycosylation in the diseased brain, and the increase in the endogenous anti-oxidant ubiquinone an attempt to protect the brain from oxidative stress, for instance, induced by lipid peroxidation.



https://en.wikipedia.org/wiki/Dolichol

Dolichol Phosphate

Dolichol monophosphate is a fatty alcohol that plays a role synthesis of the can cell wall of bacteria.



https://en.wikipedia.org/wiki/Dolichol_monophosphate

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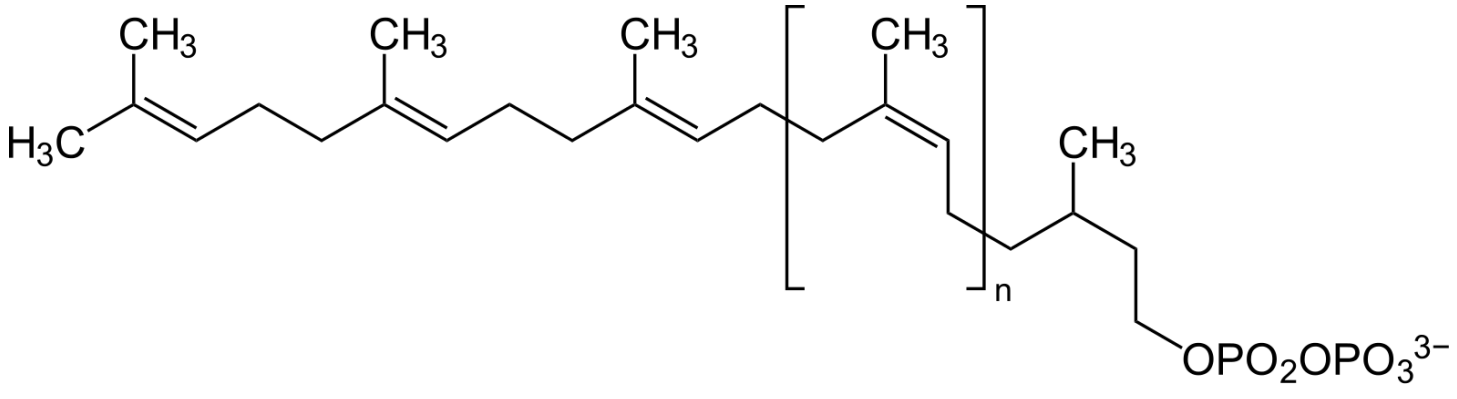
Dolichol Pyrophosphate

Dolichol pyrophosphate is a molecule in the membrane of the endoplasmic
that plays a role in N-glycosylation of proteins. The process involves “build
of the glycosyl chain on a molecule called dolichol pyrophosphate before tra
amide nitrogen of a target protein’s asparagine.



https://en.wikipedia.org/wiki/Dolichol

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Donor Chromophore

Fluorescence resonance energy transfer (FRET - also called Förster resonance energy transfer, resonance energy transfer (RET) or electronic energy transfer (EET)) is a method for determining interactions between biomolecules. In the technique, a donor chromophore and an acceptor chromophore are covalently attached to molecules of interest.

The acceptor chromophore is designed to accept energy through nonradiative dipole–dipole coupling from the donor molecule and fluoresce at a unique wavelength (red arrow) when it receives that energy from the donor.

Further, the wavelength of light that causes the donor to transfer energy (blue arrow) to the acceptor has no effect on the acceptor chromophore. The only way the acceptor can fluoresce is if it receives energy transferred from the donor. If the two are not close enough together, the donor fluoresces and emits light corresponding to the green or black arrow.

The experiment begins with donors and acceptors in a cell. Light of a wavelength that excites the donor chromophore is shined on the cell. In order for the acceptor chromophore to receive the energy from the donor molecule, the acceptor must be physically very close to it. Thus, if a protein with a donor binds with a protein with an acceptor, then energy transfer from the donor chromophore to the acceptor fluorescence can occur and the unique fluorescence of the acceptor is detected. If the two proteins do not interact together, then little or no fluorescence from the acceptor is detected.

https://en.wikipedia.org/wiki/Förster_resonance_energy_transfer

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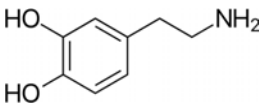
Dopamine

Dopamine (contracted from 3,4-dihydroxyphenethylamine) is an organic chemical of the catecholamine and phenethylamine families that plays several important roles in the brain and body. It is an amine synthesized by removing a carboxyl group from a molecule of its precursor chemical L-DOPA, which is synthesized in the brain and kidneys. Dopamine is also synthesized in plants and most multicellular animals. In the brain, dopamine functions as a neurotransmitter—a chemical released by neurons (nerve cells) to send signals to other nerve cells. The brain includes several distinct dopamine pathways, one of which plays a major role in reward-motivated behavior. Most types of reward increase the level of dopamine in the brain, and most addictive drugs increase dopamine neuronal activity. Other brain dopamine pathways are involved in motor control and in controlling the release of various hormones. These pathways and cell groups form a dopamine system which is neuromodulatory.

Outside the central nervous system, dopamine functions in several parts of the peripheral nervous system as a local chemical messenger. In blood vessels, it inhibits norepinephrine release and acts as a vasodilator (at normal concentrations); in the kidneys, it increases sodium excretion and urine output; in the pancreas, it reduces insulin production; in the digestive system, it reduces gastrointestinal motility and protects intestinal mucosa; and in the immune system, it reduces the activity of lymphocytes. With the exception of the blood vessels, dopamine in each of these peripheral systems is synthesized locally and exerts its effects near the cells that release it.

Several important diseases of the nervous system are associated with dysfunctions of the dopamine system, and some of the key medications used to treat them work by altering the effects of dopamine. Parkinson's disease, a degenerative condition causing tremor and motor impairment, is caused by a loss of dopamine-secreting neurons in an area of the midbrain called the substantia nigra. Its metabolic precursor L-DOPA can be manufactured, and in its pure form marketed as Levodopa is the most widely used treatment for the condition. There is evidence that schizophrenia involves altered levels of dopamine activity, and most antipsychotic drugs used to treat this are dopamine antagonists which reduce dopamine activity. Similar dopamine antagonist drugs are also some of the most effective anti-nausea agents. Restless legs syndrome and attention deficit hyperactivity disorder (ADHD) are associated with decreased dopamine activity. Dopaminergic stimulants can be addictive in high doses, but some are used at lower doses to treat ADHD. Dopamine itself is available as a manufactured medication for intravenous injection: although it cannot reach the brain from the bloodstream, its peripheral effects make it useful in the treatment of heart failure or shock, especially in newborn babies.



https://en.wikipedia.org/wiki/Dopamine

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Dopaminergic Neurons

Dopaminergic means "related to dopamine" (literally, "working on dopamine"), dopamine being a common neurotransmitter. Dopaminergic substances or actions increase dopamine-related activity in the brain. Dopaminergic brain structures facilitate dopamine-related activity. For example, certain proteins such as the dopamine transporter (DAT), vesicular monoamine transporter 2 (VMAT2), and dopamine receptors can be classified as dopaminergic, and neurons that synthesize or contain dopamine and synapses with dopamine receptors in them may also be labeled as dopaminergic.

Enzymes that regulate the biosynthesis or metabolism of dopamine such as aromatic L-amino acid decarboxylase or DOPA decarboxylase, monoamine oxidase (MAO), and catechol O-methyl transferase (COMT) may be referred to as dopaminergic as well. Also, any endogenous or exogenous chemical substance that acts to affect dopamine receptors or dopamine release through indirect actions (for example, on neurons that synapse onto neurons that release dopamine or express dopamine receptors) can also be said to have dopaminergic effects, two prominent examples being opioids, which enhance dopamine release indirectly in the reward pathways, and some substituted amphetamines, which enhance dopamine release directly by binding to and inhibiting $VMAT_2$.

https://en.wikipedia.org/wiki/Dopaminergic

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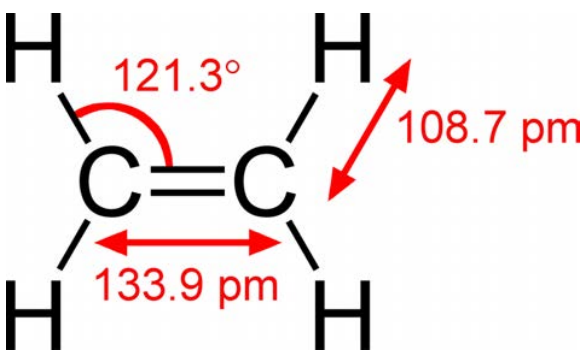
Double Bond

A double bond in chemistry is a chemical bond between two chemical elements involving four bonding electrons instead of the usual two. The most common double bond, that is between two carbon atoms, can be found in alkenes. Many types of double bonds exist between two different elements. For example, in a carbonyl group with a carbon atom and an oxygen atom. Other common double bonds are found in azo compounds (N=N), imines (C=N) and sulfoxides (S=O). In skeletal formula the double bond is drawn as two parallel lines (=) between the two connected atoms. Typographically, the equals sign is used for this. Double bonds were first introduced in chemical notation by prominent Russian chemist Alexander Butlerov.

Double bonds involving carbon are stronger than single bonds and are also shorter. The bond order is two. Double bonds are also electron-rich, which makes them reactive.



https://en.wikipedia.org/wiki/Double_bond

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Double Bonds

A double bond in chemistry is a chemical bond between two chemical elements involving four bonding electrons instead of the usual two. The most common double bond, that is between two carbon atoms, can be found in alkenes. Many types of double bonds exist between two different elements. For example, in a carbonyl group with a carbon atom and an oxygen atom. Other common double bonds are found in azo compounds (N=N), imines (C=N) and sulfoxides (S=O). In skeletal formula the double bond is drawn as two parallel lines (=) between the two connected atoms; typographically, the equals sign is used for this. Double bonds were first introduced in chemical notation by prominent Russian chemist Alexander Butlerov.

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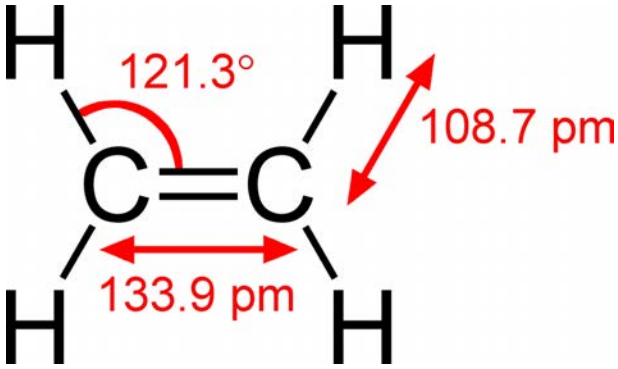

https://en.wikipedia.org/wiki/Double_bond

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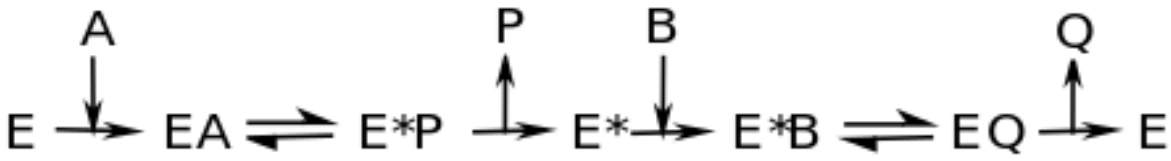
Chapter 1 - Introduction: Basic Chemistry

Double Displacement

Double displacement (also called ping-pong) is a mechanism used by some enzymes that catalyze reactions with multiple substrates. Enzymes with a ping-pong mechanism can exist in two states, E and a chemically modified form of the enzyme E*. This modified enzyme is known as an intermediate. In such mechanisms, substrate A binds, changes the enzyme to E* by, for example, transferring a chemical group to the active site, and is then released. Only after the first substrate is released can substrate B bind and react with the modified enzyme, regenerating the unmodified E form. When a set of v by [S] curves (fixed A, varying B) from an enzyme with a ping–pong mechanism are plotted in a Lineweaver–Burk plot, a set of parallel lines will be produced. This is called a secondary plot.

Enzymes with ping–pong mechanisms include some oxidoreductases such as thioredoxin peroxidase, transferases such as acylneuraminate cytidylyltransferase and serine proteases such as trypsin and chymotrypsin. Serine proteases are a very common and diverse family of enzymes, including digestive enzymes (trypsin, chymotrypsin, and elastase), several enzymes of the blood clotting cascade and many others. In these serine proteases, the E* intermediate is an acyl-enzyme species formed by the attack of an active site serine residue on a peptide bond in a protein substrate.



https://en.wikipedia.org/wiki/Enzyme_kinetics#Ping.E2.80.93pong_mechanisms

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Double helix

In molecular biology, the term double helix refers to the structure formed by do
stranded molecules of nucleic acids such as DNA. The double helical structure o
cleic acid complex arises as a consequence of its secondary structure, and is a fu
mental component in determining its tertiary structure. The term entered popu
ture with the publication in 1968 of The Double Helix: A Personal Account of th
covery of the Structure of DNA, by James Watson.

The DNA double helix polymer of nucleic acid, held together by nucleotides wh
pair together. In B-DNA, the most common double helical structure, the double
right-handed with about 10–10.5 base pairs per turn. This translates into abou
nucleotides per turn. The double helix structure of DNA contains a major groov
minor groove. In B-DNA the major groove is wider than the minor groove. Give
difference in widths of the major groove and minor groove, many proteins whic
to B-DNA do so through the wider major groove.

https://en.wikipedia.org/wiki/Nucleic_acid_double_helix

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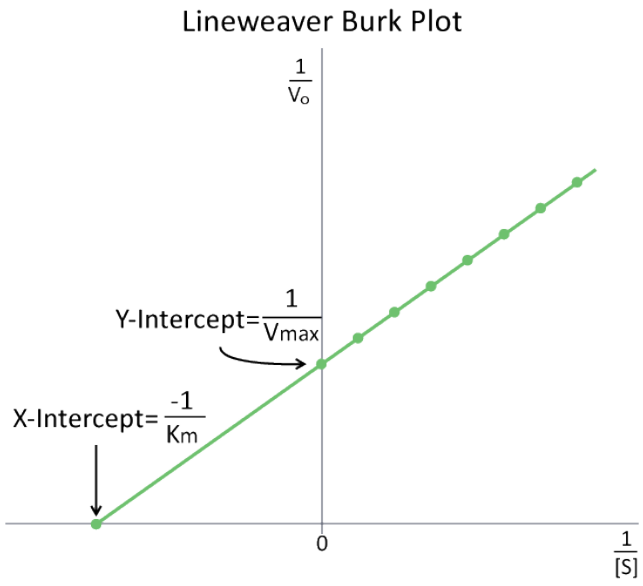
Double-reciprocal Plot

The Lineweaver–Burk plot (or double reciprocal plot) is a graphical representation of the Lineweaver–Burk equation of enzyme kinetics, described by Hans Lineweaver and Dean Burk in 1934.

The Lineweaver–Burk plot was widely used to determine important terms in enzyme kinetics, such as K_m and V_{max}, before the wide availability of powerful computers and non-linear regression software. The y-intercept of such a graph is equivalent to the inverse of V_{max}. The x-intercept of the graph represents $-1/K_m$. It also gives a quick, visual impression of the different forms of enzyme inhibition.

The double reciprocal plot distorts the error structure of the data, and it is therefore unreliable for the determination of enzyme kinetic parameters. Although it is still used for representation of kinetic data, non-linear regression or alternative linear forms of the Michaelis–Menten equation such as the Hanes-Woolf plot or Eadie–Hofstee plot are generally used for the calculation of parameters.
When used for determining the type of enzyme inhibition, the Lineweaver–Burk plot can distinguish competitive, non-competitive and uncompetitive inhibitors. Competitive inhibitors have the same y-intercept as uninhibited enzyme (since V_{max} is unaffected by competitive inhibitors the inverse of V_{max} also doesn't change) but there are different slopes and x-intercepts between the two data sets. Non-competitive inhibition produces plots with the same x-intercept as uninhibited enzyme (K_m is unaffected) but different slopes and y-intercepts. Uncompetitive inhibition causes different intercepts on both the y- and x-axes.



https://en.wikipedia.org/wiki/Lineweaver%E2%80%93Burk_plot

Downstream Promoter Elements

In molecular biology, a downstream promoter element (DPE) is a core promoter element. Like all core promoters, the DPE plays an important role in the initiation of gene transcription by RNA polymerase II.

Together with the initiator motif (Inr), another core promoter element, the DPE is recognized by the transcription factor II D (TFIID) subunits TAF6 and TAF9. It has been shown that DPE-dependent basal transcription depends highly on the Inr (and vice versa) and on correct spacing between the two elements.

The DPE consensus sequence was originally thought to be RGWCGTG, however more recent studies have suggested it to be the similar but more general sequence RGWYV(T). It is located about 28–33 nucleotides downstream of the transcription start site.

It has been shown that the DPE is about as widely used as the TATA box in *D. melanogaster*. While a DPE was found in many promoters that do not contain a TATA box, there are also promoters that contain both a TATA box and a DPE.

https://en.wikipedia.org/wiki/Downstream_promoter_element

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Chapter 7 - Information Processing: Transcription

Chapter 9 - Point by Point: Information Processing

Drosha

Drosha is a Class 2 ribonuclease III enzyme that in humans is encoded by the DROSHA (formerly RNASEN) gene. Members of the ribonuclease III superfamily of double-stranded (ds) RNA-specific endoribonucleases participate in diverse RNA maturation and decay pathways in eukaryotic and prokaryotic cells. The RNase III Drosha is the core nuclease that executes the initiation step of microRNA (miRNA) processing in the nucleus.

The microRNAs thus generated are short RNA molecules that regulate a wide variety of other genes by interacting with the RNA-induced silencing complex (RISC) to induce cleavage of complementary messenger RNA (mRNA) as part of the RNA interference pathway. A microRNA molecule is synthesized as a long RNA primary transcript known as a pri-miRNA, which is cleaved by Drosha to produce a characteristic stem-loop structure of about 70 base pairs long, known as a pre-miRNA. Drosha exists as part of a protein complex called the Microprocessor complex, which also contains the double-stranded RNA binding protein Pasha (also called DGCR8). Pasha is essential for Drosha activity and is capable of binding single-stranded fragments of the pri-miRNA that are required for proper processing.

https://en.wikipedia.org/wiki/Drosha

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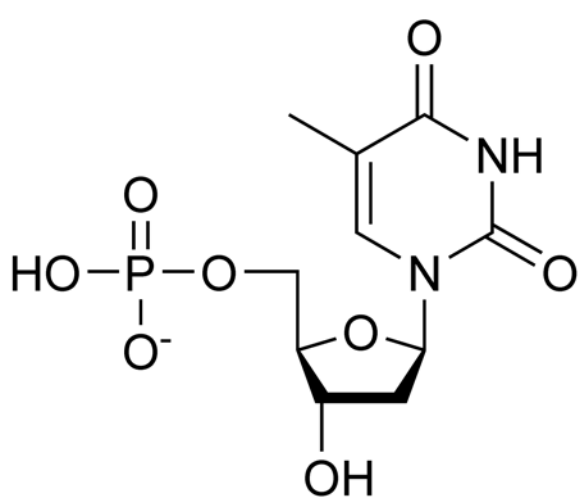
dTMP

Thymidine monophosphate (TMP), also known as thymidylic acid (conjugate base thymidylate), deoxythymidine monophosphate (dTMP), or deoxythymidylic acid (conjugate base deoxythymidylate), is a nucleotide that is used as a monomer in DNA. It is an ester of phosphoric acid with the nucleoside thymidine. dTMP consists of a phosphate group, the pentose sugar deoxyribose, and the nucleobase thymine. Unlike the other deoxyribonucleotides, thymidine monophosphate often does not contain the "deoxy" prefix in its name. Nevertheless, its symbol often includes a "d" ("dTMP").



https://en.wikipedia.org/wiki/Thymidine_monophosphate

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dTMP Kinase

dTMP kinase (EC 2.7.4.9) is an enzyme that catalyzes the chemical reaction

ATP + dTMP <=> ADP + dTDP

This enzyme belongs to the family of transferases, specifically those transfe
phosphorus-containing groups (phosphotransferases) with a phosphate gro
tor. The systematic name of this enzyme class is ATP:dTMP phosphotransfe
names in common use include thymidine monophosphate kinase, thymidyl
thymidylate monophosphate kinase, thymidylic acid kinase, thymidylic kin
oxythymidine 5'-monophosphate kinase, TMPK, and thymidine 5'-monoph
nase. This enzyme participates in pyrimidine metabolism.

https://en.wikipedia.org/wiki/DTMP_kinase

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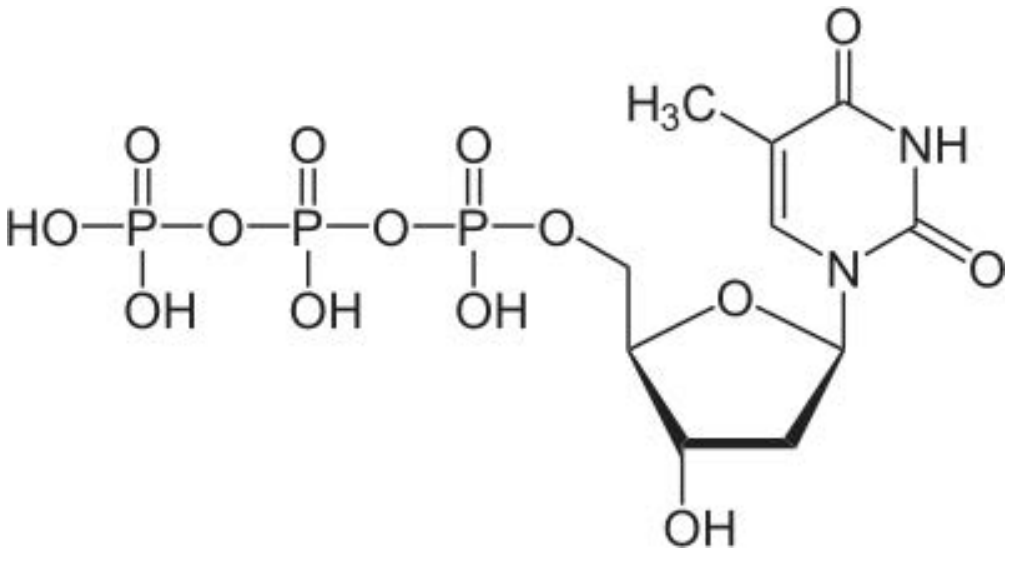
dTTP

Deoxythymidine triphosphate (dTTP) is one of the four nucleotide triphosphates that are used in the *in vivo* synthesis of DNA. Unlike the other deoxyribonucleotide triphosphates, thymidine triphosphate does not always contain the "deoxy" prefix in its name. The corresponding ribonucleoside triphosphate is called uridine triphosphate.



https://en.wikipedia.org/wiki/Thymidine_triphosphate

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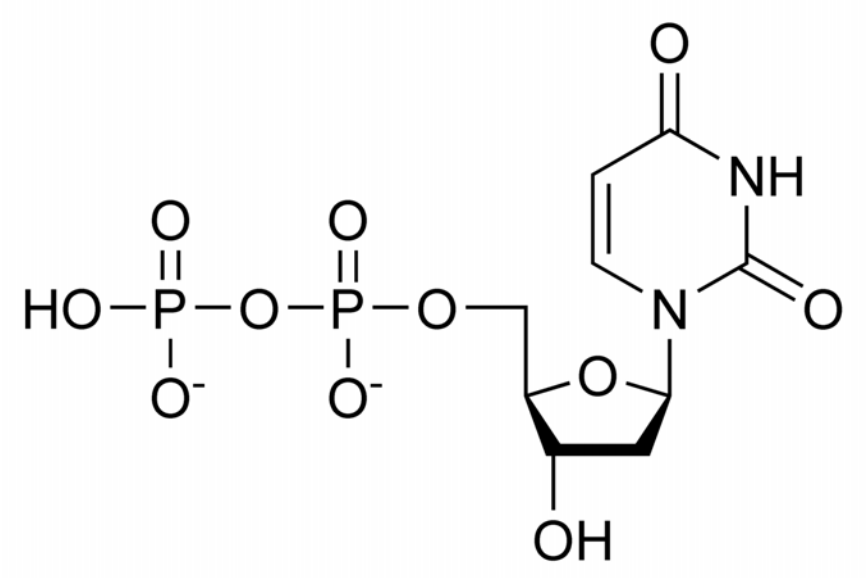
dUDP

Deoxyuridine diphosphate (dUDP) is a deoxyribonucleotide produced from UDP by
tion of the enzyme ribonucleotide reductase. dUDP is part of the metabolic pathwa
for making thymidine nucleotides. dUDP is converted next into dUTP, then to dUM
and then into dTMP.



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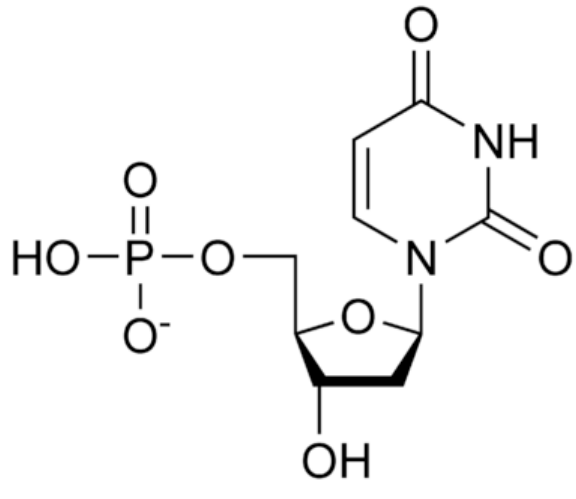
dUMP

Deoxyuridine monophosphate (dUMP), also known as deoxyuridylic acid or deoxyuridylate in its conjugate acid and conjugate base forms, respectively, is a deoxynucleotide.

It is an intermediate in the metabolism of thymidine nucleotides. Thymidylate synthase acts on it and converts it to dTMP.



https://en.wikipedia.org/wiki/Deoxyuridine_monophosphate

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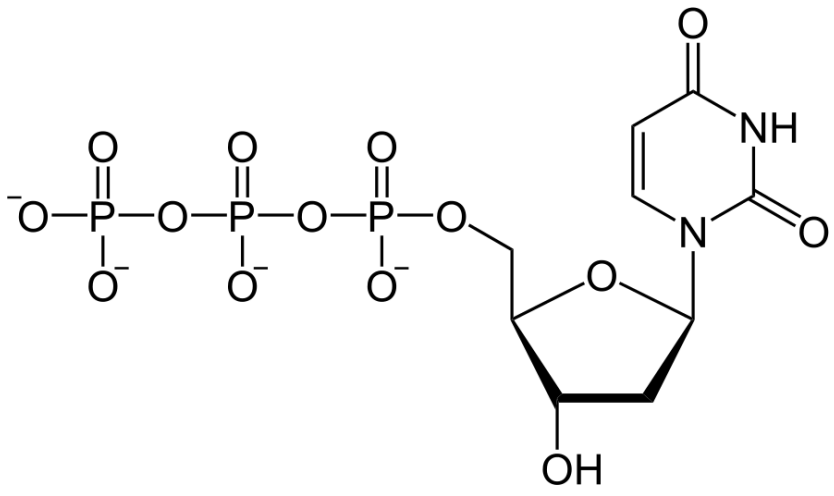
dUTP

Deoxyuridine triphosphate (dUTP) is an intermediate in synthesis of thymidine tides. It is made from dUDP by action of NDPK and is acted on by dUTPase (al called dUTP diphosphatase) to produce dUMP. dUMP is then converted to dTM action of thymidylate synthase.



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dUTPase

dUTP diphosphatase (also called dUTPase) (EC 3.6.1.23) is an enzyme that catalyzes the reaction below in thymidine metabolism

$dUTP + H_2O <-> dUMP + PP_i$

This enzyme has a dual function: on one hand, it removes dUTP from the deoxynucleotide pool, which reduces the probability of this base being incorporated into DNA by DNA polymerases, while on the other hand, it produces the dTTP precursor dUMP. Lack or inhibition of dUTPase action leads to harmful perturbations in the nucleotide pool resulting in increased uracil content of DNA that activates a hyperactive futile cycle of DNA repair.

This enzyme belongs to the family of hydrolases, specifically those acting on acid anhydrides in phosphorus-containing anhydrides. The systematic name of this enzyme class is dUTP nucleotidohydrolase. Other names in common use include deoxyuridine-triphosphatase, dUTPase, dUTP pyrophosphatase, deoxyuridine 5'-triphosphate nucleotidohydrolase, and deoxyuridine 5'-triphosphatase. This enzyme participates in pyrimidine metabolism.

https://en.wikipedia.org/wiki/DUTP_diphosphatase

Related Glossary Terms

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Dynein

Dynein is a motor protein (also called molecular motor or motor molecule) in cells which converts the chemical energy contained in ATP into the mechanical energy of intracellular movement. Dynein transports various cellular cargo by "walking" along cytoskeletal microtubules towards the minus-end of the microtubule, which is usually oriented towards the cell center. Thus, they are called "minus-end directed motors." This form of transport is known as retrograde transport. In contrast, kinesins, which are motor proteins that move toward the microtubules' plus end, are called plus-end directed motors.

Axonemal dynein causes sliding of microtubules in the axonemes of cilia and flagella and is found only in cells that have those structures.

Cytoplasmic dynein, found in all animal cells and possibly plant cells as well, performs functions necessary for cell survival such as organelle transport and centrosome assembly. Cytoplasmic dynein moves processively along the microtubule; that is, one or the other of its stalks is always attached to the microtubule so that the dynein can "walk" a considerable distance along a microtubule without detaching.

Cytoplasmic dynein helps to position the Golgi complex and other organelles in the cell. It also helps transport cargo needed for cell function such as vesicles made by the endoplasmic reticulum, endosomes, and lysosomes. Dynein is involved in the movement of chromosomes and positioning the mitotic spindles for cell division. Dynein carries organelles, vesicles and possibly microtubule fragments along the axons of neurons toward the cell body in a process called retrograde axoplasmic transport.

https://en.wikipedia.org/wiki/Dynein

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E-site

The E-site is the third and final binding site for t-RNA in the ribosome duri
synthesis. The "E" stands for exit, and is accompanied by the P-site (for pep
which is the second binding site, and the A-site (aminoacyl), which is the fi
site.

https://en.wikipedia.org/wiki/E-site

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E1

E1 is one of three subunits of the pyruvate dehydrogenase complex. It catalyzes the decarboxylation of pyruvate within the enzyme complex and transfer of the two carbon activated acetaldehyde to thiamine pyrophosphate (TPP).

The overall reaction to convert pyruvate to acetyl-AoA involves three steps, each occurring on one of the enzyme's subunits. The steps, sequentially occurring on subunits E1, E2, and E3, are 1) decarboxylation of pyruvate; 2) oxidation of the decarboxylated product (with transfer of the two carbon unit to CoASH to make acetyl-CoA); and 3) transfer of electrons to ultimately form NADH.

Phosphorylation of E1 by pyruvate dehydrogenase kinase (PDK) inactivates E1 and subsequently the entire complex. PDK is inhibited by dichloroacetic acid and pyruvate, resulting in a higher quantity of active, unphosphorylated PDH. Phosphorylation is reversed by pyruvate dehydrogenase phosphatase, which is stimulated by insulin, PEP, and AMP, but competitively inhibited by ATP, NADH, and Acetyl-CoA.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase

Related Glossary Terms

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E2

E2 (dihydrolipoamide acetyltransferase) is one of three subunits of the enzyme pyruvate dehydrogenase. It performs the oxidation of the two carbon activated acetaldehyde (hydroxyethyl group) within the enzyme complex. Lipoamide is covalently bound to E2 and it is during the transfer of the activated acetaldehyde to it from the TPP of E1 that the oxidation occurs. E2 also catalyzes transfer of the two carbon group from lipoamide to CoASH, forming acetyl-CoA.

The overall reaction to convert pyruvate to acetyl-AoA involves three steps, each occurring on one of the enzyme's subunits. The steps, sequentially occurring on subunits E1, E2, and E3, are 1) decarboxylation of pyruvate; 2) oxidation of the decarboxylated product (with transfer of the two carbon unit to CoASH to make acetyl-CoA); and 3) transfer of electrons to ultimately form NADH.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase

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E3

E3 is one of three subunits of the enzyme pyruvate dehydrogenase. It performs
dation of lipoamide by transferring electrons to FAD (forming $FADH_2$) and the
NAD^+ to form NADH.

The overall reaction to convert pyruvate to acetyl-AoA involves three steps, eac
ring on one of the enzyme's subunits. The steps, sequentially occurring on subu
E2, and E3, are 1) decarboxylation of pyruvate; 2) oxidation of the decarboxylat
uct (with transfer of the two carbon unit to CoASH to make acetyl-CoA); and 3)
fer of electrons to ultimately form NADH.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase

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Eadie-Hofstee

In biochemistry, an Eadie–Hofstee diagram (also Woolf–Eadie–Augustinsson–Hofstee or Eadie–Augustinsson plot) is a graphical representation of enzyme kinetics in which reaction rate is plotted as a function of the ratio between rate and substrate concentration:

$$v = -K_m \frac{v}{[S]} + V_{\mathbf{max}}$$

where v represents reaction rate, K_m is the Michaelis–Menten constant, [S] is the substrate concentration, and V_{max} is the maximum reaction rate.

A plot of v against v/[S] will hence yield V_{max} as the y-intercept, V_{max}/K_m as the x-intercept, and K_m as the negative slope. Like other techniques that linearize the Michaelis–Menten equation, the Eadie-Hofstee plot was used historically for rapid identification of important kinetic terms like K_m and V_{max}, but has been superseded by non-linear regression methods that are significantly more accurate and no longer computationally inaccessible. It is also more robust against error-prone data than the Lineweaver–Burk plot, particularly because it gives equal weight to data points in any range of substrate concentration or reaction rate. (The Lineweaver–Burk plot unevenly weights such points.) Both plots remain useful as a means to present data graphically.

One drawback from the Eadie–Hofstee approach is that neither ordinate nor abscissa represent independent variables: both are dependent on reaction rate. Thus any experimental error will be present in both axes. Also, experimental error or uncertainty will propagate unevenly and become larger over the abscissa thereby giving more weight to smaller values of v/[S]. Therefore, the typical measure of goodness of fit for linear regression, the correlation coefficient R, is not applicable.

https://en.wikipedia.org/wiki/Eadie–Hofstee_diagram

EcoRV

EcoRV is a type II restriction endonuclease isolated from certain strains of
coli. It has the alternative name Eco32I.

In molecular biology, it is a commonly used restriction enzyme. It creates b
The enzyme recognizes the palindromic 6-base DNA sequence 5'-GAT|ATC
makes a cut at the vertical line. The complementary sequence is then 3'-CT
The ends are blunt and can be ligated into a blunt cloning site easily but wi
ciency than sticky ends.

https://en.wikipedia.org/wiki/EcoRV

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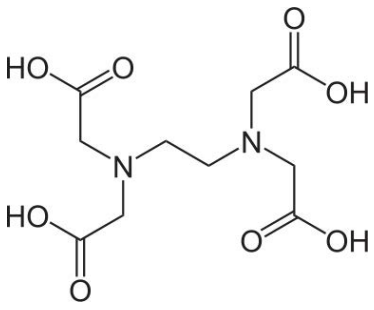
EDTA

Ethylenediaminetetraacetic acid, widely abbreviated as EDTA (for other names, see Table), is an aminopolycarboxylic acid and a colorless, water-soluble solid. Its conjugate base is named ethylenediaminetetraacetate. It is widely used to dissolve limescale. Its usefulness arises because of its role as a hexadentate ("six-toothed") ligand and chelating agent, i.e., its ability to "sequester" metal ions such as Ca^{2+} and Fe^{3+}. After being bound by EDTA, metal ions remain in solution but exhibit diminished reactivity. EDTA is produced as several salts, notably disodium EDTA and calcium disodium EDTA.

In the laboratory, EDTA is widely used for scavenging metal ions. In biochemistry and molecular biology, ion depletion is commonly used to deactivate metal-dependent enzymes, either as an assay for their reactivity or to suppress damage to DNA or proteins. In analytical chemistry, EDTA is used in complexometric titrations and analysis of water hardness or as a masking agent to sequester metal ions that would interfere with the analyses.

EDTA finds many specialized uses in the biomedical laboratories, such as in veterinary ophthalmology as an anticollagenase to prevent the worsening of corneal ulcers in animals. In tissue culture EDTA is used as a chelating agent that binds to calcium and prevents joining of cadherins between cells, preventing clumping of cells grown in liquid suspension, or detaching adherent cells for passaging. In histopathology, EDTA can be used as a decalcifying agent making it possible to cut sections using a microtome once the tissue sample is demineralized. EDTA is also known to inhibit a range of metallopeptidases, the method of inhibition occurs via the chelation of the metal ion required for catalytic activity. EDTA can also be used to test for bioavailability of heavy metals in sediments. However, EDTA may influence the bioavailability of metals in solution, which may pose concerns regarding its effects in the environment, especially given its widespread uses and applications.



https://en.wikipedia.org/wiki/Ethylenediaminetetraacetic_acid

EF-G

EF-G or elongation factor G (historically known as translocase) is a prokaryotic elongation factor and a GTPase responsible for catalyzing the coordinated movement of tRNA and mRNA through the ribosome.

The factor EF-G catalyzes the translocation of the tRNA and mRNA down the ribosome at the end of each round of polypeptide elongation. Just like the EF-Tu+tRNA+GTP complex, EF-G binds to the ribosome in its GTP-bound state. When it binds to the ribosome A-site, EF-G causes the tRNA previously occupying that site to occupy an intermediate A/P position (bound to the A site of the small ribosomal subunit and to the P site of the large subunit), and the tRNA in the P site is shifted to a P/E hybrid state. EF-G hydrolysis of GTP causes a conformation change that forces the A/P tRNA to fully occupy the P site, the P/E tRNA to fully occupy the E site (and exit the ribosome complex), and the mRNA to shift three nucleotides down relative to the ribosome due to its association with these tRNA molecules. The GDP-bound EF-G molecule then dissociates from the complex, leaving another free A-site where the elongation cycle can start again.

Apart from its role in translocation, EF-G, working together with Ribosome Recycling Factor, promotes ribosome recycling in a GTP-dependent manner.

https://en.wikipedia.org/wiki/EF-G

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Chapter 7 - Information Processing: Translation

Chapter 9 - Point by Point: Information Processing

EF-Tu

EF-Tu (elongation factor thermo unstable) is one of the prokaryotic elongation factors. Elongation factors are part of the mechanism that synthesizes new proteins by translation at the ribosome. Individual amino acid links are added to the protein chain by transfer RNA (t-RNA). Messenger RNA (mRNA) carries a codon that codes for each amino acid. t-RNA carries the amino acid and an anticodon for that amino acid. The ribosome creates a protein chain by following the mRNA code and selecting the next t-RNA and its amino acid.

The prokaryotic factor EF-Tu helps the aminoacyl-tRNA move onto a free site on the ribosome. In the cytoplasm, EF-Tu binds an aminoacylated, or charged, tRNA molecule. This complex enters the ribosome.

There are 3 tRNA attachment sites on the ribosome: aminoacyl (A), peptidyl (P) and exit (E). The tRNA complex first binds to the A site, then moves to the P site, and is released at the E site.

The tRNA anticodon domain associates with the mRNA codon domain in the ribosomal A site. If the codon-anticodon pairing is correct, EF-Tu hydrolyzes guanosine triphosphate (GTP) into guanosine diphosphate (GDP) and inorganic phosphate. This creates a conformational change in EF-Tu that causes EF-Tu to dissociate from the tRNA of the ternary complex (and therefore leave the ribosome). The aminoacyl-tRNA then fully enters the A site, where its amino acid is brought near the P site's polypeptide and the ribosome catalyzes the covalent transfer of the polypeptide onto the amino acid . The tRNA on the P site (without peptide) moves to the E site and is then released.

EF-Tu contributes to translational accuracy in three ways. It delays GTP hydrolysis if the tRNA in the ribosome’s A site does not match the mRNA codon, thus preferentially increasing the likelihood for the incorrect tRNA to leave the ribosome. It also adds a second delay (regardless of tRNA matching) after freeing itself from tRNA, before the aminoacyl-tRNA fully enters the A site. This delay period is a second opportunity for incorrectly paired tRNA (and their bound amino acids) to move out of the A site before the incorrect amino acid is irreversibly added to the polypeptidic chain. A third mechanism is the less well understood function of EF-Tu to crudely check aminoacyl-tRNA associations and reject complexes where the amino acid is not bound to the correct tRNA coding for it.

https://en.wikipedia.org/wiki/EF-Tu

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Efflux

Any movement of ions, molecules or other substances from the intracellula
the extracellular space.

https://en.wikipedia.org/wiki/Efflux

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Chapter 3 - Membranes: Transport

EGF Receptor

The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands.

The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). Mutations affecting EGFR expression or activity could result in cancer.

Mutations that lead to EGFR overexpression (known as upregulation) or overactivity have been associated with a number of cancers, including lung cancer, anal cancers and glioblastoma multiforme. These somatic mutations involving EGFR lead to its constant activation, which produces uncontrolled cell division. In glioblastoma a more or less specific mutation of EGFR, called EGFRvIII is often observed. Mutations, amplifications or misregulation of EGFR or family members are implicated in about 30% of all epithelial cancers.

https://en.wikipedia.org/wiki/Epidermal_growth_factor_receptor

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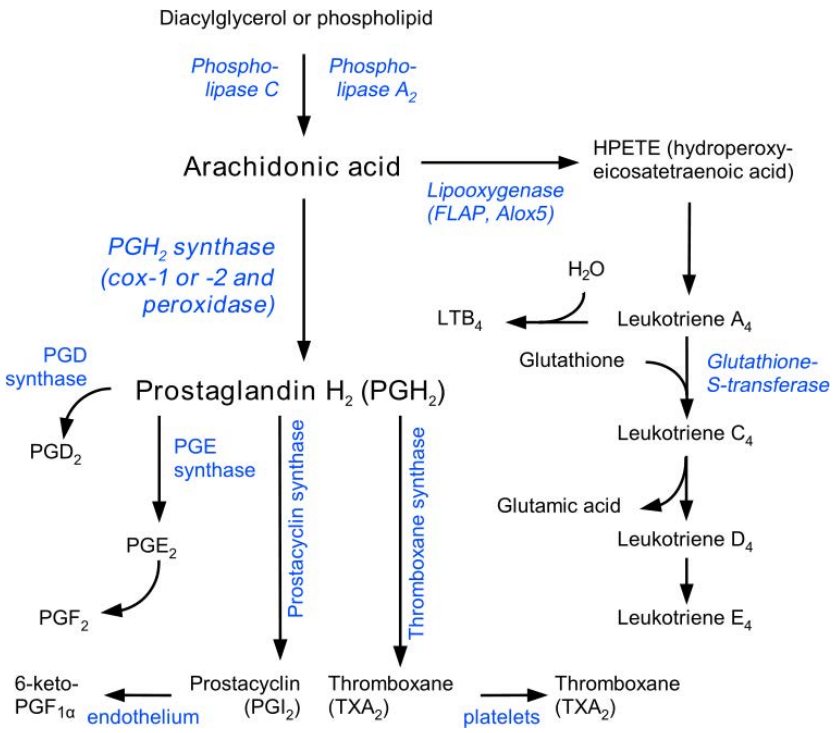
Eicosanoid

In biochemistry, eicosanoids (preferred IUPAC name icosanoids) are signaling molecules made by oxidation of 20-carbon fatty acids. They exert complex control over many bodily systems, mainly in growth during and after physical activity, inflammation or immunity after the intake of toxic compounds and pathogens, and as messengers in the central nervous system. Many are classified as hormones. The networks of controls that depend upon eicosanoids are among the most complex in the human body.

Eicosanoids are derived from either omega-3 (ω-3) or omega-6 (ω-6) fatty acids. In general, the ω-6 eicosanoids are pro-inflammatory. ω-3s are much less so. The amounts and balance of these fats in a person's diet will affect the body's eicosanoid-controlled functions, with effects on cardiovascular disease, triglycerides, blood pressure, and arthritis.

There are multiple subfamilies of eicosanoids, including the prostaglandins, thromboxanes, and leukotrienes, as well as the lipoxins and eoxins, and others. For each, there are two or three separate series, derived from either an ω-3 or an ω-6 EFA. These series' different activities largely explain the health effects of ω-3 and ω-6 fats.



https://en.wikipedia.org/wiki/Eicosanoid

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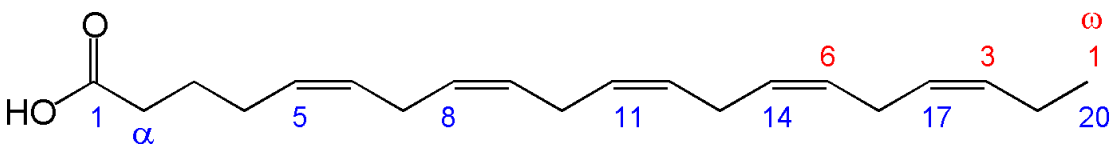
Eicosapentaenoic Acid

Eicosapentaenoic acid (EPA or also icosapentaenoic acid) is an ω-3 fatty acid. In physiological literature, it is given the name 20:5(n-3). It also has the trivial name timnodonic acid. In chemical structure, EPA is a carboxylic acid with a 20-carbon chain and five *cis* double bonds. The first double bond is located at the third carbon from the ω end.

EPA is a polyunsaturated fatty acid (PUFA) that acts as a precursor for prostaglandin-3 (which inhibits platelet aggregation), thromboxane-3, and leukotriene-5 eicosanoids. Studies of fish oil supplements, which contain EPA, have failed to support claims of preventing heart attacks or strokes.

The human body converts α-linolenic acid (ALA) to EPA. ALA is itself an essential fatty acid, an appropriate supply of which must be ensured. The efficiency of the conversion of ALA to EPA, however, is much lower than the absorption of EPA from food containing it. Because EPA is also a precursor to docosahexaenoic acid (DHA), ensuring a sufficient level of EPA on a diet containing neither EPA nor DHA is harder both because of the extra metabolic work required to synthesize EPA and because of the use of EPA to metabolize into DHA. Medical conditions like diabetes or certain allergies may significantly limit the human body's capacity for metabolization of EPA from ALA.



https://en.wikipedia.org/wiki/Eicosapentaenoic_acid

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eIFs

Eukaryotic initiation factors (eIFs) are proteins involved in the initiation phase eukaryotic translation. These proteins help stabilize the formation of the functi bosome around the start codon and also provide regulatory mechanisms in tran initiation. Several initiation factors form a complex with the small 40S ribosom subunit and Met-tRNAiMet called the 43S preinitation complex (PIC). Additior tors of the eIF4F complex (eIF4A, E, and G) recruit the 43S PIC to the five-prim structure of messenger RNA to promote ribosomal scanning along the mRNA t an AUG start codon. Recognition of the start codon by the Met-tRNAiMet prom GTP hydrolysis (or gated phosphate release) by specific initiation factors and in factor release, resulting in the 60S ribosomal subunit recruitment to form the 8 some. There exist many more eukaryotic initiation factors than prokaryotic ini factors, reflecting the greater biological complexity of eukaryotic cells. Eukaryo lation requires at least twelve eukaryotic initiation factors.

https://en.wikipedia.org/wiki/Eukaryotic_initiation_factor

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Elastase

Elastase breaks down elastin, an elastic fiber that, together with collagen, determi
the mechanical properties of connective tissue. The neutrophil form breaks down t
outer membrane protein A (OmpA) of *E. coli* and other Gram-negative bacteria.
Elastase also has the important immunological role of breaking down *Shigella* viru
lence factors. This is accomplished through the cleavage of peptide bonds in the ta
proteins. The specific peptide bonds cleaved are those on the carboxyl side of smal
drophobic amino acids such as glycine, alanine, and valine.

Elastase is inhibited by the acute-phase protein α1-antitrypsin (A1AT), which bind
most irreversibly to the active site of elastase and trypsin. A1AT is normally secrete
the liver cells into the serum. α1-antitryspin deficiency (A1AD) leads to uninhibited
struction of elastic fiber by elastase. The main result is pulmonary emphysema.

https://en.wikipedia.org/wiki/Elastase

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Elastin

Elastin is a highly elastic protein in connective tissue and allows many tissues in the body to resume their shape after stretching or contracting. Elastin helps skin to return to its original position when it is poked or pinched. Elastin is also an important load-bearing tissue in the bodies of vertebrates and used in places where mechanical energy is required to be stored. In humans, elastin is encoded by the ELN gene.

Elastic fiber is composed mainly of an amorphous component, which is extensively cross-linked elastin, and a fibrillar component, which are primarily the microfibrils such as fibrillin, both of which are made of simple amino acids such as glycine, valine, alanine, and proline. The total elastin ranges from 58 to 75% of the weight of the dry defatted artery in normal canine arteries. Comparison between fresh and digested tissues shows that, at 35% strain, a minimum of 48% of the arterial load is carried by elastin, and a minimum of 43% of the change in stiffness of arterial tissue is due to the change in elastin stiffness. Elastin is made by linking many soluble tropoelastin protein molecules, in a reaction catalyzed by lysyl oxidase, to make a massive insoluble, durable complex cross-linked by desmosine and isodesmosine in an *in vivo* Chichibabin pyridine synthesis reaction. The amino acid responsible for these cross-links is lysine. Tropoelastin is a specialized protein with a molecular weight of 64 to 66 kDa, and an irregular or random coil conformation made up of 830 amino acids.

https://en.wikipedia.org/wiki/Elastin

Related Glossary Terms

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Electrochemical Gradients

An electrochemical gradient is a gradient of electrochemical potential, usually for an ion that can move across a membrane. The gradient consists of two parts, the chemical gradient, or difference in solute concentration across a membrane, and the electrical gradient, or membrane potential (Vm). The ions move across the membrane to achieve the greatest amount of entropy in conformity with the second law of thermodynamics. When there are unequal concentrations of an ion across a permeable membrane, the ion will move across the membrane from the area of higher concentration to the area of lower concentration through simple diffusion. Ions also carry an electric charge that forms an electric potential across a membrane. If there is an unequal distribution of charges across the membrane, then the difference in electric potential generates a force that drives ion diffusion until the charges are balanced on both sides of the membrane.

In biological processes, the direction an ion moves by diffusion or active transport across a membrane is determined by the electrochemical gradient. In mitochondria and chloroplasts, proton gradients are used to generate a chemiosmotic potential that is also known as a proton motive force. This potential energy is used for the synthesis of ATP by oxidative phosphorylation.

An electrochemical gradient has two components. First, the electrical component is caused by a charge difference across the lipid membrane. Second, a chemical component is caused by a differential concentration of ions across the membrane. The combination of these two factors determines the thermodynamically favourable direction for an ion's movement across a membrane.

An electrochemical gradient is analogous to the water pressure across a hydroelectric dam. Membrane transport proteins such as the sodium-potassium pump within the membrane are equivalent to turbines that convert the water's potential energy to other forms of physical or chemical energy, and the ions that pass through the membrane are equivalent to water that ends up at the bottom of the dam. Also, energy can be used to pump water up into the lake above the dam. In similar manner, chemical energy in cells can be used to create electrochemical gradients.

https://en.wikipedia.org/wiki/Electrochemical_gradient

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Electrogenic

Electrogenic is a word used to describe membrane transport systems whose
of molecules across the membrane results in a net change in charge. The so
potassium pump, which moves three sodium ions outside of the cell in exch
two potassium ions, for example, is electrogenic.

Electrogenic is the opposite of electroneutral in that the latter involves mov
materials across a membrane with no change in charge.

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Electron Acceptor

An electron acceptor is a chemical entity that accepts electrons transferred to it
another compound. It is an oxidizing agent that, by virtue of its accepting electr
itself reduced in the process.

Examples of electron acceptors include oxygen, nitrate, iron (III), manganese (
fate, carbon dioxide, or in some microorganisms the chlorinated solvents such a
chloroethylene (PCE), trichloroethylene (TCE), dichloroethene (DCE), and viny
ride (VC). In biology, a terminal electron acceptor is a compound that receives
cepts an electron during cellular respiration or photosynthesis.

All organisms obtain energy by transferring electrons from an electron donor to
tron acceptor. During this process (electron transport chain) the electron accep
reduced and the electron donor is oxidized.

https://en.wikipedia.org/wiki/Electron_acceptor

Related Glossary Terms

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Electron Carrier

Electron carriers are molecules that accept electrons from other molecules. cules donating electrons are reduced and the carriers are, in the process, re electron carrier can transfer electrons from itself to another carrier. This h biological oxidations. For example, oxidation of pyruvate by pyruvate dehyd results in transfer of electrons to NAD^+ to form NADH. NADH, in turn, tra trons to electron carriers in Complex I of the electron transport system. Co transfers electrons to coenzyme Q and electrons move through the system f rier to another until they arrive at molecular oxygen, the terminal acceptor, cepts four electrons and four protons to form two molecules of water.

Related Glossary Terms

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Electron Donor

An electron donor is a chemical entity that donates electrons to another compound. It is a reducing agent that, by virtue of its donating electrons, is itself oxidized in the process.

In biology, electron donors release an electron during cellular respiration, resulting in the release of energy. Microorganisms, such as bacteria, obtain energy in the electron transfer processes. Through its cellular machinery, the microorganism collects the energy for its use. The final result is the electron is donated to an electron acceptor. During this process (electron transport chain) the electron donor is oxidized and the electron acceptor is reduced. Petroleum hydrocarbons, less chlorinated solvents like vinyl chloride, soil organic matter, and reduced inorganic compounds are all compounds that can act as electron donors.

In cells, foodstuffs are electron donors. Oxidation of glucose to carbon dioxide, for example, involves transfer of electrons from glucose through the electron transport system, ultimately resulting in synthesis of ATP by the process of oxidative phosphorylation.

https://en.wikipedia.org/wiki/Electron_donor

Related Glossary Terms

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Electron Microscope

An electron microscope is a microscope that uses a beam of accelerated elec
source of illumination. Because the wavelength of an electron can be up to 1
times shorter than that of visible light photons, the electron microscope has
resolving power than a light microscope and can reveal the structure of sma
A transmission electron microscope can achieve better than 50 pm resoluti
nifications of up to about 10,000,000x whereas most light microscopes are
diffraction to about 200 nm resolution and useful magnifications below 20

https://en.wikipedia.org/wiki/Electron_microscope

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Electron Transferring Flavoprotein

An electron transfer flavoprotein (ETF) or electron transfer flavoprotein co
(CETF) is a flavoprotein located on the matrix face of the inner mitochondr
brane and functions as a specific electron acceptor for primary dehydrogen
ferring the electrons to terminal respiratory systems such as electron-trans
flavoprotein dehydrogenase. ETFs provide an alternate point of entry for el
the electron transport system entering from $FADH_2$.

ETFs can be functionally classified into constitutive, "housekeeping" ETFs,
volved in the oxidation of fatty acids (Group I), and ETFs produced by som
tes under specific growth conditions, receiving electrons only from the oxid
cific substrates (Group II).

https://en.wikipedia.org/wiki/Electron-transferring_flavoprotein

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Electron Transport

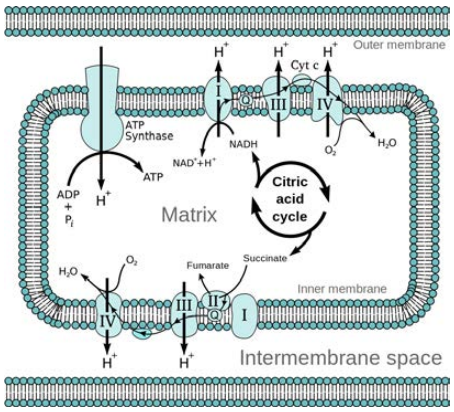
An electron transport (system) chain (ETC) is a series of compounds that transfer electrons from electron donors to electron acceptors via redox (both reduction and oxidation occurring simultaneously) reactions. They couple this electron movement with the transfer (pumping) of protons (H^+ ions) across a membrane. This creates an electrochemical proton gradient that is used to synthesize adenosine triphosphate (ATP) in the coupled process of oxidative phosphorylation. Molecules of the chain include peptides, enzymes (which are proteins or protein complexes), cytochromes and others. The final acceptor of electrons in the electron transport chain during aerobic respiration is molecular oxygen although a variety of acceptors other than oxygen exist in anaerobic respiration.

Electron transport chains are used for extracting energy via redox reactions from sunlight in photosynthesis or, such as in the case of the oxidation of sugars, cellular respiration. In eukaryotes, an important electron transport chain is found in the inner mitochondrial membrane where it serves as the site of oxidative phosphorylation through the use of ATP synthase. It is also found in the thylakoid membrane of the chloroplast in photosynthetic eukaryotes. In bacteria, the electron transport chain is located in their cell membrane.

In chloroplasts, light drives the conversion of water to oxygen and $NADP^+$ to NADPH with transfer of H^+ ions across chloroplast membranes. In mitochondria, it is the conversion of oxygen to water, NADH to NAD^+ and succinate to fumarate that are required to generate the proton gradient.

Electron transport chains are major sites of premature electron leakage to oxygen, generating superoxide and potentially resulting in increased oxidative stress.

Pictured below - the electron transport system of mitochondria.



https://en.wikipedia.org/wiki/Electron_transport_chain

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Electron Transport System

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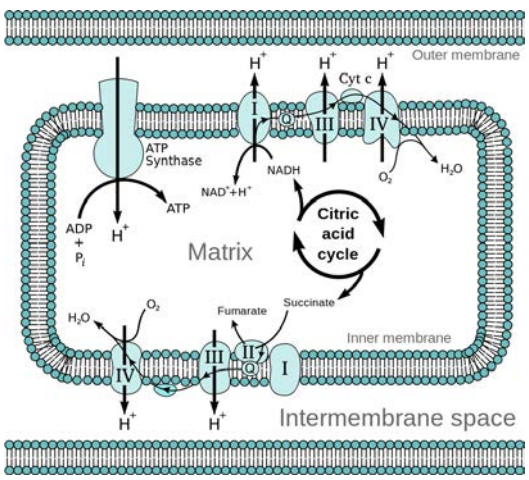

https://en.wikipedia.org/wiki/Electron_transport_chain

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Electronegativity

Electronegativity (symbol χ) is a chemical property that describes the tende
atom or a functional group to attract electrons (or electron density) towards
atom's electronegativity is affected by both its atomic number and the dista
which its valence electrons reside from the charged nucleus. The higher the
electronegativity number, the more an element or compound attracts electr
wards it.

https://en.wikipedia.org/wiki/Electronegativity

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Electroneutral

Electroneutral is a word used to describe membrane transport systems wh
ment of molecules across the membrane results in no net change in charge.
transport proteins (GLUTs) move glucose across cell membranes and no ch
charge occurs as a result of the movement, so that system is electroneutral.
tral is the opposite of electrogenic in that the latter involves movement of m
across a membrane with an accompanying change in charge.

Related Glossary Terms

Drag related terms here

Electrophilic

In chemistry, an electrophile (literally electron lover) is a reagent attracted
trons. Electrophiles are positively charged or neutral species having vacant
that are attracted to an electron rich center. It participates in a chemical rea
cepting an electron pair in order to bond to a nucleophile. Because electrop
electrons, they are Lewis acids. Most electrophiles are positively charged, h
that carries a partial positive charge, or have an atom that does not have an
electrons.

https://en.wikipedia.org/wiki/Electrophile

Related Glossary Terms

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Electrophoresis

Electrophoresis is the motion of dispersed particles relative to a fluid under
ence of a spatially uniform electric field. The term is commonly used in bioc
describe use of an electrical field to separate molecules on the basis of size o
Agarose gel electrophoresis is used to separate DNA molecules and polyacr
electrophoresis (PAGE) is used to separate small DNAs or proteins.

https://en.wikipedia.org/wiki/Electrophoresis

Related Glossary Terms

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Elongases

An elongase is an enzyme that extends the length of a fatty acid beyond tha
carbon product of the fatty acid synthase reaction. Elongases are found in t
plasmic reticulum and in the mitochondrial matrix.

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Embryogenesis

Embryogenesis is the process by which the embryo forms and develops. In
the term refers chiefly to early stages of prenatal development, whereas the
and fetal development describe later stages. Embryogenesis starts with the
of the egg cell (ovum) by a sperm cell, (spermatozoon). Once fertilized, the
ferred to as a zygote, a single diploid cell. The zygote undergoes mitotic divi
no significant growth (a process known as cleavage) and cellular differentia
ing to development of a multicellular embryo.

https://en.wikipedia.org/wiki/Embryogenesis

Related Glossary Terms

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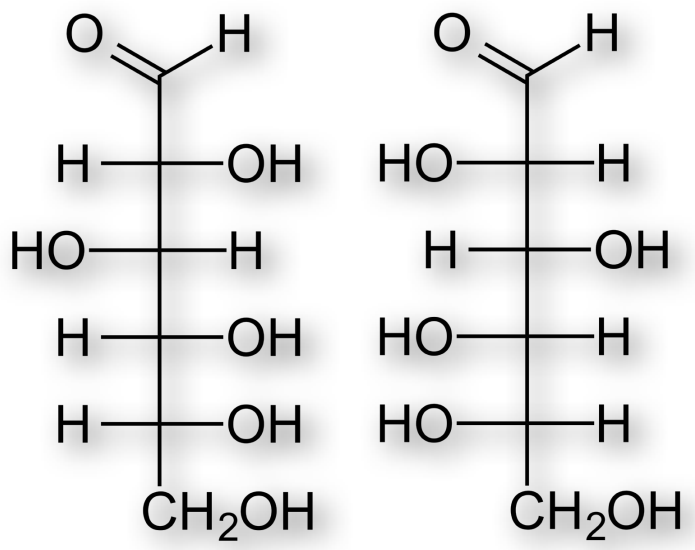
Enantiomers

The term enantiomers refer to two stereoisomers that are mirror images of each other that are non-superposable (not identical), much as one's left and right hands are the same except for being reversed along one axis (the hands cannot be made to appear identical simply by reorientation). Organic compounds that contain a chiral carbon usually have two non-superposable structures. These two structures are mirror images of each other and are, thus, commonly called enantiomorphs (enantio = opposite ; morph = form), hence this structural property is now commonly referred to as enanti-omerism.

Shown below are the enantiomers D-glucose and L-glucose.



https://en.wikipedia.org/wiki/Enantiomer

Endocannabinoids

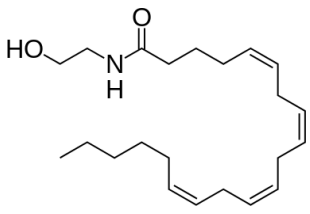
Cannabinoids are a class of diverse chemical compounds that act on cannabinoid receptors in cells that repress neurotransmitter release in the brain. Ligands for these receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured artificially). The most notable cannabinoid is the phytocannabinoid tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis. Cannabidiol (CBD) is another major constituent of the plant. There are at least 113 different cannabinoids isolated from cannabis, exhibiting varied effects.

Endocannabinoids serve as intercellular 'lipid messengers', signaling molecules that are released from one cell and activating the cannabinoid receptors present on other nearby cells. Although in this intercellular signaling role they are similar to the well-known monoamine neurotransmitters, such as acetylcholine and dopamine, endocannabinoids differ in numerous ways from them. For instance, they are used in retrograde signaling between neurons. Furthermore, endocannabinoids are lipophilic molecules that are not very soluble in water. They are not stored in vesicles, and exist as integral constituents of the membrane bilayers that make up cells. They are believed to be synthesized 'on-demand' rather than made and stored for later use. The mechanisms and enzymes underlying the biosynthesis of endocannabinoids remain elusive and continue to be an area of active research.

Anandamide is an endocannabinoid derived from arachidonic acid. It has a pharmacology similar to THC, although its chemical structure is different. Anandamide binds to the central (CB1) and, to a lesser extent, peripheral (CB_2) cannabinoid receptors, where it acts as a partial agonist. Anandamide is about as potent as THC at the CB1 receptor. Anandamide is found in nearly all tissues in a wide range of animals. Anandamide has also been found in plants, including small amounts in chocolate.

Two analogs of anandamide, 7,10,13,16-docosatetraenoylethanolamide and homo-γ-linolenoylethanolamine, have similar pharmacology. All of these are members of a family of signaling lipids called N-acylethanolamines, which also includes the noncannabimimetic palmitoylethanolamide and oleoylethanolamide, which possess anti-inflammatory and orexigenic effects, respectively. Many N-acylethanolamines have also been identified in plant seeds and in molluscs.

Shown below - anandamide.



https://en.wikipedia.org/wiki/Cannabinoid#Endocannabinoids

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Endocytosis

Endocytosis is a form of active transport in which a cell transports molecules (such as proteins) into the cell (endo- + cytosis) by engulfing them in an energy-using process. Endocytosis and its counterpart, exocytosis, are used by all cells because most chemical substances important to them are large polar molecules that cannot pass through the hydrophobic plasma or cell membrane by passive means. Endocytosis includes pinocytosis (cell drinking) and phagocytosis (cell eating).

Endocytosis pathways can be subdivided into four categories: namely, clathrin receptor-mediated endocytosis, caveolae, macropinocytosis, and phagocytosis.
• Clathrin-mediated endocytosis is mediated by small (approx. 100 nm in diameter) vesicles that have a morphologically characteristic coat made up of a complex of proteins that are mainly associated with the cytosolic protein clathrin. Clathrin-coated vesicles (CCVs) are found in virtually all cells and form domains of the plasma membrane termed clathrin-coated pits. Coated pits can concentrate large extracellular molecules that have different receptors responsible for the receptor-mediated endocytosis of ligands, e.g. low density lipoprotein, transferrin, growth factors, antibodies and many others.
• Caveolae are the most common reported non-clathrin-coated plasma membrane buds, which exist on the surface of many, but not all cell types. They consist of the cholesterol-binding protein caveolin (Vip21) with a bilayer enriched in cholesterol and glycolipids. Caveolae are small (approx. 50 nm in diameter) flask-shape pits in the membrane that resemble the shape of a cave (hence the name caveolae). They can constitute up to a third of the plasma membrane area of the cells of some tissues, being especially abundant in smooth muscle, type I pneumocytes, fibroblasts, adipocytes, and endothelial cells. Uptake of extracellular molecules is also believed to be specifically mediated via receptors in caveolae.
• Macropinocytosis, which usually occurs from highly ruffled regions of the plasma membrane, is the invagination of the cell membrane to form a pocket, which then pinches off into the cell to form a vesicle (0.5–5 µm in diameter) filled with a large volume of extracellular fluid and molecules within it (equivalent to ~100 CCVs). The filling of the pocket occurs in a non-specific manner. The vesicle then travels into the cytosol and fuses with other vesicles such as endosomes and lysosomes.
• Phagocytosis is the process by which cells bind and internalize particulate matter larger than around 0.75 µm in diameter, such as small-sized dust particles, cell debris, micro-organisms and apoptotic cells. These processes involve the uptake of larger membrane areas than clathrin-mediated endocytosis and caveolae pathway.

https://en.wikipedia.org/wiki/Endocytosis

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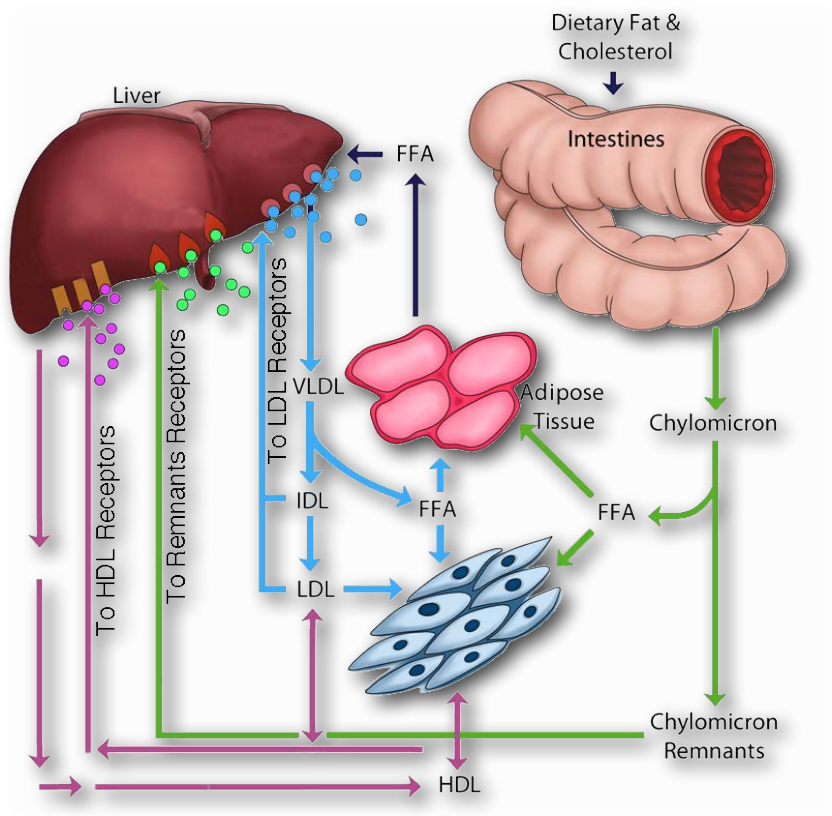
Endogenous Pathway

The endogenous pathway is one of three major pathways taken by lipids in the body. (The others are the exogenous pathway and the reverse transport pathway.)

The liver plays a central role in managing the body's needs for lipids. When lipids are needed by the body or when the capacity of the liver to contain more lipids than is supplied by the diet, the liver packages up fats and cholesteryl esters into Very Low Density Lipoprotein (VLDL) complexes. They contain the ApoB-100, ApoC-I, ApoC-II, ApoC-III, and ApoE apolipoproteins. VLDLs enter the blood and travel to muscles and adipose tissue where lipoprotein lipase is activated by ApoC-II. In the muscle cells, the released fatty acids are taken up and oxidized. By contrast, in the adipoctyes, the fatty acids are taken up and reassembled back into triacylglycerides (fats) and stored in droplets. Removal of fat from the VLDLs causes them to shrink, first to Intermediate Density Lipoprotein (IDL) complexes (also called VLDL remnants) and then to Low Density Lipoprotein (LDL) complexes.

This is accompanied by loss of apolipoproteins so that LDLs are comprised primarily of ApoB-100. This lipoprotein complex is important because cells have receptors for it to bind and internalize it by receptor-mediated endocytosis . Up until this point, cholesterol and cholesteryl esters have traveled in chylomicrons, VLDLs, and IDLs as fat has been stripped stripped away. For cholesterol compounds to get into the cell from the lipoprotein complexes, they must be internalized by cells and that is the job of receptor-mediated endocytosis.

The endogenous pathway is shown below in blue.



https://en.wikipedia.org/wiki/Lipoprotein#Endogenous_pathway

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Endonuclease

Endonucleases are enzymes that cleave the phosphodiester bond within a polynucleotide chain. Some, such as Deoxyribonuclease I, cut DNA relatively nonspecifically (without regard to sequence), while many, typically called restriction endonucleases or restriction enzymes, cleave only at very specific nucleotide sequences.

Restriction enzymes are endonucleases from eubacteria and archaea that recognize a specific DNA sequence. The nucleotide sequence recognized for cleavage by a restriction enzyme is called the restriction site. Typically, a restriction site will be a palindromic sequence about four to six nucleotides long. Most restriction endonucleases cleave the DNA strand unevenly, leaving complementary single-stranded ends. These ends can reconnect through hybridization and are termed "sticky ends". Once paired, the phosphodiester bonds of the fragments can be joined by DNA ligase. There are hundreds of restriction endonucleases known, each attacking a different restriction site. The DNA fragments cleaved by the same endonuclease can be joined together regardless of the origin of the DNA. Such DNA is called recombinant DNA - DNA formed by the joining of genes into new combinations. Restriction endonucleases (restriction enzymes) are divided into three categories, Type I, Type II, and Type III, according to their mechanism of action. These enzymes are often used in genetic engineering to make recombinant DNA for introduction into bacterial, plant, or animal cells, as well as in synthetic biology.

https://en.wikipedia.org/wiki/Endonuclease

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Endoplasmic reticulum

The endoplasmic reticulum (ER) is a type of organelle in the cells of eukaryotic organisms that forms an interconnected network of flattened, membrane-enclosed sacs or tube-like structures known as cisternae. The membranes of the ER are continuous with the outer nuclear membrane. The endoplasmic reticulum occurs in most types of eukaryotic cells, including the most primitive *Giardia*, but is absent from red blood cells and spermatozoa. There are two types of endoplasmic reticulum, rough and smooth. The outer (cytosolic) face of the rough endoplasmic reticulum is studded with ribosomes that are the sites of protein synthesis. The smooth endoplasmic reticulum lacks ribosomes and functions in lipid manufacture and metabolism, the production of steroid hormones, and detoxification.

Functions of the endoplasmic reticulum include folding of proteins in sacs called cisternae and the transport of synthesized proteins in vesicles to the Golgi apparatus. Correct folding of newly made proteins is performed by several endoplasmic reticulum chaperone proteins, including protein disulfide isomerase (PDI), ERp29, the Hsp70 family member BiP/Grp78, calnexin, calreticulin, and the peptidylpropyl isomerase family. Only properly folded proteins are transported from the rough ER to the Golgi apparatus – unfolded proteins cause an unfolded protein response as a stress response in the ER.

The smooth endoplasmic reticulum (abbreviated SER) synthesizes lipids, phospholipids, and steroids. It also carries out the metabolism of carbohydrates, detoxification of natural metabolism products and of alcohol and drugs, attachment of receptors on cell membrane proteins, and steroid metabolism. In muscle cells, it regulates calcium ion concentration. The smooth endoplasmic reticulum also contains the enzyme glucose-6-phosphatase, which converts glucose-6-phosphate to glucose, a step in gluconeogenesis. The sarcoplasmic reticulum (SR), from the Greek σάρξ sarx ("flesh"), is smooth ER found in myocytes.

The rough endoplasmic reticulum is key in:
• Manufacture of lysosomal enzymes with a mannose-6-phosphate marker added in the *cis*-Golgi network
• Manufacture of secreted proteins, either secreted constitutively with no tag or secreted in a regulatory manner involving clathrin and paired basic amino acids in the signal peptide.
• Integral membrane proteins that stay embedded in the membrane as vesicles exit and bind to new membranes. Rab proteins are key in targeting the membrane. SNAP and SNARE proteins are key in the fusion event.
• Initial glycosylation as assembly continues. This is N-linked (O-linking occurs in the Golgi).
• N-linked glycosylation: If the protein is properly folded, Oligosaccharyltransferase recognizes the AA sequence NXS or NXT (with the S/T residue phosphorylated) and adds a 14-sugar backbone (2-N-acetylglucosamine, 9-branching mannose, and 3-glucose at the end) to the side-chain nitrogen of Asn.
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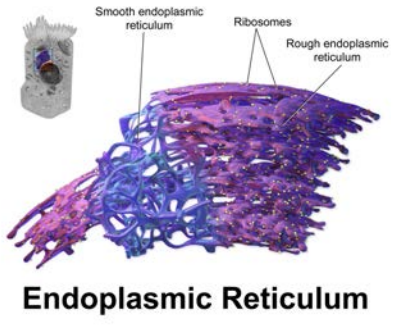

https://en.wikipedia.org/wiki/Endoplasmic_reticulum

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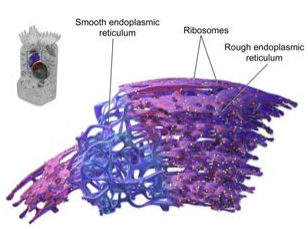

Endoplasmic Reticulum

https://en.wikipedia.org/wiki/Endoplasmic_reticulum

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Endosome

In cell biology, an endosome is a membrane-bound compartment inside eukaryotic cells. It is a compartment of the endocytic membrane transport pathway originating from the trans Golgi membrane. Molecules or ligands internalized from the plasma membrane can follow this pathway all the way to lysosomes for degradation, or they can be recycled back to the plasma membrane. Molecules are also transported to endosomes from the *trans*-Golgi network and either continue to lysosomes or recycle back to the Golgi. Endosomes can be classified as early, sorting, or late depending on their stage post internalization. Endosomes represent a major sorting compartment of the endomembrane system in cells.

Endosomes provide an environment for material to be sorted before it reaches the degradative lysosome. For example, LDL is taken into the cell by binding to the LDL receptor at the cell surface. Upon reaching early endosomes, the LDL dissociates from the receptor, and the receptor can be recycled to the cell surface. The LDL remains in the endosome and is delivered to lysosomes for processing. LDL dissociates because of the slightly acidified environment of the early endosome, generated by a vacuolar membrane proton pump V-ATPase. On the other hand, EGF and the EGF receptor have a pH-resistant bond that persists until it is delivered to lysosomes for their degradation. The mannose 6-phosphate receptor carries ligands from the Golgi destined for the lysosome by a similar mechanism.

• Early endosomes consist of a dynamic tubular-vesicular network (vesicles up to 1 µm in diameter with connected tubules of approx. 50 nm diameter). Markers include RAB5A and RAB4, transferrin and its receptor and EEA1.

• Late endosomes, also known as MVBs, are mainly spherical, lack tubules, and contain many close-packed lumenal vesicles. Markers include RAB7, RAB9, and mannose 6-phosphate receptors.

• Recycling endosomes are concentrated at the microtubule organizing center and consist of a mainly tubular network. Marker - RAB11.

https://en.wikipedia.org/wiki/Endosome

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https://en.wikipedia.org/wiki/Endosome

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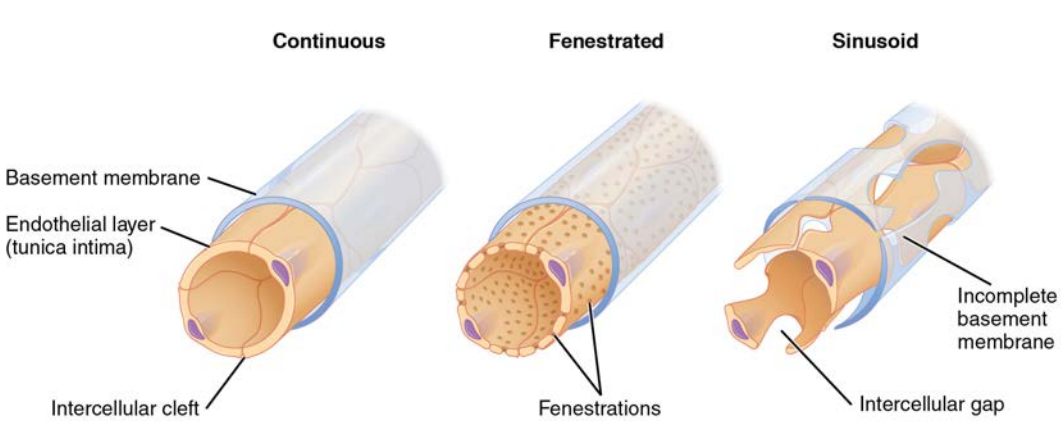
Endothelium

The endothelium is a type of tissue that lines the interior surface of blood vessels and lymphatic vessels, forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall. It is a thin layer of simple squamous cells called endothelial cells. Endothelial cells in direct contact with blood are called vascular endothelial cells, whereas those in direct contact with lymph are known as lymphatic endothelial cells.

Endothelial cells are involved in many aspects of vascular biology, including:
• Barrier function - the endothelium acts as a semi-selective barrier between the vessel lumen and surrounding tissue, controlling the passage of materials and the transit of white blood cells into and out of the bloodstream. Excessive or prolonged increases in permeability of the endothelial monolayer, as in cases of chronic inflammation, may lead to tissue edema/swelling.
• Blood clotting (thrombosis & fibrinolysis). The endothelium normally provides a non-thrombogenic surface because it contains, for example, heparan sulfate which acts as a cofactor for activating antithrombin, a protease that inactivates several factors in the coagulation cascade.
• Inflammation
• Formation of new blood vessels (angiogenesis)
• Vasoconstriction and vasodilation, and hence the control of blood pressure
• Repair of damaged or diseased organs via an injection of blood vessel cells
• Angiopoietin-2 works with VEGF to facilitate cell proliferation and migration of endothelial cells



https://en.wikipedia.org/wiki/Endothelium

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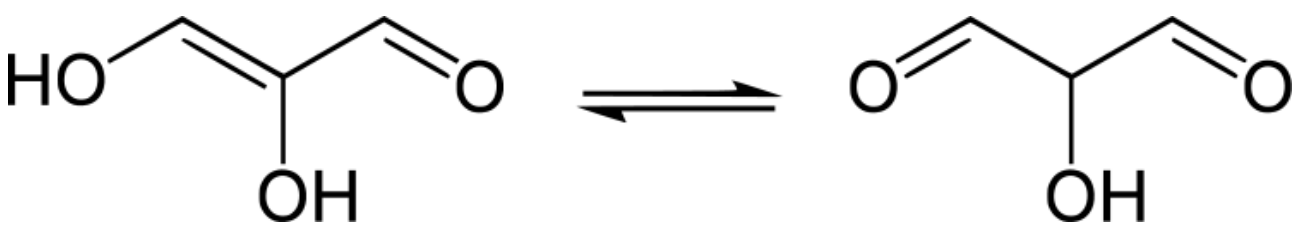
Enediol

Enediols are alkenes with a hydroxyl group on both sides of a C=C double bond. Enediols are reaction intermediates in the Lobry-de Bruyn-van Ekenstein transformation.

Enediols with a carbonyl group adjacent to the enediol group are called reductones. The enediol structure is stabilized by the resonance resulting from the tautomerism with the adjacent carbonyl. Therefore, the chemical equilibrium produces mainly the enediol form rather than the keto form. Reductones are strong reducing agents, thus efficacious antioxidants, and fairly strong acids. Examples of reductones are tartronaldehyde, reductic acid and ascorbic acid.

Shown below is aldehyde tautomerization of tartronaldehyde



https://en.wikipedia.org/wiki/Enol

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Chapter 4 - Catalysis: Basic Principles

Energy Coupling

Energy coupling is a common mechanism used in metabolism to drive energe
favorable reactions forward by coupling them to hydrolysis of a triphosphate (
drolysis, for example).

The addition of phosphate to a sugar is a common reaction that occurs in a ce
self, this process is not very energetically favorable (that is, it needs an input o
to occur). Cells overcome this energy obstacle by using ATP to “drive” the reac
energy needed to drive reactions is harvested in very controlled conditions in
This involves a process called ‘coupling’. In coupled reactions, an enzyme binc
high energy molecule (usually ATP) and the other molecule(s) involved in the

Hydrolysis of ATP provides energy for the enzyme to stimulate the reaction or
other substance(s). Without the hydrolysis of ATP (or GTP, in some cases), th
tion would not be favorable.

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Enhancers

In genetics, an enhancer is a short (50-1500 bp) region of DNA that can be bound by proteins (activators) to increase the likelihood transcription will occur at a gene. These proteins are usually referred to as transcription factors. Enhancers are generally *cis*-acting, located up to 1 Mbp (1,000,000 bp) away from the gene and can be upstream or downstream from the start site, and either in the forward or backward direction. There are hundreds of thousands of enhancers in the human genome.

In eukaryotic cells the structure of the chromatin complex of DNA is folded in a way that functionally mimics the supercoiled state characteristic of prokaryotic DNA, so although the enhancer DNA may be far from the gene in a linear way, it is spatially close to the promoter and gene. This allows it to interact with the general transcription factors and RNA polymerase II. The same mechanism holds true for silencers in the eukaryotic genome. Silencers are antagonists of enhancers that, when bound to its proper transcription factors called repressors, repress the transcription of the gene. Silencers and enhancers may be in close proximity to each other or may even be the same region only differentiated by the transcription factor the region binds to.

An enhancer may be located upstream or downstream of the gene it regulates. Furthermore, an enhancer doesn't need to be located near the transcription initiation site to affect transcription, as some have been found located in several hundred thousand base pairs upstream or downstream of the start site. Enhancers do not act on the promoter region itself, but are bound by activator proteins. These activator proteins interact with the mediator complex, which recruits polymerase II and the general transcription factors which then begin transcribing the genes. Enhancers can also be found within introns. An enhancer's orientation may even be reversed without affecting its function. Additionally, an enhancer may be excised and inserted elsewhere in the chromosome, and still affect gene transcription. That is one reason that introns polymorphisms may have effects although they are not translated. Enhancers can also be found at the exonic region of an unrelated gene and they may act on genes.

https://en.wikipedia.org/wiki/Enhancer_(genetics) on another chromosome

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Enol

Enols, or more formally, alkenols, are a type of reactive structure or intermediate in organic chemistry that is represented as an alkene (olefin) with a hydroxyl group attached to one end of the alkene double bond. The terms enol and alkenol are portmanteaus deriving from "-ene"/"alkene" and the "-ol" suffix indicating the hydroxyl group of alcohols, dropping the terminal "-e" of the first term. Generation of enols often involves removal of a hydrogen adjacent (α-) to the carbonyl group—i.e., deprotonation, its removal as a proton, H^+. When this proton is not returned at the end of the stepwise process, the result is an anion termed an enolate. The enolate structures shown are schematic. A more modern representation considers the molecular orbitals that are formed and occupied by electrons in the enolate. Similarly, generation of the enol often is accompanied by "trapping" or masking of the hydroxy group as an ether, such as a silyl enol ether.

Shown below is keto-enol tautomerization. The enol is on the right.

https://en.wikipedia.org/wiki/Enol

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Chapter 6 - Metabolism: Citric Acid Cycle & Related Pathways

Enolase

Enolase, also known as phosphopyruvate hydratase, is a metalloenzyme res
for the catalysis of the conversion of 2-phosphoglycerate (2-PG) to phospho
vate (PEP), the ninth and penultimate step of glycolysis. The chemical reac
lyzed by enolase is:

2-phospho-D-glycerate <-> Phosphoenolpyruvate + H_2O

The reaction is reversible, depending on environmental concentrations of s
The optimum pH for the human enzyme is 6.5. Enolase belongs to the fam
specifically the hydro-lyases, which cleave carbon-oxygen bonds. The syste
of this enzyme is 2-phospho-D-glycerate hydro-lyase (phosphoenolpyruvat

https://en.wikipedia.org/wiki/Enolase

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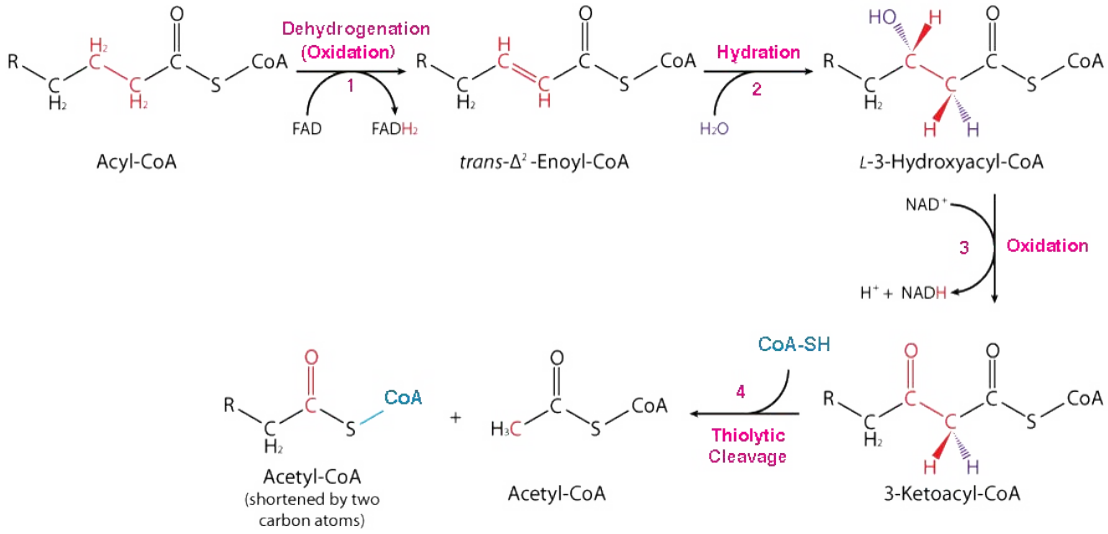
Enoyl-CoA Hydratase

Enoyl-CoA hydratase is an enzyme that hydrates the double bond between the second and third carbons on acyl-CoA. This enzyme, also known as crotonase, is essential to metabolizing fatty acids to produce both acetyl CoA and energy.

Enoyl-CoA hydratase catalyzes the second step (shown in the figure below) in the breakdown of fatty acids or the second step of β-oxidation in fatty acid metabolism shown below. Fatty acid metabolism is how our bodies turn fats or lipids into energy. When fats come into our bodies, they are generally in the form of triacyl-glycerols. These must be broken down in order for the fats to pass into our bodies. When that happens, three fatty acids are released.

In fatty acid metabolism, fatty acids are changed into fatty acyl-CoA. To do this, the carboxylate which occupies one end of the fatty acid is changed into a thioester by substituting coenzyme A for the hydroxyl group. Next the fatty acyl-CoA is oxidized and broken down into an acetyl-CoA molecule and another acyl-CoA. The acetyl CoA is then sent to the citric acid cycle while the remaining acyl-CoA is broken down further into acetyl-CoAs. The complete breakdown of a fatty acid not only generates acetyl-CoA molecules, but it also generates energy in the form of NADH. This NADH goes on to be converted into ATP which can be used in other reactions.



https://en.wikipedia.org/wiki/Enoyl-CoA_hydratase

Enthalpy

Enthalpy is a measurement of energy in a thermodynamic system. It includes th
nal energy, which is the energy required to create a system, and the amount of e
required to make room for it by displacing its environment and establishing its
and pressure.

Enthalpy is defined as a state function that depends only on the prevailing equi
state identified by the variables internal energy, pressure, and volume. It is an e
sive quantity. The unit of measurement for enthalpy in the International Systen
Units (SI) is the joule, but other historical, conventional units are still in use, su
the British thermal unit and the calorie.

https://en.wikipedia.org/wiki/Enthalpy

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Entropy

In thermodynamics, entropy (usual symbol S) is a measure of the number of microscopic configurations that correspond to a thermodynamic system in a state specified by certain macroscopic variables. For example, gas in a container with known volume, pressure, and temperature could have an enormous number of possible configurations of the individual gas molecules, and which configuration the gas is actually in may be regarded as random. Hence, entropy can be understood as a measure of molecular disorder within a macroscopic system. The second law of thermodynamics states that an isolated system's entropy never decreases. Such systems spontaneously evolve towards thermodynamic equilibrium, the state with maximum entropy. Non-isolated systems may lose entropy, provided their environment's entropy increases by at least that increment. Since entropy is a state function, the change in entropy of a system is determined by its initial and final states. This applies whether the process is reversible or irreversible. However, irreversible processes increase the combined entropy of the system and its environment.

https://en.wikipedia.org/wiki/Entropy

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Enzyme

Enzymes are macromolecular biological catalysts. Enzymes accelerate, or catalyze, chemical reactions. The molecules at the beginning of the process are called substrates and the enzyme converts these into different molecules, called products. The place on the enzyme where the reaction occurs is called the active site. Almost all metabolic processes in the cell need enzymes in order to occur at rates fast enough to sustain life. The set of enzymes made in a cell determines which metabolic pathways occur in that cell. Enzymes are known to catalyze more than 5,000 biochemical reaction types. Enzymes' specificity comes from their unique three-dimensional structures.

Like all catalysts, enzymes increase the rate of a reaction by lowering its activation energy. Some enzymes can make their conversion of substrate to product occur many millions of times faster. An extreme example is orotidine 5'-phosphate decarboxylase, which allows a reaction that would otherwise take millions of years to occur in milliseconds. Chemically, enzymes are like any catalyst and are not consumed in chemical reactions, nor do they alter the equilibrium of a reaction. Enzyme activity can be affected by other molecules. Inhibitors are molecules that decrease enzyme activity, and activators are molecules that increase activity. Many drugs and poisons are enzyme inhibitors. An enzyme's activity decreases markedly outside its optimal temperature and pH.

Enzymes serve a wide variety of functions inside living organisms. They are indispensable for signal transduction and cell regulation, often via kinases and phosphatases. They also generate movement, with myosin hydrolyzing ATP to generate muscle contraction, and also transport cargo around the cell as part of the cytoskeleton. Other ATPases in the cell membrane are ion pumps involved in active transport. Enzymes are also involved in more exotic functions, such as luciferase generating light in fireflies. Viruses can also contain enzymes for infecting cells, such as the HIV integrase and reverse transcriptase, or for viral release from cells, like the influenza virus neuraminidase.

An important function of enzymes is in the digestive systems of animals. Enzymes such as amylases and proteases break down large molecules (starch or proteins, respectively) into smaller ones, so they can be absorbed by the intestines. Starch molecules, for example, are too large to be absorbed from the intestine, but enzymes hydrolyze the starch chains into smaller molecules such as maltose and eventually glucose, which can then be absorbed. Different enzymes digest different food substances. In ruminants, which have herbivorous diets, microorganisms in the gut produce another enzyme, cellulase, to break down the cellulose cell walls of plant fiber.

https://en.wikipedia.org/wiki/Enzyme

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Enzyme Kinetics

Enzyme kinetics is the investigation of how enzymes bind substrates and turn them into products. The rate data used in kinetic analyses are commonly obtained from enzyme assays. In 1913 Leonor Michaelis and Maud Leonora Menten proposed a quantitative theory of enzyme kinetics, which is referred to as Michaelis–Menten kinetics. The major contribution of Michaelis and Menten was to think of enzyme reactions in two stages. In the first, the substrate binds reversibly to the enzyme, forming the enzyme-substrate complex. The enzyme then catalyzes the chemical step in the reaction and releases the product.

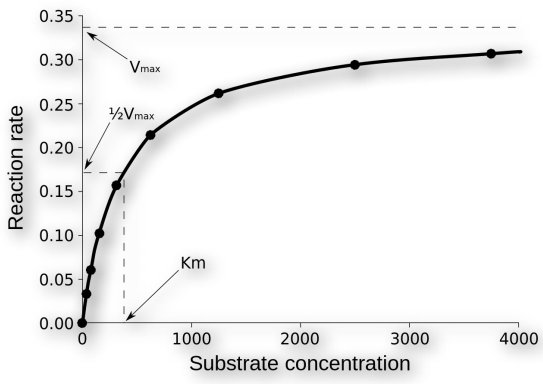
Enzyme rates depend on solution conditions and substrate concentration. To find the maximum speed of an enzymatic reaction, the substrate concentration is increased until a constant rate of product formation is seen. This is shown in the saturation curve on the right. Saturation happens because, as substrate concentration increases, more and more of the free enzyme is converted into the substrate-bound ES complex. At the maximum reaction rate (V_{max}) of the enzyme, all the enzyme active sites are bound to substrate, and the amount of ES complex is the same as the total amount of enzyme.

V_{max} is only one of several important kinetic parameters. The amount of substrate needed to achieve a given rate of reaction is also important. This is given by the Michaelis-Menten constant (K_m), which is the substrate concentration required for an enzyme to reach one-half its maximum reaction rate. Generally, each enzyme has a characteristic K_m for a given substrate. Another useful constant is k_{cat}, also called the turnover number, which is the number of substrate molecules handled by one active site per second.

The efficiency of an enzyme can be expressed in terms of k_{cat}/K_m. This is also called the specificity constant and incorporates the rate constants for all steps in the reaction up to and including the first irreversible step. Because the specificity constant reflects both affinity and catalytic ability, it is useful for comparing different enzymes against each other, or the same enzyme with different substrates. The theoretical maximum for the specificity constant is called the diffusion limit and is about 10^8 to 10^9 ($M^{-1}\,s^{-1}$). At this point every collision of the enzyme with its substrate will result in catalysis, and the rate of product formation is not limited by the reaction rate but by the diffusion rate. Enzymes with this property are called catalytically perfect or kinetically perfect. Example of such enzymes are triose-phosphate isomerase, carbonic anhydrase, acetylcholinesterase, catalase, fumarase, β-lactamase, and superoxide dismutase. The turnover of such enzymes can reach several million reactions per second.

Michaelis–Menten kinetics relies on the law of mass action, which is derived from the assumptions of free diffusion and thermodynamically driven random collision. Many biochemical or cellular processes deviate significantly from these conditions, because of macromolecular crowding and constrained molecular movement. More recent, complex extensions of the model attempt to correct for these effects.

Shown below - Velocity versus [Substrate] for a reaction.



https://en.wikipedia.org/wiki/Enzyme

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Enzymes

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https://en.wikipedia.org/wiki/Enzyme

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EP

EP is an abbreviation for the enzyme-product complex before release of the
the conclusion of the catalysis.

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Chapter 4 - Catalysis: Basic Principles

Epidermal Growth Factor

Epidermal growth factor (EGF) is a growth factor that stimulates cell growth, proliferation, and differentiation by binding to its receptor EGFR. Human EGF is a 6045-Da protein with 53 amino acid residues and three intramolecular disulfide bonds.

EGF acts by binding with high affinity to epidermal growth factor receptor (EGFR) on the cell surface. This stimulates ligand-induced dimerization, activating the intrinsic protein-tyrosine kinase activity of the receptor (see the second diagram). The tyrosine kinase activity, in turn, initiates a signal transduction cascade that results in a variety of biochemical changes within the cell – a rise in intracellular calcium levels, increased glycolysis and protein synthesis, and increases in the expression of certain genes including the gene for EGFR – that ultimately lead to DNA synthesis and cell proliferation.

https://en.wikipedia.org/wiki/Epidermal_growth_factor

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Epigenetics

Epigenetics is the study, in the field of genetics, of cellular and physiologica
typic trait variations that are caused by external or environmental factors th
genes on and off and affect how cells read genes. Hence, epigenetic researcl
describe dynamic alterations in the transcriptional potential of a cell. These
may or may not be heritable, although the use of the term "epigenetic" to de
esses that are not heritable is controversial. Unlike genetics based on chang
DNA sequence (the genotype), the changes in gene expression or cellular ph
epigenetics have other causes, thus use of the prefix epi- (Greek: επί- over,
around).

https://en.wikipedia.org/wiki/Epigenetics

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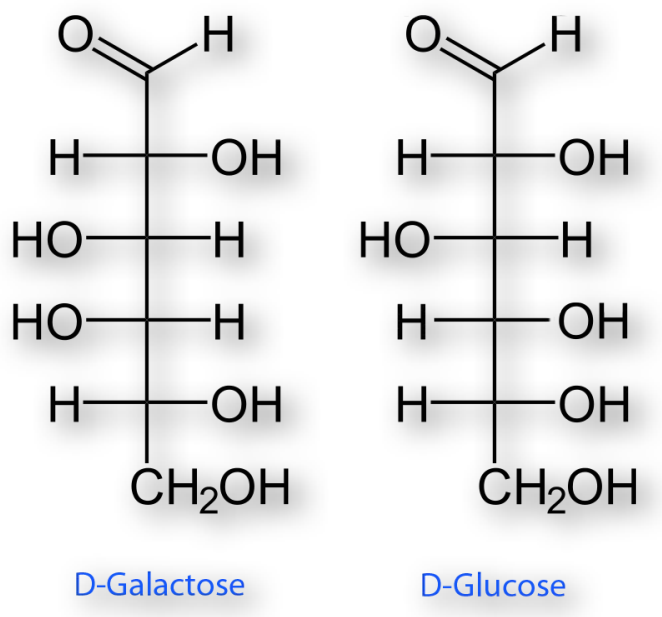
Chapter 9 - Point by Point: Metabolism

Epimers

In stereochemistry, epimer refers to one of a pair of stereoisomers. The two isomers differ in configuration at only one stereogenic center. All other stereocenters in the molecules, if any, are the same in each

The sugars glucose and galactose are epimers. In glucose, the -OH group on the first carbon is in the axial position, the direction opposite the -OH group on carbon C-4. In galactose, the -OH group is oriented in the same direction, the equatorial position.

The stereoisomers β-D-glucopyranose and β-D-mannopyranose are epimers because they differ only in the stereochemistry at the C-2 position.



D-Galactose D-Glucose

https://en.wikipedia.org/wiki/Epimer

Related Glossary Terms

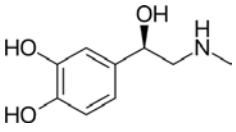
Epinephrine

Epinephrine, also known as adrenalin or adrenaline, is primarily a medication and hormone. As a medication it is used for a number of conditions including: anaphylaxis, cardiac arrest, and superficial bleeding. Inhaled epinephrine may be used to improve the symptoms of croup. It may also be used for asthma when other treatments are not effective. It is given intravenously, by injection into a muscle, by inhalation, or by injection just under the skin.

Epinephrine is normally produced by both the adrenal glands and certain neurons. It plays an important role in the fight-or-flight response by increasing blood flow to muscles, output of the heart, pupil dilation, and blood sugar. Epinephrine does this by its effects on alpha and beta receptors. It is found in many animals and some one cell organisms.

As a hormone, epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of epinephrine causes smooth muscle relaxation in the airways but causes contraction of the smooth muscle that lines most arterioles.

Epinephrine acts by binding to a variety of adrenergic receptors. Epinephrine is a nonselective agonist of all adrenergic receptors, including the major subtypes $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, and $\beta 3$.Epinephrine's binding to these receptors triggers a number of metabolic changes. Binding to α-adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle, and stimulates glycolysis and inhibits insulin-mediated glycogenesis in muscle. β adrenergic receptor binding triggers glucagon secretion in the pancreas, increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together, these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body.



https://en.wikipedia.org/wiki/Epinephrine

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Epithelial

Epithelium (epi- + thele + -ium) is one of the four basic types of animal tissue. The other three types are connective tissue, muscle tissue and nervous tissue. Epithelial tissues line the cavities and surfaces of blood vessels and organs throughout the body.

There are three principal shapes of epithelial cells: squamous, columnar, and cuboidal. These can be arranged in a single layer of cells as simple epithelium, either squamous, columnar or cuboidal, or in layers of two or more cells deep as stratified (layered), either squamous, columnar or cuboidal. All glands are made up of epithelial cells. Functions of epithelial cells include secretion, selective absorption, protection, transcellular transport, and sensing.

Epithelium lines both the outside (skin) and the inside cavities and lumina of bodies. The outermost layer of human skin is composed of dead stratified squamous, keratinized epithelial cells. Tissues that line the inside of the mouth, the esophagus and part of the rectum are composed of nonkeratinized stratified squamous epithelium. Other surfaces that separate body cavities from the outside environment are lined by simple squamous, columnar, or pseudostratified epithelial cells. Other epithelial cells line the insides of the lungs, the gastrointestinal tract, the reproductive and urinary tracts, and make up the exocrine and endocrine glands. The outer surface of the cornea is covered with fast-growing, easily regenerated epithelial cells. Endothelium (the inner lining of blood vessels, the heart, and lymphatic vessels) is a specialized form of epithelium. Another type, mesothelium, forms the walls of the pericardium, pleurae, and peritoneum.

Epithelial tissue rests on a basement membrane, which acts as a scaffolding on which epithelium can grow and regenerate after injuries. Epithelial tissue is innervated, but avascular. This epithelial tissue must be nourished by substances diffusing from the blood vessels in the underlying tissue, but they don't have their own blood supply. The basement membrane acts as a selectively permeable membrane that determines which substances will be able to enter the epithelium.

https://en.wikipedia.org/wiki/Epithelium

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Epithelium

Epithelium (epi- + thele + -ium) is one of the four basic types of animal tissue. The other three types are connective tissue, muscle tissue and nervous tissue. Epithelial tissues line the cavities and surfaces of blood vessels and organs throughout the body.

There are three principal shapes of epithelial cells: squamous, columnar, and cuboidal. These can be arranged in a single layer of cells as simple epithelium, either squamous, columnar or cuboidal, or in layers of two or more cells deep as stratified (layered), either squamous, columnar or cuboidal. All glands are made up of epithelial cells. Functions of epithelial cells include secretion, selective absorption, protection, transcellular transport, and sensing.

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Equilibrium

In a chemical reaction, chemical equilibrium is the state in which both reacta
products are present in concentrations which have no further tendency to cha
time. There are no net changes in the concentrations of the reactant(s) and pr
at equilibrium. Such a state is known as dynamic equilibrium.

https://en.wikipedia.org/wiki/List_of_types_of_equilibrium

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Equilibrium Duplicate

In a chemical reaction, chemical equilibrium is the state in which both reac
products are present in concentrations which have no further tendency to c
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at equilibrium. Such a state is known as dynamic equilibrium.

https://en.wikipedia.org/wiki/List_of_types_of_equilibrium

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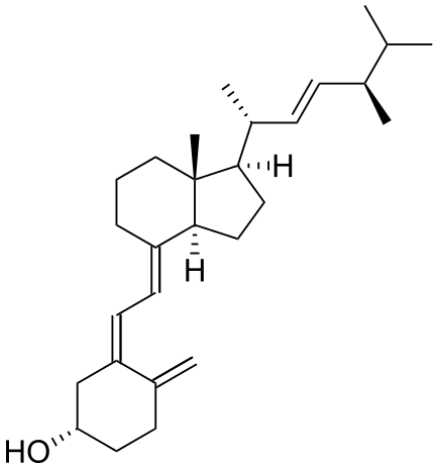
Ergocalciferol

Ergocalciferol (vitamin D_2) is a form of vitamin D. Ergocalciferol is a secosteroid formed by a photochemical bond breaking of a steroid, specifically, by the action of ultraviolet light on ergosterol. Viosterol, the name given to early preparations of irradiated ergosterol, is essentially synonymous with ergocalciferol.

Conflicting evidence exists for how similarly D2 and D3 behave in the body and whether they are equally active or efficient in production of 1,25-hydroxyvitamin D (1,25(OH)D), the active hormone. Some preliminary studies indicate D3 is more potent, while others report equal efficacy. Both forms appear to have similar efficacy in ameliorating rickets and reducing the incidence of falls in elderly patients.

The metabolism of each appears to be different, with the vitamin D binding protein possibly having greater affinity for $25(OH)D_3$ than for $25(OH)D_2$, as shown in one study. Cholecalciferol (vitamin D_3) is sensitive to UV radiation and rapidly, but reversibly, forms other sterols which can further irreversibly convert to ergosterol.



https://en.wikipedia.org/wiki/Ergocalciferol

Erwin Chargaff

Erwin Chargaff (11 August 1905 – 20 June 2002) was an Austro-Hungarian who immigrated to the United States during the Nazi era and was a professo chemistry at Columbia University medical school. Through careful experime Chargaff discovered two rules that helped lead to the discovery of the double structure of DNA.

The first rule was that in DNA the number of guanine units equals the numb sine units, and the number of adenine units equals the number of thymine u hinted at the base pair makeup of DNA.

The second rule was that the relative amounts of guanine, cytosine, adenine thymine bases varies from one species to another. This hinted that DNA rath protein could be the genetic material.

https://en.wikipedia.org/wiki/Erwin_Chargaff

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Erythropoietin

Erythropoietin is a glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow.

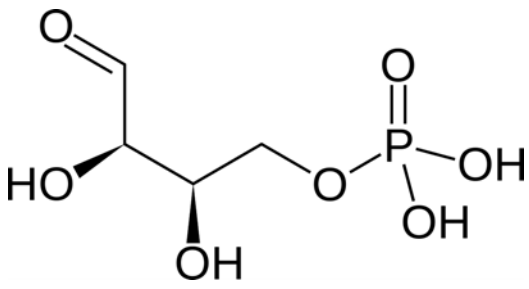
Erythropoietin is an essential hormone for red blood cell production. Without it, definitive erythropoiesis does not take place. Under hypoxic conditions, the kidney will produce and secrete erythropoietin to increase the production of red blood cells by targeting CFU-E, proerythroblast and basophilic erythroblast subsets in the differentiation. Erythropoietin has its primary effect on red blood cell progenitors and precursors (which are found in the bone marrow in humans) by promoting their survival through protecting these cells from apoptosis.

Erythropoietin has been shown to exert its effects by binding to the erythropoietin receptor (EpoR). EPO is highly glycosylated (40% of total molecular weight), with half-life in blood around five hours. EPO's half-life may vary between endogenous and various recombinant versions. Additional glycosylation or other alterations of EPO via recombinant technology have led to the increase of EPO's stability in blood (thus requiring less frequent injections). EPO binds to the erythropoietin receptor on the red cell progenitor surface and activates a JAK2 signaling cascade. High level erythropoietin receptor expression is localized to erythroid progenitor cells. While there are reports that EPO receptors are found in a number of other tissues, such as heart, muscle, kidney and peripheral/central nervous tissue, those results are confounded by nonspecificity of reagents such as anti-EpoR antibodies. In controlled experiments, EPO receptor is not detected in those tissues. In the bloodstream, red cells themselves do not express erythropoietin receptor, so cannot respond to EPO. However, indirect dependence of red cell longevity in the blood on plasma erythropoietin levels has been reported, a process termed neocytolysis.

https://en.wikipedia.org/wiki/Erythropoietin

Erythrose-4-phosphate

Erythrose-4-phosphate is a phosphate of the simple sugar erythrose. It is an intermediate in the pentose phosphate pathway and the Calvin cycle. In addition, it serves as a precursor in the biosynthesis of the aromatic amino acids tyrosine, phenylalanine, and tryptophan. It is used in the first step of the shikimate pathway. At this stage, phosphoenolpyruvate and erythrose-4-phosphate react to form 3-deoxy-D-arabinoheptulosonate-7-phosphate (DAHP), in a reaction catalyzed by the enzyme DAHP synthase.



https://en.wikipedia.org/wiki/Erythrose_4-phosphate

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle
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Chapter 9 - Point by Point: Metabolism
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Chapter 9 - Point by Point: Metabolism
Chapter 9 - Point by Point: Metabolism

ES

ES is an abbreviation for the enzyme-substrate complex, which is simply th
bound to its substrate in the process of catalysis.

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Essential Amino Acids

An essential amino acid or indispensable amino acid is an amino acid that cannot be synthesized *de novo* (from scratch) by the organism, and thus must be supplied in its diet. The nine amino acids humans cannot synthesize are phenylalanine, valine, threonine, tryptophan, methionine, leucine, isoleucine, lysine, and histidine.

Six other amino acids are considered conditionally essential in the human diet, meaning their synthesis can be limited under special pathophysiological conditions, such as prematurity in the infant or individuals in severe catabolic distress. These six are arginine, cysteine, glycine, glutamine, proline and tyrosine.

Five amino acids can be completely synthesized to meet the body's needs and are completely non-essential. These five are alanine, aspartic acid, asparagine, glutamic acid and serine.

https://en.wikipedia.org/wiki/Essential_amino_acid

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Essential Fatty Acids

Essential fatty acids, or EFAs, are fatty acids that humans and other animals must ingest because the body requires them for good health but cannot synthesize them.

The term "essential fatty acid" refers to fatty acids required for biological processes but does not include the fats that only act as fuel. Essential fatty acids should not be confused with essential oils, which are "essential" in the sense of being a concentrated essence.

Only two fatty acids are known to be essential for humans: α-linolenic acid (an ω-3 fatty acid) and linoleic acid (an ω-6 fatty acid). Some other fatty acids are sometimes classified as "conditionally essential," meaning that they can become essential under some developmental or disease conditions. Examples include docosahexaenoic acid (an ω-3 fatty acid) and gamma-linolenic acid (an ω-6 fatty acid).

When the two EFAs were discovered in 1923, they were designated "vitamin F", but in 1929, research on rats showed that the two EFAs are better classified as fats rather than vitamins.

In the body, essential fatty acids serve multiple functions. In each of these, the balance between dietary ω-3 and ω-6 strongly affects function. They are modified to make
• classic eicosanoids (affecting inflammation and many other cellular functions)
• endocannabinoids (affecting mood, behavior and inflammation)
• lipoxins - a group of eicosanoid derivatives formed via the lipoxygenase pathway from ω-6 EFAs and resolvins from ω-3 (in the presence of acetylsalicylic acid, down-regulating inflammation)
• isofurans, neurofurans, isoprostanes, hepoxilins, epoxyeicosatrienoic acids (EETs) and Neuroprotectin D
• lipid rafts (affecting cellular signaling)

They also act on DNA (activating or inhibiting transcription factors such as NF-κB, which is linked to pro-inflammatory cytokine production)

https://en.wikipedia.org/wiki/Essential_fatty_acid

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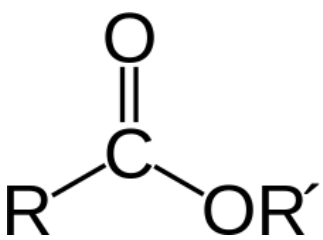
Ester

Esters are chemical compounds derived from an acid (organic or inorganic) in which at least one –OH (hydroxyl) group is replaced by an –O–alkyl (alkoxy) group. Usually, esters are derived from a carboxylic acid and an alcohol. Glycerides, which are fatty acid esters of glycerol, are important esters in biology, being one of the main classes of lipids, and making up the bulk of animal fats and vegetable oils. Esters with low molecular weight are commonly used as fragrances and found in essential oils and pheromones. Phosphoesters form the backbone of DNA molecules. Nitrate esters, such as nitroglycerin, are known for their explosive properties, while polyesters are important plastics, with monomers linked by ester moieties.



https://en.wikipedia.org/wiki/Ester

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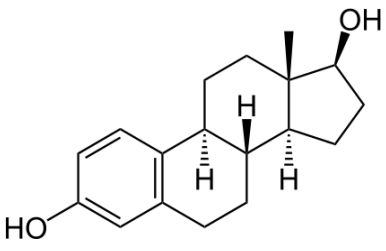
Estradiol

Estradiol, or more precisely, 17β-estradiol, is a steroid and estrogen sex hormone, and the primary female sex hormone. It is named for and is important in the regulation of the estrous and menstrual female reproductive cycles. Estradiol is essential for the development and maintenance of female reproductive tissues but it also has important effects in many other tissues including bone. While estrogen levels in men are lower compared to women, estrogens have essential functions in men as well. Estradiol is found in most vertebrates as well as many crustaceans, insects, fish, and other animal species.

In the female, estradiol acts as a growth hormone for tissue of the reproductive organs, supporting the lining of the vagina, the cervical glands, the endometrium, and the lining of the fallopian tubes. It enhances growth of the myometrium. Estradiol appears necessary to maintain oocytes in the ovary. During the menstrual cycle, estradiol produced by the growing follicle triggers, via a positive feedback system, the hypothalamic-pituitary events that lead to the luteinizing hormone surge, inducing ovulation. In the luteal phase, estradiol, in conjunction with progesterone, prepares the endometrium for implantation. During pregnancy, estradiol increases due to placental production. In baboons, blocking of estrogen production leads to pregnancy loss, suggesting estradiol has a role in the maintenance of pregnancy. Research is investigating the role of estrogens in the process of initiation of labor. Actions of estradiol are required before the exposure of progesterone in the luteal phase.

A more potent chemical derivative of estradiol, ethinyl estradiol is a major component of hormonal contraceptives. Combined forms of hormonal contraception contain ethinyl estradiol and a progestin, which both contribute to the inhibition of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), which accounts for the ability of these birth control methods to prevent ovulation and thus prevent pregnancy. Other types of hormonal birth control contain only progestins and no ethinyl estradiol.



https://en.wikipedia.org/wiki/Estradiol

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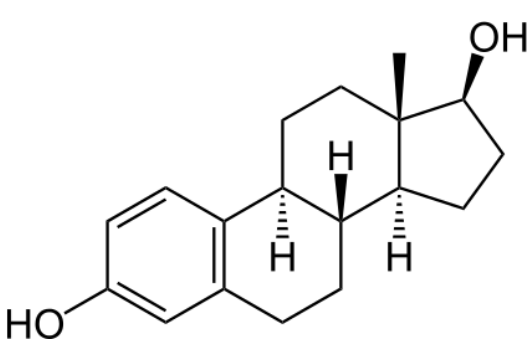
Estriol

Estriol (also oestriol or E_3) is one of the three main estrogens produced by the human body. Estriol is only produced in significant amounts during pregnancy as it is made by the placenta from 16-hydroxydehydroepiandrosterone sulfate (16-OH DHEAS), an androgen steroid made in the fetal liver and adrenal glands.

In pregnant women with multiple sclerosis, estriol reduces the disease's symptoms noticeably, according to researchers at UCLA's Geffen Medical School. Estriol can be a weak or strong estrogen depending on if it is given acutely or chronically when given to immature animals, but is an antagonist when given in combination with estradiol. Estriol may play a role in the development of breast cancer, but based on in vitro research, does appear to act as an antagonist to the G-protein coupled estrogen receptor. Though estriol is used as part of the primarily North American phenomenon of bioidentical hormone replacement therapy, it is not approved for use by the FDA or Health Canada. Though initial research in the 1970s suggested it could be used therapeutically as an estrogen, subsequent research failed to confirm this hypothesis.



https://en.wikipedia.org/wiki/Estriol

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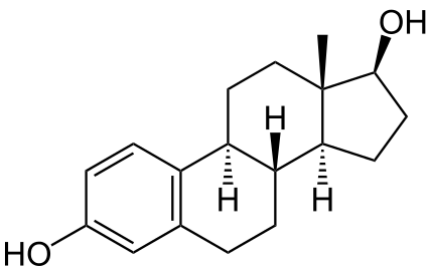
Estrogen

Estrogen is the primary female sex hormone and is responsible for development and regulation of the female reproductive system and secondary sex characteristics. Estrogen may also refer to any substance, natural or synthetic, that mimics the effects of the natural hormone. The steroid 17β-estradiol is the most potent and prevalent endogenous estrogen, although several metabolites of estradiol also have estrogenic hormonal activity.

The three major naturally occurring forms of estrogen in women are estrone (E_1), estradiol (E_2), and estriol (E_3). Another type of estrogen called estetrol (E_4) is produced only during pregnancy. Quantitatively, estrogens circulate at lower levels than androgens in both men and women. While estrogen levels are significantly lower in males compared to females, estrogens nevertheless also have important physiological roles in males.

Like all steroid hormones, estrogens readily diffuse across the cell membrane. Once inside the cell, they bind to and activate estrogen receptors (ERs) which in turn modulate the expression of many genes. Additionally, estrogens bind to and activate rapid-signaling membrane estrogen receptors (mERs), such as GPER.

The estrogen known as estradiol is shown below.



https://en.wikipedia.org/wiki/Estrogen

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Estrogen Receptors

Estrogen receptors (ERs) are a group of proteins found inside and on cells. They are receptors that are activated by the hormone estrogen (17β-estradiol). Two classes of ER exist: nuclear estrogen receptors (ERα and ERβ), which are members of the nuclear receptor family of intracellular receptors, and membrane estrogen receptors (mERs) (GPER (GPR30), ER-X, and Gq-mER), which are mostly G protein-coupled receptors.

Once activated by estrogen, the intracellular ER is able to translocate into the nucleus and bind to DNA to regulate the activity of different genes (i.e. it is a DNA-binding transcription factor). However, it also has additional functions independent of DNA binding.

In the absence of hormone, estrogen receptors are largely located in the cytosol. Hormone binding to the receptor triggers a number of events starting with migration of the receptor from the cytosol into the nucleus, dimerization of the receptor, and subsequent binding of the receptor dimer to specific sequences of DNA known as hormone response elements. The DNA/receptor complex then recruits other proteins that are responsible for the transcription of downstream DNA into mRNA and finally protein that results in a change in cell function. Estrogen receptors also occur within the cell nucleus, and both estrogen receptor subtypes have a DNA-binding domain and can function as transcription factors to regulate the production of proteins.

The receptor also interacts with activator protein 1 and Sp-1 to promote transcription, via several co-activators such as PELP-1.

https://en.wikipedia.org/wiki/Estrogen_receptor

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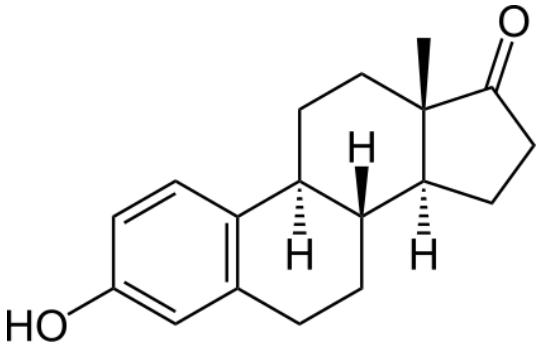
Estrone

Estrone (E_1) is an estrogenic hormone secreted by the ovary as well as adipose tissue with the chemical name of 3-hydroxyestra-1,3,5(10)-triene-17-one and the chemical formula $C_{18}H_{22}O_2$. Estrone is an odorless, solid crystalline powder, white in color with a melting point of 254.5 °C and a specific gravity of 1.23. Estrone is one of several natural estrogens, which also include estriol and estradiol. Estrone is the least abundant of the three hormones. Estradiol is present almost always in the reproductive female body, and estriol is abundant primarily during pregnancy.

Estrone is known to be a carcinogen for human females as well as a cause of breast tenderness or pain, nausea, headache, hypertension, and leg cramps in the context of non-endogenous exposure. In men, estrone has been known to cause anorexia, nausea, vomiting, and erectile dysfunction. Estrone is relevant to health and disease states because of its conversion to estrone sulfate, a long-lived derivative. Estrone sulfate acts as a reservoir that can be converted as needed to the more active estradiol. It is the predominant estrogen in postmenopausal women.



https://en.wikipedia.org/wiki/Estrone

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Ethanol

Ethanol also commonly called alcohol, ethyl alcohol, and drinking alcohol, is the principal type of alcohol found in alcoholic beverages, produced by the fermentation of sugars by yeasts. It is a neurotoxic, psychoactive drug, and one of the oldest recreational drugs. It can cause alcohol intoxication when consumed in sufficient quantity.

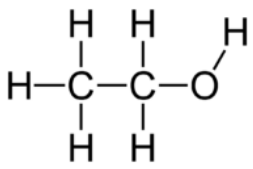
Ethanol in alcoholic beverages and fuel is produced by fermentation. Certain species of yeast (e.g., *Saccharomyces cerevisiae*) metabolizes sugar producing ethanol and carbon dioxide. The chemical equations below summarize the conversion:

$C_6H_{12}O_6 \rightarrow 2\ CH_3CH_2OH + 2\ CO_2$
$C_{12}H_{22}O_{11} + H_2O \rightarrow 4\ CH_3CH_2OH + 4\ CO_2$

Fermentation is the process of culturing yeast under favorable thermal conditions to produce alcohol. This process is carried out at around 35–40 °C (95–104 °F). Toxicity of ethanol to yeast limits the ethanol concentration obtainable by brewing; higher concentrations, therefore, are obtained by fortification or distillation. The most ethanol-tolerant yeast strains can survive up to approximately 18% ethanol by volume.

To produce ethanol from starchy materials such as cereal grains, the starch must first be converted into sugars. In brewing beer, this has traditionally been accomplished by allowing the grain to germinate, or malt, which produces the enzyme amylase. When the malted grain is mashed, the amylase converts the remaining starches into sugars.

Sugars for ethanol fermentation can be obtained from cellulose. Deployment of this technology could turn a number of cellulose-containing agricultural by-products, such as corncobs, straw, and sawdust, into renewable energy resources. Other agricultural residues such as sugar cane bagasse and energy crops such as switchgrass may also be a sources of fermentable sugars.



https://en.wikipedia.org/wiki/Ethanol

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Ethanolamine

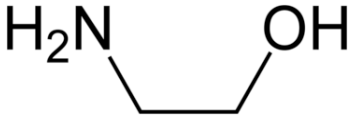
Ethanolamine, also called 2-aminoethanol or monoethanolamine (often abbreviated as ETA or MEA), is an organic chemical compound with the formula $HOCH_2CH_2NH_2$. The molecule is both a primary amine and a primary alcohol (due to a hydroxyl group).

The ethanolamines comprise a group of amino alcohols. A class of antihistamines is identified as ethanolamines, which includes carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, and doxylamine.

Ethanolamine is biosynthesized by decarboxylation of serine:

$$HOCH_2CH(CO_2H)NH_2 \rightarrow HOCH_2CH_2NH_2 + CO_2$$

Ethanolamine is the second-most-abundant head group for phospholipids, substances found in biological membranes (particularly those of procaryotes), e.g., phosphatidylethanolamine. It is also used in messenger molecules such as palmitoylethanolamide, which has an effect on CB_1 receptors.



https://en.wikipedia.org/wiki/Ethanolamine

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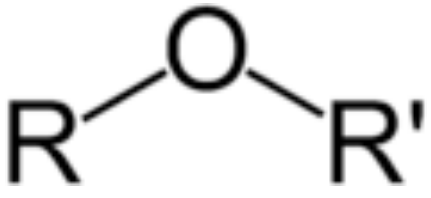
Ether

Ethers are a class of organic compounds that contain an ether group—an ox
connected to two alkyl or aryl groups—of general formula R–O–R′. These e
again be classified into two varieties. If the alkyl groups are the same on bo
the oxygen atom, then it is a simple or symmetrical ether, whereas if they a
the ethers are called mixed or unsymmetrical ethers.



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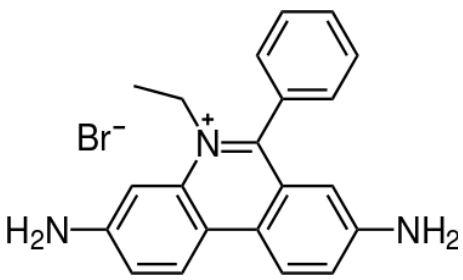
Ethidium Bromide

Ethidium bromide is an intercalating agent commonly used as a fluorescent tag (nucleic acid stain) in molecular biology laboratories for techniques such as agarose gel electrophoresis. It is commonly abbreviated as "EtBr", which is also an abbreviation for bromoethane. When exposed to ultraviolet light, it will fluoresce with an orange color, intensifying almost 20-fold after binding to DNA.

Ethidium bromide is commonly used to detect nucleic acids in molecular biology laboratories. In the case of DNA this is usually double-stranded DNA from PCRs, restriction digests, etc. Single-stranded RNA can also be detected, since it usually folds back onto itself and thus provides local base pairing for the dye to intercalate. Detection typically involves a gel containing nucleic acids placed on or under a UV lamp. Since ultraviolet light is harmful to eyes and skin, gels stained with ethidium bromide are usually viewed indirectly using an enclosed camera, with the fluorescent images recorded as photographs. Where direct viewing is needed, the viewer's eyes and exposed skin should be protected. In the laboratory the intercalating properties have long been used to minimize chromosomal condensation when a culture is exposed to mitotic arresting agents during harvest. The resulting slide preparations permit a higher degree of resolution, and thus more confidence in determining structural integrity of chromosomes upon microscopic analysis.

Ethidium bromide has also been used extensively to reduce mitochondrial DNA copy number in proliferating cells. The effect of EtBr on mitochondrial DNA is used in veterinary medicine to treat trypanosomosis in cattle, as EtBr binds molecules of kinetoplastid DNA and changes their conformation to Z-DNA form. This form inhibits replication of kinetoplastid DNA which is lethal for *trypanosomas*.



https://en.wikipedia.org/wiki/Ethidium_bromide

Eukaryotes

A eukaryote is any organism whose cells contain a nucleus and other organelles enclosed within membranes. Eukaryotes belong to the taxon *Eukarya* or *Eukaryota*. The defining feature that sets eukaryotic cells apart from prokaryotic cells (bacteria and *Archaea*) is that they have membrane-bound organelles, especially the nucleus, which contains the genetic material, and is enclosed by the nuclear envelope.

Eukaryotic cells also contain other membrane-bound organelles such as mitochondria and the Golgi apparatus. In addition, plants and algae contain chloroplasts. Eukaryotic organisms may be unicellular, or multicellular. Only eukaryotes have multicellular organisms consisting of many kinds of tissue made up of different cell types.

Eukaryotes can reproduce both asexually through mitosis and sexually through meiosis and gamete fusion. In mitosis, one cell divides to produce two genetically identical cells. In meiosis, DNA replication is followed by two rounds of cell division to produce four daughter cells each with half the number of chromosomes as the original parent cell (haploid cells). These act as sex cells (gametes – each gamete has just one complement of chromosomes, each a unique mix of the corresponding pair of parental chromosomes) resulting from genetic recombination during meiosis.

The domain Eukaryota appears to be monophyletic, and so makes up one of the three domains of life. The two other domains, Bacteria and Archaea, are prokaryotes and have none of the above features. Eukaryotes represent a tiny minority of all living things. However, due to their much larger size, eukaryotes' collective worldwide biomass is estimated at about equal to that of prokaryotes. Eukaryotes first developed approximately 1.6–2.1 billion years ago.

https://en.wikipedia.org/wiki/Eukaryote

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Eukaryotic

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https://en.wikipedia.org/wiki/Eukaryote

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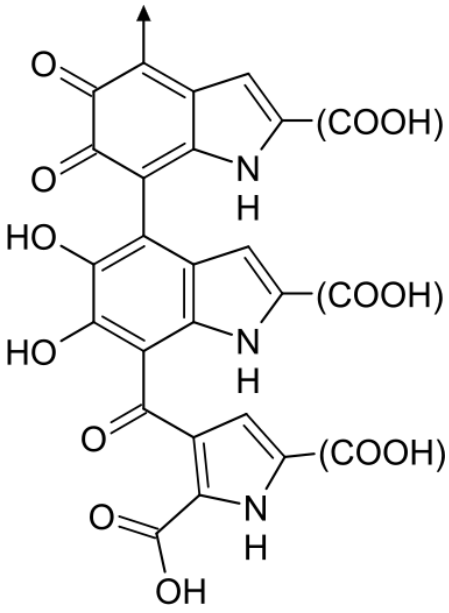
Eumelanin

Melanin is a broad term for a group of natural pigments found in most organisms (arachnids are one of the few groups in which it has not been detected). Melanin is produced by the oxidation of the amino acid tyrosine, followed by polymerization. The pigment is produced in a specialized group of cells known as melanocytes.

There are three basic types of melanin: eumelanin, pheomelanin, and neuromelanin. The most common is eumelanin, of which there are two types—brown eumelanin and black eumelanin. Pheomelanin is a cysteine-containing red polymer of benzothiazine units largely responsible for red hair, among other pigmentation. Neuromelanin is found in the brain, though its function remains obscure.

Eumelanin polymers have long been thought to comprise numerous cross-linked 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymers. There are two types of eumelanin—brown eumelanin and black eumelanin—which chemically differ from each other in their pattern of polymeric bonds. A small amount of black eumelanin in the absence of other pigments causes grey hair. A small amount of brown eumelanin in the absence of other pigments causes yellow (blond) color hair. As the body ages, it continues to produce black melanin but stops producing the brown version, explaining the grey hair common in the elderly.

Part of the structure of eumelanin is shown below



https://en.wikipedia.org/wiki/Melanin#Eumelanin

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Exclusion Limit

Size exclusion chromatography (also called molecular exclusion chromatog
exclusion chromatography, or gel filtration chromatography) is a low resolu
tion method for separating molecules on the basis of size. It works by empl
with tiny “tunnels” in them that each have a precise opening. The size of the
referred to as an “exclusion limit,” which means that molecules above a cer
lar weight will not typically fit into the tunnels and are therefore excluded f
ing through them.

https://en.wikipedia.org/wiki/Size-exclusion_chromatography

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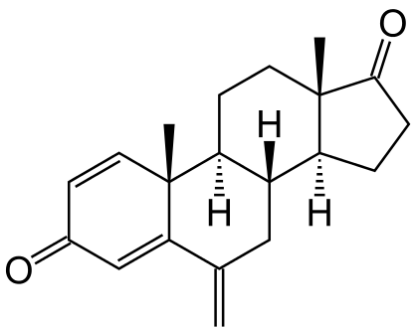
Exemestane

Exemestane (trade name Aromasin) is a drug used to treat breast cancer. It is a member of the class of drugs known as aromatase inhibitors. Some breast cancers require estrogen to grow. Those cancers have estrogen receptors (ERs), and are called ER-positive. They may also be called estrogen-responsive, hormonally-responsive, or hormone-receptor-positive. Aromatase is an enzyme that synthesizes estrogen. Aromatase inhibitors block the synthesis of estrogen. This lowers the estrogen level, and slows the growth of cancers.

The main source of estrogen is the ovaries in premenopausal women, while in postmenopausal women most of the body's estrogen is produced via the conversion of androgens into estrogen by the aromatase enzyme in the peripheral tissues (i.e. adipose tissue like that of the breast) and a number of sites in the brain. Estrogen is produced locally via the actions of the aromatase enzyme in these peripheral tissues where it acts locally. Any circulating estrogen in post-menopausal women as well as men is the result of estrogen escaping local metabolism and entering the circulatory system.

Exemestane is an irreversible, steroidal aromatase inactivator of type I, structurally related to the natural substrate 4-androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition." By being structurally similar to enzyme targets, exemestane permanently binds to the enzymes, preventing them from converting androgen into estrogen.

Type II aromatase inhibitors such as anastrozole and letrozole, by contrast, are not steroids and work by interfering with the aromatase's heme.



https://en.wikipedia.org/wiki/Exemestane

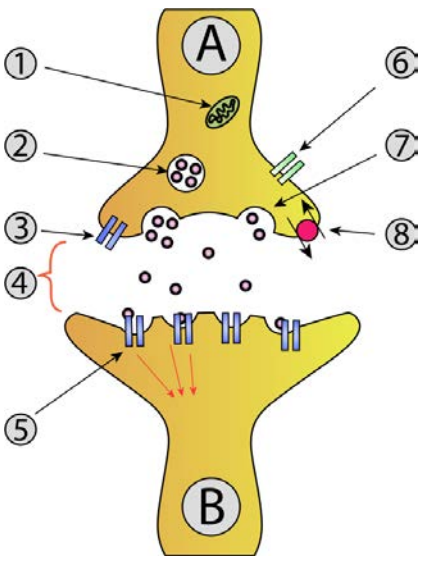
Exocytosis

Exocytosis is a form of active transport in which a cell transports molecules (such as proteins) out of the cell (exo- + cytosis) by expelling them in an energy-using process. Exocytosis and its counterpart, endocytosis, are used by all cells because most chemical substances important to them are large polar molecules that cannot pass through the hydrophobic portion of the cell membrane by passive means.

In exocytosis, membrane-bound secretory vesicles are carried to the cell membrane, and their contents (water-soluble molecules such as proteins) are secreted into the extracellular environment. This secretion is possible because the vesicle transiently fuses with the outer cell membrane.

Exocytosis is also a mechanism by which cells are able to insert membrane proteins (such as ion channels and cell surface receptors), lipids, and other components into the cell membrane. Vesicles containing these membrane components fully fuse with and become part of the outer cell membrane.

In the image below, neurotransmitters in vesicles (2) are exocytosed into the synaptic junction between nerve cells.



https://en.wikipedia.org/wiki/Exocytosis

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Chapter 9 - Point by Point: Membranes

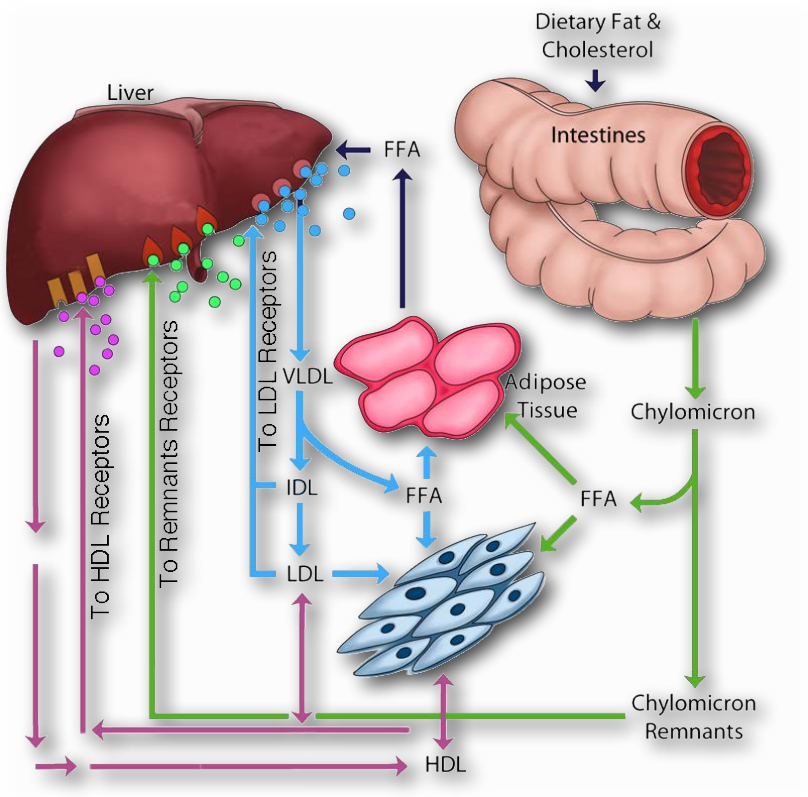
Exogenous Pathway

The exogenous pathway is one of three major pathways taken by lipids in the body. (The others are the endogenous pathway and the reverse transport pathway.)

Dietary fat entering the body from the intestinal system must be transported, as appropriate, to places needing it or storing it. This is the function of the exogenous pathway of lipid movement in the body (shown in the figure below in green). All dietary lipids (fats, cholesterol, fat soluble vitamins, and other lipids) are moved by it. In the case of dietary fat, it begins its journey after ingestion first by being solubilized by bile acids in the intestinal tract. After passing through the stomach, pancreatic lipases clip two fatty acids from the fat, leaving a monoacyl glycerol. The fatty acids and monoacyl glycerol are absorbed by intestinal cells (enterocytes) and reassembled back into a fat, and then this is mixed with phospholipids, cholesterol esters, and apolipoprotein B-48 and processed to form chylomicrons in the Golgi apparatus and smooth endoplasmic reticulum.

These are exocytosed from the cell into lymph capillaries called lacteals. The chylomicrons pass through the lacteals and enter the bloodstream via the left subclavian vein. Within the bloodstream, lipoprotein lipase breaks down the fats causing the chylomicron to shrink and become what is known as a chylomicron remnant. It retains its cholesterol and other lipid molecules.

The chylomicron remnants travel to the liver where they are absorbed. This is accomplished by receptors in the liver that recognize and bind to the ApoE of the chylomicrons. The bound complexes are then internalized by endocytosis, degraded in the lysosomes, and the cholesterol is disbursed in the cell.



https://en.wikipedia.org/wiki/Lipoprotein#Exogenous_pathway

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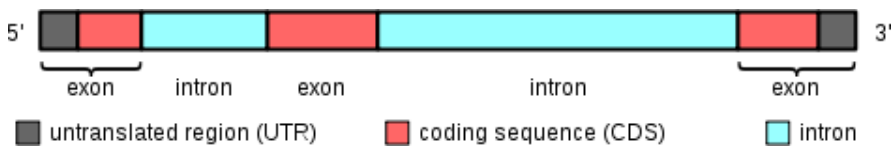
Exons

An exon is any part of a gene that will become a part of the final mature RNA produced by that gene after introns have been removed by RNA splicing. The term exon refers to both the DNA sequence within a gene and to the corresponding sequence in RNA transcripts. In RNA splicing, introns are removed and exons are covalently joined to one another as part of generating the mature messenger RNA.

In protein-coding genes, the open reading frame (ORF) that codes for a specific portion of the complete protein are located in the exons. However, the term exon is often misused to refer only to coding sequences for the final protein. This is incorrect, since many noncoding exons are known in human genes. Exons can include both sequences that code for amino acids and untranslated sequences. Stretches of unused sequence called introns are removed, and the exons are joined together to form the final functional mRNA. Some of the exons will be wholly or part of the 5' untranslated region (5' UTR) or the 3' untranslated region (3' UTR) of each transcript. The untranslated regions are important for efficient translation of the transcript and for controlling the rate of translation and half-life of the transcript. Furthermore, transcripts made from the same gene may not have the same exon structure, since parts of the mRNA could be removed by the process of alternative splicing. Some mRNA transcripts have exons with no ORFs and, thus, are sometimes referred to as non-coding RNA.



https://en.wikipedia.org/wiki/Exon

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Exonuclease

Exonucleases are enzymes that work by cleaving nucleotides one at a time from the end (exo) of a polynucleotide chain. A hydrolyzing reaction that breaks phosphodiester bonds at either the 3’ or the 5’ end occurs. Its close relative is the endonuclease, which cleaves phosphodiester bonds in the middle (endo) of a polynucleotide chain. Eukaryotes and prokaryotes have three types of exonucleases involved in the normal turnover of mRNA: 5’ to 3’ exonuclease, which is a dependent decapping protein; 3’ to 5’ exonuclease, an independent protein; and poly(A)-specific 3’ to 5’ exonuclease.

In both archaebacteria and eukaryotes, one of the main routes of RNA degradation is performed by the multi-protein exosome complex, which consists largely of 3' to 5' exoribonucleases.

DNA polymerase I also has 3' to 5' and 5' to 3' exonuclease activity, which is used in editing and proofreading DNA for errors. The 3' to 5' can only remove one mononucleotide at a time, and the 5' to 3' activity can remove mononucleotides or up to 10 nucleotides at a time.

RNA polymerase II is known to be in effect during transcriptional termination. It works with a 5’ exonuclease (human gene Xrn2) to degrade the newly formed transcript downstream, leaving the polyadenylation site and simultaneously shooting the polymerase. This process involves the exonuclease's catching up to the pol II and terminating the transcription. Pol I then synthesizes DNA nucleotides in place of the RNA primer it had just removed.

https://en.wikipedia.org/wiki/Exonuclease

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Expression Platform

Riboswitches are often conceptually divided into two parts - an aptamer an
sion platform. The aptamer directly binds the small molecule, and the expr
form undergoes structural changes in response to the changes in the aptam
pression platform is what regulates gene expression.

https://en.wikipedia.org/wiki/Riboswitch

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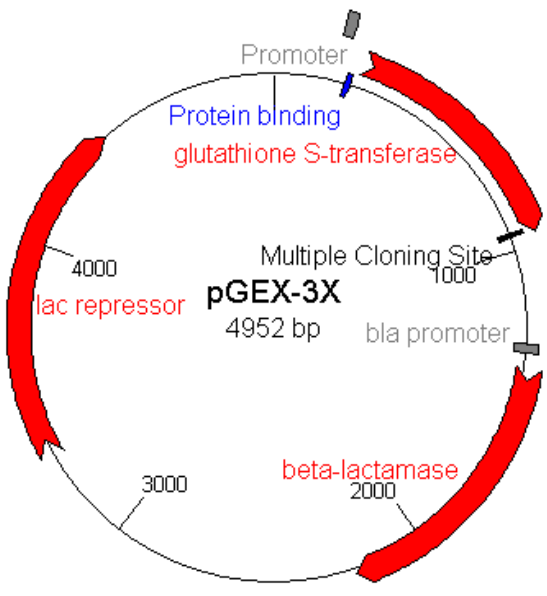
Expression Vector

An expression vector, otherwise known as an expression construct, is usually a plasmid or virus designed for gene expression in cells. The vector is used to introduce a specific gene into a target cell, and can commandeer the cell's mechanism for protein synthesis to produce the protein encoded by the gene. Expression vectors are the basic tools in biotechnology for the production of proteins. They typically contain at a minimum 1) a replication origin, 2) a (marker) gene for antibiotic resistance, and 3) a promoter active in the target cell.

The plasmid is engineered to contain regulatory sequences that act as enhancer and promoter regions and lead to efficient transcription of the gene carried on the expression vector. The goal of a well-designed expression vector is the efficient production of protein, and this may be achieved by the production of significant amount of stable messenger RNA, which can then be translated into protein. The expression of protein may be tightly controlled and protein is only produced in significant quantity when necessary through the use of an inducer, in some systems however the protein may be expressed constitutively. *Escherichia coli* is commonly used as the host for protein production, but other cell types may also be used. An example of the use of expression vector is the production of insulin, which is used for medical treatments of diabetes.

Shown below is the structure of the PGEX-3X expression vector.



https://en.wikipedia.org/wiki/Expression_vector

Extra-chromosomal DNA

Extrachromosomal DNA is any DNA that is found outside of the nucleus of a cell. It is also referred to as extranuclear DNA or cytoplasmic DNA. Most DNA in an individual genome is found in chromosomes but DNA found outside of the nucleus also serves important biological functions.

In prokaryotes, nonviral extrachromosomal DNA is primarily found in plasmids whereas in eukaryotes extrachromosomal DNA is primarily found in organelles. Mitochondrial DNA is a main source of this extrachromosomal DNA in eukaryotes. Extrachromosomal DNA is often used in research of replication because it is easy to identify and isolate.

Extrachromosomal DNA was found to be structurally different from nuclear DNA. Cytoplasmic DNA is less methylated than DNA found within the nucleus. It was also confirmed that the sequences of cytoplasmic DNA was different from nuclear DNA in the same organism, showing that cytoplasmic DNAs are not simply fragments of nuclear DNA.

Although prokaryotic organisms do not possess a membrane bound nucleus like the eukaryotes, they do contain a nucleoid region in which the main chromosome is found. Extrachromosomal DNA exists in prokaryotes outside of the nucleoid region as circular or linear plasmids. Bacterial plasmids are typically short sequences, consisting of 1 kilobase (kb) to a few hundred kb segments, and contain an origin of replication which allows the plasmid to replicate independently of the bacterial chromosome. The total number of a particular plasmid within a cell is referred to as the copy number and can range from as few as two copies per cell to as many as several hundred copies per cell.

https://en.wikipedia.org/wiki/Extrachromosomal_DNA

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Extracellular Matrix

In biology, the extracellular matrix (ECM) is a collection of extracellular molecules secreted by cells that provides structural and biochemical support to the surrounding cells. Because multicellularity evolved independently in different multicellular lineages, the composition of ECM varies between multicellular structures. However, cell adhesion, cell-to-cell communication and differentiation are common functions of the ECM.

The animal extracellular matrix includes the interstitial matrix and the basement membrane. Interstitial matrix is present between various animal cells (i.e., in the intercellular spaces). Gels of polysaccharides and fibrous proteins fill the interstitial space and act as a compression buffer against the stress placed on the ECM. Basement membranes are sheet-like depositions of ECM on which various epithelial cells rest. Each type of connective tissue in animals has a type of ECM: collagen fibers and bone mineral comprise the ECM of bone tissue. Reticular fibers and ground substance comprise the ECM of loose connective tissue and blood plasma is the ECM of blood.

The plant ECM includes cell wall components, like cellulose, in addition to more complex signaling molecules. Some single-celled organisms adopt multicelluar biofilms in which the cells are embedded in an ECM composed primarily of extracellular polymeric substances (EPS).

https://en.wikipedia.org/wiki/Extracellular_matrix

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Extremophiles

An extremophile (from Latin extremus meaning "extreme" and Greek philiā (φιλία) meaning "love") is an organism that thrives in physically or geochemically extreme conditions that are detrimental to most life on Earth. In contrast, organisms that live in more moderate environments may be termed mesophiles or neutrophiles.

Most known extremophiles are microbes. The domain *Archaea* contains renowned examples, but extremophiles are present in numerous and diverse genetic lineages of bacteria and archaeans. Furthermore, it is erroneous to use the term extremophile to encompass all archaeans, as some are mesophilic. Neither are all extremophiles unicellular; protostome animals found in similar environments include the Pompeii worm, the psychrophilic *Grylloblattidae* (insects) and Antarctic krill (a crustacean). Many would also classify tardigrades (water bears) as extremophiles, but while tardigrades can survive in extreme environments, they are not considered extremophiles because they are not adapted to live in these conditions. Their chances of dying increase the longer they are exposed to the extreme environment.

Pictured below - extremophiles living in a Yellowstone hot spring

https://en.wikipedia.org/wiki/Extremophile

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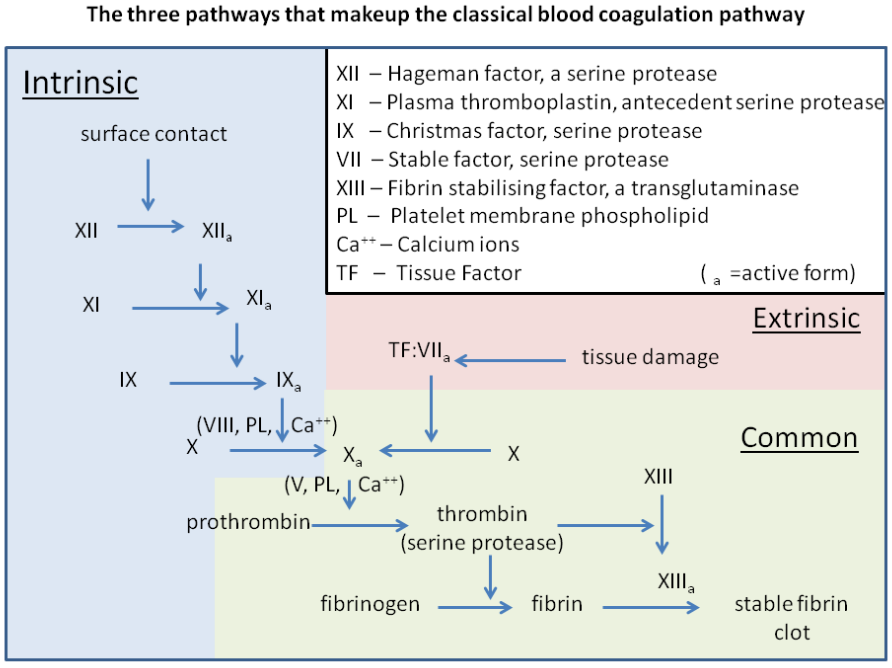
Extrinsic Pathway

In blood clotting, the main role of the tissue factor (extrinsic pathway) is to generate a "thrombin burst", a process by which thrombin, the most important constituent of the coagulation cascade in terms of its feedback activation roles, is released very rapidly. FVIIa circulates in a higher amount than any other activated coagulation factor. The process includes the following steps:

1. Following damage to the blood vessel, FVII leaves the circulation and comes into contact with tissue factor (TF) expressed on tissue-factor-bearing cells (stromal fibroblasts and leukocytes), forming an activated complex (TF-FVIIa).
2. TF-FVIIa activates FIX and FX.
3. FVII is itself activated by thrombin, FXIa, FXII and FXa.
4. The activation of FX (to form FXa) by TF-FVIIa is almost immediately inhibited by tissue factor pathway inhibitor (TFPI).
5. FXa and its co-factor FVa form the prothrombinase complex, which activates prothrombin to thrombin.
6. Thrombin then activates other components of the coagulation cascade, including FV and FVIII (which forms a complex with FIX), and activates and releases FVIII from being bound to vWF.
7. FVIIIa is the co-factor of FIXa, and together they form the "tenase" complex, which activates FX and so the cycle continues. ("Tenase" is a contraction of "ten" and the suffix "-ase" used for enzymes.)



https://en.wikipedia.org/wiki/Coagulation#Tissue_factor_pathway_.28extrinsic.29

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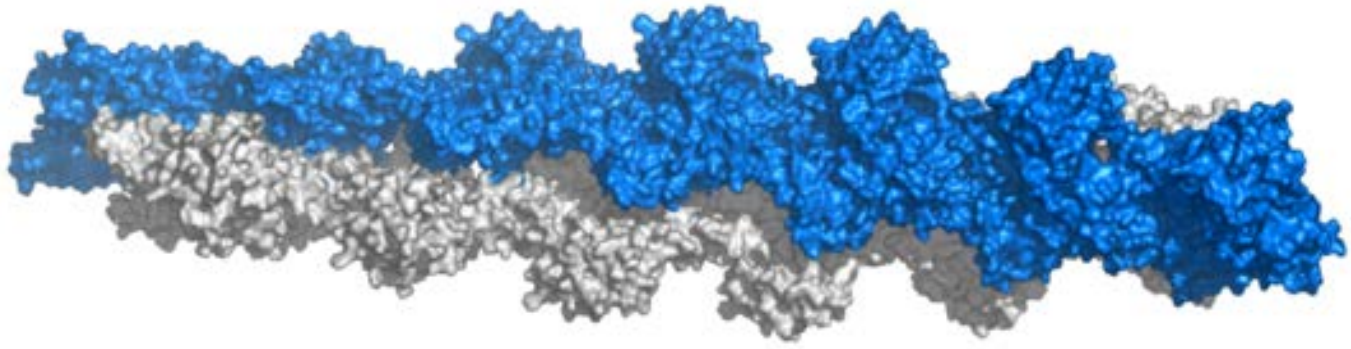
F-actin

Actin is a protein found in cells either a free monomer called G-actin (globular) or as part of a linear polymer microfilament called F-actin (filamentous), both of which are essential for such important cellular functions as the mobility and contraction of cells during cell division.

The classical description of F-actin states that it has a filamentous structure that can be considered to be a single stranded levorotatory helix with a rotation of 166° around the helical axis and an axial translation of 27.5 Å, or a single stranded dextrorotatory helix with a cross over spacing of 350-380 Å, with each actin surrounded by four more.

The F-actin polymer is considered to have structural polarity due to the fact that all the microfilament's subunits point towards the same end. This gives rise to a naming convention: the end that possesses an actin subunit that has its ATP binding site exposed is called the "(-) end", while the opposite end where the cleft is directed at a different adjacent monomer is called the "(+) end".



https://en.wikipedia.org/wiki/Actin#F-Actin

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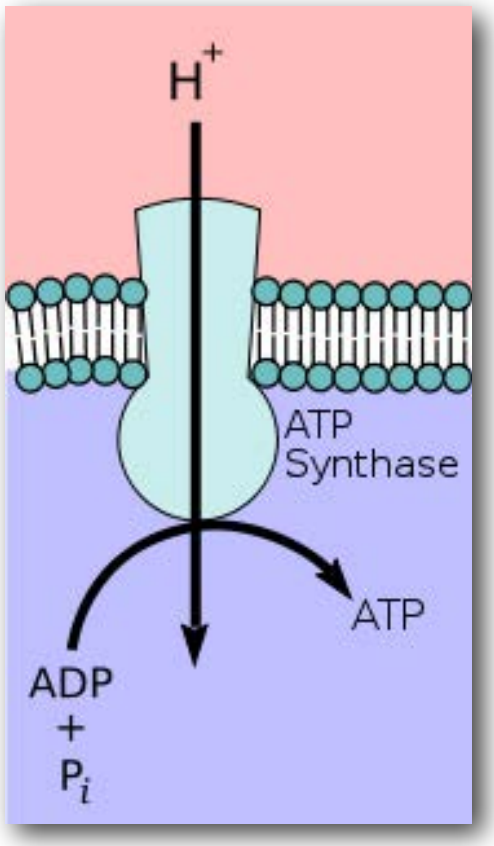
F_0

The F_0 region of ATP synthase is a proton pore that is embedded in the mitochondrial membrane. It consists of three main subunits A, B, and C, and (in humans) six additional subunits, d, e, f, g, F6, and 8 (or A6L).

According to the current model of ATP synthesis (known as the alternating catalytic model), the transmembrane potential created by (H^+) proton cations supplied by the electron transport chain, drives the (H^+) proton cations from the intermembrane space through the membrane via the F_0 region of ATP synthase. A portion of the F_0 (the ring of c-subunits) rotates as the protons pass through the membrane.



https://en.wikipedia.org/wiki/ATP_synthase#FO-ATP_Synthase_Structure

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F_1

The F_1 particle of the ATP synthase complex is large and can be seen in the
sion electron microscope by negative staining. These are particles of 9 nm d
that pepper the inner mitochondrial membrane. They were originally called
tary particles and were thought to contain the entire respiratory apparatus
chondrion, but, through a long series of experiments, Efraim Racker and hi
(who first isolated the F_1 particle in 1961) were able to show that this partic
lated with ATPase activity in uncoupled mitochondria and with the ATPase
submitochondrial particles created by exposing mitochondria to ultrasound
Pase activity was further associated with the creation of ATP by a long serie
ments in many laboratories.

https://en.wikipedia.org/wiki/ATP_synthase#F1-ATP_Synthase_structur

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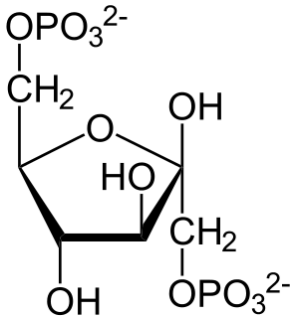
F1,6BP

Fructose 1,6-bisphosphate, also known as Harden-Young ester, is fructose sugar phosphorylated on carbons 1 and 6 (i.e., is a fructosephosphate). The β-D-form of this compound is very common in cells. The vast majority of glucose and fructose entering a cell will become converted to fructose 1,6-bisphosphate at some point.

Fructose 1,6-bisphosphate lies within the glycolysis metabolic pathway and is produced by phosphorylation of fructose 6-phosphate. It is, in turn, broken down into two compounds: glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. It is an allosteric activator of pyruvate kinase through distinct interactions of binding and allostery at the enzyme's catalytic site.

Fructose 1,6-bis(phosphate) has also been implicated in the ability to bind and sequester Fe(II), a soluble form of iron whose oxidation to the insoluble Fe(III) is capable of generating reactive oxygen species via Fenton chemistry. The ability of fructose 1,6-bis(phosphate) to bind Fe(II) may prevent such electron transfers, and thus act as an antioxidant within the body. Certain neurodegenerative diseases, like Alzheimer's and Parkinson's, have been linked to metal deposits with high iron content, although it is uncertain whether Fenton chemistry plays a substantial role in these diseases, or whether fructose 1,6-bis(phosphate) is capable of mitigating those effects.



https://en.wikipedia.org/wiki/Fructose_1,6-bisphosphate

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F1,6BPase

Fructose-1,6-bisphosphatase (F1,6BPase) is an enzyme that converts fructose-1,6-bisphosphate to fructose 6-phosphate in gluconeogenesis and the Calvin cycle which are both anabolic pathways. Fructose bisphosphatase catalyzes the reverse of the reaction which is catalyzed by phosphofructokinase in glycolysis. These enzymes only catalyze the reaction in one direction each, and are regulated by metabolites such as fructose 2,6-bisphosphate so that high activity of one of the two enzymes is accompanied by low activity of the other. More specifically, fructose 2,6-bisphosphate allosterically inhibits fructose 1,6-bisphosphatase, but activates phosphofructokinase-I. Fructose 1,6-bisphosphatase is involved in many different metabolic pathways and found in most organisms. FBPase requires metal ions for catalysis (Mg^{++} and Mn^{++} being preferred) and the enzyme is potently inhibited by Li^{+}.

https://en.wikipedia.org/wiki/Fructose_1,6-bisphosphatase

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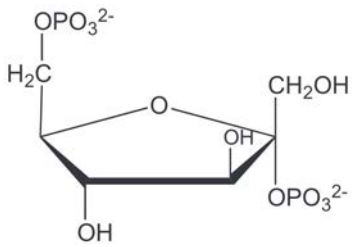
F2,6BP

Fructose-2,6-bisphosphate abbreviated Fru-2,6-P2, is a metabolite that allosterically affects the activity of the enzymes phosphofructokinase 1 (PFK-1) and fructose 1,6-bisphosphatase (FBPase-1) to regulate glycolysis and gluconeogenesis. Fru-2,6-P2 is synthesized and broken down by the bifunctional enzyme phosphofructokinase 2/fructose-2,6-bisphosphatase (PFK-2/FBPase-2).

The synthesis of Fru-2,6-P2 is performed through the phosphorylation of fructose 6-phosphate using ATP by the PFK-2 portion of the enzyme. The breakdown of Fru-2,6-P2 is catalyzed by dephosphorylation by FBPase-2 to produce Fructose 6-phosphate and P_i.

Fru-2,6-P2 strongly activates glucose breakdown in glycolysis through allosteric modulation of phosphofructokinase 1 (PFK-1). Elevated expression of Fru-2,6-P2 levels in the liver allosterically activates phosphofructokinase 1 by increasing the enzyme's affinity for fructose 6-phosphate, while decreasing its affinity for inhibitory ATP and citrate. At physiological concentration, PFK-1 is almost completely inactive, but interaction with Fru-2,6-P2 activates the enzyme to stimulate glycolysis and enhance breakdown of glucose.

The concentration of Fru-2,6-P2 in cells is controlled through regulation of the synthesis and breakdown by PFK-2/FBPase-2. The primary regulators of this are the hormones insulin, glucagon, and epinephrine which affect the enzyme through phosphorlyation/dephosphorylation reactions. Release of the hormone glucagon triggers production of cyclic adenosine monophosphate (cAMP), which activates a cAMP-dependent protein kinase. This kinase phosphorylates the PFK-2/FBPase-2 enzyme at an NH2-terminal Ser residue with ATP to activate the FBPase-2 activity and inhibit the PFK-2 activity of the enzyme, thus reducing levels of Fru-2,6-P2 in the cell. With decreasing amounts of Fru-2,6-P2, glycolysis becomes inhibited while gluconeogenesis is activated. Insulin triggers the opposite response. As a phosphoprotein phosphatase, insulin dephosphorylates the enzyme, thus activating the PFK-2 and inhibiting the FBPase-2 activities. With additional Fru-2,6-P2 present, activation of PFK-1 occurs to stimulate glycolysis while inhibiting gluconeogenesis.



https://en.wikipedia.org/wiki/Fructose_2,6-bisphosphate

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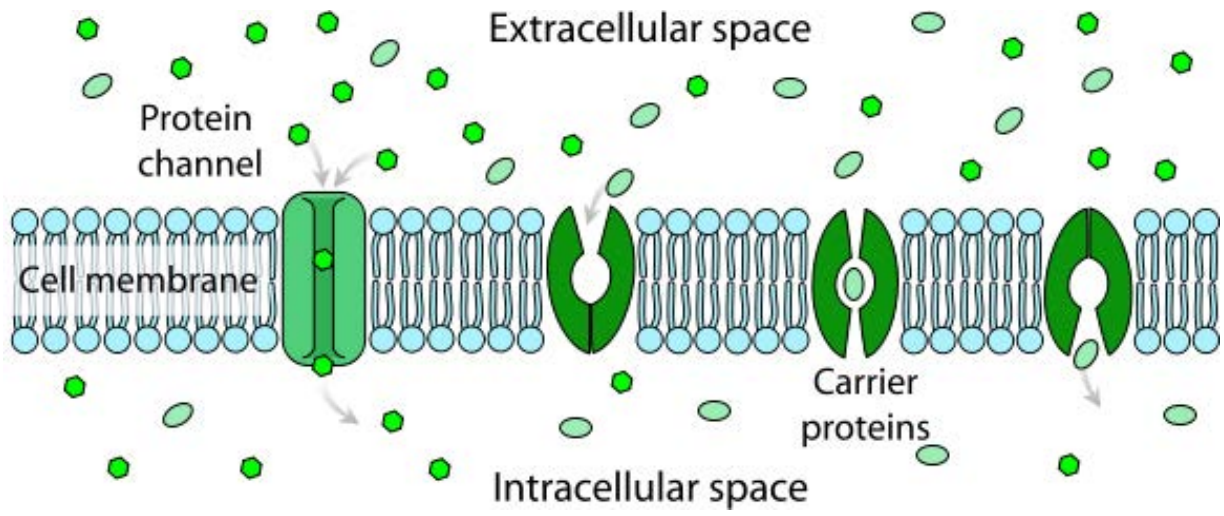
Facilitated Diffusion

Facilitated diffusion (also known as facilitated transport or passive-mediated transport) is the process of spontaneous passive transport (as opposed to active transport) of molecules or ions across a biological membrane via specific transmembrane integral proteins. Being passive, facilitated transport does not directly require chemical energy from ATP hydrolysis in the transport step itself. Rather, molecules and ions move down their concentration gradient reflecting its diffusive nature.



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Facultative Anaerobes

A facultative anaerobe is an organism that makes ATP by aerobic respiratio
is present, but is capable of switching to fermentation or anaerobic respirat
gen is absent. An obligate aerobe, by contrast, cannot make ATP in the abse
gen, and obligate anaerobes die in the presence of oxygen.

https://en.wikipedia.org/wiki/Facultative_anaerobic_organism

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FAD

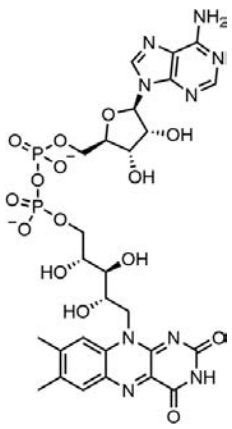
In biochemistry, flavin adenine dinucleotide (FAD) is a redox cofactor, more specifically a prosthetic group, involved in several important reactions in metabolism. FAD can exist in three (or four: flavin-N(5)-oxide) different redox states, which are the quinone, semiquinone, and hydroquinone. FAD is converted between these states by accepting or donating electrons.

FAD, in its fully oxidized form, or quinone form, accepts two electrons and two protons to become $FADH_2$ (hydroquinone form). The semiquinone ($FADH\cdot$) can be formed by either reduction of FAD or oxidation of $FADH_2$ by accepting or donating one electron and one proton, respectively. See the mechanism section below for details.

A flavoprotein is a protein that contains a flavin moiety, this may be in the form of FAD or flavin mononucleotide (FMN). There are many flavoproteins besides components of the succinate dehydrogenase complex, including α-ketoglutarate dehydrogenase and a component of the pyruvate dehydrogenase complex.

Flavin adenine dinucleotide consists of two main portions: an adenine nucleotide (adenosine monophosphate) and a flavin mononucleotide bridged together through their phosphate groups. Adenine is bound to a cyclic ribose at the 1' carbon, while phosphate is bound to the ribose at the 5' carbon to form the adenine nucledotide. Riboflavin is formed by a carbon-nitrogen (C-N) bond between a isoalloxazine and a ribitol. The phosphate group is then bound to the on the terminal ribose carbon to form a FMN. Because the bond between the isoalloxazine and the ribitol is not considered to be a glycosidic bond, the flavin mononucleotide is not truly a nucleotide. This makes the dinucleotide name misleading. However, the flavin mononucleotide group is still very close to a nucleotide in its structure and chemical properties.

FAD can be reduced to $FADH_2$ through by the addition of two H^+ and two e^-. $FADH_2$ can also be oxidized by the loss of one H+ and one e- to form FADH. The FAD form can be recreated from another loss on one H+ and one e-. FAD formation can also occur through the reduction and dehydration of flavin-N(5)-oxide. Based on the oxidation state, flavins take specific colors when in aqueous solution. FAD (fully oxidized) is yellow, FADH(half reduced) is either blue or red based on the pH, and the fully reduced form is colorless. Changing the form can have a large impact on other chemical properties. For example, FAD, the fully oxidized form is subject to nucleophilic attack, the fully reduced form, $FADH_2$ has high polarizability, while the half reduced form is unstable in aqueous solution. FAD is an aromatic ring system, whereas $FADH_2$ is not. This means that $FADH_2$ is significantly higher in energy, without the stabilization through resonance that the aromatic structure provides. $FADH_2$ is an energy-carrying molecule, because, once oxidized it regains aromaticity and releases the energy represented by this stabilization.



https://en.wikipedia.org/wiki/Flavin_adenine_dinucleotide

$FADH_2$

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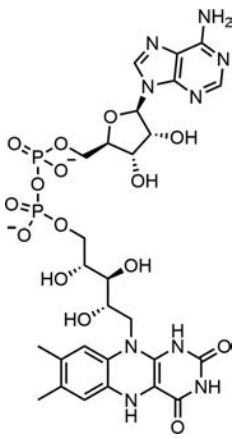

https://en.wikipedia.org/wiki/Flavin_adenine_dinucleotide

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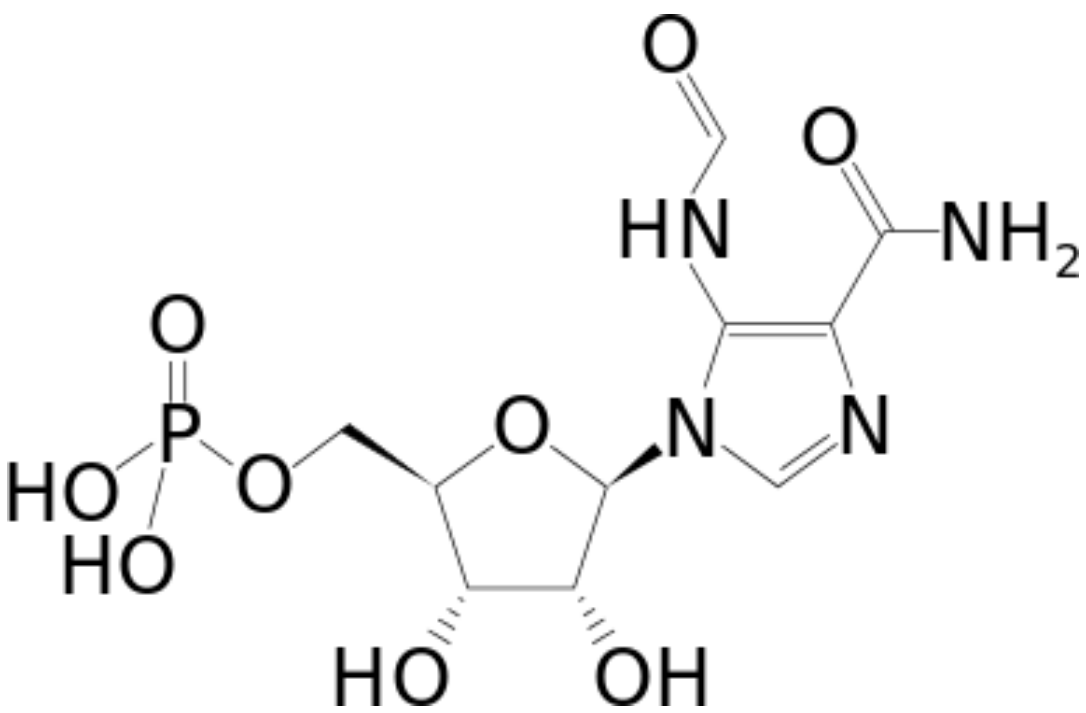
FAICAR

5-Formamidoimidazole-4-carboxamide ribotide (or FAICAR) is an intermediat
formation of purines. It is formed by the enzyme AICAR transformylase from A
and 10-formyltetrahydrofolate.



https://en.wikipedia.org/wiki/5-Formamidoimidazole-4-carboxamide_ribotid

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Familial Hypercholesterolemia

Familial hypercholesterolemia (abbreviated FH) is a genetic disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein (LDL, "bad cholesterol"), in the blood and early cardiovascular disease. Since individuals with FH underlying body biochemistry is slightly different, their high cholesterol levels are less responsive to the kinds of cholesterol control methods which are usually more effective in people without FH (such as dietary modification and statin tablets). Nevertheless, treatment (including higher statin doses) is usually effective.

Many people have mutations in the LDLR gene that encodes the LDL receptor protein, which normally removes LDL from the circulation, or apolipoprotein B (ApoB), which is the part of LDL that binds with the receptor. Mutations in other genes are rare. People who have one abnormal copy (are heterozygous) of the LDLR gene may have premature cardiovascular disease at the age of 30 to 40. Having two abnormal copies (being homozygous) may cause severe cardiovascular disease in childhood. Heterozygous FH is a common genetic disorder, inherited in an autosomal dominant pattern, occurring in 1:500 people in most countries. Homozygous FH is much rarer, occurring in 1 in a million births.

Heterozygous FH is normally treated with statins, bile acid sequestrants, or other lipid lowering agents that lower cholesterol levels. New cases are generally offered genetic counseling. Homozygous FH often does not respond to medical therapy and may require other treatments, including LDL apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation.

https://en.wikipedia.org/wiki/Familial_hypercholesterolemia

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Farnesyl Groups

A farnesyl group is a 15 carbon intermediate formed in isoprenoid synthesis linked to a pyrophosphtate and contains five carbon units from isopentenyl phate and dimethylallylpyrophosphate.

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Chapter 3 - Membranes: Basic Concepts

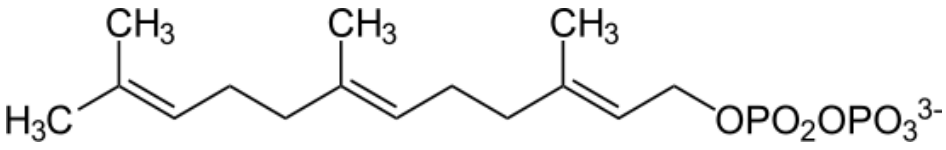
Farnesyl Pyrophosphate

Farnesyl pyrophosphate (FPP), also known as farnesyl diphosphate (FDP), is an intermediate in both the mevalonate and non-mevalonate pathways used by organisms in the biosynthesis of terpenes, terpenoids, and sterols.

It is used in the synthesis of CoQ (part of the electron transport chain), as well as being the immediate precursor of squalene (via the enzyme squalene synthase), dehydrodolichol diphosphate (a precursor of dolichol, which transports proteins to the ER lumen for N-glycosylation), and geranylgeranyl pyrophosphate (GGPP).

Farnesyl pyrophosphate synthase (a prenyl transferase) catalyzes sequential condensation reactions of dimethylallyl pyrophosphate with 2 units of 3-isopentenyl pyrophosphate to form farnesyl pyrophosphate in the following two steps:

- Dimethylallyl pyrophosphate reacts with 3-isopentenyl pyrophosphate to form geranyl pyrophosphate:
- Geranyl pyrophosphate then reacts with another molecule of 3-isopentenyl pyrophosphate to form farnesyl pyrophosphate



https://en.wikipedia.org/wiki/Farnesyl_pyrophosphate

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Fat

Fat is one of the three main macronutrients: fat, carbohydrate, and protein. Fats, also known as triglycerides or triacylglycerols, are esters of three fatty acid chains and the alcohol glycerol.

The terms "oil", "fat", and "lipid" are often confused. "Oil" normally refers to a fat with short or unsaturated fatty acid chains that is liquid at room temperature, while "fat" may specifically refer to fats that are solids at room temperature. "Lipid" is the general term, as a lipid is not necessarily a triglyceride. Fats, like other lipids, are generally hydrophobic, and are soluble in organic solvents and insoluble in water.

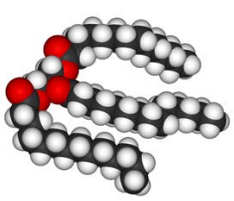
Fat is an important foodstuff for many forms of life, and fats serve both structural and metabolic functions. They are necessary part of the diet of most heterotrophs (including humans). Some fatty acids that are set free by the digestion of fats are called essential because they cannot be synthesized in the body from simpler constituents. There are two essential fatty acids (EFAs) in human nutrition: α-linolenic acid (an ω-3 fatty acid) and linoleic acid (an ω-6 fatty acid). Other lipids needed by the body can be synthesized from these and other fats. Fats and other lipids are broken down in the body by enzymes called lipases produced in the pancreas.

Fats and oils are categorized according to the number and bonding of the carbon atoms in the aliphatic chain. Fats that are saturated fats have no double bonds between the carbons in the chain. Unsaturated fats have one or more double bonded carbons in the chain. The nomenclature is based on the non-acid (non-carbonyl) end of the chain. This end is called the omega end or the n-end. Thus α-linolenic acid is called an ω-3 fatty acid because the 3rd carbon from that end is the first double bonded carbon in the chain counting from that end.

Some oils and fats have multiple double bonds and are therefore called polyunsaturated fats. Unsaturated fats can be further divided into cis fats, which are the most common in nature, and trans fats, which are rare in nature. Unsaturated fats can be altered by reaction with hydrogen effected by a catalyst. This action, called hydrogenation, tends to break all the double bonds and makes a fully saturated fat. To make vegetable shortening, then, liquid *cis*-unsaturated fats such as vegetable oils are hydrogenated to produce saturated fats, which have more desirable physical properties e.g., they melt at a desirable temperature (30–40 °C), and store well, whereas polyunsaturated oils go rancid when they react with oxygen in the air. However, *trans* fats are generated during hydrogenation as contaminants created by an unwanted side reaction on the catalyst during partial hydrogenation. Consumption of such trans fats has shown to increase the risk of coronary heart disease.

Saturated fats can stack themselves in a closely packed arrangement, so they can solidify easily and are typically solid at room temperature. For example, animal fats tallow and lard are high in saturated fatty acid content and are solids. Olive and linseed oils on the other hand are unsaturated and liquid.

Fats serve both as energy sources for the body, and as stores for energy in excess of what the body needs immediately. Each gram of fat when burned or metabolized releases about 9 food calories (37 kJ = 8.8 kcal). Fats are broken down in the healthy body to release their constituents, glycerol and fatty acids. Glycerol itself can be converted to glucose by the liver and so become a source of energy.



https://en.wikipedia.org/wiki/Fat

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Fat Catabolism

Fatty acids are released, between meals, from the fat depots in adipose tissue, where they are stored as triglycerides, as follows:
Lipolysis, the removal of the fatty acid chains from the glycerol to which they are bound in their storage form as triglycerides (or fats), is carried out by lipases.
Once freed from glycerol, the free fatty acids enter the blood, which transports them, attached to plasma albumin, throughout the body.
Long chain free fatty acids enter the metabolizing cells (i.e. most living cells in the body except red blood cells and neurons in the central nervous system) through specific transport proteins, such as the SLC27 family fatty acid transport protein.
Once inside the cell long-chain-fatty-acid—CoA ligase catalyzes the reaction between a fatty acid molecule with ATP (which is broken down to AMP and inorganic pyrophosphate) to give a fatty acyl-adenylate, which then reacts with free coenzyme A to give a fatty acyl-CoA molecule.

In order for the acyl-CoA to enter the mitochondrion the carnitine shuttle is used:
1 Acyl-CoA is transferred to the hydroxyl group of carnitine by carnitine palmitoyltransferase I, located on the cytosolic faces of the outer and inner mitochondrial membranes.
2 Acyl-carnitine is shuttled inside by a carnitine-acylcarnitine translocase, as a carnitine is shuttled outside.
3 Acyl-carnitine is converted back to acyl-CoA by carnitine palmitoyltransferase II, located on the interior face of the inner mitochondrial membrane. The liberated carnitine is shuttled back to the cytosol, as an acyl-CoA is shuttled into the matrix.

β oxidation, in the mitochondrial matrix, then cuts the long carbon chains of the fatty acids (in the form of acyl-CoA molecules) into a series of two-carbon (acetate) units, which, combined with co-enzyme A, form molecules of acetyl CoA, which condense with oxaloacetate to form citrate at the "beginning" of the citric acid cycle. It is convenient to think of this reaction as marking the "starting point" of the cycle, as this is when fuel - acetyl-CoA - is added to the cycle, which will be dissipated as CO_2 and H_2O with the release of a substantial quantity of energy captured in the form of ATP, during the course of each turn of the cycle.

Briefly, the steps in β-oxidation (the initial breakdown of free fatty acids into acetyl-CoA) are as follows:

1 Dehydrogenation by acyl-CoA dehydrogenase, yielding 1 $FADH_2$
2 Hydration by enoyl-CoA hydratase
3 Dehydrogenation by 3-hydroxyacyl-CoA dehydrogenase, yielding 1 $NADH + H^+$
4 Cleavage by thiolase, yielding 1 acetyl-CoA and a fatty acid that has now been shortened by 2 carbons (forming a new, shortened acyl-CoA)
This β-oxidation reaction is repeated until the fatty acid has been completely reduced to acetyl-CoA or, in, the case of fatty acids with odd numbers of carbon atoms, acetyl-CoA and 1 molecule of propionyl-CoA per molecule of fatty acid. Each β-oxidative cut of the acyl-CoA molecule yields 5 ATP molecules. Additional ATPs come from oxidation of the acetyl-CoA molecules in the mitochondrion.

https://en.wikipedia.org/wiki/Fatty_acid_metabolism#Fatty_acid_catabolism

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Chapter 2 - Structure & Function: Lipids

Fatal Familial Insomnia

Fatal familial insomnia (FFI) is an extremely rare autosomal dominant inh
disease of the brain. It is almost always caused by a mutation to the protein
can also develop spontaneously in patients with a non-inherited mutation v
called sporadic fatal insomnia (sFI). FFI has no known cure and involves pr
worsening insomnia, which leads to hallucinations, delirium, and confusion
like that of dementia. The average survival span for patients diagnosed with
the onset of symptoms is 18 months.

The mutated protein, called PrPSc, has been found in just 40 families worl
ing about 100 people. If only one parent has the gene, the offspring have a
inheriting it and developing the disease.

https://en.wikipedia.org/wiki/Fatal_familial_insomnia

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Chapter 2 - Structure & Function: Proteins I

Fatty Acid

In chemistry, particularly in biochemistry, a fatty acid is a carboxylic acid with a long aliphatic chain, which is either saturated or unsaturated. Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from 4 to 28. Fatty acids are usually derived from triglycerides or phospholipids. Fatty acids are important sources of fuel because, when metabolized, they yield large quantities of ATP. Many cell types can use either glucose or fatty acids for this purpose. Long-chain fatty acids cannot cross the blood–brain barrier and so cannot be used as fuel by the cells of the central nervous system, but medium-chain fatty acids octanoic acid and heptanoic acid can be used, in addition to glucose and ketone bodies.

Saturated fatty acids have no double bonds. Thus, saturated fatty acids are saturated with hydrogen (since double bonds reduce the number of hydrogens on each carbon). Because saturated fatty acids have only single bonds, each carbon atom within the chain has 2 hydrogen atoms (except for the ω carbon at the end that has 3 hydrogens).

Unsaturated fatty acids have one or more double bonds between carbon atoms.
The two carbon atoms in the chain that are bound next to either side of the double bond can occur in a *cis* or *trans* configuration.

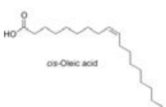
A *cis* configuration means that the two hydrogen atoms adjacent to the double bond stick out on the same side of the chain. The rigidity of the double bond freezes its conformation and, in the case of the *cis* isomer, causes the chain to bend and restricts the conformational freedom of the fatty acid. The more double bonds the chain has in the cis configuration, the less flexibility it has. When a chain has many cis bonds, it becomes quite curved in its most accessible conformations. For example, oleic acid, with one double bond, has a "kink" in it, whereas linoleic acid, with two double bonds, has a more pronounced bend. α-linolenic acid, with three double bonds, favors a hooked shape. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer, or triglycerides in lipid droplets, *cis* bonds limit the ability of fatty acids to be closely packed, and therefore can affect the melting temperature of the membrane or of the fat.

A *trans* configuration, by contrast, means that the adjacent two hydrogen atoms lie on opposite sides of the chain. As a result, they do not cause the chain to bend much, and their shape is similar to straight saturated fatty acids. In most naturally occurring unsaturated fatty acids, each double bond has three n carbon atoms after it, for some n, and all are *cis* bonds. Most fatty acids in the *trans* configuration are not found in nature and are the result of human processing (e.g., hydrogenation).

The differences in geometry between the various types of unsaturated fatty acids, as well as between saturated and unsaturated fatty acids, play an important role in biological processes, and in the construction of biological structures (such as cell membranes).

Fatty acids that are required by the human body but cannot be made in sufficient quantity from other substrates, and therefore must be obtained from food, are called essential fatty acids. There are two series of essential fatty acids: one has a double bond three carbon atoms removed from the methyl end. The other has a double bond six carbon atoms removed from the methyl end. Humans lack the ability to introduce double bonds in fatty acids beyond carbons 9 and 10, as counted from the carboxylic acid side. Two essential fatty acids are linoleic acid (LA) and α-linolenic acid (ALA). They are widely distributed in plant oils. The human body has a limited ability to convert ALA into the longer-chain ω-3 fatty acids — eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can also be obtained from fish.

trans-Oleic acid



cis-Oleic acid

https://en.wikipedia.org/wiki/Fatty_acid

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Fatty Acid Oxidation

In biochemistry and metabolism, β-oxidation is the catabolic process by which fatty acid molecules are broken down in the cytosol in prokaryotes and in the mitochondria in eukaryotes to generate acetyl-CoA, which enters the citric acid cycle, and NADH and $FADH_2$, which are co-enzymes used in the electron transport chain. It is named as such because the β carbon of the fatty acid undergoes oxidation to a carbonyl group. Various mechanisms have evolved to handle the large variety of fatty acids.

From the cytosol, the following processes bring fatty acids into the mitochondrial matrix so that β-oxidation can take place.
1 - Acyl-CoA is transferred to the hydroxyl group of carnitine by carnitine palmitoyltransferase I, located on the cytosolic faces of the outer and inner mitochondrial membranes.
2 - Acyl-carnitine is shuttled inside by a carnitine-acylcarnitine translocase, as a carnitine is shuttled outside.
3 - Acyl-carnitine is converted back to acyl-CoA by carnitine palmitoyltransferase II, located on the interior face of the inner mitochondrial membrane. The liberated carnitine is shuttled back to the cytosol, as an acyl-carnitine is shuttled into the matrix.

Once the fatty acid is inside the mitochondrial matrix, β-oxidation occurs by cleaving two carbons every cycle to form acetyl-CoA. The process consists of 4 steps.
1 - A long-chain fatty acid is dehydrogenated to create a trans double bond between C_2 and C_3. This is catalyzed by acyl CoA dehydrogenase to produce *trans*-Δ2-enoyl CoA. It uses FAD as an electron acceptor and it is reduced to FADH2.
2 - *Trans*-Δ2-enoyl CoA is hydrated at the double bond to produce L-3-hydroxyacyl CoA by enoyl-CoA hydratase.
3 - L-3-hydroxyacyl CoA is dehydrogenated again to create 3-ketoacyl CoA by 3-hydroxyacyl CoA dehydrogenase. This enzyme uses NAD as an electron acceptor.
4 - Thiolysis occurs between C_2 and C_3 (α and β carbons) of 3-ketoacyl CoA. Thiolase enzyme catalyzes the reaction when a new molecule of coenzyme A breaks the bond by nucleophilic attack on C_3. This releases the first two carbon units, as acetyl CoA, and a fatty acyl CoA minus two carbons. The process continues until all of the carbons in the fatty acid are turned into acetyl CoA.

Fatty acids are oxidized by most of the tissues in the body. However, some tissues such as the red blood cells (which do not contain mitochondria), and cells of the central nervous system (because fatty acids cannot cross the blood-brain barrier into the interstitial fluids that bathe these cells) do not use fatty acids for their energy requirements, but instead use carbohydrates.

https://en.wikipedia.org/wiki/Beta_oxidation

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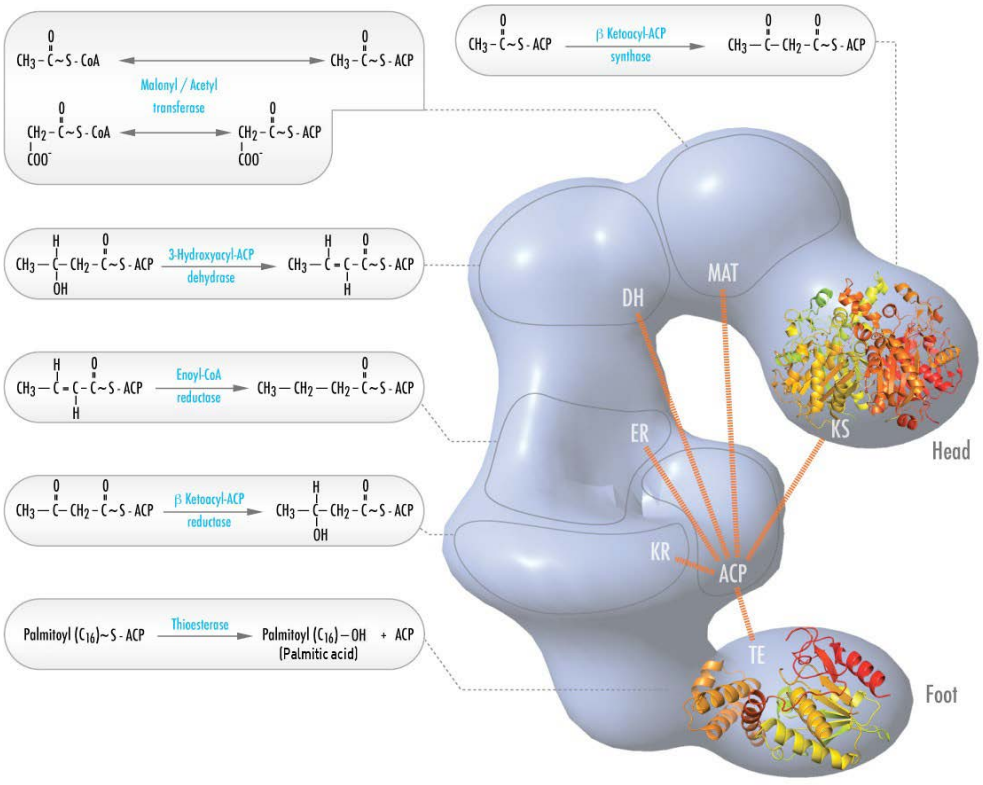
Fatty Acid Synthase

Fatty acid synthase (FAS) is an enzyme that in humans is encoded by the FASN gene. Fatty acid synthase is a multi-enzyme protein that catalyzes fatty acid synthesis. It is not a single enzyme but a whole enzymatic system composed of two identical 272 kDa multifunctional polypeptides, in which substrates are handed from one functional domain to the next.

Its main function is to catalyze the synthesis of palmitate (C16:0, a long-chain saturated fatty acid) from acetyl-CoA and malonyl-CoA, in the presence of NADPH.

Mammalian FAS consists of a homodimer of two identical protein subunits, in which three catalytic domains in the N-terminal section (-ketoacyl synthase (KS), malonyl/acetyltransferase (MAT), and dehydrase (DH)), are separated by a core region of 600 residues from four C-terminal domains (enoyl reductase (ER), -ketoacyl reductase (KR), acyl carrier protein (ACP) and thioesterase (TE)).

The conventional model for organization of FAS (see the 'head-to-tail' model on the right) is largely based on the observations that the bifunctional reagent 1,3-dibromopropanone (DBP) is able to crosslink the active site cysteine thiol of the KS domain in one FAS monomer with the phosphopantetheine prosthetic group of the ACP domain in the other monomer. Complementation analysis of FAS dimers carrying different mutations on each monomer has established that the KS and MAT domains can cooperate with the ACP of either monomer. A reinvestigation of the DBP crosslinking experiments revealed that the KS active site Cys161 thiol could be crosslinked to the ACP 4'-phosphopantetheine thiol of either monomer. In addition, it has been recently reported that a heterodimeric FAS containing only one competent monomer is capable of palmitate synthesis.



https://en.wikipedia.org/wiki/Fatty_acid_synthase

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Fatty Acid Synthesis

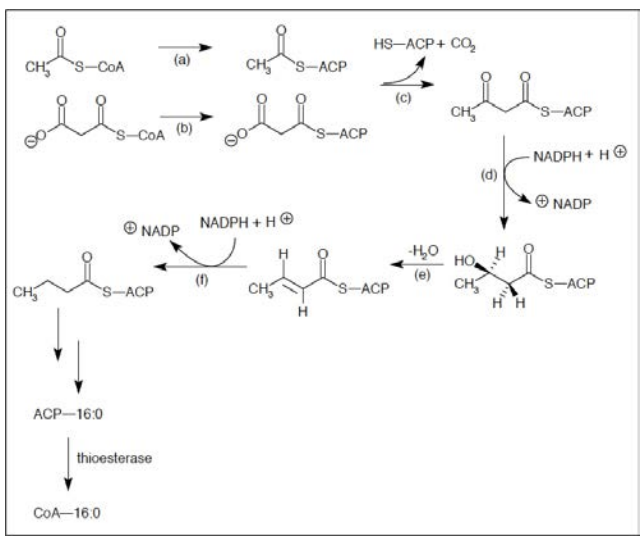
Fatty acid synthesis is the creation of fatty acids from acetyl-CoA, via malonyl-CoA, through the action of enzymes called fatty acid synthases. This process takes place in the cytoplasm of the cell. Most of the acetyl-CoA which is converted into fatty acids is derived from carbohydrates via the glycolytic pathway. The glycolytic pathway also provides the glycerol with which three fatty acids can combine (by means of ester bonds) to form triglycerides (also known as "triacylglycerols", "neutral fats" - to distinguish them from fatty "acids" - or simply as "fat"), the final product of the lipogenic process.

Much like β-oxidation, straight-chain fatty acid synthesis occurs via the six recurring reactions shown below, until the 16-carbon palmitic acid is produced.

The diagrams presented show how fatty acids are synthesized in microorganisms and list the enzymes found in *Escherichia coli*. These reactions are performed by fatty acid synthase II (FASII), which in general contain multiple enzymes that act as one complex. FASII is present in prokaryotes, plants, fungi, and parasites, as well as in mitochondria.

In animals, as well as some fungi such as yeast, these same reactions occur on fatty acid synthase I (FASI), a large dimeric protein that has all of the enzymatic activities required to create a fatty acid. FASI is less efficient than FASII. However, it allows for the formation of more molecules, including "medium-chain" fatty acids via early chain termination.

Once a 16:0 carbon fatty acid has been formed, it can undergo a number of modifications, resulting in desaturation and/or elongation. Elongation, starting with stearate (18:0), is performed mainly in the ER by several membrane-bound enzymes. The enzymatic steps involved in the elongation process are principally the same as those carried out by FAS, but the four principal successive steps of the elongation are performed by individual proteins, which may be physically associated.



https://en.wikipedia.org/wiki/Fatty_acid_synthesis

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Feedback Inhibition

Enzyme inhibitors also occur naturally and are involved in the regulation o
lism. For example, enzymes in a metabolic pathway can be inhibited by dow
products. This type of negative feedback (called feedback inhibition) slows
tion line when products begin to build up and is an important way to maint
stasis in a cell.

https://en.wikipedia.org/wiki/Enzyme_inhibitor

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Feedforward Activation

Feedforward activation occurs when a metabolite activates an enzyme that
reaction further ahead in the metabolic pathway in which the metabolite is
example, fructose 1,6-bisphophatase (F1,6BP) the fourth metabolite in glyc
vates pyruvate kinase, the enzyme catalyzing the tenth reaction of the the p
This has the effect of “pulling” the entire pathway forwards by reducing the
tion of metabolites after F1,6BP.

Related Glossary Terms

Drag related terms here

Fermentation

Fermentation is a metabolic process that converts sugar to acids, gases, or alcohol when oxygen is not available. It occurs in yeast and bacteria, and also in oxygen-starved muscle cells, as in the case of lactic acid fermentation.

Fermentation takes place when the electron transport chain is unusable (often due to lack of a final electron receptor, such as oxygen), and becomes the cell's primary means of ATP (energy) production. It turns NADH and pyruvate produced in glycolysis into NAD^+ and an organic molecule.

Humans have used fermentation to produce food and beverages since the Neolithic age. For example, fermentation is used for preservation in a process that produces lactic acid as found in such sour foods as pickled cucumbers, kimchi and yogurt (see fermentation in food processing), as well as for producing alcoholic beverages such as wine (see fermentation in winemaking) and beer. Fermentation can even occur within the stomachs of animals, such as humans.

https://en.wikipedia.org/wiki/Fermentation

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Ferredoxin

Ferredoxins are iron-sulfur proteins that mediate electron transfer in a range of meta
bolic reactions.

Ferredoxins are small proteins containing iron and sulfur atoms organized as iron-
sulfur clusters. These biological "capacitors" can accept or discharge electrons, with tl
effect of a change in the oxidation state of the iron atoms between +2 and +3. In this
way, ferredoxin acts as an electron transfer agent in biological redox reactions.

https://en.wikipedia.org/wiki/Ferredoxin

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Ferredoxin: $NADP^+$ Oxidoreductase

Ferredoxin-NADP+ reductase, abbreviated FNR, is an enzyme that catalyzes the chemical reaction:

2 reduced Ferredoxin + $NADP^+$ + H^+ <---> 2 oxidized Ferredoxin + NADPH

This enzyme belongs to the family of oxidoreductases, that use iron-sulfur proteins as electron donors and NAD^+ or $NADP^+$ as electron acceptors.

During photosynthesis, electrons are removed from water and transferred (ultimately) to the single electron carrier ferredoxin. Ferredoxin: $NADP^+$ reductase then transfers an electron from each of two ferredoxin molecules to a single molecule of the two electron carrier NADPH. FNR utilizes FAD, which can exist in an oxidized state, single electron reduced semiquinone state, and fully reduced state to mediate this electron transfer.

FNR has an induced-fit mechanism of catalysis. Binding of ferredoxin to the enzyme causes the formation of a hydrogen bond between a glutamate residue (E312) and a serine residue (S96) in the active site. The glutamate residue is highly conserved because it both stabilizes the semiquinone form of FAD and is a proton donor/acceptor in the reaction. The rate limiting step of the electron transfer reaction is the release of the first oxidized ferredoxin molecule after the reduction of FAD with one electron. This step is inhibited by the presence of oxidized ferredoxin and stimulated by the presence of $NADP^+$. The binding of $NADP^+$ to the enzyme lowers the binding affinity of the enzyme for ferredoxin.

This reaction can also operate in reverse to generate reduced ferredoxin, which can then be used in a variety of biosynthetic pathways. Some bacteria and algae use the molecule flavodoxin instead of ferredoxin as the single electron carrier molecule to be reduced or oxidized.

Ferredoxin: $NADP^+$ reductase is the last enzyme in the transfer of electrons during photosynthesis from photosystem I to NADPH. The NADPH is then used as a reducing equivalent in the reactions of the Calvin cycle.

https://en.wikipedia.org/wiki/Ferredoxin—NADP(%2B)_reductase

Related Glossary Terms

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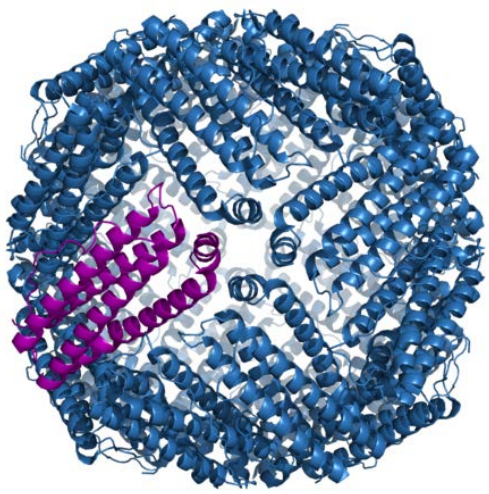
Ferritin

Ferritin is a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion. The protein is produced by almost all living organisms, including algae, bacteria, higher plants, and animals. In humans, it acts as a buffer against iron deficiency and iron overload. Ferritin is found in most tissues as a cytosolic protein, but small amounts are secreted into the serum where it functions as an iron carrier. Plasma ferritin is also an indirect marker of the total amount of iron stored in the body, hence serum ferritin is used as a diagnostic test for iron deficiency anemia.

Ferritin is a globular protein complex consisting of 24 protein subunits and is the primary intracellular iron-storage protein in both prokaryotes and eukaryotes, keeping iron in a soluble and non-toxic form. Ferritin that is not combined with iron is called apoferritin.



https://en.wikipedia.org/wiki/Ferritin

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Fetal Hemoglobin

Fetal hemoglobin (also hemoglobin F, HbF, or $\alpha 2\gamma 2$) is the main oxygen transport protein in the human fetus during the last seven months of development in the uterus and persists in the newborn until roughly 6 months old. Functionally, fetal hemoglobin differs most from adult hemoglobin in that it is able to bind oxygen with greater affinity than the adult form, giving the developing fetus better access to oxygen from the mother's bloodstream.

In newborns, fetal hemoglobin is nearly completely replaced by adult hemoglobin by approximately 6 months postnatally, except in a few thalassemia cases in which there may be a delay in cessation of HbF production until 3–5 years of age. In adults, fetal hemoglobin production can be reactivated pharmacologically, which is useful in the treatment of diseases such as sickle-cell disease.

When fetal hemoglobin production is switched off after birth, normal children begin producing adult hemoglobin (HbA). Children with sickle-cell disease instead begin producing a defective form of hemoglobin called hemoglobin S which aggregates together and forms filaments that cause red blood cells to change their shape from round to sickle-shaped. These defective red blood cells have a greater tendency to stack on top of one another and block blood vessels. These invariably lead to so-called painful vaso-occlusive episodes, which are a hallmark of the disease.

If fetal hemoglobin remains the predominant form of hemoglobin after birth, the number of painful episodes decreases in patients with sickle-cell disease. Hydroxyurea promotes the production of fetal hemoglobin and can thus be used to treat sickle-cell disease. The fetal hemoglobin's reduction in the severity of the disease comes from its ability to inhibit the formation of hemoglobin aggregates within red blood cells which also contain hemoglobin S. Combination therapy with hydroxyurea and recombinant erythropoietin—rather than treatment with hydroxyurea alone—has been shown to further elevate hemoglobin F levels and to promote the development of HbF-containing F-cells.

https://en.wikipedia.org/wiki/Fetal_hemoglobin

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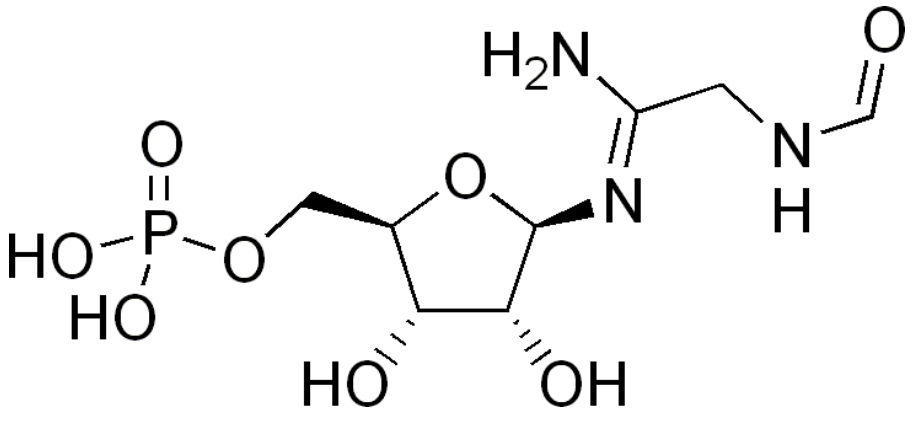
fGAM

5'-PhosphoribosylformylglycinamidineFGAM) is an intermediate in the of purines.



https://en.wikipedia.org/wiki/5%27-Phosphoribosylformylglycinamidine

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Fibrin

Fibrin (also called Factor Ia) is a fibrous, non-globular protein involved in the clotting of blood. It is formed by the action of the protease thrombin on fibrinogen which causes it to polymerize. The polymerized fibrin together with platelets forms a hemostatic plug or clot over a wound site.

When the lining of a blood vessel is broken, platelets are attracted forming a platelet plug. These platelets have thrombin receptors on their surfaces that bind serum thrombin molecules which in turn convert soluble fibrinogen in the serum into fibrin at the wound site. Fibrin forms long strands of tough insoluble protein that are bound to the platelets. Factor XIII completes the cross-linking of fibrin so that it hardens and contracts. The cross-linked fibrin forms a mesh atop the platelet plug that completes the clot.

https://en.wikipedia.org/wiki/Fibrin

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Fibrinogen

Fibrinogen (factor I) is a glycoprotein in vertebrates that helps in the formation of blood clots. The fibrinogen molecule is a soluble, large, and complex 340 kDa plasma glycoprotein, that is converted by thrombin into fibrin during blood clot formation. It has a rod-like shape with dimensions of 9 × 47.5 × 6 nm and it shows a negative net charge at physiological pH (IP at pH 5.2). Fibrinogen is synthesized in the liver by the hepatocytes. The concentration of fibrinogen in the blood plasma is 200–400 mg/dL (normally measured using the Clauss method).

During normal blood coagulation, a coagulation cascade activates the zymogen prothrombin by converting it into the serine protease thrombin. Thrombin then converts the soluble fibrinogen into insoluble fibrin strands. These strands are then cross-linked by factor XIII to form a blood clot. FXIIIa stabilizes fibrin further by incorporation of the fibrinolysis inhibitors α-2-antiplasmin and TAFI (thrombin activatable fibrinolysis inhibitor, procarboxypeptidase B), and binding to several adhesive proteins of various cells. Both the activation of factor XIII by thrombin and plasminogen activator (t-PA) are catalyzed by fibrin. Fibrin specifically binds the activated coagulation factors factor Xa and thrombin and entraps them in the network of fibers, thus functioning as a temporary inhibitor of these enzymes, which stay active and can be released during fibrinolysis. Research from 2011 has shown that fibrin plays a key role in the inflammatory response and development of rheumatoid arthritis.

https://en.wikipedia.org/wiki/Fibrinogen

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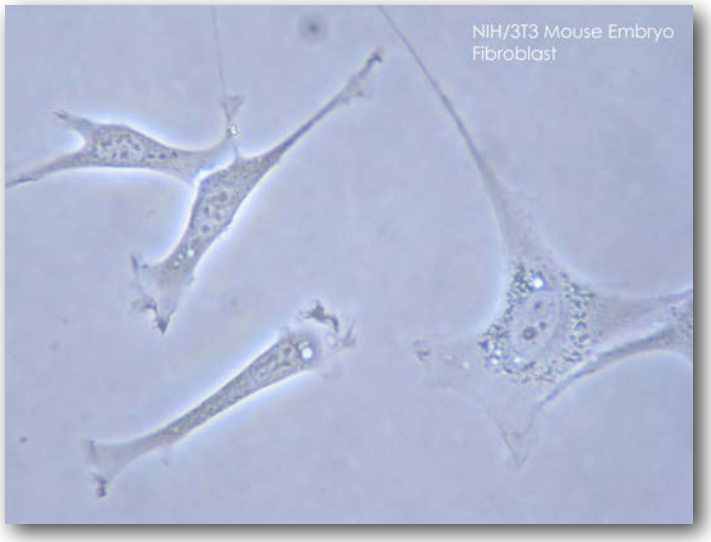
Fibroblasts

A fibroblast is a type of cell that synthesizes the extracellular matrix and collagen, the structural framework (stroma) for animal tissues, and plays a critical role in wound healing. Fibroblasts are the most common cells of connective tissue in animals.

The main function of fibroblasts is to maintain the structural integrity of connective tissues by continuously secreting precursors of the extracellular matrix. Fibroblasts secrete the precursors of all the components of the extracellular matrix, primarily the ground substance and a variety of fibers. The composition of the extracellular matrix determines the physical properties of connective tissues.
Like other cells of connective tissue, fibroblasts are derived from primitive mesenchyme. Thus they express the intermediate filament protein vimentin, a feature used as a marker to distinguish their mesodermal origin. However, this test is not specific as epithelial cells cultured *in vitro* on adherent substratum may also express vimentin after some time.

In certain situations epithelial cells can give rise to fibroblasts, a process called epithelial-mesenchymal transition (EMT). Conversely, fibroblasts in some situations may give rise to epithelia by undergoing a mesenchymal to epithelial transition (MET) and organizing into a condensed, polarized, laterally connected true epithelial sheet. This process is seen in many developmental situations (e.g. nephron and notocord development), as well as in wound healing and tumorigenesis.



https://en.wikipedia.org/wiki/Fibroblast

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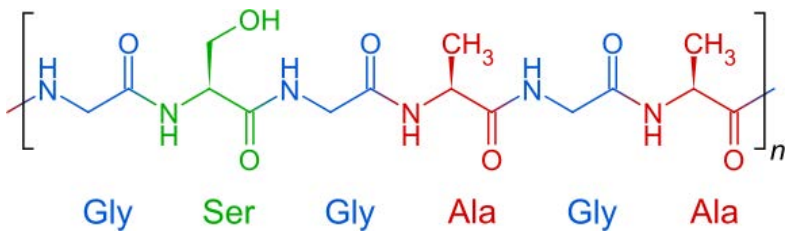
Fibroin

Fibroin is an insoluble protein present in silk created by spiders, the larvae of Bombyx mori, other moth genera such as *Antheraea, Cricula*, *Samia* and *Gonometa*, and numerous other insects. Silk in its raw state consists of two main proteins, sericin and fibroin, with a glue-like layer of sericin coating two singular filaments of fibroin called brins.

The fibroin protein consists of layers of antiparallel β sheets. Its primary structure mainly consists of the recurrent amino acid sequence (Gly-Ser-Gly-Ala-Gly-Ala)n. The high glycine (and, to a lesser extent, alanine) content allows for tight packing of the sheets, which contributes to silk's rigid structure and tensile strength. A combination of stiffness and toughness make it a material with applications in several areas, including biomedicine and textile manufacture.

Fibroin is known to arrange itself in three structures, called silk I, II, and III. Silk I is the natural form of fibroin, as emitted from the *Bombyx mori* silk glands. Silk II refers to the arrangement of fibroin molecules in spun silk, which has greater strength and is often used in various commercial applications. Silk III is a newly discovered structure of fibroin. Silk III is formed principally in solutions of fibroin at an interface (i.e. air-water interface, water-oil interface, etc.).

Below, the repeating sequence structure of fibroin is shown.



https://en.wikipedia.org/wiki/Fibroin

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Fibronectin

Fibronectin is a high-molecular weight (~440kDa) glycoprotein of the extracellular matrix that binds to membrane-spanning receptor proteins called integrins. Similar to integrins, fibronectin binds extracellular matrix components such as collagen, fibrin, and heparan sulfate proteoglycans (e.g. syndecans).

Fibronectin exists as a protein dimer, consisting of two nearly identical monomers linked by a pair of disulfide bonds. The fibronectin protein is produced from a single gene, but alternative splicing of its pre-mRNA leads to the creation of several isoforms.

Fibronectin plays a major role in cell adhesion, growth, migration, and differentiation, and it is important for processes such as wound healing and embryonic development. Altered fibronectin expression, degradation, and organization has been associated with a number of pathologies, including cancer and fibrosis.

https://en.wikipedia.org/wiki/Fibronectin

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Fibrous Protein

Scleroproteins or fibrous proteins constitute one of the three main types of proteins (alongside globular and membrane proteins). There are many scleroprotein superfamilies including keratin, collagen, elastin, and fibroin. The roles of such proteins include protection and support, forming connective tissue, tendons, bone matrices, and muscle fiber.

A scleroprotein forms long protein filaments, which are shaped like rods or wires. Scleroproteins are structural proteins or storage proteins that are typically inert and water-insoluble. A scleroprotein occurs as an aggregate due to hydrophobic side chains that protrude from the molecule.

A scleroprotein's peptide sequence often has limited residues with repeats. These can form unusual secondary structures, such as a collagen helix. The structures often feature cross-links between chains (e.g., cys-cys disulfide bonds between keratin chains).

Scleroproteins tend not to denature as easily as globular proteins.

https://en.wikipedia.org/wiki/Scleroprotein

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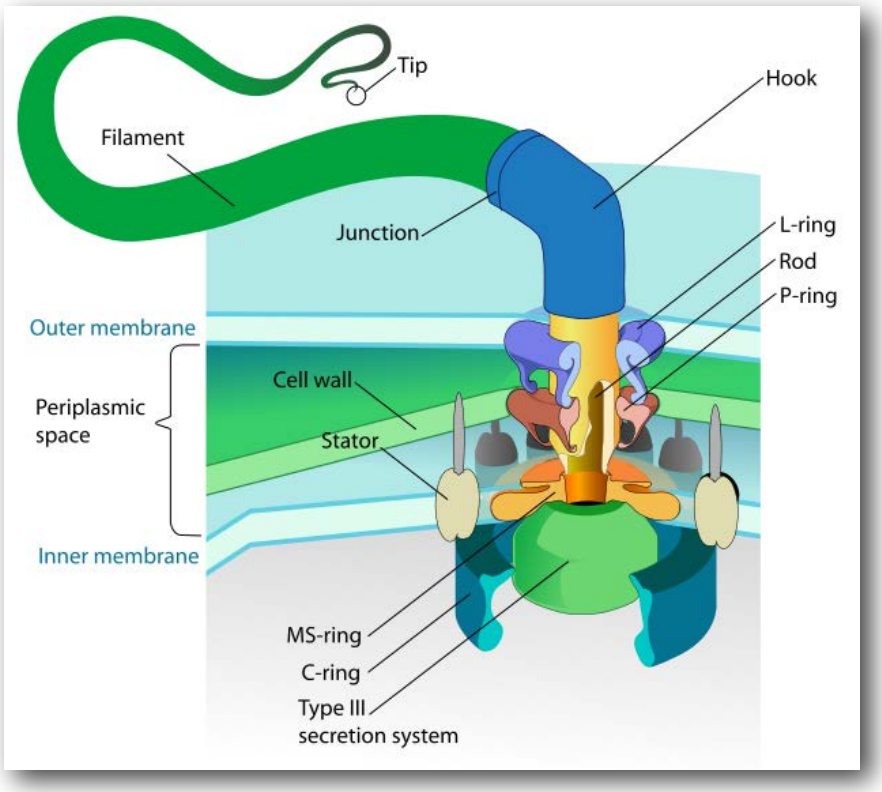
Flagella

A flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells. The primary role of the flagellum is locomotion but it also often has function as a sensory organelle, being sensitive to chemicals and temperatures outside the cell. Flagella are organelles defined by function rather than structure. There are large differences between different types of flagella. The prokaryotic and eukaryotic flagella differ greatly in protein composition, structure, and mechanism of propulsion. However, both can be used for swimming.



https://en.wikipedia.org/wiki/Flagellum

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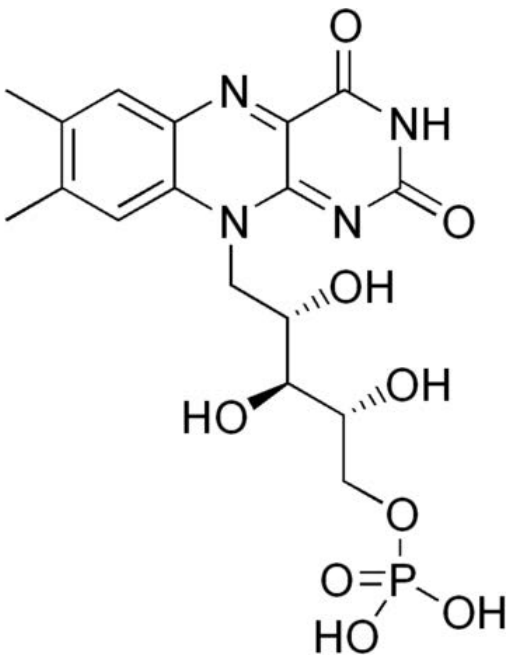
Flavin Mononucleotide

Flavin mononucleotide (FMN), or riboflavin-5′-phosphate, is a biomolecule produced from riboflavin (vitamin B_2) by the enzyme riboflavin kinase and functions as prosthetic group of various oxidoreductases including NADH dehydrogenase as well as cofactor in biological blue-light photo receptors. During the catalytic cycle, a reversible interconversion of the oxidized (FMN), semiquinone (FMNH•) and reduced ($FMNH_2$) forms occurs in the various oxidoreductases. FMN is a stronger oxidizing agent than NAD and is particularly useful because it can take part in both one- and two-electron transfers.



https://en.wikipedia.org/wiki/Flavin_mononucleotide

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Flavonoids

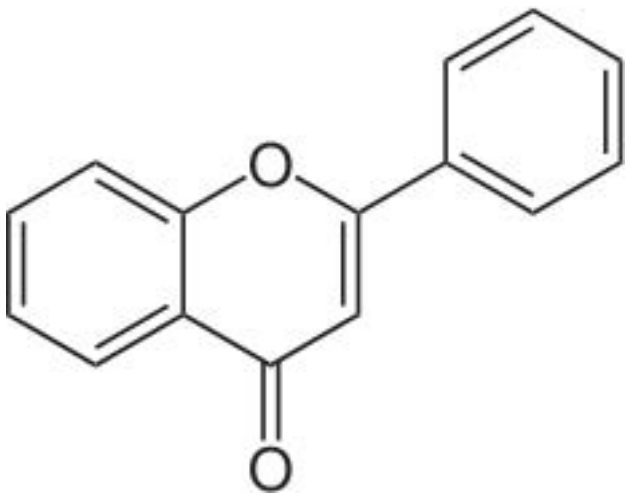
Flavonoids (or bioflavonoids) are a class of plant and fungus secondary metabolites. Chemically, they have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and heterocyclic ring (C). This carbon structure can be abbreviated C_6-C_3-C_6. According to the IUPAC nomenclature, they can be classified into:

• flavonoids or bioflavonoids (flavon backbone shown below)

• isoflavonoids, derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure

• neoflavonoids, derived from 4-phenylcoumarine (4-phenyl-1,2-benzopyrone) structure

The three flavonoid classes above are all ketone-containing compounds, and as such, are anthoxanthins (flavones and flavonols). This class was the first to be termed bioflavonoids.



https://en.wikipedia.org/wiki/Flavonoid

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Flavoproteins

Flavoproteins are proteins that contain a nucleic acid derivative of riboflavin: the flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN).
Flavoproteins are involved in a wide array of biological processes, including, but by no means limited to, bioluminescence, removal of radicals contributing to oxidative stress, photosynthesis, DNA repair, and apoptosis. The spectroscopic properties of the flavin cofactor make it a natural reporter for changes occurring within the active site. This makes flavoproteins one of the most-studied enzyme families.

The flavoprotein family contains a diverse range of enzymes, including:
• Epidermin biosynthesis protein, EpiD, which has been shown to be a flavoprotein that binds FMN. This enzyme catalyzes the removal of two reducing equivalents from the cysteine residue of the C-terminal meso-lanthionine of epidermin to form a --C==C-- double bond.
• The B chain of dipicolinate synthase, an enzyme which catalyzes the formation of dipicolinic acid from dihydroxydipicolinic acid.
• Phenylacrylic acid decarboxylase EC 4.1.1.-, and enzyme which confers resistance to cinnamic acid in yeast

https://en.wikipedia.org/wiki/Flavoprotein

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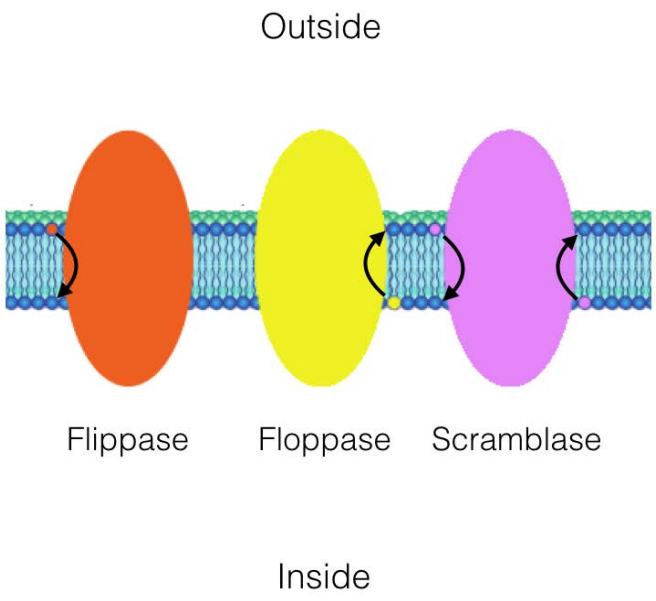
Flippase

Flippases are transmembrane lipid transporter proteins located in the membrane responsible for aiding the movement of phospholipid molecules between the two leaflets that compose a cell's membrane (transverse diffusion, also known as a "flip-flop" transition). The possibility of active maintenance of an asymmetric distribution of molecules in the phospholipid bilayer was predicted in the early 1970s by Mark Bretscher. Although phospholipids diffuse rapidly in the plane of the membrane, their polar head groups cannot pass easily through the hydrophobic center of the bilayer, limiting their diffusion in this dimension. Some flippases are energy-independent and bidirectional, causing reversible equilibration of phospholipid between the two sides of the membrane, whereas others are energy-dependent and unidirectional, using energy from ATP hydrolysis to pump the phospholipid in a preferred direction. Flippases are described as transporters that move lipids from the exoplasmic to the cytosolic face, while floppases transport in the reverse direction.



https://en.wikipedia.org/wiki/Flippase

Related Glossary Terms

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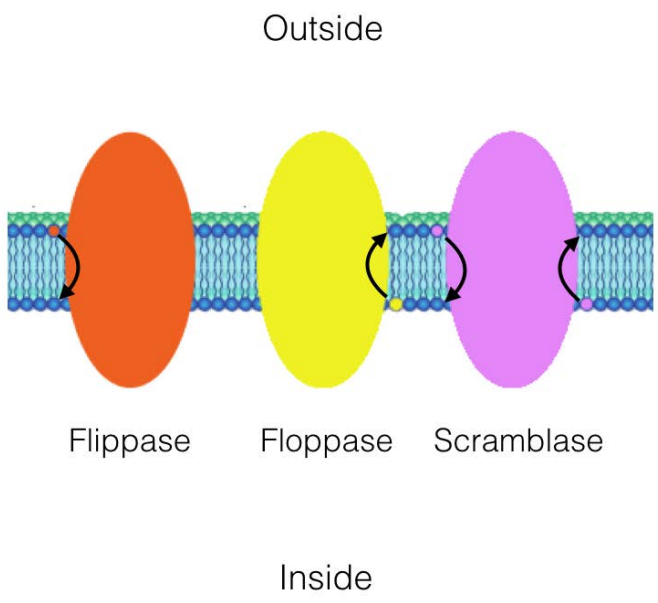
Floppase

Flippases are transmembrane lipid transporter proteins located in the membrane responsible for aiding the movement of phospholipid molecules between the two leaflets that compose a cell's membrane (transverse diffusion, also known as a "flip-flop" transition). The possibility of active maintenance of an asymmetric distribution of molecules in the phospholipid bilayer was predicted in the early 1970s by Mark Bretscher. Although phospholipids diffuse rapidly in the plane of the membrane, their polar head groups cannot pass easily through the hydrophobic center of the bilayer, limiting their diffusion in this dimension. Some flippases are energy-independent and bidirectional, causing reversible equilibration of phospholipid between the two sides of the membrane, whereas others are energy-dependent and unidirectional, using energy from ATP hydrolysis to pump the phospholipid in a preferred direction. Flippases are described as transporters that move lipids from the exoplasmic to the cytosolic face, while floppases transport in the reverse direction.



https://en.wikipedia.org/wiki/Flippase

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Chapter 9 - Point by Point: Membranes

Fluorescence

Fluorescence is the emission of light by a substance that has absorbed light
electromagnetic radiation. It is a form of luminescence. In most cases, the e
has a longer wavelength, and therefore lower energy, than the absorbed rad
most striking example of fluorescence occurs when the absorbed radiation
traviolet region of the spectrum, and thus invisible to the human eye, while
light is in the visible region, which gives the fluorescent substance a distinc
can only be seen when exposed to UV light.

https://en.wikipedia.org/wiki/Fluorescence

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Fluorescence Recovery After Photobleaching

Fluorescence recovery after photobleaching (FRAP) denotes an optical tech
ble of quantifying the two dimensional lateral diffusion of a molecularly thi
taining fluorescently labeled probes, or to examine single cells. This techni
useful in biological studies of cell membrane diffusion and protein binding.
tion, surface deposition of a fluorescing phospholipid bilayer (or monolaye
characterization of hydrophilic (or hydrophobic) surfaces in terms of surfa
and free energy.

https://en.wikipedia.org/wiki/Fluorescence_recovery_after_photobleachi

Related Glossary Terms

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Fluorescence Resonance Energy Transfer

Fluorescence resonance energy transfer (FRET) is a mechanism describing
transfer between two light-sensitive molecules (chromophores). A donor ch
phore, initially in its electronic excited state, may transfer energy to an acce
mophore through nonradiative dipole–dipole coupling. The efficiency of th
transfer is inversely proportional to the sixth power of the distance betwee
acceptor, making FRET extremely sensitive to small changes in distance.

Measurements of FRET efficiency can be used to determine if two fluoroph
within a certain distance of each other. Such measurements are used as a re
in fields including biology and chemistry.

https://en.wikipedia.org/wiki/Förster_resonance_energy_transfer

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Related Glossary Terms

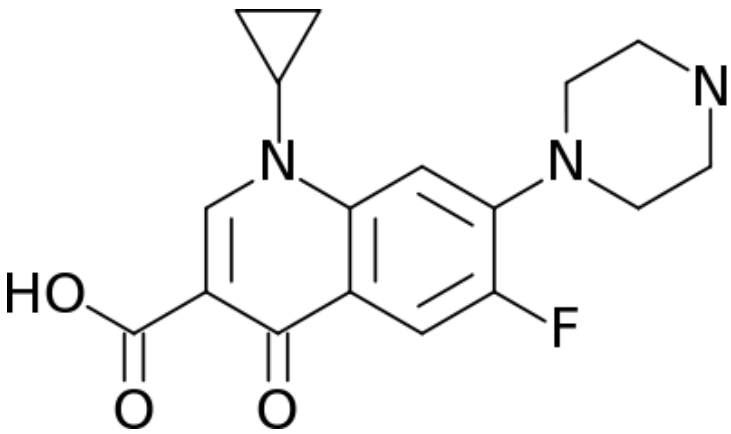
Drag related terms here

Fluoroquinolone

The quinolones are a family of synthetic broad-spectrum antibiotic drugs. Quinolones, and derivatives, have also been isolated from natural sources (such as plants, animals and bacteria) and can act as natural antimicrobials and/or signaling molecules.

Quinolones exert their antibacterial effect by preventing bacterial DNA from unwinding and duplicating. The majority of quinolones in clinical use are fluoroquinolones, which have a fluorine atom attached to the central ring system, typically at the 6-position or C-7 position. Most of them are named with the -oxacin suffix.

Shown below is ciprofloxacin, a fluoroquinolone.



https://en.wikipedia.org/wiki/Quinolone

Related Glossary Terms

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Foam Cells

Foam cells are fat-laden macrophages seen in atherosclerosis. They are an indication of plaque build-up, or atherosclerosis, which is commonly associated with increased risk of heart attack and stroke.

Foam cells are formed when the body sends macrophages to the location of a fatty deposit on the blood vessel walls. The macrophage surrounds the fatty material in an attempt to destroy it. The cell becomes filled with lipids (fats). The lipids surrounded by the macrophage give it a “foamy” appearance.

In chronic hyperlipidemia, lipoproteins aggregate within the intima of blood vessels and become oxidized by the action of oxygen free radicals generated either by macrophages or endothelial cells. The macrophages engulf oxidized low-density lipoproteins (LDLs) by endocytosis via scavenger receptors, which are distinct from LDL receptors. The oxidized LDL accumulates in the macrophages and other phagocytes, which are then known as foam cells. Foam cells form the fatty streaks of the plaques of atheroma in the tunica intima of arteries.

Low-density lipoprotein (LDL) cholesterol is contained by a foam cell. LDL is also known as “bad” cholesterol. It becomes a marker for atherosclerosis. Foam cells are the body’s way of trying to get rid of bad cholesterol from the blood vessels. Foam cells do not give off any explicit signs or symptoms, but they are part of the origin of atherosclerosis. Foam cells are very small in size and can only be truly detected by examining a fatty plaque under a microscope after it is removed from the body. HDL cholesterol is good cholesterol and it removes harmful bad cholesterol from where it does not belong.

Foam cells are not dangerous as such, but can become a problem when they accumulate at particular foci thus creating a necrotic center of atherosclerosis. If the fibrous cap that prevents the necrotic center from spilling into the lumen of a vessel ruptures, a thrombus can form which can lead to emboli occluding smaller vessels. The occlusion of small vessels results in ischemia, and contributes to stroke and myocardial infarction, two of the leading causes of cardiovascular-related death.

https://en.wikipedia.org/wiki/Foam_cell

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Focal Adhesion Structures

In cell biology, focal adhesions are large macromolecular assemblies through which mechanical force and regulatory signals are transmitted between the extracellular matrix (ECM) and an interacting cell. More precisely, focal adhesions are the sub-cellular structures that mediate the regulatory effects (i.e., signaling events) of a cell in response to ECM adhesion.

Focal adhesions are integrin-containing, multi-protein structures that form mechanical links between intracellular actin bundles and the extracellular substrate in many cell types. Focal adhesions are large, dynamic protein complexes through which the cytoskeleton of a cell connects to the ECM. They are limited to clearly defined ranges of the cell, at which the plasma membrane closes to within 15 nm of the ECM substrate. Focal adhesions are in a state of constant flux. Proteins associate and disassociate with it continually as signals are transmitted to other parts of the cell, relating to anything from cell motility to cell cycle. Focal adhesions can contain over 100 different proteins, which suggests a considerable functional diversity. More than anchoring the cell, they function as signal carriers (sensors), which inform the cell about the condition of the ECM and thus affect their behavior. In sessile cells, focal adhesions are quite stable under normal conditions, while in moving cells their stability is diminished: this is because in motile cells, focal adhesions are being constantly assembled and disassembled as the cell establishes new contacts at the leading edge, and breaks old contacts at the trailing edge of the cell. One example of their important role is in the immune system, in which white blood cells migrate along the connective endothelium following cellular signals to damaged biological tissue.

https://en.wikipedia.org/wiki/Focal_adhesion

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Focal Adhesions

In cell biology, focal adhesions are large macromolecular assemblies through which mechanical force and regulatory signals are transmitted between the extracellular matrix (ECM) and an interacting cell. More precisely, focal adhesions are the sub-cellular structures that mediate the regulatory effects (i.e., signaling events) of a cell in response to ECM adhesion.

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https://en.wikipedia.org/wiki/Focal_adhesion

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Folate

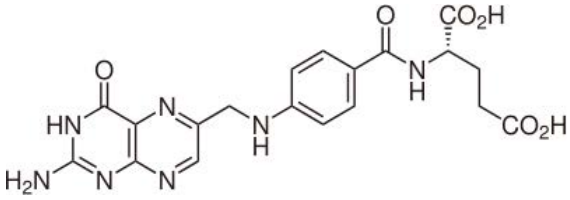
Folic acid (conjugate base folate) is a B vitamin. It is also referred to as vitamin M, vitamin B_9, vitamin B_c (or folacin), pteroyl-L-glutamic acid, and pteroyl-L-glutamate.

Food supplement manufacturers often use the term folate for something different from "pure" folic acid. In chemistry, folate refers to the deprotonated ion, and folic acid to the neutral molecule—which both coexist in water.

Folate indicates a collection of "folates" that is not chemically well-characterized, including other members of the family of pteroylglutamates, or mixtures of them, having various levels of reduction of the pteridine ring, one-carbon substitutions and different numbers of glutamate residues.
Folic acid is synthetically produced, and used in fortified foods and supplements on the theory that it is converted into folate. However, folic acid is a synthetic oxidized form, not significantly found in fresh natural foods. To be used it must be converted to tetrahydrofolate (tetrahydrofolic acid) by dihydrofolate reductase (DHFR). Increasing evidence suggests that this process may be slow in humans.

A lack of dietary folates can lead to folate deficiency. A complete lack of dietary folate takes months before deficiency develops as normal individuals have about 500–20,000 micrograms (µg) of folate in body stores. This deficiency can result in many health problems, the most notable one being neural tube defects in developing embryos—a relatively rare birth defect affecting 300,000 (0.2%) births globally each year and 3,000 pregnancies in the United States each year.

The structure of folic acid is shown below.



https://en.wikipedia.org/wiki/Folic_acid

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Folded Protein

Protein folding is the physical process by which a protein chain acquires its native
dimensional structure, a conformation that is usually biologically functional, in ar
peditious and reproducible manner. It is the physical process by which a polypept
folds into its characteristic and functional three-dimensional structure from rando
coil.

The correct three-dimensional structure is essential to function, although some pa
of functional proteins may remain unfolded, so that protein dynamics is importan
Failure to fold into native structure generally produces inactive proteins, but in so
instances misfolded proteins have modified or toxic functionality. Several neurode
erative and other diseases are believed to result from the accumulation of amyloid
brils formed by misfolded proteins. Many allergies are caused by incorrect folding
some proteins, because the immune system does not produce antibodies for certai
protein structures.

https://en.wikipedia.org/wiki/Protein_folding

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Folding

Protein folding is the physical process by which a protein chain acquires its native 3-dimensional structure, a conformation that is usually biologically functional, in an expeditious and reproducible manner. It is the physical process by which a polypeptide folds into its characteristic and functional three-dimensional structure from random coil.

The correct three-dimensional structure is essential to function, although some parts of functional proteins may remain unfolded, so that protein dynamics is important. Failure to fold into native structure generally produces inactive proteins, but in some instances misfolded proteins have modified or toxic functionality. Several neurodegenerative and other diseases are believed to result from the accumulation of amyloid fibrils formed by misfolded proteins. Many allergies are caused by incorrect folding of some proteins, because the immune system does not produce antibodies for certain protein structures.

https://en.wikipedia.org/wiki/Protein_folding

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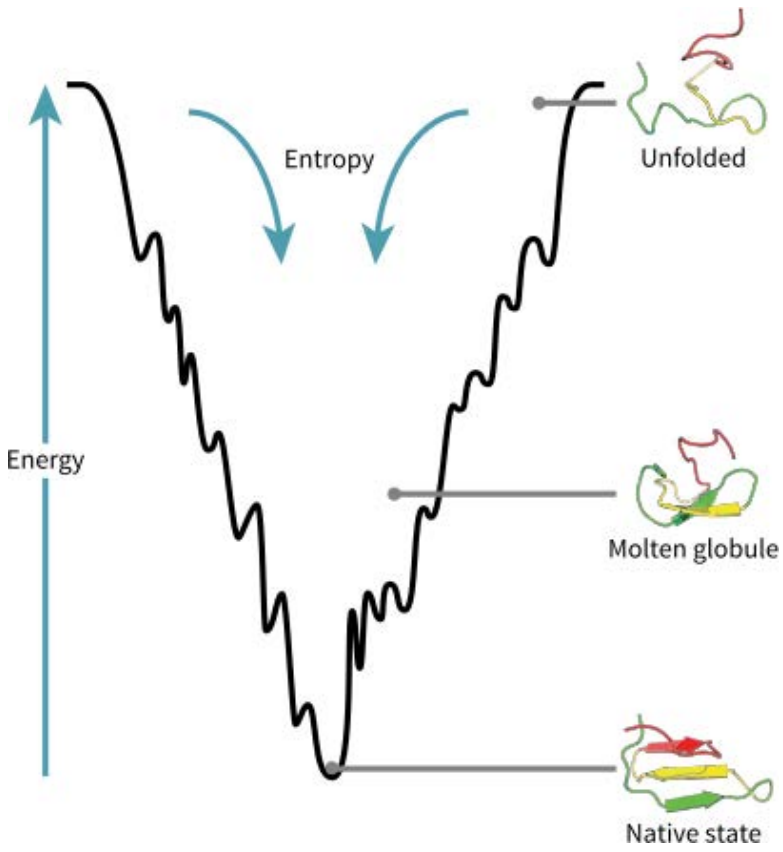
Folding funnel

The folding funnel hypothesis is a specific version of the energy landscape theory of protein folding, which assumes that a protein's native state corresponds to its free energy minimum under the solution conditions usually encountered in cells. Although energy landscapes may be "rough", with many non-native local minima in which partially folded proteins can become trapped, the folding funnel hypothesis assumes that the native state is a deep free energy minimum with steep walls, corresponding to a single well-defined tertiary structure.



https://en.wikipedia.org/wiki/Folding_funnel

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Chapter 2 - Structure & Function: Proteins I

Chapter 9 - Point by Point: Structure and Function

Follicle-stimulating Hormone

Follicle-stimulating hormone (FSH) is a gonadotropin, a glycoprotein polyp
mone. FSH is synthesized and secreted by the gonadotropic cells of the ante
tary gland, and regulates the development, growth, pubertal maturation, ar
tive processes of the body. FSH and luteinizing hormone (LH) work togethe
productive system.

https://en.wikipedia.org/wiki/Follicle-stimulating_hormone

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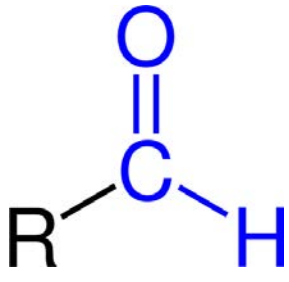
Formyl

A formyl functional group consists of a carbonyl bonded to a hydrogen. Wh
to an R group, a formyl group is called an aldehyde.



https://en.wikipedia.org/wiki/Formylation

Related Glossary Terms

Drag related terms here

Formylated

The addition of a formyl functional group is termed formylation. A formyl functi
group consists of a carbonyl bonded to a hydrogen. When attached to an R group
formyl group is called an aldehyde.

Formylation has been identified in several critical biological processes. Two form
tion reactions occur in the *de novo* biosynthesis of purines. These reactions are c
lyzed by the enzymes glycinamide ribonucleotide (GAR) transformylase and 5-
aminoimidazole-4-carboxyamide ribotide (AICAR) transformylase.

The methionine initiator tRNA is also formylated.

More recently, formylation has been discovered to be a histone modification, wh
may modulate gene expression.

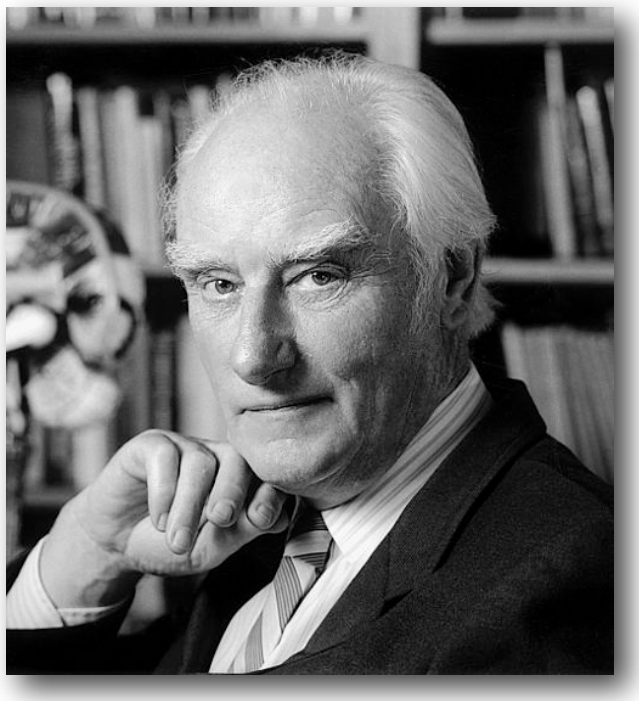
https://en.wikipedia.org/wiki/Formylation

Related Glossary Terms

Drag related terms here

Francis Crick

Francis Harry Compton Crick (8 June 1916 – 28 July 2004) was a British molecular biologist, biophysicist, and neuroscientist, most noted for being a co-discoverer of the structure of the DNA molecule in 1953 with James Watson. Together with Watson and Maurice Wilkins, he was jointly awarded the 1962 Nobel Prize in Physiology or Medicine "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material".



https://en.wikipedia.org/wiki/Francis_Crick

Related Glossary Terms

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FRAP

Fluorescence recovery after photobleaching (FRAP) denotes an optical tech
ble of quantifying the two dimensional lateral diffusion of a molecularly thi
taining fluorescently labeled probes, or to examine single cells. This techni
useful in biological studies of cell membrane diffusion and protein binding.
tion, surface deposition of a fluorescing phospholipid bilayer (or monolaye
characterization of hydrophilic (or hydrophobic) surfaces in terms of surfa
and free energy.

https://en.wikipedia.org/wiki/Fluorescence_recovery_after_photobleachi

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Chapter 3 - Membranes: Basic Concepts

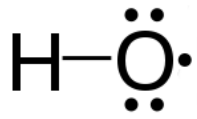
Free Radical

A radical (more precisely, a free radical) is an atom, molecule, or ion that has unpaired valence electrons. With some exceptions, these unpaired electrons make free radicals highly chemically reactive towards other substances, or even towards themselves: their molecules will often spontaneously dimerize or polymerize if they come in contact with each other. Most radicals are reasonably stable only at very low concentrations in inert media or in a vacuum.

A notable example of a free radical is the hydroxyl radical (shown below), a molecule that has one unpaired electron on the oxygen atom. Two other examples are triplet oxygen and triplet carbene ($:CH_2$) which have two unpaired electrons. In contrast, the hydroxyl anion (HO^-) is not a radical, since the unpaired electron is resolved by the addition of an electron. Singlet oxygen and singlet carbene are not radicals as the two electrons are paired.

Free radicals may be created in a number of ways, including synthesis with very dilute or rarefied reagents, reactions at very low temperatures, or breakup of larger molecules. The latter can be affected by any process that puts enough energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions. Indeed, radicals are intermediate stages in many chemical reactions.

Free radicals play an important role in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes. In living organisms, the free radicals superoxide and nitric oxide and their reaction products regulate many processes, such as control of vascular tone and thus blood pressure. They also play a key role in the intermediary metabolism of various biological compounds. Such radicals can even be messengers in a process dubbed redox signaling. A radical may be trapped within a solvent cage or be otherwise bound.



https://en.wikipedia.org/wiki/Radical_(chemistry)

Related Glossary Terms

Fructokinase

Fructokinase also known as D-fructokinase or D-fructose (D-mannose) kinase, zyme of the liver, intestine, and kidney cortex. Fructokinase is in a family of enz called transferases, meaning that this enzyme transfers functional groups. It is considered a phosphotransferase (or, frequently, a kinase) since it specifically t a phosphate group. Fructokinase specifically catalyzes the transfer of a phospha group from ATP (the substrate) to fructose as the initial step in its utilization. T main role of fructokinase is in carbohydrate metabolism, more specifically, sucr and fructose metabolism. The reaction equation is as follows:

ATP + D-fructose = ADP + D-fructose 1-phosphate.

This is notable because in most tissues this reaction is catalyzed by hexokinase, ing instead fructose 6-phosphate.

https://en.wikipedia.org/wiki/Fructokinase

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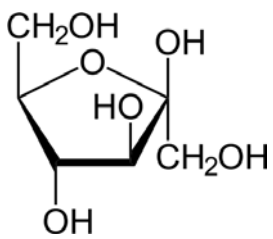
Fructose

Fructose, or fruit sugar, is a simple ketonic monosaccharide found in many plants, where it is often bonded to glucose to form the disaccharide sucrose. It is one of the three dietary monosaccharides, along with glucose and galactose, that are absorbed directly into the bloodstream during digestion. Fructose was discovered by French chemist Augustin-Pierre Dubrunfaut in 1847. The name "fructose" was coined in 1857 by the English chemist William Miller. Pure, dry fructose is a very sweet, white, odorless, crystalline solid and is the most water-soluble of all the sugars. Fructose is found in honey, tree and vine fruits, flowers, berries, and most root vegetables.

Fructose exists in foods either as a monosaccharide (free fructose) or as a unit of a disaccharide (sucrose). Free fructose is absorbed directly by the intestine. When fructose is consumed in the form of sucrose, it is digested (broken down) and then absorbed as free fructose. As sucrose comes into contact with the membrane of the small intestine, the enzyme sucrase catalyzes the cleavage of sucrose to yield one glucose unit and one fructose unit, which are then each absorbed. After absorption, it enters the hepatic portal vein and is directed toward the liver.

There are speculations that excessive fructose consumption is a cause of insulin resistance, obesity, elevated LDL cholesterol and triglycerides, leading to metabolic syndrome, type 2 diabetes, and cardiovascular disease. However, the UK's Scientific Advisory Committee on Nutrition in 2015 disputed the claims, demonstrating that "there is insufficient evidence to demonstrate that fructose intake... leads to adverse health outcomes independent of any effects related to its presence as a component of total and free sugars.



https://en.wikipedia.org/wiki/Fructose

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Fructose 1,6-bisphosphatase

Fructose-1,6-bisphosphatase (F1,6BPase) is an enzyme that converts fructo
bisphosphate to fructose 6-phosphate in gluconeogenesis and the Calvin cy
are both anabolic pathways. Fructose bisphosphatase catalyzes the reverse
tion which is catalyzed by phosphofructokinase in glycolysis. These enzyme
lyze the reaction in one direction each, and are regulated by metabolites su
tose 2,6-bisphosphate so that high activity of one of the two enzymes is acc
by low activity of the other. More specifically, fructose 2,6-bisphosphate all
inhibits fructose 1,6-bisphosphatase, but activates phosphofructokinase-I. I
1,6-bisphosphatase is involved in many different metabolic pathways and fo
most organisms. FBPase requires metal ions for catalysis (Mg^{++} and Mn^{++} b
ferred) and the enzyme is potently inhibited by Li^{+}.

https://en.wikipedia.org/wiki/Fructose_1,6-bisphosphatase

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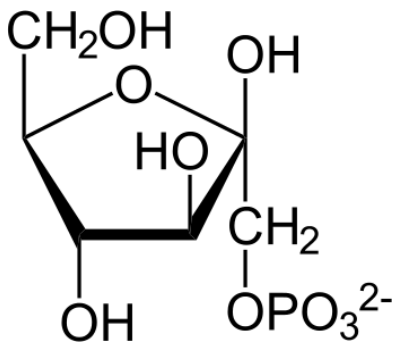
Fructose-1-phosphate

Fructose-1-phosphate is a derivative of fructose. It is generated mainly by hepatic fructokinase but is also generated in smaller amounts in the small intestinal mucosa and proximal epithelium of the renal tubule. It is an important intermediate of glucose metabolism. Because fructokinase has a high V_{max} fructose entering cells is quickly phosphorylated to fructose 1-phosphate. In this form it is usually accumulated in the liver until it undergoes further conversion by aldolase B (the rate limiting enzyme of fructose metabolism).

Aldolase B converts it into glyceraldehyde and dihydroxyacetone phosphate (DHAP). Glyceraldehyde is then phosphorylated by triose kinase to glyceraldehyde 3-phosphate.



https://en.wikipedia.org/wiki/Fructose_1-phosphate

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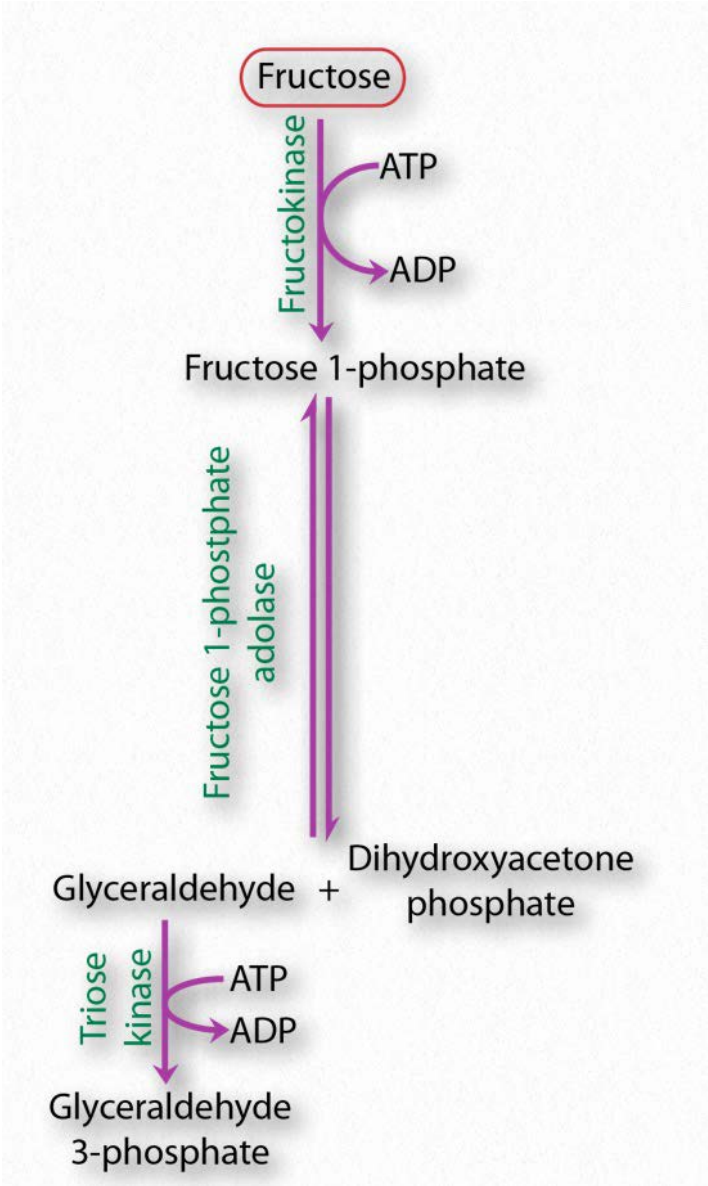
Fructose-1-phosphate Aldolase

Fructose-1-phosphate aldolase catalyzes the reaction below. It is notable in allowing metabolism of fructose to bypass PFK and Hexokinase regulation of glycolysis.



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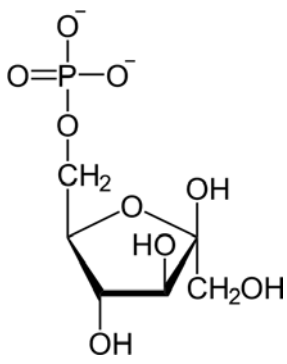
Fructose-6-phosphate

Fructose 6-phosphate (F6P) is fructose sugar phosphorylated on carbon 6 (i.e., is a fructosephosphate). The β-D-form of this compound is very common in cells. The vast majority of glucose and fructose entering a cell will become converted to this at some point.

Fructose 6-phosphate lies within the glycolysis metabolic pathway and is produced by isomerization of glucose 6-phosphate. It is in turn further phosphorylated to fructose-1,6-bisphosphate.

F6P can be produced from mannose-6-phosphate action of mannose isomerase.



https://en.wikipedia.org/wiki/Fructose_6-phosphate

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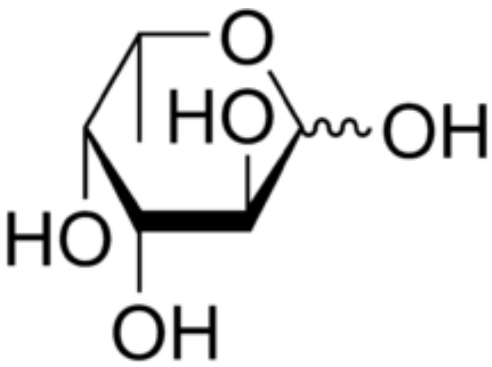
Fucose

Fucose is a hexose deoxy sugar with the chemical formula $C_6H_{12}O_5$. It is found on N-linked glycans on the mammalian, insect and plant cell surface, and is the fundamental sub-unit of the fucoidan polysaccharide. $\alpha(1\rightarrow3)$ linked core fucose is a suspected carbohydrate antigen for IgE-mediated allergy.

Two structural features distinguish fucose from other six-carbon sugars present in mammals: the lack of a hydroxyl group on the carbon at the 6-position (C-6) (thereby making it a deoxy sugar) and the L-configuration. It is equivalent to 6-deoxy-L-galactose.

In the fucose-containing glycan structures, fucosylated glycans, fucose can exist as a terminal modification or serve as an attachment point for adding other sugars. In human N-linked glycans, fucose is most commonly linked α-1,6 to the reducing terminal β-N-acetylglucosamine. However, fucose at the non-reducing termini linked α-1,2 to galactose forms the H antigen, the substructure of the A and B blood group antigens.

Fucose is released from fucose-containing polymers by an enzyme called α-fucosidase. L-Fucose is claimed to have application in cosmetics, pharmaceuticals, and dietary supplements. However, these claims are often not supported by peer-reviewed scientific studies.



https://en.wikipedia.org/wiki/Fucose

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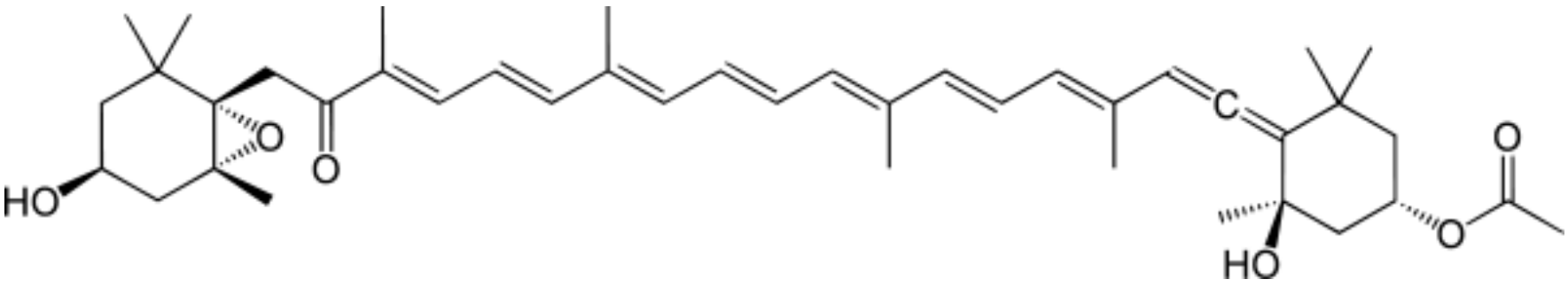
Fucoxanthin

Fucoxanthin is a xanthophyll, with formula $C_{42}H_{58}O_6$. It is found as an acce
ment in the chloroplasts of brown algae and most other heterokonts, giving
brown or olive-green color. Fucoxanthin absorbs light primarily in the blue
yellow-green part of the visible spectrum, peaking at around 510-525 nm by
timates and absorbing significantly in the range of 450 to 540 nm.



https://en.wikipedia.org/wiki/Fucoxanthin

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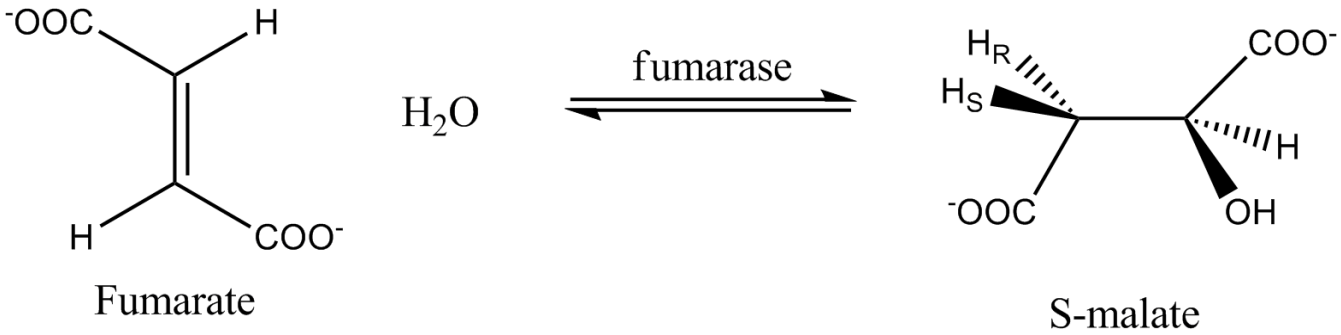
Chapter 5 - Energy: Photophosphorylation

Fumarase

Fumarase (or fumarate hydratase) is an enzyme that catalyzes the reversible hydration/dehydration of fumarate to malate. Fumarase comes in two forms: mitochondrial and cytosolic. The mitochondrial isoenzyme is involved in the citric acid cycle and the cytosolic isoenzyme is involved in the metabolism of amino acids and fumarate. Subcellular localization is established by the presence of a signal sequence on the amino terminus in the mitochondrial form, while subcellular localization in the cytosolic form is established by the absence of the signal sequence found in the mitochondrial variety.

This enzyme participates in two metabolic pathways: citric acid cycle, reductive citric acid cycle (CO_2 fixation), and is also important in renal cell carcinoma. Mutations in this gene have been associated with the development of leiomyomas in the skin and uterus in combination with renal cell carcinoma.



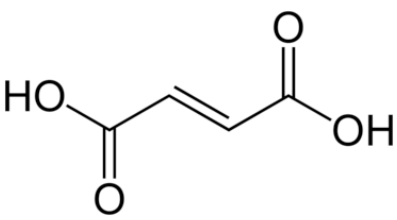
Fumarate S-malate

https://en.wikipedia.org/wiki/Fumarase

Related Glossary Terms

Fumarate

Fumaric acid or *trans*-butenedioic acid is the chemical compound with the formula $HO_2CCH=CHCO_2H$. This white crystalline compound is one of two isomeric unsaturated dicarboxylic acids, the other being maleic acid. In fumaric acid the carboxylic acid groups are *trans* (E) and in maleic acid they are *cis* (Z). Fumaric acid has a fruit-like taste. The salts and esters are known as fumarates.



https://en.wikipedia.org/wiki/Fumaric_acid

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Fungal

A fungus is any member of the group of eukaryotic organisms that includes unicellular microorganisms such as yeasts and molds, as well as multicellular fungi that produce familiar fruiting forms known as mushrooms. These organisms are classified as a kingdom, Fungi, which is separate from the other eukaryotic life kingdoms of plants and animals.

One difference that places fungi in a different kingdom is that its cell walls contain chitin, unlike the cell walls of plants, bacteria and some protists. Similar to animals, fungi are heterotrophs, that is, they acquire their food by absorbing dissolved molecules, typically by secreting digestive enzymes into their environment. Growth is their means of mobility, except for spores, which may travel through the air or water (a few of which are flagellated). Fungi are the principal decomposers in ecological systems. These and other differences place fungi in a single group of related organisms, named the *Eumycota* (true fungi or *Eumycetes*), that share a common ancestor (is a monophyletic group), an interpretation that is also strongly supported by molecular phylogenetics. This fungal group is distinct from the structurally similar myxomycetes (slime molds) and oomycetes (water molds). The discipline of biology devoted to the study of fungi is known as mycology (from the Greek μύκης, mukēs, meaning "fungus"). In the past, mycology was regarded as a branch of botany; today it is a separate kingdom in biological taxonomy. Fungi are genetically more closely related to animals than to plants.

https://en.wikipedia.org/wiki/Fungus

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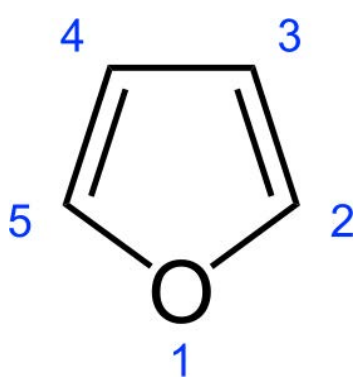
Furan

Furan is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen. The class of compounds containing suc rings are also referred to as furans.

Furan is a colorless, flammable, highly volatile liquid with a boiling point close to ro temperature. It is soluble in common organic solvents, including alcohol, ether, and acetone, but is slightly soluble in water. It is toxic and may be carcinogenic in human Furan is used as a starting point to other specialty chemicals.



https://en.wikipedia.org/wiki/Furan

Related Glossary Terms

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Chapter 2 - Structure & Function: Carbohydrates

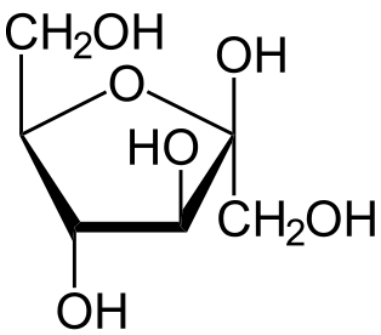
Furanoses

A furanose is a collective term for carbohydrates that have a chemical structure that includes a five-membered ring system consisting of four carbon atoms and one oxygen atom. The name derives from its similarity to the oxygen heterocycle furan, but the furanose ring does not have double bonds.

The chemical structure of fructose in its furanose form is shown below.

A furanose ring is a cyclic hemiacetal of an aldopentose or a cyclic hemiketal of a ketohexose. A furanose ring structure consists of four carbon and one oxygen atom with the anomeric carbon to the right of the oxygen. The highest numbered chiral carbon (typically to the left of the oxygen in a Haworth projection) determines whether or not the structure has a d-configuration or L-configuration. In an l-configuration furanose, the substituent on the highest numbered chiral carbon is pointed downwards out of the plane, and in a D-configuration furanose, the highest numbered chiral carbon is facing upwards.

The furanose ring will have either α or β configuration, depending on which direction the anomeric hydroxy group is pointing. In a d-configuration furanose, α configuration has the hydroxy pointing down, and β has the hydroxy pointing up. It is the opposite in an l-configuration furanose. Typically, the anomeric carbon undergoes mutarotation in solution, and the result is an equilibrium mixture of α-β configurations.



https://en.wikipedia.org/wiki/Furanose

Related Glossary Terms

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Futile Cycle

A futile cycle, also known as a substrate cycle, occurs when two metabolic pathways run simultaneously in opposite directions and have no overall effect other than to dissipate energy in the form of heat. For example, if glycolysis and gluconeogenesis were to be active at the same time, glucose would be converted to pyruvate by glycolysis and then converted back to glucose by gluconeogenesis, with an overall consumption of ATP. Futile cycles may have a role in metabolic regulation, where a futile cycle would be a system oscillating between two states and very sensitive to small changes in the activity of any of the enzymes involved. The cycle does generate heat, and may be used to maintain thermal homeostasis, for example in the brown adipose tissue of young mammals, or to generate heat rapidly, for example in insect flight muscles and in hibernating animals during periodical arousal from torpor. It has been reported that the glucose metabolism substrate cycle is not a futile cycle but a regulatory process. For example, when energy is suddenly needed, ATP is replaced by AMP, a much more reactive adenine.

https://en.wikipedia.org/wiki/Futile_cycle

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Futile Cycles

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https://en.wikipedia.org/wiki/Futile_cycle

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G protein Coupled Receptors

G protein–coupled receptors (GPCRs), also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptor, and G protein–linked receptors (GPLR), constitute a large protein family of receptors, that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times.

There are two principal signal transduction pathways involving the G protein–coupled receptors:

- the cAMP signal pathway and
- the phosphatidylinositol signal pathway.

https://en.wikipedia.org/wiki/G_protein–coupled_receptor

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G-actin

Actin is a globular multi-functional protein that forms microfilaments. It can be p
sent as either a free monomer called G-actin (globular) or as part of a linear polym
microfilament called F-actin (filamentous), both of which are essential for such im
tant cellular functions as the mobility and contraction of cells during cell division.

Scanning electron microscope images indicate that G-actin has a globular structur
However, X-ray crystallography shows that each of these globules consists of two
separated by a cleft. This structure represents the “ATPase fold”, which is a center
enzymatic catalysis that binds ATP and Mg^{2+} and hydrolyzes the former to ADP pl
phosphate. This fold is a conserved structural motif that is also found in other pro
that interact with triphosphate nucleotides such as hexokinase (an enzyme used in
ergy metabolism) or in Hsp70 proteins (a protein family that play an important pa
protein folding). G-actin is only functional when it contains either ADP or ATP in
cleft but the form that is bound to ATP predominates in cells when actin is presen
its free state.

https://en.wikipedia.org/wiki/Actin

Related Glossary Terms

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G-protein

G proteins, also known as guanine nucleotide-binding proteins, are a family of proteins that act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli outside a cell to its interior. Their activity is regulated by factors that control their ability to bind to and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP). When they are bound to GTP, they are 'on', and, when they are bound to GDP, they are 'off'. G proteins belong to the larger group of enzymes called GTPases.

There are two classes of G proteins. The first function as monomeric small GTPases, while the second form and function as heterotrimeric G protein complexes. The latter class of complexes is made up of alpha (α), beta (β) and gamma (γ) subunits. In addition, the β and γ subunits can form a stable dimeric complex referred to as the β-γ complex.

G proteins located within the cell are activated by G protein-coupled receptors (GPCRs) that span the cell membrane. Signaling molecules bind to a domain of the GPCR located outside the cell, and an intracellular GPCR domain then in turn activates a particular G protein. Some inactive-state GPCRs have also been shown to be "pre-coupled" with G proteins. The G protein activates a cascade of further signaling events that finally results in a change in cell function. G protein-coupled receptor and G proteins working together transmit signals from many hormones, neurotransmitters, and other signaling factors. G proteins regulate metabolic enzymes, ion channels, transporter proteins, and other parts of the cell machinery, controlling transcription, motility, contractility, and secretion, which in turn regulate diverse systemic functions such as embryonic development, learning and memory, and homeostasis.

https://en.wikipedia.org/wiki/G_protein

Related Glossary Terms

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G-protein Coupled Receptor Kinase

G protein-coupled receptor kinases (GRKs, GPCRKs) are a family of protein
that regulate the activity of G protein-coupled receptors (GPCRs) by phospho
their intracellular domains after their associated G proteins have been releas
tivated.

The phosphorylated serine and threonine residues act as binding sites for ar
teins that prevent the reassociation of the G proteins with their receptors, th
venting reactivation of the signaling pathway.

GRKs regulate also cellular responses independent of their kinase activity. In
lar, G protein-coupled receptor kinase 2 interacts with a diverse repertoire o
GPCR substrates.

https://en.wikipedia.org/wiki/G_protein-coupled_receptor_kinase

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G-Protein Coupled Receptors

G protein–coupled receptors (GPCRs), also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptor, and G protein–linked receptors (GPLR), constitute a large protein family of receptors, that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times.

There are two principal signal transduction pathways involving the G protein–coupled receptors:

- the cAMP signal pathway and
- the phosphatidylinositol signal pathway.

https://en.wikipedia.org/wiki/G_protein–coupled_receptor

Related Glossary Terms

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Index Find Term

G6P Dehydrogenase

Glucose-6-phosphate dehydrogenase (G6PD or G6PDH) is a cytosolic enzyme tha
lyzes the chemical reaction

D-glucose 6-phosphate + $NADP^+$ <---> 6-phospho-D-glucono-1,5-lactone + NADP
H^+

This enzyme participates in the pentose phosphate pathway, a metabolic pathway
supplies reducing energy to cells (such as erythrocytes) by maintaining the level o
co-enzyme nicotinamide adenine dinucleotide phosphate (NADPH). The NADPH
turn maintains the level of glutathione in these cells that helps protect the red bloo
cells against oxidative damage from compounds like hydrogen peroxide. Of greate
quantitative importance is the production of NADPH for tissues actively engaged
synthesis of fatty acids and/or isoprenoids, such as the liver, mammary glands, ad
tissue, and the adrenal glands. G6PD reduces $NADP^+$ to NADPH while oxidizing
glucose-6-phosphate.

https://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase

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Chapter 6 - Metabolism: Sugars

G6Pase

Glucose 6-phosphatase (G6Pase) is an enzyme that hydrolyzes glucose-6-phospl
resulting in the creation of a phosphate group and free glucose. Glucose is then e
ported from the cell via glucose transporter membrane proteins. This catalysis c
pletes the final step in gluconeogenesis and glycogenolysis and therefore plays a
role in the homeostatic regulation of blood glucose levels.

Glucose-6-phosphatase consists of 357 amino acids, and is anchored to the endo
mic reticulum (ER) by nine transmembrane helices. Its N-terminal and active si
found on the lumen side of the ER and its C-terminus projects into the cytoplasr
to its tight association to the ER, the exact structure of glucose-6-phosphatase re
unknown. However, sequence alignment has shown that glucose-6-phosphatase
structurally similar to the active site of the vanadium-containing chloroperoxida
found in *Curvularia inaequalis*.

https://en.wikipedia.org/wiki/Glucose_6-phosphatase

Related Glossary Terms

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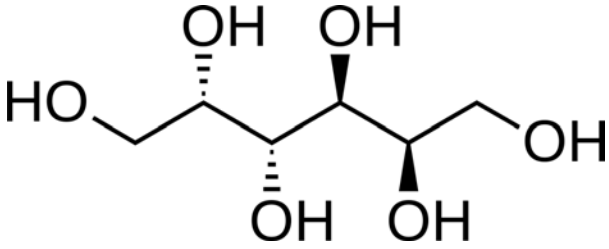
Galactitol

Galactitol (dulcitol) is a sugar alcohol, the reduction product of galactose. In people with galactokinase deficiency, a form of galactosemia, excess dulcitol forms in the lens of the eye leading to cataracts.

Galactitol is produced from galactose in a reaction catalyzed by aldose reductase. Galactose itself comes from the metabolism of the disaccharide lactose into glucose and galactose.

The other common galactose metabolism defect is a defect in galactose-1-phosphate uridylyltransferase, an autosomal recessive disorder, which also causes a buildup of galactitol as a result of increased concentrations of galactose-1-phosphate and galactose. The toxicity associated with galactose-1-phosphate uridylyltransferase deficiency is associated with symptoms of hepatosplenomegaly and mental retardation in addition to the cataracts caused by galactitol buildup.



https://en.wikipedia.org/wiki/Galactitol

Related Glossary Terms

Drag related terms here

Galactokinase

Galactokinase is an enzyme (phosphotransferase) that facilitates the phosp
of α-D-galactose to galactose 1-phosphate at the expense of one molecule of
tokinase catalyzes the second step of the Leloir pathway, a metabolic pathw
most organisms for the catabolism of β-D-galactose to glucose 1-phosphate

The Leloir pathway catalyzes the conversion of galactose to glucose. Galacto
in dairy products, as well as in fruits and vegetables, and can be produced e
nously in the breakdown of glycoproteins and glycolipids. Three enzymes a
in the Leloir pathway: galactokinase, galactose-1-phosphate uridylyltransfe
UDP-galactose 4-epimerase. Galactokinase catalyzes the first committed st
tose catabolism, forming galactose 1-phosphate

https://en.wikipedia.org/wiki/Galactokinase

Related Glossary Terms

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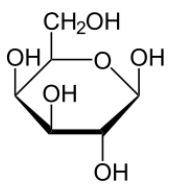
Galactose

Galactose (galacto- + -ose, "milk sugar"), sometimes abbreviated Gal, is a monosaccharide sugar that is less sweet than glucose and fructose. It is a C-4 epimer of glucose.

Galactose is a monosaccharide. When combined with glucose (monosaccharide), through a condensation reaction, the result is the disaccharide lactose. The hydrolysis of lactose to glucose and galactose is catalyzed by the enzymes lactase and β-galactosidase. The latter is produced by the lac operon in *Escherichia coli*.

In nature, lactose is found primarily in milk and milk products. Consequently, various food products made with dairy-derived ingredients, e.g. breads and cereals, can contain lactose. Galactose metabolism, which converts galactose into glucose, is carried out by the three principal enzymes in a mechanism known as the Leloir pathway. The enzymes are listed in the order of the metabolic pathway: galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), and UDP-galactose-4'-epimerase (GALE).

In the human body, glucose is changed into galactose via hexoneogenesis to enable the mammary glands to secrete lactose. However, most lactose in breast milk is synthesized from galactose taken up from the blood, and only 35±6% is made from galactose from *de novo* synthesis. Glycerol also contributes some to the mammary galactose production.



https://en.wikipedia.org/wiki/Galactose

Related Glossary Terms

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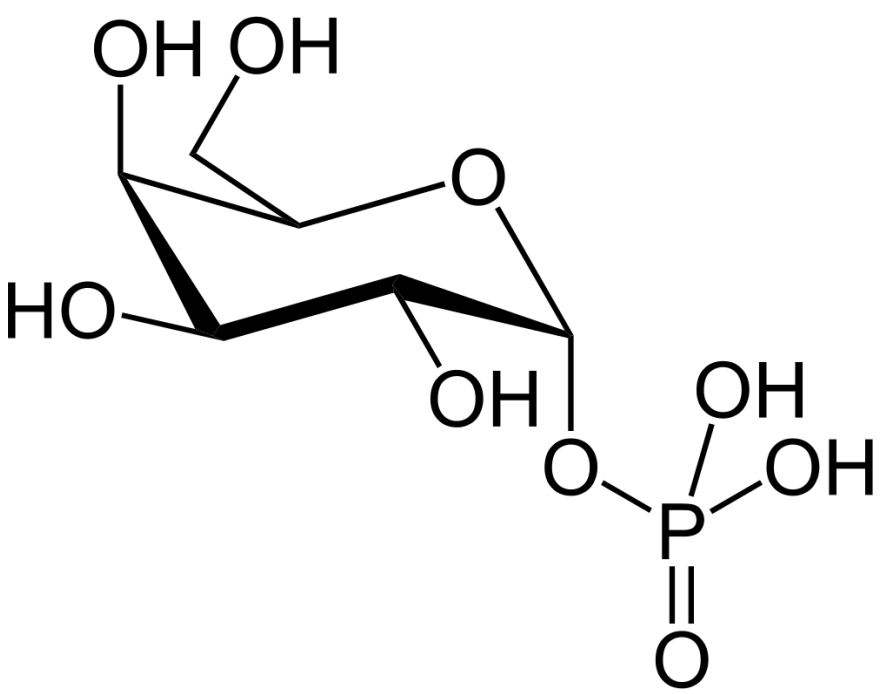
Galactose-1-phosphate

D-Galactose-1-phosphate is an intermediate in the intraconversion of glucose and
lactose. It is formed from galactose by galactokinase.



https://en.wikipedia.org/wiki/Galactose_1-phosphate

Related Glossary Terms

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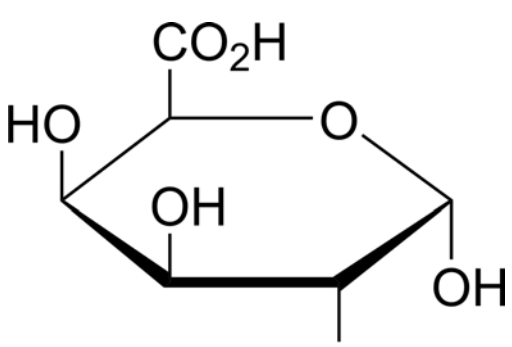
Index Find Term

Galacturonic Acid

D-Galacturonic acid is a sugar acid, an oxidized form of D-galactose. It is the main
ponent of pectin, in which it exists as the polymer polygalacturonic acid. In its ope
form, it has an aldehyde group at C_1 and a carboxylic acid group at C_6. Other oxidiz
forms of D-galactose are D-galactonic acid (carboxylic group at C_1) and meso-
galactaric acid (mucic acid) (carboxylic groups at C_1 and C_6). It is also a uronic acid
hexuronic acid. Naturally occurring uronic acids are D-glucuronic acid, D-galactur
acid, L-iduronic acid and D-mannuronic acid.



https://en.wikipedia.org/wiki/D-Galacturonic_acid

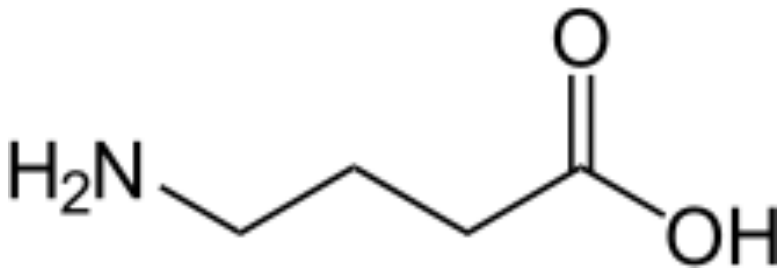
Related Glossary Terms

Drag related terms here

Gamma-aminobutyric Acid

γ-Aminobutyric acid (γ-Aminobutyric acid) is the chief inhibitory neurotransm
the mammalian central nervous system. It plays the principal role in reducing
ronal excitability throughout the nervous system. In humans, GABA is also di
sponsible for the regulation of muscle tone.

GABA is also found in plants. It is the most abundant amino acid in the apopl
matoes. It has also a role in cell signaling in plants.



https://en.wikipedia.org/wiki/Gamma-Aminobutyric_acid

Related Glossary Terms

Drag related terms here

Gamma-glutamylcysteine Synthetase

Glutamate Cysteine Ligase (GCL), previously known as γ-glutamylcysteine
(GCS), is the first enzyme of the cellular glutathione (GSH) biosynthetic pa
catalyzes the chemical reaction:

L-glutamate + L-cysteine + ATP <---> γ-glutamyl cysteine + ADP + Pi

GSH, and by extension GCL, is critical to cell survival. Nearly every eukaryo
from plants to yeast to humans, expresses a form of the GCL protein for the
synthesizing GSH.

https://en.wikipedia.org/wiki/Glutamate–cysteine_ligase

Related Glossary Terms

Drag related terms here

Gamma-secretase

γ secretase is a multi-subunit protease complex, itself an integral membran
that cleaves single-pass transmembrane proteins at residues within the tra
brane domain. Proteases of this type are known as intramembrane protease
well-known substrate of γ secretase is amyloid precursor protein, a large in
brane protein that, when cleaved by both γ and β secretase, produces a sho
acid peptide called amyloid β whose abnormally folded fibrillar form is the
component of amyloid plaques found in the brains of Alzheimer's disease p
secretase is also critical in the related processing of several other type I inte
brane proteins, such as Notch, ErbB4, E-cadherin, N-cadherin, ephrin-B2,

https://en.wikipedia.org/wiki/Gamma_secretase

Related Glossary Terms

Drag related terms here

Gamma-turns

A turn is an element of secondary structure in proteins where the polypeptide chain reverses its overall direction.

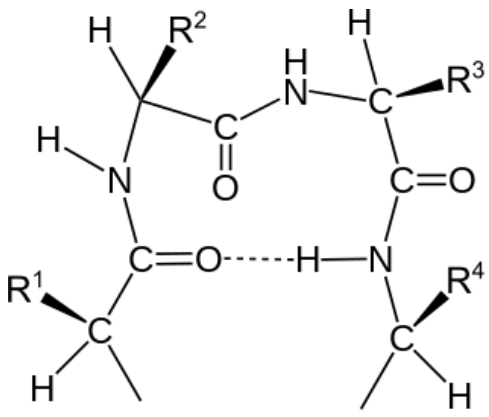
Turns are classified according to the separation between the two end residues:
In an α-turn the end residues are separated by four peptide bonds

(i --> i +/- 4).

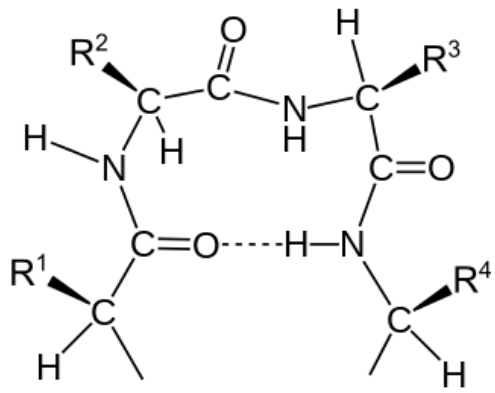
•In a γ-turn, by two bonds

(i --> i +/- 2).

Shown below is a β turn



ß turn: Type I



ß turn: Type II

https://en.wikipedia.org/wiki/Turn_(biochemistry)

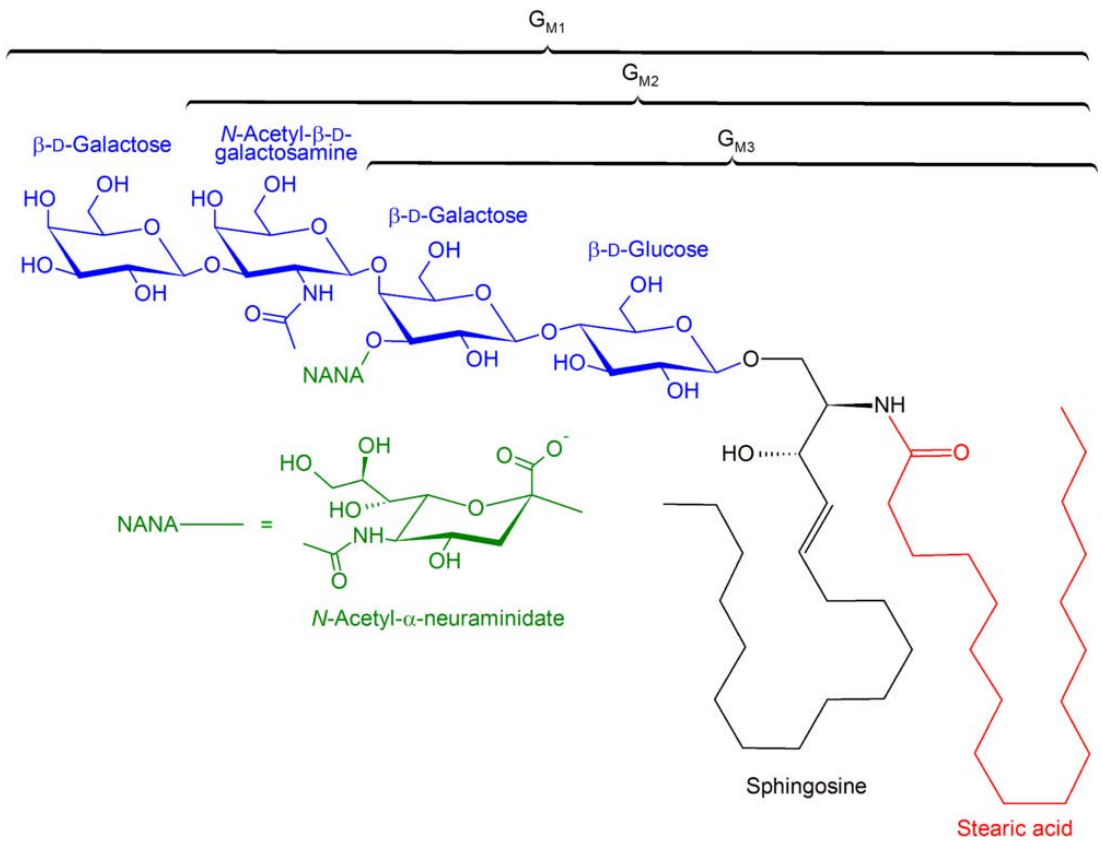
Related Glossary Terms

Ganglioside

A ganglioside is a molecule composed of a glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids (e.g. n-acetylneuraminic acid, NANA) linked on the sugar chain. NeuNAc, an acetylated derivative of the carbohydrate sialic acid, makes the head groups of gangliosides anionic at pH 7, which distinguishes them from globosides.

The oligosaccharide groups on gangliosides extend well beyond the surfaces of the cell membranes, and act as distinguishing surface markers that can serve as specific determinants in cellular recognition and cell-to-cell communication. These carbohydrate head groups also act as specific receptors for certain pituitary glycoprotein hormones and certain bacterial protein toxins such as cholera toxin.

The functions of gangliosides as specific determinants suggest its important role in the growth and differentiation of tissues as well as in carcinogenesis. It has been found that tumor formation can induce the synthesis of a new complement of ganglioside, and very low concentrations of a specific ganglioside can induce differentiation of cultured neuronal tumor cells. Gangliosides G_{M1}, G_{M2}, and G_{M3} are shown below.



https://en.wikipedia.org/wiki/Ganglioside

Related Glossary Terms

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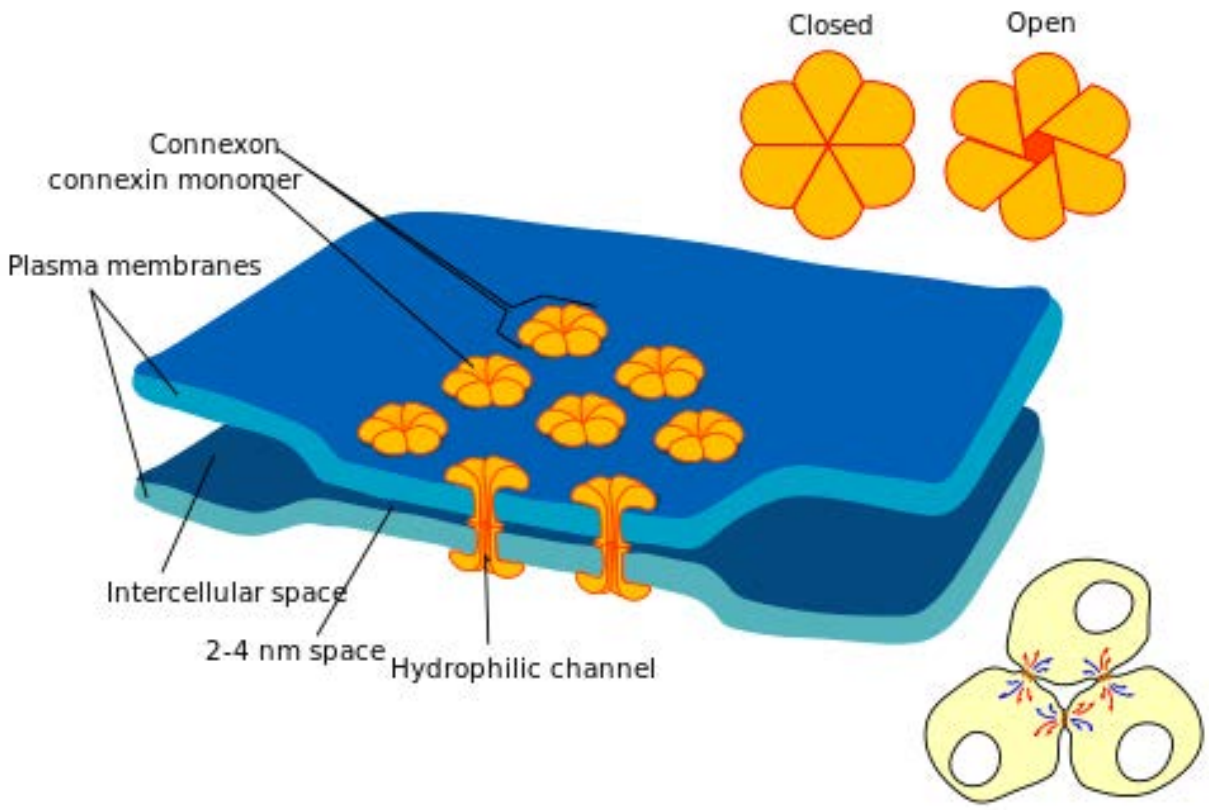
Gap Junctions

A gap junction may also be called a nexus or macula communicans. When found in nerves it may also be called an electrical synapse. While an ephapse has some similarities to a gap junction, by modern definition the two are different.

Gap junctions are a specialized intercellular connection between a multitude of animal cell-types. They directly connect the cytoplasm of two cells, which allows various molecules, ions and electrical impulses to directly pass through a regulated gate between cells.



https://en.wikipedia.org/wiki/Gap_junction

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GAR Synthetase

Phosphoribosylamine-glycine ligase, also known as glycinamide ribonucleotide synthetase (GARS), is an enzyme that catalyzes the chemical reaction:

ATP + 5-phospho-D-ribosylamine + glycine <---> ADP + phosphate + N1-(5-phospho-D-ribosyl)glycinamide

which is the second step in purine biosynthesis. This enzyme belongs to the family of ligases, specifically those forming generic carbon-nitrogen bonds.
In bacteria, GARS is a monofunctional enzyme (encoded by the purD gene). The purD genes often contain PurD RNA motif in their 5' UTR. In yeast, GARS is part of a bifunctional enzyme (encoded by the ADE5/7 gene) in conjunction with phosphoribosylformylglycinamidine cyclo-ligase (AIRS). In higher eukaryotes,including humans, GARS is part of a trifunctional enzyme in conjunction with AIRS and with phosphoribosylglycinamide formyltransferase (GART), forming GARS-AIRS-GART.

In humans, the gene that codes for GARS-AIRS-GART is on chromosome 21, and individuals with Down Syndrome have higher purine levels, which has been correlated with mental retardation. Thus, studies have been conducted to investigate its involvement in Down Syndrome. It has been found that GARS is expressed for longer in individuals with Down Syndrome than in unaffected individuals. In unaffected individuals, GARS is highly expressed in the cerebellum before birth but is barely expressed by three weeks after birth. In individuals with Down Syndrome, GARS expression continues until at least seven weeks after birth. This suggests that GARS may be a main contributor to the development of Down Syndrome. However, so far no mutations to GARS have been identified that could change its function and cause Down Syndrome related mental retardation

https://en.wikipedia.org/wiki/Phosphoribosylamine—glycine_ligase

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Gated Ion Channels

Ion channels are pore-forming membrane proteins whose functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume. Ion channels are present in the membranes of all cells. Ion channels are considered to be one of the two traditional classes of ionophoric proteins, with the other class known as ion transporters (including the sodium-potassium pump, sodium-calcium exchanger, and sodium-glucose transport proteins, amongst others).

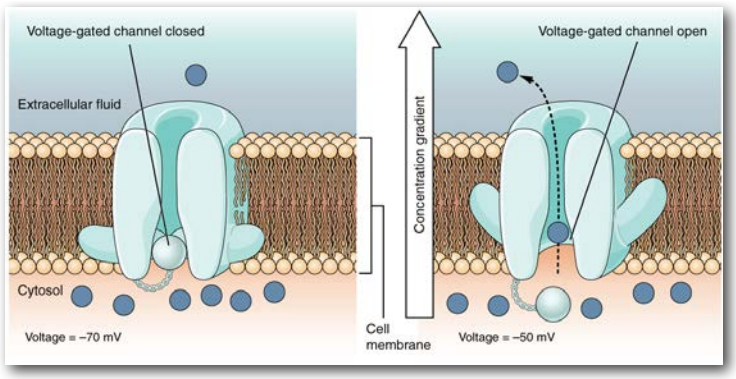
There are two distinctive features of ion channels that differentiate them from other types of ion transporter proteins:

1 The rate of ion transport through the channel is very high (often 10^6 ions per second or greater).
2 Ions pass through channels down their electrochemical gradient, which is a function of ion concentration and membrane potential, "downhill", without the input (or help) of metabolic energy (e.g. ATP, co-transport mechanisms, or active transport mechanisms).

Ion channels are located within the plasma membrane of nearly all cells and many intracellular organelles. They are often described as narrow, water-filled tunnels that allow only ions of a certain size and/or charge to pass through. This characteristic is called selective permeability. The archetypal channel pore is just one or two atoms wide at its narrowest point and is selective for specific species of ion, such as sodium or potassium. However, some channels may be permeable to the passage of more than one type of ion, typically sharing a common charge: positive (cations) or negative (anions). Ions often move through the segments of the channel pore in single file nearly as quickly as the ions move through free solution. In many ion channels, passage through the pore is governed by a "gate", which may be opened or closed in response to chemical or electrical signals, temperature, or mechanical force.

Ion channels are integral membrane proteins, typically formed as assemblies of several individual proteins. Such "multi-subunit" assemblies usually involve a circular arrangement of identical or homologous proteins closely packed around a water-filled pore through the plane of the membrane or lipid bilayer. For most voltage-gated ion channels, the pore-forming subunit(s) are called the α subunit, while the auxiliary subunits are denoted β, γ, and so on.

Because channels underlie the nerve impulse and because "transmitter-activated" channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. Indeed, numerous toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails, and others) work by modulating ion channel conductance and/or kinetics. In addition, ion channels are key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. In the search for new drugs, ion channels are a frequent target.



https://en.wikipedia.org/wiki/Ion_channel

Related Glossary Terms

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Index Find Term

GC Box

In molecular biology, a GC box is a distinct pattern of nucleotides found in
moter region of some eukaryotic genes upstream of the TATA box and appr
110 bases upstream from the transcription initiation site. It has a consensus
GGGCGG which is position dependent and orientation independent. The G
are bound by transcription factors and have similar functions to enhancers

https://en.wikipedia.org/wiki/GC_box

Related Glossary Terms

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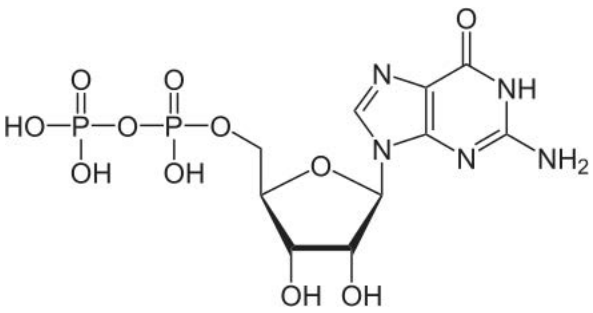
GDP

Guanosine diphosphate, abbreviated GDP, is a nucleoside diphosphate. It is an ester of pyrophosphoric acid with the nucleoside guanosine. GDP consists of the pyrophosphate group, the pentose sugar ribose, and the nucleobase guanine.

GDP is the product of GTP dephosphorylation by GTPases, e.g., the G-proteins that are involved in signal transduction. GDP is converted into GTP with the help of pyruvate kinase and phosphoenolpyruvate.



https://en.wikipedia.org/wiki/Guanosine_diphosphate

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GDP-glucose

GDP-glucose is an activated intermediate that can donate a glucose to a gro
lose chain in cellulose biosynthesis.

https://en.wikipedia.org/wiki/Cellulose_synthase_(UDP-forming)

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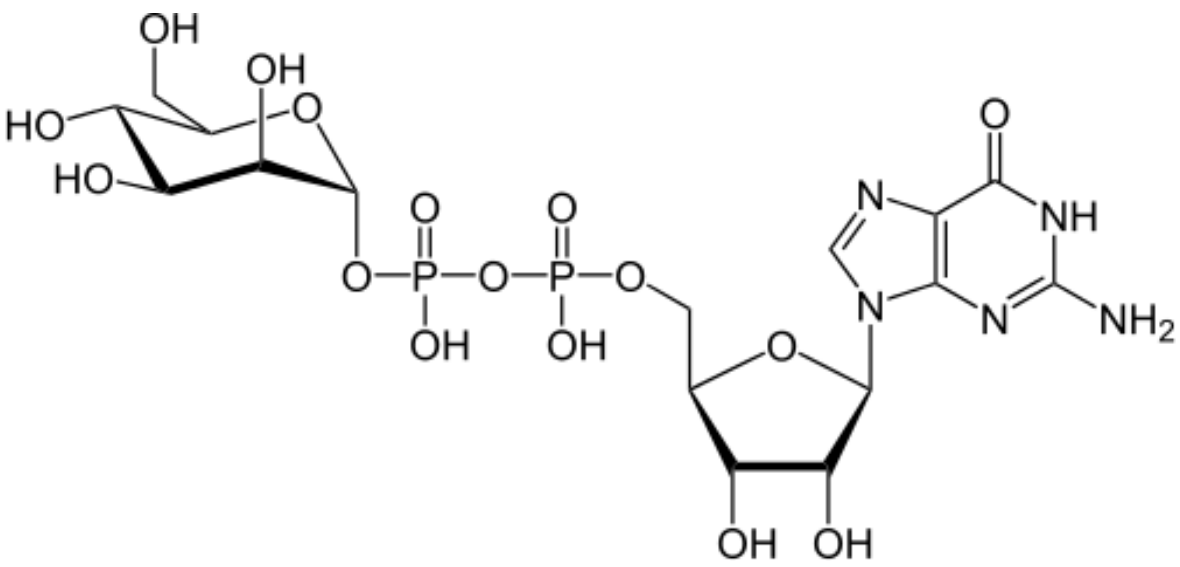
GDP-mannose

Guanosine diphosphate mannose or GDP-mannose is a nucleotide sugar that is a sub strate for glycosyltransferase reactions in metabolism. This compound is a substrate for enzymes called mannosyltransferases.

GDP-mannose is produced from GTP and mannose-6-phosphate by the enzyme mannose-1-phosphate guanylyltransferase.



https://en.wikipedia.org/wiki/Guanosine_diphosphate_mannose

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Gene

A gene is a locus (or region) of DNA that encodes a functional RNA or protein product, and is the molecular unit of heredity. The transmission of genes to an organism's offspring is the basis of the inheritance of phenotypic traits. Most biological traits are under the influence of polygenes (many different genes) as well as the gene–environment interactions. Some genetic traits are instantly visible, such as eye color or number of limbs, and some are not, such as blood type, risk for specific diseases, or the thousands of basic biochemical processes that comprise life.

Genes can acquire mutations in their sequence, leading to different variants, known as alleles, in the population. These alleles encode slightly different versions of a protein, which cause different phenotype traits. Colloquial usage of the term "having a gene" (e.g., "good genes," "hair color gene") typically refers to having a different allele of the gene. Genes evolve due to natural selection or survival of the fittest of the alleles.
The concept of a gene continues to be refined as new phenomena are discovered.

For example, regulatory regions of a gene can be far removed from its coding regions, and coding regions can be split into several exons. Some viruses store their genome in RNA instead of DNA and some gene products are functional non-coding RNAs. Therefore, a broad, modern working definition of a gene is any discrete locus of heritable, genomic sequence which affect an organism's traits by being expressed as a functional product or by regulation of gene expression.

https://en.wikipedia.org/wiki/Gene

Related Glossary Terms

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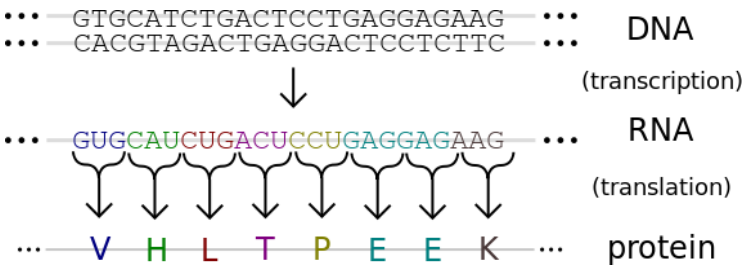
Gene Expression

Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as transfer RNA (tRNA) or small nuclear RNA (snRNA) genes, the product is a functional RNA. The process of gene expression is used by all known life—eukaryotes (including multicellular organisms), prokaryotes (bacteria and archaea), and utilized by viruses—to generate the macromolecular machinery for life.



https://en.wikipedia.org/wiki/Gene_expression

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Gene Silencing

Gene silencing is a general term used to describe the regulation of gene expression. In particular, this term refers to the ability of a cell to prevent the expression of a certain gene. Gene silencing can occur during either transcription or translation and is often used in research. In particular, methods used to silence genes are being increasingly used to produce therapeutics to combat cancer and diseases, such as infectious diseases and neurodegenerative disorders.

Gene silencing is often considered the same as gene knockout. When genes are silenced, their expression is reduced. In contrast, when genes are knocked out, they are completely erased from the organism's genome and, thus, have no expression. Gene silencing is considered a gene knockdown mechanism since the methods used to silence genes, such as RNAi, CRISPR, or siRNA, generally reduce the expression of a gene by at least 70% but do not completely eliminate it. Methods using gene silencing are often considered better than gene knockouts since they allow researchers to study essential genes that are required for the animal models to survive and cannot be removed. In addition, they provide a more complete view on the development of diseases since diseases are generally associated with genes that have a reduced expression.

https://en.wikipedia.org/wiki/Gene_silencing

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General Transcription Factors

General transcription factors (GTFs), also known as basal transcriptional factors, are a class of protein transcription factors that bind to specific sites (promoter) on DNA to activate transcription of genetic information from DNA to messenger RNA. GTFs, RNA polymerase, and the mediator multiple protein complex constitute the basic transcriptional apparatus that bind to the promoter, then start transcription. GTFs are also intimately involved in the process of gene regulation, and most are required for life.

A transcription factor is a protein that binds to specific DNA sequences (enhancer or promoter), alone or with other proteins in a complex, to control the rate of transcription of genetic information from DNA to messenger RNA by promoting as an activator or blocking as a repressor the recruitment of RNA polymerase. As a class of protein, general transcription factors bind to promoters along the DNA sequence or form a large transcription preinitiation complex to activate transcription. General transcription factors are necessary for transcription to occur.

In bacteria, transcription initiation requires an RNA polymerase and a single GTF: sigma factor.

In archaea and eukaryotes, transcription initiation requires an RNA polymerase and a set of multiple GTFs to form a transcription preinitiation complex. The Transcription initiation by eukaryotic RNA polymerase II involves the following GTFs:

- TFIIA
- TFIIB
- TFIID
- TFIIE
- TFIIF
- TFIIH

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Genes

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https://en.wikipedia.org/wiki/Gene

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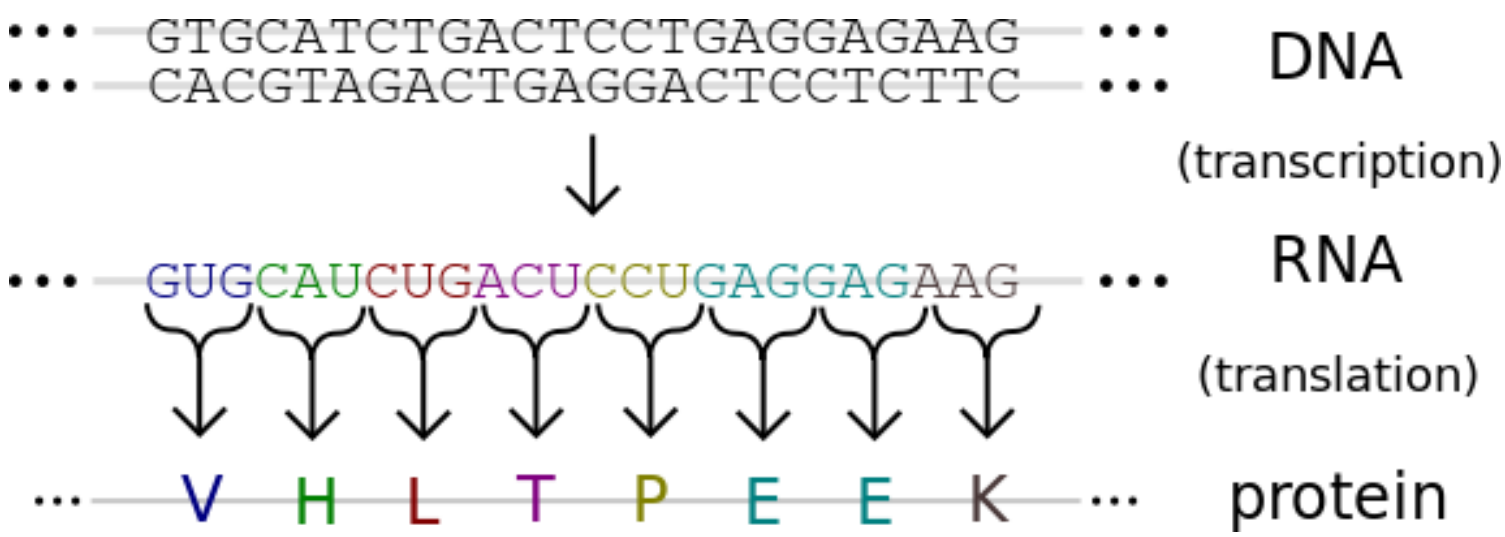
Genetic Code

The genetic code is the set of rules by which information encoded within genetic material (DNA or mRNA sequences) can be both translated into proteins by living cells or transcribed into non-coding RNAs that serve as regulatory tools in gene regulation. Biological decoding is accomplished by the ribosome, which links amino acids in an order specified by mRNA, using transfer RNA (tRNA) molecules to carry amino acids and to read the mRNA three nucleotides at a time. The genetic code is highly similar among all organisms and can be expressed in a simple table with 64 entries.



https://en.wikipedia.org/wiki/Genetic_code

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Genome

In modern molecular biology and genetics, the genome is the genetic material of an organism. It consists of DNA (or RNA in RNA viruses). The genome includes both the genes, (the coding regions), the noncoding DNA and the genomes of the mitochondria and chloroplasts.

Some organisms have multiple copies of chromosomes: diploid, triploid, tetraploid and so on. In classical genetics, in a sexually reproducing organism (typically eukarya) the gamete has half the number of chromosomes of the somatic cell and the genome is a full set of chromosomes in a diploid cell. The halving of the genetic material in gametes is accomplished by the segregation of homologous chromosomes during meiosis. In haploid organisms, including cells of bacteria, archaea, and in organelles including mitochondria and chloroplasts, or viruses, that similarly contain genes, the single or set of circular or linear chains of DNA (or RNA for some viruses), likewise constitute the genome. The term genome can be applied specifically to mean what is stored on a complete set of nuclear DNA (i.e., the "nuclear genome") but can also be applied to what is stored within organelles that contain their own DNA, as with the "mitochondrial genome" or the "chloroplast genome". Additionally, the genome can comprise non-chromosomal genetic elements such as viruses, plasmids, and transposable elements.

Typically, when it is said that the genome of a sexually reproducing species has been "sequenced", it refers to a determination of the sequences of one set of autosomes and one of each type of sex chromosome, which together represent both of the possible sexes. Even in species that exist in only one sex, what is described as a "genome sequence" may be a composite read from the chromosomes of various individuals. Colloquially, the phrase "genetic makeup" is sometimes used to signify the genome of a particular individual or organism. The study of the global properties of genomes of related organisms is usually referred to as genomics, which distinguishes it from genetics which generally studies the properties of single genes or groups of genes.

Both the number of base pairs and the number of genes vary widely from one species to another, and there is only a rough correlation between the two (an observation known as the C-value paradox). At present, the highest known number of genes is around 60,000, for the protozoan causing trichomoniasis (see List of sequenced eukaryotic genomes), almost three times as many as in the human genome.

https://en.wikipedia.org/wiki/Genome

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Genomics

Genomics is a discipline in genetics that applies recombinant DNA, DNA se
methods, and bioinformatics to sequence, assemble, and analyze the functi
structure of genomes (the complete set of DNA within a single cell of an org
vances in genomics have triggered a revolution in discovery-based research
stand even the most complex biological systems such as the brain. The field
efforts to determine the entire DNA sequence of organisms and fine-scale g
ping. The field also includes studies of intragenomic phenomena such as he
tasis, pleiotropy and other interactions between loci and alleles within the g
contrast, the investigation of the roles and functions of single genes is a pri
of molecular biology or genetics and is a common topic of modern medical
cal research.

https://en.wikipedia.org/wiki/Genomics

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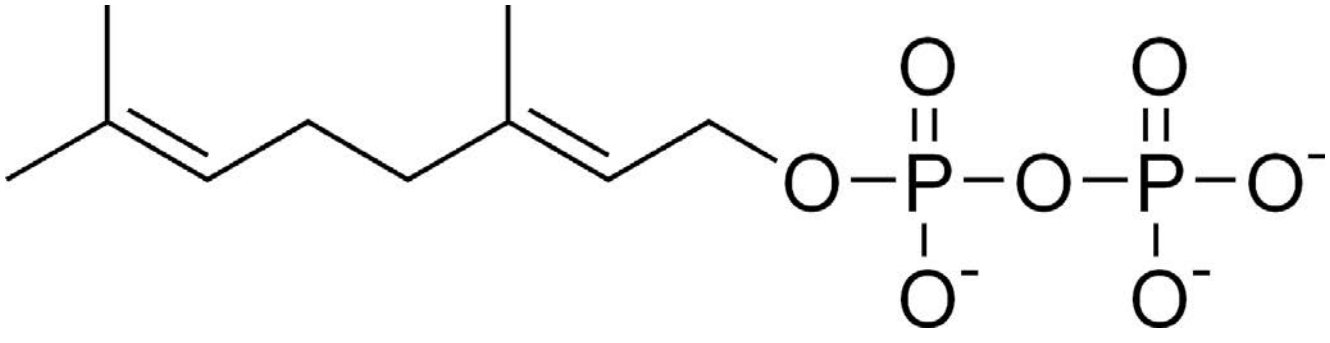
Geranyl Pyrophosphate

Geranyl pyrophosphate (GPP), also known as geranyl diphosphate (GDP), i
mediate in the HMG-CoA reductase pathway used by organisms in the bios
farnesyl pyrophosphate, geranylgeranyl pyrophosphate, cholesterol, terpen
penoids.



https://en.wikipedia.org/wiki/Geranyl_pyrophosphate

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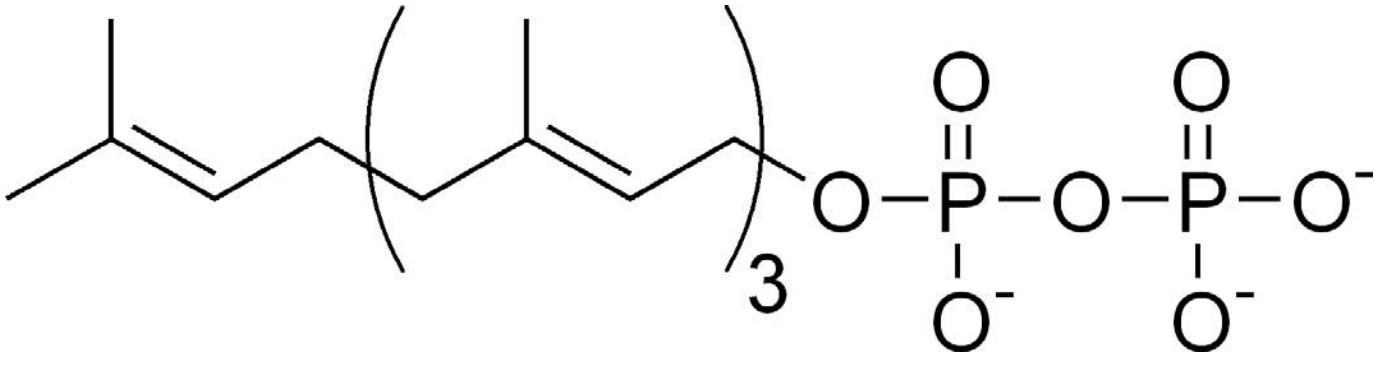
Geranylgeranyl Pyrophosphate

Geranylgeranyl pyrophosphate is an intermediate in the biosynthesis of sor
and terpenoids. In plants it is also the precursor to carotenoids, gibberellin
ols, and chlorophylls. It is also a precursor to geranylgeranylated proteins,
primary use in human cells.



https://en.wikipedia.org/wiki/Geranylgeranyl_pyrophosphate

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Ghrelin

Ghrelin (pronounced GREL-in), the "hunger hormone", also known as lenomorelin (INN), is a peptide hormone produced by ghrelinergic cells in the gastrointestinal trac which functions as a neuropeptide in the central nervous system. Besides regulating a petite, ghrelin also plays a significant role in regulating the distribution and rate of use of energy.

When the stomach is empty, ghrelin is secreted. When the stomach is stretched, secre tion stops.a It acts on hypothalamic brain cells both to increase hunger, and to increas gastric acid secretion and gastrointestinal motility to prepare the body for food intake

https://en.wikipedia.org/wiki/Ghrelin

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Gibbs Free Energy

In thermodynamics, the Gibbs free energy (IUPAC recommended name: Gibbs energy or Gibbs function; also known as free enthalpy to distinguish it from Helmholtz free energy) is a thermodynamic potential that measures the maximum or reversible work that may be performed by a thermodynamic system at a constant temperature and pressure (isothermal, isobaric). Just as in mechanics, where potential energy is defined as capacity to do work, similarly different potentials have different meanings.

The Gibbs free energy (kJ in SI units) is the maximum amount of non-expansion work that can be extracted from a thermodynamically closed system (one that can exchange heat and work with its surroundings, but not matter); this maximum can be attained only in a completely reversible process. When a system changes from a well-defined initial state to a well-defined final state, the Gibbs free energy change ΔG equals the work exchanged by the system with its surroundings, minus the work of the pressure forces, during a reversible transformation of the system from the initial state to the final state.

https://en.wikipedia.org/wiki/Gibbs_free_energy

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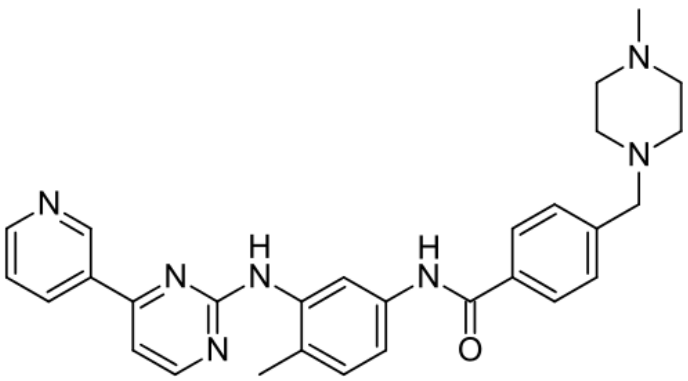
Gleevec

Imatinib (INN), marketed by Novartis as Gleevec (Canada, South Africa and the USA) or Glivec (Australia, Europe and Latin America), investigational name STI-571, is a tyrosine-kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML).

Imatinib kills cancer cells by turning off tyrosine kinase. In order to survive, cells need signaling through proteins (signal cascade) to keep them alive. Some of the proteins in this cascade use a phosphate group as an "on" switch. This phosphate group is added by a tyrosine kinase enzyme. In healthy cells, these tyrosine kinase enzymes are turned on and off as needed. In Ph-positive CML cells, one tyrosine kinase enzyme, BCR-Abl, is stuck on the "on" position, and keeps adding phosphate groups. Imatinib blocks this BCR-Abl enzyme, and stops it from adding phosphate groups. As a result, these cells stop growing, and even die by a process of cell death (apoptosis). Because the BCR-Abl tyrosine kinase enzyme exists only in cancer cells and not in healthy cells, imatinib works as a form of targeted therapy—only cancer cells are killed through the drug's action. In this regard, imatinib was one of the first cancer therapies to show the potential for such targeted action, and is often cited as a paradigm for research in cancer therapeutics.

Due in large part to the development of Gleevec and related drugs having a similar mechanism of action, the five year survival rate for people with chronic myeloid leukemia nearly doubled from 31% in 1993 (before Gleevec's 2001 FDA approval) to 59% for those diagnosed between 2003 and 2009. Compared to older drugs imatinib has a relatively benign side effect profile, allowing many patients to live a normal lifestyle. Median survival for imatinib-treated people with gastrointestinal stromal tumors (GIST) is nearly 5 years compared to 9 to 20 months in the pre-imatinib-era.



https://en.wikipedia.org/wiki/Imatinib

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Glia

Glial cells, sometimes called neuroglia or simply glia, are non-neuronal cell
tain homeostasis, form myelin, and provide support and protection for neu
central and peripheral nervous systems. In the central nervous system, glia
clude oligodendrocytes, astrocytes, ependymal cells and microglia, and in t
eral nervous system glial cells include Schwann cells and satellite cells.

Neuroscience currently identifies four main functions of glial cells:

1. To surround neurons and hold them in place
2. To supply nutrients and oxygen to neurons
3. To insulate one neuron from another
4. To destroy pathogens and remove dead neurons.

https://en.wikipedia.org/wiki/Neuroglia

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Globin

The globins are a family of globular proteins, which are thought to share a common ancestor. These proteins all incorporate the globin fold, a series of eight α helical segments. Two prominent members of this family include myoglobin and hemoglobin, which both bind the heme prosthetic group. Both of these proteins are reversible oxygen binders.

Globins are heme-containing proteins involved in binding and/or transporting oxygen. They belong to a very large and well studied family that is widely distributed in many organisms.

Globins evolved from a common ancestor and can be divided into three groups: single-domain globins, and two types of chimeric globins, flavohaemoglobins and globin-coupled sensors. Bacteria have all three types of globins, while archaea lack flavohaemoglobins, and eukaryotes lack globin-coupled sensors. Several functionally different haemoglobins can coexist in the same species. Eight globins are known to occur in vertebrates: androglobin, cytoglobin, globin E, globin X, globin Y, haemoglobin, myoglobin and neuroglobin.

https://en.wikipedia.org/wiki/Globin

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Globular

Globular proteins or spheroproteins are spherical ("globe-like") proteins and are one of the common protein types (the others being fibrous, disordered and membrane proteins). Globular proteins are somewhat water-soluble (forming colloids in water), unlike the fibrous or membrane proteins. There are multiple fold classes of globular proteins, since there are many different architectures that can fold into a roughly spherical shape.

The spherical structure is induced by the protein's tertiary structure. The molecule's apolar (hydrophobic) amino acids are bounded towards the molecule's interior whereas polar (hydrophilic) amino acids are bound outwards, allowing dipole-dipole interactions with the solvent, which explains the molecule's solubility.

Globular proteins are only marginally stable because the free energy released when the protein folded into its native conformation is relatively small. This is because protein folding requires entropic cost. As a primary sequence of a polypeptide chain can form numerous conformations, native globular structure restricts its conformation to a few only. It results in a decrease in randomness, although non-covalent interactions such as hydrophobic interactions stabilize the structure.

https://en.wikipedia.org/wiki/Globular_protein

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Chapter 2 - Structure & Function: Proteins I

Globular Protein

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https://en.wikipedia.org/wiki/Globular_protein

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Glucagon

Glucagon is a peptide hormone, produced by α cells of the pancreas. It works to raise the concentration of glucose in the bloodstream. Its effect is opposite that of insulin, which lowers the glucose.

The pancreas releases glucagon when the concentration of glucose in the bloodstream falls too low. Glucagon causes the liver to convert stored glycogen into glucose, which is released into the bloodstream. High blood-glucose levels stimulate the release of insulin. Insulin allows glucose to be taken up and used by insulin-dependent tissues. Thus, glucagon and insulin are part of a feedback system that keeps blood glucose levels at a stable level. It increases energy expenditure and is elevated under conditions of stress. Glucagon belongs to a family of several other related hormones.

Glucagon generally elevates the concentration of glucose in the blood by promoting gluconeogenesis and glycogenolysis. Glucose is stored in the liver in the form of the polysaccharide glycogen, which is a glucan (a polymer made up of glucose molecules). Liver cells (hepatocytes) have glucagon receptors. When glucagon binds to the glucagon receptors, the liver cells convert the glycogen into individual glucose molecules and release them into the bloodstream, in a process known as glycogenolysis. As these stores become depleted, glucagon then encourages the liver and kidney to synthesize additional glucose by gluconeogenesis. Glucagon turns off glycolysis in the liver, causing glycolytic intermediates to be shuttled to gluconeogenesis.

Glucagon also regulates the rate of glucose production through lipolysis. Glucagon induces lipolysis in humans under conditions of insulin suppression (such as diabetes mellitus type 1).

https://en.wikipedia.org/wiki/Glucagon

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Glucocorticoid Hormones

Glucocorticoids (GCs) are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor (GR), that is present in almost every vertebrate animal cell. The name glucocorticoid (glucose + cortex + steroid) is composed from its role in regulation of glucose metabolism, synthesis in the adrenal cortex, and its steroidal structure. A less common synonym is glucocorticosteroid. GCs are part of the feedback mechanism in the immune system which reduces certain aspects of immune function, such as reduction of inflammation.

https://en.wikipedia.org/wiki/Glucocorticoid

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Glucocorticoid Receptor

The glucocorticoid receptor (GR, or GCR) also known as NR3C1 (nuclear receptor sub family 3, group C, member 1) is the receptor to which cortisol and other glucocorticoids bind.

The GR is expressed in almost every cell in the body and regulates genes controlling the development, metabolism, and immune response. Because the receptor gene is expressed in several forms, it has many different (pleiotropic) effects in different parts of the body.

When the GR binds to glucocorticoids, its primary mechanism of action is the regulation of gene transcription. The unbound receptor resides in the cytosol of the cell. After the receptor is bound to glucocorticoid, the receptor-glucorticoid complex can take either of two paths. The activated GR complex up-regulates the expression of anti-inflammatory proteins in the nucleus or represses the expression of pro-inflammatory proteins in the cytosol (by preventing the translocation of other transcription factors from the cytosol into the nucleus).

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Glucogenic

A material that is glucogenic is capable of favoring the production of glucose
sis of glucose occurs in gluconeogesis. Gluconeogenesis (GNG) is a metabol
that results in the generation of glucose from certain non-carbohydrate carb
strates. From breakdown of proteins, these substrates include glucogenic ar
(although not ketogenic amino acids); from breakdown of lipids (such as tri
they include glycerol (although not fatty acids); and from other steps in met
they include pyruvate and lactate.

https://en.wikipedia.org/wiki/Gluconeogenesis

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Glucokinase

Glucokinase is an enzyme that facilitates phosphorylation of glucose to glucose-6-phosphate. Glucokinase occurs in cells in the liver, pancreas, gut, and brain of humans and most other vertebrates. In each of these organs it plays an important role in the regulation of carbohydrate metabolism by acting as a glucose sensor, triggering shifts in metabolism or cell function in response to rising or falling levels of glucose, such as occur after a meal or when fasting. Mutations of the gene for this enzyme can cause unusual forms of diabetes or hypoglycemia.

Glucokinase (GK) is a hexokinase isozyme, related homologously to at least three other hexokinases. All of the hexokinases can mediate phosphorylation of glucose to glucose-6-phosphate (G6P), which is the first step of both glycogen synthesis and glycolysis. However, glucokinase is coded by a separate gene and its distinctive kinetic properties allow it to serve a different set of functions. Glucokinase has a lower affinity for glucose than the other hexokinases do, and its activity is localized to a few cell types, leaving the other three hexokinases as more important preparers of glucose for glycolysis and glycogen synthesis for most tissues and organs. Because of this reduced affinity, the activity of glucokinase, under usual physiological conditions, varies substantially according to the concentration of glucose.

https://en.wikipedia.org/wiki/Glucokinase

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Gluconeogenesis

Gluconeogenesis (GNG) is a metabolic pathway that results in the generation of glucose from certain non-carbohydrate carbon substrates. From breakdown of proteins, these substrates include glucogenic amino acids (although not ketogenic amino acids). From breakdown of lipids (such as triglycerides), they include glycerol (although not fatty acids). From other steps in metabolism they include pyruvate and lactate.

Gluconeogenesis is one of several main mechanisms used by humans and many other animals to maintain blood glucose levels, avoiding low levels (hypoglycemia). Other means include the degradation of glycogen (glycogenolysis), fatty acid breakdown.

Gluconeogenesis is a ubiquitous process, present in plants, animals, fungi, bacteria, and other microorganisms. In vertebrates, gluconeogenesis takes place mainly in the liver and, to a lesser extent, in the cortex of the kidneys. In ruminants, this tends to be a continuous process. In many other animals, the process occurs during periods of fasting, starvation, low-carbohydrate diets, or intense exercise. The process is highly endergonic until it is coupled to the hydrolysis of ATP or GTP, effectively making the process exergonic. For example, the pathway leading from pyruvate to glucose-6-phosphate requires 4 molecules of ATP and 2 molecules of GTP to proceed spontaneously. Gluconeogenesis is often associated with ketosis. Gluconeogenesis is also a target of therapy for type 2 diabetes, such as the antidiabetic drug, metformin, which inhibits glucose formation and stimulates glucose uptake by cells. In ruminants, because metabolizable dietary carbohydrates tend to be metabolized by rumen organisms, gluconeogenesis occurs regardless of fasting, low-carbohydrate diets, exercise, etc.

https://en.wikipedia.org/wiki/Gluconeogenesis

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Chapter 6 - Metabolism: Sugars
Chapter 6 - Metabolism: Citric Acid Cycle & Related Pathways
Chapter 6 - Metabolism: Citric Acid Cycle & Related Pathways
Chapter 6 - Metabolism: Citric Acid Cycle & Related Pathways
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Glucosamine-6-phosphate

Glucosamine-6-phosphate is a precursor of N-acetylglucosamine and is an ate in synthesis of the peptidoglycan cell wall layer of bacteria.

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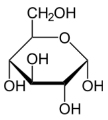
Glucose

Glucose is a sugar with the molecular formula C6H12O6. The suffix "-ose" is a chemical classifier, denoting a carbohydrate. It is also known as grape sugar. With 6 carbon atoms, it is classed as a hexose, a sub-category of monosaccharides. α-D-glucose is one of the 16 aldose stereoisomers. The D-isomer (D-glucose), also known as dextrose, occurs widely in nature, but the L-isomer (L-glucose) does not. Glucose is made during photosynthesis from water and carbon dioxide, using energy from sunlight. The reverse of the photosynthesis reaction, which releases this energy, is a very important source of power for cellular respiration. Glucose is stored as a polymer, in plants as starch and in animals as glycogen, for times when the organism will need it. Glucose circulates in the blood of animals as blood sugar. Glucose can be obtained by hydrolysis of carbohydrates such as milk, cane sugar, maltose, cellulose, glycogen etc. It is however, manufactured by hydrolysis of cornstarch by steaming and diluting acid.

Glucose is the most widely used aldohexose in living organisms. One possible explanation for this is that glucose has a lower tendency than other aldohexoses to react non-specifically with the amine groups of proteins. This reaction – glycation – impairs or destroys the function of many proteins. Glucose's low rate of glycation can be attributed to it having a more stable cyclic form compared to other aldohexoses, which means it spends less time than they do in its reactive open-chain form. The reason for glucose having the most stable cyclic form of all the aldohexoses is that its hydroxy groups (with the exception of the hydroxy group on the anomeric carbon of D-glucose) are in the equatorial position. Many of the long-term complications of diabetes (e.g., blindness, renal failure, and peripheral neuropathy) are probably due to the glycation of proteins or lipids. In contrast, enzyme-regulated addition of sugars to protein is called glycosylation and is essential for the function of many proteins.



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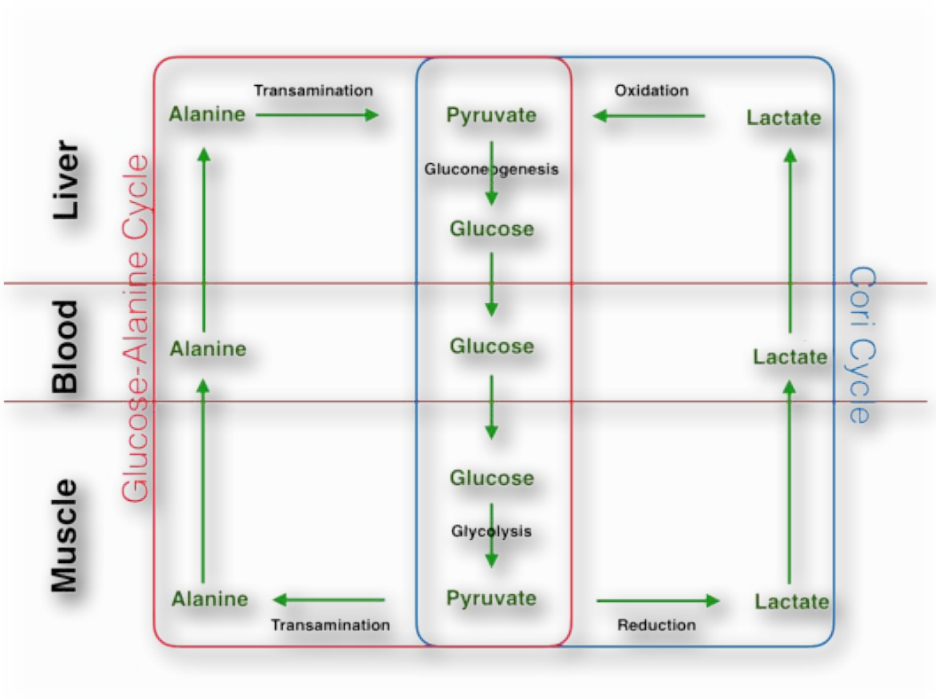
Glucose Alanine Cycle

The Cahill cycle, also known as the alanine cycle or glucose-alanine cycle, is the series of reactions in which amino groups and carbons from muscle are transported to the liver. When muscles degrade amino acids for energy needs, the resulting nitrogen is transaminated to pyruvate to form alanine. This alanine is shuttled to the liver where the nitrogen enters the urea cycle and the pyruvate is used to make glucose.

The Cahill cycle is less productive than the Cori cycle, which uses lactate, since a by-product of energy production from alanine is production of urea. Removal of the urea is energy-dependent, requiring four "high-energy" phosphate bonds (3 ATP hydrolyzed to 2 ADP and one AMP), thus the net ATP produced is less than that found in the Cori cycle. However, unlike in the Cori cycle, NADH is conserved because lactate is not formed. This allows for it to be oxidized via the electron transport chain. This pathway requires the presence of alanine aminotransferase, which is restricted to tissues such as muscle, liver, and the intestine. Therefore, this pathway is used instead of the Cori cycle only when an aminotransferase is present and when there is a need to transfer ammonia to the liver.
The alanine cycle also serves other purposes:

- Recycles carbon skeletons between muscle and liver
- Transports ammonium to the liver and is converted into urea.



https://en.wikipedia.org/wiki/Cahill_cycle

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Glucose Metabolism

Carbohydrate metabolism denotes the various biochemical processes responsib
the formation, breakdown and interconversion of carbohydrates in living organ

The most important carbohydrate is glucose, a simple sugar (monosaccharide)
metabolized by nearly all known organisms. Glucose and other carbohydrates a
of a wide variety of metabolic pathways across species: plants synthesize carboh
from carbon dioxide and water by photosynthesis storing the absorbed energy i
nally, often in the form of starch or lipids. Plant components are consumed by a
and fungi, and used as fuel for cellular respiration. Oxidation of one gram of ca
drate yields approximately 4 kcal of energy, while the oxidation of one gram of
yields about 9 kcal. Energy obtained from metabolism (e.g., oxidation of glucos
usually stored temporarily within cells in the form of ATP. Organisms capable o
bic respiration metabolize glucose and oxygen to release energy with carbon dio
and water as byproducts.

https://en.wikipedia.org/wiki/Carbohydrate_metabolism

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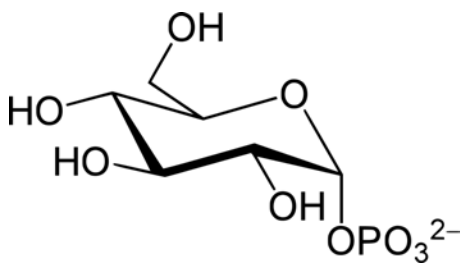
Glucose-1-phosphate

Glucose 1-phosphate (also called Cori ester or G1P) is a glucose molecule with a phosphate group on the 1'-carbon. It can exist in either the α- or β-anomeric form.

Catabolically, G1P is the direct product of the reaction in which glycogen phosphorylase cleaves off a molecule of glucose from a greater glycogen structure.
To be utilized in cellular catabolism it must first be converted to glucose 6-phosphate by the enzyme phosphoglucomutase. One reason that cells form glucose 1-phosphate instead of glucose during glycogen breakdown is that the very polar phosphorylated glucose cannot leave the cell membrane and so is marked for intracellular catabolism.

In glycogen synthesis, free glucose 1-phosphate can react with UTP to form UDP-glucose, by using the enzyme UDP-glucose pyrophosphorylase. It can then return to the greater glycogen structure via glycogen synthase.



https://en.wikipedia.org/wiki/Glucose_1-phosphate

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Glucose-6-phosphate

Glucose 6-phosphate (also known as Robison ester) is glucose sugar phosphorylated on carbon 6. This compound is very common in cells as the vast majority of glucose entering a cell will become phosphorylated in this way.

Because of its prominent position in cellular chemistry, glucose 6-phosphate has many possible fates within the cell. It lies at the start of two major metabolic pathways: glycolysis and the pentose phosphate pathway. In addition to these metabolic pathways, glucose 6-phosphate may also be converted to glycogen or starch for storage. This storage is in the liver and muscles in the form of glycogen for most multicellular animals, and in intracellular starch or glycogen granules for most other organisms.

Glycolysis

If the cell needs energy or carbon skeletons for synthesis then glucose 6-phosphate is targeted for glycolysis. Glucose 6-phosphate is first isomerized to fructose 6-phosphate by phosphoglucose isomerase.

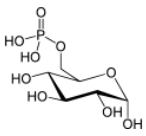
Pentose Phosphate Pathway

When the ratio of $NADP^+$: NADPH increases, the body realizes it needs to produce more NADPH (a reducing agent for several reactions like fatty acid synthesis and glutathione reduction in erythrocytes). This will cause the G6P to be dehydrogenated by glucose 6-phosphate dehydrogenase. This irreversible reaction is the initial step of the pentose phosphate pathway, which generates the useful cofactor NADPH as well as ribulose-5-phosphate, a carbon source for the synthesis of other molecules. Also, if the body needs nucleotide precursors of DNA for growth and synthesis, G6P will also be dehydrogenated and enter the pentose phosphate pathway.

Glycogen Synthesis

If blood glucose levels are high, the body needs a way to store the excess glucose. After being converted to G6P, the molecule can be turned into glucose-1-phosphate by phosphoglucomutase. Glucose-1-phosphate can then be combined with uridine triphosphate (UTP) to form UDP-glucose, driven by the hydrolysis of UTP, releasing phosphate. Now, the activated UDP-glucose can add to a growing glycogen molecule with the help of glycogen synthase. This is a very efficient storage mechanism for glucose since it costs the body only 1 ATP to store the 1 glucose molecule and virtually no energy to remove it from storage. It is important to note that glucose-6-phosphate is an allosteric activator of glycogen synthase, which makes sense because when the level of glucose is high the body should store the excess glucose as glycogen. On the other hand, glycogen synthase is inhibited when it is phosphorylated by protein kinase during times of high stress or low levels of blood glucose, via hormone induction by glucagon or adrenaline.

When the body needs glucose for energy, glycogen phosphorylase, with the help of an orthophosphate, can cleave away a molecule from the glycogen chain. The cleaved molecule is in the form of glucose-1-phosphate, which can be converted into G6P by phosphoglucomutase. Next, the phosphoryl group on G6P can be cleaved by glucose-6-phosphatase so that a free glucose can be formed. This free glucose can pass through membranes and can enter the bloodstream to travel to other places in the body.



https://en.wikipedia.org/wiki/Glucose_6-phosphate

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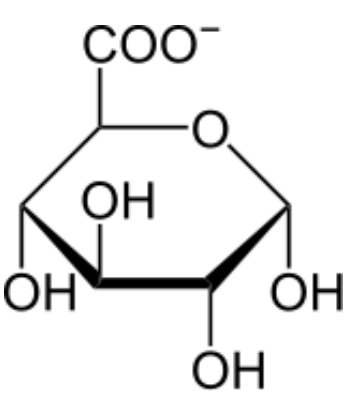
Glucuronic Acid

Glucuronic acid is a uronic acid that was first isolated from urine (hence the name). It is found in many gums such as Gum arabic (ca. 18 %) and Xanthan, and is important for the metabolism of microorganisms, plants and animals.

Glucuronic acid is a sugar acid derived from glucose, with its sixth carbon atom oxidized to a carboxylic acid. In living beings, this primary oxidation occurs with UDP-α-D-glucose (UDPG), not with the free sugar.

Glucuronic acid is a common building block of proteoglycans and glycoglycerolipids such as:
• Heparin is an inhibitor of blood coagulation, and occurs in mast cells, lung and liver.
• Chondroitin sulfate is found in large quantities in cartilage, aorta, connective tissue, bone, and skin.
• Dermatan sulfate is a proteoglycan in skin, heart, and blood vessels.
• Keratan sulfate being found in the cornea, cartilage, and bone.
• Hyaluronic acid occurs in large quantities in connective tissues, skin, cartilage, and synovial fluid.
• Glycoglycerolipids of glucuronic or galacturonic acids form the cell walls of bacteria.



https://en.wikipedia.org/wiki/Glucuronic_acid

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Glutamate Dehydrogenase

Glutamate dehydrogenase (GLDH) is an enzyme, present in most microbes and the mitochondria of eukaryotes, as are some of the other enzymes required for urea synthesis, that converts glutamate to α-ketoglutarate, and vice versa. In animals, the produced ammonia is usually used as a substrate in the urea cycle. Typically, the α-ketoglutarate to glutamate reaction does not occur in mammals, as glutamate dehydrogenase equilibrium favors the production of ammonia and α-ketoglutarate.

Glutamate dehydrogenase also has a very low affinity for ammonia (high Michaelis constant of about 1 mM), and therefore toxic levels of ammonia would have to be present in the body for the reverse reaction to proceed (that is, α-ketoglutarate and ammonia to glutamate and $NAD(P)^+$). In bacteria, the ammonia is assimilated to amino acids via glutamate and aminotransferases. In plants, the enzyme can work in either direction depending on environment and stress. Transgenic plants expressing microbial GLDHs are improved in tolerance to herbicide, water deficit, and pathogen infections. They are more nutritionally valuable.

https://en.wikipedia.org/wiki/Glutamate_dehydrogenase

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Glutamate-5-kinase

In enzymology, a glutamate 5-kinase (EC 2.7.2.11) is an enzyme that catalyz
chemical reaction:

ATP + L-glutamate <---> ADP + L-glutamate 5-phosphate

This enzyme participates in urea cycle and metabolism of amino groups.

https://en.wikipedia.org/wiki/Glutamate_5-kinase

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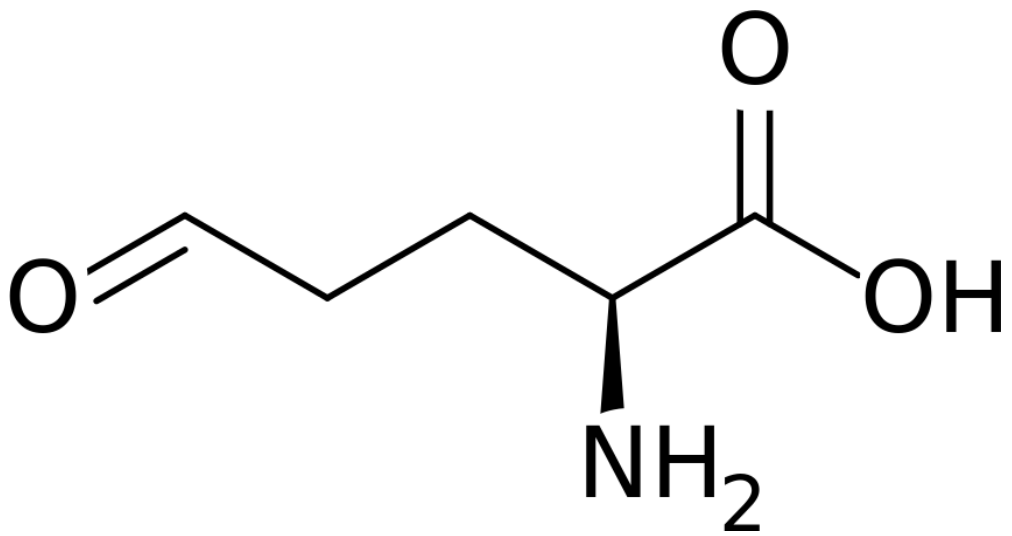
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Glutamate-5-semialdehyde

Glutamate-5-semialdehyde is a non-proteinogenic amino acid involved in t
thesis of proline and arginine (via ornithine), as well as in the biosynthesis
ics, such as carbapenems. It is synthesized by the reduction of glutamyl-5-p
by glutamate-5-semialdehyde dehydrogenase.



https://en.wikipedia.org/wiki/Glutamate-5-semialdehyde

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Glutamate-5-semialdehydy Dehydrogenase

In enzymology, a glutamate-5-semialdehyde dehydrogenase is an enzyme t
lyzes the chemical reaction:

L-glutamate 5-semialdehyde + P_i + $NADP^+$ <---> L-glutamyl 5-phosphate +
H^+

This enzyme belongs to the family of oxidoreductases, specifically those act
aldehyde or oxo group of donor with NAD^+ or $NADP^+$ as acceptor.

https://en.wikipedia.org/wiki/Glutamate-5-semialdehyde_dehydrogenase

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Glutamic Acid

Glutamic acid (abbreviated as Glu or E - encoded by the codons GAA or GAG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated –COO– form under biological conditions), and a side chain carboxylic acid, classifying it as a polar negatively charged (at physiological pH), aliphatic amino acid. It is non-essential in humans, meaning the body can synthesize it.

Glutamate is a key compound in cellular metabolism. In humans, dietary proteins are broken down by digestion into amino acids, which serve as metabolic fuel for other functional roles in the body. A key process in amino acid degradation is transamination, in which the amino group of an amino acid is transferred to an α-ketoacid, typically catalyzed by a transaminase. The reaction can be generalized as such:

R_1-amino acid + R_2-α-ketoacid ⇌ R_1-α-ketoacid + R_2-amino acid

A very common α-keto acid is α-ketoglutarate, an intermediate in the citric acid cycle. Transamination of α-ketoglutarate gives glutamate. The resulting α-ketoacid product is often a useful one as well, which can contribute as fuel or as a substrate for further metabolism processes. Examples are as follows:

Alanine + α-ketoglutarate ⇌ Pyruvate + Glutamate

Aspartate + α-ketoglutarate ⇌ Oxaloacetate + Glutamate

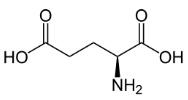
Both pyruvate and oxaloacetate are key components of cellular metabolism, contributing as substrates or intermediates in fundamental processes such as glycolysis, gluconeogenesis, and the citric acid cycle.

Glutamate also plays an important role in the body's disposal of excess or waste nitrogen. Glutamate undergoes deamination, an oxidative reaction catalyzed by glutamate dehydrogenase, as follows:

Glutamate + H_2O + $NADP^+$ → α-ketoglutarate + NADPH + NH_3 + H^+

Ammonia (as ammonium) is then excreted predominantly as urea, synthesized in the liver. Transamination can thus be linked to deamination, effectively allowing nitrogen from the amine groups of amino acids to be removed, via glutamate as an intermediate, and finally excreted from the body in the form of urea.

Glutamate is also a neurotransmitter, which makes it one of the most abundant molecules in the brain. Malignant brain tumors known as glioma or glioblastoma exploit this phenomenon by using glutamate as an energy source, especially when these mutations become more dependent on glutamate due to mutations in the gene IDH1.



https://en.wikipedia.org/wiki/Glutamic_acid

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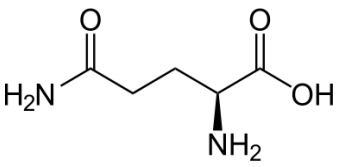
Glutamine

Glutamine (abbreviated as Gln or Q; encoded by the codons CAA and CAG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain amide which replaces the side chain hydroxyl of glutamic acid with an amine functional group, classifying it as a charge neutral, polar (at physiological pH) amino acid. It is non-essential and conditionally essential in humans, meaning the body can usually synthesize sufficient amounts of it, but in some instances of stress, the body's demand for glutamine increases and glutamine must be obtained from the diet.

Glutamine plays a role in a variety of biochemical functions:
- Protein synthesis, as any other of the 20 proteinogenic amino acids
- Lipid synthesis, especially by cancer cells.
- Regulation of acid-base balance in the kidney by producing ammonium
- Cellular energy, as a source, next to glucose
- Nitrogen donation for many anabolic processes, including the synthesis of purines
- Carbon donation, as a source, refilling the citric acid cycle
- Nontoxic transporter of ammonia in the blood circulation



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Glutamine Synthetase

Glutamine synthetase (GS) is an enzyme that plays an essential role in the metabolism of nitrogen by catalyzing the condensation of glutamate and ammonia to form glutamine:

Glutamate + ATP + NH_3 → Glutamine + ADP + P_i

Glutamine Synthetase uses ammonia produced by nitrate reduction, amino acid degradation, and photorespiration. The amide group of glutamate is a nitrogen source for the synthesis of glutamine pathway metabolites.

Other reactions may take place via GS. Competition between ammonium ion and water, their binding affinities, and the concentration of ammonium ion, influences glutamine synthesis and glutamine hydrolysis. Glutamine is formed if an ammonium ion attacks the acyl-phosphate intermediate, while glutamate is remade if water attacks the intermediate. Ammonium ion binds more strongly than water to GS due to electrostatic forces between a cation and a negatively charged pocket. Another possible reaction is upon NH_2OH binding to GS, rather than NH_4^+, yields γ-glutamylhydroxamate.

GS is present predominantly in the brain, kidneys, and liver. GS in the brain participates in the metabolic regulation of glutamate, the detoxification of brain ammonia, the assimilation of ammonia, recyclization of neurotransmitters, and termination of neurotransmitter signals. GS, in the brain, is found primarily in astrocytes. Astrocytes protect neurons against excitotoxicity by taking up excess ammonia and glutamate. In hyperammonemic environments (high levels of ammonia), astroglial swelling occurs. Different perspectives have approached the problem of astroglial swelling. One study shows that morphological changes occur that increase GS expression in glutamatergic areas or other adaptations that alleviates high levels of glutamate and ammonia. Another perspective is that astrocyte swelling is due to glutamine accumulation. To prevent increased levels of cortical glutamate and cortical water content, a study has been conducted to prevent GS activity in rats by the use of MSO.

https://en.wikipedia.org/wiki/Glutamine_synthetase

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Glutaredoxin

Glutaredoxins are small redox enzymes of approximately one hundred amino-acid residues that use glutathione as a cofactor. Glutaredoxins are oxidized by substrates, and reduced non-enzymatically by glutathione. In contrast to thioredoxins, which are reduced by thioredoxin reductase, no oxidoreductase exists that specifically reduces glutaredoxins. Instead, glutaredoxins are reduced by the oxidation of glutathione. Oxidized glutathione is then regenerated by glutathione reductase. Together these components compose the glutathione system.
Like thioredoxin, which functions in a similar way, glutaredoxin possesses an active center disulfide bond. It exists in either a reduced or an oxidized form where the two cysteine residues are linked in an intramolecular disulfide bond. Glutaredoxins function as electron carriers in the glutathione-dependent synthesis of deoxyribonucleotides by the enzyme ribonucleotide reductase. Moreover, GRX act in antioxidant defence by reducing dehydroascorbate, peroxiredoxins, and methionine sulfoxide reductase. Beside their function in antioxidant defence, bacterial and plant GRX were shown to bind iron-sulfur clusters and to deliver the cluster to enzymes on demand.

https://en.wikipedia.org/wiki/Glutaredoxin

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Chapter 6 - Metabolism: Nucleotides

Glutathione

Glutathione (GSH) is an important antioxidant in plants, animals, fungi, and some bacteria and archaea, preventing damage to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides and heavy metals. It is a tripeptide with a γ peptide linkage between the carboxyl group of the glutamate side-chain and the amine group of cysteine (which is attached by normal peptide linkage to a glycine).

Thiol groups are reducing agents, existing at a concentration around 5 mM in animal cells. Glutathione reduces disulfide bonds formed within cytoplasmic proteins to cysteines by serving as an electron donor. In the process, glutathione is converted to its oxidized form, glutathione disulfide (GSSG), also called L-(–)-glutathione.

Once oxidized, glutathione can be reduced back by glutathione reductase, using NADPH as an electron donor. The ratio of reduced glutathione to oxidized glutathione within cells is often used as a measure of cellular toxicity.

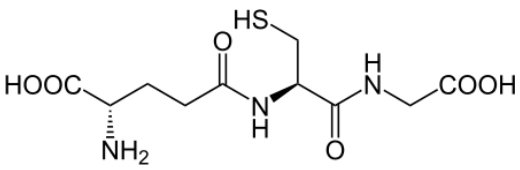
Glutathione exists in both reduced (GSH) and oxidized (GSSG) states. In the reduced state, the thiol group of cysteine is able to donate a reducing equivalent ($H^+ + e^-$) to other unstable molecules, such as reactive oxygen species. In donating an electron, glutathione itself becomes reactive, but readily reacts with another reactive glutathione to form glutathione disulfide (GSSG). Such a reaction is probable due to the relatively high concentration of glutathione in cells (up to 5 mM in the liver).

Generally, interactions between GSH and other molecules with higher relative electrophilicity deplete GSH levels within the cell. An exception to this case involves the sensitivity of GSH to the electrophilic compound's relative concentration. In high concentrations, the organic molecule Diethyl maleate fully depleted GSH levels in cells. However, in low concentrations, a minor decease in cellular GSH levels was followed by a two-fold increase.

GSH can be regenerated from GSSG by the enzyme glutathione reductase (GSR): NADPH reduces FAD present in GSR to produce a transient FADH-anion. This anion then quickly breaks a disulfide bond (Cys58 - Cys63) and leads to Cys63's nucleophilically attacking the nearest sulfide unit in the GSSG molecule (promoted by His467), which creates a mixed disulfide bond (GS-Cys58) and a GS-anion. His467 of GSR then protonates the GS-anion to form the first GSH. Next, Cys63 nucleophilically attacks the sulfide of Cys58, releasing a GS-anion, which, in turn, picks up a solvent proton and is released from the enzyme, thereby creating the second GSH. So, for every GSSG and NADPH, two reduced GSH molecules are gained, which can again act as antioxidants scavenging reactive oxygen species in the cell.

In healthy cells and tissue, more than 90% of the total glutathione pool is in the reduced form (GSH) and less than 10% exists in the disulfide form (GSSG). An increased GSSG-to-GSH ratio is considered indicative of oxidative stress.
Glutathione has multiple functions:

- It is the major endogenous antioxidant produced by the cells, participating directly in the neutralization of free radicals and reactive oxygen compounds, as well as maintaining exogenous antioxidants such as vitamins C and E in their reduced (active) forms.
- Regulation of the nitric oxide cycle is critical for life, but can be problematic if unregulated.
- It is used in metabolic and biochemical reactions such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport, and enzyme activation. Thus, every system in the body can be affected by the state of the glutathione system, especially the immune system, the nervous system, the gastrointestinal system, and the lungs.
- It has a vital function in iron metabolism. Yeast cells depleted of or containing toxic levels of GSH show an intense iron starvation-like response and impairment of the activity of extramitochondrial ISC enzymes, followed by death.



https://en.wikipedia.org/wiki/Glutathione

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Glutathione Peroxidase

Glutathione peroxidase (GPx) is the general name of an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage. The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water.

The main reaction that glutathione peroxidase catalyzes is:

$2GSH + H_2O_2 \rightarrow GS–SG + 2H_2O$

where GSH represents reduced monomeric glutathione, and GS–SG represents glutathione disulfide. The mechanism involves oxidation of the selenol of a selenocysteine residue by hydrogen peroxide. This process gives the derivative with a selenenic acid (RSeOH) group. The selenenic acid is then converted back to the selenol by a two step process that begins with reaction with GSH to form the GS-SeR and water. A second GSH molecule reduces the GS-SeR intermediate back to the selenol, releasing GS-SG as the by-product. A simplified representation is shown below:

$RSeH + H_2O_2 \rightarrow RSeOH + H_2O$
$RSeOH + GSH \rightarrow GS\text{-}SeR + H_2O$
$GS\text{-}SeR + GSH \rightarrow GS\text{-}SG + RSeH$

Glutathione reductase then reduces the oxidized glutathione to complete the cycle:

$GS–SG + NADPH + H^+ \rightarrow 2\ GSH + NADP^+$.

It has been shown that low levels of glutathione peroxidase as measured in the serum may be a contributing factor to vitiligo. Lower plasma glutathione peroxide levels were also observed in patients with type 2 diabetes with macroalbuminuria and this was correlated to the stage of diabetic nephropathy. In one study, the activity of glutathione peroxidase along with other antioxidant enzymes such as superoxide dismutase and catalase was not associated with coronary heart disease risk in women. Glutathione peroxidase activity was found to be much lower in patients with relapsing-remitting multiple sclerosis. One study has suggested that glutathione peroxidase and superoxide dismutase polymorphisms play a role in the development of celiac disease.

https://en.wikipedia.org/wiki/Glutathione_peroxidase

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Glutathione Reductase

Glutathione reductase (GR) also known as glutathione-disulfide reductase (GSR) is an enzyme that in humans is encoded by the GSR gene. Glutathione reductase catalyzes the reduction of glutathione disulfide (GSSG) to the sulfhydryl form glutathione (GSH), which is a critical molecule in resisting oxidative stress and maintaining the reducing environment of the cell. Glutathione reductase functions as dimeric disulfide oxidoreductase and utilizes an FAD prosthetic group and NADPH to reduce one molar equivalent of GSSG to two molar equivalents of GSH.

Glutathione plays a key role in maintaining proper function and preventing oxidative stress in human cells. It can act as a scavenger for hydroxyl radicals, singlet oxygen, and various electrophiles. Reduced glutathione reduces the oxidized form of the enzyme glutathione peroxidase, which in turn reduces hydrogen peroxide (H2O2), a dangerously reactive species within the cell. In addition, it plays a key role in the metabolism and clearance of xenobiotics, acts as a cofactor in certain detoxifying enzymes, participates in transport, and regenerates antioxidants such and Vitamins E and C to their reactive forms. The ratio of GSSG/GSH present in the cell is a key factor in properly maintaining the oxidative balance of the cell, that is, it is critical that the cell maintains high levels of the reduced glutathione and a low level of the oxidized Glutathione disulfide. This narrow balance is maintained by glutathione reductase, which catalyzes the reduction of GSSG to GSH.

https://en.wikipedia.org/wiki/Glutathione_reductase

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Glutathione Synthetase

Glutathione synthetase (GSS) is the second enzyme in the glutathione (GSH) biosynthesis pathway. It catalyzes the condensation of γ-glutamylcysteine and glycine, to form glutathione. Glutathione synthetase is also a potent antioxidant. It is found in a large number of species including bacteria, yeast, mammals, and plants.

Glutathione synthetase is important for a variety of biological functions in multiple organisms. In *Arabidopsis thaliana*, low levels of glutathione synthetase have resulted in increased vulnerability to stressors such as heavy metals, toxic organic chemicals, and oxidative stress. The presence of a thiol functional group allows its product GSH to serve both as an effective oxidizing and reducing agent in numerous biological scenarios. Thiols can easily accept a pair of electrons and become oxidized to disulfides, and the disulfides can be readily reduced to regenerate thiols. Additionally, the thiol side chain of cysteines serve as potent nucleophiles and react with oxidants and electrophilic species that would otherwise cause damage to the cell. Interactions with certain metals also stabilize thiolate intermediates.

In humans, glutathione synthetase functions in a similar manner. Its product GSH participates in cellular pathways involved in homeostasis and cellular maintenance. For instance, glutathione peroxidases catalyze the oxidation of GSH to glutathione disulfide (GSSG) by reducing free radicals and reactive oxygen species such as hydrogen peroxide. Glutathione S-transferases uses GSH to clean up various metabolites, xenobiotics, and electrophiles to mercapturates for excretion. Because of its antioxidant role, GSS mostly produce GSH inside the cytoplasm of liver cells and imported to mitochondria where detoxification occurs. GSH is also essential for the activation of the immune system to generate robust defense mechanisms against invading pathogens. GSH is capable of preventing infection from the influenza virus.

https://en.wikipedia.org/wiki/Glutathione_synthetase

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

GLUTs

Glucose transporters are a wide group of membrane proteins that facilitate the transport of glucose over a plasma membrane. Because glucose is a vital source of energy for all life, these transporters are present in all phyla. The GLUT or SLC2A family are a protein family that is found in most mammalian cells. 12 GLUTS are encoded by human genome. GLUT is a type of uniporter transporter protein.

GLUTs are integral membrane proteins that contain 12 membrane-spanning helices with both the amino and carboxyl termini exposed on the cytoplasmic side of the plasma membrane. GLUT proteins transport glucose and related hexoses according to a model of alternate conformation, which predicts that the transporter exposes a single substrate binding site toward either the outside or the inside of the cell. Binding of glucose to one site provokes a conformational change associated with transport, and releases glucose to the other side of the membrane. The inner and outer glucose-binding sites are, it seems, located in transmembrane segments 9, 10, 11. Also, the QLS motif located in the seventh transmembrane segment could be involved in the selection and affinity of transported substrate.

https://en.wikipedia.org/wiki/Glucose_transporter

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Glycans

The terms glycan and polysaccharide are defined by IUPAC as synonyms mea
"compounds consisting of a large number of monosaccharides linked glycosi
However, in practice the term glycan may also be used to refer to the carbohy
tion of a glycoconjugate, such as a glycoprotein, glycolipid, or a proteoglycan,
the carbohydrate is only an oligosaccharide. Glycans usually consist solely of
glycosidic linkages of monosaccharides.

Glycans can be found attached to proteins as in glycoproteins and proteoglyc
general, they are found on the exterior surface of cells. O- and N-linked glyca
very common in eukaryotes but may also be found, although less commonly,
karyotes.

https://en.wikipedia.org/wiki/Glycan

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Glycation

Glycation (sometimes called non-enzymatic glycosylation) is the result of the covalent bonding of a protein or lipid molecule with a sugar molecule, such as or glucose, without the controlling action of an enzyme. All blood sugars are r molecules. Glycation may occur either inside the body (endogenous glycation side the body (exogenous glycation).

Enzyme-controlled addition of sugars to protein or lipid molecules is termed tion. Glycation is a haphazard process that impairs the functioning of biomol whereas glycosylation occurs at defined sites on the target molecule and is re order for the molecule to function. Much of the early laboratory research wor tose glycations used inaccurate assay techniques that led to drastic underesti the importance of fructose in glycation.

https://en.wikipedia.org/wiki/Glycation

Related Glossary Terms

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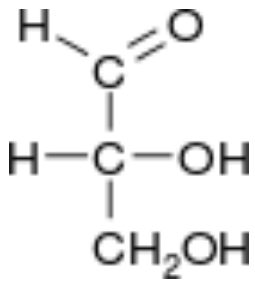
Glyceraldehyde

Glyceraldehyde (glyceral) is a triose monosaccharide with chemical formula
is the simplest of all common aldoses. It is a sweet, colorless, crystalline sol
intermediate compound in carbohydrate metabolism. The word comes fro
ing glycerol and aldehyde, as glyceraldehyde is glycerol with one hydroxym
oxidized to an aldehyde.



https://en.wikipedia.org/wiki/Glyceraldehyde

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Glyceraldehyde 3-phosphate Dehydrogenase

Glyceraldehyde 3-phosphate dehydrogenase (abbreviated as GAPDH or less commonly as G3PDH) is an enzyme of ~37kDa that catalyzes the sixth step of glycolysis and thus serves to break down glucose for energy and carbon molecules. In addition to this long established metabolic function, GAPDH has recently been implicated in several non-metabolic processes, including transcription activation, initiation of apoptosis, ER to Golgi vesicle shuttling, and fast axonal, or axoplasmic transport. In sperm, a testis-specific isoenzyme GAPDHS is expressed.

As its name indicates, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) catalyzes the conversion of glyceraldehyde 3-phosphate to D-glycerate 1,3-bisphosphate. This is the 6th step in the glycolytic breakdown of glucose, an important pathway of energy and carbon molecule supply which takes place in the cytosol of eukaryotic cells. The conversion occurs in two coupled steps. The first is favorable and allows the second unfavorable step to occur.

GAPDH can itself activate transcription. The OCA-S transcriptional coactivator complex contains GAPDH and lactate dehydrogenase, two proteins previously only thought to be involved in metabolism. GAPDH moves between the cytosol and the nucleus and may thus link the metabolic state to gene transcription.
In 2005, Hara et al. showed that GAPDH initiates apoptosis. This is not a third function, but can be seen as an activity mediated by GAPDH binding to DNA like in transcription activation, discussed above. The study demonstrated that GAPDH is S-nitrosylated by NO in response to cell stress, which causes it to bind to the protein SIAH1, a ubiquitin ligase. The complex moves into the nucleus where Siah1 targets nuclear proteins for degradation, thus initiating controlled cell shutdown. In subsequent study the group demonstrated that deprenyl, which has been used clinically to treat Parkinson's disease, strongly reduces the apoptotic action of GAPDH by preventing its S-nitrosylation and might thus be used as a drug.

GAPDH acts as reversible metabolic switch under oxidative stress. When cells are exposed to oxidants, they need excessive amounts of the antioxidant cofactor NADPH. In the cytosol, NADPH is reduced from $NADP^+$ by several enzymes, three of them catalyze the first steps of the Pentose phosphate pathway. Oxidant-treatments cause an inactivation of GAPDH. This inactivation re-routes temporally the metabolic flux from glycolysis to the Pentose Phosphate Pathway, allowing the cell to generate more NADPH. Under stress conditions, NADPH is needed by some antioxidant-systems including glutaredoxin and thioredoxin as well as being essential for the recycling of gluthathione.

GAPDH also appears to be involved in the vesicle transport from the endoplasmic reticulum (ER) to the Golgi apparatus which is part of shipping route for secreted proteins. It was found that GAPDH is recruited by rab2 to the vesicular-tubular clusters of the ER where it helps to form COP 1 vesicles. GAPDH is activated via tyrosine phosphorylation by Src.

GAPDH, like many other enzymes, has multiple functions. In addition to catalyzing the 6th step of glycolysis, recent evidence implicates GAPDH in other cellular processes.GAPDH has been described to exhibit higher order multifunctionality in the context of maintaining cellular iron homeostasis. This came as a surprise to researchers but it makes evolutionary sense to re-use and adapt existing proteins instead of evolving a novel protein from scratch.

https://en.wikipedia.org/wiki/Glyceraldehyde_3-phosphate_dehydrogenase

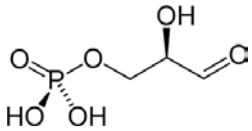
Glyceraldehyde-3-phosphate

Glyceraldehyde 3-phosphate, also known as triose phosphate or 3-phosphoglyceraldehyde and abbreviated as GLYAL3P, G3P, GA3P, GADP, GAP, TP, GALP or PGAL, is a chemical compound that occurs as an intermediate in several central metabolic pathways of all organisms. It is a phosphate ester of the 3-carbon sugar glyceraldehyde and has chemical formula $C_3H_7O_6P$.

During plant photosynthesis, 2 molecules of glycerate 3-phosphate (GP - also known as 3-phosphoglycerate) are produced by the first step of the light-independent reactions when ribulose 1,5-bisphosphate (RuBP) and carbon dioxide are catalyzed by the rubisco enzyme. The GP is converted to D-glyceraldehyde 3-phosphate (G3P) using the energy in ATP and the reducing power of NADPH as part of the Calvin cycle. This returns ADP, phosphate ions Pi, and $NADP^+$ to the light-dependent reactions of photosynthesis for their continued function. RuBP is regenerated for the Calvin cycle to continue.

G3P is generally considered the prime end-product of photosynthesis and it can be used as an immediate food nutrient, combined and rearranged to form monosaccharide sugars, such as glucose, which can be transported to other cells, or packaged for storage as insoluble polysaccharides such as starch.

Balance sheet
6 CO_2 + 6 RuBP (+ energy from 12 ATP and 12 NADPH) →12 G3P (3-carbon)
10 G3P (+ energy from 6 ATP) → 6 RuBP (i.e. starting material regenerated)
2 G3P → glucose (6-carbon).



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https://en.wikipedia.org/wiki/Glyceraldehyde_3-phosphate_dehydrogenase

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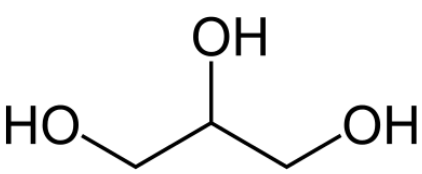
Chapter 3 - Membranes: Other Considerations

Glycerol

Glycerol (also called glycerine) is a simple polyol (sugar alcohol) compound. It is a colorless, odorless, viscous liquid that is sweet-tasting and non-toxic. It is widely used in the food industry as a sweetener and humectant and in pharmaceutical formulations. Glycerol has three hydroxyl groups that are responsible for its solubility in water and its hygroscopic nature. The glycerol backbone is central to all lipids known as triglycerides.

Glycerol is a precursor for synthesis of triacylglycerols and of phospholipids in the liver and adipose tissue. When the body uses stored fat as a source of energy, glycerol and fatty acids are released into the bloodstream. Circulating glycerol does not glycate proteins as do glucose or fructose, and does not lead to the formation of advanced glycation endproducts (AGEs). In some organisms, the glycerol component can enter the glycolysis pathway directly and, thus, provide energy for cellular metabolism (or, potentially, be converted to glucose through gluconeogenesis).

Before glycerol can enter the pathway of glycolysis or gluconeogenesis (depending on physiological conditions), it must be converted to the intermediate glyceraldehyde 3-phosphate.



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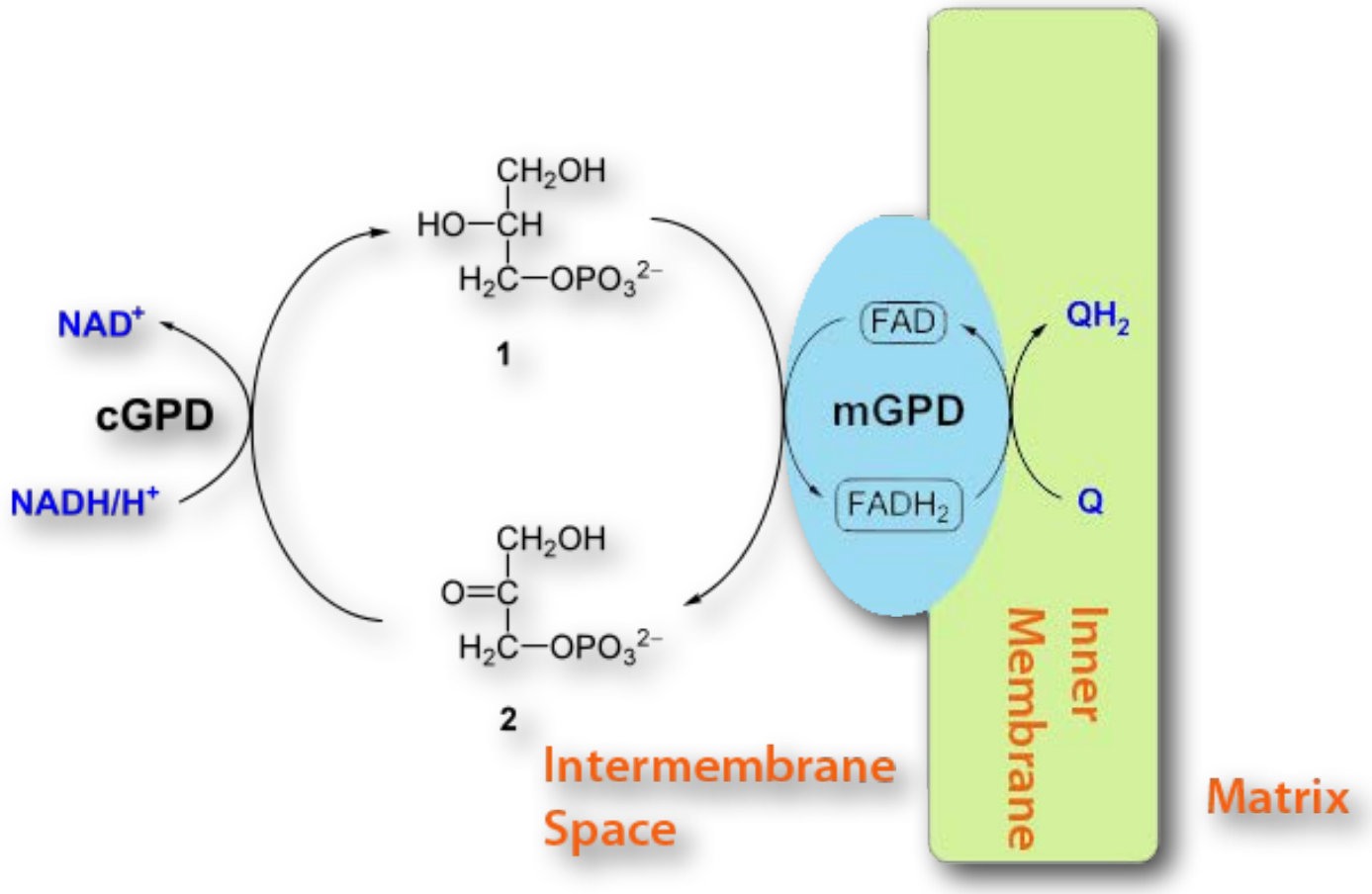
Glycerol Phosphate Shuttle

The glycerol-3-phosphate shuttle is a mechanism that regenerates NAD^+ from NADH, a by-product of glycolysis. Its importance in transporting reducing equivalents is secondary to the malate-aspartate shuttle.



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Chapter 3 - Membranes: Other Considerations

Chapter 9 - Point by Point: Membranes

Chapter 9 - Point by Point: Membranes

Glycerol-3-phosphate

sn-Glycerol 3-phosphate is a phosphoric ester of glycerol, which is a component of glycerophospholipids.

Glycerol 3-phosphate is synthesized by reducing dihydroxyacetone phosphate (DHAP), a glycolysis intermediate, with glycerol-3-phosphate dehydrogenase. DHAP and thus glycerol 3-phosphate is also possible to be synthesized from amino acids and citric acid cycle intermediates via glyceroneogenesis pathway.

Glycerol 3-phosphate is a starting material for *de novo* synthesis of glycerolipids.

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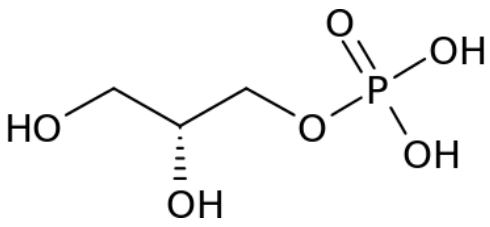
It is also synthesized by phosphorylating glycerol generated upon hydrolyzing fats with glycerol kinase, and can feed into glycolysis or glyconeogenesis pathways.

Glycerol 3-phosphate is a starting material for *de novo* synthesis of glycerolipids. In eukaryotes, it is first acylated on its sn-1 position by an ER- or mitochondrial membrane enzyme, glycerol-3-phosphate O-acyltransferase, and another acyl group is then added on the sn-2 position making phosphatidic acids.

Some fungi have glycerol-1-phosphatase, which removes the phosphate group of glycerol 3-phosphate to generate glycerol. They can perform glycerol fermentation producing glycerol from glucose through glycolysis pathway.



https://en.wikipedia.org/wiki/Glycerol_3-phosphate

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Glycerol-3-phosphate Dehydrogenase

Glycerol-3-phosphate dehydrogenase (GPDH) is an enzyme that catalyzes t
ble redox conversion of dihydroxyacetone phosphate (aka glycerone phospl
dated) to sn-glycerol 3-phosphate.
Glycerol-3-phosphate dehydrogenase serves as a major link between carbol
tabolism and lipid metabolism. It is also a major contributor of electrons to
tron transport chain in the mitochondria.

GPDH plays a major role in lipid biosynthesis. Through the reduction of dil
tone phosphate into glycerol 3-phosphate, GPDH allows the prompt depho
tion of glycerol 3-phosphate into glycerol. Additionally, GPDH is responsib
taining the redox potential across the inner mitochondrial membrane in gly

https://en.wikipedia.org/wiki/Glycerol-3-phosphate_dehydrogenase

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Glycerol-3-phosphate O-acyl Transferase

In enzymology, a glycerol-3-phosphate O-acyltransferase is an enzyme that
the chemical reaction:

Acyl-CoA + sn-glycerol 3-phosphate <---> CoASH + 1-acyl-sn-glycerol 3-ph

The reaction it catalyzes is important for synthesis of phosphatidic acid and

https://en.wikipedia.org/wiki/Glycerol-3-phosphate_O-acyltransferase

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Glycerophospholipid

Glycerophospholipids or phosphoglycerides are glycerol-based phospholipids. They are the main components of biological membranes.

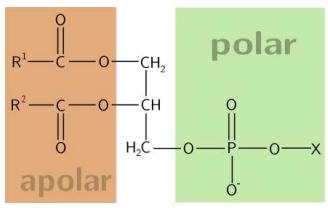
The term glycerophospholipid signifies any derivative of glycerophosphoric acid that contains at least one O-acyl, or O-alkyl, or O-alk-1'- enyl residue attached to the glycerol moiety.

Plasmalogens are a type of phosphoglyceride. The first carbon of glycerol has a hydrocarbon chain attached via an ether, not ester, linkage. The linkages are more resistant to chemical attack than ester linkages are. The second (central) carbon atom has a fatty acid linked by an ester. The third carbon links to an ethanolamine or choline by means of a phosphate ester. These compounds are key components of the membranes of muscles and nerves.

Phosphatidates are lipids in which the first two carbon atoms of the glycerol are fatty acid esters, and the third is a phosphate ester. The phosphate serves as a link to another alcohol-usually ethanolamine, choline, serine, or a carbohydrate. The identity of the alcohol determines the subcategory of the phosphatidate. There is a negative charge on the phosphate and, in the case of choline or serine, a positive quaternary ammonium ion. (Serine also has a negative carboxylate group.) The presence of charges give a "head" with an overall charge. The phosphate ester portion ("head") is hydrophilic, whereas the remainder of the molecule, the fatty acid "tail", is hydrophobic. These are important components for the formation of lipid bilayers. Phosphatidylethanoamines, phosphatidylcholines, and other phospholipids are examples of phosphatidates.

Phosphatidylcholines are lecithins. Choline is the alcohol, with a positively charged quaternary ammonium, bound to the phosphate, with a negative charge. Lecithins are present in all living organisms. An egg yolk has a high concentration of lecthins- which are commercially important as an emulsifying agent in products such as mayonnaise. Lecithins are also present in brain and nerve tissue.

There are many other phospholipids, some of which are glycolipids. The glycolipids include phosphatidyl sugars where the alcohol functional group is part of a carbohydrate. Phosphatidyl sugars are present in plants and certain microorganisms. A carbohydrate is very hydrophilic due to the large number of hydroxyl groups present.



https://en.wikipedia.org/wiki/Glycerophospholipid

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Glycerophospholipids

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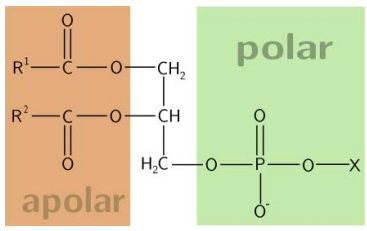

https://en.wikipedia.org/wiki/Glycerophospholipid

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Glycine

Glycine (abbreviated as Gly or G) is the smallest of the 20 amino acids commonly found in proteins, and indeed is the smallest possible (having a hydrogen substituent as its side-chain). Most proteins incorporate only small quantities of glycine. A notable exception is collagen, which contains about 35% glycine. The formula is NH_2CH_2COOH. Its codons are GGU, GGC, GGA, GGG of the genetic code.

Glycine is a colorless, sweet-tasting crystalline solid. It is unique among the proteinogenic amino acids in that it is achiral. It can fit into hydrophilic or hydrophobic environments, due to its minimal side chain of only one hydrogen atom. The acyl radical is glycyl.

Synthesis

Glycine is not essential to the human diet, as it is biosynthesized in the body from the amino acid serine, which is in turn derived from 3-phosphoglycerate, but the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. In most organisms, the enzyme serine hydroxymethyltransferase catalyzes this transformation via the cofactor pyridoxal phosphate:

Serine + Tetrahydrofolate → Glycine + N_5,N_{10}-Methylene tetrahydrofolate + H_2O

In the liver of vertebrates, glycine synthesis is catalyzed by glycine synthase. This conversion is readily reversible:

CO_2 + NH_4^+ + N_5,N_{10}-Methylene tetrahydrofolate + NADH + H^+ → Glycine + Tetrahydrofolate + NAD^+

Degradation

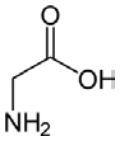
Glycine is degraded via three pathways. The predominant pathway in animals and plants involves the glycine cleavage enzyme:

Glycine + Tetrahydrofolate + NAD^+ → CO_2 + NH_4^+ + N_5,N_{10}-Methylene Tetrahydrofolate + NADH + H^+

In the second pathway, glycine is degraded in two steps. The first step is the reverse of glycine biosynthesis from serine with serine hydroxymethyl transferase. Serine is then converted to pyruvate by serine dehydratase.

In the third pathway of glycine degradation, glycine is converted to glyoxylate by D-amino acid oxidase. Glyoxylate is then oxidized by hepatic lactate dehydrogenase to oxalate in an NAD^+-dependent reaction.

The half-life of glycine and its elimination from the body varies significantly based on dose. In one study, the half-life was between 0.5 and 4.0 hours.



https://en.wikipedia.org/wiki/Glycine

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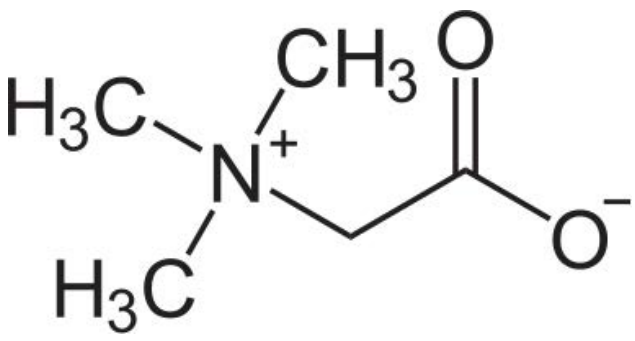
Glycine Betaine

Trimethylglycine (TMG) is an amino acid derivative that occurs in plants. Trimethylglycine was the first betaine discovered. Originally it was simply called betaine because, in the 19th century, it was discovered in sugar beets. Since then, many other betaines have been discovered, and the more specific name glycine betaine distinguishes this one.

TMG is an important cofactor in methylation, a process that occurs in every cell of mammals to synthesize and donate methyl groups (CH_3) for other processes in the body. These processes include the synthesis of neurotransmitters such as dopamine and serotonin. Methylation is also required for the biosynthesis of melatonin and the electron transport chain constituent coenzyme Q_{10}.



https://en.wikipedia.org/wiki/Trimethylglycine

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Glycine Synthase

The glycine cleavage system (GCS) is also known as the glycine decarboxyla
or GDC. The system is a series of enzymes that are triggered in response to
trations of the amino acid glycine. The same set of enzymes is sometimes re
glycine synthase when it runs in the reverse direction to form glycine. Th
cleavage system is composed of four proteins: the T-protein, P-protein, L-p
H-protein. They do not form a stable complex, so it is more appropriate to
tem" instead of a "complex". The H-protein is responsible for interacting w
other proteins and acts as a shuttle for some of the intermediate products i
carboxylation. In both animals and plants the glycine cleavage system is loc
tached to the inner membrane of the mitochondria.

https://en.wikipedia.org/wiki/Glycine_cleavage_system

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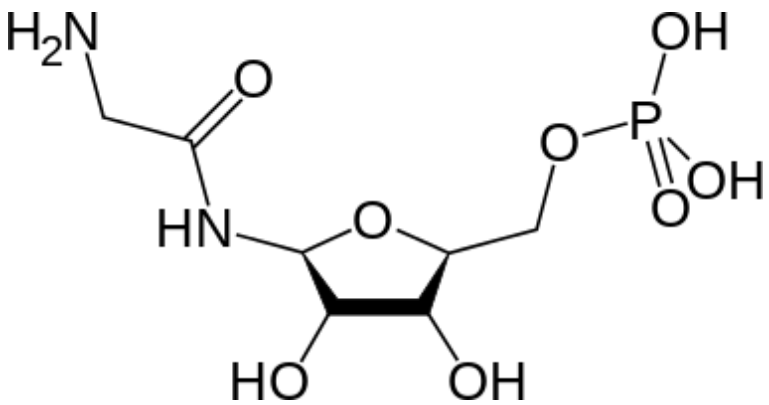
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Glycineamide Ribonucleotide

Glycineamide ribonucleotide (or GAR) is an intermediate in *de novo* purine biosynthesis.

It is formed from phosphoribosylamine by the enzyme phosphoribosylamine—glycine ligase. In the next step of purine biosynthesis the enzyme phosphoribosylglycinamide formyltransferase acts on GAR to form FGAR.

GAR formation is stimulated by luteinizing hormone (LH) and chorionic gonadotropin (HCG) via activation of Glc-6-P-dehydrogenase.



https://en.wikipedia.org/wiki/Glycineamide_ribonucleotide

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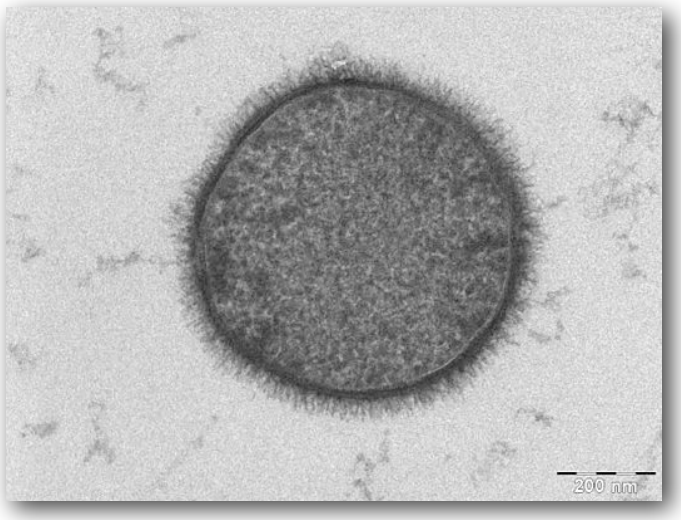
Glycocalyx

The glycocalyx is a glycoprotein-polysaccharide covering that surrounds the cell membranes of some bacteria, epithelia and other cells.

Most animal epithelial cells have a fuzz-like coat on the external surface of their plasma membranes. This coating consists of several carbohydrate moieties of membrane glycolipids and glycoproteins, which serve as backbone molecules for support. Generally, the carbohydrate portion of the glycolipids found on the surface of plasma membranes helps these molecules contribute to cell-cell recognition, communication, and intercellular adhesion.

The glycocalyx is a type of identifier that the body uses to distinguish between its own healthy cells and transplanted tissues, diseased cells, or invading organisms. Included in the glycocalyx are cell-adhesion molecules that enable cells to adhere to each other and guide the movement of cells during embryonic development. The glycocalyx plays a major role in regulation of endothelial vascular tissue, including the modulation of red blood cell volume in capillaries.

The slime on the outside of a fish is an example of glycocalyx. The term was initially applied to the polysaccharide matrix coating epithelial cells, but its functions have been discovered to go well beyond that. The glycocalyx surrounding a *Bacillus subtilis* bacterium is shown below.



https://en.wikipedia.org/wiki/Glycocalyx

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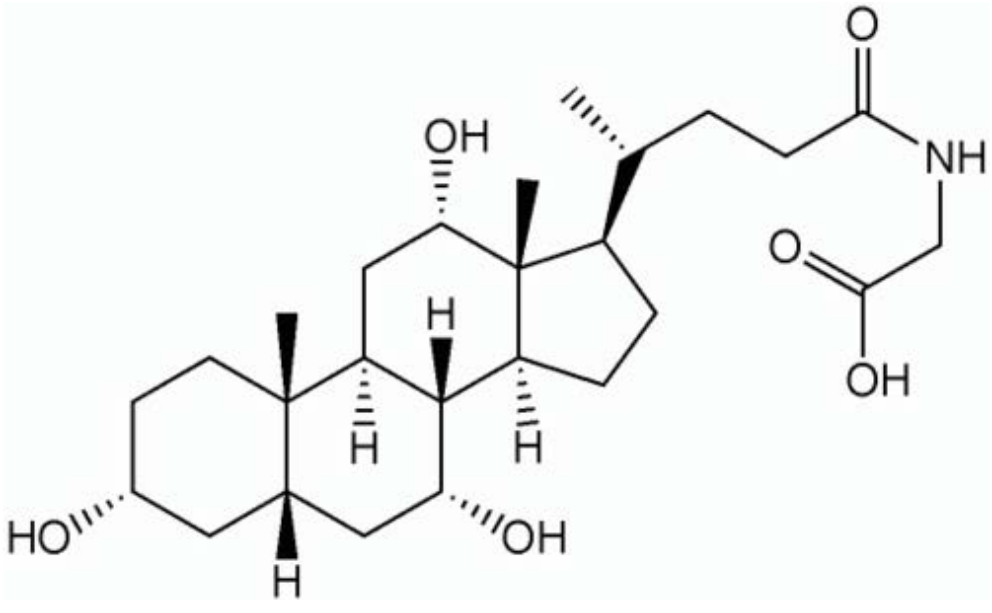
Glycocholic Acid

Glycocholic acid, or cholylglycine, is a crystalline bile acid involved in the e
tion of fats. It occurs as a sodium salt in the bile of mammals. It is a conjug
acid with glycine. Its anion is called glycocholate.



https://en.wikipedia.org/wiki/Glycocholic_acid

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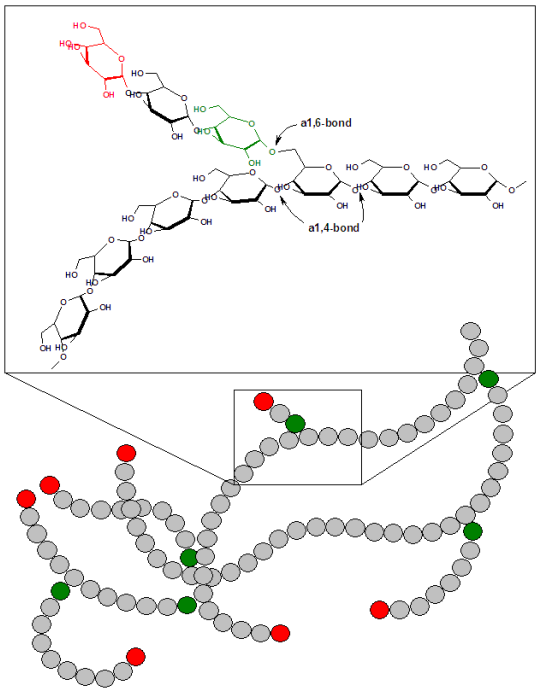
Glycogen

Glycogen is a multibranched polysaccharide of glucose that serves as a form of energy storage in animals and fungi. The polysaccharide structure represents the main storage form of glucose in the body.

In humans, glycogen is made and stored primarily in the cells of the liver and the muscles hydrated with three or four parts of water. Glycogen functions as the secondary long-term energy storage, with the primary energy stores being fats held in adipose tissue. Muscle glycogen is converted into glucose by muscle cells, and liver glycogen converts to glucose for use throughout the body including the central nervous system.

Glycogen is the analogue of starch, a glucose polymer that functions as energy storage in plants. It has a structure similar to amylopectin (a component of starch), but is more extensively branched and compact than starch. Both are white powders in their dry state. Glycogen is found in the form of granules in the cytosol/cytoplasm in many cell types, and plays an important role in the glucose cycle. Glycogen forms an energy reserve that can be quickly mobilized to meet a sudden need for glucose, but one that is less compact than the energy reserves of triglycerides (lipids).

In the liver, glycogen can comprise from 5 to 6% of its fresh weight (100–120 g in an adult). Only the glycogen stored in the liver can be made accessible to other organs. In the muscles, glycogen is found in a low concentration (1-2% of the muscle mass). The amount of glycogen stored in the body—especially within the muscles, liver, and red blood cells—mostly depends on physical training, basal metabolic rate, and eating habits. Small amounts of glycogen are found in the kidneys, and even smaller amounts in certain glial cells in the brain and white blood cells. The uterus also stores glycogen during pregnancy to nourish the embryo.



https://en.wikipedia.org/wiki/Glycogen

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Glycogen Metabolism

Glycogen is cleaved from the nonreducing ends of the chain by the enzyme glycogen phosphorylase to produce monomers of glucose-1-phosphate:

Glucose-1-phosphate is then converted to glucose 6-phosphate (G6P) by phosphoglucomutase. A special debranching enzyme is needed to remove the α(1-6) branches in branched glycogen and reshape the chain into a linear polymer. The G6P monomers produced have three possible fates:

- G6P can continue on the glycolysis pathway and be used as fuel.
- G6P can enter the pentose phosphate pathway via the enzyme glucose-6-phosphate dehydrogenase to produce NADPH and 5-carbon sugars.

In the liver and kidney, G6P can be dephosphorylated back to glucose by the enzyme glucose 6-phosphatase. This is the final step in the gluconeogenesis pathway.

Glycogen synthesis is, unlike its breakdown, endergonic - it requires the input of energy. Energy for glycogen synthesis comes from uridine triphosphate (UTP), which reacts with glucose-1-phosphate, forming UDP-glucose, in a reaction catalyzed by UTP—glucose-1-phosphate uridylyltransferase. Glycogen is synthesized from monomers of UDP-glucose initially by the protein glycogenin, which has two tyrosine anchors for the reducing end of glycogen, since glycogenin is a homodimer. After about eight glucose molecules have been added to a tyrosine residue, the enzyme glycogen synthase progressively lengthens the glycogen chain using UDP-glucose, adding α(1→4)-bonded glucose. The glycogen branching enzyme catalyzes the transfer of a terminal fragment of six or seven glucose residues from a nonreducing end to the C-6 hydroxyl group of a glucose residue deeper into the interior of the glycogen molecule. The branching enzyme can act upon only a branch having at least 11 residues, and the enzyme may transfer to the same glucose chain or adjacent glucose chains.

https://en.wikipedia.org/wiki/Glycogen#Metabolism

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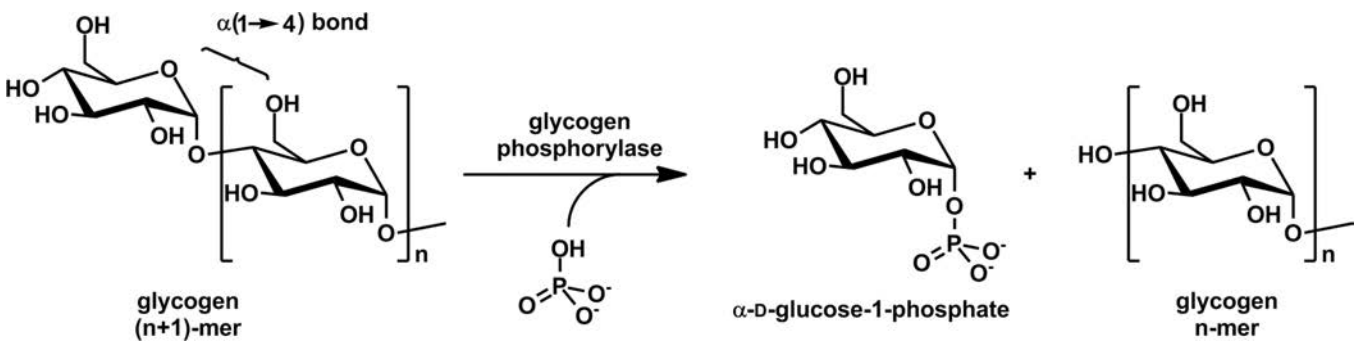
Glycogen Phosphorylase

Glycogen phosphorylase is one of the phosphorylase enzymes. Glycogen phosphorylase catalyzes the rate-limiting step in glycogenolysis in animals by releasing glucose-1-phosphate from the terminal α-1,4-glycosidic bond. Glycogen phosphorylase is also studied as a model protein regulated by both reversible phosphorylation and allosteric effects.



https://en.wikipedia.org/wiki/Glycogen_phosphorylase

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Glycogen Synthase

Glycogen synthase (UDP-glucose-glycogen glucosyltransferase) is a glycosyltransferase enzyme (EC 2.4.1.11) that catalyzes the reaction of UDP-glucose and (1,4-α-D-glucosyl)n to yield UDP and (1,4-α-D-glucosyl)n+1.

In other words, this enzyme converts excess glucose residues one by one into a polymeric chain for storage as glycogen. Glycogen synthase concentration is highest in the bloodstream 30 to 60 minutes following intense exercise. It is a key enzyme in glycogenesis.

The reaction is highly regulated by allosteric effectors such as glucose-6-phosphate (which allows glycogen synthase to operate as a glucose-6-phosphate sensor), by phosphorylation reactions (catalyzed by GSK3, see below), and indirectly triggered by the hormone insulin, which is secreted by the pancreas in response to elevated blood glucose levels. Phosphorylation of glycogen synthase decreases its activity. The enzyme also cleaves the ester bond between the C1 position of glucose and the pyrophosphate of UDP itself.

The control of glycogen synthase is a key step in regulating glycogen metabolism and glucose storage. Glycogen synthase is directly regulated by glycogen synthase kinase 3 (GSK-3), AMPK, protein kinase A (PKA), and casein kinase 2 (CK2). Each of these protein kinases lead to phosphorylated and catalytically inactive glycogen synthase.

For enzymes in the GT3 family, these regulatory kinases inactivate glycogen synthase by phosphorylating it at the N-terminal of the 25th residue and the C-terminal of the 120th residue. Glycogen synthase is also regulated by protein phosphatase 1 (PP1), which activates glycogen synthase via dephosphorylation. PP1 is targeted to the glycogen pellet by four targeting subunits, GM, GL, PTG and R6. These regulatory enzymes are regulated by insulin and glucagon signaling pathways.

https://en.wikipedia.org/wiki/Glycogen_synthase

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Glycogen Synthase Kinase 3

Glycogen synthase kinase 3 is a serine/threonine protein kinase that media
tion of phosphate molecules onto serine and threonine amino acid residues
covered in 1980 as a regulatory kinase for its namesake, Glycogen synthase
since been identified as a kinase for over forty different proteins in a variety
ent pathways. In mammals GSK-3 is encoded by two known genes, GSK-3 α
and GSK-3 β (GSK3B). GSK-3 has recently been the subject of much resear
it has been implicated in a number of diseases, including Type II diabetes (
mellitus type 2), Alzheimer's Disease, inflammation, cancer, and bipolar dis

https://en.wikipedia.org/wiki/GSK-3

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Chapter 6 - Metabolism: Nucleotides

Glycogenin

Glycogenin is an enzyme involved in converting glucose to glycogen. It acts as a primer, by polymerizing the first few glucose molecules, after which other enzymes take over. It is a homodimer of 37-kDa subunits and is classified as a glycosyltransferase.

It catalyzes the chemical reaction:

UDP-α-D-glucose + Glycogenin <---> UDP + α-D-glucosylglycogenin

The main enzyme involved in glycogen polymerization, glycogen synthase, can only add to an existing chain of at least 4 glucose residues. Glycogenin acts as the primer, to which further glucose monomers may be added. It achieves this by catalyzing the addition of glucose to itself (autocatalysis) by first binding glucose from UDP-glucose to the hydroxyl group of Tyr-194. Seven more glucoses can be added, each derived from UDP-glucose, by glycogenin's glucosyltransferase activity. Once sufficient residues have been added, glycogen synthase takes over extending the chain. Glycogenin remains covalently attached to the reducing end of the glycogen molecule.

https://en.wikipedia.org/wiki/Glycogenin

Related Glossary Terms

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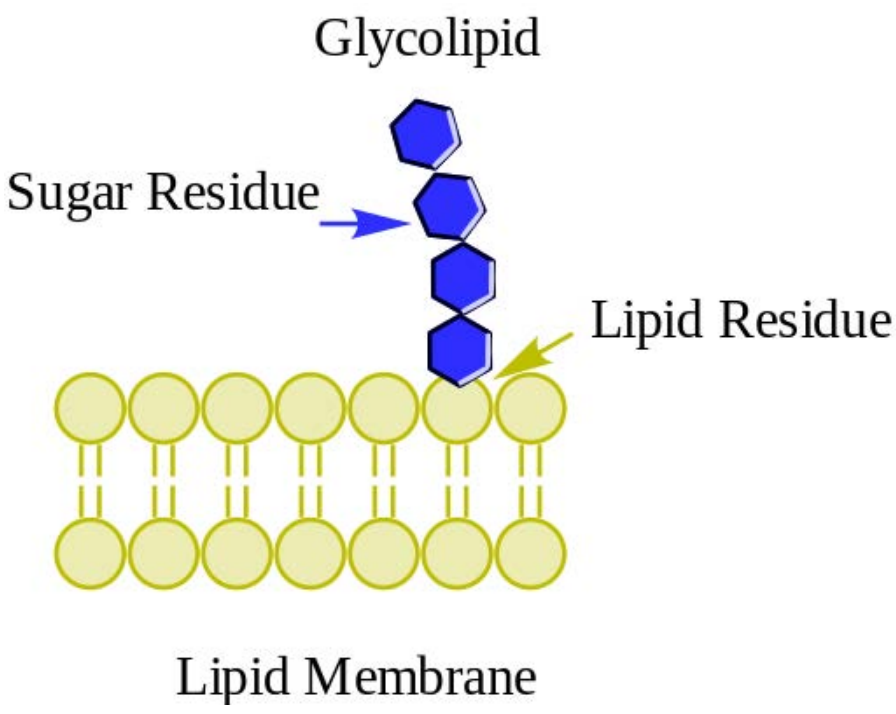
Glycolipids

Glycolipids are lipids with a carbohydrate attached by a glycosidic bond. Their role is to serve as markers for cellular recognition and also to provide energy. The carbohydrates are found on the outer surface of all eukaryotic cell membranes. They extend from the phospholipid bilayer into the aqueous environment outside the cell where it acts as a recognition site for specific chemicals as well as helping to maintain the stability of the membrane and attaching cells to one another to form tissues.



https://en.wikipedia.org/wiki/Glycolipid

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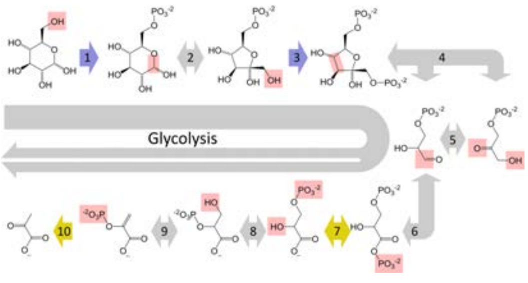
Glycolysis

Glycolysis is the metabolic pathway that converts glucose $C_6H_{12}O_6$, into pyruvate, $CH_3COCOO^- + H^+$. The free energy released in this process is used to form the high-energy compounds ATP (adenosine triphosphate) and NADH (reduced nicotinamide adenine dinucleotide).

Glycolysis is a determined sequence of ten enzyme-catalyzed reactions. The intermediates provide entry points to glycolysis. For example, most monosaccharides, such as fructose and galactose, can be converted to one of these intermediates. The intermediates may also be directly useful. For example, the intermediate dihydroxyacetone phosphate (DHAP) is a source of the glycerol that combines with fatty acids to form fat.

Glycolysis is an oxygen independent metabolic pathway, meaning that it does not use molecular oxygen (i.e. atmospheric oxygen) for any of its reactions. However the products of glycolysis (pyruvate and NADH + H^+) are sometimes disposed of using atmospheric oxygen. When molecular oxygen is used in the disposal of the products of glycolysis the process is usually referred to as aerobic, whereas if the disposal uses no oxygen the process is said to be anaerobic.
Thus, glycolysis occurs, with variations, in nearly all organisms, both aerobic and anaerobic. The wide occurrence of glycolysis indicates that it is one of the most ancient metabolic pathways. Indeed, the reactions that constitute glycolysis and its parallel pathway, the pentose phosphate pathway, occur metal-catalyzed under the oxygen-free conditions of the Archean oceans, also in the absence of enzymes. Glycolysis could thus have originated from chemical constraints of the prebiotic world.

Glycolysis occurs in most organisms in the cytosol of the cell. The most common type of glycolysis is the Embden–Meyerhof–Parnas (EMP pathway), which was discovered by Gustav Embden, Otto Meyerhof, and Jakub Karol Parnas. Glycolysis also refers to other pathways, such as the Entner–Doudoroff pathway and various heterofermentative and homofermentative pathways. However, the discussion here will be limited to the Embden–Meyerhof–Parnas pathway.



https://en.wikipedia.org/wiki/Glycolysis

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Glycophorin

A Glycophorin is a sialoglycoprotein of the membrane of a red blood cell. It
membrane-spanning protein and carries sugar molecules. It is heavily glyco
(60%). Glycophorins are rich in sialic acid, which gives the red blood cells a
hydrophilic-charged coat. This enables them to circulate without adhering
cells or vessel walls.

https://en.wikipedia.org/wiki/Glycophorin

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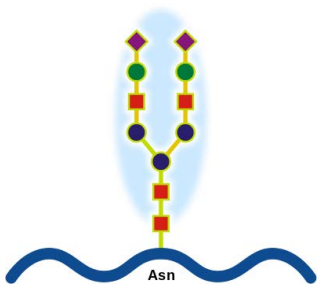
Glycoprotein

Glycoproteins are proteins that contain oligosaccharide chains (glycans) covalently attached to polypeptide side-chains. The carbohydrate is attached to the protein in a co-translational or post-translational modification. This process is known as glycosylation. Secreted extracellular proteins are often glycosylated.

In proteins that have segments extending extracellularly, the extracellular segments are also often glycosylated. Glycoproteins are also often important integral membrane proteins, where they play a role in cell–cell interactions. It is important to distinguish endoplasmic reticulum-based glycosylation of the secretory system without of reversible cytosolic/nuclear glycosylation. Glycoprotein of the cytosol and nucleus can be modified through the reversible addition of a single GlcNAc residues that is consider reciprocal to phosphorylation and the functions of these are likely to be additional regulatory mechanism that controls phosphorylation-based signaling. In contrast, classical secretory glycosylation can be structurally essential. For example, inhibition of asparagine-linked, i.e. N-linked, glycosylation can prevent glycoprotein folding and full inhibition can be toxic to an individual cell. In contrast, perturbations of terminal processing, which occurs in the Golgi apparatus, is dispensable for isolated cells(as evidence by survival with glycosides inhibitors) but can lead to human disease (Congenital disorders of glycosylation) and can be lethal in animal models. It is therefore likely that the fine processing of glycans is important for endogeneous functionality, such as cell trafficking, but that this is likely to have been secondary to its role in host-pathogen interactions. A famous example of this latter effect is the ABO blood system.

An N-linked glycoprotein is depicted below.



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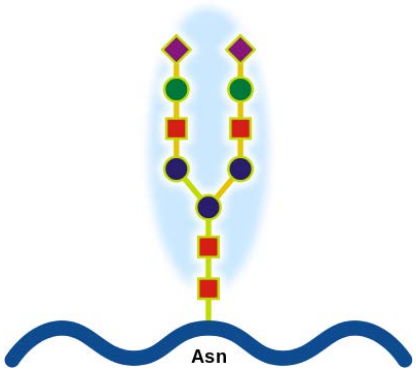

https://en.wikipedia.org/wiki/Glycoprotein

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Glycosaminoglycan

Glycosaminoglycans (GAGs) or mucopolysaccharides are long unbranched polysaccharides consisting of a repeating disaccharide unit. The repeating unit (except for keratan) consists of an amino sugar (N-acetylglucosamine or N-acetylgalactosamine) along with a uronic sugar (glucuronic acid or iduronic acid) or galactose. Glycosaminoglycans are highly polar and attract water. They are therefore useful to the body as a lubricant or as a shock absorber.

Glycosaminoglycans have high degrees of heterogeneity with regards to molecular mass, disaccharide construction, and sulfation due to the fact that GAG synthesis, unlike proteins or nucleic acids, is not template driven, and dynamically modulated by processing enzymes.

Based on core disaccharide structures, GAGs are classified into four groups. Heparin/heparan sulfate (HSGAGs) and chondroitin sulfate/dermatan sulfate (CSGAGs) are synthesized in the Golgi apparatus, where protein cores made in the rough endoplasmic reticulum are posttranslationally modified with O-linked glycosylations by glycosyltransferases forming proteoglycans. Keratan sulfate may modify core proteins through N-linked glycosylation or O-linked glycosylation of the proteoglycan. The fourth class of GAG, hyaluronic acid, is not synthesized by the Golgi, but rather by integral membrane synthases which immediately secrete the dynamically elongated disaccharide chain.

HSGAG and CSGAG modified proteoglycans first begin with a consensus Ser-Gly/Ala-X-Gly motif in the core protein. Construction of a tetrasaccharide linker that consists of -GlcAβ1–3Galβ1–3Galβ1–4Xylβ1-O-(Ser)-, where xylosyltransferase, β4-galactosyl transferase (GalTI),β3-galactosyl transferase (GalT-II), and β3-GlcA transferase (GlcAT-I) transfer the four monosaccharides, begins synthesis of the GAG modified protein. The first modification of the tetrasaccharide linker determines whether the HSGAGs or CSGAGs will be added. Addition of a GlcNAc promotes the addition of HSGAGs while addition of GalNAc to the tetrasaccharide linker promotoes CSGAG development. GlcNAcT-I transfers GlcNAc to the tetrasaccahride linker, which is distinct from glycosyltransferase GlcNAcT-II, the enzyme that is utilized to build HSGAGs. Interestingly, EXTL2 and EXTL3, two genes in the EXT tumor suppressor family, have been shown to have GlcNAcT-I activity. Conversely, GalNAc is transferred to the linker by the enzyme GalNAcT to initiate synthesis of CSGAGs, an enzyme which may or may not have distinct activity compared to the GalNAc transferase activity of chondroitin synthase.

https://en.wikipedia.org/wiki/Glycosaminoglycan

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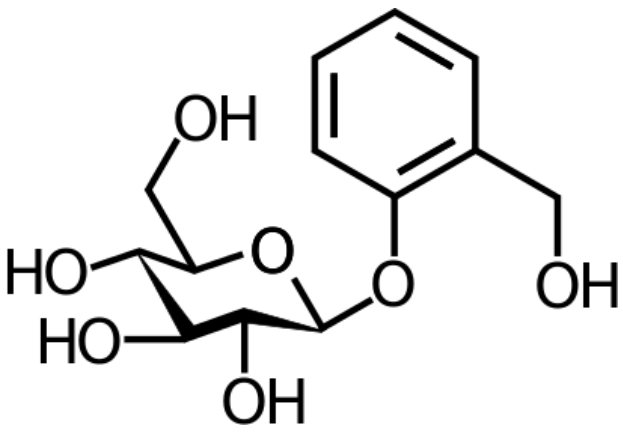
Glycoside

In chemistry, a glycoside is a molecule in which a sugar is bound to another functional group via a glycosidic bond. Glycosides play numerous important roles in living organisms. Many plants store chemicals in the form of inactive glycosides. These can be activated by enzyme hydrolysis, which causes the sugar part to be broken off, making the chemical available for use. Many such plant glycosides are used as medications. In animals and humans, poisons are often bound to sugar molecules as part of their elimination from the body.

In formal terms, a glycoside is any molecule in which a sugar group is bonded through its anomeric carbon to another group via a glycosidic bond. Glycosides can be linked by an O- (an O-glycoside), N- (a glycosylamine), S-(a thioglycoside), or C- (a C-glycoside) glycosidic bond.

Salicin, an aspirin-like glycoside, is depicted below.



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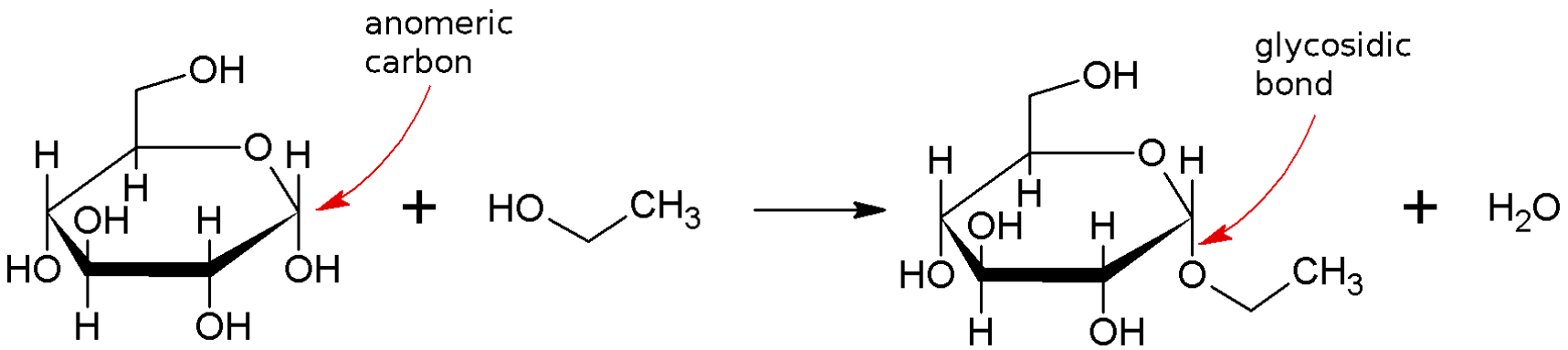
Glycosidic

In chemistry, a glycosidic bond or glycosidic linkage is a type of covalent bond that joins a carbohydrate (sugar) molecule to another group, which may or may not be a other carbohydrate.

A glycosidic bond is formed between the hemiacetal or hemiketal group of a saccha (or a molecule derived from a saccharide) and the hydroxyl group of some compour such as an alcohol. A substance containing a glycosidic bond is a glycoside.



https://en.wikipedia.org/wiki/Glycosidic_bond

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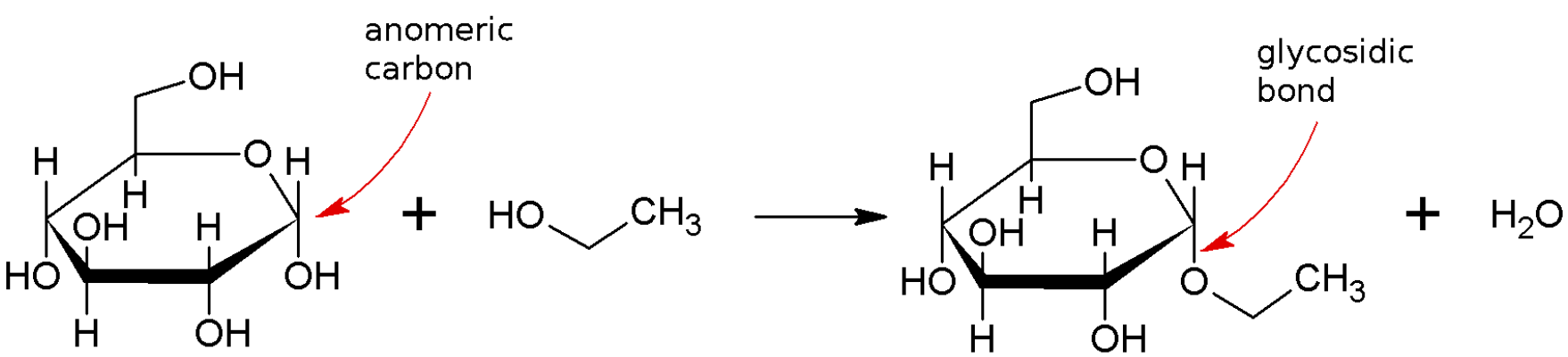

https://en.wikipedia.org/wiki/Glycosidic_bond

Related Glossary Terms

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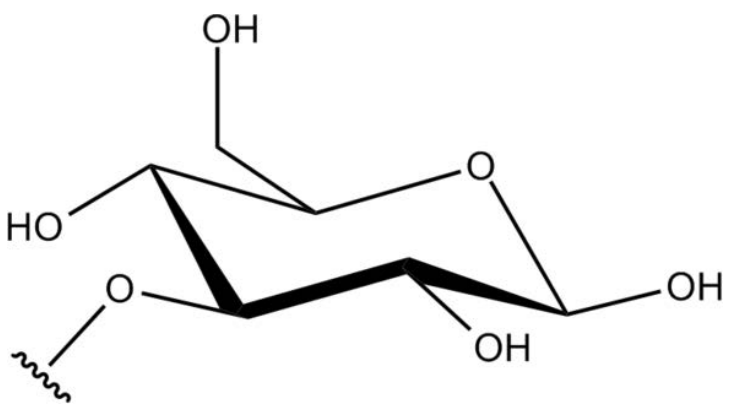
Glycosyl

A glycosyl group is a univalent free radical or substituent structure obtained by
ing the hemiacetal hydroxyl group from the cyclic form of a monosaccharide ar
tension, of a lower oligosaccharide. Glycosyl also reacts with inorganic acids, su
phosphoric acid, forming an ester such as glucose 1-phosphate.

In the image below, the β-D-glucopyranosyl group was obtained by the remova
hemiacetal hydroxyl group from β-D-glucopyranose.



https://en.wikipedia.org/wiki/Glycosyl

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Glycosylation

Glycosylation is the reaction in which a carbohydrate, i.e. a glycosyl donor, is attached to a hydroxyl or other functional group of another molecule (a glycosyl acceptor). In biology glycosylation mainly refers in particular to the enzymatic process that attaches glycans to proteins, lipids, or other organic molecules. This enzymatic process produces one of the fundamental biopolymers found in cells (along with DNA, RNA, and proteins). Glycosylation is a form of co-translational and post-translational modification. Glycans serve a variety of structural and functional roles in membrane and secreted proteins. The majority of proteins synthesized in the rough ER undergo glycosylation. It is an enzyme-directed site-specific process, as opposed to the non-enzymatic chemical reaction of glycation. Glycosylation is also present in the cytoplasm and nucleus as the O-GlcNAc modification. Aglycosylation is a feature of engineered antibodies to bypass glycosylation.

Five classes of glycans are produced:
• N-linked glycans attached to a nitrogen of asparagine or arginine side-chains. N-linked glycosylation requires participation of a special lipid called dolichol phosphate.
• O-linked glycans attached to the hydroxyl oxygen of serine, threonine, tyrosine, hydroxylysine, or hydroxyproline side-chains, or to oxygens on lipids such as ceramide
• Phospho-glycans linked through the phosphate of a phospho-serine
• C-linked glycans, a rare form of glycosylation where a sugar is added to a carbon on a tryptophan side-chain
• Glypiation, which is the addition of a GPI anchor that links proteins to lipids through glycan linkages.

https://en.wikipedia.org/wiki/Glycosylation

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Glycosylphosphatidylinositol

Glycosylphosphatidylinositol (GPI anchor) is a glycolipid that can be attached to the C-terminus of a protein during posttranslational modification. Proteins containing a GPI anchor (called glypiated) play key roles in a wide variety of biological processes. It is composed of a phosphatidylinositol group linked through a carbohydrate-containing linker (glucosamine and mannose glycosidically bound to the inositol residue) and via an ethanolamine phosphate (EtNP) bridge to the C-terminal amino acid of a mature protein. The two fatty acids within the hydrophobic phosphatidyl-inositol group anchor the protein to the cell membrane.

Glypiated (GPI-linked) proteins contain a signal sequence, thus directing them to the endoplasmic reticulum (ER). The protein is co-translationally inserted in the ER membrane and is attached to the ER membrane by its hydrophobic C terminus. The majority of the protein extends into the ER lumen. The hydrophobic C-terminal sequence is then cleaved off and replaced by the GPI-anchor. As the protein processes through the secretory pathway, it is transferred via vesicles to the Golgi apparatus and finally to the plasma membrane where it remains attached to the exterior leaflet of the cell membrane. Since the glypiation is the sole means of attachment of such proteins to the membrane, cleavage of the group by phospholipases will result in controlled release of the protein from the membrane. The latter mechanism is used *in vitro*, i.e., the membrane proteins released from the membranes in the enzymatic assay are glypiated proteins.

Phospholipase C (PLC) is an enzyme that is known to cleave the phospho-glycerol bond found in GPI-anchored proteins. Treatment with PLC will cause release of GPI-linked proteins from the outer cell membrane. The T-cell marker Thy-1 and acetylcholinesterase, as well as both intestinal and placental alkaline phosphatases, are known to be GPI-linked and are released by treatment with PLC. GPI-linked proteins are thought to be preferentially located in lipid rafts, suggesting a high level of organization within plasma membrane microdomains.

https://en.wikipedia.org/wiki/Glycophosphatidylinositol

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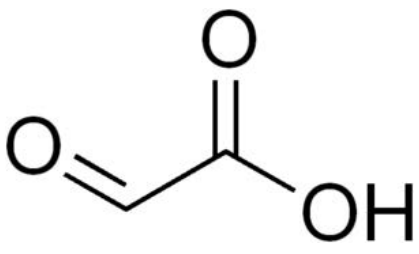
Glyoxylate

Glyoxylic acid or oxoacetic acid is an organic compound. Together with acetic acid, glycolic acid, and oxalic acid, glyoxylic acid is one of the C2 carboxylic acids. It is a colorless solid that occurs naturally and is useful industrially.

The conjugate base of gloxylic acid is known as glyoxylate and is the form that the compound exists in solution at neutral pH. Glyoxylate is an intermediate of the glyoxylate cycle, which enables organisms, such as bacteria, fungi, and plants to convert fatty acids into carbohydrates. Glyoxylate is the byproduct of the amidation process in biosynthesis of several amidated peptides.



https://en.wikipedia.org/wiki/Glyoxylic_acid

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Glyoxylate Cycle

The glyoxylate cycle, a variation of the tricarboxylic acid cycle, is an anabolic pathway occurring in plants, bacteria, protists, and fungi. The glyoxylate cycle centers on the conversion of acetyl-CoA to succinate for the synthesis of carbohydrates. In microorganisms, the glyoxylate cycle allows cells to utilize simple carbon compounds as a carbon source when complex sources such as glucose are not available. The cycle is generally assumed to be absent in animals, with the exception of nematodes at the early stages of embryogenesis. In recent years, however, the detection of malate synthase (MS) and isocitrate lyase (ICL), key enzymes involved in the glyoxylate cycle, in some animal tissue has raised questions regarding the evolutionary relationship of enzymes in bacteria and animals and suggests that animals encode alternative enzymes of the cycle that differ in function from known MS and ICL in non-metazoan species.

The glyoxylate cycle utilizes five of the eight enzymes associated with the tricarboxylic acid cycle: citrate synthase, aconitase, succinate dehydrogenase, fumarase, and malate dehydrogenase. The two cycles differ in that in the glyoxylate cycle, isocitrate is converted into glyoxylate and succinate by ICL instead of into α-ketoglutarate. This bypasses the decarboxylation steps that take place in the TCA cycle, allowing simple carbon compounds to be used in the later synthesis of macromolecules, including glucose. Glyoxylate is subsequently combined with acetyl-CoA to produce malate, catalyzed by MS. Malate is also formed in parallel from succinate by the action of succinate dehydrogenase and fumarase.

https://en.wikipedia.org/wiki/Glyoxylate_cycle

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Glyoxysome

Glyoxysomes are specialized peroxisomes found in plants (particularly in th
age tissues of germinating seeds) and also in filamentous fungi. As in all pe
in glyoxysomes the fatty acids are hydrolyzed to acetyl-CoA by peroxisomal
oxidation enzymes. Besides peroxisomal functions, glyoxysomes possess ac
the key enzymes of glyoxylate cycle (isocitrate lyase and malate synthase) w
plish the glyoxylate cycle bypass.

Thus, glyoxysomes (as all peroxisomes) contain enzymes that initiate the br
fatty acids and additionally possess the enzymes to produce intermediate p
the synthesis of sugars by gluconeogenesis. The seedling uses these sugars s
from fats until it is mature enough to produce them by photosynthesis.

https://en.wikipedia.org/wiki/Glyoxysome

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https://en.wikipedia.org/wiki/Glyoxysome

Related Glossary Terms

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Glypiation

Glypiation is the covalent bond of a glycosylphosphatidylinositol (GPI) anchor and is a common post-translational modification that localizes proteins to cell membranes. This special kind of glycosylation is widely detected on surface glycoproteins in eukaryotes and some *Archaea*.

GPI anchors consist of a phosphoethanolamine linker that binds to the C-terminus of target proteins. Glycan's core structure has a phospholipid tail that anchors the structure to the membrane.

Both the lipid moiety of the tail and the sugar residues in the glycan core has considerable variation, demonstrating vast functional diversity that includes signal transduction, cell adhesion and immune recognition. GPI anchors can also be cleaved by enzymes such as phospholipase C to regulate the localization of proteins that are anchored at the plasma membrane.

https://en.wikipedia.org/wiki/Glypiation

Related Glossary Terms

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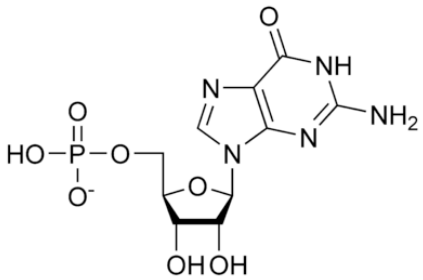
GMP

Guanosine monophosphate (GMP), also known as 5'-guanidylic acid or guanylic acid (conjugate base guanylate), is a nucleotide that is used as a monomer in RNA. It is an ester of phosphoric acid with the nucleoside guanosine. GMP consists of the phosphate group, the pentose sugar ribose, and the nucleobase guanine. Hence it is a ribonucleoside monophosphate. Guanosine monophosphate is commercially produced by microbial fermentation.

Guanosine monophosphate in the form of its salts, such as disodium guanylate (E627), dipotassium guanylate (E628) and calcium guanylate (E629), are food additives used as flavor enhancers to provide the umami taste. It is often used in synergy with disodium inosinate. The combination is known as disodium 5'-ribonucleotides. Disodium guanylate is often found in instant noodles, potato chips and snacks, savoury rice, tinned vegetables, cured meats, and packet soup.

As it is a fairly expensive additive, it is usually not used independently of glutamic acid or monosodium glutamate (MSG), which also contribute umami. If inosinate and guanylate salts are present in a list of ingredients but MSG does not appear to be, the glutamic acid is likely provided as part of another ingredient, such as a processed soy protein complex (hydrolyzed soy protein), autolyzed yeast or soy sauce.



https://en.wikipedia.org/wiki/Guanosine_monophosphate

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GMP Reductase

GMP reductase (Guanosine 5'-monophosphate oxidoreductase) is an enzy
lyzes the irreversible and NADPH-dependent reductive deamination of GM

NADPH + Guanosine 5-phosphate <=> $NADP^+$ + inosine 5-phosphate + N

It converts nucleobase, nucleoside and nucleotide derivatives of G to A nuc
and maintains intracellular balance of A and G nucleotides.

https://en.wikipedia.org/wiki/GMP_reductase

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GMP Synthase

Guanosine monophosphate synthetase, also known as GMPS is an enzyme verts xanthosine monophosphate to guanosine monophosphate. In the *de n* sis of purine nucleotides, IMP is the branch point metabolite at which point way diverges to the synthesis of either guanine or adenine nucleotides. In t nucleotide pathway, there are 2 enzymes involved in converting IMP to GM IMP dehydrogenase (IMPD1), which catalyzes the oxidation of IMP to XMP synthetase, which catalyzes the amination of XMP to GMP.

https://en.wikipedia.org/wiki/GMP_synthase_(glutamine—hydrolysing)

Related Glossary Terms

Drag related terms here

Golden Rice

Golden rice is a variety of rice (*Oryza sativa*) produced through genetic engineering to biosynthesize β-carotene, a precursor of vitamin A, in the edible parts of rice. It is intended to produce a fortified food to be grown and consumed in areas with a shortage of dietary vitamin A, a deficiency which is estimated to kill 670,000 children under the age of 5 each year.

Golden rice differs from its parental strain by the addition of three β-carotene biosynthesis genes. The rice plant can naturally produce β-carotene in its leaves, where it is involved in photosynthesis. However, the plant does not normally produce the pigment in the endosperm, where photosynthesis does not occur.

https://en.wikipedia.org/wiki/Golden_rice

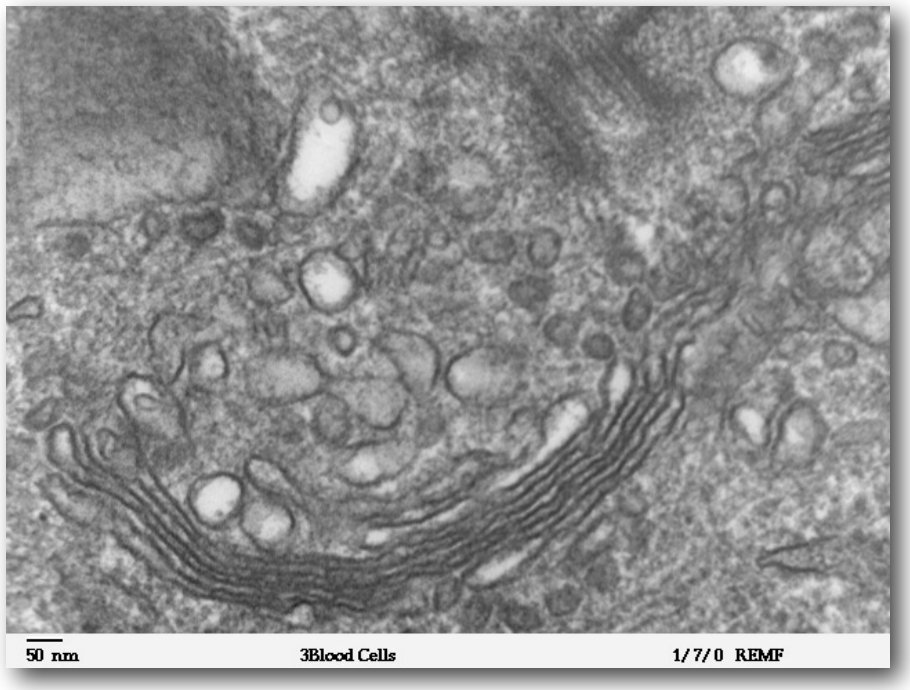
Related Glossary Terms

Golgi

The Golgi apparatus, also known as the Golgi complex, Golgi body, or simply the Golgi, is an organelle found in most eukaryotic cells. It was identified in 1897 by the Italian physician Camillo Golgi and named after him in 1898.

Part of the cellular endomembrane system, the Golgi apparatus packages proteins into membrane-bound vesicles inside the cell before the vesicles are sent to their destination. The Golgi apparatus resides at the intersection of the secretory, lysosomal, and endocytic pathways. It is of particular importance in processing proteins for secretion, containing a set of glycosylation enzymes that attach various sugar monomers to proteins as the proteins move through the apparatus.

The image below shows the Golgi as a set of flattened disks near the bottom.



https://commons.wikimedia.org/wiki/File:Human_leukocyte,_showing_golgi_-_TEM.jpg

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Related Glossary Terms

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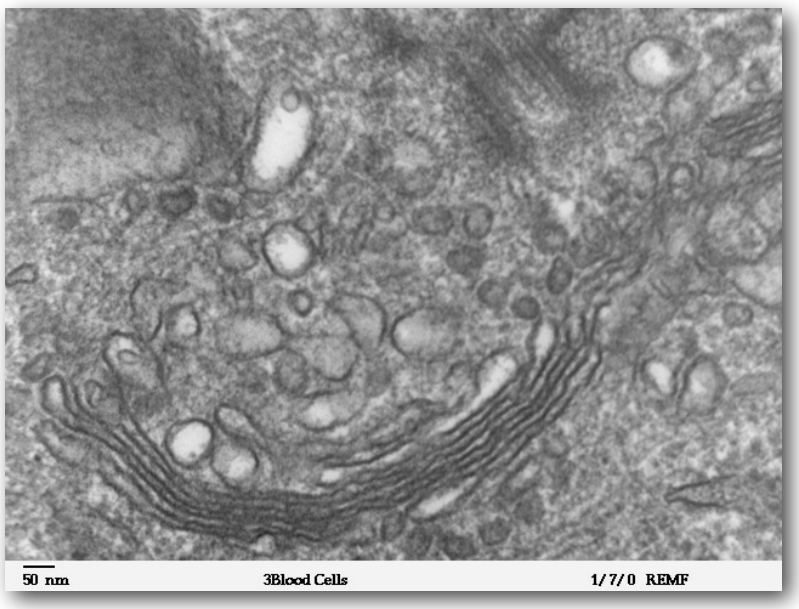

https://commons.wikimedia.org/wiki/File:Human_leukocyte,_showing_golgi_-_TEM.jpg

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Gopalasamudram Ramachandran

Gopalasamudram Narayana Ramachandran, or G.N. Ramachandran, FRS (8 October 1922 – 7 April 2001) was an Indian physicist who was known for his work that led to his creation of the Ramachandran plot for understanding peptide structure. He was the first to propose a triple-helical model for the structure of collagen and subsequently went on to make other major contributions in biology and physics. Leading scientists including Professor Linus Pauling and Professor Francis Crick regarded Professor Ramchandran as a Nobel Prize caliber scientist of great reputation.

https://en.wikipedia.org/wiki/G._N._Ramachandran

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Chapter 2 - Structure & Function: Proteins I

Gp41

Gp41 also known as glycoprotein 41 is a subunit of the envelope protein complex of r roviruses, including human immunodeficiency virus (HIV). Gp41 is a transmembran protein that contains several sites within its ectodomain that are required for infecti of host cells.

The interaction of gp41 fusion peptides with the target cell causes a formation of an i termediate, pre-hairpin structure which bridges and fuses the viral and host mem- branes together. The pre-hairpin structure has a relatively long half-life which makes a target for therapeutic intervention and inhibitory peptides.

Enfuvirtide (also known as T-20) is a fusion inhibitor drug that binds to the pre- hairpin structure and prevents membrane fusion and HIV-1 entry to the cell. The vul nerability of this structure has initiated development towards a whole spectrum of fu sion preventing drugs. A variety of naturally-occurring molecules have also been shown to bind gp41 and prevent HIV-1 entry.

https://en.wikipedia.org/wiki/Gp41

Related Glossary Terms

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Chapter 2 - Structure & Function: Carbohydrates

Gp120

Envelope glycoprotein GP120 (or gp120) is a glycoprotein exposed on the s
the HIV envelope. The 120 in its name comes from its molecular weight of 1
Gp120 is essential for virus entry into cells as it plays a vital role in attachm
cific cell surface receptors.

Gp120 is anchored to the viral membrane, or envelope, via non-covalent bo
the transmembrane glycoprotein, gp41. Three gp120s and gp41s combine in
heterodimers to form the envelope spike, which mediates attachment to an
the host cell.

https://en.wikipedia.org/wiki/Envelope_glycoprotein_GP120

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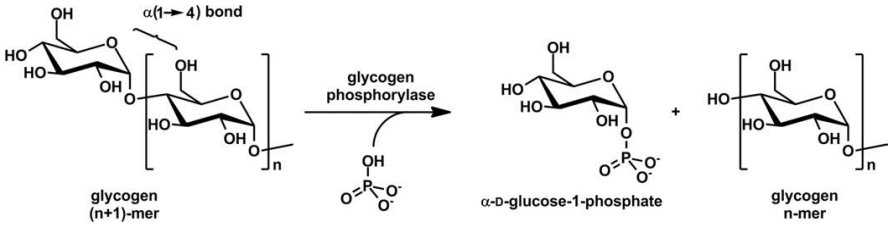
GP_a

Glycogen phosphorylase a (GP_a) is a phosphroylated form of glycogen phoshorylase, the primary enzyme in glycogen breakdown. It catalyzes the phosphorolysis of glycogen (uses a phosphate for cleavage) to yield glucose-1-phosphate and a glycogen molecule shortened by one residue.



Glycogen phosphorylase is regulated by both allosteric control and by phosphorylation.

Hormones such as epinephrine, insulin and glucagon regulate glycogen phosphorylase using second messenger amplification systems that are linked to G proteins. Glucagon activates adenylate cyclase through a seven transmembrane receptor coupled to Gs which, in turn, activates adenylate cyclase to increase intracellular concentrations of cAMP. cAMP binds to and releases an active form of protein kinase A (PKA). Next, PKA phosphorylates phosphorylase kinase, which, in turn, phosphorylates glycogen phosphorylase b, transforming it into the active glycogen phosphorylase a. This phosphorylation is added onto the glycogen phosphorylase b serine 14. In the liver, glucagon activates another G-protein-linked receptor that triggers a different cascade, resulting in the activation of Phospholipase C (PLC). PLC indirectly causes the release of calcium from the hepatocytes' endoplasmic reticulum into the cytosol. The increased calcium availability binds to the calmodulin subunit and activates glycogen phosphorylase kinase. Glycogen phosphorylase kinase activates glycogen phosphorylase in the same manner mentioned previously.

Glycogen phosphorylase b is not always inactive in muscle, as it can be activated allosterically by AMP. An increase in AMP concentration, which occurs during strenuous exercise, signals energy demand. AMP activates glycogen phosphorylase b by changing its conformation from a tense to a relaxed form. This relaxed form has similar enzymatic properties as the phosphorylated enzyme. An increase in ATP concentration opposes this activation by displacing AMP from the nucleotide binding site, indicating sufficient energy stores.

Upon eating a meal, there is a release of insulin, signaling glucose availability in the blood. Insulin indirectly activates PP-1 and phosphodiesterase. The PP-1 directly dephosphorylates glycogen phosphorylase a, reforming the inactive glycogen phosphorylase b. The phosphodiesterase converts cAMP to AMP. This activity removes the second messenger (generated by glucagon and epinephrine) and inhibits PKA. In this manner, PKA can no longer cause the phosphorylation cascade that ends with formation of (active) glycogen phosphorylase a. These modifications initiated by insulin end glycogenolysis in order to preserve what glycogen stores are left in the cell and trigger glycogenesis (rebuilding of glycogen).
Phosphorylase a and phosphorylase b each exist in two forms a T (tense) inactive state and R (relaxed) state. Phosphorylase b is normally in the T state, inactive due to the physiological presence of ATP and Glucose 6 phosphate, and Phosphorylase a is normally in the R state (active).

An isoenzyme of glycogen phosphorylase exists in the liver sensitive to glucose concentration, as the liver acts as a glucose exporter. In essence, liver phosphorylase is responsive to glucose, which causes a very responsive transition from the R to T form, inactivating it. Furthermore, liver phosphorylase is insensitive to AMP.

https://en.wikipedia.org/wiki/Glycogen_phosphorylase

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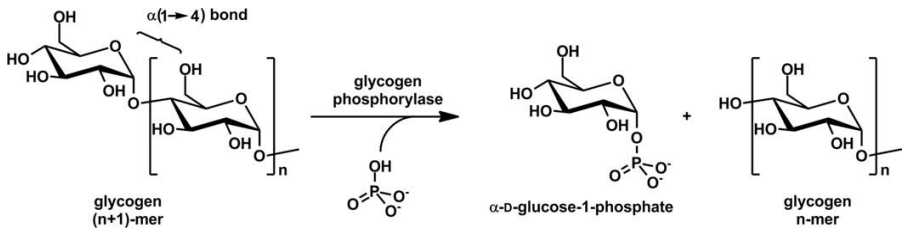

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https://en.wikipedia.org/wiki/Glycogen_phosphorylase

Related Glossary Terms

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GPI Anchor

Glycosylphosphatidylinositol (GPI anchor) is a glycolipid that can be attached to the C-terminus of a protein during posttranslational modification. Proteins containing a GPI anchor play key roles in a wide variety of biological processes. It is composed of a phosphatidylinositol group linked through a carbohydrate-containing linker (glucosamine and mannose glycosidically bound to the inositol residue) and via an ethanolamine phosphate (EtNP) bridge to the C-terminal amino acid of a mature protein. The two fatty acids within the hydrophobic phosphatidyl-inositol group anchor the protein to the cell membrane.

Glypiated (GPI-linked) proteins contain a signal sequence, thus directing them to the endoplasmic reticulum (ER). The protein is co-translationally inserted in the ER membrane and is attached to the ER membrane by its hydrophobic C terminus. The majority of the protein extends into the ER lumen. The hydrophobic C-terminal sequence is then cleaved off and replaced by the GPI-anchor. As the protein processes through the secretory pathway, it is transferred via vesicles to the Golgi apparatus and finally to the plasma membrane where it remains attached to the exterior leaflet of the cell membrane. Since the glypiation is the sole means of attachment of such proteins to the membrane, cleavage of the group by phospholipases will result in controlled release of the protein from the membrane. The latter mechanism is used *in vitro*. That is, the membrane proteins released from the membranes in the enzymatic assay are glypiated protein.

Phospholipase C (PLC) is an enzyme that is known to cleave the phospho-glycerol bond found in GPI-anchored proteins. Treatment with PLC will cause release of GPI-linked proteins from the outer cell membrane. The T-cell marker Thy-1 and acetylcholinesterase, as well as both intestinal and placental alkaline phosphatases, are known to be GPI-linked and are released by treatment with PLC. GPI-linked proteins are thought to be preferentially located in lipid rafts, suggesting a high level of organization within plasma membrane microdomains.

https://en.wikipedia.org/wiki/Glycophosphatidylinositol

Related Glossary Terms

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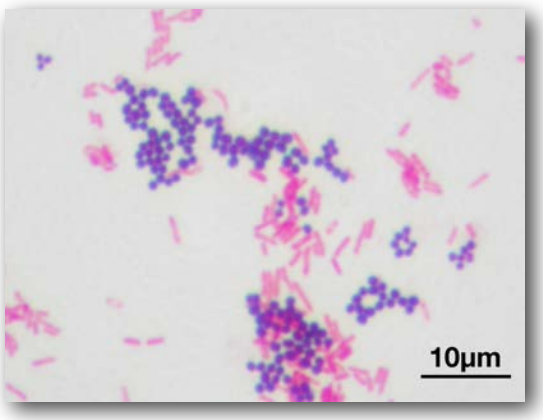
Chapter 3 - Membranes: Other Considerations

Gram Negative Bacteria

Gram-negative bacteria are a group of bacteria that do not retain the crystal violet stain used in the Gram staining method of bacterial differentiation. They are characterized by their cell membranes, which are composed of a thin peptidoglycan cell wall sandwiched between an inner cytoplasmic cell membrane and a bacterial outer membrane.

Gram-negative bacteria display the following characteristics:
1 - An inner cell membrane is present (cytoplasmic)
2 - A thin peptidoglycan layer is present (This is much thicker in gram-positive bacteria)
3 - Has outer membrane containing lipopolysaccharides (LPS, which consists of lipid A, core polysaccharide, and O antigen) in its outer leaflet and phospholipids in the inner leaflet
4 - Porins exist in the outer membrane, which act like pores for particular molecules
5 - Between the outer membrane and the cytoplasmic membrane there is a space filled with a concentrated gel-like substance called periplasm
6 - The S-layer is directly attached to the outer membrane rather than to the peptidoglycan
7 - If present, flagella have four supporting rings instead of two
8 - Teichoic acids or lipoteichoic acids are absent
9 - Lipoproteins are attached to the polysaccharide backbone
10 - Some contain Braun's lipoprotein, which serves as a link between the outer membrane and the peptidoglycan chain by a covalent bond
11 - Most, with very few exceptions, do not form spores

Pictured below are Gram positive (pink) and Gram negative (purple) bacteria.



https://en.wikipedia.org/wiki/Gram-negative_bacteria

Related Glossary Terms

Drag related terms here

Gram Positive Bacteria

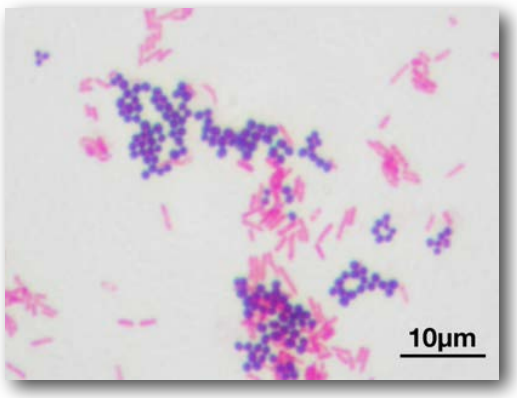
Gram-positive bacteria are bacteria that give a positive result in the Gram stain test. Gram-positive bacteria take up the crystal violet stain used in the test, and then appear to be purple-colored when seen through a microscope. This is because the thick peptidoglycan layer in the bacterial cell wall retains the stain after it is washed away from the rest of the sample, in the decolorization stage of the test.

Despite their thicker peptidoglycan layer, gram-positive bacteria are more receptive to antibiotics than gram-negative, due to the absence of the outer membrane.

In general, the following characteristics are present in gram-positive bacteria:
1 - Cytoplasmic lipid membrane
2 - Thick peptidoglycan layer
3 - Teichoic acids and lipoids are present, forming lipoteichoic acids, which serve as chelating agents, and also for certain types of adherence.
4 - Peptidoglycan chains are cross-linked to form rigid cell walls by a bacterial enzyme DD-transpeptidase.
5 - A much smaller volume of periplasm than that in gram-negative bacteria.

Only some species have a capsule usually consisting of polysaccharides. Also only some species are flagellates, and when they do have flagella they only have two basal body rings to support them (gram-negative have four). Both gram-positive and gram-negative bacteria commonly have a surface layer called an S-layer. In gram-positive bacteria, the S-layer is attached to the peptidoglycan layer (in gram-negative bacteria, the S-layer is attached directly to the outer membrane). Specific to gram-positive bacteria is the presence of teichoic acids in the cell wall. Some of these are lipoteichoic acids, which have a lipid component in the cell membrane that can assist in anchoring the peptidoglycan.

Pictured below are Gram positive (pink) and Gram negative (purple) bacteria.



https://en.wikipedia.org/wiki/Gram-positive_bacteria

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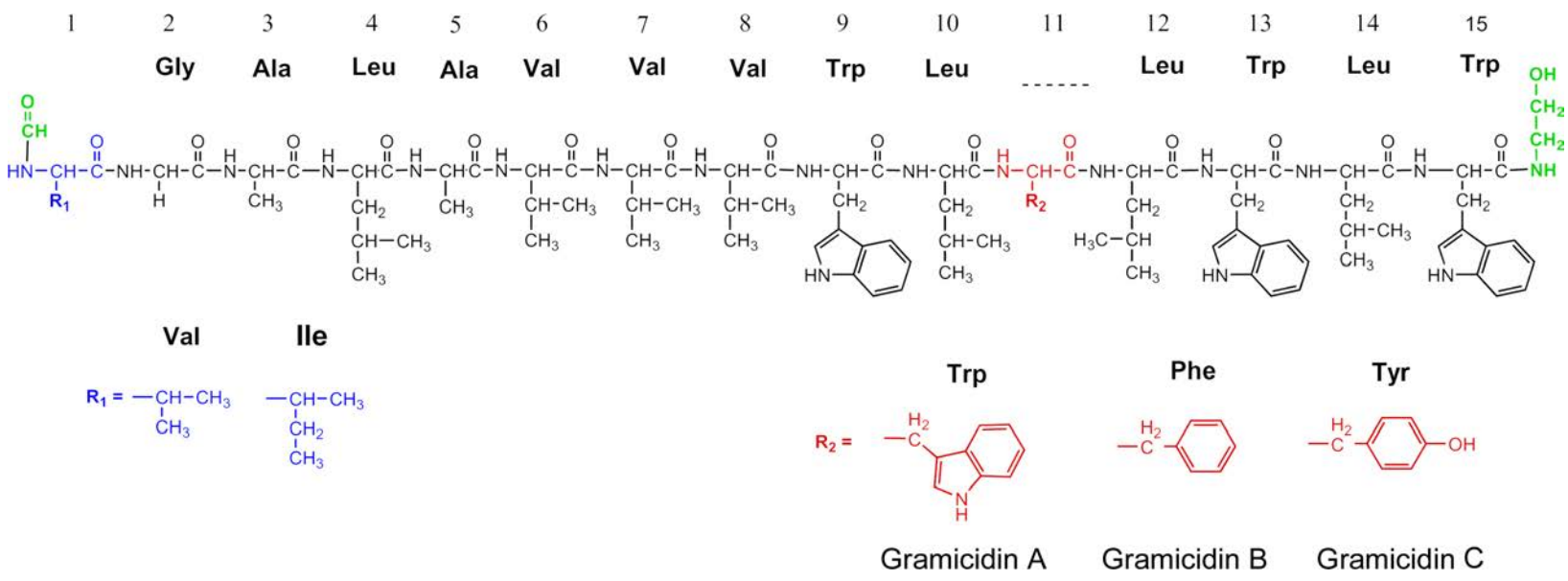
Gramicidins

Gramicidin is a heterogeneous mixture of three antibiotic compounds, gramicidins A, B and C, making up 80%, 6%, and 14%, respectively, all of which are obtained from the soil bacterial species *Bacillus brevis* and called collectively gramicidin D. Gramicidin D contains linear pentadecapeptides, that is chains made up of 15 amino acids.

Gramicidin is active against Gram-positive bacteria, except for the Gram-positive bacilli, and against select Gram-negative organisms, such as *Neisseria* bacteria. Its therapeutic use is limited to topical application, as it induces hemolysis in lower concentrations than bacteria cell death, so it cannot be administered internally. Since the exterior epidermis is composed of dead cells, applying it to the surface of the skin will not cause harm.



https://en.wikipedia.org/wiki/Gramicidin

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Chapter 3 - Membranes: Transport

Chapter 9 - Point by Point: Membranes

Granzyme B

Granzyme B is a serine protease most commonly found in the granules of cytotoxic lymphocytes (CTLs), natural killer cells (NK cells) and cytotoxic T cells. It is secreted by these cells along with the pore forming protein perforin to mediate apoptosis in target cells.

Granzyme B has also more recently found to be produced by a wide range of non-cytotoxic cells ranging from basophils and mast cells to smooth muscle cells. The secondary functions of granzyme B are also numerous. Granzyme B has shown to be involved in inducing inflammation by stimulating cytokine release and is also involved in extracellular matrix remodeling.

Granzyme B is released with perforin which inserts into a target cell's plasma membrane forming a pore. Perforin has a radius of 5.5 nm and granzyme B has a stokes radius of 2.5 nm and can therefore pass through the perforin pore into the target to be destroyed.

Alternatively, once released, granzyme B can bind to negatively charged heparan sulphate containing receptors on a target cell and become endocytosed. The vesicles that carry the enzyme inside then burst, exposing granzyme b to the cytoplasm and its substrates. Hsp-70 has also been linked to aiding granzyme B entry.

Granzyme B has also been proposed to enter a target by first exchanging its bound serglycin for negative phospholipids in a target's plasma membrane. Entry then occurs by the less selective process of absorptive pinocytosis.

Once inside the target cell granzyme B can cleave and activate initiator caspases 8 and 10, and executioner caspases 3 and 7 which trigger apoptosis. Caspase 7 is the most sensitive to granzyme B and caspases 3, 8, and 10 are only cleaved to intermediate fragments and need further cleavage for full activation.

https://en.wikipedia.org/wiki/Granzyme_B

Related Glossary Terms

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Chapter 4 - Catalysis: Mechanism

GroEL

GroEL belongs to the chaperonin family of molecular chaperones, and is found in a large number of bacteria. It is required for the proper folding of many proteins. To function properly, GroEL requires the lid-like cochaperonin protein complex GroES. In eukaryotes the proteins Hsp60 and Hsp10 are structurally and functionally nearly identical to GroEL and GroES, respectively.

Within the cell, the process of GroEL/ES mediated protein folding involves multiple rounds of binding, encapsulation, and release of substrate protein. Unfolded substrate proteins bind to a hydrophobic binding patch on the interior rim of the open cavity of GroEL, forming a binary complex with the chaperonin. Binding of substrate protein in this manner, in addition to binding of ATP, induces a conformational change that allows association of the binary complex with a separate lid structure, GroES. Binding of GroES to the open cavity of the chaperonin induces the individual subunits of the chaperonin to rotate such that the hydrophobic substrate binding site is removed from the interior of the cavity, causing the substrate protein to be ejected from the rim into the now largely hydrophilic chamber.

The hydrophilic environment of the chamber favors the burying of hydrophobic residues of the substrate, inducing substrate folding. Hydrolysis of ATP and binding of a new substrate protein to the opposite cavity sends an allosteric signal causing GroES and the encapsulated protein to be released into the cytosol. A given protein will undergo multiple rounds of folding, returning each time to its original unfolded state, until the native conformation or an intermediate structure committed to reaching the native state is achieved. Alternatively, the substrate may succumb to a competing reaction, such as misfolding and aggregation with other misfolded proteins.

https://en.wikipedia.org/wiki/GroEL

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GroES

Heat shock 10 kDa protein 1 (Hsp10) also known as chaperonin 10 (cpn10) or early-pregnancy factor (EPF) is a protein that in humans is encoded by the HSPE1 gene. The homolog in *E. coli* is GroES that is a chaperonin which usually works in conjunction with GroEL.

GroES exists as a ring-shaped oligomer of between six to eight identical subunits, while the 60 kDa chaperonin (cpn60 - or groEL in bacteria) forms a structure comprising 2 stacked rings, each ring containing 7 identical subunits. These ring structures assemble by self-stimulation in the presence of Mg2+-ATP. The central cavity of the cylindrical cpn60 tetradecamer provides an isolated environment for protein folding whilst cpn-10 binds to cpn-60 and synchronizes the release of the folded protein in an Mg^{++}-ATP dependent manner. The binding of cpn10 to cpn60 inhibits the weak ATPase activity of cpn60.

Escherichia coli GroES has also been shown to bind ATP cooperatively, and with an affinity comparable to that of GroEL. Each GroEL subunit contains three structurally distinct domains: an apical, an intermediate and an equatorial domain. The apical domain contains the binding sites for both GroES and the unfolded protein substrate. The equatorial domain contains the ATP-binding site and most of the oligomeric contacts. The intermediate domain links the apical and equatorial domains and transfers allosteric information between them. The GroEL oligomer is a tetradecamer, cylindrically shaped, that is organized in two heptameric rings stacked back to back. Each GroEL ring contains a central cavity, known as the `Anfinsen cage', that provides an isolated environment for protein folding. The identical 10 kDa subunits of GroES form a dome-like heptameric oligomer in solution. ATP binding to GroES may be important in charging the seven subunits of the interacting GroEL ring with ATP, to facilitate cooperative ATP binding and hydrolysis for substrate protein release.

https://en.wikipedia.org/wiki/GroES

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Growth Factor

A growth factor is a naturally occurring substance capable of stimulating cellular growth, proliferation, healing, and cellular differentiation. Usually it is a protein or a steroid hormone. Growth factors are important for regulating a variety of cellular processes.

Growth factors typically act as signaling molecules between cells. Examples are cytokines and hormones that bind to specific receptors on the surface of their target cells.

Growth factor is sometimes used interchangeably among scientists with the term cytokine. Historically, cytokines were associated with hematopoietic (blood forming) cells and immune system cells (e.g., lymphocytes and tissue cells from spleen, thymus, and lymph nodes). For the circulatory system and bone marrow in which cells can occur in a liquid suspension and not bound up in solid tissue, it makes sense for them to communicate by soluble, circulating protein molecules. However, as different lines of research converged, it became clear that some of the same signaling proteins the hematopoietic and immune systems used were also being used by all sorts of other cells and tissues, during development and in the mature organism.

While growth factor implies a positive effect on cell division, cytokine is a neutral term with respect to whether a molecule affects proliferation. While some cytokines can be growth factors, such as G-CSF and GM-CSF, others have an inhibitory effect on cell growth or proliferation. Some cytokines, such as Fas ligand, are used as "death" signals. They cause target cells to undergo programmed cell death or apoptosis.

https://en.wikipedia.org/wiki/Growth_factor

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GTP

Guanosine-5'-triphosphate (GTP) is a purine nucleoside triphosphate. It can act as a substrate for the synthesis of RNA during the transcription process of DNA during DNA replication. Its structure is similar to that of the guanine nucleobase, the only difference being that nucleotides like GTP have a ribose sugar and three phosphates, with the nucleobase attached to the 1' and the triphosphate moiety attached to the 5' carbons of the ribose.

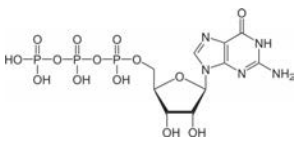
It also has the role of a source of energy or an activator of substrates in metabolic reactions, like that of ATP, but more specific. It is used as a source of energy for protein synthesis and gluconeogenesis.

GTP is essential to signal transduction, in particular with G-proteins, in second-messenger mechanisms where it is converted to guanosine diphosphate (GDP) through the action of GTPases.

GTP is involved in energy transfer within the cell. For instance, a GTP molecule is generated by one of the enzymes in the citric acid cycle. This is tantamount to the generation of one molecule of ATP, since GTP is readily converted to ATP with nucleoside-diphosphate kinase (NDK).

During the elongation stage of translation, GTP is used as an energy source for the binding of a new amino-bound tRNA to the A site of the ribosome. GTP is also used as an energy source for the translocation of the ribosome towards the 3' end of the mRNA.

During microtubule polymerization, each heterodimer formed by an α and a β tubulin molecule carries two GTP molecules, and the GTP is hydrolyzed to GDP when the tubulin dimers are added to the plus end of the growing microtubule. Such GTP hydrolysis is not mandatory for microtubule formation, but it appears that only GDP-bound tubulin molecules are able to depolymerize. Thus, a GTP-bound tubulin serves as a cap at the tip of microtubule to protect from depolymerization. Once the GTP is hydrolyzed, the microtubule begins to depolymerize and shrink rapidly.



https://en.wikipedia.org/wiki/Guanosine_triphosphate

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GTPase

GTPases (singular GTPase) are a large family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP). The GTP binding and hydrolysis takes place in the highly conserved G domain common to all GTPases.

GTPases play an important role in:
• Signal transduction at the intracellular domain of transmembrane receptors, including recognition of taste, smell and light.
• Protein biosynthesis (a.k.a. translation) at the ribosome.
• Control and differentiation during cell division.
• Translocation of proteins through membranes.
Transport of vesicles within the cell. (GTPases control assembly of vesicle coats.)

All regulatory GTPases have a common mechanism that enables them to switch a signal transduction chain on and off. Toggling the switch is performed by the unidirectional change of the GTPase from the active, GTP-bound form to the inactive, GDP-bound form by hydrolysis of the GTP through intrinsic GTPase-activity, effectively switching the GTPase off. This reaction is initiated by GTPase-activating proteins (GAPs), coming from another signal transduction pathway. It can be reversed (switching the GTPase on again) by Guanine nucleotide exchange factors (GEFs), which cause the GDP to dissociate from the GTPase, leading to its association with a new GTP. This closes the cycle to the active state of the GTPase. The irreversible hydrolysis of the GTP to GDP forces the cycle to run only in one direction. Only the active state of the GTPase can transduce a signal to a reaction chain.

https://en.wikipedia.org/wiki/GTPase

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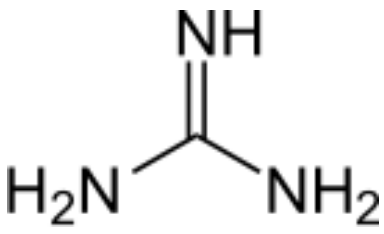
Guanidinium

Guanidine is protonated in physiological conditions. This conjugate acid is called the guanidinium cation, $[CH_6N_3]+$. It is a highly stable +1 cation in aqueous solution due to the efficient resonance stabilization of the charge and efficient solvation by water molecules. As a result, its pKa is 13.6 meaning that guanidine is a very strong base in water.

Guanidinium chloride has chaotropic properties and is used to denature proteins. Guanidine hydrochloride is known to denature proteins with a linear relationship between concentration and free energy of unfolding. In aqueous solutions containing 6 M guanidinium chloride, almost all proteins lose their entire secondary structure and become randomly coiled peptide chains. Guanidinium thiocyanate is also used for its denaturing effect on various biological samples. Guanidine hydrochloride is used as an adjuvant in treatment of botulism, introduced in 1968, but now its role is considered controversial - because in some patients there was no improvement after this drug administration.



https://en.wikipedia.org/wiki/Guanidine#Guanidinium_salts

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Guanine

Guanine (G, Gua) is one of the four main nucleobases found in the nucleic acids DNA and RNA, the others being adenine, cytosine, and thymine (uracil in RNA). In DNA, guanine is paired with cytosine. With the formula C5H5N5O, guanine is a derivative of purine, consisting of a fused pyrimidine-imidazole ring system with conjugated double bonds. Being unsaturated, the bicyclic molecule is planar. The guanine nucleoside is called guanosine.

Guanine, along with adenine and cytosine, is present in both DNA and RNA, whereas thymine is usually seen only in DNA, and uracil only in RNA. Guanine has two tautomeric forms, the major keto form (see figures) and rare enol form. It binds to cytosine through three hydrogen bonds. In cytosine, the amino group acts as the hydrogen bond donor and the C-2 carbonyl and the N-3 amine as the hydrogen-bond acceptors. Guanine has the C-6 carbonyl group that acts as the hydrogen bond acceptor, while a group at N-1 and the amino group at C-2 act as the hydrogen bond donors.

https://en.wikipedia.org/wiki/Guanine

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Guanine Deaminase

Guanine deaminase also known as cypin, guanase, guanine aminase, GAH, nine aminohydrolase is an aminohydrolase enzyme which converts guanine thine. Cypin is a major cytosolic protein that interacts with PSD-95. It pron ized microtubule assembly in neuronal dendrites.

https://en.wikipedia.org/wiki/Guanine_deaminase

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Chapter 6 - Metabolism: Nucleotides

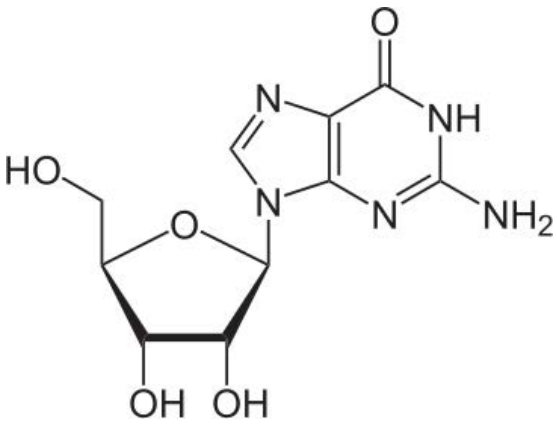
Chapter 9 - Point by Point: Metabolism

Guanosine

Guanosine is a purine nucleoside comprising guanine attached to a ribose (ribofuranose) ring via a β-N_9-glycosidic bond. Guanosine can be phosphorylated to become guanosine monophosphate (GMP), cyclic guanosine monophosphate (cGMP), guanosine diphosphate (GDP), and guanosine triphosphate (GTP). These forms play important roles in various biochemical processes such as synthesis of nucleic acids and proteins, photosynthesis, muscle contraction, and intracellular signal transduction (cGMP). When guanine is attached by its N_9 nitrogen to the C_1 carbon of a deoxyribose ring it is known as deoxyguanosine.

The antiviral drug aciclovir, often used in herpes treatment, and the anti-HIV drug abacavir, are structurally similar to guanosine.

Guanosine is required for an RNA splicing reaction in mRNA, when a "self-splicing" intron removes itself from the mRNA message by cutting at both ends, re-ligating, and leaving just the exons on either side to be translated into protein.



https://en.wikipedia.org/wiki/Guanosine

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Guide RNA

The term “guide RNA” is used to refer to three things in molecular biology.

First, guide RNAs (aka gRNA) are the RNAs that guide the insertion or deletion of uridine residues into mitochondrial mRNAs in kinetoplastid protists in the process known as RNA editing.

Second in the process of RNA silencing, the term guide RNA refers to the strand of RNA in the RISC complex that is retained (the other strand is the passenger and it is released) and used to base pair with a target RNA.

Third, in the CRISPR/Cas9 technique, a guide RNA is the molecule used to target a location in a DNA for cutting by Cas9.

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Gyrase

DNA gyrase, also known as topoisomerase II or simply as gyrase, is an enzyme that relieves strain while double-stranded DNA is being unwound by helicase. This causes negative supercoiling of the DNA. The gyrase supercoils (or relaxes positive supercoils) into DNA by looping the template so as to form a crossing, then cutting one of the double helices and passing the other through it before releasing the break, changing the linking number by two in each enzymatic step.

This process occurs in prokaryotes (in particular, in bacteria), whose single circular DNA is cut by DNA gyrase and the two ends are then twisted around each other to form supercoils. Gyrase has been found in the apicoplast of the malarial parasite Plasmodium falciparum, a unicellular eukaryote. Bacterial DNA gyrase is the target of many antibiotics, including nalidixic acid, novobiocin, and ciprofloxacin.

The unique ability of gyrase to introduce negative supercoils into DNA is what allows bacterial DNA to have free negative supercoils. The ability of gyrase to relax positive supercoils comes into play during DNA replication and prokaryotic transcription. The right-handed nature of the DNA double helix causes positive supercoils to accumulate ahead of a translocating enzyme, in the case of DNA replication, a DNA polymerase. The ability of gyrase (and topoisomerase IV) to relax positive supercoils allows superhelical tension ahead of the polymerase to be released so that replication can continue.

https://en.wikipedia.org/wiki/DNA_gyrase

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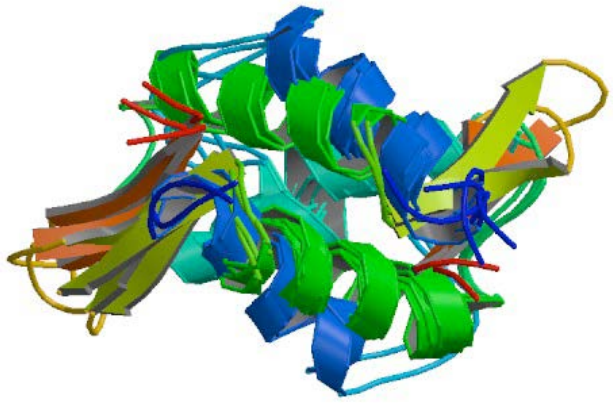
H_1

Histone H_1 is one of the five main histone protein families which are components of chromatin in eukaryotic cells. Though highly conserved, it is nevertheless the most variable histone in sequence across species.

Unlike the other histones, H_1 does not make up the nucleosome "bead". Instead, it sits on top of the structure, keeping in place the DNA that has wrapped around the nucleosome. H_1 is present in half the amount of the other four histones, which contribute two molecules to each nucleosome bead. In addition to binding to the nucleosome, the H_1 protein binds to the "linker DNA" (approximately 20-80 nucleotides in length) region between nucleosomes, helping stabilize the zig-zagged 30 nm chromatin fiber.

It is uncertain whether H_1 promotes a solenoid (DNA)-like chromatin fiber, in which exposed linker DNA is shortened, or whether it merely promotes a change in the angle of adjacent nucleosomes, without affecting linker length. Nuclease digestion and DNA footprinting experiments suggest that the globular domain of histone H_1 localizes near the nucleosome dyad, where it protects approximately 15-30 base pairs of additional DNA.



https://en.wikipedia.org/wiki/Histone_H1

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H_{2A}

Histone H_{2A} is one of the five main histone proteins involved in the structure of chromatin in eukaryotic cells.

H_{2A} consists of a main globular domain and a long N-terminal tail or C-terminal on one end of the molecule. The N-terminal tail or C-terminal tail is the location of post-translational modification. Thus far, researchers have not identified any secondary structures that arise in the tail. H_{2A} utilizes a protein fold known as the 'histone fold.' The histone fold is a three-helix core domain that is connected by two loops. This connection forms a 'handshake arrangement.' Most notably, this is termed the helix-turn-helix motif, which allows for dimerization with H_{2B}. The 'histone fold' is conserved among H_{2A} at the structural level. However the genetic sequence that encodes for this structure differs between variants.

Histone H_{2A} is composed of non-allelic variants. The term "Histone H_{2A}" is intentionally non-specific and refers to a variety of closely related proteins that vary often by only a few amino acids. Notable variants include $H_{2A.1}$, $H_{2A.2}$, $H_{2A.X}$, and $H_{2A.Z}$.

Changes in variant composition occur in differentiating cells. This was observed in differentiating neurons during synthesis and turnover. Changes in variant composition were seen among the $H_{2A.1}$ histone. The only variant that remained constant in the neural differentiation was variant H_{2AZ}. H_{2AZ} is a variant that exchanges with conventional H_{2A} core protein. This variant is important for gene silencing.

https://en.wikipedia.org/wiki/Histone_H2A

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H_{2B}

Histone H_{2B} is one of the 5 main histone proteins involved in the structure of chromatin in eukaryotic cells. Featuring a main globular domain and long N-terminal and C-terminal tails, H_{2B} is involved with the structure of the nucleosomes.

Histone H_{2B} is a lightweight structural protein made of 126 amino acids. Many of these amino acids have a basic pH, which allows them to interact with the negatively charged phosphate groups in DNA. Along with a central globular domain, histone H_{2B} has two flexible histone tails that extend outwards – one at the N-terminal end and one at C-terminal end. These are highly involved in condensing chromatin from the beads-on-a-string conformation to a 30-nm fiber. Similar to other histone proteins, histone H_{2B} has a distinct histone fold that is optimized for histone-histone as well as histone-DNA interactions.

Two copies of histone H_{2B} come together with two copies each of histone H_{2A}, histone H_3, and histone H_4 to form the octamer core of the nucleosome to give structure to DNA. To facilitate this formation, histone H_{2B} first binds to histone H_{2A} to form a heterodimer. Two of these heterodimers then bind together with a heterotetramer made of histone H_3 and histone H_4, giving the nucleosome its characteristic disk shape. Chromatin is then wrapped around the entire nucleosome in groups of approximately 160 base pairs of DNA. The wrapping continues until all chromatin has been packaged with the nucleosomes.

https://en.wikipedia.org/wiki/Histone_H2B

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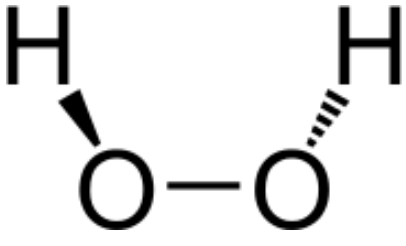
H_2O_2

Hydrogen peroxide is a chemical compound with the formula H_2O_2. In its pure form, it is a colorless liquid, slightly more viscous than water. However, for safety reasons it is normally used as an aqueous solution. Hydrogen peroxide is the simplest peroxide (a compound with an oxygen–oxygen single bond) and finds use as a strong oxidizer, bleaching agent and disinfectant. Concentrated hydrogen peroxide, or "high-test peroxide", is a reactive oxygen species and has been used as a propellant in rocketry.

Hydrogen peroxide is often described as being "water but with one more oxygen atom", a description that can give the incorrect impression of significant chemical similarity between the two compounds. While they have a similar melting point and appearance, pure hydrogen peroxide will explode if heated to boiling, will cause serious contact burns to the skin and can set materials alight on contact. For these reasons it is usually handled as a dilute solution (household grades are typically 3–6% in the U.S. and somewhat higher in Europe). Its chemistry is dominated by the nature of its unstable peroxide bond.



https://en.wikipedia.org/wiki/Hydrogen_peroxide

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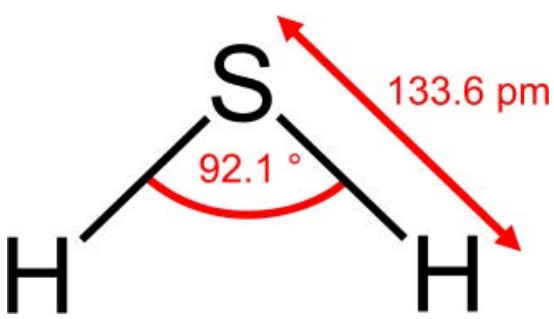
H_2S

Hydrogen sulfide is the chemical compound with the formula H_2S. It is a colorless gas with the characteristic foul odor of rotten eggs. It is heavier than air, very poisonous, corrosive, flammable, and explosive.

Hydrogen sulfide often results from the prokaryotic breakdown of organic matter in the absence of oxygen gas, such as in swamps and sewers. This process is commonly known as anaerobic digestion. H_2S also occurs in volcanic gases, natural gas, and in some sources of well water. The human body produces small amounts of H_2S and uses it as a signaling molecule.



https://en.wikipedia.org/wiki/Hydrogen_sulfide

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G - G

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

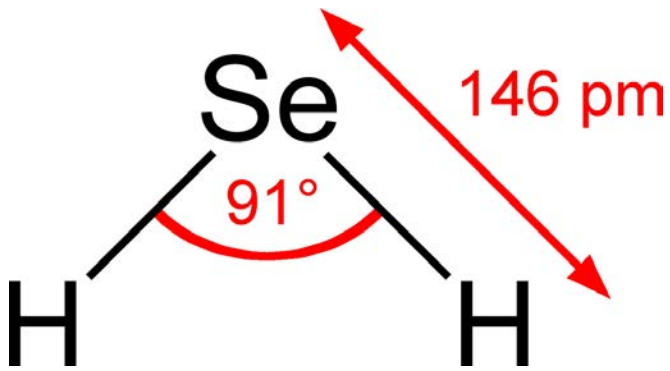
Chapter 9 - Short & Sweet: Energy

Chapter 9 - Point by Point: Metabolism

Chapter 9 - Point by Point: Metabolism

H_2Se

Hydrogen selenide is an inorganic compound with the formula H_2Se. It is t
(and virtually the only) hydride of selenium. H_2Se is a colorless, flammable
standard conditions. It is the most toxic selenium compound with an expos
0.05 ppm over an 8-hour period. Even at extremely low concentrations, thi
pound has a very irritating smell resembling that of decayed horseradish or
gas', but smells of rotten eggs at higher concentrations.



https://en.wikipedia.org/wiki/Hydrogen_selenide

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

H_3

Histone H_3 is one of the five main histone proteins involved in the structure of chr
tin in eukaryotic cells. Featuring a main globular domain and a long N-terminal ta
H_3 is involved with the structure of the nucleosomes of the 'beads on a string' stru
ture. Histone proteins are highly post-translationally modified however Histone H
the most extensively modified of the five histones. The term "Histone H3" alone is
posely ambiguous in that it does not distinguish between sequence variants or mo
cation state. Histone H_3 is an important protein in the emerging field of epigenetic
where its sequence variants and variable modification states are thought to play a
in the dynamic and long term regulation of genes.

The N-terminal meme of histone H_3 protrudes from the globular nucleosome core
can undergo several different types of post-translational modification that influen
lular processes. These modifications include the covalent attachment of methyl or
tyl groups to lysine and arginine amino acids and the phosphorylation of serine or
threonine.

https://en.wikipedia.org/wiki/Histone_H3

Related Glossary Terms

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H_4

Histone H_4 is one of the five main histone proteins involved in the structure
tin in eukaryotic cells. Featuring a main globular domain and a long N-term
H_4 is involved with the structure of the nucleosome of the 'beads on a string
tion. Histone proteins are highly post-translationally modified. Covalently
modifications include acetylation and methylation of the N-terminal tails. T
fications may alter expression of genes located on DNA associated with its
tone octamer. Histone H_4 is an important protein in the structure and funct
matin, where its sequence variants and variable modification states are tho
a role in the dynamic and long term regulation of genes.

https://en.wikipedia.org/wiki/Histone_H4

Related Glossary Terms

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H_5

The histone H_1 family in animals includes multiple H_1 isoforms that can be
in different or overlapping tissues and developmental stages within a single
The reason for these multiple isoforms remains unclear, but both their evol
conservation from sea urchin to humans as well as significant differences in
amino acid sequences suggest that they are not functionally equivalent. One
histone H_5, which is only found in avian erythrocytes, which are unlike mam
erythrocytes in that they have nuclei.

https://en.wikipedia.org/wiki/Histone_H1

Related Glossary Terms

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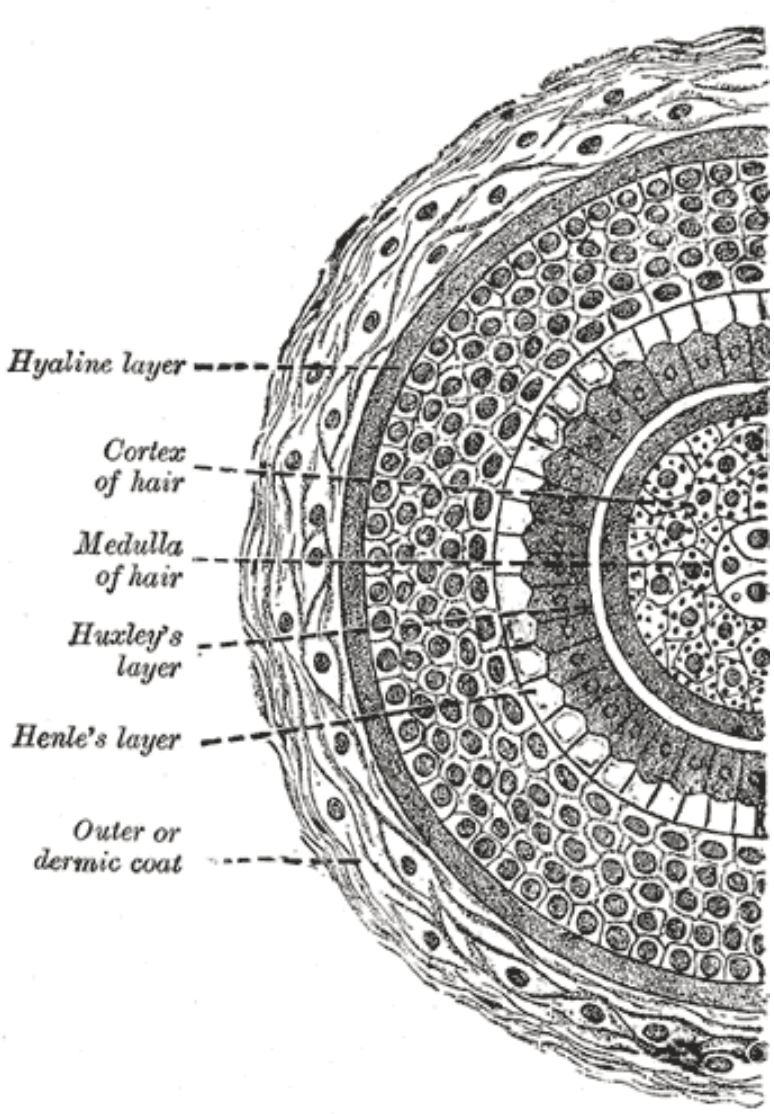
Hair

Hair is a protein filament that grows from follicles found in the dermis, or skin. Hair is one of the defining characteristics of mammals. The human body, apart from areas of glabrous skin, is covered in follicles which produce thick terminal and fine vellus hair. Most common interest in hair is focused on hair growth, hair types and hair care, but hair is also an important biomaterial primarily composed of protein, notably keratin. Shown below is a cross-section of a human hair.



https://en.wikipedia.org/wiki/Hair

Handedness

Helices can be either right-handed or left-handed. With the line of sight alo
lix's axis, if a clockwise screwing motion moves the helix away from the obs
it is called a right-handed helix; if towards the observer, then it is a left-han
Handedness (or chirality) is a property of the helix, not of the perspective: a
handed helix cannot be turned to look like a left-handed one unless it is vie
mirror, and vice versa.

Handedness is also a consideration for asymmetric carbons - carbons boun
ferent molecules. The 3D configuration of these carbons can occur in two c
forms - commonly called D and L in biochemistry.

https://en.wikipedia.org/wiki/Helix

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Chapter 1 - Introduction: Basic Chemistry

HbA

Hemoglobin A (HbA), also known as adult hemoglobin or $\alpha_2\beta_2$, is the most
man hemoglobin tetramer, comprising over 97% of the total red blood cell
It consists of two α chains and two β chains.

https://en.wikipedia.org/wiki/Hemoglobin_A

Related Glossary Terms

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HbS

In people heterozygous for HgbS (carriers of sickling hemoglobin), the poly
problems are minor, because the normal allele is able to produce over 50%
globin. In people homozygous for HgbS, the presence of long-chain polyme
distort the shape of the red blood cell from a smooth doughnut-like shape t
and full of spikes, making it fragile and susceptible to breaking within capil
ers have symptoms only if they are deprived of oxygen (for example, while
mountain) or while severely dehydrated. The sickle-cell disease occurs whe
amino acid, glutamic acid, is replaced by valine to change its structure and
As such, sickle-cell anemia is also known as E6V. Valine is hydrophobic, ca
moglobin to collapse on itself occasionally. The structure is not changed oth
When enough hemoglobin collapses on itself the red blood cells become sic

https://en.wikipedia.org/wiki/Sickle-cell_disease

Related Glossary Terms

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HCl

The compound hydrogen chloride has the chemical formula HCl. At room te
ture, it is a colorless gas, which forms white fumes of hydrochloric acid upon
with atmospheric humidity. Hydrogen chloride gas and hydrochloric acid ar
tant in technology and industry. Hydrochloric acid, the aqueous solution of h
chloride, is also commonly given the formula HCl.

Hydrogen chloride is a diatomic molecule, consisting of a hydrogen atom H a
rine atom Cl connected by a covalent single bond. Since the chlorine atom is
more electronegative than the hydrogen atom, the covalent bond between th
oms is quite polar. Consequently, the molecule has a large dipole moment wi
tive partial charge ($\delta-$) at the chlorine atom and a positive partial charge ($\delta+$
drogen atom. In part because of its high polarity, HCl is very soluble in wate
other polar solvents).

https://en.wikipedia.org/wiki/Hydrogen_chloride

Related Glossary Terms

Drag related terms here

HDL

High-density lipoproteins (HDL) are one of the five major groups of lipoproteins. Lipoproteins are complex particles composed of multiple proteins which transport all fat molecules (lipids) around the body within the water outside cells. They are typically composed of 80-100 proteins per particle (organized by one, two or three ApoA, more as the particles enlarge picking up and carrying more fat molecules) and transporting up to hundreds of fat molecules per particle. Unlike the larger lipoprotein particles which deliver fat molecules to cells, HDL particles remove fat molecules from cells which need to export molecules. The molecules carried include cholesterol, phospholipids, and triglycerides. Amounts of each are quite variable.

Increasing concentrations of HDL particles are strongly associated with decreasing accumulation of atherosclerosis within the walls of arteries. This is important because atherosclerosis eventually results in sudden plaque ruptures, cardiovascular disease, stroke and other vascular diseases. HDL particles are sometimes referred to as "good cholesterol" because they can transport fat molecules out of artery walls, reduce macrophage accumulation, and thus help prevent or even regress atherosclerosis. However, studies have shown that HDL-lacking mice still have the ability to transport cholesterol to bile, suggesting that there are alternative mechanisms for cholesterol removal.

https://en.wikipedia.org/wiki/High-density_lipoprotein

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https://en.wikipedia.org/wiki/High-density_lipoprotein

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Heat Shock

Heat shock is the effect of subjecting a cell to a higher temperature than that of th
ideal body temperature of the organism from which the cell line was derived.

The cellular response to heat shock includes the transcriptional up-regulation of g
encoding heat shock proteins (HSPs) as part of the cell's internal repair mechanis
They are also called stress-proteins. and respond to heat, cold and oxygen depriva
by activating several cascade pathways. HSPs are also present in cells under perfe
normal conditions. Some HSPs, called chaperones, ensure that the cell's proteins
the right shape and in the right place at the right time. For example, HSPs help ne
misfolded proteins to fold into their correct three-dimensional conformations, wh
essential for their function. They also shuttle proteins from one compartment to a
other inside the cell, and target old or terminally misfolded proteins to proteases f
degradation. Heat shock proteins are also believed to play a role in the presentatio
pieces of proteins (or peptides) on the cell surface to help the immune system rec
nize diseased cells.

https://en.wikipedia.org/wiki/Heat_shock

Related Glossary Terms

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Hedgehog Protein

The Hedgehog signaling pathway is a signaling pathway that transmits info
embryonic cells required for proper development. Different parts of the em
different concentrations of hedgehog signaling proteins. The pathway also l
the adult. Diseases associated with the malfunction of this pathway include
carcinoma.

The Hedgehog signaling pathway is one of the key regulators of animal dev
and is present in all bilaterians. The pathway takes its name from its polype
ligand, an intercellular signaling molecule called Hedgehog (Hh) found in f
the genus *Drosophila*. Hh is one of *Drosophila's* segment polarity gene pro
volved in establishing the basis of the fly body plan. The molecule remains
during later stages of embryogenesis and metamorphosis.

https://en.wikipedia.org/wiki/Hedgehog_signaling_pathway

Related Glossary Terms

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Helicase

Helicases are a class of enzymes vital to all living organisms. Their main function is to unpackage an organism's genes. They are motor proteins that move directionally along a nucleic acid phosphodiester backbone, separating two annealed nucleic acid strands (i.e., DNA, RNA, or RNA-DNA hybrid) using energy derived from ATP hydrolysis. There are many helicases resulting from the great variety of processes in which strand separation must be catalyzed. Approximately 1% of eukaryotic genes code for helicases. The human genome codes for 95 non-redundant helicases: 64 RNA helicases and 31 DNA helicases. Many cellular processes, such as DNA replication, transcription, translation, recombination, DNA repair, and ribosome biogenesis involve the separation of nucleic acid strands that necessitates the use of helicases.

Helicases are often used to separate strands of a DNA double helix or a self-annealed RNA molecule using the energy from ATP hydrolysis, a process characterized by the breaking of hydrogen bonds between annealed nucleotide bases. They also function to remove nucleic acid-associated proteins and catalyze homologous DNA recombination. Metabolic processes of RNA such as translation, transcription, ribosome biogenesis, RNA splicing, RNA transport, RNA editing, and RNA degradation are all facilitated by helicases. Helicases move incrementally along one nucleic acid strand of the duplex with a directionality and processivity specific to each particular enzyme.

Helicases adopt different structures and oligomerization states. Whereas DnaB-like helicases unwind DNA as donut-shaped hexamers, other enzymes have been shown to be active as monomers or dimers. Studies have shown that helicases may act passively, waiting for uncatalyzed unwinding to take place and then translocating between displaced strands, or can play an active role in catalyzing strand separation using the energy generated in ATP hydrolysis. In the latter case, the helicase acts comparably to an active motor, unwinding and translocating along its substrate as a direct result of its ATPase activity. Helicases may process much faster *in vivo* than *in vitro* due to the presence of accessory proteins that aid in the destabilization of the fork junction.

https://en.wikipedia.org/wiki/Helicase

Related Glossary Terms

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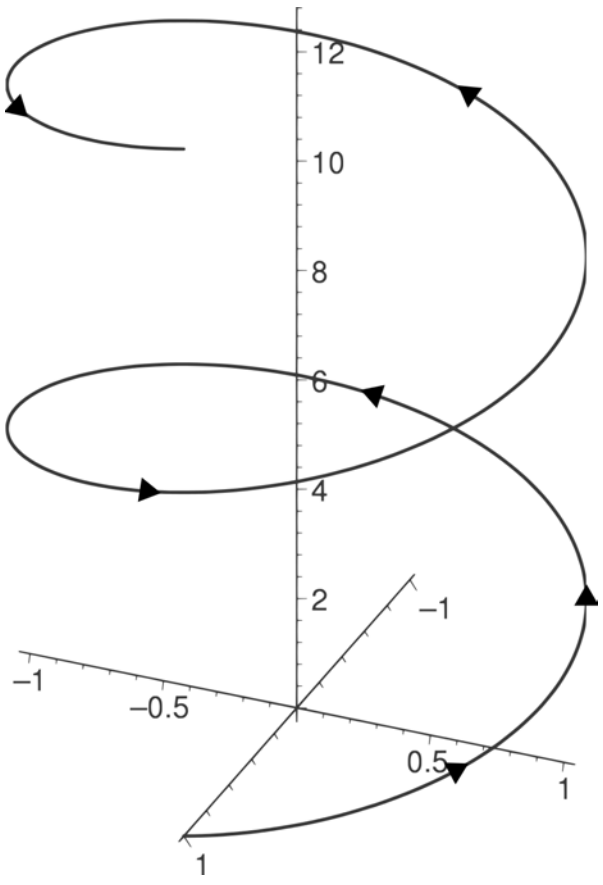
Helix

A helix is a type of smooth space curve, i.e. a curve in three-dimensional space. It has the property that the tangent line at any point makes a constant angle with a fixed line called the axis. Examples of helices are coil springs and the handrails of spiral staircases. Helices are important in biology, as the DNA molecule is formed as two intertwined helices, and many proteins have helical substructures, known as α-helices. A right-handed helix is shown below.



https://en.wikipedia.org/wiki/Helix

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Helix-turn-helix

In proteins, the helix-turn-helix (HTH) is a major structural motif capable
DNA. It is composed of two α helices joined by a short strand of amino acid
found in many proteins that regulate gene expression.

https://en.wikipedia.org/wiki/Helix-turn-helix

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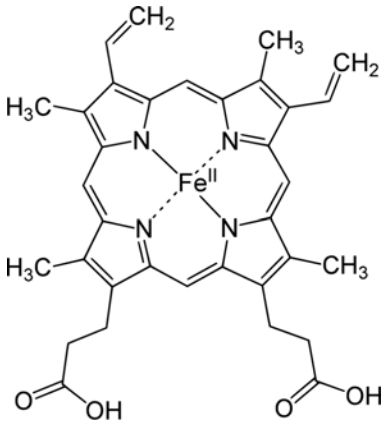
Chapter 2 - Structure and Function: Proteins

Chapter 9 - Point by Point: Structure and Function

Heme

Heme is a cofactor consisting of an Fe^{++} (ferrous or iron) ion contained in the center of a large heterocyclic organic ring called a porphyrin, made up of four pyrrolic groups joined together by methine bridges. Not all porphyrins contain iron, but a substantial fraction of porphyrin-containing metalloproteins have heme as their prosthetic group. These are known as hemoproteins. Hemes are most commonly recognized as components of hemoglobin, the red pigment in blood, but are also found in a number of other biologically important hemoproteins such as myoglobin, cytochrome, catalase, heme peroxidase, and endothelial nitric oxide synthase. Shown below is heme b.



https://en.wikipedia.org/wiki/Heme

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Heme Oxygenase

Heme oxygenase (HO) is an enzyme that catalyzes the degradation of heme
duces biliverdin, ferrous iron, and carbon monoxide. Heme oxygenase clea
heme ring at the α-methene bridge to form either biliverdin or, if the heme
tached to a globin, verdoglobin. Biliverdin is subsequently converted to bili
biliverdin reductase.

https://en.wikipedia.org/wiki/Heme_oxygenase

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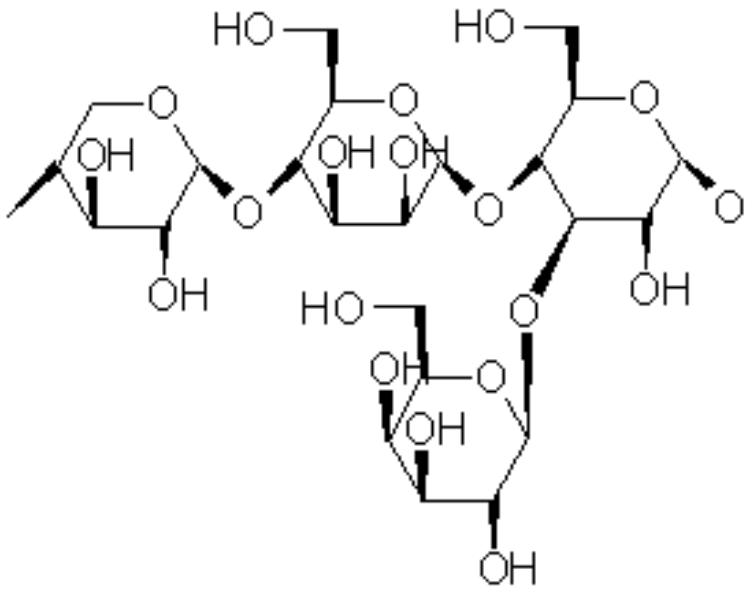
Chapter 6 - Metabolism: Other Lipids

Hemicellulose

A hemicellulose (also known as polyose) is any of several heteropolymers (matrix polysaccharides), such as arabinoxylans, present along with cellulose in almost all plant cell walls. While cellulose is crystalline, strong, and resistant to hydrolysis, hemicellulose has a random, amorphous structure with little strength. It is easily hydrolyzed by dilute acid or base as well as myriad hemicellulase enzymes.



- Xylose - ß(1,4) - Mannose - ß(1,4) - Glucose -
- alpha(1,3) - Galactose

Hemicellulose

https://en.wikipedia.org/wiki/Hemicellulose

Related Glossary Terms

Drag related terms here

Hemiterpenes

Hemiterpenes consist of a single isoprene unit. Isoprene itself is considered
hemiterpene, but oxygen-containing derivatives such as prenol and isovale
hemiterpenoids.

https://en.wikipedia.org/wiki/Terpene

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Hemocyanin

Hemocyanins (also spelled haemocyanins and abbreviated Hc) are proteins that transport oxygen throughout the bodies of some invertebrate animals. These metalloproteins contain two copper atoms that reversibly bind a single oxygen molecule (O_2). They are second only to hemoglobin in frequency of use as an oxygen transport molecule. Unlike the hemoglobin in red blood cells found in vertebrates, hemocyanins are not bound to blood cells but are instead suspended directly in the hemolymph. Oxygenation causes a color change between the colorless Cu(I) deoxygenated form and the blue Cu(II) oxygenated form.

Hemocyanins are found only in the *Mollusca* and *Arthropoda*: the earliest hemocyanins were found in the snail *Helix pomatia* (a mollusc) and in the horseshoe crab (an arthropod). They were subsequently found to be common among crustaceans and are utilized by some land arthropods such as the tarantula *Eurypelma californicum*, the emperor scorpion, and the centipede *Scutigera coleoptrata*. Also, larval storage proteins in many insects appear to be derived from hemocyanins.

Although the respiratory function of hemocyanin is similar to that of hemoglobin, there are a significant number of differences in its molecular structure and mechanism. Whereas hemoglobin carries its iron atoms in porphyrin rings (heme groups), the copper atoms of hemocyanin are bound as prosthetic groups coordinated by histidine residues. The active site of hemocyanin is composed of a pair of copper(I) cations which are directly coordinated to the protein through the driving force of imidazolic rings of six histidine residues. It has been noted that species using hemocyanin for oxygen transportation include crustaceans living in cold environments with low oxygen pressure. Under these circumstances hemoglobin oxygen transportation is less efficient than hemocyanin oxygen transportation. Nevertheless there are also terrestrial arthropods using hemocyanin, notably spiders and scorpions, that live in warm climates.

Most hemocyanins bind with oxygen non-cooperatively and are roughly one-fourth as efficient as hemoglobin at transporting oxygen per amount of blood. Hemoglobin binds oxygen cooperatively due to steric conformation changes in the protein complex, which increases hemoglobin's affinity for oxygen when partially oxygenated. In some hemocyanins of horseshoe crabs and some other species of arthropods, cooperative binding is observed, with Hill coefficients of 1.6 - 3.0. Hill coefficients vary depending on species and laboratory measurement settings. Hemoglobin, for comparison, has a Hill coefficient of usually 2.8 - 3.0. In these cases of cooperative binding hemocyanin was arranged in protein sub-complexes of 6 subunits (hexamer) each with one oxygen binding site. Binding of oxygen on one unit in the complex would increase the affinity of the neighboring units. Each hexamer complex was arranged together to form a larger complex of dozens of hexamers. In one study, cooperative binding was found to be dependent on hexamers being arranged together in the larger complex, suggesting cooperative binding between hexamers. Hemocyanin oxygen-binding profile is also affected by dissolved salt ion levels and pH.

https://en.wikipedia.org/wiki/Hemocyanin

Hemoglobin

Hemoglobin is the iron-containing oxygen-transport metalloprotein in the red blood cells of all vertebrates (with the exception of the fish family *Channichthyidae*) as well as the tissues of some invertebrates. Hemoglobin in the blood carries oxygen from the respiratory organs (lungs or gills) to the rest of the body (i.e. the tissues). There it releases the oxygen to permit aerobic respiration to provide energy to power the functions of the organism in the process called metabolism.

In mammals, the protein makes up about 96% of the red blood cells' dry content (by weight), and around 35% of the total content (including water). Hemoglobin has an oxygen-binding capacity of 1.34 mL O_2 per gram, which increases the total blood oxygen capacity seventy-fold compared to dissolved oxygen in blood. The mammalian hemoglobin molecule can bind (carry) up to four oxygen molecules.

Hemoglobin is involved in the transport of other gases: It carries some of the body's respiratory carbon dioxide (about 20–25% of the total) as carbaminohemoglobin, in which CO_2 is bound to the globin protein. The molecule also carries the important regulatory molecule nitric oxide bound to a globin protein thiol group, releasing it at the same time as oxygen.

Hemoglobin is also found outside red blood cells and their progenitor lines. Other cells that contain hemoglobin include the A_9 dopaminergic neurons in the substantia nigra, macrophages, alveolar cells, and mesangial cells in the kidney. In these tissues, hemoglobin has a non-oxygen-carrying function as an antioxidant and a regulator of iron metabolism.

Hemoglobin and hemoglobin-like molecules are also found in many invertebrates, fungi, and plants. In these organisms, hemoglobins may carry oxygen, or they may act to transport and regulate other small molecules and ions such as carbon dioxide, nitric oxide, hydrogen sulfide and sulfide. A variant of the molecule, called leghemoglobin, is used to scavenge oxygen away from anaerobic systems, such as the nitrogen-fixing nodules of leguminous plants, before the oxygen can poison (deactivate) the system.

https://en.wikipedia.org/wiki/Hemoglobin

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Hemophilia

Hemophilia (also spelled haemophilia) is a group of hereditary genetic diso
impairs the body's ability to control blood clotting, which is used to stop ble
a blood vessel is broken. Haemophilia A (clotting factor VIII deficiency) is t
common form of the disorder, present in about 1 in 5,000–10,000 male bir
philia B (factor IX deficiency) occurs in around 1 in about 20,000–34,000

https://en.wikipedia.org/wiki/Haemophilia

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Henderson Hasselbalch Equation

The Henderson–Hasselbalch equation describes the derivation of pH as a measure of acidity (using pKa, the negative log of the acid dissociation constant) in biological and chemical systems. The equation is also useful for estimating the pH of a buffer solution and finding the equilibrium pH in acid-base reactions (it is widely used to calculate the isoelectric point of proteins).
The equation is given by:

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log_{10}\left(\frac{[\mathrm{A}^-]}{[\mathrm{HA}]}\right)$$

Here, [HA] is the molar concentration of the undissociated weak acid, [A^-] is the molar concentration (molarity, M) of this acid's conjugate base and pKa is –log10 Ka where Ka is the acid dissociation constant, that is:

$$\mathrm{p}K_\mathrm{a} = -\log_{10}(K_\mathrm{a}) = -\log_{10}\left(\frac{[\mathrm{H_3O^+}][\mathrm{A}^-]}{[\mathrm{HA}]}\right)$$

for the non-specific Brønsted acid-base reaction:

$$\mathrm{HA} + \mathrm{H_2O} \rightleftharpoons \mathrm{A}^- + \mathrm{H_3O}^+$$

In these equations, A^- denotes the ionic form of the relevant acid. Bracketed quantities such as [base] and [acid] denote the molar concentration of the quantity enclosed.

https://en.wikipedia.org/wiki/Henderson–Hasselbalch_equation

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https://en.wikipedia.org/wiki/Henderson–Hasselbalch_equation

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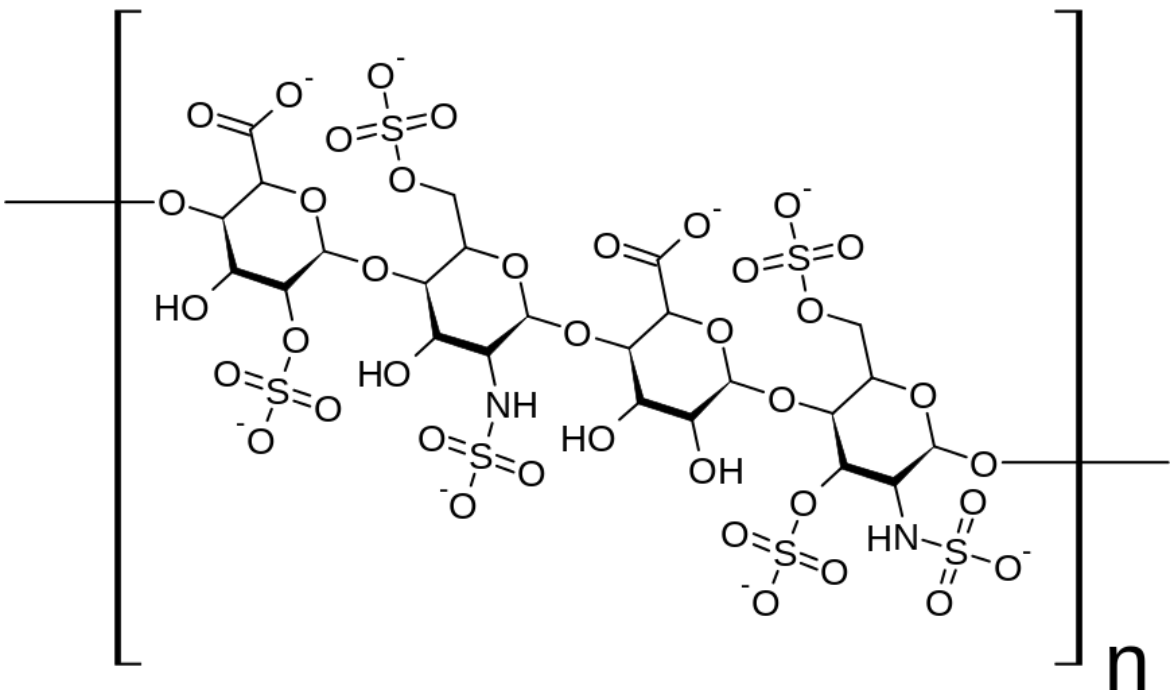
Chapter 1 - Introduction: Water and Buffers

Heparan Sulfate

Heparan sulfate (HS) is a linear polysaccharide found in all animal tissues. It occurs as a proteoglycan (HSPG) in which two or three HS chains are attached in close proximity to cell surface or extracellular matrix proteins. It is in this form that HS binds to a variety of protein ligands and regulates a wide variety of biological activities, including developmental processes, angiogenesis, blood coagulation, abolishing detachment activity by GrB (Granzyme B), and tumor metastasis. HS has been shown to serve as cellular receptor for a number of viruses including the respiratory syncytial virus (Hallak et al. 2000). The structure of a heparan sulfate subunit is shown below.



https://en.wikipedia.org/wiki/Heparan_sulfate

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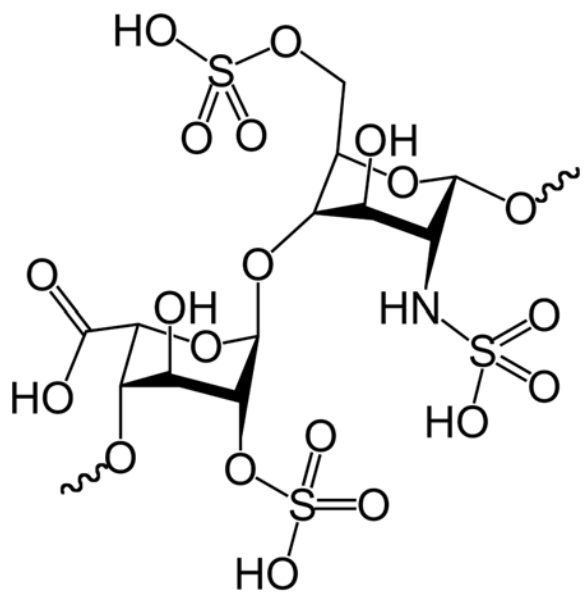
Heparin

Heparin is a widely used injectable blood thinner. It is used to treat and prevent deep vein thrombosis and pulmonary embolism (collectively known as venous thromboembolism) and is also used as part of the treatment of myocardial infarction and unstable angina. Heparin is used on the inside surfaces of various devices such as test tubes and kidney dialysis machines.

Heparin's normal role in the body is unclear. Heparin is usually stored within the secretory granules of mast cells and released only into the vasculature at sites of tissue injury. It has been proposed that, rather than anticoagulation, the main purpose of heparin is defense at such sites against invading bacteria and other foreign materials. The repeating unit of a heparin polymer is shown below.



https://en.wikipedia.org/wiki/Heparin

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Herceptin

Trastuzumab, sold under the brandname Herceptin among others, is a monoclonal antibody that interferes with the HER2/neu receptor. Its main use is to treat certain breast cancers.

The HER receptors are proteins that are embedded in the cell membrane and communicate molecular signals from outside the cell (molecules called EGFs) to inside the cell, and turn genes on and off. The HER protein, Human Epidermal Growth Factor Receptor, binds to Human Epidermal Growth Factor, and stimulates cell proliferation. In some cancers, notably certain types of breast cancer, HER2 is over-expressed, and causes cancer cells to reproduce uncontrollably.

The HER2 gene (also known as HER2/neu and ErbB2 gene) is amplified in 20-30% of early-stage breast cancers. The HER2 pathway promotes cell growth and division when it is functioning normally. However, when it is overexpressed, cell growth accelerates beyond its normal limits. In some types of cancer the pathway is exploited to promote rapid cell growth and proliferation and hence tumor formation. The EGF pathway includes the receptors HER1 (EGFR), HER2, HER3, and HER4. The binding of EGF to HER is required to activate the pathway. The pathway initiates the MAP Kinase pathway as well as the PI3 Kinase/AKT pathway, which in turn activates the NF-κB pathway. In cancer cells the HER2 protein can be expressed up to 100 times more than in normal cells (2 million versus 20,000 per cell). This overexpression leads to strong and constant proliferative signaling and hence tumor formation. Overexpression of HER2 also causes deactivation of checkpoints, allowing for even greater increases in proliferation.

Trastuzumab binds to domain IV of the extracellular segment of the HER2/neu receptor. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle so there is reduced proliferation. It has been suggested that trastuzumab does not alter HER-2 expression, but downregulates activation of AKT. In addition, trastuzumab suppresses angiogenesis both by induction of antiangiogenic factors and repression of pro-angiogenic factors. It is thought that a contribution to the unregulated growth observed in cancer could be due to proteolytic cleavage of HER2/neu that results in the release of the extracellular domain.

Experiments in laboratory animals indicate that antibodies, including trastuzumab, when bound to a cell, induce immune cells to kill that cell, and that such antibody-dependent cell-mediated cytotoxicity is another important mechanism of action.

https://en.wikipedia.org/wiki/Trastuzumab

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Heterochromatin

Heterochromatin is a tightly packed form of DNA, which comes in multiple varieties. Because it is tightly packed, it is inaccessible to polymerases and is therefore not transcribed, (or so we thought. According to Volpe et al, and many other papers since, we see that much of this DNA is in fact transcribed, however it is continuously turned over via a RITS pathway) . These varieties lie on a continuum between the two extremes of constitutive and facultative heterochromatin. Both play a role in the expression of genes.

Chromatin is found in two varieties: euchromatin and heterochromatin. Originally, the two forms were distinguished cytologically by how intensely they stained – the euchromatin is less intense, while heterochromatin stains intensely, indicating tighter packing. Heterochromatin is usually localized to the periphery of the nucleus. Despite this early dichotomy, recent evidence in both animals and plants has suggested that there are more than two distinct heterochromatin states, and it may in fact exist in four or five 'states', each marked by different combinations of epigenetic marks.

Heterochromatin mainly consists of genetically inactive satellite sequences, and many genes are repressed to various extents, although some cannot be expressed in euchromatin at all. Both centromeres and telomeres are heterochromatic, as is the Barr body of the second, inactivated X-chromosome in a female.

https://en.wikipedia.org/wiki/Heterochromatin

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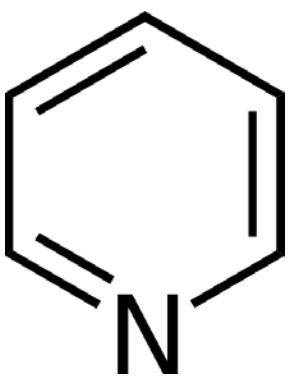
Chapter 9 - Point by Point: Structure and Function

Heterocyclic

A heterocyclic compound or ring structure is a cyclic compound that has at least two different elements as members of its ring(s). Heterocyclic chemist branch of chemistry dealing with the synthesis, properties and applications heterocycles. In contrast, the rings of homocyclic compounds consist entire of the same element. One heterocyclic compound is shown below.



https://en.wikipedia.org/wiki/Heterocyclic_compound

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Heterotrophic

A heterotroph is an organism that cannot fix carbon and uses organic carbo
growth. Heterotrophs can be further divided based on how they obtain ene
heterotroph uses light for energy, then it is considered a photoheterotroph,
heterotroph uses chemical energy, it is considered a chemoheterotroph.

https://en.wikipedia.org/wiki/Heterotroph

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heterotroph uses chemical energy, it is considered a chemoheterotroph.

https://en.wikipedia.org/wiki/Heterotroph

Related Glossary Terms

Drag related terms here

Heterotropic

A heterotropic allosteric modulator is a regulatory molecule that is not the substrate. It may be either an activator or an inhibitor of the enzyme. For ex CO_2, and 2,3-bisphosphoglycerate are heterotropic allosteric modulators of bin.

https://en.wikipedia.org/wiki/Allosteric_regulation#Types_of_allosteric_

Related Glossary Terms

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Heterotropic Effectors

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substrate. It may be either an activator or an inhibitor of the enzyme. For e
CO_2, and 2,3-bisphosphoglycerate are heterotropic allosteric modulators of
bin.

https://en.wikipedia.org/wiki/Allosteric_regulation#Types_of_allosteric_

Related Glossary Terms

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Heterozygous

A diploid organism is heterozygous at a gene locus when its cells contain tw
alleles of a gene. The cell or organism is called a heterozygote specifically fo
in question, therefore, heterozygosity refers to a specific genotype. Heteroz
types are represented by a capital letter (representing the dominant allele)
case letter (representing the recessive allele), such as "Rr" or "Ss". Alternati
erozygote for gene "R" is assumed to be "Rr". The capital letter is usually w

If the trait in question is determined by simple (complete) dominance, a he
will express only the trait coded by the dominant allele, and the trait coded
sive allele will not be present. In more complex dominance schemes the res
erozygosity can be more complex.

https://en.wikipedia.org/wiki/Zygosity#Heterozygous

Related Glossary Terms

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Hexokinase

A hexokinase is an enzyme that phosphorylates hexoses (six-carbon sugars), forming hexose phosphate. In most organisms, glucose is the most important substrate of hexokinases, and glucose-6-phosphate is the most important product. Hexokinase can transfer an inorganic phosphate group from ATP to a substrate.

Genes that encode hexokinase have been discovered in every domain of life, and exist among a variety of species that range from bacteria, yeast, and plants to humans and other vertebrates. They are categorized as actin fold proteins, sharing a common ATP binding site core that is surrounded by more variable sequences which determine substrate affinities and other properties.

Several hexokinase isoforms or isozymes that provide different functions can occur in a single species.

https://en.wikipedia.org/wiki/Hexokinase

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Hexoses

In bio-organic chemistry, a hexose is a monosaccharide with six carbon atoms, having the chemical formula $C_6H_{12}O_6$. Hexoses are classified by functional group, with aldohexoses having an aldehyde at position 1, and ketohexoses having a ketone at position 2.

Hexoses play a key role in several different biochemical pathways, including cellular energy release, signaling, carbohydrate synthesis, and the regulation of gene expression. The most common hexoses in biological systems are D-galactose, D-glucose and D-mannose.

Researchers have used computational algorithms to model protein-galactose, protein-glucose and protein-mannose binding-sites. Individual hexoses share multiple physiochemical similarities leading to the development of a general protein-hexose binding-site model.

https://en.wikipedia.org/wiki/Hexose

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High Density Lipoprotein

High-density lipoproteins (HDL) are one of the five major groups of lipoproteins. Lipoproteins are complex particles composed of multiple proteins which transport all fat molecules (lipids) around the body within the water outside cells. They are typically composed of 80-100 proteins per particle (organized by one, two or three ApoA, more as the particles enlarge picking up and carrying more fat molecules) and transporting up to hundreds of fat molecules per particle. Unlike the larger lipoprotein particles which deliver fat molecules to cells, HDL particles remove fat molecules from cells which need to export fat molecules. The fats carried include cholesterol, phospholipids, and triglycerides. Amounts of each are quite variable.

Increasing concentrations of HDL particles are strongly associated with decreasing accumulation of atherosclerosis within the walls of arteries. This is important because atherosclerosis eventually results in sudden plaque ruptures, cardiovascular disease, stroke and other vascular diseases. HDL particles are sometimes referred to as "good cholesterol" because they can transport fat molecules out of artery walls, reduce macrophage accumulation, and thus help prevent or even regress atherosclerosis. However, studies have shown that HDL-lacking mice still have the ability to transport cholesterol to bile, suggesting that there are alternative mechanisms for cholesterol removal.

https://en.wikipedia.org/wiki/High-density_lipoprotein

Related Glossary Terms

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High Density Lipoprotein Complexes

High-density lipoproteins (HDL) are one of the five major groups of lipoproteins. Lipoproteins are complex particles composed of multiple proteins which transport all fat molecules (lipids) around the body within the water outside cells. They are typically composed of 80-100 proteins per particle (organized by one, two or three ApoA. More as the particles enlarge picking up and carrying more fat molecules) and transporting up to hundreds of fat molecules per particle. Unlike the larger lipoprotein particles which deliver fat molecules to cells, HDL particles remove fat molecules from cells which need to export fat molecules. The fats carried include cholesterol, phospholipids, and triglycerides. Amounts of each are quite variable.

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https://en.wikipedia.org/wiki/High-density_lipoprotein

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Hind III

HindIII (pronounced "Hin Dee Three") is a type II site-specific deoxyribonuclease restriction enzyme isolated from *Haemophilus influenzae* that cleaves the DNA palindromic sequence AAGCTT in the presence of the cofactor Mg^{++} via hydrolysis.

HindIII restrictions process results in formation of overhanging palindromic sticky ends. The cleavage of this sequence between the AA's results in 5' overhangs on the DNA called sticky ends:

5'-A |A G C T T-3'
3'-T T C G A| A-5'

Restriction endonucleases are used as defense mechanisms in prokaryotic organisms in the restriction modification system. Their primary function is to protect the host genome against invasion by foreign DNA, primarily bacteriophage DNA. There is also evidence that suggests the restriction enzymes may act alongside modification enzymes as selfish elements, or may be involved in genetic recombination and transposition.

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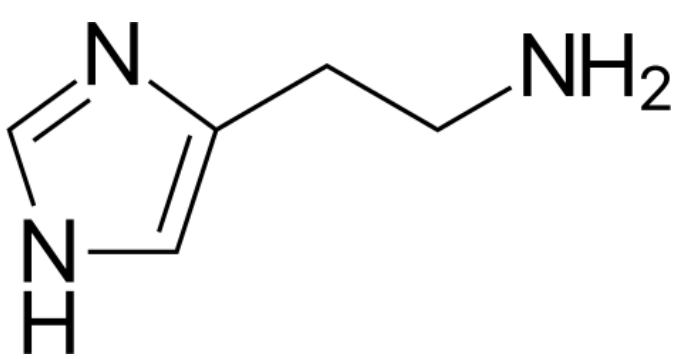
Histamine

Histamine is an organic nitrogenous compound involved in local immune res
well as regulating physiological function in the gut and acting as a neurotrans
Histamine is involved in the inflammatory response and has a central role as
tor of pruritus. As part of an immune response to foreign pathogens, histami
duced by basophils and by mast cells found in nearby connective tissues. His
creases the permeability of the capillaries to white blood cells and some prote
low them to engage pathogens in the infected tissues.



https://en.wikipedia.org/wiki/Histamine

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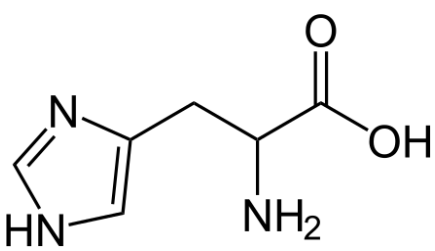
Histidine

Histidine (abbreviated as His or H; encoded by the codons CAU and CAC) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH3^+$ form under biological conditions), a carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain imidazole, which can be positively charged.

The conjugate acid (protonated form) of the imidazole side chain in histidine has a pKa of approximately 6.0. This means that, at physiologically relevant pH values, relatively small shifts in pH will change its average charge. Below a pH of 6, the imidazole ring is mostly protonated as described by the Henderson–Hasselbalch equation. When protonated, the imidazole ring bears two NH bonds and has a positive charge. The positive charge is equally distributed between both nitrogens and can be represented with two equally important resonance structures. As the pH increases past approximately 6, one of the protons is lost. The remaining proton of the now-neutral imidazole ring can reside on either nitrogen, giving rise to what are known as the N_1-H or N_3-H tautomers. The N_3-H tautomer is protonated on the #3 nitrogen, farther from the amino acid backbone bearing the amino and carboxyl groups, whereas the N_1-H tautomer is protonated on the nitrogen nearer the backbone.



https://en.wikipedia.org/wiki/Histidine

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Histidine Tagging

A polyhistidine-tag is an amino acid motif in proteins that consists of at least six histidine (His) residues, often at the N- or C-terminus of the protein. It is also known as hexa histidine-tag, 6xHis-tag, His6 tag and by the trademarked name His-tag (registered by EMD Biosciences).

Polyhistidine-tags are often used for affinity purification of polyhistidine-tagged recombinant proteins expressed in *Escherichia coli* and other prokaryotic expression systems. Bacterial cells are harvested via centrifugation and the resulting cell pellet lysed either by physical means or by means of detergents and enzymes such as lysozyme or any combination of these. At this stage raw lysate contains the recombinant protein among many other proteins originating from the bacterial host. This mixture is incubated with an affinity resin containing bound bivalent nickel or cobalt ions, which are available commercially in different varieties. Nickel and cobalt have similar properties and as they are adjacent period 4 transition metals ((v. iron triad)). These resins are generally sepharose/agarose functionalized with a chelator, such as iminodiacetic acid (Ni-IDA) and nitrilotriacetic acid (Ni-NTA) for nickel and carboxylmethylaspartate (Co-CMA) for cobalt, which the polyhistidine-tag binds with micromolar affinity. The resin is then washed with phosphate buffer to remove proteins that do not specifically interact with the cobalt or nickel ion. With Ni-based methods, washing efficiency can be improved by the addition of 20 mM imidazole (proteins are usually eluted with 150-300 mM imidazole). Generally nickel-based resins have higher binding capacity, while cobalt-based resins offer the highest purity. The purity and amount of protein can be assessed by SDS-PAGE and Western blotting.

Affinity purification using a polyhistidine-tag usually results in relatively pure protein when the recombinant protein is expressed in prokaryotic organisms. Depending on downstream applications, including the purification of protein complexes to study protein interactions, purification from higher organisms such as yeasts or other eukaryotes may require a tandem affinity purification using two tags to yield higher purity. Alternatively, single-step purification using immobilized cobalt ions rather than nickel ions generally yields a substantial increase in purity and requires lower imidazole concentrations for elution of the his-tagged protein.

Polyhistidine-tagging is the option of choice for purifying recombinant proteins in denaturing conditions because its mode of action is dependent only on the primary structure of proteins. Generally for this sort of a technique, histidine binding is titrated using pH instead of imidazole binding—at a high pH, histidine binds to nickel or cobalt, but at low pH (~6 for cobalt and ~4 for nickel), histidine becomes protonated and is competed off of the metal ion. Compare this to antibody purification and GST purification, a prerequisite to which is the proper (native) folding of proteins involved.

https://en.wikipedia.org/wiki/Polyhistidine-tag

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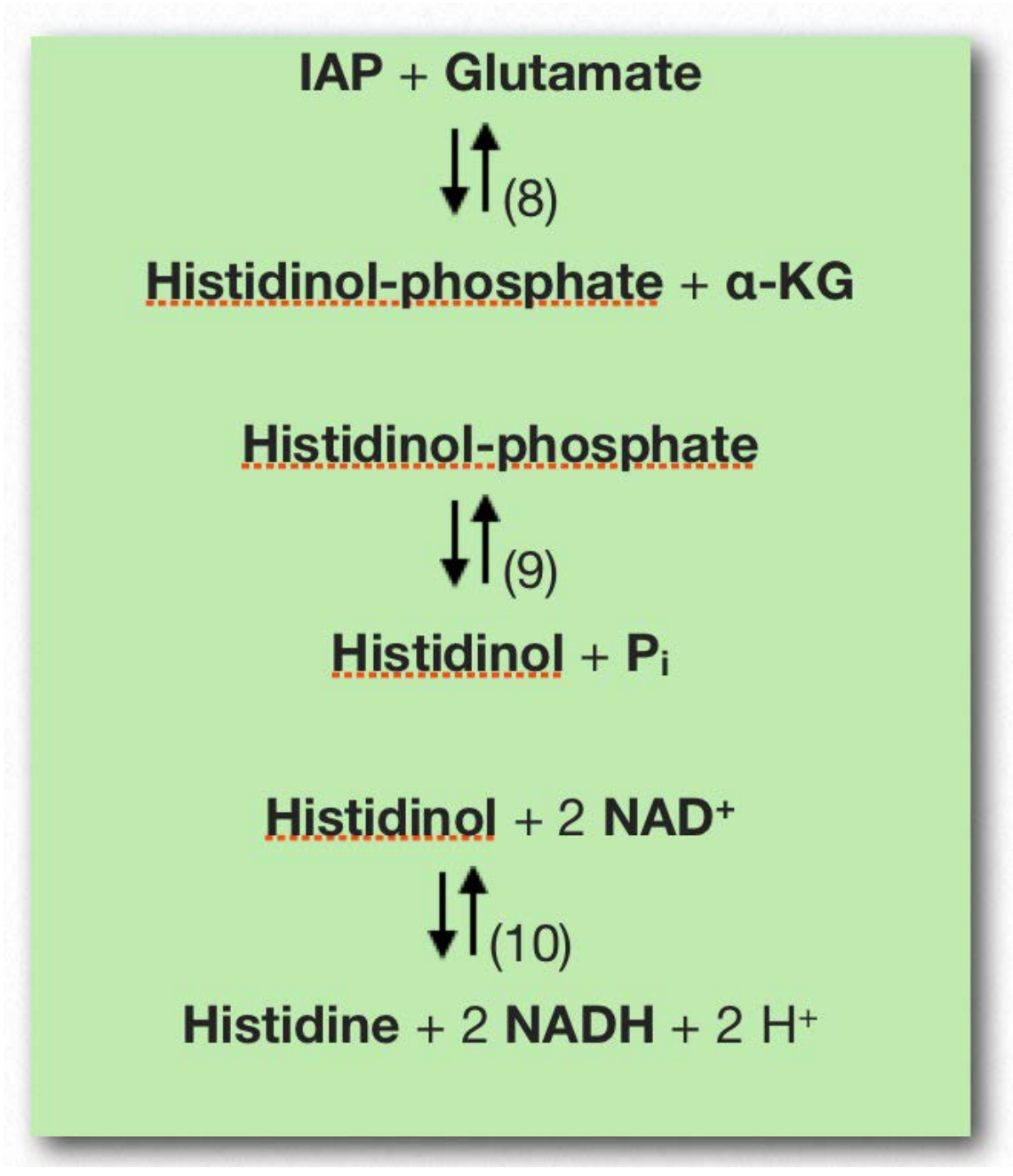
Chapter 8 - Basic Techniques
Chapter 9 - Point by Point: Techniques

Histidinol

Histidinol is an intermediate in the biosynthesis of the amino acid histidine. It is the immediate precursor of histidine.



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Histidinol Dehydrogenase

Histidinol dehydrogenase (HIS4) (HDH) (EC 1.1.1.23) is an enzyme that ca
chemical reaction

L-histidinol + 2 NAD^+ <---> L-histidine + 2 NADH + 2 H^+

The two substrates of this enzyme are L-histidinol and NAD^+, and its 3 pro
histidine, NADH, and H^+.

Histidinol dehydrogenase catalyzes the terminal step in the biosynthesis of
bacteria, fungi, and plants, the four-electron oxidation of L-histidinol to his

https://en.wikipedia.org/wiki/Histidinol_dehydrogenase

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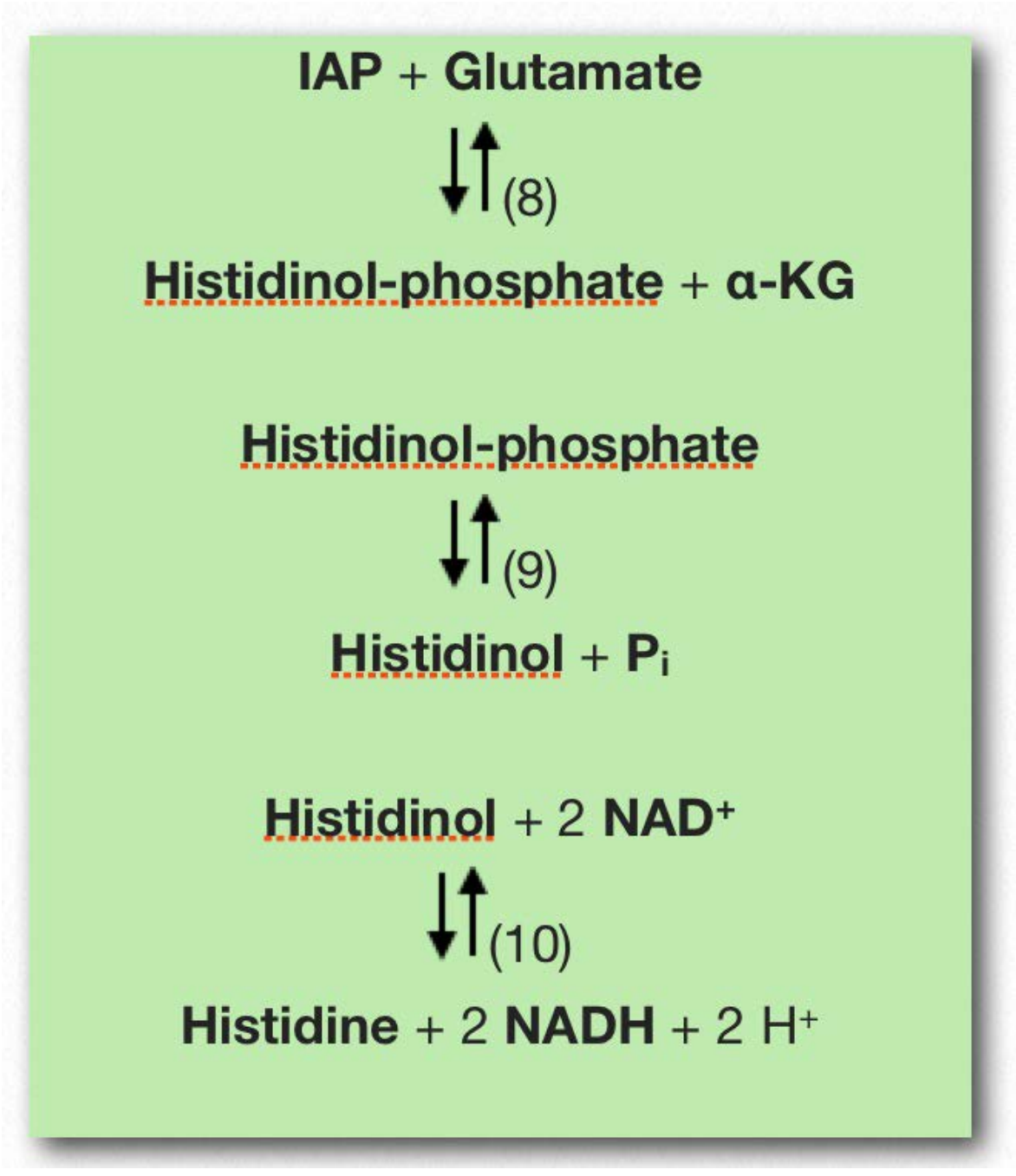
Histidinol-phosphate

Histidinol-phosphate is an intermediate in the biosynthesis of the amino acid histidine.



Related Glossary Terms

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Histidinol-phosphate Aminotransferase

Histidinol-phosphate transaminase (EC 2.6.1.9) is an enzyme that catalyzes the chemical reaction

L-histidinol phosphate + 2-oxoglutarate <---> 3-(imidazol-4-yl)-2-oxopropyl phosphate + L-glutamate

The two substrates of this enzyme are L-histidinol phosphate and 2-oxoglutarate and its two products are 3-(imidazol-4-yl)-2-oxopropyl phosphate and L-glutamate.

This enzyme belongs to the family of transferases, specifically the transaminases, which transfer nitrogenous groups. The systematic name of this enzyme class is L-histidinol-phosphate:2-oxoglutarate aminotransferase. Other names in common use include imidazolylacetolphosphate transaminase, glutamic-imidazoleacetol phosphate transaminase, histidinol phosphate aminotransferase, imidazoleacetol phosphate transaminase, L-histidinol phosphate aminotransferase, histidine:imidazoleacetol phosphate transaminase, IAP transaminase, and imidazolylacetolphosphate aminotransferase. This enzyme participates in 5 metabolic pathways: histidine metabolism, tyrosine metabolism, phenylalanine metabolism, phenylalanine, tyrosine and tryptophan biosynthesis, and novobiocin biosynthesis. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Histidinol-phosphate_transaminase

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Histidinol-phosphate Phosphatase

Histidinol-phosphatase (EC 3.1.3.15) is an enzyme that catalyzes the chemi

L-histidinol-phosphate + H_2O <---> L-histidinol + P_i

This enzyme belongs to the family of hydrolases, to be specific, those acting
phoric monoester bonds. The systematic name of this enzyme class is L-his
phosphate phosphohydrolase. Other names in common use include histidin
phate phosphatase, L-histidinol phosphate phosphatase, histidinolphospha
phatase, HPpase, and histidinolphosphatase. This enzyme participates in h
tabolism.

https://en.wikipedia.org/wiki/Histidinol-phosphatase

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

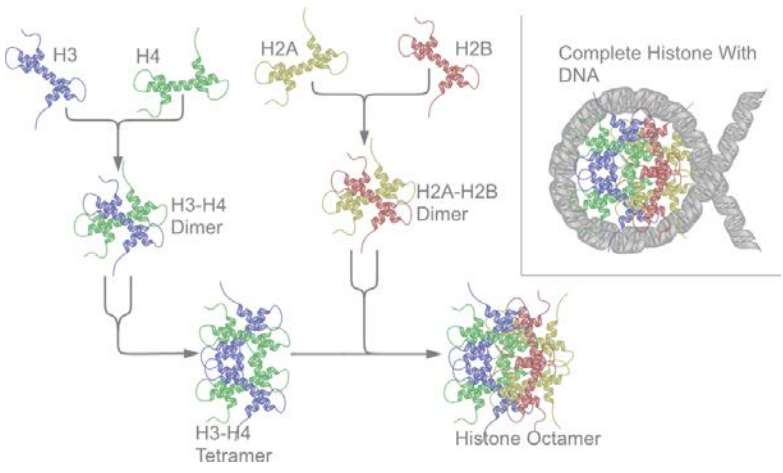
Histone

Histones are highly alkaline proteins found in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes. They are the chief protein components of chromatin, acting as spools around which DNA winds, and playing a role in gene regulation. Without histones, the unwound DNA in chromosomes would be very long (a length to width ratio of more than 10 million to 1 in human DNA). For example, each human cell has about 1.8 meters of DNA, (~6 ft) but wound on the histones it has about 90 micrometers (0.09 mm) of chromatin, which, when duplicated and condensed during mitosis, result in about 120 micrometers of chromosomes.

Five major families of histones exist: H1/H5, H2A, H2B, H3 and H4. Histones H2A, H2B, H3 and H4 are known as the core histones, while histones H1 and H5 are known as the linker histones.

The core histones all exist as dimers, which are similar in that they all possess the histone fold domain - three α helices linked by two loops. It is this helical structure that allows for interaction between distinct dimers, particularly in a head-tail fashion (also called the handshake motif). The resulting four distinct dimers then come together to form one octameric nucleosome core, approximately 63 Angstroms in diameter (a solenoid (DNA)-like particle). 147 base pairs of DNA wrap around this core particle 1.65 times in a left-handed super-helical turn to give a particle of around 100 Angstroms across. The linker histone H1 binds the nucleosome at the entry and exit sites of the DNA, thus locking the DNA into place and allowing the formation of higher order structure. The most basic such formation is the 10 nm fiber or beads on a string conformation. This involves the wrapping of DNA around nucleosomes with approximately 50 base pairs of DNA separating each pair of nucleosomes (also referred to as linker DNA). Higher-order structures include the 30 nm fiber (forming an irregular zigzag) and 100 nm fiber, these being the structures found in normal cells. During mitosis and meiosis, the condensed chromosomes are assembled through interactions between nucleosomes and other regulatory proteins.

https://en.wikipedia.org/wiki/Histone



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Histone Acetyl Transferase

Histone acetyltransferases (HATs) are enzymes that acetylate conserved lysine amino acids on histone proteins by transferring an acetyl group from acetyl CoA to form ε-N-acetyllysine. DNA is wrapped around histones, and, by transferring an acetyl group to the histones, genes can be turned on and off. In general, histone acetylation increases gene expression.

In general, histone acetylation is linked to transcriptional activation and associated with euchromatin. When it was first discovered, it was thought that acetylation of lysine neutralizes the positive charge normally present, thus reducing affinity between histone and (negatively charged) DNA, which renders DNA more accessible to transcription factors. Research has emerged, since, to show that lysine acetylation and other posttranslational modifications of histones generate binding sites for specific protein–protein interaction domains, such as the acetyllysine-binding bromodomain. Histone acetyltransferases can also acetylate non-histone proteins, such as nuclear receptors and other transcription factors to facilitate gene expression.

Histone acetyltransferases serve many biological roles inside the cell. Chromatin is a combination of proteins and DNA found in the nucleus, and it undergoes many structural changes as different cellular events such as DNA replication, DNA repair, and transcription occur. Chromatin in the cell can be found in two states: condensed and uncondensed. The latter, known as euchromatin, is transcriptionally active, whereas the former, known as heterochromatin, is transcriptionally inactive. Histones comprise the protein portion of chromatin. There are five different histone proteins: H1, H2A, H2B, H3, and H4. A core histone is formed when two of each histone subtype, excluding H1, form a quaternary complex. This octameric complex, in association with the 147 base pairs of DNA coiled around it, forms the nucleosome. Histone H1 locks the nucleosome complex together, and it is the last protein to bind in the complex.

Histones tend to be positively charged proteins with N-terminal tails that stem from the core. The phosphodiester backbone of DNA is negative, which allows for strong ionic interactions between histone proteins and DNA. Histone acetyltransferases transfer an acetyl group to specific lysine residues on histones, which neutralizes their positive charge and thus reduces the strong interactions between the histone and DNA. Acetylation is also thought to perturb interactions between individual nucleosomes and act as interaction sites for other DNA-associated proteins.

There can be different levels of histone acetylation as well as other types of modifications, allowing the cell to have control over the level of chromatin packing during different cellular events such as replication, transcription, recombination, and repair. Acetylation is not the only regulatory post-translational modification to histones that dictates chromatin structure. Methylation, phosphorylation, ADP-ribosylation, and ubiquitination have also been reported. These combinations of different covalent modifications on the N-terminal tails of histones have been referred to as the histone code, and it is thought that this code may be heritable and preserved in the next cell generation.

H3 and H4 histone proteins are the primary targets of HATs, but H2A and H2B are also acetylated in vivo. Lysines 9, 14, 18, and 23 of H3 and lysines 5, 8, 12, and 16 of H4 are all targeted for acetylation. Lysines 5, 12, 15, and 20 are acetylated on histone H2B, while only lysines 5 and 9 have been observed to be acetylated on histone H2A.

https://en.wikipedia.org/wiki/Histone_acetyltransferase

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Histone Deacetylases

Histone deacetylases (EC 3.5.1.98, HDAC) are a class of enzymes that remove acetyl groups (O=C-CH3) from an ε-N-acetyl lysine amino acid on a histone, allowing the histones to wrap the DNA more tightly. This is important because DNA is wrapped around histones, and DNA expression is regulated by acetylation and de-acetylation. Its action is opposite to that of histone acetyltransferase. HDAC proteins are now also called lysine deacetylases (KDAC), to describe their function rather than their target, which also includes non-histone proteins.

Histone tails are normally positively charged due to amine groups present on their lysine and arginine amino acids. These positive charges help the histone tails to interact with and bind to the negatively charged phosphate groups on the DNA backbone. Acetylation, which occurs normally in a cell, neutralizes the positive charges on the histone by changing amines into amides and decreases the ability of the histones to bind to DNA. This decreased binding allows chromatin expansion, permitting genetic transcription to take place. Histone deacetylases remove those acetyl groups, increasing the positive charge of histone tails and encouraging high-affinity binding between the histones and DNA backbone. The increased DNA binding condenses DNA structure, preventing transcription.

Histone acetylation plays an important role in the regulation of gene expression. Hyperacetylated chromatin is transcriptionally active, and hypoacetylated chromatin is silent. A study on mice found that a specific subset of mouse genes (7%) was deregulated in the absence of HDAC1. Their study also found a regulatory crosstalk between HDAC1 and HDAC2 and suggest a novel function for HDAC1 as a transcriptional coactivator. HDAC1 expression was found to be increased in the prefrontal cortex of schizophrenia subjects, negatively correlating with the expression of GAD67 mRNA.

https://en.wikipedia.org/wiki/Histone_deacetylase

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Histone Demethylases

Demethylases are enzymes that remove methyl (CH3-) groups from nucleic acids, teins (in particular histones), and other molecules. Demethylase enzymes are imp tant in epigenetic modification mechanisms. The demethylase proteins alter trans tional regulation of the genome by controlling the methylation levels that occur or DNA and histones and, in turn, regulate the chromatin state at specific gene loci w organisms.

For many years histone methylation was thought to be irreversible, due to the fact the half-life of the histone methylation was approximately equal to the half-life of tones themselves. In 2004, Shi et al. published their discovery of the histone deme lase LSD1 (later classified as KDM1A), a nuclear amine oxidase homolog. With the found interest in epigenetics, many more families of histone demethylases have be found. Defined by their mechanisms, two main classes of histone demethylases ex flavin adenine dinucleotide (FAD)-dependent amine oxidase, and an Fe(II) and α- ketoglutarate-dependent dioxygenase.

https://en.wikipedia.org/wiki/Demethylase

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Histone Methyltransferases

Histone methyltransferases (HMT) are histone-modifying enzymes (e.g., histone-lysine N-methyltransferases and histone-arginine N-methyltransferases), that catalyze the transfer of one, two, or three methyl groups to lysine and arginine residues of histone proteins. The attachment of methyl groups occurs predominantly at specific lysine or arginine residues on histones H3 and H4. Two major types of histone methyltranferases exist, lysine-specific (which can be SET (Su(var)3-9, Enhancer of Zeste, Trithorax) domain containing or non-SET domain containing) and arginine-specific. In both types of histone methyltransferases, cofactor S-Adenosyl methionine (SAM) serves as a cofactor and methyl donor group. In eukaryotic cells, the genome is tightly condensed into chromatin (composed of DNA and histone proteins), so enzymes, such as histone methyltransferases, must overcome this inaccessibility. Histone methyltransferase does so by modifying histones at certain sites through methylation. Methylation of histones is important biologically because it is the principal epigenetic modification of chromatin that determines gene expression, genomic stability, stem cell maturation, cell lineage development, genetic imprinting, DNA methylation, and cell mitosis.

There are two different types of protein arginine methyltransferases (PRMTs) and three types of methylation that can occur at arginine residues on histone tails.

Histone methylation plays an important role in epigenetic gene regulation. Methylated histones can either repress or activate transcription as different experimental findings suggest. For example, it is likely that the methylation of lysine 9 on histone H3 (H3K9me3) in the promoter region of genes prevents excessive expression of these genes and, therefore, delays cell cycle transition and/or proliferation.

https://en.wikipedia.org/wiki/Histone_methyltransferase

Related Glossary Terms

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HIV-1 Protease

HIV-1 protease is a retroviral aspartyl protease (retropepsin) that is essenti
life-cycle of HIV, the retrovirus that causes AIDS. HIV protease cleaves new
sized polyproteins at the appropriate places to create the mature protein co
of an infectious HIV virion. Without effective HIV protease, HIV virions re
fectious. Thus, mutation of HIV protease's active site or inhibition of its act
rupts HIV's ability to replicate and infect additional cells, making HIV prot
tion the subject of considerable pharmaceutical research.

https://en.wikipedia.org/wiki/HIV-1_protease

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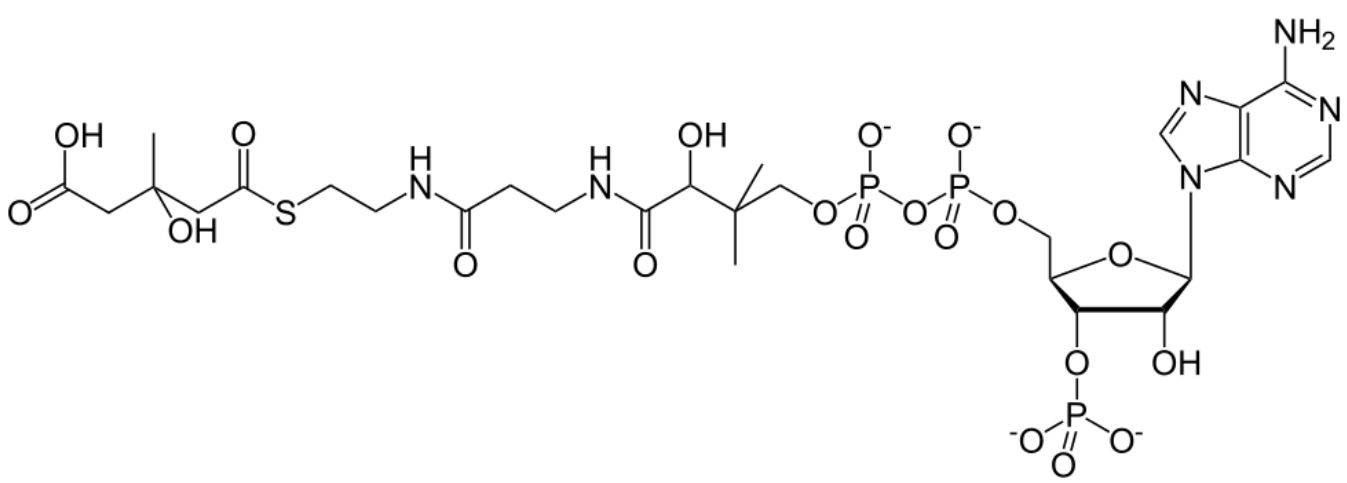
HMG-CoA

HMG-CoA (or 3-hydroxy-3-methylglutaryl-coenzyme A) is an intermediate in the mevalonate and ketogenesis pathways. It is formed from acetyl CoA and acetoacetyl CoA by HMG-CoA synthase.

It is also an intermediate in the metabolism of leucine. Its immediate precursor is 3-methylglutaconyl CoA.



https://en.wikipedia.org/wiki/HMG-CoA

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HMG-CoA Reductase

HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, officially abbreviated HMGCR) is the rate-controlling enzyme (NADH-dependent) of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids. Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low density lipoprotein (LDL) via the LDL receptor as well as oxidized species of cholesterol. Competitive inhibitors of the reductase induce the expression of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, an important determinant of atherosclerosis. This enzyme is thus the target of the widely available cholesterol-lowering drugs known collectively as the statins.

HMG-CoA reductase is anchored in the membrane of the endoplasmic reticulum, and was long regarded as having seven transmembrane domains, with the active site located in a long carboxyl terminal domain in the cytosol. More recent evidence shows it to contain eight transmembrane domains.

https://en.wikipedia.org/wiki/HMG-CoA_reductase

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HMG-CoA Synthase

In molecular biology, Hydroxymethylglutaryl-CoA synthase or HMG-CoA s
an enzyme which catalyzes the reaction in which Acetyl-CoA condenses wit
acetoacetyl-CoA to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). It i
reaction in the mevalonate-dependent isoprenoid biosynthesis pathway. H
an intermediate in both cholesterol synthesis and ketogenesis. This reactio
activated in patients with diabetes mellitus type 1 if left untreated, due to p
sulin deficiency and the exhaustion of substrates for gluconeogenesis and t
cle, notably oxaloacetate. This results in shunting of excess acetyl-CoA into
synthesis pathway via HMG-CoA, leading to the development of diabetic ke

https://en.wikipedia.org/wiki/Hydroxymethylglutaryl-CoA_synthase

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Chapter 6 - Metabolism: Other Lipids

Chapter 9 - Point by Point: Metabolism

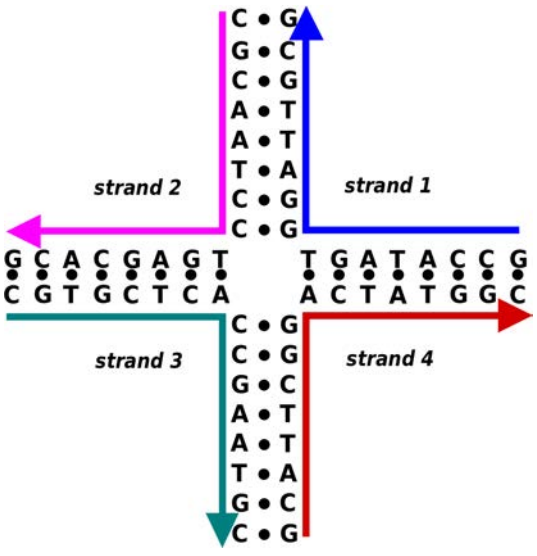
Holliday Junction

A Holliday junction is a branched nucleic acid structure that contains four double-stranded arms joined together. These arms may adopt one of several conformations depending on buffer salt concentrations and the sequence of nucleobases closest to the junction. The structure is named after the molecular biologist Robin Holliday, who proposed its existence in 1964.

In biology, Holliday junctions are a key intermediate in many types of genetic recombination, as well as in double-strand break repair. These junctions usually have a symmetrical sequence and are thus mobile, meaning that the four individual arms may slide though the junction in a specific pattern that largely preserves base pairing. Additionally, four-arm junctions similar to Holliday junctions appear in some functional RNA molecules.

The Holliday junction is a key intermediate in homologous recombination, a biological process that increases genetic diversity by shifting genes between two chromosomes, as well as site-specific recombination events involving integrases. They are additionally involved in repair of double-strand breaks. In addition, cruciform structures involving Holliday junctions can arise to relieve helical strain in symmetrical sequences in DNA supercoils. While four-arm junctions also appear in functional RNA molecules, such as U1 spliceosomal RNA and the hairpin ribozyme of the tobacco ringspot virus, these usually contain unpaired nucleotides in between the paired double-helical domains, and thus do not strictly adopt the Holliday structure.

The Holliday junctions in homologous recombination are between identical or nearly identical sequences, leading to a symmetric arrangement of sequences around the central junction. This allows a branch migration process to occur where the strands move through the junction point. Cleavage, or resolution, of the Holliday junction can occur in two ways. Cleavage of the original set of strands leads to two molecules that may show gene conversion but not chromosomal crossover, while cleavage of the other set of two strands causes the resulting recombinant molecules to show crossover. All products, regardless of cleavage, are heteroduplexes in the region of Holliday junction migration.



https://en.wikipedia.org/wiki/Holliday_junction

Holoenzymes

Enzymes that require a cofactor but do not have one bound are called apoe
apoproteins. An enzyme together with the cofactor(s) required for activity i
holoenzyme (or haloenzyme). The term holoenzyme can also be applied to
that contain multiple protein subunits, such as the DNA polymerases. Her
zyme is the complete complex containing all the subunits needed for activit

https://en.wikipedia.org/wiki/Enzyme

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Chapter 4 - Catalysis: Basic Principles

Homeostasis

Homeostasis or homoeostasis is the property of a system in which variables
lated so that internal conditions remain stable and relatively constant. Exar
meostasis include the regulation of temperature and the balance between a
alkalinity (pH). Human homeostasis is the process that maintains the stabi
human body's internal environment in response to changes in external con

Homeostasis requires a sensor to detect changes in the condition to be regu
trol center, and an effector mechanism that can vary that condition, and a r
feedback connection between the two.

https://en.wikipedia.org/wiki/Homeostasis

Related Glossary Terms

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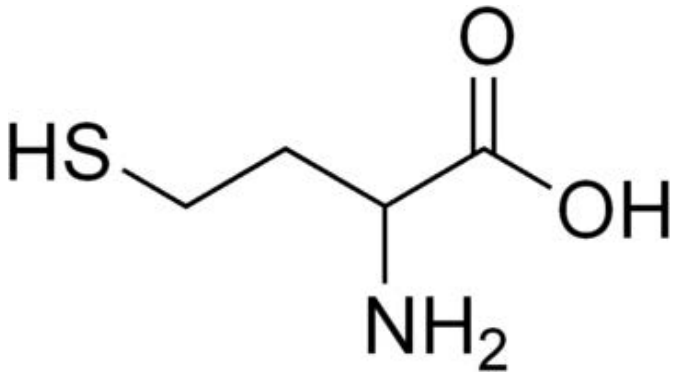
Homocysteine

Homocysteine is a non-protein α-amino acid. It is a homologue of the amino acid cysteine, differing by an additional methylene bridge (-CH2-). It is biosynthesized from methionine by the removal of its terminal Cε methyl group. Homocysteine can be recycled into methionine or converted into cysteine with the aid of certain B-vitamins.



https://en.wikipedia.org/wiki/Homocysteine

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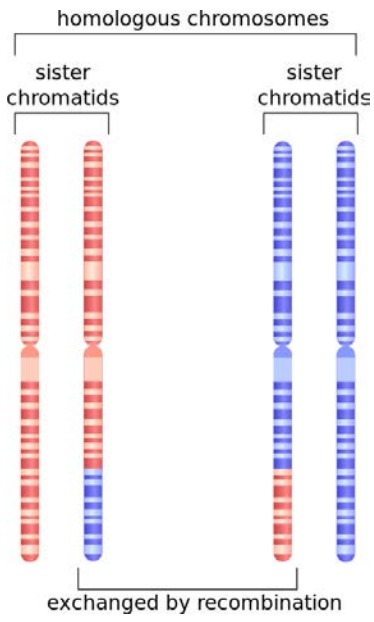
Homologous Recombination

Homologous recombination is a type of genetic recombination in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. It is most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks. Homologous recombination also produces new combinations of DNA sequences during meiosis, the process by which eukaryotes make gamete cells, like sperm and egg cells in animals. These new combinations of DNA represent genetic variation in offspring, which in turn enables populations to adapt during the course of evolution. Homologous recombination is also used in horizontal gene transfer to exchange genetic material between different strains and species of bacteria and viruses.

Although homologous recombination varies widely among different organisms and cell types, most forms involve the same basic steps. After a double-strand break occurs, sections of DNA around the 5' ends of the break are cut away in a process called resection. In the strand invasion step that follows, an overhanging 3' end of the broken DNA molecule then "invades" a similar or identical DNA molecule that is not broken. After strand invasion, the further sequence of events may follow either of two main pathways discussed below (see Models) - the DSBR (double-strand break repair) pathway or the SDSA (synthesis-dependent strand annealing) pathway. Homologous recombination that occurs during DNA repair tends to result in non-crossover products, in effect restoring the damaged DNA molecule as it existed before the double-strand break.

Homologous recombination is conserved across all three domains of life as well as viruses, suggesting that it is a nearly universal biological mechanism. The discovery of genes for homologous recombination in protists—a diverse group of eukaryotic microorganisms—has been interpreted as evidence that meiosis emerged early in the evolution of eukaryotes. Since their dysfunction has been strongly associated with increased susceptibility to several types of cancer, the proteins that facilitate homologous recombination are topics of active research.



https://en.wikipedia.org/wiki/Homologous_recombination

Related Glossary Terms

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Homoserine Dehydrogenase

In enzymology, a homoserine dehydrogenase is an enzyme that catalyzes th
reaction

L-homoserine + $NAD(P)^+$ <---> L-aspartate 4-semialdehyde + NAD(P)H +

The 2 substrates of this enzyme are L-homoserine and NAD^+ (or $NADP^+$), a
products are L-aspartate 4-semialdehyde, NADH (or NADPH), and H^+.

Homoserine dehydrogenase catalyzes the third step in the aspartate pathwa
NAD(P)-dependent reduction of aspartate β-semialdehyde into homoserine
ine is an intermediate in the biosynthesis of threonine, isoleucine, and meth

https://en.wikipedia.org/wiki/Homoserine_dehydrogenase

Related Glossary Terms

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Index Find Term

Homoserine Kinase

Homoserine kinase is an enzyme that catalyzes the chemical reaction

ATP + L-homoserine <---> ADP + O-phospho-L-homoserine

The two substrates of this enzyme are ATP and L-homoserine, and its two pr
ADP and O-phospho-L-homoserine.

This enzyme belongs to the family of transferases, specifically those transfer
phosphorus-containing groups (phosphotransferases) with an alcohol group
tor. The systematic name of this enzyme class is ATP:L-homoserine O-
phosphotransferase. Other names in common use include homoserine kinas
phorylating), and HSK. This enzyme participates in glycine, serine and threo
tabolism.

https://en.wikipedia.org/wiki/Homoserine_kinase

Related Glossary Terms

Drag related terms here

Homoserine O-transsuccinylase

Homoserine O-succinyltransferase is an enzyme that catalyzes the reaction

Succinyl-CoA + L-homoserine <---> CoASH + O-succinyl-L-homoserine

The substrates of this enzyme are succinyl-CoA and L-homoserine, and the
ucts are CoASH and O-succinyl-L-homoserine.

This enzyme belongs to the family of transferases, specifically those acyltra
transferring groups other than aminoacyl groups. The systematic name of t
class is succinyl-CoA:L-homoserine O-succinyltransferase. Other names in
use include homoserine O-transsuccinylase, and homoserine succinyltrans
enzyme participates in methionine metabolism and sulfur metabolism.

https://en.wikipedia.org/wiki/Homoserine_O-succinyltransferase

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Related Glossary Terms

Drag related terms here

Homotropic

A homotropic allosteric modulator is a substrate for its target enzyme, as w
latory molecule of the enzyme's activity. It is typically an activator of the en
example, aspartate is a substrate and homotropic effector of aspartate trans
lase (ATCase).

https://en.wikipedia.org/wiki/Allosteric_regulation#Types_of_allosteric_

Related Glossary Terms

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Homotropic Effectors

A homotropic allosteric modulator (effector) is a substrate for its target enz
well as a regulatory molecule of the enzyme's activity. It is typically an activ
enzyme. For example, aspartate is a substrate and homotropic effector of as
transcarbamoylase (ATCase).

https://en.wikipedia.org/wiki/Allosteric_regulation#Types_of_allosteric_

Related Glossary Terms

Drag related terms here

Homozygotes

A cell is said to be homozygous for a particular gene when identical alleles o
are present on both homologous chromosomes. The cell or organism in que
called a homozygote. True breeding organisms are always homozygous for
that are to be held constant.

https://en.wikipedia.org/wiki/Zygosity#Homozygous

Related Glossary Terms

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Hormone

A hormone is any member of a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behavior. Hormones have diverse chemical structures, mainly of 3 classes: eicosanoids, steroids, and amino acid derivatives (amines, peptides, and proteins). The glands that secrete hormones comprise the endocrine signaling system. The term hormone is sometimes extended to include chemicals produced by cells that affect the same cell (autocrine or intracrine signaling) or nearby cells (paracrine signaling).

https://en.wikipedia.org/wiki/Hormone

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Hormone-response Elements

A hormone response element (HRE) is a short sequence of DNA within the
of a gene that is able to bind a specific hormone receptor complex and there
late transcription. The sequence is most commonly a pair of inverted repea
by three nucleotides, which also indicates that the receptor binds as a dime
cally, HRE responds to steroid hormones, as the activated steroid receptor
scription factor binding HRE. This regulates the transcription of genes sign
steroid hormone.

A gene may have many different response elements, allowing complex cont
erted over the level and rate of transcription.

HRE are used in transgenic animal cells as inducers of gene expression.
Examples of HREs include estrogen response elements (EREs) and androg
elements (AREs).

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Hormone-sensitive Triacylglycerol Lipase

Hormone-sensitive lipase also previously known as cholesteryl ester hydrolase
is an enzyme that, in humans, is encoded by the LIPE gene.

HSL is an intracellular neutral lipase that is capable of hydrolyzing a variety of
The enzyme has a long and a short form. The long form is expressed in steroid
tissues such as testis, where it converts cholesteryl esters to free cholesterol fo
hormone production. The short form is expressed in adipose tissue, among oth
where it hydrolyzes stored triglycerides to free fatty acids.

https://en.wikipedia.org/wiki/Hormone-sensitive_lipase

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Hormones

A hormone is any member of a class of signaling molecules produced by gla
ticellular organisms that are transported by the circulatory system to target
gans to regulate physiology and behavior. Hormones have diverse chemical
mainly of 3 classes: eicosanoids, steroids, and amino acid derivatives (amin
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by cells that affect the same cell (autocrine or intracrine signaling) or nearb
acrine signaling).

https://en.wikipedia.org/wiki/Hormone

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Hox

Hox genes (a subset of homeotic genes) are a group of related genes that contro
body plan of an embryo along the cranio-caudal (head-tail) axis. After the embr
segments have formed, the Hox proteins determine the type of segment structu
legs, antennae, and wings in fruit flies or the different types of vertebrae in hum
that will form on a given segment. Hox proteins thus confer segmental identity,
not form the actual segments themselves.
Hox genes are defined as having the following properties:

- Their protein product is a transcription factor
- They contain a DNA sequence known as the homeobox

In many animals, the organization of the Hox genes in the chromosome is the s
the order of their expression along the anterior-posterior axis of the developing
mal, and are thus said to display colinearity.

https://en.wikipedia.org/wiki/Hox_gene

Related Glossary Terms

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HPLC

High-performance liquid chromatography (HPLC; formerly referred to as h
pressure liquid chromatography), is a technique in analytical chemistry use
rate, identify, and quantify each component in a mixture. It relies on pump
pressurized liquid solvent containing the sample mixture through a column
a solid adsorbent material. Each component in the sample interacts slightly
with the adsorbent material, causing different flow rates for the different co
and leading to the separation of the components as they flow out the colum

https://en.wikipedia.org/wiki/High-performance_liquid_chromatography

Related Glossary Terms

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Hsp40

In molecular biology, chaperone DnaJ, also known as Hsp40 (heat shock protein 40 kD), is a molecular chaperone protein. Molecular chaperones are a diverse family of proteins that function to protect proteins from irreversible aggregation during synthesis and in times of cellular stress.

Molecular chaperones are a diverse family of proteins that function to protect proteins from irreversible aggregation during synthesis and in times of cellular stress. The bacterial molecular chaperone DnaK is an enzyme that couples cycles of ATP binding, hydrolysis, and ADP release by an N-terminal ATP-hydrolizing domain to cycles of sequestration and release of unfolded proteins by a C-terminal substrate binding domain. Dimeric GrpE is the co-chaperone for DnaK, and acts as a nucleotide exchange factor, stimulating the rate of ADP release 5000-fold. DnaK is itself a weak ATPase. ATP hydrolysis by DnaK is stimulated by its interaction with another co-chaperone, DnaJ. Thus the co-chaperones DnaJ and GrpE are capable of tightly regulating the nucleotide-bound and substrate-bound state of DnaK in ways that are necessary for the normal housekeeping functions and stress-related functions of the DnaK molecular chaperone cycle.

https://en.wikipedia.org/wiki/Chaperone_DnaJ

Related Glossary Terms

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Hsp70

The 70 kilodalton heat shock proteins (Hsp70s) are a family of conserved ubiquitously expressed heat shock proteins. Proteins with similar structure exist in virtually all living organisms. The Hsp70s are an important part of the cell's machinery for protein folding, and help to protect cells from stress.

Members of the Hsp70 family are very strongly upregulated by heat stress and toxic chemicals, particularly heavy metals such as arsenic, cadmium, copper, mercury, etc.

When not interacting with a substrate peptide, Hsp70 is usually in an ATP bound state. Hsp70 by itself is characterized by a very weak ATPase activity, such that spontaneous hydrolysis will not occur for many minutes. As newly synthesized proteins emerge from the ribosomes, the substrate binding domain of Hsp70 recognizes sequences of hydrophobic amino acid residues, and interacts with them. This spontaneous interaction is reversible, and in the ATP bound state Hsp70 may relatively freely bind and release peptides. However, the presence of a peptide in the binding domain stimulates the ATPase activity of Hsp70, increasing its normally slow rate of ATP hydrolysis. When ATP is hydrolyzed to ADP the binding pocket of Hsp70 closes, tightly binding the now-trapped peptide chain. Further speeding ATP hydrolysis are the so-called J-domain cochaperones: primarily Hsp40 in eukaryotes, and DnaJ in prokaryotes. These cochaperones dramatically increase the ATPase activity of Hsp70 in the presence of interacting peptides.

By binding tightly to partially synthesized peptide sequences (incomplete proteins), Hsp70 prevents them from aggregating and being rendered nonfunctional. Once the entire protein is synthesized, a nucleotide exchange factor (BAG-1 and HspBP1 are among those which have been identified) stimulates the release of ADP and binding of fresh ATP, opening the binding pocket. The protein is then free to fold on its own, or to be transferred to other chaperones for further processing. HOP (the Hsp70/Hsp90 Organizing Protein) can bind to both Hsp70 and Hsp90 at the same time, and mediates the transfer of peptides from Hsp70 to Hsp90.

Hsp70 also aids in transmembrane transport of proteins, by stabilizing them in a partially folded state. Hsp70 proteins can act to protect cells from thermal or oxidative stress. These stresses normally act to damage proteins, causing partial unfolding and possible aggregation. By temporarily binding to hydrophobic residues exposed by stress, Hsp70 prevents these partially denatured proteins from aggregating, and allows them to refold. Low ATP is characteristic of heat shock and sustained binding is seen as aggregation suppression, while recovery from heat shock involves substrate binding and nucleotide cycling. In a thermophile anaerobe (Thermotoga maritima) the Hsp70 demonstrates redox sensitive binding to model peptides, suggesting a second mode of binding regulation based on oxidative stress.

https://en.wikipedia.org/wiki/Hsp70

Related Glossary Terms

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Hsp90

Hsp90 (heat shock protein 90) is a chaperone protein that assists other proteins to fold properly, stabilizes proteins against heat stress, and aids in protein degradation. It also stabilizes a number of proteins required for tumor growth, which is why Hsp90 inhibitors are investigated as anti-cancer drugs.

Heat shock proteins, as a class, are among the most highly expressed cellular proteins across all species. As their name implies, heat shock proteins protect cells when stressed by elevated temperatures. They account for 1–2% of total protein in unstressed cells. However, when cells are heated, the fraction of heat shock proteins increases to 4–6% of cellular proteins.

Heat shock protein 90 (Hsp90) is one of the most common of the heat-related proteins. The "90" comes from the fact that it weighs roughly 90 kiloDaltons. A 90 kDa protein is considered fairly large for a non-fibrous protein. Hsp90 is found in bacteria and all branches of eukarya, but it is apparently absent in archaea. Whereas cytoplasmic Hsp90 is essential for viability under all conditions in eukaryotes, the bacterial homologue HtpG is dispensable under non-heat stress conditions.

The glucocorticoid receptor (GR) is the most thoroughly studied example of a steroid receptor whose function is crucially dependent on interactions with Hsp90. In the absence of the steroid hormone cortisol, GR resides in the cytosol complexed with several chaperone proteins including Hsp90. These chaperones maintain the GR in a state capable of binding hormone.

https://en.wikipedia.org/wiki/Hsp90

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Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a hormone produced by the embry
implantation. The presence of hCG is detected in pregnancy tests. Some can
mors produce this hormone. Therefore, elevated levels measured when the
not pregnant can lead to a cancer diagnosis. However, it is not known whet
duction is a contributing cause or an effect of tumorigenesis. The pituitary a
hCG, known as luteinizing hormone (LH), is produced in the pituitary glan
and females of all ages.

https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin

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Chapter 2 - Structure & Function: Carbohydrates

Human EGF Receptor

The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands.

The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). Mutations affecting EGFR expression or activity could result in cancer.

Mutations that lead to EGFR overexpression (known as upregulation) or overactivity have been associated with a number of cancers, including lung cancer, anal cancers and glioblastoma multiforme. These somatic mutations involving EGFR lead to its constant activation, which produces uncontrolled cell division. In glioblastoma a more or less specific mutation of EGFR, called EGFRvIII is often observed. Mutations, amplifications or misregulations of EGFR or family members are implicated in about 30% of all epithelial cancers.

https://en.wikipedia.org/wiki/Epidermal_growth_factor_receptor

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Related Glossary Terms

Drag related terms here

Human Genome

The human genome is the complete set of nucleic acid sequence for human
piens), encoded as DNA within the 23 chromosome pairs in cell nuclei and
DNA molecule found within individual mitochondria. Human genomes inc
protein-coding DNA genes and noncoding DNA. Haploid human genomes,
contained in germ cells (the egg and sperm gamete cells created in the meio
sexual reproduction before fertilization creates a zygote) consist of three bil
base pairs, while diploid genomes (found in somatic cells) have twice the D
While there are significant differences among the genomes of human indivi
the order of 0.1%), these are considerably smaller than the differences betw
mans and their closest living relatives, the chimpanzees (approximately 4%
bos.

https://en.wikipedia.org/wiki/Human_genome

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Chapter 2 - Structure and Function: Proteins

Humans

Modern humans (*Homo sapiens*, primarily ssp. *Homo sapiens sapiens*) are
tant members of *Hominina* clade (or human clade), a branch of the taxono
Hominini belonging to the family of great apes. They are characterized by e
and bipedal locomotion; manual dexterity and increased tool use, compare
animals; and a general trend toward larger, more complex brains and socie

https://en.wikipedia.org/wiki/Human

Related Glossary Terms

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Huntingtin

The huntingtin gene, also called the HTT or HD (Huntington disease) gene, is ("interesting transcript 15") gene, which codes for a protein called the huntin tein. The gene and its product are under heavy investigation as part of Huntin disease clinical research and the suggested role for huntingtin in long-term m storage.

It is variable in its structure, as the many polymorphisms of the gene can lead able numbers of glutamine residues present in the protein. In its wild-type (n form, it contains 6-35 glutamine residues. However, in individuals affected by ton's disease (an autosomal dominant genetic disorder), it contains more than mine residues (highest reported repeat length is about 250). Its commonly us is derived from this disease. Previously, the IT15 label was commonly used.

https://en.wikipedia.org/wiki/Huntingtin

Related Glossary Terms

Drag related terms here

Hyaluronic Acid

Hyaluronic acid (HA/conjugate base hyaluronate), also called hyaluronan, is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is unique among glycosaminoglycans in that it is nonsulfated, forms in the plasma membrane instead of the Golgi, and can be very large, with its molecular weight often reaching the millions. One of the chief components of the extracellular matrix, hyaluronan contributes significantly to cell proliferation and migration, and may also be involved in the progression of some malignant tumors.

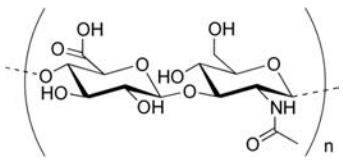
Hyaluronic acid is an important component of articular cartilage, where it is present as a coat around each cell (chondrocyte). When aggrecan monomers bind to hyaluronan in the presence of HAPLN1 (Hyaluronanic acid and proteoglycan link protein 1), large, highly negatively charged aggregates form. These aggregates imbibe water and are responsible for the resilience of cartilage (its resistance to compression). The molecular weight (size) of hyaluronan in cartilage decreases with age, but the amount increases.

Hyaluronanic acid is also a major component of skin, where it is involved in tissue repair. When skin is exposed to excessive UVB rays, it becomes inflamed (sunburn) and the cells in the dermis stop producing as much hyaluronan, and increase the rate of its degradation. Hyaluronan degradation products then accumulate in the skin after UV exposure.

While it is abundant in extracellular matrices, hyaluronan also contributes to tissue hydrodynamics, movement and proliferation of cells, and participates in a number of cell surface receptor interactions, notably those including its primary receptors, CD44 and RHAMM. Upregulation of CD44 itself is widely accepted as a marker of cell activation in lymphocytes. Hyaluronan's contribution to tumor growth may be due to its interaction with CD44. Receptor CD44 participates in cell adhesion interactions required by tumor cells.

Although hyaluronan binds to receptor CD44, there is evidence hyaluronan degradation products transduce their inflammatory signal through toll-like receptor 2 (TLR2), TLR4 or both TLR2, and TLR4 in macrophages and dendritic cells. TLR and hyaluronan play a role in innate immunity.
There are limitations including the *in vivo* loss of this compound limiting the duration of effect.

The repeating unit of hyaluronic acid is shown below.



https://en.wikipedia.org/wiki/Hyaluronic_acid

Related Glossary Terms

Hyaluronidases

The hyaluronidases (EC 3.2.1.35) are a family of enzymes that degrade hyaluronic acid. Karl Meyer classified these enzymes in 1971 into three distinct groups, a scheme based on the enzyme reaction products. The three main types of hyaluronidases are two classes of eukaryotic endoglycosidase hydrolases and a prokaryotic lyase-type of glycosidase.

In most mammalian fertilization, hyaluronidase is released by the acrosome of the sperm cell after it has reached the oocyte, by digesting hyaluronan in the corona radiata, thus enabling conception. Gene-targeting studies show that hyaluronidases such as PH20 are not essential for fertilization, although exogenous hyaluronidases can disrupt the cumulus matrix.

The majority of mammalian ova are covered in a layer of granulosa cells intertwined in an ECM that contains a high concentration of hyaluronan. When a capacitated sperm reaches the ovum, it is able to penetrate this layer with the assistance of hyaluronidase enzymes present on the surface of the sperm. Once this occurs, the sperm is capable of binding with the zona pellucida, and the acrosome reaction can occur.

https://en.wikipedia.org/wiki/Hyaluronidase

Related Glossary Terms

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Hybridization

In molecular biology, hybridization (or hybridisation) is a phenomenon in which single-stranded deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) molecules anneal to complementary DNA or RNA. Though a double-stranded DNA sequence is generally stable under physiological conditions, changing these conditions in the laboratory (generally by raising the surrounding temperature) will cause the molecules to separate into single strands. These strands are complementary to each other but may also be complementary to other sequences present in their surroundings. Lowering the surrounding temperature allows the single-stranded molecules to anneal or “hybridize” to each other.

DNA replication and transcription of DNA into RNA both rely upon nucleotide hybridization, as do molecular biology techniques including Southern blots and Northern blots, the polymerase chain reaction (PCR), and most approaches to DNA sequencing.

Hybridization is a basic property of nucleotide sequences and is taken advantage of in numerous molecular biology techniques. Overall genetic relatedness of two species can be determined by hybridizing segments of their DNA (DNA-DNA hybridization). Due to sequence similarity between closely related organisms, higher temperatures are required to melt such DNA hybrids when compared to more distantly related organisms. A variety of different methods use hybridization to pinpoint the origin of a DNA sample, including the polymerase chain reaction (PCR). In another technique, short DNA sequences are hybridized to cellular mRNAs to identify expressed genes. Pharmaceutical drug companies are exploring the use of antisense RNA to bind to undesired mRNA, preventing the ribosome from translating the mRNA into protein.

https://en.wikipedia.org/wiki/Nucleic_acid_hybridization

Related Glossary Terms

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Chapter 2 - Structure and Function: Nucleic Acids

Hydration

In chemistry, a hydration reaction is a chemical reaction in which a substar
bines with water. In organic chemistry, water is added to an unsaturated su
which is usually an alkene or an alkyne. This type of reaction is employed in
to produce ethanol, isopropanol, and 2-butanol.

Hydration of double bonds occurs as a step in biochemistry oxidative pathw
clude the citric acid cycle (hydration of fumarate) and fatty acid oxidation (
of the *trans* intermediate).

https://en.wikipedia.org/wiki/Hydration_reaction

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Hydration Shell

A solvation shell is a shell of any chemical species that acts as a solvent and
a solute species. When the solvent is water it is often referred to as a hydrat
hydration sphere.

A classic example is when water molecules form a sphere around a metal io
tronegative oxygen atom contained in the water molecule is attracted electr
to the positive charge on the metal ion. The result is a solvation shell of wat
cules that surround the ion. This shell can be several molecules thick, depe
the charge of the ion.

The hydration shell is a factor in the exclusion of sodium ions from potassiu
nels.

https://en.wikipedia.org/wiki/Solvation_shell

Related Glossary Terms

Drag related terms here

Hydrogen Bonding

A hydrogen bond is the electrostatic attraction between polar groups that occurs when a hydrogen (H) atom bound to a highly electronegative atom such as nitrogen (N), oxygen (O) or fluorine (F) experiences attraction to some other nearby highly electronegative atom.

These hydrogen-bond attractions can occur between molecules (intermolecular) or within different parts of a single molecule (intramolecular). Depending on geometry and environmental conditions, the hydrogen bond may be worth between 5 and 30 kJ/mole in thermodynamic terms. This makes it stronger than a van der Waals interaction, but weaker than covalent or ionic bonds. This type of bond can occur in inorganic molecules such as water and in organic molecules like DNA and proteins.

Intermolecular hydrogen bonding is responsible for the high boiling point of water (100 °C) compared to the other group 16 hydrides that have no hydrogen bonds. Hydrogen bonding also plays an important role in determining the three-dimensional structures adopted by proteins and nucleic bases. In these macromolecules, bonding between parts of the same macromolecule cause it to fold into a specific shape, which helps determine the molecule's physiological or biochemical role. For example, the double helical structure of DNA is due largely to hydrogen bonding between its base pairs (as well as Pi stacking interactions), which link one complementary strand to the other and enable replication.

In the secondary structure of proteins, hydrogen bonds form between the backbone oxygens and amide hydrogens. When the spacing of the amino acid residues participating in a hydrogen bond occurs regularly between positions i and i + 4, an α helix is formed. When the spacing is less, between positions i and i + 3, then a 310 helix is formed. When two strands are joined by hydrogen bonds involving alternating residues on each participating strand, a β sheet is formed. Hydrogen bonds also play a part in forming the tertiary structure of protein through interaction of R-groups.

The role of hydrogen bonds in protein folding has also been linked to osmolyte-induced protein stabilization. Protective osmolytes, such as trehalose and sorbitol, shift the protein folding equilibrium toward the folded state, in a concentration dependent manner. While the prevalent explanation for osmolyte action relies on excluded volume effects, that are entropic in nature, recent Circular dichroism (CD) experiments have shown osmolyte to act through an enthalpic effect. The molecular mechanism for their role in protein stabilization is still not well established, though several mechanism have been proposed. Recently, computer molecular dynamics simulations suggested that osmolytes stabilize proteins by modifying the hydrogen bonds in the protein hydration layer.

https://en.wikipedia.org/wiki/Hydrogen_bond

Related Glossary Terms

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Hydrogen Bonds

A hydrogen bond is the electrostatic attraction between polar groups that occurs when a hydrogen (H) atom bound to a highly electronegative atom such as nitrogen (N), oxygen (O) or fluorine (F) experiences attraction to some other nearby highly electronegative atom.

These hydrogen-bond attractions can occur between molecules (intermolecular) or within different parts of a single molecule (intramolecular). Depending on geometry and environmental conditions, the hydrogen bond may be worth between 5 and 30 kJ/mole in thermodynamic terms. This makes it stronger than a van der Waals interaction, but weaker than covalent or ionic bonds. This type of bond can occur in inorganic molecules such as water and in organic molecules like DNA and proteins.

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https://en.wikipedia.org/wiki/Hydrogen_bond

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Hydrogen Sulfide

Hydrogen sulfide is the chemical compound with the formula H_2S. It is a co
with the characteristic foul odor of rotten eggs. It is heavier than air, very p
corrosive, flammable, and explosive.

Hydrogen sulfide often results from the prokaryotic breakdown of organic r
the absence of oxygen gas, such as in swamps and sewers. This process is c
known as anaerobic digestion. The human body produces small amounts of
uses it as a signaling molecule.

https://en.wikipedia.org/wiki/Hydrogen_sulfide

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Hydrolysis

The term hydrolysis refers to using a molecule of water to break a bond. Hydrolysis can break bonds in proteins, nucleic acids, carbohydrates and fats. When a carbohydrate is broken into its component sugar molecules by hydrolysis (e.g. sucrose being broken down into glucose and fructose), this is termed saccharification. Generally, hydrolysis or saccharification is a step in the degradation of a substance.

Hydrolysis can be the reverse of a condensation reaction in which two molecules join together into a larger one and eject a water molecule. Thus hydrolysis adds water to break down, whereas condensation builds up by removing water.

https://en.wikipedia.org/wiki/Hydrolysis

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Hydrolysis of Fat

The term hydrolysis refers to using a molecule of water to break a bond. Hydrolysis can break bonds in proteins, nucleic acids, carbohydrates and fats. When a carbohydrate is broken into its component sugar molecules by hydrolysis (e.g. sucrose being broken down into glucose and fructose), this is termed saccharification. Generally, hydrolysis or saccharification is a step in the degradation of a substance.

Hydrolysis can be the reverse of a condensation reaction in which two molecules join together into a larger one and eject a water molecule. Thus hydrolysis adds water to break down, whereas condensation builds up by removing water.

Perhaps the oldest commercially practiced example of ester hydrolysis is saponification (formation of soap). It is the hydrolysis of a triglyceride (fat) with an aqueous base such as sodium hydroxide (NaOH). During the process, glycerol is formed, and the fatty acids react with the base, converting them to salts. These salts are called soaps, commonly used in households.

https://en.wikipedia.org/wiki/Hydrolysis#Esters_and_amides

Related Glossary Terms

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Hydrophilic

A hydrophile is a molecule or other molecular entity that is attracted to, and tends to be dissolved by water.

A hydrophilic molecule or portion of a molecule is one whose interactions with water and other polar substances are more thermodynamically favorable than their interactions with oil or other hydrophobic solvents. They are typically charge-polarized and capable of hydrogen bonding. This makes these molecules soluble not only in water but also in other polar solvents.

Hydrophilic molecules (and portions of molecules) can be contrasted with hydrophobic molecules (and portions of molecules). In some cases, both hydrophilic and hydrophobic properties occur in a single molecule. An example of these amphiphilic molecules is the lipids that comprise the cell membrane. Another example is soap, which has a hydrophilic head and a hydrophobic tail, allowing it to dissolve in both water and oil.

Hydrophilic and hydrophobic molecules are also known as polar molecules and nonpolar molecules, respectively. Some hydrophilic substances do not dissolve. This type of mixture is called a colloid.

An approximate rule of thumb for hydrophilicity of organic compounds is that solubility of a molecule in water is more than 1 mass % if there is at least one neutral hydrophile group per 5 carbons, or at least one electrically charged hydrophile group per 7 carbons.

Hydrophilic substances (ex: salts) can seem to attract water out of the air. Sugar is also hydrophilic, and like salt is sometimes used to draw water out of foods. Sugar sprinkled on cut fruit will "draw out the water" through hydrophilia, making the fruit mushy and wet, as in a common strawberry compote recipe.

https://en.wikipedia.org/wiki/Hydrophile

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Hydrophilicity

Hydrophilicity refers to the hydrophilic nature of a substance.

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https://en.wikipedia.org/wiki/Hydrophile

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Chapter 9 - Point by Point: Structure and Function

Hydrophobic

In chemistry, hydrophobicity is the physical property of a molecule (known as a hydrophobe) that is seemingly repelled from a mass of water. (Strictly speaking, there is no repulsive force involved. It is an absence of attraction.)

Hydrophobic molecules tend to be non-polar and, thus, prefer other neutral molecules and non-polar solvents. Hydrophobic molecules in water often cluster together, forming micelles. Water on hydrophobic surfaces will exhibit a high contact angle.

Examples of hydrophobic molecules include the alkanes, oils, fats, and greasy substances in general. Hydrophobic materials are used for oil removal from water, the management of oil spills, and chemical separation processes to remove non-polar substances from polar compounds.

https://en.wikipedia.org/wiki/Hydrophobe

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Hydrophobic Effect

The hydrophobic effect is the observed tendency of nonpolar substances to
in aqueous solution and exclude water molecules. This occurs because inter
tween the hydrophobic molecules enable the displaced water molecules to r
gen bonds more freely with each other and increase the number of hydroge
they are involved with, thereby decreasing the overall free energy. The word
bic literally means "water-fearing," and it describes the segregation and app
sion between water and nonpolar substances.

https://en.wikipedia.org/wiki/Hydrophobic_effect

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Hydrophobicity

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management of oil spills, and chemical separation processes to remove non-polar su
stances from polar compounds.

https://en.wikipedia.org/wiki/Hydrophobe

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Hydroxide

Hydroxide is a diatomic anion with chemical formula OH^-. It consists of an
hydrogen atom held together by a covalent bond, and carries a negative ele
It is an important but usually minor constituent of water. It functions as a b
ligand, a nucleophile and a catalyst. The hydroxide ion forms salts, some of
sociate in aqueous solution, liberating solvated hydroxide ions. Sodium hyd
multi-million-ton per annum commodity chemical. A hydroxide attached to
electropositive center may itself ionize, liberating a hydrogen cation (H^+), m
parent compound an acid.

https://en.wikipedia.org/wiki/Hydroxide

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Hydroxyethyl

Hydroxyethyl-TPP, also known as activated acetaldehyde, is an intermediat
carboxylation of pyruvate. When oxidized, it yields acetyl-CoA. It can relea
hyde in bacterial fermentation which is subsequently reduced to ethanol.

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Related Glossary Terms

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Hydroxyl

A hydroxyl or hydroxy group is a chemical functional group containing one oxygen atom connected by a covalent bonding to one hydrogen atom (–OH). It is sometimes called the alcohol functional group because when bonded to carbon in a molecule that otherwise contains only hydrogen and carbon the hydroxy (not hydroxyl) group defines the molecule as an alcohol, resulting in a name ending in -ol. A hydroxyl group bonded covalently to the carbon of a carbonyl group (C=O) produces a carboxyl group (C(O)OH) that is the defining group of a carboxylic acid. When the –OH group participates in an ionic bond, the [OH^-] anion is called the hydroxide ion. As a free radical, it is the hydroxyl radical.

https://en.wikipedia.org/wiki/Hydroxyl

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Hydroxyl Radical

The hydroxyl radical, •OH, is the neutral form of the hydroxide ion (OH^-). radicals are highly reactive (easily becoming hydroxyl groups) and consequ lived. However, they form an important part of radical chemistry. Most no droxyl radicals are produced from the decomposition of hydroperoxides (R atmospheric chemistry, by the reaction of excited atomic oxygen with wate

https://en.wikipedia.org/wiki/Hydroxyl_radical

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Hydroxylation

Hydroxylation is a chemical process that introduces a hydroxyl group (-OH) into an organic compound. In biochemistry, hydroxylation reactions are often facilitated by enzymes called hydroxylases. Hydroxylation is the first step in the oxidative degradation of organic compounds in air. It is extremely important in detoxification since hydroxylation converts lipophilic compounds into water-soluble (hydrophilic) products that are more readily excreted. Some drugs (e.g. steroids) are activated or deactivated by hydroxylation.

https://en.wikipedia.org/wiki/Hydroxylation

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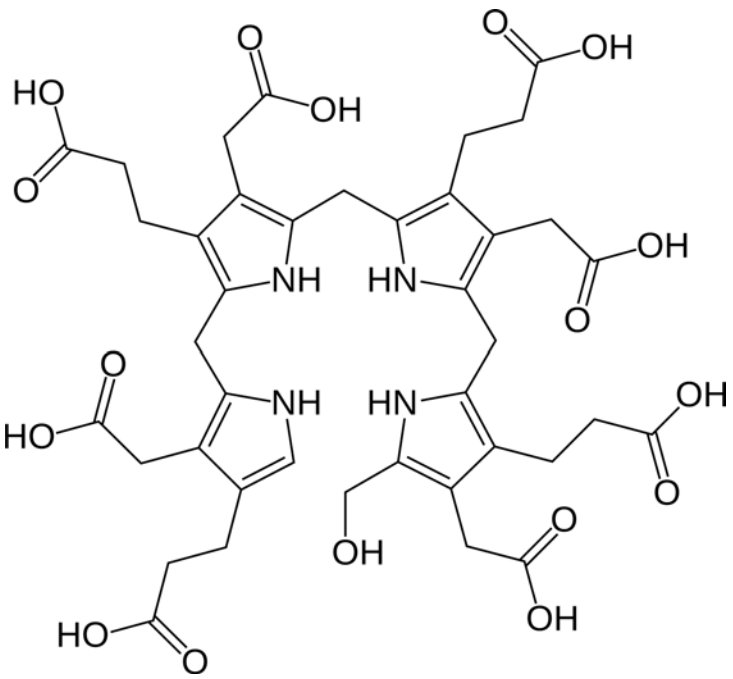
Hydroxylmethylbilane

Hydroxymethylbilane (HMB), also known as preuroporphyrinogen, is a molecule in
volved in the metabolism of porphyrin. In the third step, it is generated by the enzy
porphobilinogen deaminase, and in the next step the enzyme uroporphyrinogen III
thase converts it into uroporphyrinogen III. In general, defects of heme synthesis a
formation of HMB lead to photosensitivity.



https://en.wikipedia.org/wiki/Hydroxymethylbilane

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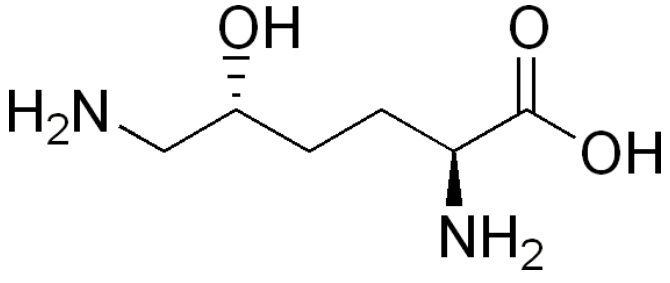
Chapter 6 - Metabolism: Other Lipids

Chapter 9 - Point by Point: Metabolism

Hydroxylysine

Hydroxylysine (Hyl) is an amino acid with the molecular formula $C_6H_{14}N_2O_3$. I
first discovered in 1921 by Donald Van Slyke as the 5-Hydroxylysine form. It ar
from a post-translational hydroxy modification of lysine. It is most widely know
component of collagen.

Hydroxylysine is biosynthesized from lysine via oxidation by lysyl hydroxylase
zymes. The most common form is the (5R) stereoisomer found in collagen.



https://en.wikipedia.org/wiki/Hydroxylysine

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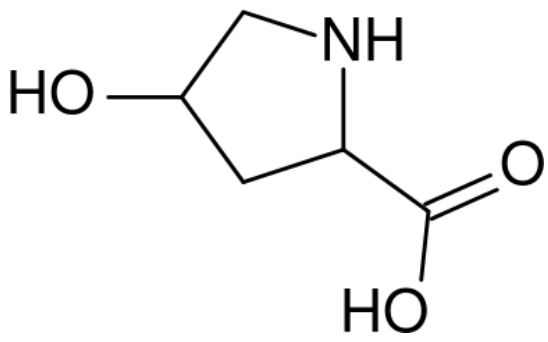
Hydroxyproline

(2S,4R)-4-Hydroxyproline, or L-hydroxyproline (C5H9O3N), is a common non-proteinogenic amino acid, abbreviated as Hyp, e.g., in Protein Data Bank.

Hydroxyproline is produced by hydroxylation of the amino acid proline by the enzyme prolyl hydroxylase following protein synthesis (as a post-translational modification). The enzyme catalyzed reaction takes place in the lumen of the endoplasmic reticulum. Although it is not directly incorporated into proteins, hydroxyproline comprises roughly 4% of all amino acids found in animal tissue, an amount greater than seven other amino acids that are translationally incorporated.



https://en.wikipedia.org/wiki/Hydroxyproline

Related Glossary Terms

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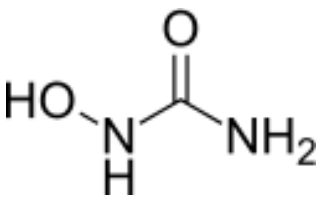
Hydroxyurea

Hydroxycarbamide (INN, BAN) or hydroxyurea (USAN, AAN) is an antineoplastic drug used in myeloproliferative disorders, specifically polycythemia vera and essential thrombocythemia. It is also used to reduce the rate of painful attacks in sickle-cell disease and has antiretroviral properties in diseases such as HIV/AIDS.

Hydroxycarbamide decreases the production of deoxyribonucleotides via inhibition of the enzyme ribonucleotide reductase by scavenging tyrosyl free radicals as they are involved in the reduction NDPs.

In the treatment of sickle-cell disease, hydroxycarbamide increases the concentration of fetal hemoglobin. The precise mechanism of action is not yet clear, but it appears that hydroxycarbamide increases nitric oxide levels, causing soluble guanylyl cyclase activation with a resultant rise in cyclic GMP, and the activation of γ globin chain synthesis necessary for fetal hemoglobin production (which inhibits the formation of sickle hemoglobin aggregates). A few red cell clones called F cells are progeny of a small pool of immature committed erythroid precursors (BFU-e) that retain the ability to produce HbF.

Hydroxyurea is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system.



https://en.wikipedia.org/wiki/Hydroxycarbamide

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Hyperbolic

In mathematics, a hyperbola is a type of smooth curve lying in a plane, defi
geometric properties or by equations for which it is the solution set. A hype
two pieces, called connected components or branches, that are mirror imag
other and resemble two infinite bows. The hyperbola is one of the three kin
section, formed by the intersection of a plane and a double cone.

Similar to a parabola, a hyperbola is an open curve, meaning that it continu
nitely to infinity, rather than closing on itself as an ellipse does. A hyperbol
two disconnected curves called its arms or branches.

https://en.wikipedia.org/wiki/Hyperbola

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Hypercalcemia

Hypercalcemia is an elevated calcium (Ca^{++}) level in the blood. (Normal ra
10.4 mg/dL or 2.2–2.5 mmol/L.) It can be an asymptomatic laboratory find
cause an elevated calcium level is often indicative of other diseases, a worku
be undertaken if it persists. It can be due to excessive skeletal calcium relea
creased intestinal calcium absorption, or decreased renal calcium excretion

https://en.wikipedia.org/wiki/Hypercalcaemia

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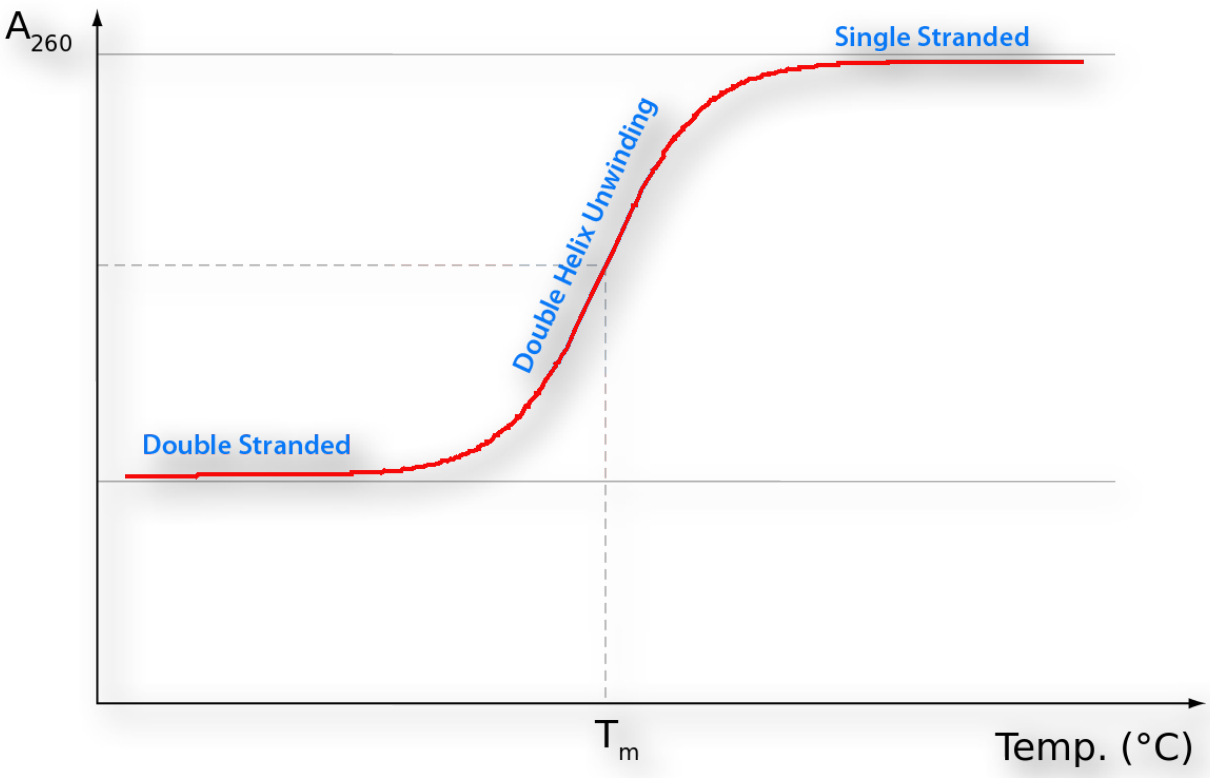
Hyperchromic Effect

Hyperchromicity is the increase of absorbance (optical density) of a material. The most famous example is the hyperchromicity of DNA that occurs when the DNA duplex is denatured. The UV absorption is increased when the two single DNA strands are being separated, either by heat or by addition of denaturant or by increasing the pH level. The opposite, a decrease of absorbance is called hypochromicity.



https://en.wikipedia.org/wiki/Hyperchromicity

Related Glossary Terms

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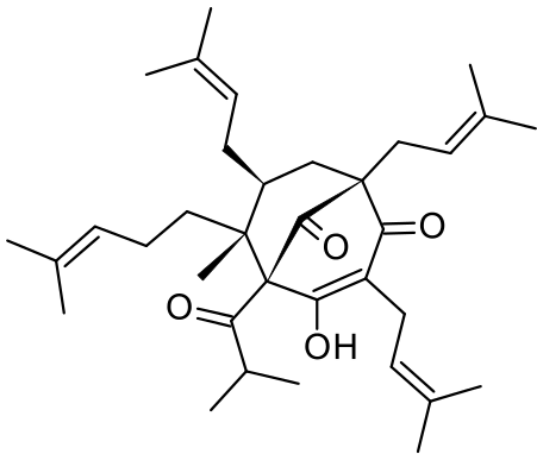
Hyperforin

Hyperforin is a phytochemical produced by some of the members of the plant genus Hypericum, notably Hypericum perforatum (St John's wort).

Hyperforin is a prenylated phloroglucinol derivative that is unstable in the presence of light and oxygen.

Hyperforin is believed to be the primary active constituent responsible for the antidepressant and anxiolytic properties of the extracts of St. John's wort. It acts as a reuptake inhibitor of monoamines, including serotonin, norepinephrine, dopamine, and of GABA and glutamate, with IC50 values of 0.05-0.10 µg/mL for all compounds, with the exception of glutamate, which is in the 0.5 µg/mL range. Hyperforin also inhibits the reuptake of glycine and choline (IC50=8.5µM). It also modulates acetylcholine release in rat hippocampus and facilitates acetylcholine release in the striatum. It appears to exert these effects by activating the transient receptor potential ion channel TRPC6. Activation of TRPC6 induces the entry of sodium and calcium into the cell which causes inhibition of monoamine reuptake. It also antagonizes the NMDA receptor, AMPA receptor and GABA receptors.

https://en.wikipedia.org/wiki/Hyperforin



Related Glossary Terms

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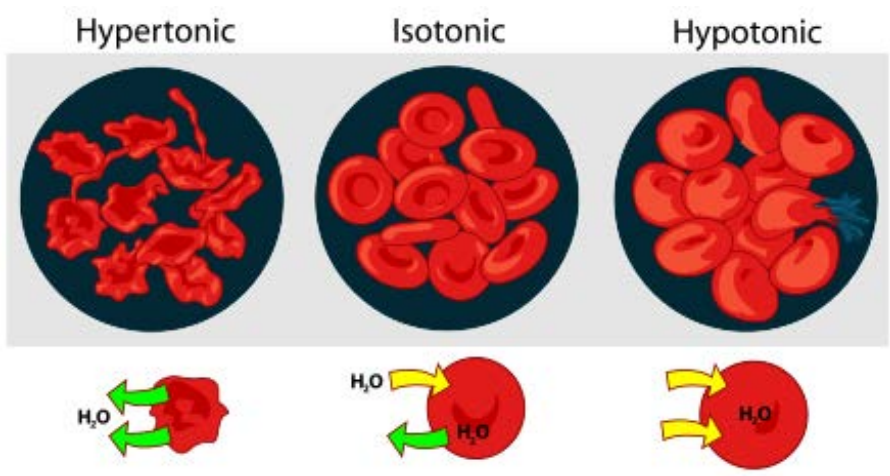
Hypertonic

Hypertonic refers to a greater concentration. In biology, a hypertonic solution is one with a higher concentration of solutes outside the cell than inside the cell. When a cell is immersed into a hypertonic solution, the tendency is for water to flow out of the cell in order to balance the concentration of the solutes. Likewise, the cytosol of the cell is conversely categorized as hypotonic, opposite of the outer solution.

When plant cells are in a hypertonic solution, the flexible cell membrane pulls away from the rigid cell wall, but remains joined to the cell wall at points called plasmodesmata. The cell takes on the appearance of a pincushion, and the plasmodesmata almost cease to function because they become constricted: a condition known as plasmolysis. In plant cells the terms isotonic, hypotonic and hypertonic cannot strictly be used accurately because the pressure exerted by the cell wall significantly affects the osmotic equilibrium point.



https://en.wikipedia.org/wiki/Tonicity#Hypertonicity

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Hypothalamus

The hypothalamus (from Greek ὑπό, "under" and θάλαμος, thalamus) is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland (hypophysis).
The hypothalamus is located below the thalamus and is part of the limbic system. In the terminology of neuroanatomy, it forms the ventral part of the diencephalon. All vertebrate brains contain a hypothalamus. In humans, it is the size of an almond.

The hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, called releasing hormones or hypothalamic hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, important aspects of parenting and attachment behaviors, thirst, fatigue, sleep, and circadian rhythms.

The hypothalamus has a central neuroendocrine function, most notably by its control of the anterior pituitary, which in turn regulates various endocrine glands and organs. Releasing hormones (also called releasing factors) are produced in hypothalamic nuclei then transported along axons to either the median eminence or the posterior pituitary, where they are stored and released as needed.

https://en.wikipedia.org/wiki/Hypothalamus

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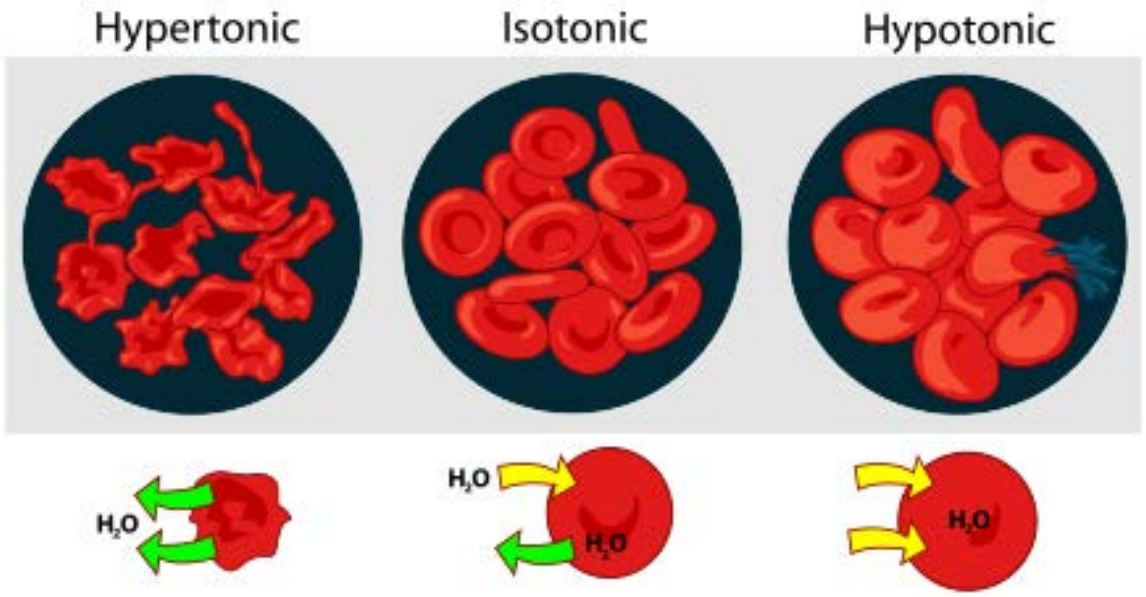
Chapter 2 - Structure & Function: Lipids
Chapter 6 - Metabolism: Fats and Fatty Acids

Hypotonic

Hypotonic refers to a lesser concentration. In biology, a hypotonic solution ha
concentration of solutes outside the cell than inside the cell. In an attempt to
the concentrations of solutes inside and outside the cell, water will rush into t
and can cause it to burst.



https://en.wikipedia.org/wiki/Tonicity#Hypotonicity

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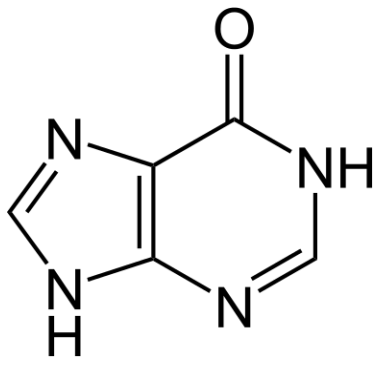
Chapter 3 - Membranes: Basic Concepts

Chapter 9 - Point by Point: Membranes

Hypoxanthine

Hypoxanthine is a naturally occurring purine derivative. It is occasionally found as a constituent of nucleic acids, where it is present in the anticodon of tRNA in the form of its nucleoside inosine. It has a tautomer known as 6-hydroxypurine. Hypoxanthine is a necessary additive in certain cell, bacteria, and parasite cultures as a substrate and nitrogen source.



https://en.wikipedia.org/wiki/Hypoxanthine

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Hypoxanthine/guanine Phosphoribosyltransferase

Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is an enzyme encoded in humans by the HPRT1 gene.

HGPRT is a transferase that catalyzes conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate. This reaction transfers the 5-phosphoribosyl group from 5-phosphoribosyl 1-pyrophosphate (PRPP) to the purine. HGPRT plays a central role in the generation of purine nucleotides through the purine salvage pathway.

HGPRTase functions primarily to salvage purines from degraded DNA to reintroduce into purine synthetic pathways. In this role, it catalyzes the reaction between guanine and phosphoribosyl pyrophosphate (PRPP) to form GMP, or between hypoxanthine and phosphoribosyl pyrophosphate (PRPP) to form inosine monophosphate.

https://en.wikipedia.org/wiki/Hypoxanthine-guanine_phosphoribosyltransferase

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Hypoxia

Hypoxia (also known as hypoxiation) is a condition in which the body or a region of the body is deprived of adequate oxygen supply. Hypoxia may be classified as either generalized, affecting the whole body, or local, affecting a region of the body. Although hypoxia is often a pathological condition, variations in arterial oxygen concentrations can be part of the normal physiology, for example, during hypoventilation training or strenuous physical exercise.

Hypoxia differs from hypoxemia and anoxemia in that hypoxia refers to a state in which oxygen supply is insufficient, whereas hypoxemia and anoxemia refer specifically to states that have low or zero arterial oxygen supply. Hypoxia in which there is complete deprivation of oxygen supply is referred to as anoxia.

Generalized hypoxia occurs in healthy people when they ascend to high altitude, where it causes altitude sickness leading to potentially fatal complications: high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). Hypoxia also occurs in healthy individuals when breathing mixtures of gasses with a low oxygen content, e.g. while diving underwater especially when using closed-circuit rebreather systems that control the amount of oxygen in the supplied air. A mild and non-damaging intermittent hypoxia is used intentionally during altitude trainings to develop an athletic performance adaptation at both the systemic and cellular level.

Hypoxia is also a serious consequence of preterm birth in the neonate. The main cause for this is that the lungs of the human fetus are among the last organs to develop during pregnancy. To assist the lungs to distribute oxygenated blood throughout the body, infants at risk of hypoxia are often placed inside an incubator capable of providing continuous positive airway pressure (also known as a humidicrib).

https://en.wikipedia.org/wiki/Hypoxia_(medical)

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Hypoxia-inducible Factor

Hypoxia-inducible factors (HIFs) are transcription factors that respond to c
available oxygen in the cellular environment, to be specific, to decreases in
hypoxia.

The HIF signaling cascade mediates the effects of hypoxia, the state of low c
centration, on the cell. Hypoxia often keeps cells from differentiating. How
poxia promotes the formation of blood vessels, and is important for the for
vascular system in embryos, and cancer tumors. The hypoxia in wounds als
the migration of keratinocytes and the restoration of the epithelium.

https://en.wikipedia.org/wiki/Hypoxia-inducible_factors

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https://en.wikipedia.org/wiki/Hypoxia-inducible_factors

Related Glossary Terms

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I-cell Disease

Inclusion-cell (I-cell) disease, also referred to as mucolipidosis II (ML II), is
lysosomal storage disease family and results from a defective phosphotransf
enzyme of the Golgi apparatus). This enzyme transfers phosphate to mannos
on specific proteins, and serves as a marker for them to be targeted to lysoso
within the cell. Without this marker, the proteins are instead excreted outsid
cell—the default pathway for proteins moving through the Golgi apparatus. I
cannot function without these proteins, which function as catabolic enzymes
normal breakdown of substances (e.g. oligosaccharides, lipids, and glycosam
cans) in various tissues throughout the body (i.e. fibroblasts). As a result, a b
these substances occurs within lysosomes because they cannot be degraded,
in the characteristic I-cells, or "inclusion cells." These cells can be identified
microscope. In addition, the defective lysosomal enzymes normally found or
lysosomes are instead found in high concentrations in the blood.

https://en.wikipedia.org/wiki/I-cell_disease

Related Glossary Terms

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IAP

Imidazole acetol phosphate (IAP) is an intermediate in the biosynthesis of histidine. It is formed from imidazole glycerol phosphate (IGP) in the following reaction

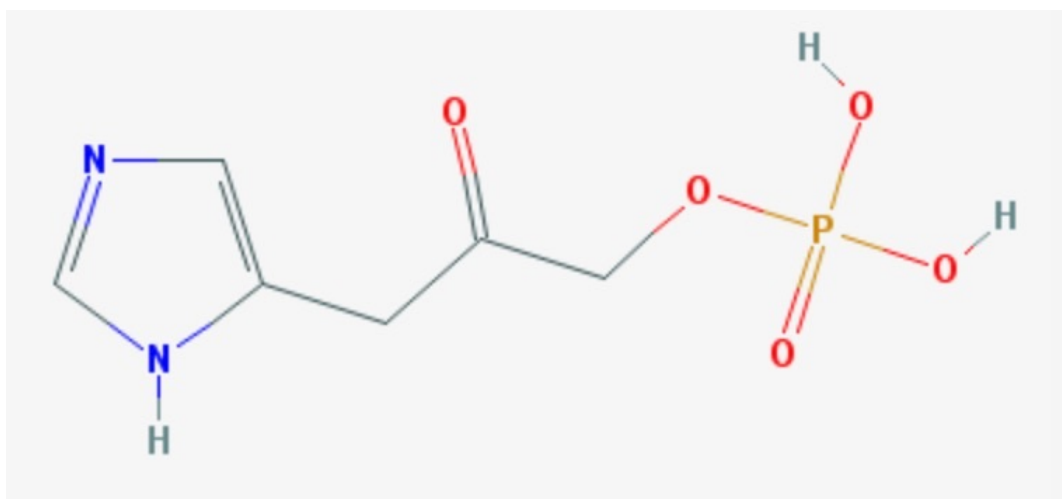
IGP

IAP

and then converted to histidinol phosphate in the following reaction

IAP + Glutamate

Histidinol-phosphate + α-KG



Related Glossary Terms

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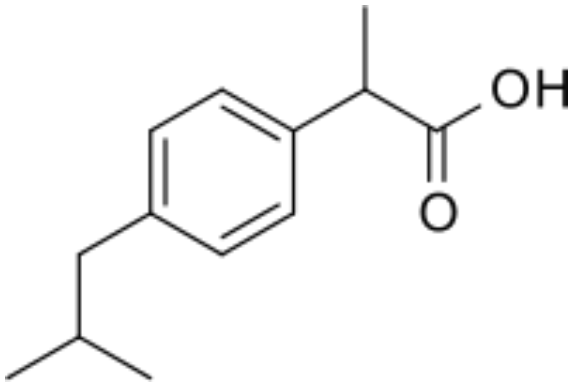
Ibuprofen

Ibuprofen, from isobutylphenylpropanoic acid, is a nonsteroidal anti-inflammatory drug (NSAID) used for treating pain, fever, and inflammation. This includes painful menstrual periods, migraines, and rheumatoid arthritis. About 60% of people improve with any given NSAID, and it is recommended that if one does not work, then another should be tried. It may also be used to close a patent ductus arteriosus in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the COX enzymes, which convert arachidonic acid to prostaglandin H_2 (PGH_2). PGH_2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A_2 (which stimulates platelet aggregation, leading to the formation of blood clots).



https://en.wikipedia.org/wiki/Ibuprofen

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IDLs

Intermediate-density lipoproteins (IDLs) belong to the lipoprotein particle family and are formed from the degradation of very low-density lipoproteins. IDL is one of the five major groups of lipoproteins (chylomicrons, VLDL, IDL, LDL, HDL) that enable fats and cholesterol to move within the water-based solution of the bloodstream. Each native IDL particle consists of protein that encircles various fatty acids, enabling, as a water-soluble particle, these fatty acids to travel in the aqueous blood environment as part of the fat transport system within the body. Their size is, in general, 25 to 35 nm in diameter, and they contain primarily a range of triacylglycerols and cholesterol esters. They are cleared from the plasma into the liver by receptor-mediated endocytosis, or further degraded to form LDL particles.

Although one might intuitively assume that "intermediate-density" refers to a density between that of high-density and low-density lipoproteins, it in fact refers to a density between that of low-density and very-low-density lipoproteins. Lipoproteins are classified as less dense when the fat to protein ratio is increased.

In general, IDL, somewhat similar to low-density lipoprotein (LDL), transports a variety of triglyceride fats and cholesterol and, like LDL, can also promote the growth of atheroma.

https://en.wikipedia.org/wiki/Intermediate-density_lipoprotein

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Related Glossary Terms

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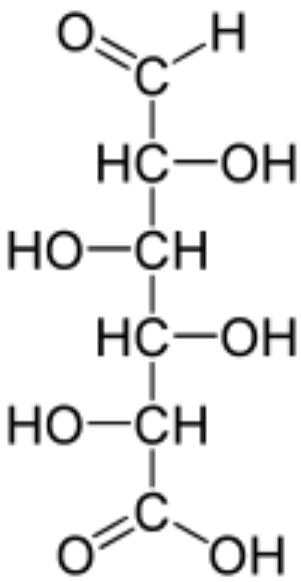
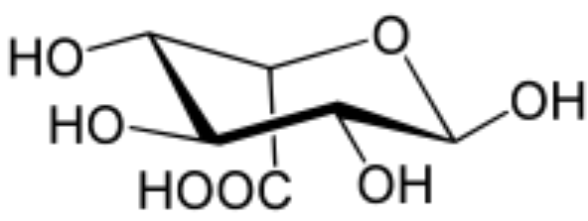
Iduronic Acid

L-Iduronic acid (IdoA) is the major uronic acid component of the glycosaminoglycans (GAGs) dermatan sulfate, and heparin. It is also present in heparan sulfate although here in a minor amount relative to its carbon-5 epimer glucuronic acid.
IdoA is a hexapyranose sugar. Most hexapyranoses are stable in one of two chair conformations 1C4 or 4C1. L-iduronate is different and adopts more than one solution conformation, with an equilibrium existing between three low-energy conformers. These are the 1C4 and 4C1 chair forms and an additional 2S0 skew-boat conformation.
IdoA may be modified by the addition of an O-sulfate group at carbon position 2 to form 2-O-sulfo-L-iduronic acid (IdoA2S).





https://en.wikipedia.org/wiki/Iduronic_acid

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Chapter 2 - Structure & Function: Carbohydrates
Chapter 2 - Structure & Function: Carbohydrates
Chapter 9 - Point by Point: Structure and Function

IF1

Prokaryotes require the use of three initiation factors: IF1, IF2, and IF3, for translation.

IF1 associates with the 30S ribosomal subunit in the A site and prevents an aminoacyl-tRNA from entering. It modulates IF2 binding to the ribosome by increasing its affinity. It may also prevent the 50S subunit from binding, stopping the formation of the 70S subunit. It also contains a β-domain fold common for nucleic acid binding proteins.

IF2 binds to an initiator tRNA and controls the entry of that tRNA into the ribosome. IF2, bound to GTP, binds to the 30S P site. After associating with the 30S subunit, fMet-tRNAf binds to the IF2 then IF2 transfers the tRNA into the partial P site. When the 50S subunit joins, it hydrolyzes GTP to GDP and Pi, causing a conformational change in the IF2 that causes IF2 to release and allow the 70S subunit to form.

IF3 is not universally found in all bacterial species but in E. coli it is required for the 30S subunit to bind to the initiation site in mRNA. In addition, it has several other jobs including stabilization of free 30S subunits, facilitation of 30S subunits binding to mRNA and checking for accuracy against the first aminoacyl-tRNA. It also allows for rapid codon-anticodon pairing for the initiator tRNA to bind quickly to. IF3 is required by the small subunit to form initiation complexes, but has to be released to allow the 50S subunit to bind.

https://en.wikipedia.org/wiki/Prokaryotic_initiation_factor

Related Glossary Terms

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IF2

Prokaryotes require the use of three initiation factors: IF1, IF2, and IF3, for translation.

IF1 associates with the 30S ribosomal subunit in the A site and prevents an aminoacyl-tRNA from entering. It modulates IF2 binding to the ribosome by increasing its affinity. It may also prevent the 50S subunit from binding, stopping the formation of the 70S subunit. It also contains a β-domain fold common for nucleic acid binding proteins.

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https://en.wikipedia.org/wiki/Prokaryotic_initiation_factor

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IF3

Prokaryotes require the use of three initiation factors: IF1, IF2, and IF3, for translation.

IF1 associates with the 30S ribosomal subunit in the A site and prevents an aminoacyl-tRNA from entering. It modulates IF2 binding to the ribosome by increasing its affinity. It may also prevent the 50S subunit from binding, stopping the formation of the 70S subunit. It also contains a β-domain fold common for nucleic acid binding proteins.

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https://en.wikipedia.org/wiki/Prokaryotic_initiation_factor

Related Glossary Terms

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IgA

Immunoglobulin A (IgA, also referred to as sIgA) is an antibody that plays a critical role in immune function in the mucous membranes. More IgA is produced in mucos linings than all other types of antibody combined. Between three and five grams are secreted into the intestinal lumen each day. This accumulates up to 15% of the total i munoglobulin produced in the entire body.

IgA has two subclasses (IgA1 and IgA2) and can exist in a dimeric form called secret IgA (sIgA). In its secretory form, IgA is the main immunoglobulin found in mucous s cretions, including tears, saliva, sweat, colostrum and secretions from the genitouri- nary tract, gastrointestinal tract, prostate and respiratory epithelium. It is also found in small amounts in blood. The secretory component of sIgA protects the immuno- globulin from being degraded by proteolytic enzymes, thus sIgA can survive in the harsh gastrointestinal tract environment and provide protection against microbes th multiply in body secretions. sIgA can also inhibit inflammatory effects of other immu noglobulins. IgA is a poor activator of the complement system, and opsonises only weakly. Its heavy chains are of the type α.

https://en.wikipedia.org/wiki/Immunoglobulin_A

Related Glossary Terms

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IgD

Immunoglobulin D (IgD) is an antibody isotype that makes up about 1% of proteins in the plasma membranes of mature B-lymphocytes where it is usually coexpressed with another cell surface antibody called IgM. IgD is also produced in a secreted form that is found in very small amounts in blood serum, representing 0.25% of immunoglobulins in serum. Relative molecular mass and half-life of sIgD is 185 kDa and 2.8 days, respectively. Secreted IgD is produced as a monomeric antibody with two heavy chains of the delta (δ) class, and two Ig light chains.

In B cells, IgD's function is to signal the B cells to be activated. By being activated, they are ready to take part in the defense of the body in the immune system. During B-cell differentiation, IgM is the exclusive isotype expressed by immature B cells. IgD starts to be expressed when the B-cell exits the bone marrow to populate peripheral lymphoid tissues. When a B-cell reaches its mature state, it co-expresses both IgM and IgD. It is not well understood whether IgM and IgD antibodies are functionally different on B cells. Cδ knockout mice (mice that have been genetically altered so that they do not produce IgD) have no major B-cell intrinsic defects. IgD may have some role in allergic reactions.

https://en.wikipedia.org/wiki/Immunoglobulin_D

Related Glossary Terms

Drag related terms here

IgE

Immunoglobulin E (IgE) is a kind of antibody (or immunoglobulin (Ig) "iso
has only been found in mammals. Monomers of IgE consist of two heavy ch
chain) and two light chains, with the ε chain containing 4 Ig-like constant d
(Cε1-Cε4). IgE's main function is immunity to parasites such as helminths l
soma mansoni, *Trichinella spiralis*, and *Fasciola hepatica*. IgE is utilized d
mune defense against certain protozoan parasites such as Plasmodium falc

IgE also has an essential role in type I hypersensitivity, which manifests var
gic diseases, such as allergic asthma, most types of sinusitis, allergic rhiniti
gies, and specific types of chronic urticaria and atopic dermatitis. IgE also p
otal role in responses to allergens, such as: anaphylactic drugs, bee stings, a
preparations used in desensitization immunotherapy.

https://en.wikipedia.org/wiki/Immunoglobulin_E

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IgG

Immunoglobulin G (IgG) is a type of antibody. It is a protein complex composed of four peptide chains—two identical heavy chains and two identical light chains arranged in a Y-shape typical of antibody monomers. Each IgG has two antigen binding sites. Representing approximately 75% of serum antibodies in humans, IgG is the most common type of antibody found in the circulation. IgG molecules are created and released by plasma B cells.

Antibodies are major components of humoral immunity. IgG is the main type of antibody found in blood and extracellular fluid allowing it to control infection of body tissues. By binding many kinds of pathogens such as viruses, bacteria, and fungi, IgG protects the body from infection. It does this through several mechanisms: IgG-mediated binding of pathogens causes their immobilization and binding together via agglutination. IgG coating of pathogen surfaces (known as opsonization) allows their recognition and ingestion by phagocytic immune cells. IgG activates the classical pathway of the complement system, a cascade of immune protein production that results in pathogen elimination. IgG also binds and neutralizes toxins. IgG also plays an important role in antibody-dependent cell-mediated cytotoxicity (ADCC) and intracellular antibody-mediated proteolysis, in which it binds to TRIM21 (the receptor with greatest affinity to IgG in humans) in order to direct marked virions to the proteasome in the cytosol. IgG is also associated with type II and type III hypersensitivity reactions.

https://en.wikipedia.org/wiki/Immunoglobulin_G

Related Glossary Terms

IgM

Immunoglobulin M, or IgM for short, is a basic antibody that is produced b
IgM is by far the physically largest antibody in the human circulatory syste
first antibody to appear in response to initial exposure to an antigen. The sp
where plasmablasts responsible for antibody production reside, is the majo
cific IgM production.

IgM forms polymers where multiple immunoglobulins are covalently linke
with disulfide bonds, mostly as a pentamer but also as a hexamer. IgM has
mass of approximately 970 kDa (in its pentamer form). Because each mono
two antigen binding sites, a pentameric IgM has 10 binding sites. Typically,
IgM cannot bind 10 antigens at the same time because the large size of mos
hinders binding to nearby sites.

https://en.wikipedia.org/wiki/Immunoglobulin_M

Related Glossary Terms

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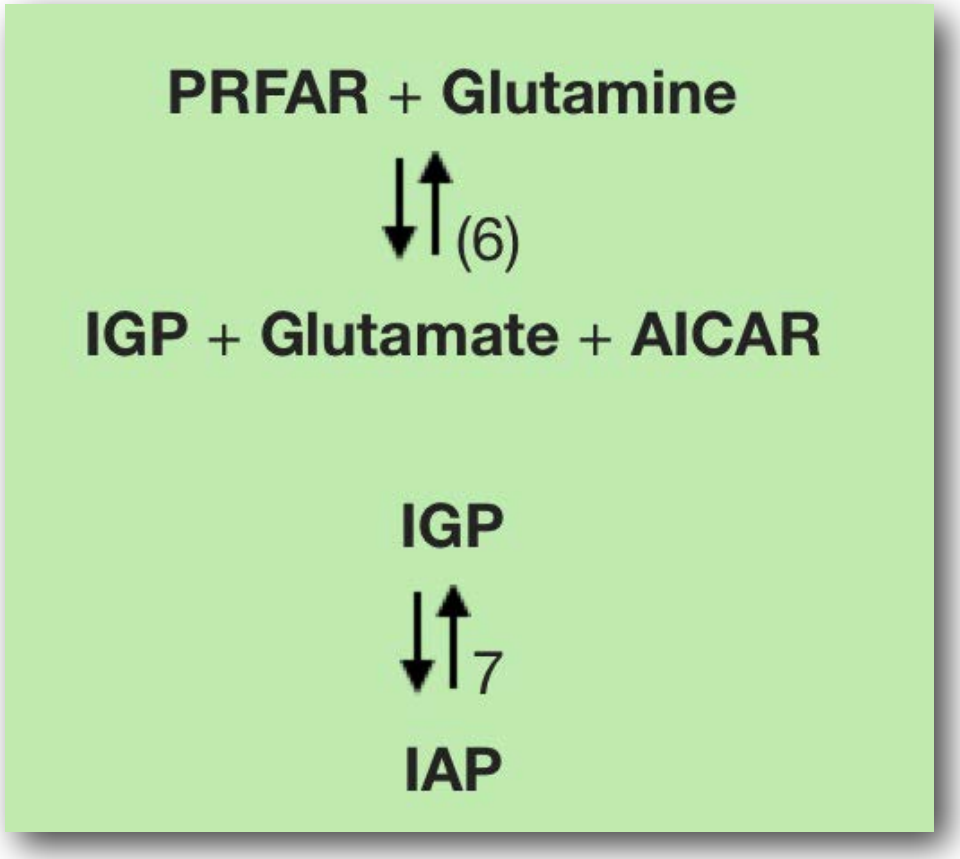
IGP

Imidazol glycerol phosphate (IGP) is an intermediate in histidine biosynthesis. Rea
tions it participates in in the pathway are shown below.



PRFAR = (N′-[(5-phosphoribulosyl)formimino]-5-aminoimidazole-4-carboxamide
ribonucleotide
IGP = Imidazole glycerol-phosphate
AICAR = 5′-phosphoribosyl-4-carboximide-5-aminoimidazole

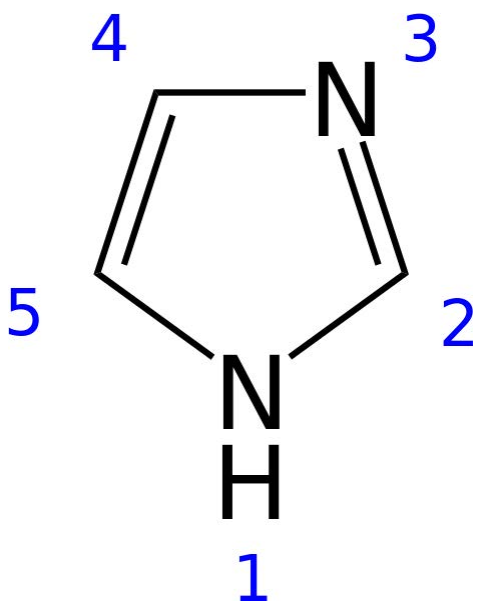
Related Glossary Terms

Drag related terms here

Imidazole

Imidazole is an organic compound with the formula $(CH)_2N(NH)CH$. It is a white or colorless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and having non-adjacent nitrogen atoms.

Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles, share the 1,3-C3N2 ring but feature varied substituents. This ring system is present in important biological building-blocks, such as histidine, and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.



https://en.wikipedia.org/wiki/Imidazole

Related Glossary Terms

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Imidazole Glycerol-phosphate Dehydratase

Imidazoleglycerol-phosphate dehydratase is an enzyme that catalyzes the c
action:

D-erythro-1-(imidazol-4-yl)glycerol 3-phosphate <---> 3-(imidazol-4-yl)-2
phosphate + H_2O

This reaction is the sixth step in the biosynthesis of histidine in bacteria, fu
plants.

https://en.wikipedia.org/wiki/Imidazoleglycerol-phosphate_dehydratase

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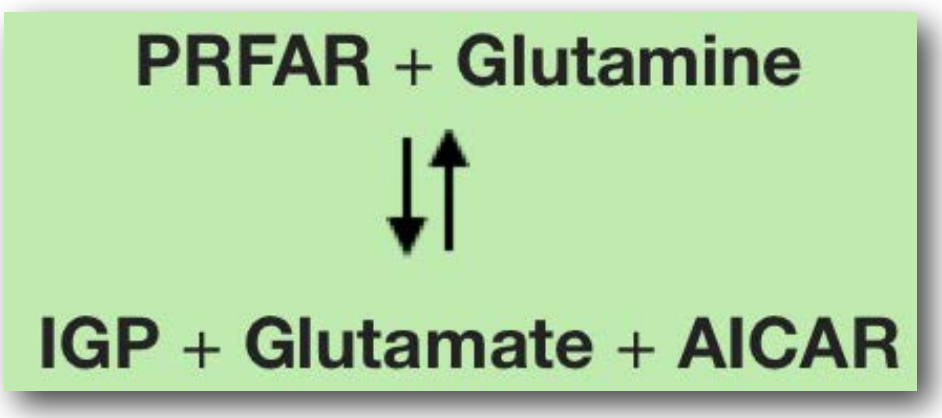
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Imidazole glycerol-phosphate synthase

Imidazole glycerol-phosphate synthase is an enzyme that catalyzes synthesis of imidazole glycerol phosphate in biosynthesis of histidine. The reaction catalyzed is below.



(PRFAR = N′-[(5-phosphoribulosyl)formimino]-5-aminoimidazole-4-carboxamide) ribonucleotide)

From http://www.ncbi.nlm.nih.gov/pubmed/11591353
“Imidazole glycerol phosphate synthase catalyzes a two-step reaction of histidine biosynthesis at the bifurcation point with the purine *de novo* pathway. The enzyme is a new example of intermediate channeling by glutamine amidotransferases in which ammonia generated by hydrolysis of glutamine is channeled to a second active site where it acts as a nucleophile. In this case, ammonia reacts in a cyclase domain to produce imidazole glycerol phosphate and an intermediate of purine biosynthesis. The enzyme is also a potential target for drug and herbicide development since the histidine pathway does not occur in mammals.”

Related Glossary Terms

Drag related terms here

Immune system

The immune system is a system of many biological structures and processes
organism that protects against disease. To function properly, an immune sys
detect a wide variety of agents, known as pathogens, from viruses to parasiti
and distinguish them from the organism's own healthy tissue. In many speci
mune system can be classified into subsystems, such as the innate immune s
sus the adaptive immune system, or humoral immunity versus cell-mediated
nity. In humans, the blood–brain barrier, blood–cerebrospinal fluid barrier,
lar fluid–brain barriers separate the peripheral immune system from the neu
mune system which protects the brain.

https://en.wikipedia.org/wiki/Immune_system

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Immunity

In biology, immunity is the balanced state of having adequate biological defenses to fight infection, disease, or other unwanted biological invasion, while having adequate tolerance to avoid allergy, and autoimmune diseases.

The basic premise for the division of the immune system into innate and adaptive components comes down to the innate system being composed of primitive bone marrow cells that are programmed to recognise foreign substances and react, versus the adaptive system being composed of more advanced lymphatic cells that are programmed to recognize self substances and don't react. The reaction to foreign substances is etymologically described as inflammation, meaning to set on fire, while the non-reaction to self substances is etymologically described as immunity, meaning to exempt. The interaction of these two components of the immune system creates a dynamic biological environment where "Health" can be seen as an active physical state where what is self is immunologically spared, and what is foreign is inflammatorily and immunologically eliminated. Extending this concept, "Disease" then can arise when what is foreign cannot be eliminated, or what is self is not spared.

https://en.wikipedia.org/wiki/Immunity_(medical)

Related Glossary Terms

Drag related terms here

Immunoglobulin

An antibody (Ab), also known as an immunoglobulin (Ig), is a large, Y-shaped prote produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses. The antibody recognizes a uniqu molecule of the harmful agent, called an antigen, via the variable region. Each tip o the "Y" of an antibody contains a paratope (analogous to a lock) that is specific for particular epitope (similarly analogous to a key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antib can tag a microbe or an infected cell for attack by other parts of the immune system can neutralize its target directly (for example, by blocking a part of a microbe that i sential for its invasion and survival). Depending on the antigen, the binding may im pede the biological process causing the disease or may recruit macrophages to dest the foreign substance. The ability of an antibody to communicate with the other co nents of the immune system is mediated via its Fc region (located at the base of the "Y"), which contains a conserved glycosylation site involved in these interactions. T production of antibodies is the main function of the humoral immune system.

https://en.wikipedia.org/wiki/Antibody

Related Glossary Terms

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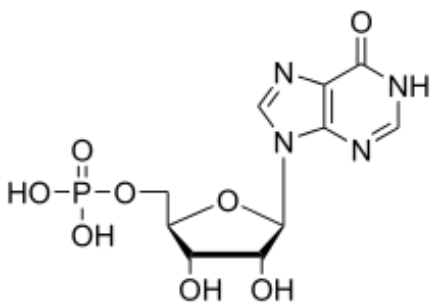
IMP

Inosinic acid or inosine monophosphate (IMP) is a nucleoside monophosphate. Inosinic acid is important in metabolism. It is the ribonucleotide of hypoxanthine and the first nucleotide formed during the synthesis of purine. IMP is formed by the deamination of adenosine monophosphate, and is hydrolyzed from inosine. IMP is an intermediate ribonucleoside monophosphate in purine metabolism.



https://en.wikipedia.org/wiki/Inosinic_acid

Related Glossary Terms

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IMP Dehydrogenase

IMP dehydrogenase EC 1.1.1.205 (Inosine-5'-monophosphate dehydrogenase) (Inosinic acid dehydrogenaseis) (IMPDH) an enzyme that converts inosine monophosphate to xanthosine monophosphate:

Inosine 5'-phosphate + NAD+ + H_2O <=> Xanthosine 5'-phosphate + NADH + H^+

It catalyzes the rate-limiting reaction of *de novo* GTP biosynthesis.
IMP dehydrogenase is associated with cell proliferation and is a possible target for cancer chemotherapy. Mammalian and bacterial IMPDHs are tetramers of identical chains. There are two IMP dehydrogenase isozymes in humans. IMP dehydrogenase nearly always contains a long insertion that has two CBS domains within it.

The structure of this enzyme is composed of a TIM barrel domain with two CBS domains inserted within a loop.

https://en.wikipedia.org/wiki/IMP_dehydrogenase

Related Glossary Terms

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In situ

The term *in situ* is used to describe something in its original, untouched/ur
dition - “as it is”.

Related Glossary Terms

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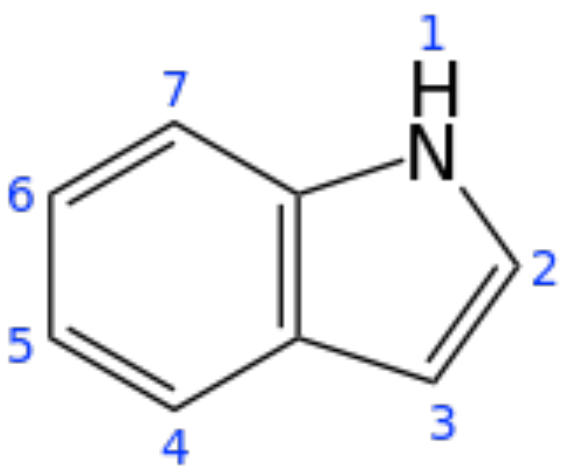
Indole

Indole is an aromatic heterocyclic organic compound. It has a bicyclic struct
sisting of a six-membered benzene ring fused to a five-membered nitrogen-c
pyrrole ring. Indole is widely distributed in the natural environment and can
duced by a variety of bacteria. As an intercellular signal molecule, indole regu
ous aspects of bacterial physiology, including spore formation, plasmid stabi
tance to drugs, biofilm formation, and virulence. The amino acid tryptophan
dole derivative and the precursor of the neurotransmitter serotonin.



https://en.wikipedia.org/wiki/Indole

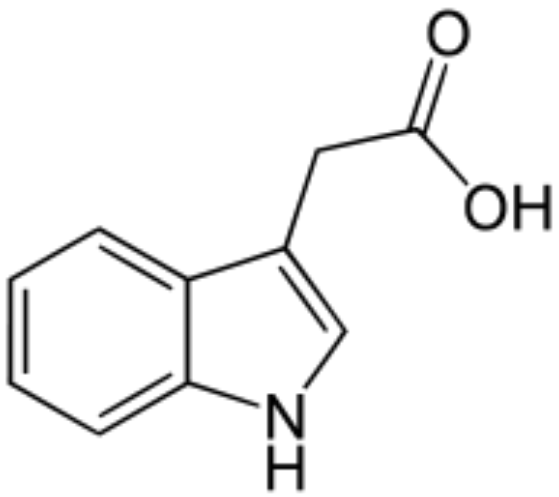
Related Glossary Terms

Drag related terms here

Indole-3-acetic Acid

Indole-3-acetic acid (IAA) is the most common, naturally-occurring, plant hormone of the auxin class. It is the best known of the auxins, and has been the subject of extensive studies by plant physiologists. Chemically, IAA is a carboxylic acid in which the carboxyl group is attached through a methylene group to the C-3 position of an indole ring. In appearance, IAA is a colorless solid.

As all auxins, IAA has many different effects, such as inducing cell elongation and cell division with all subsequent results for plant growth and development. On a larger scale, IAA serves as signaling molecule necessary for development of plant organs and coordination of growth.



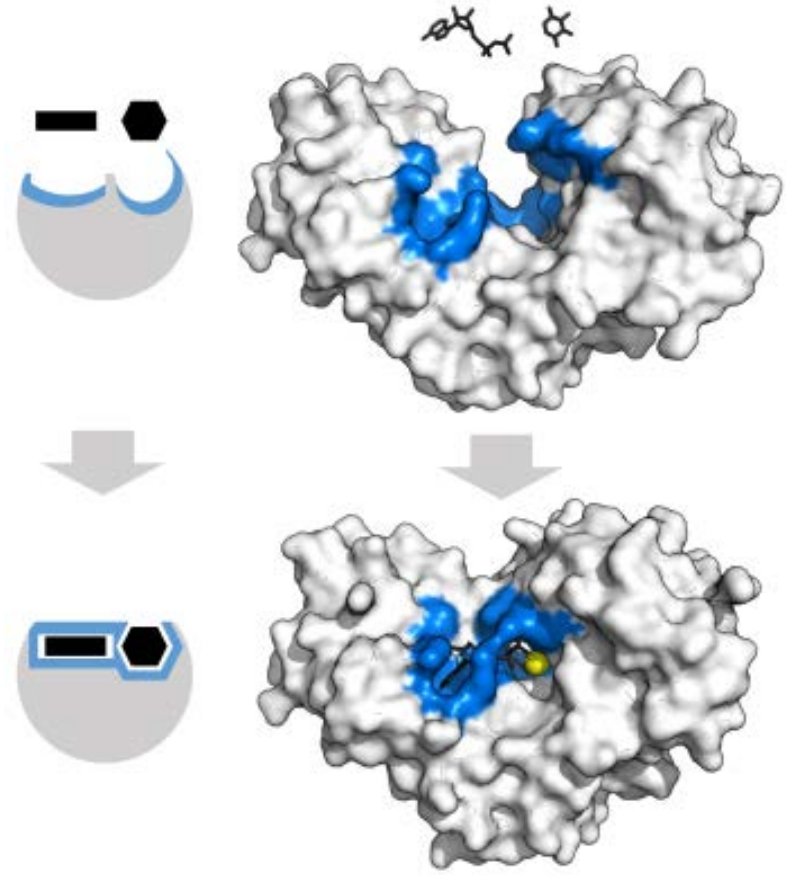
https://en.wikipedia.org/wiki/Indole-3-acetic_acid

Related Glossary Terms

Drag related terms here

Induced Fit

The favored model for the enzyme-substrate interaction is the induced fit model.This model proposes that the initial interaction between enzyme and substrate is relatively weak, but that these weak interactions rapidly induce conformational changes in the enzyme that strengthen binding. The scheme below depicts conformational changes in the enzyme hexokinase upon binding of substrate.



https://en.wikipedia.org/wiki/Enzyme_catalysis#Induced_fit

Related Glossary Terms

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Index Find Term

Inducer

In molecular biology, an inducer is a molecule that regulates gene expressio
ducer can bind to repressors or activators. Inducers function by disabling r
The gene is expressed because an inducer binds to the repressor. The bindi
ducer to the repressor prevents the repressor from binding to the operator.
lymerase can then begin to transcribe operon genes.

Inducers also function by binding to activators. Activators generally bind p
vator DNA sequences unless an inducer is present. Activator binds to an in
the complex binds to the activation sequence and activates target gene. Re
inducer stops transcription.

https://en.wikipedia.org/wiki/Inducer

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Inflammation

Inflammation (Latin, inflammatio) is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.
Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

https://en.wikipedia.org/wiki/Inflammation

Related Glossary Terms

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Inhibitors of Electron Transport

Electron transport inhibitors are molecules that bind to and prevent the mo
electrons through electron transport complexes in the inner mitochondrial
A few are listed below

Complex I - rotenone, amytal
Complex II - malonate
Complex III - Antimycin A
Complex IV - carbon monoxide, azide, cyanide

Related Glossary Terms

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Initiator tRNA

An initiator tRNA is the tRNA that binds to the P site of the ribosome durin
tion of translation. It is linked to a methionine or, in the case or prokaryote
methionine. The initiator tRNA is slightly different in structure from the tR
ing methionine for incorporation into internal sites in a protein.

Related Glossary Terms

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Innate Immune System

The innate immune system, also known as the nonspecific immune system or in-born immunity system, is an important subsystem of the overall immune system that comprises the cells and mechanisms that defend the host from infection by other organisms. The cells of the innate system recognize and respond to pathogens in a generic way, but, unlike the adaptive immune system, the system does not confer long-lasting or protective immunity to the host. Innate immune systems provide immediate defense against infection, and are found in all classes of plant and animal life.

The innate immune system is an evolutionarily older defense strategy, and is the dominant immune system found in plants, fungi, insects, and primitive multicellular organisms.

The major functions of the vertebrate innate immune system include:
• Recruiting immune cells to sites of infection, through the production of chemical factors, including specialized chemical mediators, called cytokines
• Activation of the complement cascade to identify bacteria, activate cells, and promote clearance of antibody complexes or dead cells
• Identification and removal of foreign substances present in organs, tissues, the blood and lymph, by specialized white blood cells
• Activation of the adaptive immune system through a process known as antigen presentation
• Acting as a physical and chemical barrier to infectious agents.

https://en.wikipedia.org/wiki/Innate_immune_system

Related Glossary Terms

Inner Leaflet

The lipid bilayer consists of two layers- an outer leaflet and an inner leaflet. Th
ponents of bilayers are distributed unequally between the two surfaces to create
metry between the outer and inner surfaces. This asymmetric organization is im
tant for cell functions such as cell signaling. The asymmetry of the biological me
brane reflects the different functions of the two leaflets of the membrane. As see
the fluid membrane model of the phospholipid bilayer, the outer leaflet and inn
let of the membrane are asymmetrical in their composition. Certain proteins ar
rest only on one surface of the membrane and not the other.

https://en.wikipedia.org/wiki/Biological_membrane

In human red blood cells, the inner (cytoplasmic) leaflet is composed mostly of
phatidylethanolamine, phosphatidylserine and phosphatidylinositol and its pho
lated derivatives.

https://en.wikipedia.org/wiki/Lipid_bilayer

Related Glossary Terms

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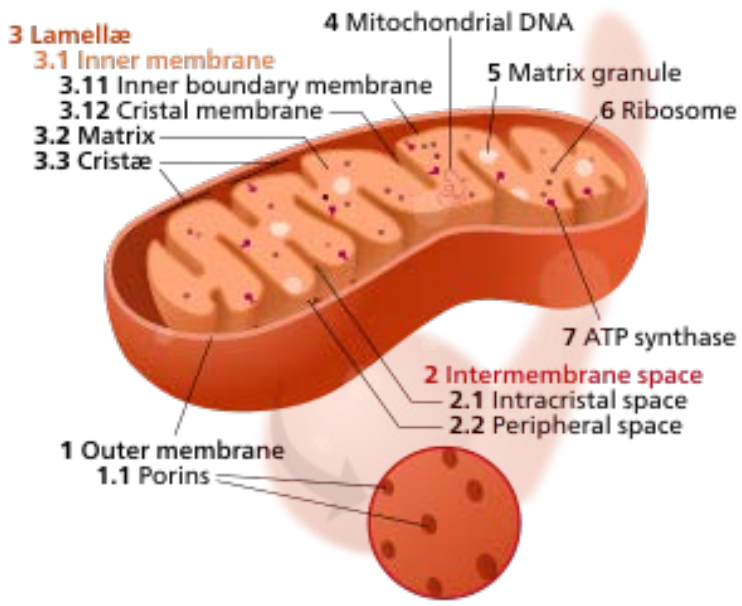
Inner Membrane

Inner membrane, as used in this book, refers to the inner mitochondrial membrane (IMM) which separates the mitochondrial matrix from the intermembrane space.

The structure of the inner mitochondrial membrane is extensively folded and compartmentalized. The numerous invaginations of the membrane are called cristae, separated by crista junctions from the inner boundary membrane juxtaposed to the outer membrane. Cristae significantly increase the total membrane surface area compared to a smooth inner membrane and thereby the available working space.

The inner membrane creates two compartments. The region between the inner and outer membrane, called the intermembrane space which is largely continuous with the cytosol, and the more sequestered space inside the inner membrane, called matrix.



https://en.wikipedia.org/wiki/Inner_mitochondrial_membrane

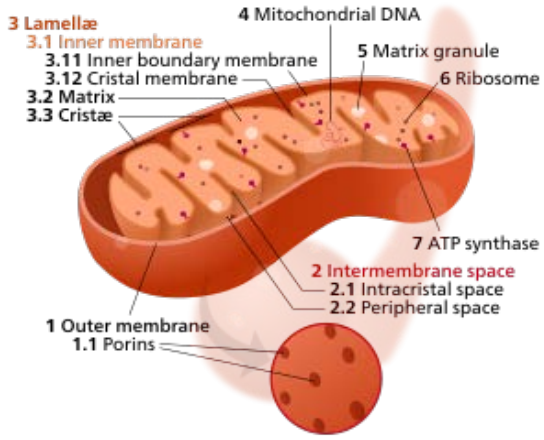
Related Glossary Terms

Inner Membrane of the Mitochondrion

The inner membrane of the mitochondrion separates the mitochondrial matrix from the intermembrane space.

The structure of the inner mitochondrial membrane is extensively folded and compartmentalized. The numerous invaginations of the membrane are called cristae, separated by crista junctions from the inner boundary membrane juxtaposed to the outer membrane. Cristae significantly increase the total membrane surface area compared to a smooth inner membrane and thereby the available working space.

The inner membrane creates two compartments. The region between the inner and outer membrane, called the intermembrane space which is largely continuous with the cytosol, and the more sequestered space inside the inner membrane, called matrix.



https://en.wikipedia.org/wiki/Inner_mitochondrial_membrane

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Inner Mitochondrial Membrane

The inner mitochondrial membrane (IMM) separates the mitochondrial matrix from the intermembrane space.

The structure of the inner mitochondrial membrane is extensively folded and compartmentalized. The numerous invaginations of the membrane are called cristae, separated by crista junctions from the inner boundary membrane juxtaposed to the outer membrane. Cristae significantly increase the total membrane surface area compared to a smooth inner membrane and thereby the available working space.

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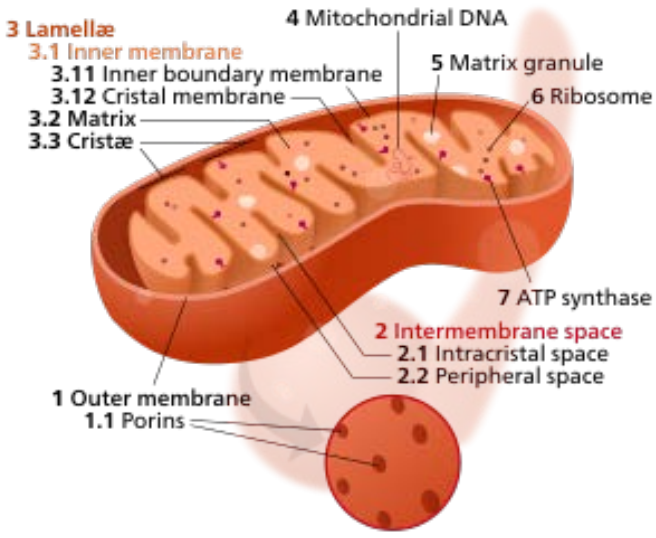

https://en.wikipedia.org/wiki/Inner_mitochondrial_membrane

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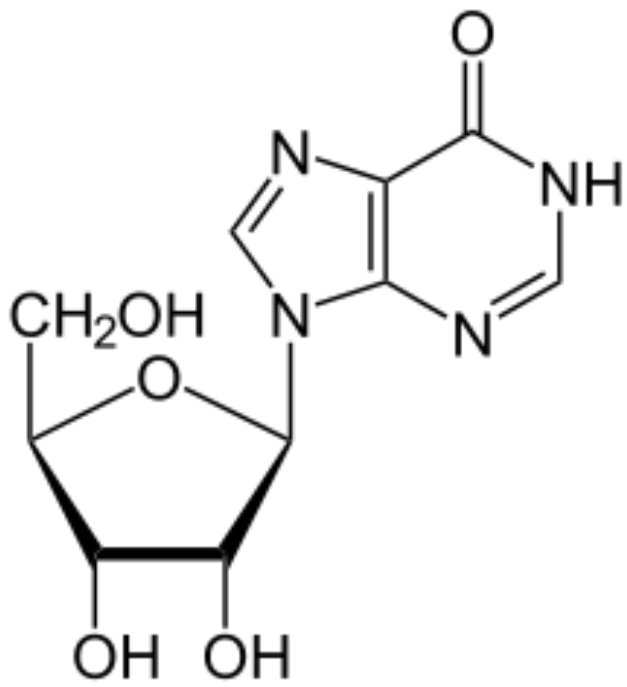
Inosine

Inosine is a nucleoside that is formed when hypoxanthine is attached to a ribose ring (also known as a ribofuranose) via a β-N9-glycosidic bond.

Inosine is commonly found in tRNAs and is essential for proper translation of the genetic code in wobble base pairs. Phosphorylation of inosine creates the nucleotide inosine monophosphate (IMP).



https://en.wikipedia.org/wiki/Inosine

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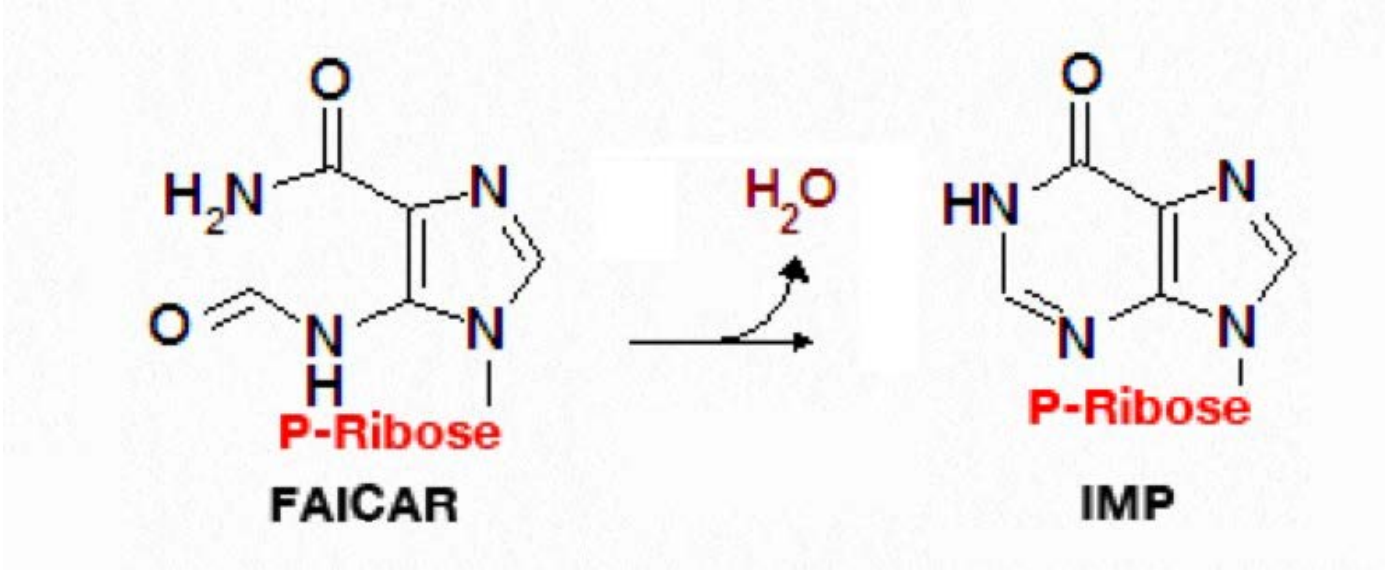
Inosine Monophosphate Synthase

In *de novo* purine biosynthsis, inosine monophosphate (IMP) synthase cata
formation of IMP from FAICAR (5-Formamidoimidazole-4-carboxamide r



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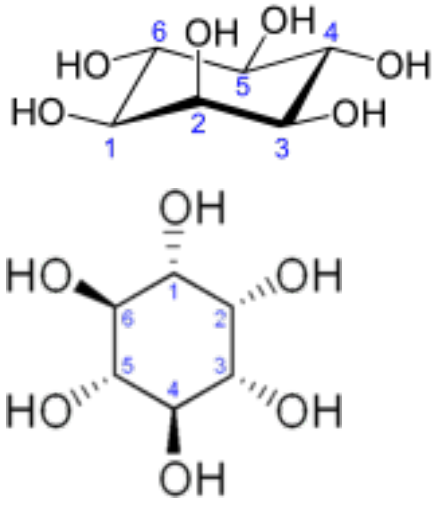
Chapter 6 - Metabolism: Nucleotides

Inositol

Inositol or cyclohexane-1,2,3,4,5,6-hexol is a chemical compound with formula $C_6H_{12}O_6$ or $(\text{-CHOH-})_6$, a six-fold alcohol (polyol) of cyclohexane. It exists in nine possible stereoisomers, of which the most prominent form, widely occurring in nature, is *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol, or myo-inositol (former names meso-inositol or i-inositol). Inositol is a sugar alcohol. Its taste has been assayed at half the sweetness of table sugar (sucrose).



https://en.wikipedia.org/wiki/Inositol

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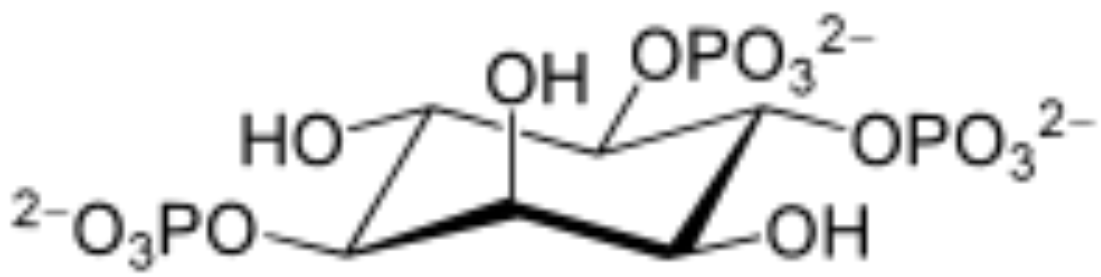
Inositol-1,4,5-trisphosphate

Inositol trisphosphate or inositol 1,4,5-trisphosphate (also commonly know
phoinositol - abbreviated $InsP_3$ or Ins_3P or IP_3), together with diacylglycero
a secondary messenger molecule used in signal transduction and lipid signa
logical cells. While DAG stays inside the membrane, IP_3 is soluble and diffu
the cell. It is made by hydrolysis of phosphatidylinositol 4,5-bisphosphate (
phospholipid that is located in the plasma membrane, by phospholipase C (



https://en.wikipedia.org/wiki/Inositol_trisphosphate

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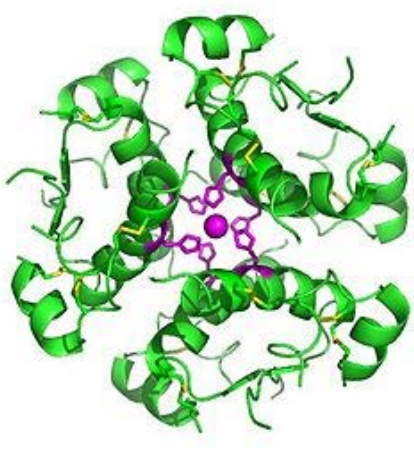
Chapter 2 - Structure & Function: Lipids

Chapter 2 - Structure & Function: Lipids

Insulin

Insulin (from the Latin, *insula* meaning island) is a peptide hormone produced by β cells in the pancreas, and by Brockmann body in some teleost fish. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver. Insulin counters the effects of glucagon or epinephrine by stimulating dephosphorylation of proteins in the kinase cascade.



https://en.wikipedia.org/wiki/Insulin

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Insulin Receptor

The insulin receptor (IR) is a transmembrane receptor that is activated by ins
IGF-I, IGF-II and belongs to the large class of tyrosine kinase receptors. Meta
the insulin receptor plays a key role in the regulation of glucose homeostasis,
tional process that under degenerate conditions may result in a range of clinic
festations including diabetes and cancer.

Biochemically, the insulin receptor is encoded by a single gene INSR, from wh
nate splicing during transcription results in either IR-A or IR-B isoforms. Dow
post-translational events of either isoform result in the formation of a proteol
cleaved α and β subunit, which upon combination are ultimately capable of h
hetero-dimerization to produce the ≈320 kDa disulfide-linked transmembran
receptor.

https://en.wikipedia.org/wiki/Insulin_receptor

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Insulin Receptor Substrate

Insulin receptor substrate (IRS) is an important ligand in the insulin respo
man cells.

IRS-1, for example, is an IRS protein that contains a phosphotyrosine bindi
(PTB-domain). In addition, the insulin receptor contains a NPXY motif. Th
domain binds the NPXY sequence. Thus, the insulin receptor binds IRS. IR
important biological functions for both metabolic and mitogenic (growth p
pathways: mice deficient of IRS1 have only a mild diabetic phenotype, but a
nounced growth impairment, i.e., IRS-1 knockout mice only reach 50% of t
normal mice.

https://en.wikipedia.org/wiki/Insulin_receptor_substrate

Related Glossary Terms

Drag related terms here

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nounced growth impairment, i.e., IRS-1 knockout mice only reach 50% of t
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https://en.wikipedia.org/wiki/Insulin_receptor_substrate

Related Glossary Terms

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Insulin Resistance

Insulin resistance (IR) is generally regarded as a pathological condition in which cells fail to respond to the normal actions of the hormone insulin. The body produces insulin when glucose starts to be released into the bloodstream from the digestion of the carbohydrates we have eaten. Normally this insulin response triggers glucose being taken into body cells, to be used for energy, and inhibits the body from using fat as energy. The level of glucose in the blood decreases as a result, staying within the normal range even when a large amount of carbohydrates is consumed. When the body produces insulin under conditions of insulin resistance, the cells in the body are resistant to the insulin and are unable to use it as effectively, leading to high blood sugar. Beta cells in the pancreas subsequently increase their production of insulin, further contributing to a high blood insulin level. This often remains undetected and can contribute to a diagnosis of Type 2 diabetes or latent autoimmune diabetes of adults. Although this type of chronic insulin resistance is harmful, during acute illness it is actually a well-evolved protective mechanism. Recent investigations have revealed that insulin resistance helps to conserve the brain's glucose supply by preventing muscles from taking up excessive glucose. Insulin resistance should even be strengthened under harsh metabolic conditions such as pregnancy, during which the expanding fetal brain demands more glucose.

Insulin resistance implies that the body's cells (primarily muscle) lose sensitivity to insulin, a hormone secreted by the pancreas to promote glucose utilization. At the molecular level, a cell senses insulin through insulin receptors, with the signal propagating through a cascade of molecules collectively known as PI3K/Akt/mTOR signaling pathway. Recent studies suggested that the pathway may operate as a bistable switch under physiologic conditions for certain types of cells, and insulin response may well be a threshold phenomenon. The pathway's sensitivity to insulin may be blunted by many factors such as free fatty acids, causing insulin resistance. From a broader perspective, however, sensitivity tuning (including sensitivity reduction) is a common practice for an organism to adapt to the changing environment or metabolic conditions. Pregnancy, for example, is a prominent change of metabolic conditions, under which the mother has to reduce her muscles' insulin sensitivity to spare more glucose for the brains (the mother's brain and the fetal brain). This can be achieved through raising the response threshold (i.e., postponing the onset of sensitivity) by secreting placental growth factor to interfere with the interaction between insulin receptor substrate (IRS) and PI3K, which is the essence of the so-called adjustable threshold hypothesis of insulin resistance.

https://en.wikipedia.org/wiki/Insulin_resistance

Insulin Signaling

Activation of insulin receptors leads to internal cellular mechanisms that directly affect glucose uptake by regulating the number and operation of protein molecules in the cell membrane that transport glucose into the cell.

Insulin binds to the extracellular portion of the α subunits of the insulin receptor. This, in turn, causes a conformational change in the insulin receptor that activates the kinase domain residing on the intracellular portion of the β subunits. The activated kinase domain autophosphorylates tyrosine residues on the C-terminus of the receptor as well as tyrosine residues in the IRS-1 protein.

1 Phosphorylated IRS-1, in turn, binds to and activates phosphoinositol 3 kinase (PI_3K)
2 PI_3K catalyzes the reaction $PIP_2 + ATP \rightarrow PIP_3 + ADP$
3 PIP_3 activates protein kinase B (PKB)
4 PKB phosphorylates glycogen synthase kinase (GSK) and thereby inactivates GSK
5 GSK can no longer phosphorylate glycogen synthase (GS)
6 Unphosphorylated GS makes more glycogen
7 PKB also facilitates vesicle fusion, resulting in an increase in GLUT4 transporters in the plasma membrane

https://en.wikipedia.org/wiki/Insulin#Signal_transduction

Related Glossary Terms

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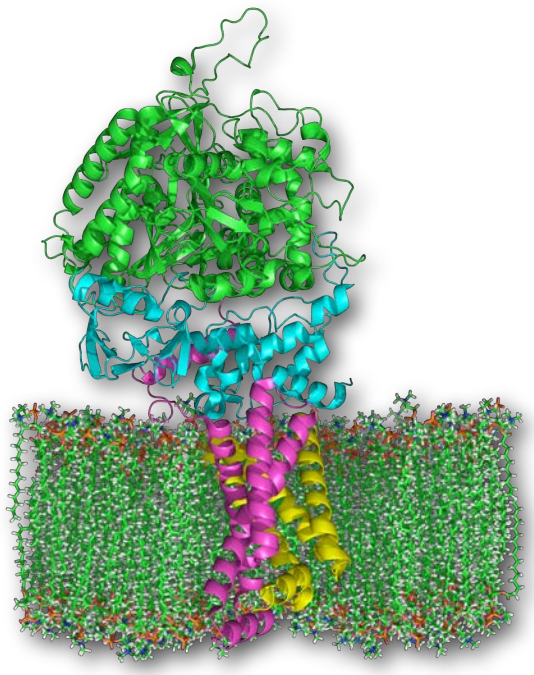
Integral Membrane Proteins

An integral membrane protein (IMP) is a type of membrane protein that is permanently attached to the biological membrane. All transmembrane proteins are IMPs, but not all IMPs are transmembrane proteins. IMPs comprise a significant fraction of the proteins encoded in an organism's genome. Proteins that cross the membrane are surrounded by "annular" lipids (see annular lipid shell), which are defined as lipids that are in direct contact with a membrane protein. Such proteins can be separated from the biological membranes only using detergents, nonpolar solvents, or sometimes denaturing agents. In the image below, the IMP known as Complex II in the inner mitochondrial membrane is depicted. The lipid bilayer is at the bottom in green.



https://en.wikipedia.org/wiki/Integral_membrane_protein

Related Glossary Terms

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Integrin

Integrins are transmembrane receptors that are the bridges for cell-cell and cell-
extracellular matrix (ECM) interactions. When triggered, integrins in turn trigge
chemical pathways to the interior (signal transduction), such as the chemical cor
tion and mechanical status of the ECM, which results in a response (activation of
scription) such as regulation of the cell cycle, cell shape, and/or motility or new r
tors being added to the cell membrane. This allows rapid and flexible responses t
events at the cell surface, for example to signal platelets to initiate an interaction
coagulation factors.

https://en.wikipedia.org/wiki/Integrin

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events at the cell surface, for example to signal platelets to initiate an interac
coagulation factors.

https://en.wikipedia.org/wiki/Integrin

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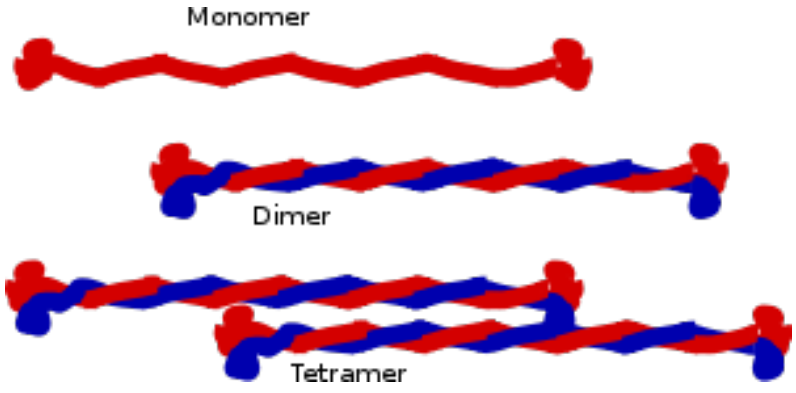
Intermediate Filaments

Intermediate filaments (IFs) are cytoskeletal components found in the cells of many animal species. They are composed of a family of related proteins sharing common structural and sequence features. Intermediate filaments have an average diameter of 10 nanometers, which is between that of 7 nm actin (microfilaments), and that of 25 nm microtubules, and they were initially designated 'intermediate' because their average diameter is between those of narrower microfilaments (actin) and wider myosin filaments found in muscle cells. Most types of intermediate filaments are cytoplasmic, but one type, the lamins, are nuclear.



https://en.wikipedia.org/wiki/Intermediate_filament

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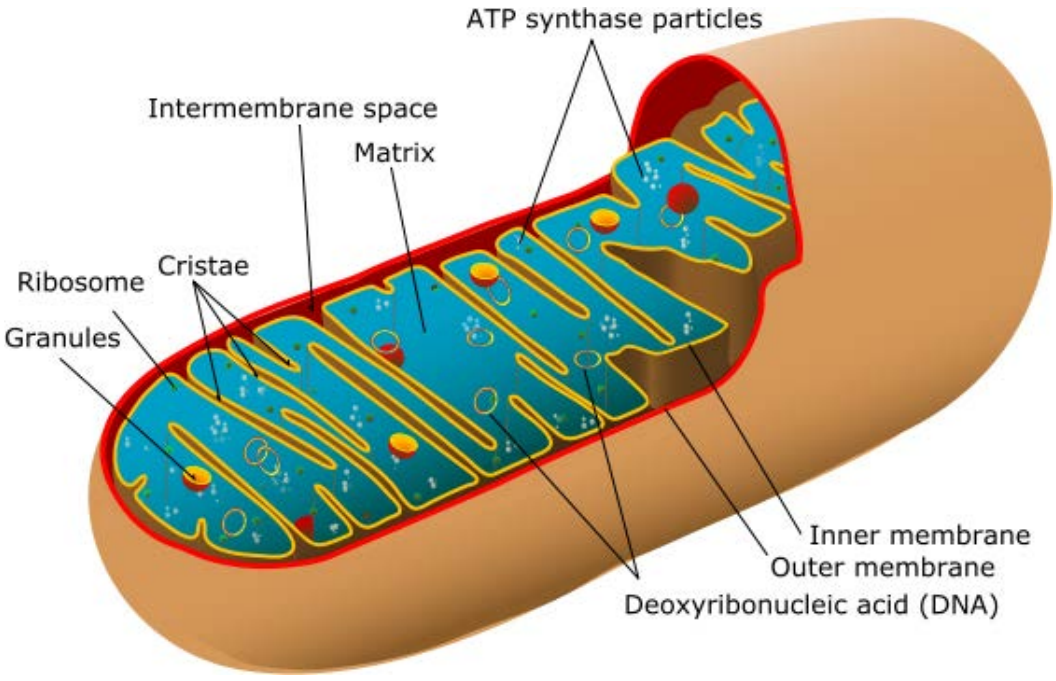
Intermembrane Space

The intermembrane space (IMS) is the region between the inner membrane and the outer membrane of a mitochondrion or a chloroplast. The main function of mitochondrial intermembrane space is related to oxidative phosphorylation. It is to this region that protons are pumped during electron transport and from which they re-enter the matrix in the process of oxidative phosphorylation.



https://en.wikipedia.org/wiki/Intermembrane_space

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Chapter 3 - Membranes: Other Considerations

Intrinsic Pathway

In molecular biology, the term intrinsic pathway may refer to multiple casc
tein interactions.

- The intrinsic pathway of apoptosis refers to cell death initiated by change
  chondria, also known as the mitochondrial pathway or intracellular pathw
  sic apoptosis.
- The intrinsic pathway of blood coagulation is also known as the contact ac
  pathway and refers to a cascade of enzymatic reactions resulting in blood

https://en.wikipedia.org/wiki/Intrinsic_pathway

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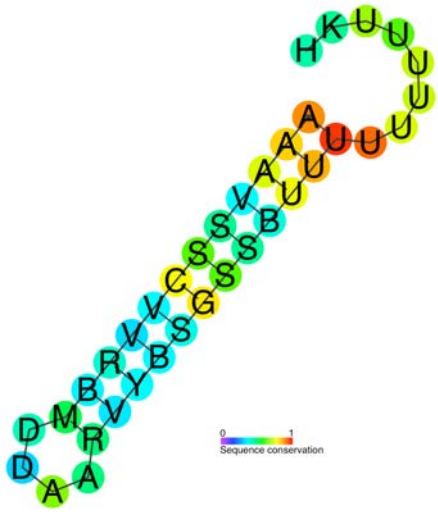
Intrinsic Terminators

Intrinsic termination (also called Rho-independent termination) is a mechanism in prokaryotes that causes RNA transcription to be stopped. In this mechanism, the mRNA contains a sequence that can base pair with itself to form a stem-loop structure 7-20 base pairs in length that is also rich in cytosine-guanine base pairs. C-G base pairs have significant base-stacking interactions (especially repeated G-C pairs) and can form three hydrogen bonds between each other, resulting in a stable RNA duplex. Following the stem-loop structure is a chain of uracil residues. The bonds between uracil and adenine are very weak. A protein bound to RNA polymerase (nusA) binds to the stem-loop structure tightly enough to cause the polymerase to temporarily stall. This pausing of the polymerase coincides with transcription of the poly-uracil sequence. The weak Adenine-Uracil bonds lower the energy of destabilization for the RNA-DNA duplex, allowing it to unwind and dissociate from the RNA polymerase.

Stem-loop structures that are not followed by a poly-Uracil sequence cause the RNA polymerase to pause, but it will typically continue transcription after a brief time because the duplex is too stable to unwind far enough to cause termination. Rho-independent transcription termination is a frequent mechanism underlying the activity of *cis*-acting RNA regulatory elements, such as riboswitches.

Shown below - predicted conserved secondary structure and sequence conservation annotation for 90 bacterial Rho-independent termination elements.



https://en.wikipedia.org/wiki/Intrinsic_termination

Related Glossary Terms

Intrinsically Disordered Proteins

An intrinsically disordered protein (IDP) is a protein that lacks a fixed or ordered three-dimensional structure. IDPs cover a spectrum of states from fully unstructured to partially structured and include random coils, (pre-)molten globules, and large multi-domain proteins connected by flexible linkers. They constitute one of the main types of protein (alongside globular, fibrous and membrane proteins).

Many disordered proteins have the binding affinity with their receptors regulated by post-translational modification, thus it has been proposed that the flexibility of disordered proteins facilitates the different conformational requirements for binding the modifying enzymes as well as their receptors. Intrinsic disorder is particularly enriched in proteins implicated in cell signaling, transcription and chromatin remodeling functions.

Many unstructured proteins undergo transitions to more ordered states upon binding to their targets (e.g. Molecular Recognition Features (MoRFs)). The coupled folding and binding may be local, involving only a few interacting residues, or it might involve an entire protein domain. It was recently shown that the coupled folding and binding allows the burial of a large surface area that would be possible only for fully structured proteins if they were much larger. Moreover, certain disordered regions might serve as "molecular switches" in regulating certain biological function by switching to ordered conformation upon molecular recognition like small molecule-binding, DNA/RNA binding, ion interactions etc.

https://en.wikipedia.org/wiki/Intrinsically_disordered_proteins

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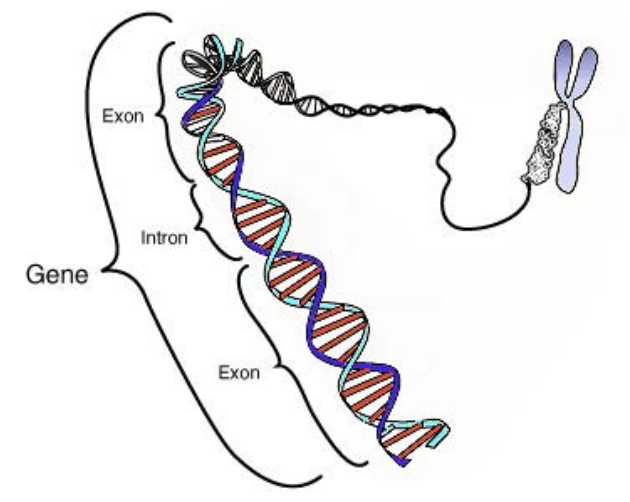
Intron

An intron is any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product. The term intron refers to both the DNA sequence within a gene and the corresponding sequence in RNA transcripts. Sequences that are joined together in the final mature RNA after RNA splicing are exons.

Introns are found in the genes of most organisms and many viruses, and can be located in a wide range of genes, including those that generate proteins, ribosomal RNA (rRNA), and transfer RNA (tRNA). When proteins are generated from intron-containing genes, RNA splicing takes place as part of the RNA processing pathway that follows transcription and precedes translation.



https://en.wikipedia.org/wiki/Intron

Related Glossary Terms

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Iodine

Iodine is a chemical element with symbol I and atomic number 53. The nar
Greek ἰοειδής ioeidēs, meaning violet or purple, due to the color of iodine v

Iodine is required by higher animals for synthesizing thyroid hormones, wh
the element. Because of this function, radioisotopes of iodine are concentra
thyroid gland along with nonradioactive iodine. If inhaled, the radioisotope
which has a high fission product yield, concentrates in the thyroid, and can
died with non-radioactive potassium iodide treatment.

https://en.wikipedia.org/wiki/Iodine

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Ion

An ion is an atom or a molecule in which the total number of electrons is no
the total number of protons, giving the atom or molecule a net positive or n
trical charge. Ions can be created, by either chemical or physical means, via

https://en.wikipedia.org/wiki/Ion

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Ion Channels

Ion channels are pore-forming membrane proteins whose functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume. Ion channels are present in the membranes of all cells. Ion channels are considered to be one of the two traditional classes of ionophoric proteins, with the other class known as ion transporters (including the sodium-potassium pump, sodium-calcium exchanger, and sodium-glucose transport proteins, amongst others).

There are two distinctive features of ion channels that differentiate them from other types of ion transporter proteins:

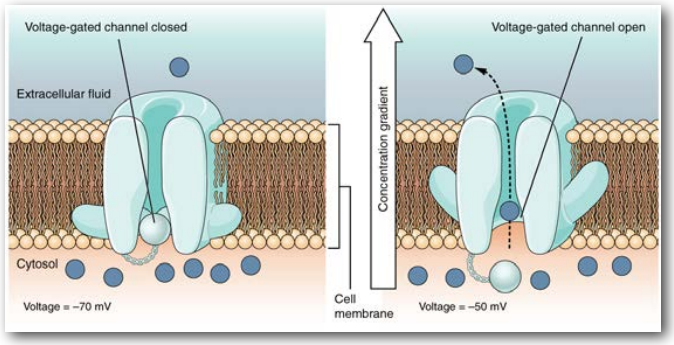
1 The rate of ion transport through the channel is very high (often 10^6 ions per second or greater).
2 Ions pass through channels down their electrochemical gradient, which is a function of ion concentration and membrane potential, "downhill", without the input (or help) of metabolic energy (e.g. ATP, co-transport mechanisms, or active transport mechanisms).

Ion channels are located within the plasma membrane of nearly all cells and many intracellular organelles. They are often described as narrow, water-filled tunnels that allow only ions of a certain size and/or charge to pass through. This characteristic is called selective permeability. The archetypal channel pore is just one or two atoms wide at its narrowest point and is selective for specific species of ion, such as sodium or potassium. However, some channels may be permeable to the passage of more than one type of ion, typically sharing a common charge: positive (cations) or negative (anions). Ions often move through the segments of the channel pore in single file nearly as quickly as the ions move through free solution. In many ion channels, passage through the pore is governed by a "gate", which may be opened or closed in response to chemical or electrical signals, temperature, or mechanical force.

Ion channels are integral membrane proteins, typically formed as assemblies of several individual proteins. Such "multi-subunit" assemblies usually involve a circular arrangement of identical or homologous proteins closely packed around a water-filled pore through the plane of the membrane or lipid bilayer. For most voltage-gated ion channels, the pore-forming subunit(s) are called the α subunit, while the auxiliary subunits are denoted β, γ, and so on.

Because channels underlie the nerve impulse and because "transmitter-activated" channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. Indeed, numerous toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails, and others) work by modulating ion channel conductance and/or kinetics. In addition, ion channels are key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic β-cell insulin release. In the search for new drugs, ion channels are a frequent target.

Depicted below is a voltage gated ion channel



https://en.wikipedia.org/wiki/Ion_channel

Ion Exchange Chromatography

Ion chromatography (or ion-exchange chromatography) is a chromatography process that separates ions and polar molecules based on their affinity to the ion exchanger. It works on almost any kind of charged molecule—including large proteins, small nucleotides, and amino acids. It is often used in protein purification, water analysis, and quality control. The water-soluble and charged molecules such as proteins, amino acids, and peptides bind to moieties which is oppositely charged by forming covalent bonds to the insoluble stationary phase. The equilibrated stationary phase consists of an ionizable functional group where the targeted molecules of a mixture to be separated and quantified can bind while passing through the column. This method applies the idea of the interaction between molecules and the stationary phase which are charged oppositely to each other.

Cation exchange chromatography is used when the desired molecules to separate are cations, and an anion exchange chromatography is to separate anions meaning that the beads in the column contain positively charged functional groups to attract the anions. The bound molecules then can be eluted and collected using an eluant which contains anions and cations by running higher concentration of ions through the column or changing pH of the column. One of the primary advantages for the use of ion chromatography is only one interaction involved during the separation as opposed to other separation techniques. Therefore, ion chromatography may have higher matrix tolerance.

https://en.wikipedia.org/wiki/Ion_chromatography

Related Glossary Terms

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Ion Gradients

An electrochemical (ion) gradient is a gradient of electrochemical potential
an ion that can move across a membrane. The gradient consists of two part
cal potential and a difference in the chemical concentration across a memb
difference of electrochemical potentials can be interpreted as a type of pote
available for work in a cell. The energy is stored in the form of chemical pot
which accounts for an ion's concentration gradient across a cell membrane,
static energy, which accounts for an ion's tendency to move under influence
transmembrane potential.

https://en.wikipedia.org/wiki/Electrochemical_gradient

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Ionic

The term ionic related to a molecule having the qualities of an ion - being charg
chemistry, an ionic compound is a chemical compound comprising ions held to
by electrostatic forces termed ionic bonding. The compound is neutral overall,
sists of positively charged ions called cations and negatively charged ions called
These can be simple ions such as the sodium (Na^+) and chloride (Cl^-) in sodium
ride, or polyatomic species such as the ammonium (NH_4^+) and carbonate (CO_3
in ammonium carbonate. Individual ions within an ionic compound usually ha
ple nearest neighbors, so are not considered to be part of molecules, but instead
a continuous three-dimensional network, usually in a crystalline structure.

https://en.wikipedia.org/wiki/Ionic_compound

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Ionic Interactions

The term ionic interactions relates to attractive and repulsive forces arising
positely charged ion or similarly charged ions respectively. Ionic interactio
of the forces helping to stabilize tertiary and quaternary structures in prote

Related Glossary Terms

Drag related terms here

Ionization

Ionization is the process by which an atom or a molecule acquires a negative or po
tive charge by gaining or losing electrons to form ions, often in conjunction with o
chemical changes. Ionization can result from the loss of an electron after collision
with subatomic particles, collisions with other atoms, molecules and ions, or throu
the interaction with light.

https://en.wikipedia.org/wiki/Ionization

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Ionize

Ionizing occurs when an atom or a molecule acquires a negative or positive
gaining or losing electrons to form ions, often in conjunction with other che
changes. Ionization can result from the loss of an electron after collisions w
tomic particles, collisions with other atoms, molecules and ions, or through
tion with light.

https://en.wikipedia.org/wiki/Ionization

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Ionophores

An ionophore is a chemical species that reversibly binds ions. Many ionoph
lipid-soluble entities that transport ions across a cell membrane. Ionophore
"ion carrier" as these compounds catalyze ion transport across hydrophobic
branes such as liquid polymeric membranes (carrier-based ion selective ele
lipid bilayers found in the living cells or synthetic vesicles (liposomes).

https://en.wikipedia.org/wiki/Ionophore

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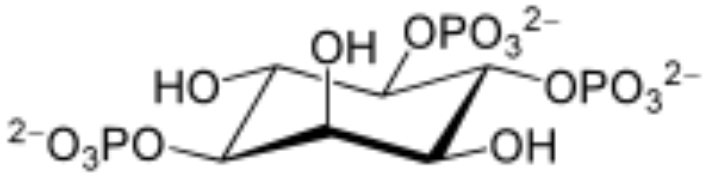
IP_3

Inositol trisphosphate or inositol 1,4,5-trisphosphate (also commonly know
phoinositol - abbreviated $InsP_3$ or Ins_3P or IP_3), together with diacylglycero
a secondary messenger molecule used in signal transduction and lipid signa
logical cells. While DAG stays inside the membrane, IP_3 is soluble and diffu
the cell. It is made by hydrolysis of phosphatidylinositol 4,5-bisphosphate (
phospholipid that is located in the plasma membrane, by phospholipase C (



https://en.wikipedia.org/wiki/Inositol_trisphosphate

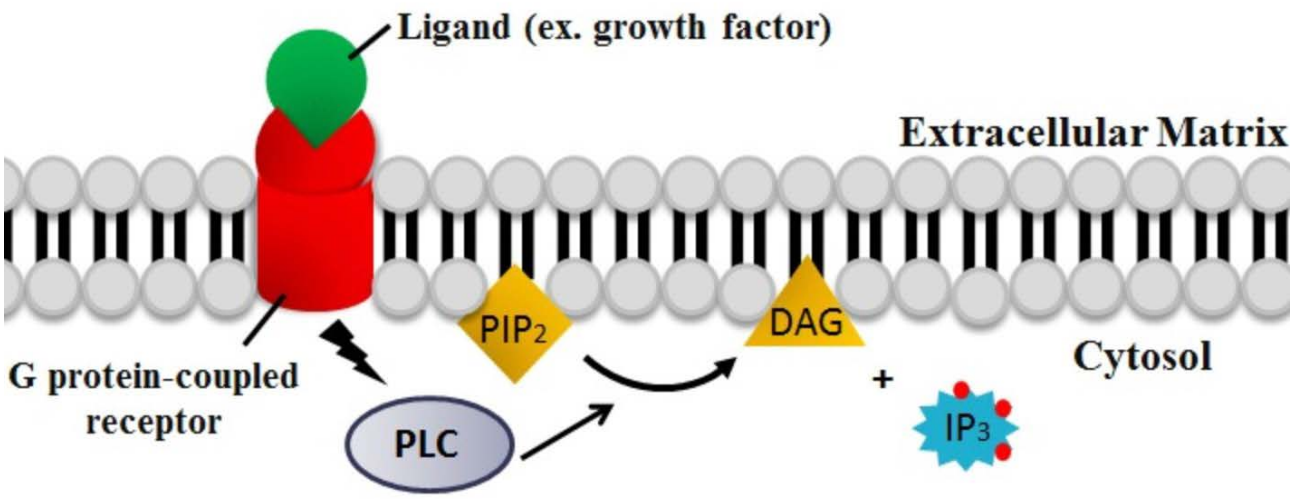
Related Glossary Terms

Drag related terms here

IP3/DAG System

The two products of the Phospholipase C (PLC) catalyzed reaction, DAG and IP3, are important second messengers that control diverse cellular processes and are substrates for synthesis of other important signaling molecules. When PIP2 is cleaved, DAG remains bound to the membrane, and IP3 is released as a soluble structure into the cytosol. IP3 then diffuses through the cytosol to bind to IP3 receptors, particularly calcium channels in the smooth endoplasmic reticulum (ER). This causes the cytosolic concentration of calcium to increase, causing a cascade of intracellular changes and activity.

In addition, calcium and DAG together work to activate protein kinase C, which goes on to phosphorylate other molecules, leading to altered cellular activity. End-effects include taste, tumor promotion, as well as vesicle exocytosis, superoxide production from NADPH oxidase, and JNK activation.



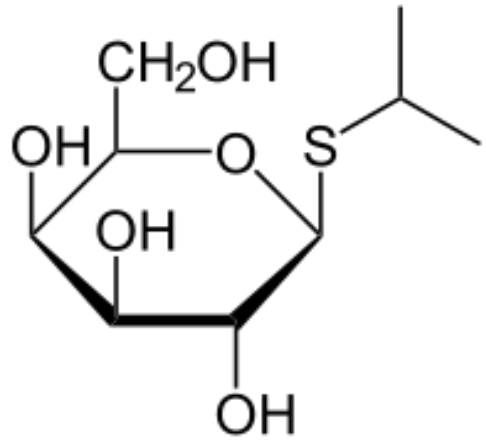
https://en.wikipedia.org/wiki/Phospholipase_C#Effects

Related Glossary Terms

IPTG

Isopropyl β-D-1-thiogalactopyranoside (IPTG, also known as lad-y) is a molecular biology reagent. This compound is a molecular mimic of allolactose, a lactose metabolite that triggers transcription of the lac operon, and it is therefore used to induce protein expression where the gene is under the control of the lac operator.

IPTG is an effective inducer of protein expression in the concentration range of 100 µM to 1.0 mM. Concentration used depends on the strength of induction required, as well as the genotype of cells or plasmid used. If lacIq, a mutant that over-produces the lac repressor, is present, then a higher concentration of IPTG may be necessary.



https://en.wikipedia.org/wiki/Isopropyl_ β-D-1-thiogalactopyranoside

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IRE-binding Protein

ACO1, or IRP1, is a bifunctional protein that functions as an iron-responsive element (IRE)-binding protein involved in the control of iron metabolism by binding mRNA to repress translation or degradation. It functions also as the cytoplasmic isoform of aconitase. Aconitases are iron-sulfur proteins that require a 4Fe-4S cluster for their enzymatic activity, in which they catalyze conversion of citrate to isocitrate.

Cells have advanced mechanisms for sensing their own need for iron. In human cells, the best-characterized iron-sensing mechanism is the result of post-transcriptional regulation of mRNA (the chemical instructions derived from DNA genes to make proteins). Sequences of mRNA called iron-responsive elements (IREs) are contained within the mRNA sequences that code for transferrin receptors and for ferritin. Iron-responsive element-binding protein (IRE-BP) binds to these mRNA sequences. On its own, the IRE-BP binds to the IREs of ferritin and transferrin receptor mRNA. But, when iron binds to the IRE-BP, the IRE-BP changes shape with the result that the IRE-BPs can no longer bind the ferritin mRNA. This liberates the mRNA to direct the cell to make more ferritin. In other words, when there is high iron in the cell, the iron itself causes the cell to produce more iron storage molecules.

Transferrin receptor production depends on a similar mechanism. But this one has the opposite trigger, and the opposite ultimate effect. IRE-BPs without iron bind to the IREs on transferrin receptor mRNA. But those IREs have a different effect: When the IRE-BP binds to these sites, the binding not only allows for translation but also stabilizes the mRNA molecule so it can stay intact for longer.

In low-iron conditions, IRE-BPs allow the cell to keep producing transferrin receptors. And more transferrin receptors make it easier for the cell to bring in more iron from transferrin-iron complexes circulating outside the cell. But, as iron binds to more and more IRE-BPs, they change shape and unbind the transferrin receptor mRNA. The transferrin receptor mRNA is rapidly degraded without the IRE-BP attached to it. The cell stops producing transferrin receptors.

When the cell has obtained more iron than it can bind up with ferritin or heme molecules, more and more iron will bind to the IRE-BPs. That will stop transferrin receptor production. And iron-IRE-BP binding will also start ferritin production.
When the cell is low on iron, less and less iron will bind to IRE-BPs. The IRE-BPs without iron will bind to transferrin receptor mRNA.

https://en.wikipedia.org/wiki/Iron-responsive_element-binding_protein

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Iron

Iron is a chemical element with symbol Fe (from Latin: ferrum) and atomic
26. It is a metal in the first transition series. It is by mass the most commor
on Earth, forming much of Earth's outer and inner core. It is the fourth mo
element in the Earth's crust.

Iron is a micronutrient important for production of heme, iron sulfur prote
tochromes. Its two oxidation states (Fe^{++} and Fe^{+++}) allow iron to perform
transfers in the electron transport system.

https://en.wikipedia.org/wiki/Iron

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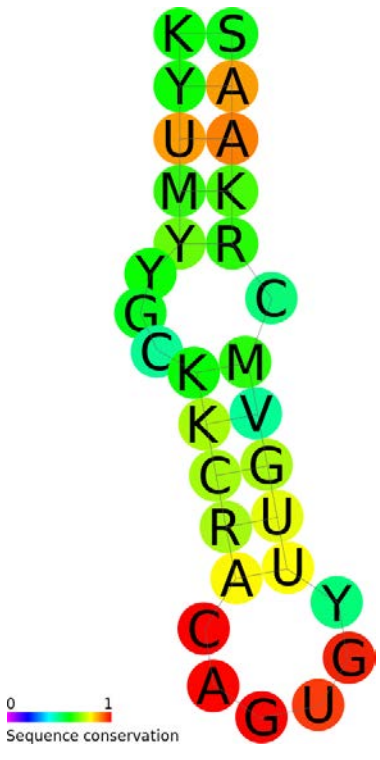
Chapter 2 - Structure and Function: Proteins

Iron Response Element

The Iron response element or Iron-responsive element (IRE) is a short conserved stem-loop which is bound by iron response proteins (IRPs, also named IRE-BP or IRBP). The IRE is found in UTRs (untranslated regions) of various mRNAs whose products are involved in iron metabolism. For example, the mRNA of ferritin (an iron storage protein) contains one IRE in its 5' UTR. When iron concentration is low, IRPs bind the IRE in the ferritin mRNA and cause reduced translation rates. In contrast, binding to multiple IREs in the 3' UTR of the transferrin receptor (involved in iron acquisition) leads to increased mRNA stability.

In high iron conditions in humans, IRP1 binds with an iron-sulphur complex [4Fe-4S] and adopts an aconitase conformation unsuitable for IRE binding. In contrast, IRP2 is degraded in high iron conditions. There is variation in affinity between different IREs and different IRPs. Some IREs can also be affected by alternative gene splicing.

The upper helix of the known IREs shows stronger conservation of structure compared to the lower helix. The bases composing the helixes are variable. The mid-stem bulged C is a highly characteristic feature (though this has been seen to be a G in the ferritin IRE for lobster.) The apical loop of the known IREs all consist of either the AGA or AGU triplet. This is pinched by a paired G-C and there is additionally a bulged U, C or A in the upper helix. The crystal structure and NMR data show a bulged U in the lower stem of the ferritin IRE.

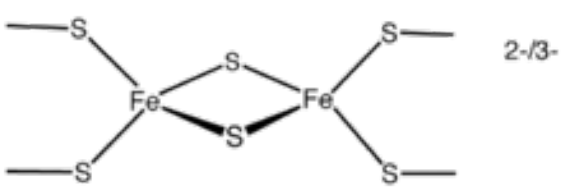


https://en.wikipedia.org/wiki/Iron_response_element

Iron-sulfur Centers

Iron–sulfur proteins are proteins characterized by the presence of iron–sulfur clusters containing sulfide-linked di-, tri-, and tetrairon centers in variable oxidation states. Iron–sulfur clusters are found in a variety of metalloproteins, such as the ferredoxins, as well as NADH dehydrogenase, hydrogenases, coenzyme Q – cytochrome c reductase, succinate – coenzyme Q reductase and nitrogenase. Iron–sulfur clusters are best known for their role in the oxidation-reduction reactions of mitochondrial electron transport.

Both Complex I and Complex II of oxidative phosphorylation have multiple Fe–S clusters. They have many other functions including catalysis as illustrated by aconitase, generation of radicals as illustrated by SAM-dependent enzymes, and as sulfur donors in the biosynthesis of lipoic acid and biotin. Additionally, some Fe–S proteins regulate gene expression. Fe–S proteins are vulnerable to attack by biogenic nitric oxide. In most Fe–S proteins, the terminal ligands on Fe are thiolate, but exceptions exist.



https://en.wikipedia.org/wiki/Iron–sulfur_protein

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Iron-sulfur Proteins

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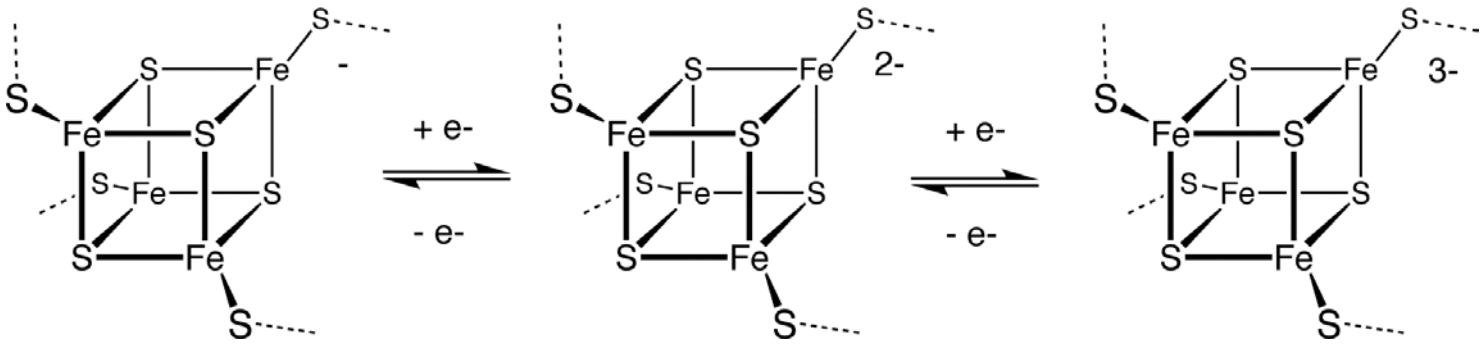
The prevalence of these proteins on the metabolic pathways of most organisms leads some scientists to theorize that iron–sulfur compounds had a significant role in the origin of life in the iron–sulfur world theory.



https://en.wikipedia.org/wiki/Iron–sulfur_protein

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IRS-1

Insulin receptor substrate 1 (IRS-1) is a signaling adapter protein that in hu
coded by the IRS-1 gene. It contains a single pleckstrin homology (PH) dom
N-terminus and a PTB domain ca. 40 residues downstream of this. Togethe
IRS_3 (pseudogene) and IRS4, it is homologous to the *Drosophila* protein ch
disruption extends the median lifespan of flies up to 48%. Similarly, Irs1 m
experience moderate life extension and delayed age-related pathologies.

https://en.wikipedia.org/wiki/IRS1

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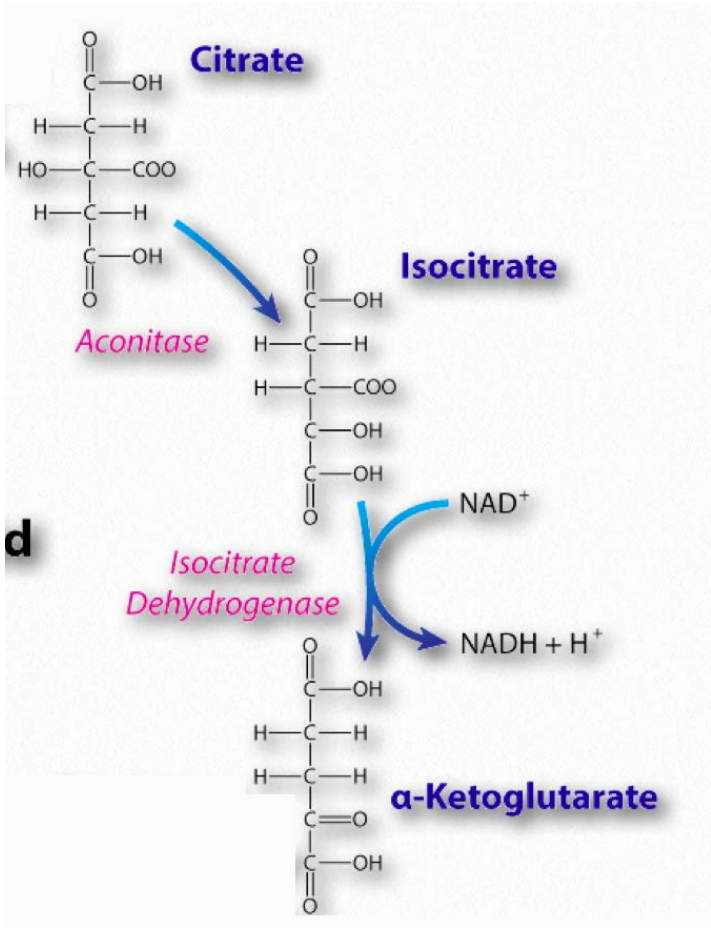
Chapter 2 - Structure and Function: Proteins

Isocitrate

Isocitric acid is an organic compound closely related to citric acid. Salts and esters of isocitric acid are known as isocitrates. The isocitrate anion is a substrate of the citric acid cycle. Isocitrate is formed from citrate with the help of the enzyme aconitase, and is acted upon by isocitrate dehydrogenase.



https://en.wikipedia.org/wiki/Isocitric_acid

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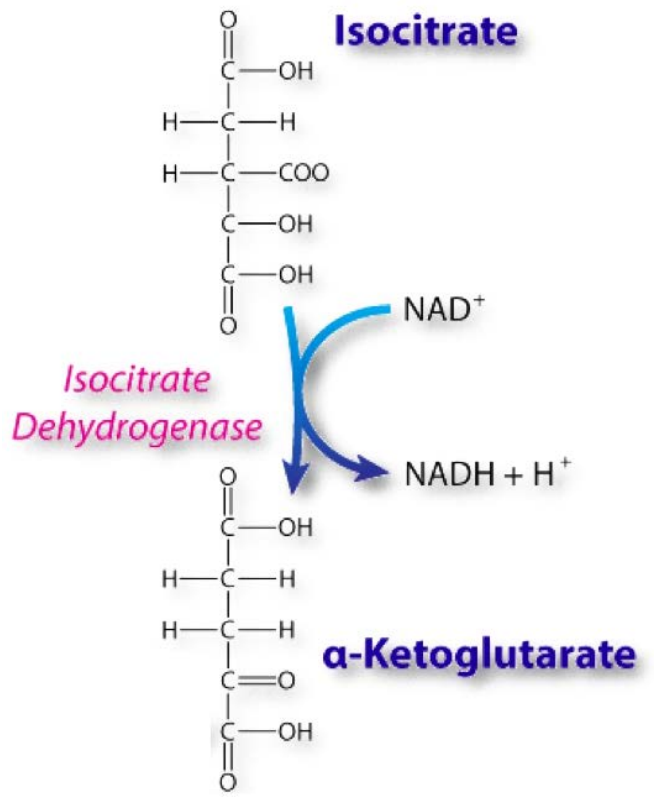
Isocitrate Dehydrogenase

Isocitrate dehydrogenase (IDH) (EC 1.1.1.42) and (EC 1.1.1.41) is an enzyme that catalyzes the oxidative decarboxylation of isocitrate, producing α-ketoglutarate (α-ketoglutarate) and CO_2. This is a two-step process, which involves oxidation of isocitrate (a secondary alcohol) to oxalosuccinate (a ketone), followed by the decarboxylation of the carboxyl group β to the ketone, forming α-ketoglutarate. In humans, IDH exists in three isoforms: IDH3 catalyzes the third step of the citric acid cycle while converting NAD^+ to NADH in the mitochondria. The isoforms IDH1 and IDH2 catalyze the same reaction outside the context of the citric acid cycle and use $NADP^+$ as a cofactor instead of NAD^+. They localize to the cytosol as well as the mitochondrion and peroxisome.



https://en.wikipedia.org/wiki/Isocitrate_dehydrogenase

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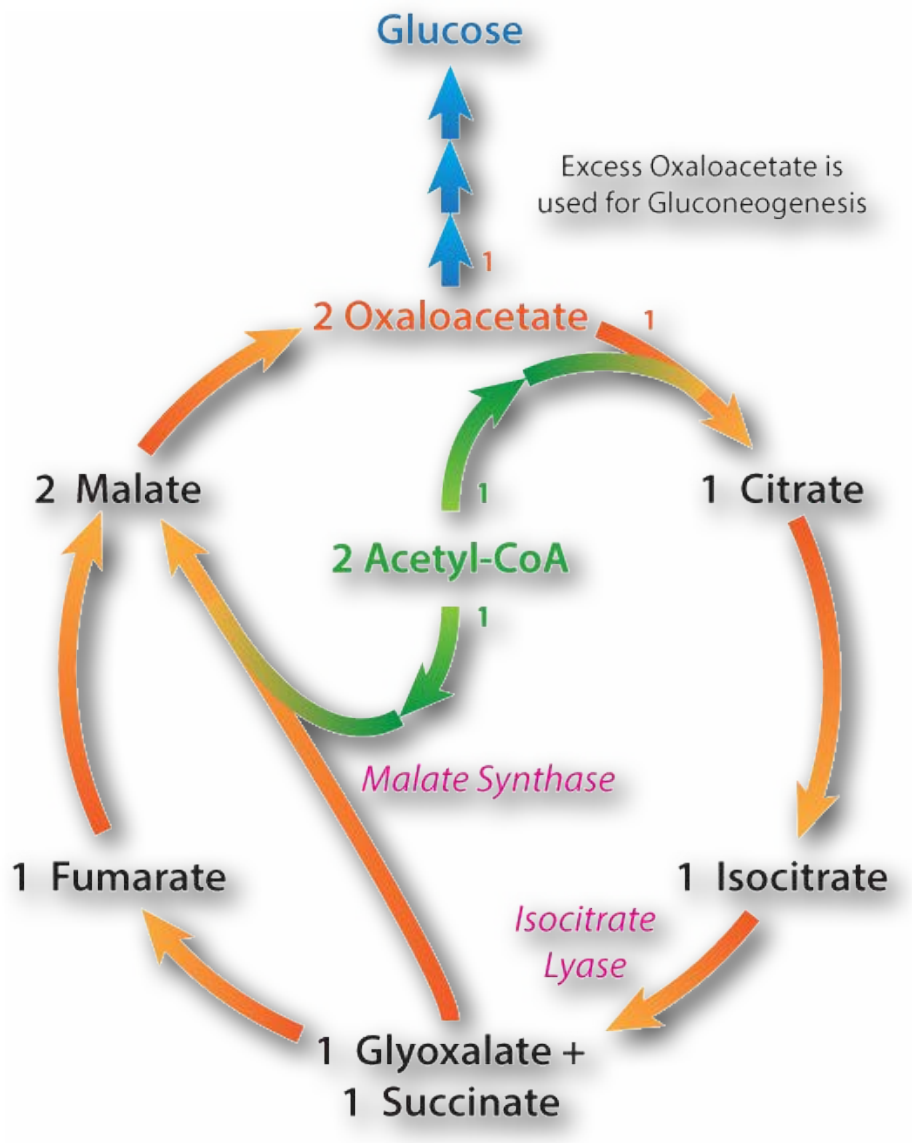
Isocitrate Lyase

Isocitrate lyase (EC 4.1.3.1), or ICL, is an enzyme in the glyoxylate cycle that catalyzes the cleavage of isocitrate to succinate and glyoxylate. Together with malate synthase, it bypasses the two decarboxylation steps of the citric acid cycle and is used by bacteria, fungi, and plants.



https://en.wikipedia.org/wiki/Isocitrate_lyase

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Isoelectric Focusing

Isoelectric focusing (IEF), also known as electrofocusing, is a technique for s
different molecules by differences in their isoelectric point (pI). It is a type o
trophoresis, usually performed on proteins in a gel, that takes advantage of
that overall charge on the molecule of interest is a function of the pH of its s
ings.

Isoelectric focusing is the first step in the technique of 2D gel electrophoresi

https://en.wikipedia.org/wiki/Isoelectric_focusing

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Isoelectric Point

The isoelectric point (pI, pH(I), IEP), is the pH at which a particular molecule carries no net electrical charge. The standard nomenclature to represent the isoelectric point is pH(I), although pI is also commonly seen. The net charge on a molecule is affected by pH of its surrounding environment and can become more positively or negatively charged due to the gain or loss, respectively, of protons (H^+).

The pI value can affect the solubility of a molecule at a given pH. Such molecules have minimum solubility in water or salt solutions at the pH that corresponds to their pI and often precipitate out of solution. Biological amphoteric molecules such as proteins contain both acidic and basic functional groups. Amino acids that make up proteins may be positive, negative, neutral, or polar in nature, and together give a protein its overall charge. At a pH below their pI, proteins carry a net positive charge. Above their pI they carry a net negative charge. Proteins can, thus, be separated by net charge in a polyacrylamide gel using either preparative gel electrophoresis or isoelectric focusing, which uses a pH gradient to separate proteins. Isoelectric focusing is also the first step in 2-D gel polyacrylamide gel electrophoresis.

https://en.wikipedia.org/wiki/Isoelectric_point

Related Glossary Terms

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Isoform

Protein isoforms, or "protein variants" are several different forms of protei
from the same gene. Through RNA splicing mechanisms in eukaryotic cells
mRNAs for the same gene can have different protein-coding segments (exo
different parts of exons from RNA joined together to form different mRNA
and thus different protein forms. Each unique sequence produces a specific
protein. Among all RNA splicing mechanisms, alternative splicing is the mo
nate one which is responsible for most of protein isoforms.

https://en.wikipedia.org/wiki/Protein_isoform

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nate one which is responsible for most of protein isoforms.

https://en.wikipedia.org/wiki/Protein_isoform

Related Glossary Terms

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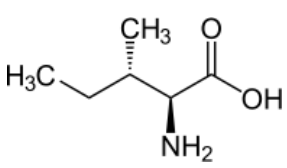
Isoleucine

Isoleucine (abbreviated as Ile or I) encoded by the codons AUU, AUC, and AUA is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $–NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $–COO^-$ form under biological conditions), and a hydrocarbon side chain, classifying it as a non-polar, uncharged(at physiological pH), aliphatic amino acid. It is essential in humans, meaning the body cannot synthesize it, and must be ingested in our diet. Isoleucine is synthesized from pyruvate employing leucine biosynthesis enzymes in other organisms such as bacteria.

Inability to break down isoleucine, along with other amino acids, is associated with the disease called Maple Syrup Urine Disease, which results in discoloration and a sweet smell in the patient's urine, which is where the name comes from. However in severe cases, MSUD can lead to damage to the brain cells and ultimately death.

Isoleucine is both a glucogenic and a ketogenic amino acid. After transamination with α-ketoglutarate the carbon skeleton can be converted into either Succinyl CoA, and fed into the TCA cycle for oxidation or converted into oxaloacetate for gluconeogenesis (hence glucogenic). It can also be converted into Acetyl CoA and fed into the TCA cycle by condensing with oxaloacetate to form citrate. In mammals Acetyl CoA cannot be converted back to carbohydrate but can be used in the synthesis of ketone bodies or fatty acids, hence ketogenic.

Biotin, sometimes referred to as Vitamin B_7 or Vitamin H, is an absolute requirement for the full catabolism of isoleucine (as well as leucine). Without adequate biotin, the human body will be unable to fully break down isoleucine and leucine molecules. This can lead to numerous physiological issues (related to muscle maintenance and protein synthesis, lipid metabolism, and fatty acid metabolism) as well as cognitive issues resulting from general metabolic pathway failure and the irritating effects of hydroxyisovalerate, a byproduct of incomplete isoleucine catabolism. Isovaleric acidemia is an example of a disorder caused by incomplete catabolism of leucine.



https://en.wikipedia.org/wiki/Isoleucine

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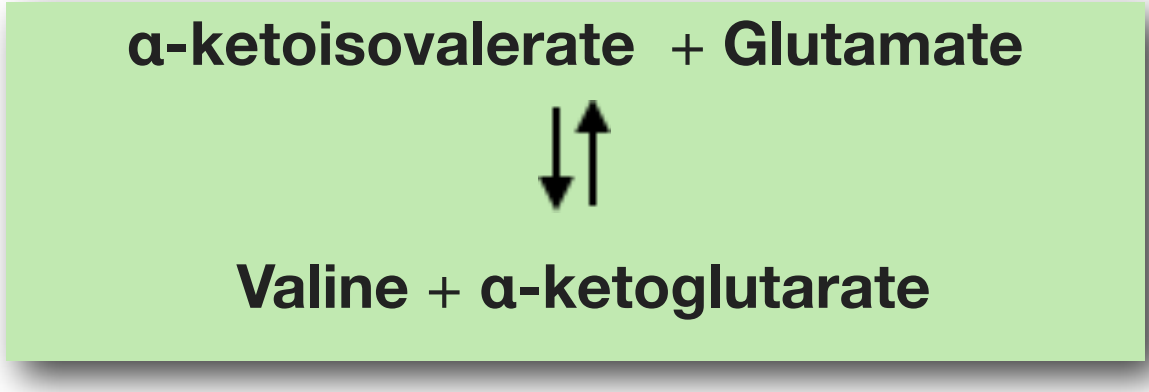
Isoleucine Aminotransferase

Isoleucine aminotranferase is a transaminase that catalyzes the last step in thesis of valine. It is shown below.



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Isomerase

Isomerases are a general class of enzymes which convert a molecule from one is
to another. Isomerases can either facilitate intramolecular rearrangements in w
bonds are broken and formed or they can catalyze conformational changes. The
eral form of such a reaction is as follows:

A–B → B–A

There is only one substrate yielding one product. This product has the same mo
formula as the substrate but differs in bond connectivity or spatial arrangement
Isomerases catalyze reactions across many biological processes, such as in glyco
and carbohydrate metabolism.

A good example of an isomerase is phosphoglucoisomerase from glycolysis, whi
terconverts glucose-6-phosphate and fructose-6-phosphate.

https://en.wikipedia.org/wiki/Isomerase

Related Glossary Terms

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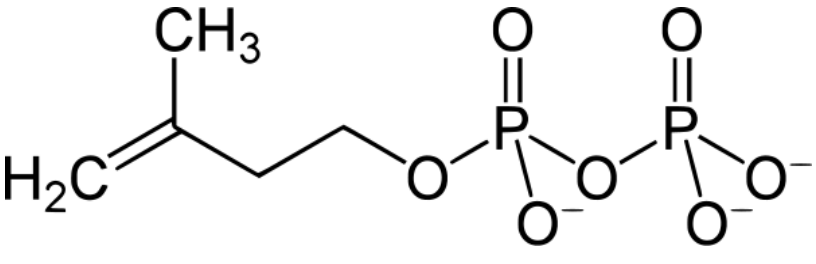
Isopentenyl Pyrophosphate

Isopentenyl pyrophosphate (IPP, isopentenyl diphosphate, or IDP) is an intermediate in the classical, HMG-CoA reductase pathway (commonly called the mevalonate pathway), and is used by organisms in the biosynthesis of terpenes and terpenoids. IPP is formed from acetyl-CoA via the mevalonate pathway (the "upstream" part), and then is isomerized to dimethylallyl pyrophosphate by the enzyme isopentenyl pyrophosphate isomerase.



https://en.wikipedia.org/wiki/Isopentenyl_pyrophosphate

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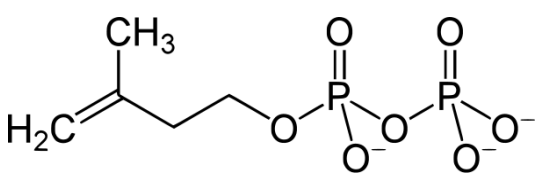
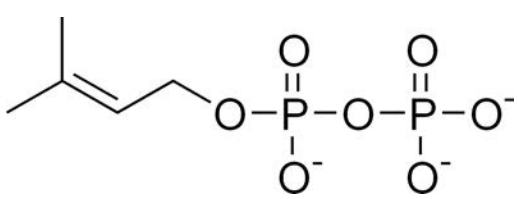
Isoprene

The isoprene skeleton can be found in naturally occurring compounds called terpenes (also known as isoprenoids), but these compounds do not arise from isoprene itself. Terpenes can be viewed as multiples of isoprene subunits, and this perspective is the cornerstone of the "isoprene rule". The precursor to isoprene units in biological systems is dimethylallyl pyrophosphate (DMAPP - bottom figure below) and its isomer isopentenyl pyrophosphate (IPP - top figure below). The plural “isoprenes” is sometimes used to refer to terpenes in general. Isoprene chains are commonly found in numerous biologically active oligomers such as Vitamin A. Similarly, natural rubber is composed of linear polyisoprene chains of very high molecular weight and other natural molecules.





https://en.wikipedia.org/wiki/Isoprene

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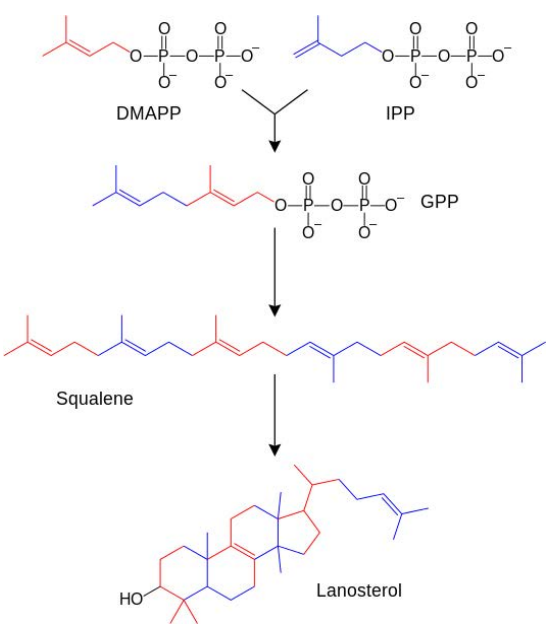
Isoprenoid

The terpenoids, sometimes called isoprenoids, are a large and diverse class of naturally occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways. Most are multicyclic structures that differ from one another not only in functional groups but also in their basic carbon skeletons. These lipids can be found in all classes of living things, and are the largest group of natural products. About 60% of known natural products are terpenoids.

Plant terpenoids are used extensively for their aromatic qualities and play a role in traditional herbal remedies. Terpenoids contribute to the scent of eucalyptus, the flavors of cinnamon, cloves, and ginger, the yellow color in sunflowers, and the red color in tomatoes. Well-known terpenoids include citral, menthol, camphor, salvinorin A in the plant Salvia divinorum, the cannabinoids found in cannabis, ginkgolide and bilobalide found in Ginkgo biloba, and the curcuminoids found in turmeric and mustard seed.

The steroids and sterols in animals are biologically produced from terpenoid precursors. Sometimes terpenoids are added to proteins, e.g., to enhance their attachment to the cell membrane; this is known as isoprenylation.

A simplified isopreonid synthesis pathway is below.



https://en.wikipedia.org/wiki/Terpenoid

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Isopropylmalate Dehydratase

Isopropylmalate dehydratse catalyzes the reaction below in the biosynthesi
The enzyme is an aconitase analog and accomplishes its catalysis via dehyd

α-isopropylmalate

β-isopropylmalate.

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Isopropylmalate Dehydrogenase

3-Isopropylmalate dehydrogenase (EC 1.1.1.85) is an enzyme that catalyzes the
cal reactions below. The enzyme catalyzes a reaction in the biosynthesis of vali
leucine shown in green at the bottom. It is the third reaction shown in the list.

(2R,3S)-3-isopropylmalate + NAD^+ <=> 4-methyl-2-oxopentanoate + CO_2 + N
(2R,3S)-3-isopropylmalate + NAD^+ <=> (2S)-2-isopropyl-3-oxosuccinate + H
NADH
(2S)-2-isopropyl-3-oxosuccinate + H^+ <=> 4-methyl-2-oxopentanoate + CO_2

β-isopropylmalate + NAD^+

α-ketoisocaproate + NADH

https://en.wikipedia.org/wiki/3-Isopropylmalate_dehydrogenase

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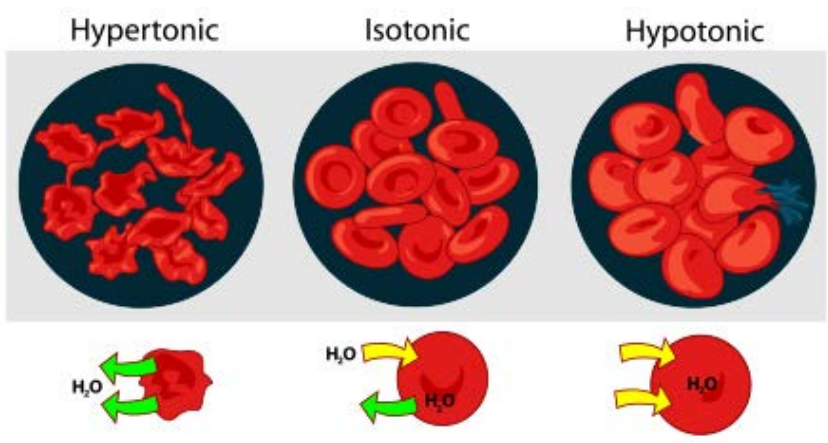
Related Glossary Terms

Drag related terms here

Isotonic

An isotonic solution is one in which its effective osmole concentration is the same as the solute concentration of a cell. In this case the cell neither swells nor shrinks because there is no concentration gradient for water across the cell membrane. Water molecules diffuse through the plasma membrane in both directions, and as the rate of water diffusion is the same in each direction that cell will neither gain nor lose water. An ISO-osmolar solution can be hypotonic if the solute is able to penetrate the cell membrane. For example an ISO-osmolar urea solution is hypotonic to red blood cells causing their lysis. This is due to urea entering the cell down its concentration gradient followed by water. For example, the osmolarity of normal saline, 9 grams NaCl dissolved in water to a total volume of one litre, is a close approximation to the osmolarity of NaCl in blood (about 290 mOsm/L). Thus, normal saline is almost isotonic to blood plasma. Both sodium and chloride ions cannot freely pass through the plasma membrane as opposed to urea.



https://en.wikipedia.org/wiki/Tonicity#Isotonicity

Related Glossary Terms

Drag related terms here

Isozyme

Isozymes (also known as isoenzymes or more generally as multiple forms of enz
are enzymes that differ in amino acid sequence but catalyze the same chemical
tion. These enzymes usually display different kinetic parameters (e.g. different
ues), or different regulatory properties. The existence of isozymes permits the f
tuning of metabolism to meet the particular needs of a given tissue or developm
stage (for example lactate dehydrogenase (LDH)).

In biochemistry, isozymes (or isoenzymes) are isoforms (closely related variant
zymes. In many cases, they are coded for by homologous genes that have diverg
time. Although, strictly speaking, allozymes represent enzymes from different a
the same gene, and isozymes represent enzymes from different genes that proc
catalyze the same reaction, the two words are usually used interchangeably.

https://en.wikipedia.org/wiki/Isozyme

Related Glossary Terms

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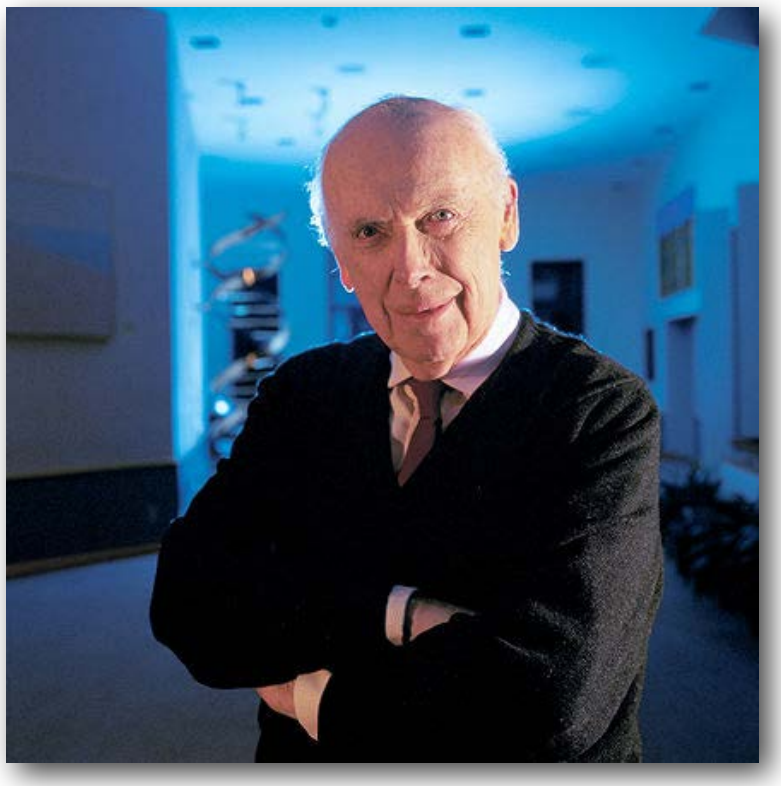
Chapter 6 - Metabolism: Nucleotides

James Watson

James Dewey Watson (born April 6, 1928) is an American molecular biologist, geneticist and zoologist, best known as one of the co-discoverers of the structure of DNA in 1953 with Francis Crick. Watson, Crick, and Maurice Wilkins were awarded the 1962 Nobel Prize in Physiology or Medicine "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material".



https://en.wikipedia.org/wiki/James_Watson

Related Glossary Terms

Drag related terms here

Jun-B

Transcription factor jun-B is a protein that in humans is encoded by the JU
Transcription factor jun-B is a transcription factor involved in regulating ge
following the primary growth factor response. It binds to the DNA sequenc
TGA[CG]TCA-3'.

https://en.wikipedia.org/wiki/JUNB

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Chapter 2 - Structure and Function: Proteins

Junk DNA

Junk DNA is term given originally to describe the large number of sequences in non-coding eukaryotic DNA for which no function was apparent.

According to T. Ryan Gregory, a genomic biologist, the first explicit discussion of the nature of junk DNA was done by David Comings in 1972 and he applied the term to all noncoding DNA. The term was formalized in 1972 by Susumu Ohno, who noted that the mutational load from deleterious mutations placed an upper limit on the number of functional loci that could be expected given a typical mutation rate. Ohno hypothesized that mammal genomes could not have more than 30,000 loci under selection before the "cost" from the mutational load would cause an inescapable decline in fitness, and eventually extinction. This prediction remains robust, with the human genome containing approximately 20,000 genes. Another source for Ohno's theory was the observation that even closely related species can have widely (orders-of-magnitude) different genome sizes, which had been dubbed the C-value paradox in 1971.

Though the fruitfulness of the term "junk DNA" has been questioned on the grounds that it provokes a strong a priori assumption of total non-functionality and though some have recommended using more neutral terminology such as "noncoding DNA" instead. "Junk DNA" remains a label for the portions of a genome sequence for which no discernible function has been identified and that through comparative genomics analysis appear under no functional constraint suggesting that the sequence itself has provided no adaptive advantage.

Since the late 70s it has become apparent that the majority of non-coding DNA in large genomes finds its origin in the selfish amplification of transposable elements, of which W. Ford Doolittle and Carmen Sapienza in 1980 wrote in the journal Nature: "When a given DNA, or class of DNAs, of unproven phenotypic function can be shown to have evolved a strategy (such as transposition) which ensures its genomic survival, then no other explanation for its existence is necessary." The amount of junk DNA can be expected to depend on the rate of amplification of these elements and the rate at which non-functional DNA is lost. In the same issue of Nature, Leslie Orgel and Francis Crick wrote that junk DNA has "little specificity and conveys little or no selective advantage to the organism". The term occurs mainly in popular science and in a colloquial way in scientific publications, and it has occasionally[quantify] been suggested that its connotations may have delayed interest in the biological functions of noncoding DNA.

Several lines of evidence indicate that some "junk DNA" sequences are likely to have unidentified functional activity and that the process of exaptation of fragments of originally selfish or non-functional DNA has been commonplace throughout evolution. In 2012, the ENCODE project, a research program supported by the National Human Genome Research Institute, reported that 76% of the human genome's noncoding DNA sequences were transcribed and that nearly half of the genome was in some way accessible to genetic regulatory proteins such as transcription factors.

However, the suggestion by ENCODE that over 80% of the human genome is biochemically functional has been criticized by other scientists, who argue that neither accessibility of segments of the genome to transcription factors nor their transcription guarantees that those segments have biochemical function and that their transcription is selectively advantageous. Furthermore, the much lower estimates of functionality prior to ENCODE were based on genomic conservation estimates across mammalian lineages.

Kallikrein

Kallikreins are a subgroup of serine proteases, enzymes capable of cleaving
bonds in proteins. In humans, plasma kallikrein (KLKB1) has no known pa
while tissue kallikrein-related peptidases (KLKs) encode a family of fifteen
lated serine proteases. These genes are localized to chromosome 19q13, for
largest contiguous cluster of proteases within the human genome. Kallikrei
sponsible for the coordination of various physiological functions including
sure, semen liquefaction and skin desquamation.

https://en.wikipedia.org/wiki/Kallikrein

Related Glossary Terms

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K_{cat}

In enzymology, turnover number (also termed k_{cat}) is defined as the maxim
of chemical conversions of substrate molecules per second that a single cata
will execute for a given enzyme concentration. It can be calculated from th
reaction rate and catalyst site concentration as follows:

$K_{cat} = V_{max}/[E_t]$,

where $[E_t]$ is the total enzyme concentration.

For example, carbonic anhydrase has a turnover number of 400,000 to 600
which means that each carbonic anhydrase molecule can produce up to 600
cules of product (bicarbonate ions) per enzyme molecule per second.

Related Glossary Terms

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K_{cat} / K_m

In the field of biochemistry, K_{cat}/K_m (also called the specificity constant or kine
ciency), is a measure of how efficiently an enzyme converts substrates into proc
comparison of specificity constants can also be used as a measure of the prefere
an enzyme for different substrates (i.e., substrate specificity). The higher the sp
constant, the more the enzyme "prefers" that substrate.

For a kinetically perfect enzyme, every encounter between enzyme and substra
to product and hence the reaction velocity is only limited by the rate the enzym
counters substrate in solution. Hence the upper limit for is equal to rate of sub
diffusion which is between10^8 and 10^9 $s^{-1}M^{-1}$

https://en.wikipedia.org/wiki/Specificity_constant

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K_d

In studying proteins and ligands, it is important to understand the “tightness” with which a protein (P) “holds onto” a ligand (L). This is measured with the dissociation constant (K_d).

The formation of a ligand-protein complex LP occurs as

$$L + P <=> LP$$

The dissociation of the complex, therefore, is the reverse of this, or

$$LP <=> L + P$$

so the corresponding dissociation constant is defined as

$$K_d = [L][P]/[LP]$$

where [L], [P], and [LP] are the molar concentrations of the protein, ligand and the complex when they are joined together.

Smaller values of K_d indicate tight binding, whereas larger values indicate loose binding. The dissociation constant is the inverse of the association constant.

$$K_a = 1/K_d$$

Where multiple molecules bond together, such as

$$JxKy <=> xJ + yK$$

(complex JxKy is breaking down down into x subunits of J and y subunits of K)

the dissociation constant is then defined as

$$K_d = [J]^x[K]^y/[JxKy]$$

where [J], [K], and [JxKy] are the concentrations of J, K, and the complex JxKy, respectively.

K_{eq}

The equilibrium constant, K_{eq}, of a chemical reaction is the value of the rea
tient when the reaction has reached equilibrium. An equilibrium constant v
pendent of the analytical concentrations of the reactant and product specie
ture, but depends on temperature and on ionic strength. Known equilibriu
values can be used to determine the composition of a system at equilibrium

For a reaction [A] <=> [B],

K_{eq} = [B]/[A]

https://en.wikipedia.org/wiki/Equilibrium_constant

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Keratan Sulfate

Keratan sulfate (KS), also called keratosulfate, is any of several sulfated gly
glycans (structural carbohydrates) that have been found especially in the co
lage, and bone. It is also synthesized in the central nervous system where it
pates both in development and in the glial scar formation following an inju
sulfates are large, highly hydrated molecules which in joints can act as a cus
sorb mechanical shock.

https://en.wikipedia.org/wiki/Keratan_sulfate

Related Glossary Terms

Drag related terms here

Keratins

Keratin is one of a family of fibrous structural proteins. Keratin is the prote
tects epithelial cells from damage or stress that has potential to kill the cell.
key structural material making up the outer layer of human skin. It is the k
tural component of hair and nails, and it provides the necessary strength ar
ness for masticatory organs, such as the tongue and the hard palate. Keratin
mers assemble into bundles to form intermediate filaments, which are toug
strong unmineralized tissues found in reptiles, birds, amphibians, and man
only other biological matter known to approximate the toughness of keratin
is chitin.

https://en.wikipedia.org/wiki/Keratin

Related Glossary Terms

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Ketogenic

Ketogenesis is the biochemical process by which organisms produce a grou
stances collectively known as ketone bodies by the breakdown of fatty acids
ess supplies energy to certain organs (particularly the brain) under circums
as fasting, but insufficient ketogenesis can cause hypoglycemia and excessiv
tion of ketone bodies leads to a dangerous state known as ketoacidosis.

https://en.wikipedia.org/wiki/Ketogenesis

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Ketogenic Diet

The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet th
cine is used primarily to treat difficult-to-control (refractory) epilepsy in ch
diet forces the body to burn fats rather than carbohydrates.

Normally, the carbohydrates contained in food are converted into glucose, w
then transported around the body and is particularly important in fueling b
function. However, if there is very little carbohydrate in the diet, the liver co
into fatty acids and ketone bodies. The ketone bodies pass into the brain an
glucose as an energy source. An elevated level of ketone bodies in the blood
known as ketosis, leads to a reduction in the frequency of epileptic seizures

https://en.wikipedia.org/wiki/Ketogenic_diet

Related Glossary Terms

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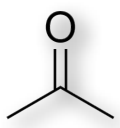
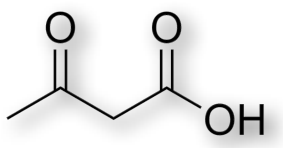
Ketone Bodies

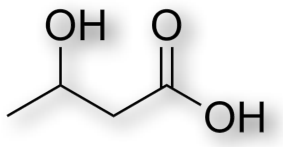
Ketone bodies are three water-soluble molecules (acetoacetate, β-hydroxybutyrate, and their spontaneous breakdown product, acetone) that are produced by the liver from fatty acids during periods of low food intake (fasting), carbohydrate restrictive diets, starvation, prolonged intense exercise, or in untreated (or inadequately treated) type 1 diabetes mellitus. These ketone bodies are readily picked up by the extra-hepatic tissues, and converted into acetyl-CoA which then enters the citric acid cycle and is oxidized in the mitochondria for energy.

In the brain, ketone bodies are also used to make acetyl-CoA into long-chain fatty acids. The latter cannot be obtained from the blood, because they cannot pass through the blood–brain barrier.

Three ketone bodies are depicted below. From top to bottom, they are acetone, acetoacetate, and β-hydroxybutyrate.







https://en.wikipedia.org/wiki/Ketone_bodies

Related Glossary Terms

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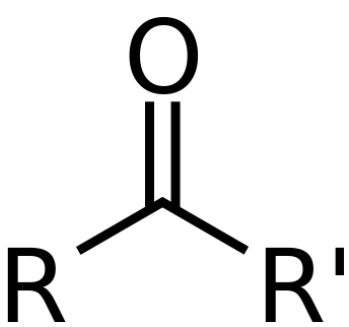
Ketones

In chemistry, a ketone is an organic compound with the structure RC(=O)R', where R and R' can be a variety of carbon-containing substituents. Ketones and aldehydes are simple compounds that contain a carbonyl group (a carbon-oxygen double bond). They are considered "simple" because they do not have reactive groups like –OH or –Cl attached directly to the carbon atom in the carbonyl group, as in carboxylic acids containing –COOH. Many ketones are known and many are of great importance in industry and in biology. Examples include many sugars (ketoses) and the industrial solvent acetone, which is the smallest ketone.



https://en.wikipedia.org/wiki/Ketone

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Ketose

A ketose is a monosaccharide containing one ketone group per molecule. With three carbon atoms, dihydroxyacetone is the simplest of all ketoses ar only one having no optical activity. Ketoses can isomerize into an aldose wh bonyl group is located at the end of the molecule. Such ketoses are reducing Fructose is the most common ketose.

https://en.wikipedia.org/wiki/Ketose

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Ketosis

Ketosis is a metabolic state in which most of the body's energy supply comes from ketone bodies in the blood, in contrast to a state of glycolysis in which blood glucose provides most of the energy. Ketosis is generally better known to the laypeople as acetone breath - a common symptom of progressing diabetes mellitus type II advanced stage. It is characterized by serum concentrations of ketone bodies over 0.5 mM, with low and stable levels of insulin and blood glucose. The condition is almost always generalized with hyperketonemia, that is, an elevated level of ketone bodies in the blood throughout the body.

Ketone bodies are formed by ketogenesis when liver glycogen stores are depleted (or from metabolizing medium-chain triglycerides). The main ketone bodies used for energy are acetoacetate and β-hydroxybutyrate, and the levels of ketone bodies are regulated mainly by insulin and glucagon. Most cells in the body can use both glucose and ketone bodies for fuel, and during ketosis, free fatty acids and glucose synthesis (gluconeogenesis) fuel the remainder.

Longer-term ketosis may result from fasting or staying on a low-carbohydrate diet, and deliberately induced ketosis serves as a medical intervention for intractable epilepsy. In glycolysis, higher levels of insulin promote storage of body fat and block release of fat from adipose tissues, while in ketosis, fat reserves are readily released and consumed. For this reason, ketosis is sometimes referred to as the body's "fat burning" mode.

https://en.wikipedia.org/wiki/Ketosis

Related Glossary Terms

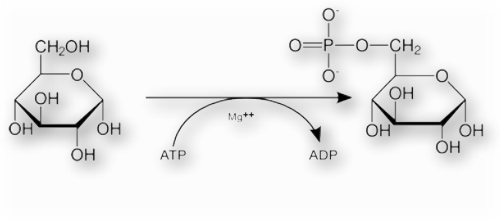
Kinase

A kinase is an enzyme that catalyzes the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific substrates. This process is known as phosphorylation, where the substrate gains a phosphate group and the high-energy ATP molecule donates a phosphate group. This transesterification produces a phosphorylated substrate and ADP. Conversely, it is referred to as dephosphorylation when the phosphorylated substrate donates a phosphate group and ADP gains a phosphate group (producing a dephosphorylated substrate and the high energy molecule of ATP). These two processes, phosphorylation and dephosphorylation, occur four times during glycolysis.

Kinases are part of the larger family of phosphotransferases. Kinases are not to be confused with phosphorylases, which catalyze the addition of inorganic phosphate groups to an acceptor, nor with phosphatases, which remove phosphate groups. The phosphorylation state of a molecule, whether it be a protein, lipid, or carbohydrate, can affect its activity, reactivity, and its ability to bind other molecules. Therefore, kinases are critical in metabolism, cell signaling, protein regulation, cellular transport, secretory processes, and many other cellular pathways.

Kinases mediate the transfer of a phosphate moiety from a high energy molecule (such as ATP) to their substrate molecule, as seen in the figure below. Kinases are needed to stabilize this reaction because the phosphoanhydride bond contains a high level of energy. Kinases properly orient their substrate and the phosphoryl group within their active sites, which increases the rate of the reaction. Additionally, they commonly use positively charged amino acid residues, which electrostatically stabilize the transition state by interacting with the negatively charged phosphate groups. Alternatively, some kinases utilize bound metal cofactors in their active sites to coordinate the phosphate groups.

Kinases are used extensively to transmit signals and regulate complex processes in cells. Phosphorylation of molecules can enhance or inhibit their activity and modulate their ability to interact with other molecules. The addition and removal of phosphoryl groups provides the cell with a means of control because various kinases can respond to different conditions or signals. Mutations in kinases that lead to a loss-of-function or gain-of-function can cause cancer and disease in humans, including certain types of leukemia and neuroblastomas, glioblastoma, spinocerebellar ataxia (type 14), forms of agammaglobulinaemia, and many others.



https://en.wikipedia.org/wiki/Kinase

Related Glossary Terms

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Kinesin

A kinesin is a protein belonging to a class of motor proteins found in eukaryotic c

Kinesins move along microtubule (MT) filaments, and are powered by the hydrol
adenosine triphosphate (ATP) (thus kinesins are ATPases). The active movement
kinesins supports several cellular functions including mitosis, meiosis and transp
cellular cargo, such as in axonal transport. Most kinesins walk towards the positiv
of a microtubule, which, in most cells, entails transporting cargo such as protein a
membrane components from the center of the cell towards the periphery. This fo
transport is known as anterograde transport. In contrast, dyneins are motor prote
that move toward the microtubules' negative end.

https://en.wikipedia.org/wiki/Kinesin

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K_m

The Michaelis constant K_m is the substrate concentration at which the reaction rate is half of V_{max} and is an inverse measure of the substrate's affinity for the enzyme—as a small K_m indicates high affinity, meaning that the rate will approach with lower than those reactions with a larger. The value of K_m is dependent on both the enzyme and the substrate, as well as conditions such as temperature and pH.

For an enzymatic reaction obeying Michaelis-Menten kinetics,

$$v = \frac{d[P]}{dt} = \frac{V_{\mathbf{max}}[S]}{K_{\mathrm{M}} + [S]}.$$

This equation is called Michaelis–Menten equation. Here, V_{max} represents the maximum rate achieved by the system, at maximum saturation of the substrate concentration. The Michaelis constant K_M is the substrate concentration at which the reaction rate is half of . Biochemical reactions involving a single substrate are often assumed to follow Michaelis–Menten kinetics, without regard to the model's underlying assumptions.

https://en.wikipedia.org/wiki/Michaelis–Menten_kinetics

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Kozak Sequence

The Kozak consensus sequence, Kozak consensus or Kozak sequence, is a sequence which occurs on eukaryotic mRNA and has the consensus (gcc)gccRccAUGG. The Kozak consensus sequence plays a major role in the initiation of the translation process. The sequence was named after the person who brought it to prominence, Marilyn Kozak.

This sequence on an mRNA molecule is recognized by the ribosome as the translational start site, from which a protein is coded by that mRNA molecule. The ribosome requires this sequence, or a possible variation (see below) to initiate translation. The Kozak sequence is not to be confused with the ribosomal binding site (RBS), that being either the 5' cap of a messenger RNA or an Internal ribosome entry site (IRES).

In vivo, this site is often not matched exactly on different mRNAs and the amount of protein synthesized from a given mRNA is dependent on the strength of the Kozak sequence. Some nucleotides in this sequence are more important than others. The AUG is most important because it is the actual initiation codon encoding a methionine amino acid at the N-terminus of the protein. (Rarely, CUG is used as an initiation codon, encoding a leucine instead of the typical methionine.) The A nucleotide of the "AUG" is referred to as number 1. For a 'strong' consensus, the nucleotides at positions +4 (i.e. G in the consensus) and -3 (i.e. either A or G in the consensus) relative to the number 1 nucleotide must both match the consensus (there is no number 0 position). An 'adequate' consensus has only 1 of these sites, while a 'weak' consensus has neither. The cc at -1 and -2 are not as conserved, but contribute to the overall strength. There is also evidence that a G in the -6 position is important in the initiation of translation.

There are examples *in vivo* of each of these types of Kozak consensus, and they probably evolved as yet another mechanism of gene regulation. Lmx1b is an example of a gene with a weak Kozak consensus sequence. For initiation of translation from such a site, other features are required in the mRNA sequence in order for the ribosome to recognize the initiation codon.

https://en.wikipedia.org/wiki/Kozak_consensus_sequence

Related Glossary Terms

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Chapter 9 - Point by Point: Information Processing

Kuru

Kuru is an incurable degenerative neurological disorder endemic to tribal r
Papua New Guinea. It is a type of transmissible spongiform encephalopathy
a prion found in humans.

The term "kuru" derives from the Fore word "kuria/guria" ("to shake"), a re
the body tremors that are a classic symptom of the disease. It is also known
Fore as the "laughing sickness" due to the pathologic bursts of laughter peo
display when afflicted with the disease. It is now widely accepted that kuru
mitted among members of the Fore tribe of Papua New Guinea via funerary
ism.

https://en.wikipedia.org/wiki/Kuru_(disease)

Related Glossary Terms

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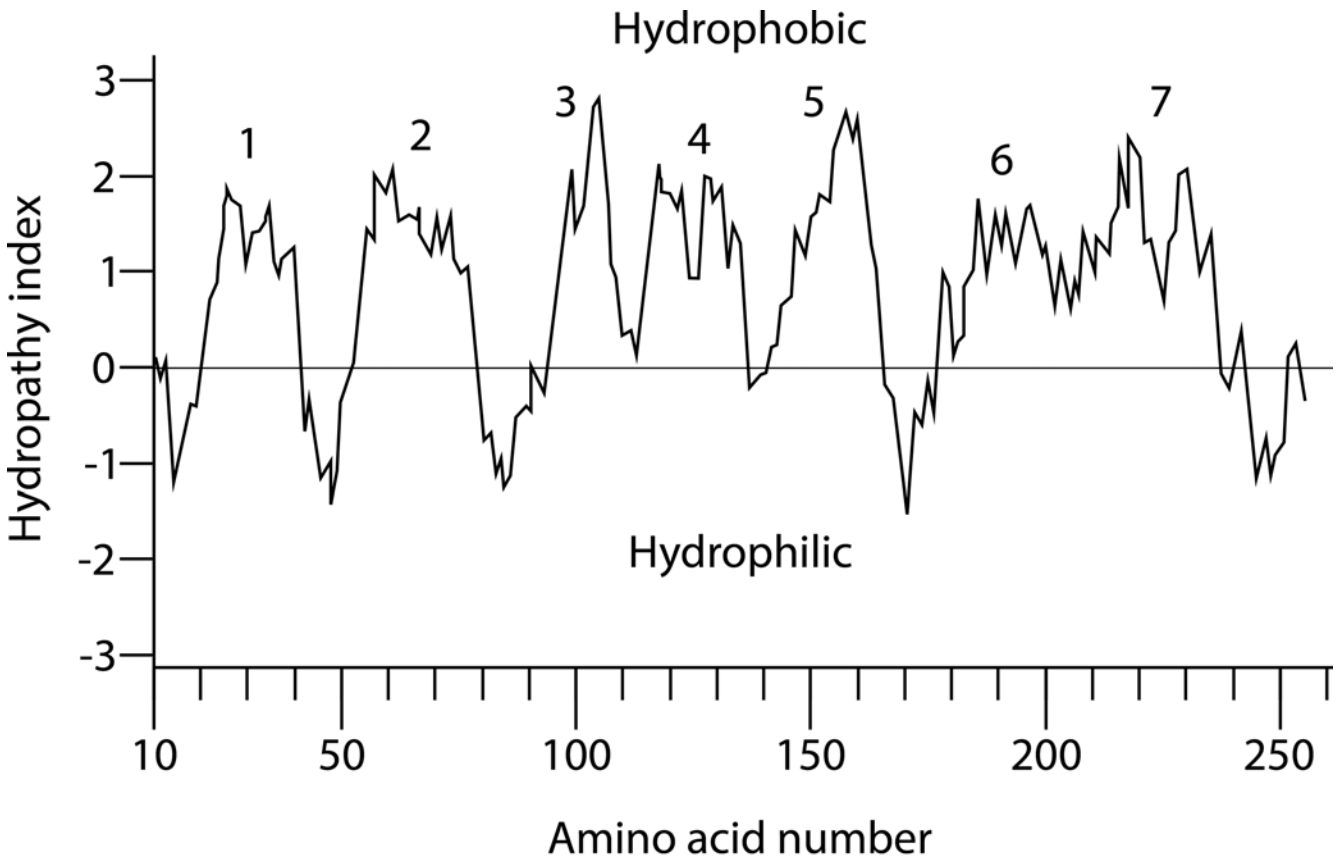
Chapter 2 - Structure & Function: Proteins I

Kyte-Doolittle

A hydrophilicity plot is a quantitative analysis of the degree of hydrophobicity or hydrophilicity of amino acids of a protein. It is used to characterize or identify possible structure or domains of a protein.

The plot has amino acid sequence of a protein on its x-axis, and degree of hydrophobicity and hydrophilicity on its y-axis. There is a number of methods to measure the degree of interaction of polar solvents such as water with specific amino acids. For instance, the Kyte-Doolittle scale indicates hydrophobic amino acids, whereas the Hopp-Woods scale measures hydrophilic residues.



Bacteriorhodopsin

https://en.wikipedia.org/wiki/Hydrophilicity_plot

L = T + W

Analysis of DNA topology uses three values:

L = linking number - the number of times one DNA strand wraps around the othe
is an integer for a closed loop and constant for a closed topological domain.

T = twist - total number of turns in the double stranded DNA helix. This will norm
tend to approach the number of turns that a topologically open double stranded D
helix makes free in solution: number of bases/10.5, assuming there are no interca
ing agents (e.g., ethidium bromide) or other elements modifying the stiffness of th
DNA.

W = writhe - number of turns of the double stranded DNA helix around the superl
cal axis

$L = T + W$ and $\Delta L = \Delta T + \Delta W$

https://en.wikipedia.org/wiki/Nucleic_acid_double_helix

Related Glossary Terms

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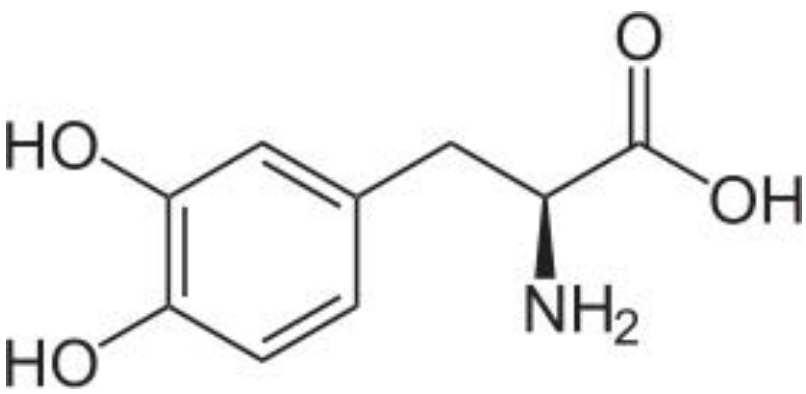
Chapter 2 - Structure and Function: Nucleic Acids

L-dopa

L-DOPA (alt., L-3,4-dihydroxyphenylalanine) is a chemical that is made and used as part of the normal biology of humans, some animals and plants. Some animals and humans make it via biosynthesis from the amino acid L-tyrosine. L-DOPA is the precursor to the neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) collectively known as catecholamines. Furthermore, L-DOPA itself mediates neurotrophic factor release by the brain and CNS. L-DOPA can be manufactured and in its pure form is sold as a psychoactive drug with the INN levodopa; trade names include Sinemet, Pharmacopa, Atamet, Stalevo, Madopar, and Prolopa. As a drug, it is used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia.



https://en.wikipedia.org/wiki/L-DOPA

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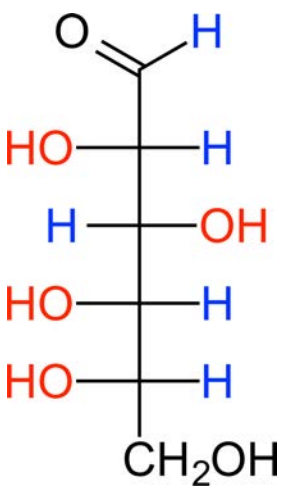
L-glucose

L-Glucose is an organic compound with formula $C_6H_{12}O_6$, specifically one of the aldo-hexose monosaccharides. As the L-isomer of glucose, it is the enantiomer of the more common D-glucose.

L-Glucose does not occur naturally in higher living organisms, but can be synthesized in the laboratory. L-Glucose is indistinguishable in taste from D-glucose, but cannot b used by living organisms as source of energy because it cannot be phosphorylated by hexokinase, the first enzyme in the glycolysis pathway.



https://en.wikipedia.org/wiki/L-Glucose

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Chapter 2 - Structure & Function: Carbohydrates

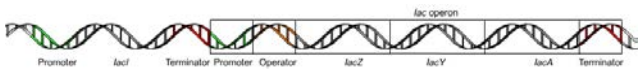
Lac operon

The lac operon (lactose operon) is an operon required for the transport and metabolism of lactose in *Escherichia coli* and many other enteric bacteria. Although glucose is the preferred carbon source for most bacteria, the lac operon allows for the effective digestion of lactose when glucose is not available.

Gene regulation of the lac operon was the first genetic regulatory mechanism to be understood clearly, so it has become a foremost example of prokaryotic gene regulation. It is often discussed in introductory molecular and cellular biology classes at universities for this reason.

The lac operon consists of three structural genes, and a promoter, a terminator, regulator, and an operator. The three structural genes are: lacZ, lacY, and lacA.
• lacZ encodes β-galactosidase (LacZ), an intracellular enzyme that cleaves the disaccharide lactose into glucose and galactose.
• lacY encodes lactose permease (LacY), a transmembrane symporter that pumps β-galactosides into the cell using a proton gradient in the same direction.
lacA encodes galactoside O-acetyltransferase (LacA), an enzyme that transfers an acetyl group from acetyl-CoA to β-galactosides.

Only lacZ and lacY appear to be necessary for lactose catabolism.



Specific control of the lac genes depends on the availability of the substrate lactose to the bacterium. The proteins are not produced by the bacterium when lactose is unavailable as a carbon source. The lac genes are organized into an operon. That is, they are oriented in the same direction immediately adjacent on the chromosome and are co-transcribed into a single polycistronic mRNA molecule. Transcription of all genes starts with the binding of the enzyme RNA polymerase (RNAP), a DNA-binding protein, which binds to a specific DNA binding site, the promoter, immediately upstream of the genes. Binding of RNA polymerase to the promoter is aided by the cAMP-bound catabolite activator protein (CAP, also known as the cAMP receptor protein). However, the lacI gene (regulatory gene for lac operon) produces a protein that blocks RNAP from binding to the promoter of the operon. This protein can only be removed when allolactose binds to it, and inactivates it. The protein that is formed by the lacI gene is known as the lac repressor. The type of regulation that the lac operon undergoes is referred to as negative inducible, meaning that the gene is turned off by the regulatory factor (lac repressor) unless some molecule (lactose) is added. Because of the presence of the lac repressor protein, genetic engineers who replace the lacZ gene with another gene will have to grow the experimental bacteria on agar with lactose available on it. If they do not, the gene they are trying to express will not be expressed as the repressor protein is still blocking RNAP from binding to the promoter and transcribing the gene. Once the repressor is removed, RNAP then proceeds to transcribe all three genes (lacZYA) into mRNA. Each of the three genes on the mRNA strand has its own Shine-Dalgarno sequence, so the genes are independently translated.The DNA sequence of the *E. coli* lac operon, the lacZYA mRNA, and the lacI genes are available from GenBank.

The first control mechanism is the regulatory response to lactose, which uses an intracellular regulatory protein called the lactose repressor to hinder production of β-galactosidase in the absence of lactose. The lacI gene coding for the repressor lies nearby the lac operon and is always expressed (constitutive). If lactose is missing from the growth medium, the repressor binds very tightly to a short DNA sequence just downstream of the promoter near the beginning of lacZ called the lac operator. The repressor binding to the operator interferes with binding of RNAP to the promoter, and therefore mRNA encoding LacZ and LacY is only made at very low levels. When cells are grown in the presence of lactose, however, a lactose metabolite called allolactose, made from lactose by the product of the lacZ gene, binds to the repressor, causing an allosteric shift. Thus altered, the repressor is unable to bind to the operator, allowing RNAP to transcribe the lac genes and thereby leading to higher levels of the encoded proteins.

The second control mechanism is a response to glucose, which uses the catabolite activator protein (CAP) homodimer to greatly increase production of β-galactosidase in the absence of glucose. Cyclic adenosine monophosphate (cAMP) is a signal molecule whose prevalence is inversely proportional to that of glucose. It binds to the CAP, which in turn allows the CAP to bind to the CAP binding site (a 16 bp DNA sequence upstream of the promoter on the left in the diagram below, about 60 bp upstream of the transcription start site), which assists the RNAP in binding to the DNA. In the absence of glucose, the cAMP concentration is high and binding of CAP-cAMP to the DNA significantly increases the production of β-galactosidase, enabling the cell to hydrolyze lactose and release galactose and glucose.

https://en.wikipedia.org/wiki/Lac_operon

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Lac Repressor

The lac repressor is a DNA-binding protein which inhibits the expression of genes co
ing for proteins involved in the metabolism of lactose in bacteria. These genes are re-
pressed when lactose is not available to the cell, ensuring that the bacterium only in-
vests energy in the production of machinery necessary for uptake and utilization of la
tose when lactose is present. When lactose becomes available, it is converted into allo
lactose, which inhibits the lac repressor's DNA binding ability. Loss of DNA binding b
the lac repressor is required for transcriptional activation of the operon.

https://en.wikipedia.org/wiki/Lac_repressor

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Lac-Z

LacZ is a part of the lac operon, which is an operon required for the transport
tabolism of lactose in *Escherichia coli* and many other enteric bacteria.

The gene product of lacZ is β-galactosidase which cleaves lactose, a disacchari
glucose and galactose. It will also cleave an artificial substrate known as X-Ga
one product of that reaction produces a blue color. X-Gal is therefore a useful
strate for easily measuring the amount of β-galactosidase in a sample.

https://en.wikipedia.org/wiki/Lac_operon

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Lactase

Lactase is an enzyme produced by many organisms. It is located in the brus
the small intestine of humans and other mammals. Lactase is essential to th
digestion of whole milk. It breaks down lactose, a sugar which gives milk it
ness. Lacking lactase, a person consuming dairy products may experience t
toms of lactose intolerance. Lactase can be purchased as a food supplement
added to milk to produce "lactose-free" milk products.

https://en.wikipedia.org/wiki/Lactase

Related Glossary Terms

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Lactate

During power exercises such as sprinting, when the rate of demand for energy is high, glucose is broken down and oxidized to pyruvate, and lactate is then produced from the pyruvate faster than the body can process it, causing lactate concentrations to rise. The production of lactate is beneficial because it regenerates NAD^+ (pyruvate is reduced to lactate while NADH is oxidized to NAD^+), which is used up in oxidation of glyceraldehyde 3-phosphate during production of pyruvate from glucose, and this ensures that energy production is maintained and exercise can continue. (During intense exercise, the respiratory chain cannot keep up with the amount of hydrogen atoms that join to form NADH, and cannot regenerate NAD^+ quickly enough.) The resulting lactate can be used in these ways:

• Oxidation back to pyruvate by well-oxygenated muscle cells, heart cells, and brain cells
• Pyruvate is then directly used to fuel the citric acid cycle
• Conversion to glucose via gluconeogenesis in the liver and release back into circulation via the Cori cycle

If blood glucose concentrations are high, the glucose can be used to build up the liver's glycogen stores.

https://en.wikipedia.org/wiki/Lactic_acid

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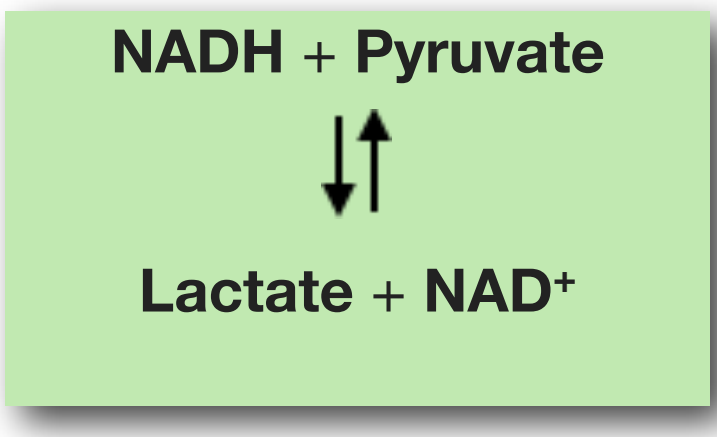
Lactate Dehydrogenase

Lactate dehydrogenase (LDH or LD) is an enzyme found in nearly all living o
mals, plants, and prokaryotes). LDH catalyzes the conversion of lactate to py
and back, as it converts NAD^+ to NADH and back. A dehydrogenase is an enz
transfers a hydride from one molecule to another.



https://en.wikipedia.org/wiki/Lactate_dehydrogenase

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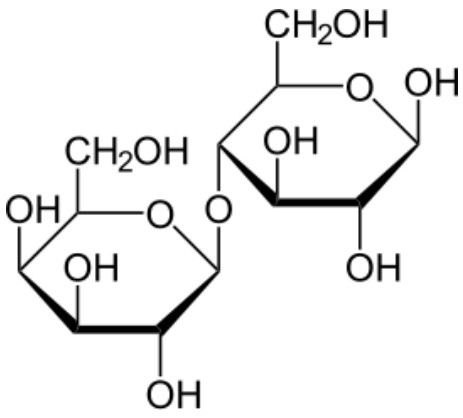
Lactose

Lactose is a disaccharide sugar derived from galactose and glucose that is found in milk. Lactose makes up around 2–8% of milk (by weight), although the amount varies among species and individuals, and milk with a reduced amount of lactose also exists. It is extracted from sweet or sour whey. The name comes from lac (gen. lactis), the Latin word for milk, plus the -ose ending used to name sugars. It has a formula of $C_{12}H_{22}O_{11}$, making it an isomer of sucrose.



https://en.wikipedia.org/wiki/Lactose

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Lactose Permease

Lactose permease is a membrane protein which is a member of the major facili
perfamily. Lactose permease is an integral membrane protein that can be classi
a symporter, which uses the proton gradient towards the cell to transport β-
galactosides such as lactose in the same direction into the cell.

Lactose permease is the lacY gene of the lac operon. In the transport performe
tose permease, sugar lies in a pocket in the center of the protein which is access
from the periplasm. On binding, a large conformational change takes place whi
makes the sugar binding site accessible from the cytoplasm.

Mechanism: hydrogen from the outside of the cell binds to a carboxyl group on
zyme that allows it to undergo a conformational change. This form of lactose pe
can bind lactose from outside the cell. The enzyme then everts and lactose is tra
ported inward.

https://en.wikipedia.org/wiki/Lactose_permease

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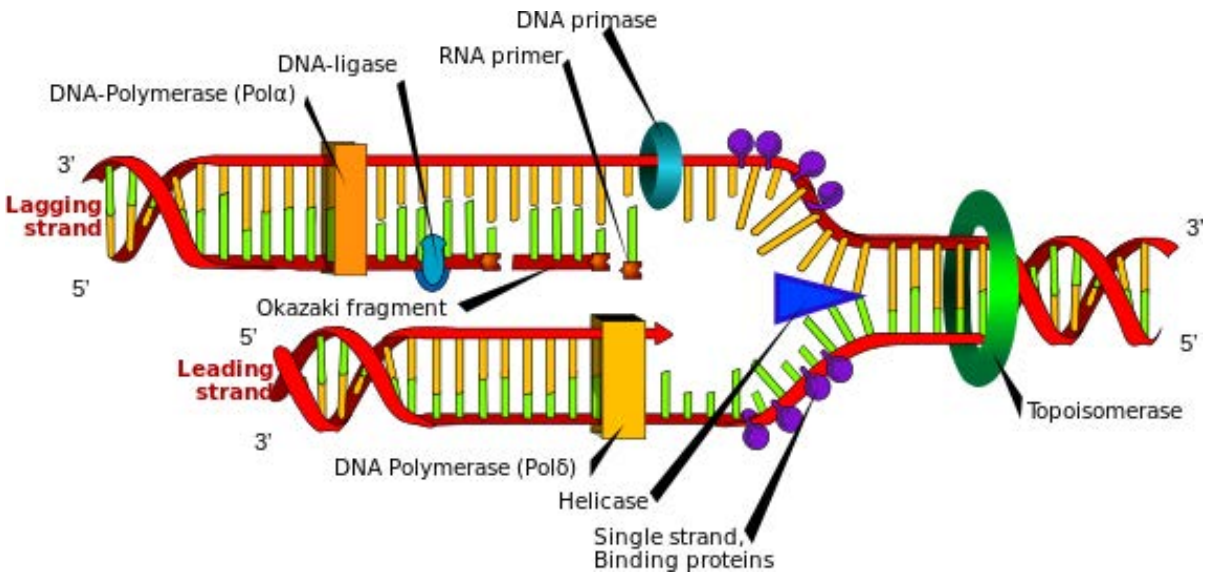
Lagging Strand

The lagging strand is the strand of nascent DNA whose direction of synthesis is opposite to the direction of the growing replication fork. Because of its orientation, replication of the lagging strand is more complicated as compared to that of the leading strand.

The lagging strand is synthesized in short, separated segments. On the lagging strand template, a primase "reads" the template DNA and initiates synthesis of a short complementary RNA primer. A DNA polymerase extends the primed segments, forming Okazaki fragments. The RNA primers are then removed and replaced with DNA, and the fragments of DNA are joined together by DNA ligase.
DNA polymerase III (in prokaryotes) or Pol δ (in eukaryotes) is responsible for extension of the primers added during replication of the lagging strand. Primer removal is performed by DNA polymerase I (in prokaryotes) and Pol δ (in eukaryotes). Eukaryotic primase is intrinsic to Pol α. In eukaryotes, pol ε helps with repair during DNA replication.

The lagging strand in the figure that follows is being synthesized from the top strand.



https://en.wikipedia.org/wiki/DNA_replication#Replication_fork

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Laminin

Laminins are high-molecular weight (~400kDa) proteins of the extracellular matri
They are a major component of the basal lamina (one of the layers of the basement
membrane), a protein network foundation for most cells and organs. The laminins
an important and biologically active part of the basal lamina, influencing cell differ
tiation, migration, and adhesion.

The laminin family of glycoproteins are an integral part of the structural scaffoldin
almost every tissue of an organism. They are secreted and incorporated into cell-
associated extracellular matrices. Laminin is vital for the maintenance and surviva
tissues. Defective laminins can cause muscles to form improperly, leading to a form
muscular dystrophy, lethal skin blistering disease (junctional epidermolysis bullos
and defects of the kidney filter (nephrotic syndrome).

https://en.wikipedia.org/wiki/Laminin

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Lamins

Nuclear lamins, also known as Class V intermediate filaments, are fibrous p
viding structural function and transcriptional regulation in the cell nucleus
lamins interact with membrane-associated proteins to form the nuclear lam
interior of the nuclear envelope. They are involved in the disassembling and
of the nuclear envelope during mitosis, as well as the positioning of nuclear

https://en.wikipedia.org/wiki/Lamin

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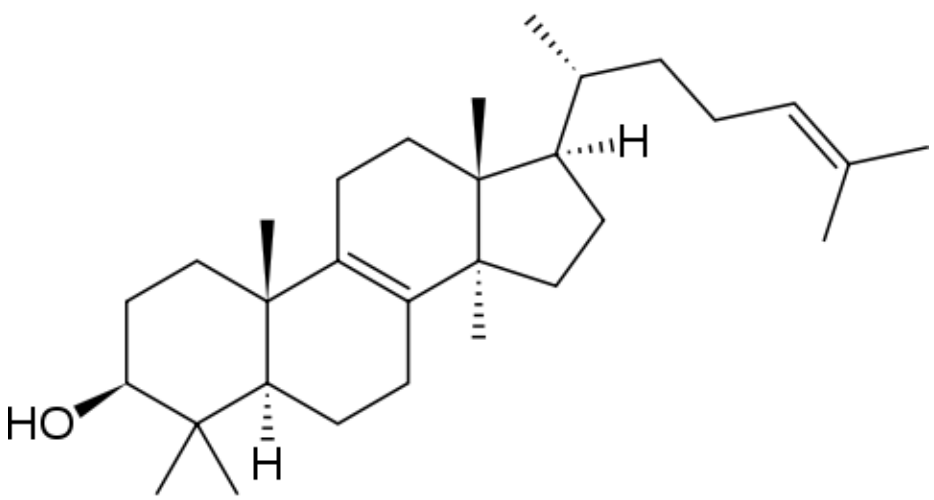
Lanosterol

Lanosterol is a tetracyclic triterpenoid and is the compound from which all an
fungi steroids are derived. By contrast plant steroids are produced via cycloar

Preliminary studies in dogs and rabbits have shown that lanosterol can preve
even reverse cataract formation.



https://en.wikipedia.org/wiki/Lanosterol

Related Glossary Terms

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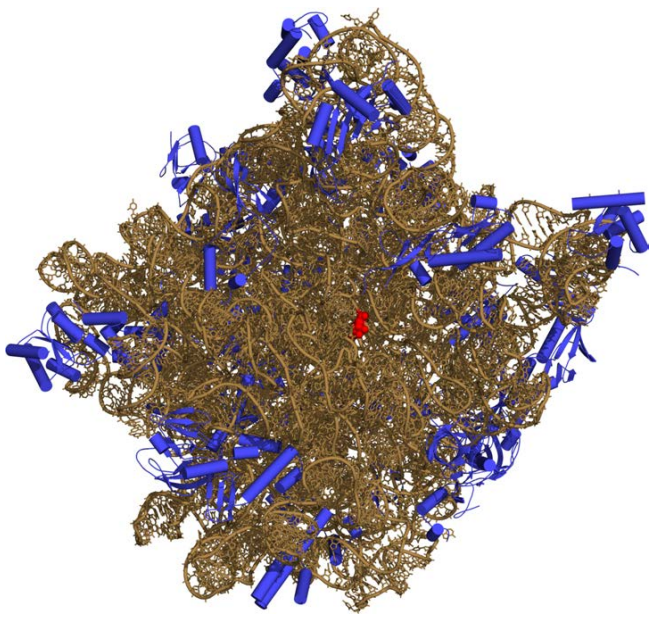
Large Subunit

Prokaryotes have 70S ribosomes, each consisting of a small (30S) and a large (50S) subunit. Their small subunit has a 16S RNA subunit (consisting of 1540 nucleotides) bound to 21 proteins. The large subunit is composed of a 5S RNA subunit (120 nucleotides), a 23S RNA subunit (2900 nucleotides) and 31 proteins.

The 50S subunit is primarily composed of proteins but also contains single-stranded RNA known as ribosomal RNA (rRNA). rRNA forms secondary and tertiary structures to maintain the structure and carry out the catalytic functions of the ribosome. 50S includes the activity that catalyzes peptide bond formation (peptidyl transfer reaction), prevents premature polypeptide hydrolysis, provides a binding site for the G-protein factors (assists initiation, elongation, and termination), and helps protein folding after synthesis.

Eukaryotes have 80S ribosomes, each consisting of a small (40S) and large (60S) subunit. Their 40S subunit has an 18S RNA (1900 nucleotides) and 33 proteins. The large subunit is composed of a 5S RNA (120 nucleotides), 28S RNA (4700 nucleotides), a 5.8S RNA (160 nucleotides) subunits and 46 proteins.



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Lateral Diffusion

Lateral diffusion describes the movement of lipids in the lipid bilayer of membr
The entire membrane is held together via non-covalent interaction of hydropho
tails, however the structure is quite fluid and not fixed rigidly in place. Under p
logical conditions phospholipid molecules in the cell membrane are in the liqui
talline state. It means the lipid molecules are free to diffuse and exhibit rapid la
fusion along the layer in which they are present. However, the exchange of phos
pholipid molecules between intracellular and extracellular leaflets of the bilaye
very slow process. Lipid rafts and caveolae are examples of cholesterol-enriched
domains in the cell membrane. Also, a fraction of the lipid in direct contact with
gral membrane proteins, which is tightly bound to the protein surface is called a
lipid shell. It behaves as a part of protein complex.

https://en.wikipedia.org/wiki/Cell_membrane#Lipids

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LDL

Low-density lipoprotein (LDL) is one of the five major groups of lipoprotein. These groups, from least dense to most dense, are chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein and high-density lipoprotein (HDL).

LDL particles pose a risk for cardiovascular disease when they invade the endothelium and become oxidized, since the oxidized forms are more easily retained by the proteoglycans. A complex set of biochemical reactions regulates the oxidation of LDL particles, chiefly stimulated by presence of necrotic cell debris and free radicals in the endothelium. Increasing concentrations of LDL particles are strongly associated with increasing rates of accumulation of atherosclerosis within the walls of arteries over time, eventually resulting in sudden plaque ruptures and triggering clots within the artery opening, or a narrowing or closing of the opening, i.e. cardiovascular disease, stroke, and other vascular disease complications.

https://en.wikipedia.org/wiki/Low-density_lipoprotein

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LDL Receptor

The Low-Density Lipoprotein (LDL) Receptor is a mosaic protein of 839 amino
(after removal of 21-amino acid signal peptide) that mediates the endocytosis o
cholesterol-rich LDL. It is a cell-surface receptor that recognizes the apoprotein
which is embedded in the outer phospholipid layer of LDL particles. The recept
recognizes the apoE protein found in chylomicron remnants and VLDL remnan
(IDL). In humans, the LDL receptor protein is encoded by the LDLR gene. It be
to the Low density lipoprotein receptor gene family.

The LDL receptor is implicate in familial hypercholesterolemia. Absence or lac
citon of the receptor is a cause of the genetic disease.

https://en.wikipedia.org/wiki/LDL_receptor

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LDLs

Low-density lipoprotein (LDL) is one of the five major groups of lipoprotein. These groups, from least dense to most dense, are chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein and high-density lipoprotein (HDL).

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https://en.wikipedia.org/wiki/Low-density_lipoprotein

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Le Chatelier’s Principle

In chemistry, Le Châtelier's principle, also called Chatelier's principle or "T
rium Law", can be used to predict the effect of a change in conditions on a c
equilibrium. The principle is named after Henry Louis Le Châtelier and sor
Karl Ferdinand Braun who discovered it independently. It can be stated as:

When any system at equilibrium is subjected to change in concentration, te
volume, or pressure, then the system readjusts itself to (partially) countera
of the applied change and a new equilibrium is established or whenever a sy
equilibrium is disturbed the system will adjust itself in such a way that the
change will be nullified.

https://en.wikipedia.org/wiki/Le_Chatelier%27s_principle

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Leader Sequence

The 5' untranslated region (5′ UTR) (also known as a Leader Sequence or Leader RNA) is the region of an mRNA that is directly upstream from the initiation codon. This region is important for the regulation of translation of a transcript by differing mechanisms in viruses, prokaryotes and eukaryotes. While called untranslated, the 5′ UTR or a portion of it is sometimes translated into a protein product. This product can then regulate the translation of the main coding sequence of the mRNA. In many other organisms, however, the 5′ UTR is completely untranslated, instead forming complex secondary structure to regulate translation. The 5′ UTR has been found to interact with proteins relating to metabolism and proteins translate sequences within the 5′ UTR. In addition, this region has been involved in transcription regulation, such as the sex-lethal gene in *Drosophila*. Regulatory elements within 5' UTRs have also been linked to mRNA export.

The 5′ UTR begins at the transcription start site and ends one nucleotide (nt) before the initiation sequence (usually AUG) of the coding region. In prokaryotes, the length of the 5′ UTR tends to be 3-10 nucleotides long, while in eukaryotes it tends to be anywhere from 100 to several thousand nucleotides long. For example, the ste11 transcript in *Schizosaccharomyces pombe* has a 2273 nucleotide 5′ UTR while the lac operon in *Escherichia coli* only has 7 nucleotides in its 5′ UTR. The differing sizes are likely due to the complexity of the eukaryotic regulation which the 5′ UTR holds, as well as the larger preinitiation complex which must form to begin translation.

The elements of a eukaryotic and prokaryotic 5′ UTR differ greatly. The prokaryotic 5′ UTR contains a ribosome binding site (RBS), also known as the Shine Dalgarno sequence (AGGAGGU), which is usually 3-10 base pairs upstream from the initiation codon. In contrast, the eukaryotic 5′ UTR contains the Kozak consensus sequence (ACCAUGG), which contains the initiation codon. The eukaryotic 5′ UTR also contains cis-acting regulatory elements called upstream open reading frames (uORFs) and upstream AUGs and termination codons (uAUGs), which have a great impact on the regulation of translation (see below). Unlike prokaryotes, 5' UTRs can harbor introns in eukaryotes. In humans, ~35% of all genes harbor introns within the 5' UTR.

https://en.wikipedia.org/wiki/Five_prime_untranslated_region

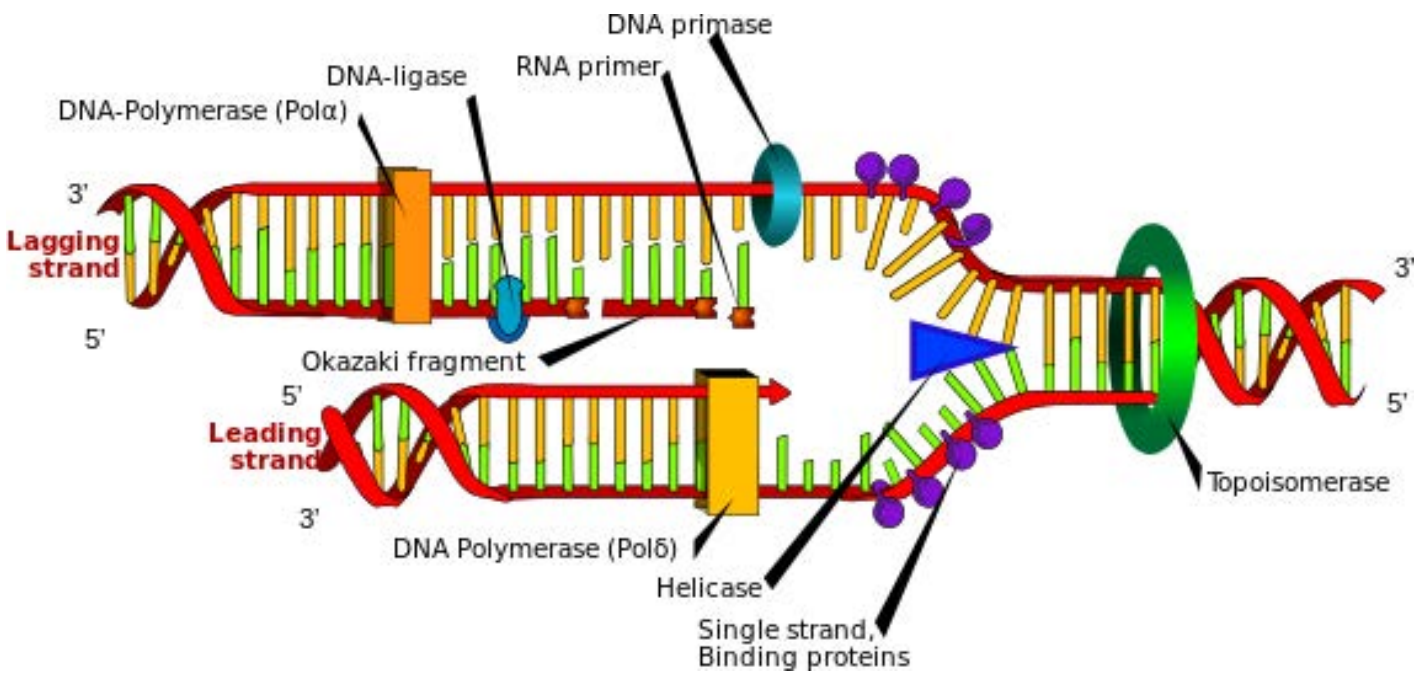
Related Glossary Terms

Leading Strand

The leading strand is the strand of nascent DNA which is being synthesized in the same direction as the growing replication fork. A polymerase "reads" the leading strand template and adds complementary nucleotides to the nascent leading strand on a continuous basis.

The polymerase involved in leading strand synthesis is DNA polymerase III (DNA Pol III) in prokaryotes. In eukaryotes, leading strand synthesis is thought to be conducted by Pol ε, however this view has been recently challenged, suggesting a role for Pol δ.

In the figure below, the leading strand is being synthesized from the bottom strand.



https://en.wikipedia.org/wiki/DNA_replication#Replication_fork

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Leaflet

When phospholipids are exposed to water, they self-assemble into a two-la
with the hydrophobic tails pointing toward the center of the sheet. This arr
results in two “leaflets” that are each a single molecular layer.

https://en.wikipedia.org/wiki/Lipid_bilayer

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Chapter 3 - Membranes: Basic Concepts

Lecithin

The term lecithin is a non-specific term to refer to a group of phospholipid
lated compounds. Lecithins are usually phospholipids, composed of phosp
with choline, glycerol or other fatty acids usually glycolipids or triglyceride.

https://en.wikipedia.org/wiki/Lecithin

Related Glossary Terms

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Lecithin-cholesterol Acyl Transferase

Lecithin–cholesterol acyltransferase (LCAT, also called phosphatidylcholin
acyltransferase) is an enzyme that converts free cholesterol into cholesteryl
more hydrophobic form of cholesterol), which is then sequestered into the
lipoprotein particle, eventually making the newly synthesized HDL spherica
ing the reaction to become unidirectional since the particles are removed fr
face. The enzyme is bound to high-density lipoproteins (HDLs) and low-de
proteins in the blood plasma.

https://en.wikipedia.org/wiki/Lecithin–cholesterol_acyltransferase

Related Glossary Terms

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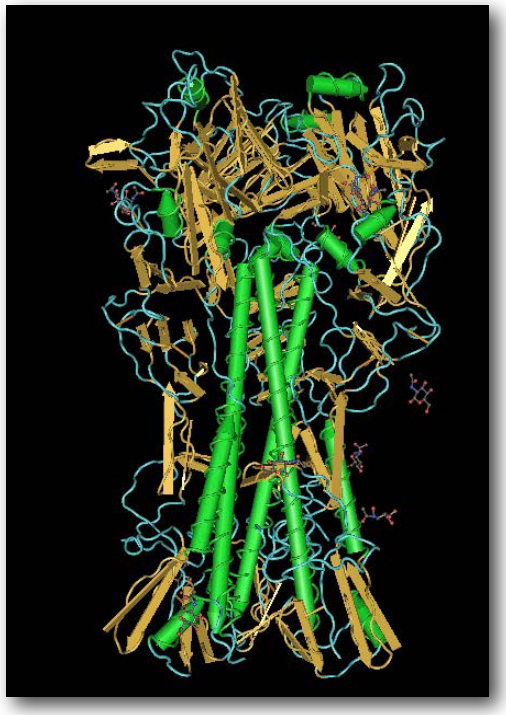
Lectins

Lectins are carbohydrate-binding proteins, macromolecules that are highly specific for sugar moieties. Lectins should neither be confused with glycoproteins (proteins containing sugar chains or residues), lecithins (fatty substances in animals and plants), nor leptin (the regulator of appetite and hunger, metabolism, and behavior).

Long before a deeper understanding of their numerous biological functions, the plant lectins, also known as phytohemagglutinins, were noted for their particular high specificity for foreign glycoconjugates (e.g. those of fungi, invertebrates, and animals). and used in biomedicine for blood cell testing and in biochemistry for fractionation.

Lectins perform recognition on the cellular and molecular level and play numerous roles in biological recognition phenomena involving cells, carbohydrates, and proteins. Lectins also mediate attachment and binding of bacteria and viruses to their intended targets. For example, it is hypothesized that some hepatitis C viral glycoproteins attach to C-type lectins on the host cell surface (liver cells) for infection.

Lectins may be disabled by specific mono- and oligosaccharides, which bind to ingested lectins from grains, legume, nightshade plants and dairy. Binding can prevent their attachment to the carbohydrates within the cell membrane. Some lectins may be powerful toxins as for instance ricin, and others have been incorporated into genetically engineered crops to transfer traits, such as resistance to pests and resistance to herbicides.



https://en.wikipedia.org/wiki/Lectin

Left-handed

Helices can be either right-handed or left-handed. With the line of sight alo
lix's axis, if a clockwise screwing motion moves the helix away from the obs
it is called a right-handed helix. If towards the observer, then it is a left-ha
Handedness (or chirality) is a property of the helix, not of the perspective: a
handed helix cannot be turned to look like a left-handed one unless it is vie
mirror, and vice versa.

https://en.wikipedia.org/wiki/Helix

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Leptin

Leptin , the "satiety hormone,"[a] is a hormone made by adipose cells that helps to regulate energy balance by inhibiting hunger. Leptin is opposed by the actions of the hormone ghrelin, the "hunger hormone". Both hormones act on receptors in the arcuate nucleus of the hypothalamus to regulate appetite to achieve energy homeostasis. In obesity, a decreased sensitivity to leptin occurs, resulting in an inability to detect satiety despite high energy stores.

https://en.wikipedia.org/wiki/Leptin

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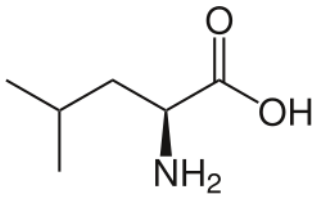
Leucine

Leucine (abbreviated as Leu or L; encoded by the six codons UUA, UUG, CUU, CUC, CUA, and CUG) is an α-amino acid used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and an isobutyl side chain, classifying it as a nonpolar (at physiological pH) amino acid. It is essential in humans—meaning the body cannot synthesize it and thus must obtain it from the diet.



https://en.wikipedia.org/wiki/Leucine

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Leucine Aminotransferase

Leucine transaminase (EC 2.6.1.6) is an enzyme that catalyzes the biochemical synthesis reaction for making leucine

α-ketoisocaproate + **Glutamate**

⇅

Leucine + **α-ketoglutarate**

This enzyme belongs to the family of transferases, specifically the transaminases, which transfer nitrogenous groups. The systematic name of this enzyme class is L-leucine:2-oxoglutarate aminotransferase. Other names in common use include L-leucine aminotransferase, leucine 2-oxoglutarate transaminase, leucine aminotransferase, and leucine-α-ketoglutarate transaminase. This enzyme participates in 3 metabolic pathways: valine, leucine and isoleucine degradation, valine, leucine and isoleucine biosynthesis, and pantothenate and coa biosynthesis. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Leucine_transaminase

Related Glossary Terms

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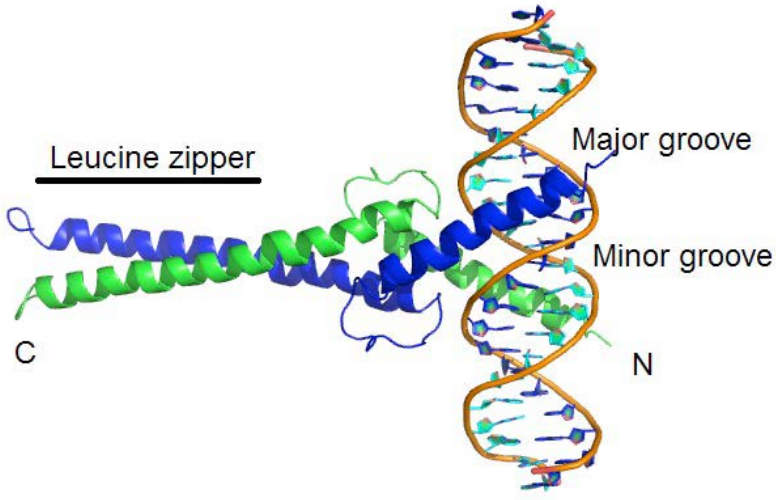
Leucine Zipper

A leucine zipper, aka leucine scissors, is a common three-dimensional structural motif in proteins. They were first described by Landschulz and collaborators in 1988 when they found that an enhancer binding protein had a very characteristic 30-amino acid segment and the display of these amino acid sequences on an idealized α helix revealed a periodic repetition of leucine residues at every seventh position over a distance covering eight helical turns. The polypeptide segments containing these periodic arrays of leucine residues were proposed to exist in an α-helical conformation and the leucine side chains from one α helix interdigitate with those from the α helix of a second polypeptide, facilitating dimerization.

Leucine zippers are a dimerization domain of the bZIP (Basic-region leucine zipper) class of eukaryotic transcription factors. The bZIP domain is 60 to 80 amino acids in length with a highly conserved DNA binding basic region and a more diversified leucine zipper dimerization region. The leucine zipper is a common three-dimensional structural motif in proteins and it has that name because leucines occur every seven amino acids in the dimerization domain. The localization of the leucines are critical for the DNA binding to the proteins. Leucine zippers are present in both eukaryotic and prokaryotic regulatory proteins, but are mainly a feature of eukaryotes. They can also be annotated simply as ZIPs, and ZIP-like motifs have been found in proteins other than transcription factors and are thought to be one of the general protein modules for protein-protein interactions.



https://en.wikipedia.org/wiki/Leucine_zipper

Related Glossary Terms

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Leucocytes

White blood cells (WBCs), also called leukocytes or leucocytes, are the cells
mune system that are involved in protecting the body against both infectiou
and foreign invaders. All white blood cells are produced and derived from a
tent cell in the bone marrow known as a hematopoietic stem cell. Leukocyte
throughout the body, including the blood and lymphatic system.

https://en.wikipedia.org/wiki/White_blood_cell

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Chapter 1 - Chemistry, Buffers, and Energy

Leukocytes

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https://en.wikipedia.org/wiki/White_blood_cell

Related Glossary Terms

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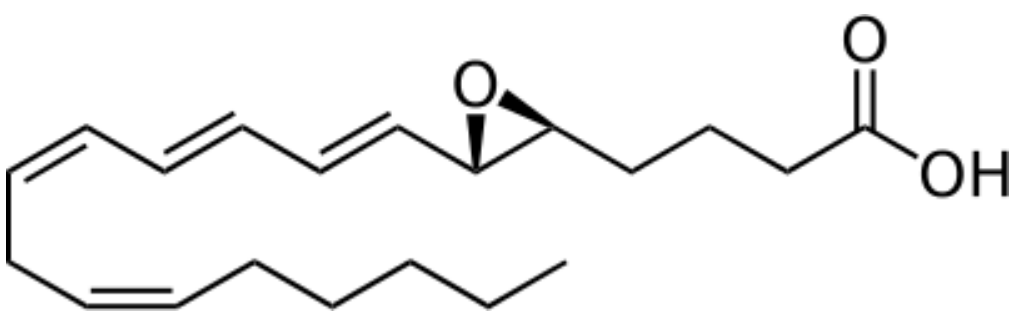
Leukotrienes

Leukotrienes are a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of the essential fatty acids arachidonic acid (AA) and eicosapentanoic acid (EPA) by the enzyme arachidonate 5-lipoxygenase. As their name implies, leukotrienes were first discovered in leukocytes, but have since been found in other immune cells.

Leukotrienes use lipid signaling to convey information to either the cell producing them (autocrine signaling) or neighboring cells (paracrine signaling) in order to regulate immune responses. Leukotriene production is usually accompanied by the production of histamine and prostaglandins, which also act as inflammatory mediators. Leukotriene A_4 is depicted below.



https://en.wikipedia.org/wiki/Leukotriene

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Leventhal’s Paradox

Levinthal's paradox is a thought experiment, also constituting a self-referen
theory of protein folding. In 1969, Cyrus Levinthal noted that, because of th
number of degrees of freedom in an unfolded polypeptide chain, the molecu
astronomical number of possible conformations. If a protein were to attain
folded configuration by sequentially sampling all the possible conformation
require a time longer than the age of the universe to arrive at its correct nat
mation. The "paradox" is that most small proteins fold spontaneously on a
or even microsecond time scale. The solution to this paradox has been estal
computational approaches to protein structure prediction.

https://en.wikipedia.org/wiki/Levinthal%27s_paradox

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LexA

Repressor LexA or LexA is a transcriptional repressor (EC 3.4.21.88) that represses SOS response genes coding primarily for error-prone DNA polymerases, DNA repair enzymes and cell division inhibitors. LexA forms *de facto* a two-component regulatory system with RecA, which senses DNA damage at stalled replication forks, forming monofilaments and acquiring an active conformation capable of binding to LexA and causing LexA to cleave itself, in a process called autoproteolysis.

DNA damage can be inflicted by the action of antibiotics, bacteriophages and UV light. Of potential clinical interest is the induction of the SOS response by antibiotics, such as ciprofloxacin. Bacteria require topoisomerases such as DNA gyrase or topoisomerase IV for DNA replication. Antibiotics such as ciprofloxacin are able to prevent the action of these molecules by attaching themselves to the gyrase - DNA complex, leading to replication fork stall and the induction of the SOS response. The expression of error-prone polymerases under the SOS response increases the basal mutation rate of bacteria. While mutations are often lethal to the cell, they can also enhance survival. In the specific case of topoisomerases, some bacteria have mutated one of their amino acids so that the ciproflaxin can only create a weak bond to the topoisomerase. This is one of the methods that bacteria use to become resistant to antibiotics. Ciprofloxacin treatment can therefore potentially lead to the generation of mutations that may render bacteria resistant to ciprofloxacin. In addition, ciprofloxacin has also been shown to induce via the SOS response dissemination of virulence factors and antibiotic resistance determinants, as well as the activation of integron integrases, potentially increasing the likelihood of acquisition and dissemination of antibiotic resistance by bacteria.

Impaired LexA proteolysis has been shown to interfere with ciprofloxacin resistance. This offers potential for combination therapy that combines quinolones with strategies aimed at interfering with the action of LexA, either directly or via RecA.

LexA contains a DNA binding domain. The winged HTH motif of LexA is a variant form of the helix-turn-helix DNA binding motif. it is usually located at the N-terminus of the protein.

Library

As used in molecular biology, a library is a term used to describe a complete
of something. A genomic library, for example, is a complete collection of D
genome. A cDNA library is a complete collection of all of the cDNAs (made
mRNAs) of an organism. Libraries are commonly collected in a large numb
rial cells which contain the relevant nucleic acid fragments in plasmids or r
tors.

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Ligand

In biochemistry and pharmacology, a ligand is a substance that forms a cor
biomolecule to serve a biological purpose. In protein-ligand binding, the lig
ally a molecule which produces a signal by binding to a site on a target prot
binding typically results in a change of conformation of the target protein.

https://en.wikipedia.org/wiki/Ligand_(biochemistry)

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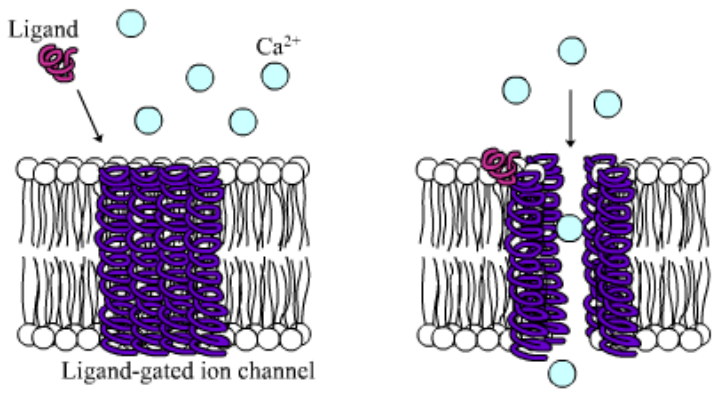
Ligand-gated Ion Channels

Ligand-gated ion channels (LGICs) are a group of transmembrane ion channel proteins which open to allow ions such as Na^+, K^+, Ca^{++}, or Cl^- to pass through the membrane in response to the binding of a chemical messenger (i.e. a ligand), such as a neurotransmitter.

These proteins are typically composed of at least two different domains: a transmembrane domain which includes the ion pore, and an extracellular domain which includes the ligand binding location (an allosteric binding site). This modularity has enabled a 'divide and conquer' approach to finding the structure of the proteins (crystallizing each domain separately). The function of such receptors located at synapses is to convert the chemical signal of presynaptically released neurotransmitter directly and very quickly into a postsynaptic electrical signal. Many LGICs are additionally modulated by allosteric ligands, by channel blockers, ions, or the membrane potential. LGICs are classified into three superfamilies which lack evolutionary relationship: Cys-loop receptors, Ionotropic glutamate receptors and ATP-gated channels.

LGICs can be contrasted with metabotropic receptors (which use second messenger activated ion channels), voltage-gated ion channels (which open and close depending on membrane potential), and stretch-activated ion channels (which open and close depending on mechanical deformation of the cell membrane).



https://en.wikipedia.org/wiki/Ligand-gated_ion_channel

Ligands

In biochemistry and pharmacology, a ligand is a substance that forms a com
biomolecule to serve a biological purpose. In protein-ligand binding, the lig
ally a molecule which produces a signal by binding to a site on a target prot
binding typically results in a change of conformation of the target protein.

https://en.wikipedia.org/wiki/Ligand_(biochemistry)

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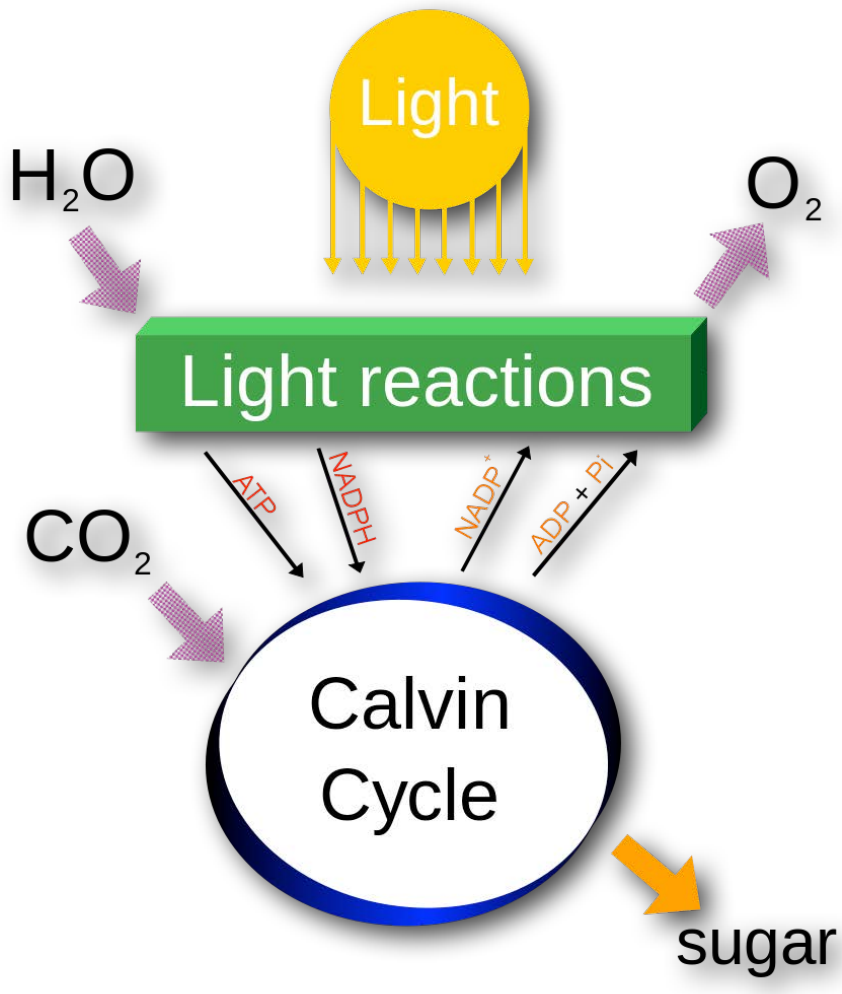
Light Cycle

In photosynthesis, the light-dependent reactions take place on the thylakoid membranes. There are four major protein complexes in the thylakoid membrane: Photosystem II (PSII), Cytochrome b6f complex, Photosystem I (PSI), and ATP synthase. These four complexes work together to ultimately create the products ATP and NADPH.



https://en.wikipedia.org/wiki/Light-dependent_reactions

Related Glossary Terms

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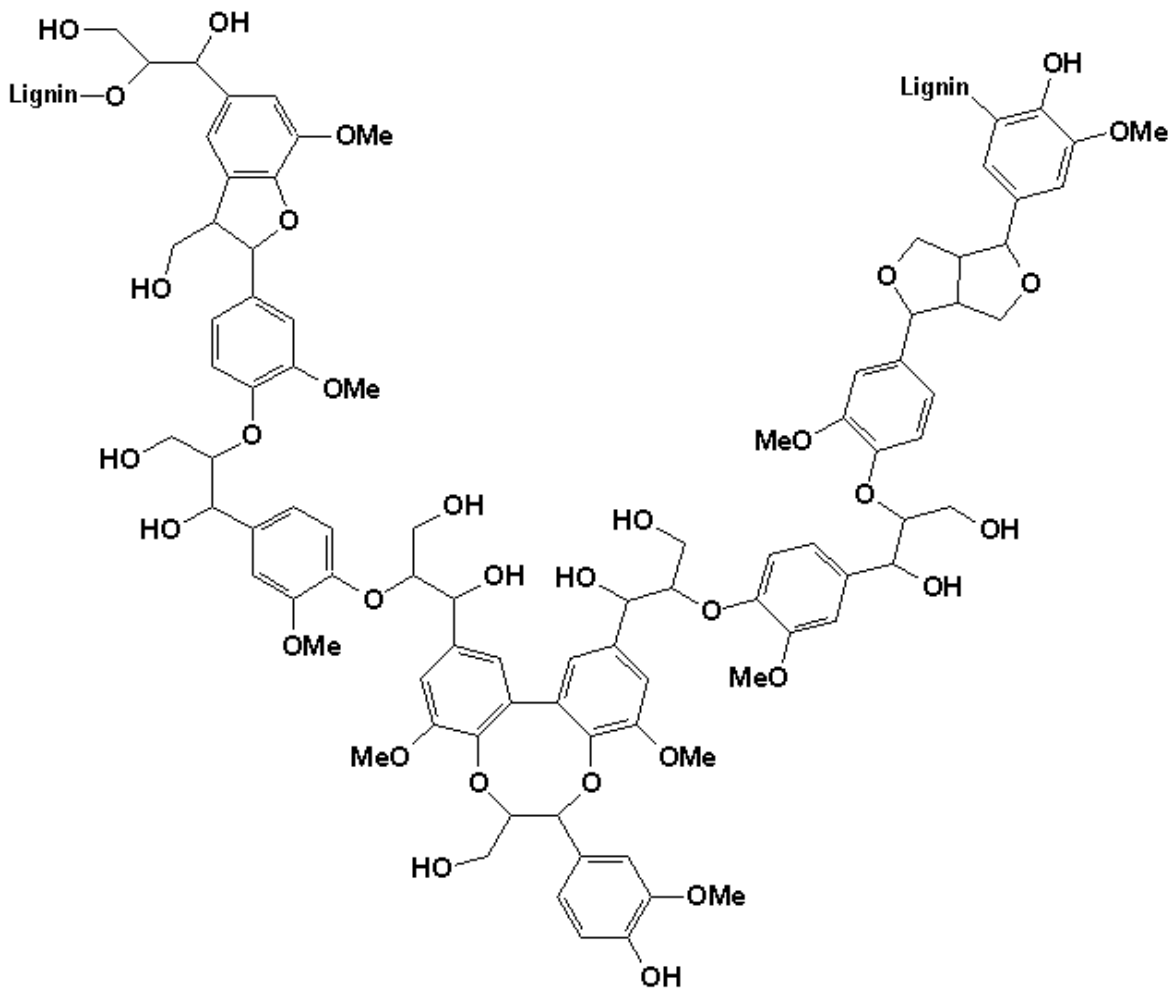
Lignin

Lignin is a class of complex organic polymers that form important structural materials in the support tissues of vascular plants and some algae. Lignins are particularly important in the formation of cell walls, especially in wood and bark, because they lend rigidity and do not rot easily. Chemically, lignins are cross-linked phenolic polymers. A small segment of one is depicted below.



https://en.wikipedia.org/wiki/Lignin

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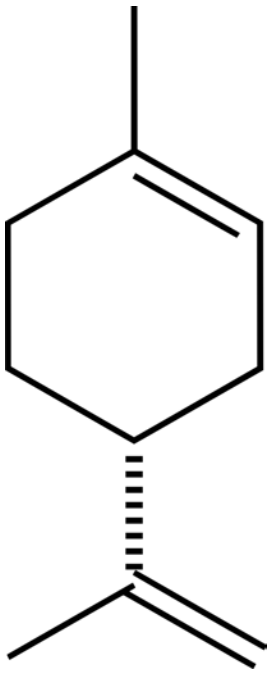
Limonene

Limonene is a colorless liquid hydrocarbon classified as a cyclic terpene. Th
common d-isomer possesses a strong smell of oranges.



https://en.wikipedia.org/wiki/Limonene

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Linalool

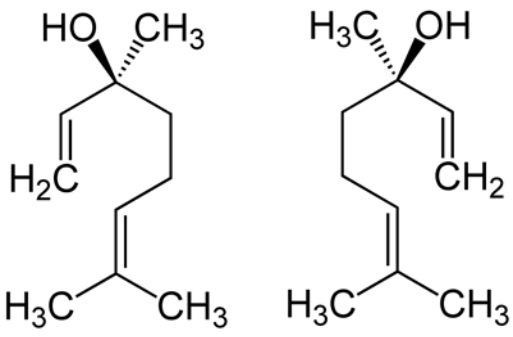
Linalool is a naturally occurring terpene alcohol chemical found in many flowers and spice plants with many commercial applications, the majority of which are based on its pleasant scent (floral, with a touch of spiciness). It has other names such as β-linalool, linalyl alcohol, linaloyl oxide, p-linalool, allo-ocimenol, and 3,7-dimethyl-1,6-octadien-3-ol.

Over 200 species of plants produce linalool, mainly from the families Lamiaceae (mints, scented herbs), Lauraceae (laurels, cinnamon, rosewood), and Rutaceae (citrus fruits), but also birch trees and other plants, from tropical to boreal climate zones. It has also been found in some fungi and cannabis.

Linalool has a stereoisomeric center at C_3 and therefore there are two stereoisomers: (R)-(–)-linalool is also known as licareol and (S)-(+)-linalool is also known as coriandrol. In the figure below, the S form is on the left.

Both enantiomeric forms are found in nature: (S)-linalool is found, for example, as a major constituent of the essential oils of coriander (Coriandrum sativum L. family *Apiaceae*) seed, palmarosa [*Cymbopogon martinii var martinii* (Roxb.) Wats., family *Poaceae*], and sweet orange (*Citrus sinensis Osbeck*, family *Rutaceae*) flowers. (R)-linalool is present in lavender (*Lavandula officinalis Chaix*, family *Lamiaceae*), bay laurel (*Laurus nobilis*, family *Lauraceae*), and sweet basil (*Ocimum basilicum*, family *Lamiaceae*), among others.

Each enantiomer evokes different neural responses in humans, and therefore are classified as possessing distinct scents. (S)-(+)-Linalool is perceived as sweet, floral, petitgrain-like (odor threshold 7.4 ppb) and the (R)-form as more woody and lavender-like (odor threshold 0.8 ppb).



https://en.wikipedia.org/wiki/Linalool

LINEs

Transposons and retrotransposons are mobile genetic elements. Retrotrans
peated sequences, which include long interspersed nuclear elements (LINE
interspersed nuclear elements (SINEs), account for a large proportion of th
sequences in many species. Alu sequences, classified as a short intersperse
ment, are the most abundant mobile elements in the human genome. Some
have been found of SINEs exerting transcriptional control of some protein-
genes.

https://en.wikipedia.org/wiki/Noncoding_DNA

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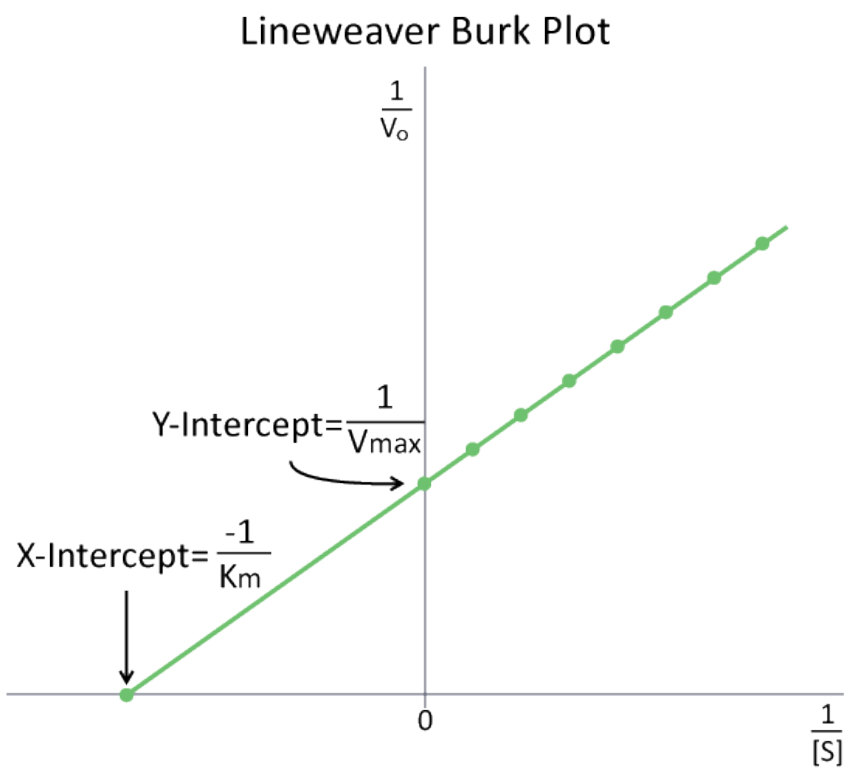
Lineweaver-Burk

The Lineweaver–Burk plot (or double reciprocal plot) is a graphical representation of the Lineweaver–Burk equation of enzyme kinetics, described by Hans Lineweaver and Dean Burk in 1934.

The Lineweaver–Burk plot was widely used to determine important terms in enzyme kinetics, such as K_m and V_{max}, before the wide availability of powerful computers and non-linear regression software. The y-intercept of such a graph is equivalent to the inverse of V_{max}. The x-intercept of the graph represents $-1/K_m$. It also gives a quick, visual impression of the different forms of enzyme inhibition.

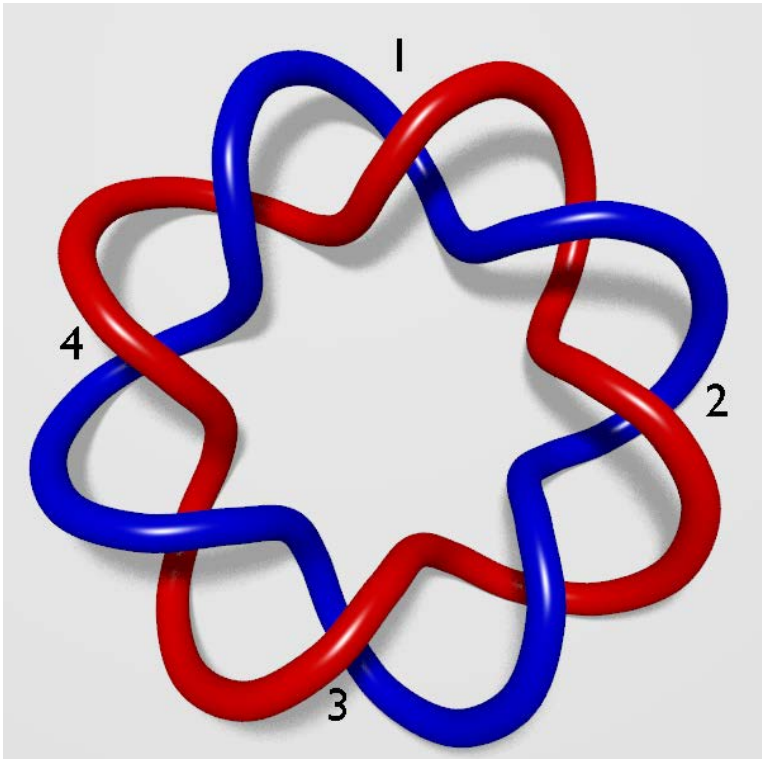


https://en.wikipedia.org/wiki/Lineweaver–Burk_plot

Related Glossary Terms

Linking Number

Analysis of DNA topology uses: L = linking number - the number of times one DNA strand wraps around the other. It is an integer for a closed loop and constant for a closed topological domain. The two curves in the figure below have a linking number of four.



https://en.wikipedia.org/wiki/Nucleic_acid_double_helix

Related Glossary Terms

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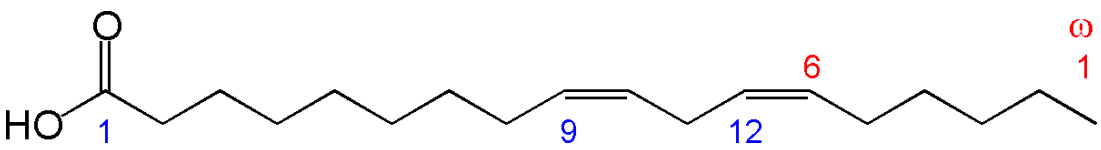
Linoleate

LA is a polyunsaturated ω-6 fatty acid used in the biosynthesis of arachidonic acid (AA) and thus some prostaglandins, leukotrienes (LTA, LTB, LTC), and thromboxane (TXA). It is found in the lipids of cell membranes. It is abundant in many nuts, fatty seeds (flax seeds, hemp seeds, poppy seeds, sesame seeds, etc.) and their derived vegetable oils, comprising over half (by weight) of poppy seed, safflower, sunflower, corn, and soybean oils.

LA is converted by various lipoxygenases, cyclooxygenases, certain cytochrome P450 enzymes (the CYP monooxygenases), and non-enzymatic autooxidation mechanisms to mono-hydroxyl products viz., 13-Hydroxyoctadecadienoic acid and 9-Hydroxyoctadecadienoic acid. These two hydroxy metabolites are enzymatically oxidized to their keto metabolites, 13-oxo-octadecadienoic acid and 9-oxo-octadecdienoic acid. Certain cytochrome P450 enzymes, the CYP epoxygenases, metabolize LA to epoxide products viz., its 12,13-epoxide, Vernolic acid and its 9,10-epoxide, Coronaric acid. All of these LA products have bioactivity and are implicated in human physiology and pathology as indicated in the cited linkages.

Linoleic acid is an essential fatty acid that must be consumed for proper health. A diet only deficient in linoleate (the salt form of the acid) causes mild skin scaling, hair loss, and poor wound healing in rats.

Along with oleic acid, linoleic acid is released by cockroaches upon death which has the effect of preventing other roaches from entering the area. This is similar to the mechanism found in ants and bees, which release oleic acid upon death.



https://en.wikipedia.org/wiki/Linoleic_acid

Related Glossary Terms

Drag related terms here

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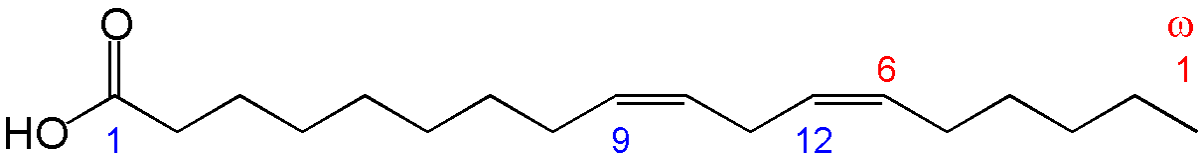

https://en.wikipedia.org/wiki/Linoleic_acid

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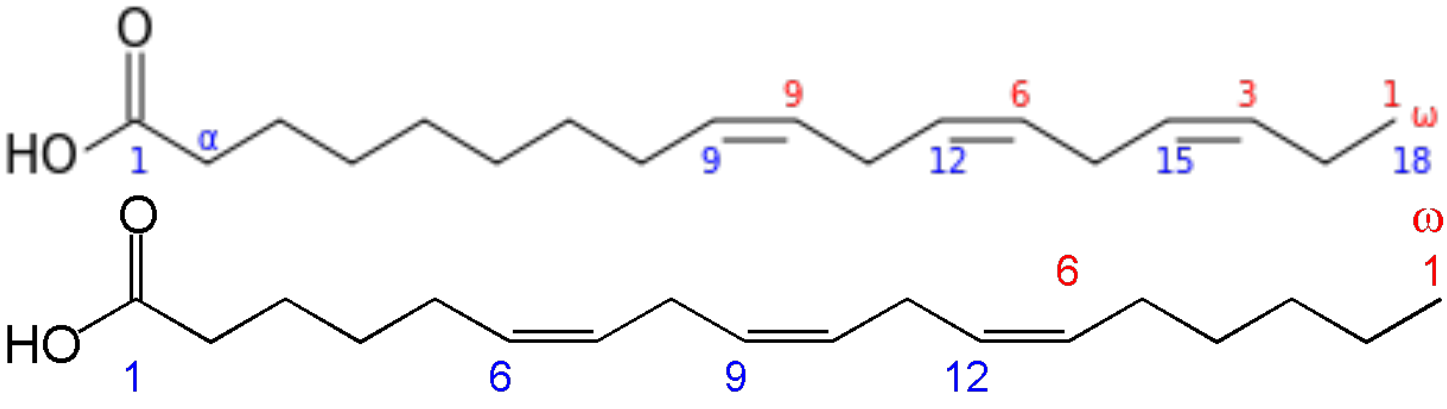
Linolenate

Linolenate (in the form of esters of linolenic acid) is often found in vegetable oils. ditionally, such fatty acylates are reported as the fatty acids:

α-Linolenic acid, an omega-3 (n-3) fatty acid
γ-Linolenic acid, an omega-6 (n-6) fatty acid



https://en.wikipedia.org/wiki/Linolenic_acid

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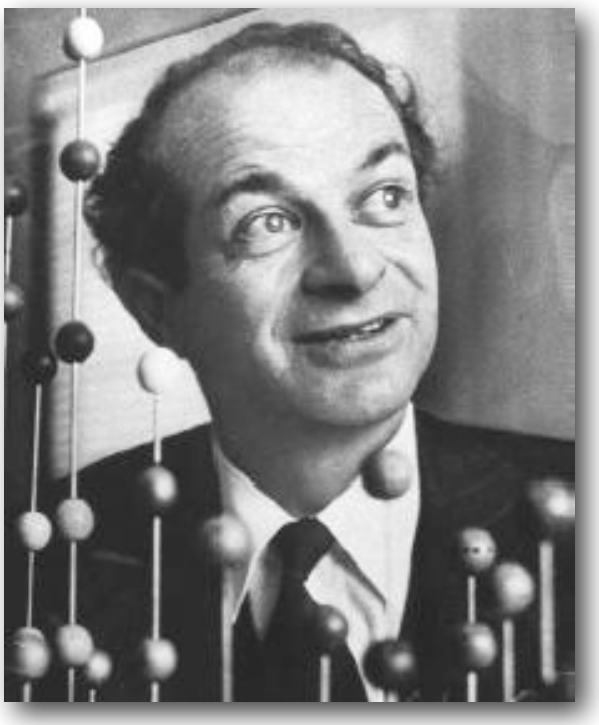
Linus Pauling

Linus Carl Pauling (February 28, 1901 – August 19, 1994) was an American chemist, biochemist, peace activist, author, and educator. Pauling was one of the founders of the fields of quantum chemistry and molecular biology.

Part of Pauling's work on the nature of the chemical bond led to his introduction of the concept of orbital hybridization. Another area which he explored was the relationship between ionic bonding, where electrons are transferred between atoms, and covalent bonding, where electrons are shared between atoms on an equal basis. Pauling showed that these were merely extremes, between which most actual cases of bonding fall. It was here especially that Pauling's electronegativity concept was particularly useful; the electronegativity difference between a pair of atoms will be the surest predictor of the degree of ionicity of the bond.



https://en.wikipedia.org/wiki/Linus_Pauling

Related Glossary Terms

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Lipase

A lipase is an enzyme that catalyzes the hydrolysis of fats (lipids). Lipases a
class of the esterases.

Lipases perform essential roles in the digestion, transport and processing o
ids (e.g. triglycerides, fats, oils) in most, if not all, living organisms. Genes e
pases are even present in certain viruses.

https://en.wikipedia.org/wiki/Lipase

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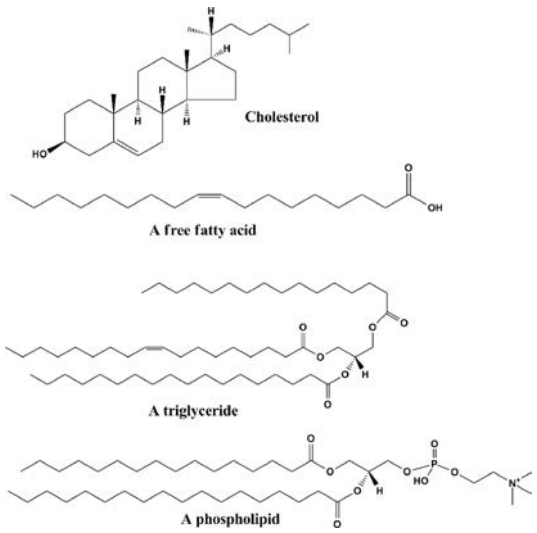
Lipid

Lipids are a group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids, and others. The main biological functions of lipids include storing energy, signaling, and acting as structural components of cell membranes. Lipids may be broadly defined as hydrophobic or amphiphilic small molecules. The amphiphilic nature of some lipids allows them to form structures such as vesicles, multilamellar/unilamellar liposomes, or membranes in an aqueous environment.

Common lipids are shown below.



https://en.wikipedia.org/wiki/Lipid

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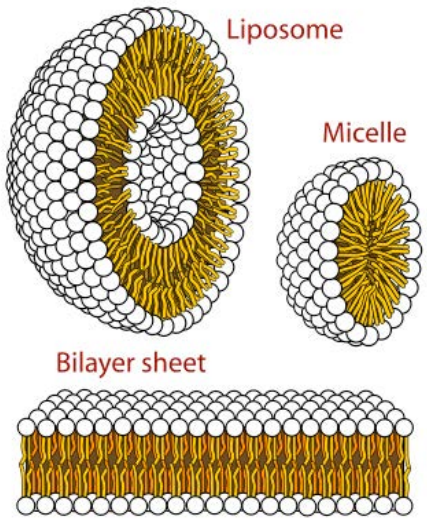
Lipid Bilayer

The lipid bilayer is a thin polar membrane made of two layers of lipid molecules. These membranes are flat sheets that form a continuous barrier around all cells. The lipid bilayer is the barrier that keeps ions, proteins and other molecules where they are needed and prevents them from diffusing into areas where they should not be.



https://en.wikipedia.org/wiki/Lipid_bilayer

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Lipid Metabolism

Lipid metabolism is the synthesis and degradation of lipids in cells. The types of lipids involved include:

- Bile salts
- Cholesterols
- Eicosanoids
- Glycolipids
- Ketone bodies
- Fatty acids - see also fatty acid metabolism
- Phospholipids
- Sphingolipids
- Steroid - see also steroidogenesis
- Triacylglycerols (fats)

https://en.wikipedia.org/wiki/Lipid_metabolism

Related Glossary Terms

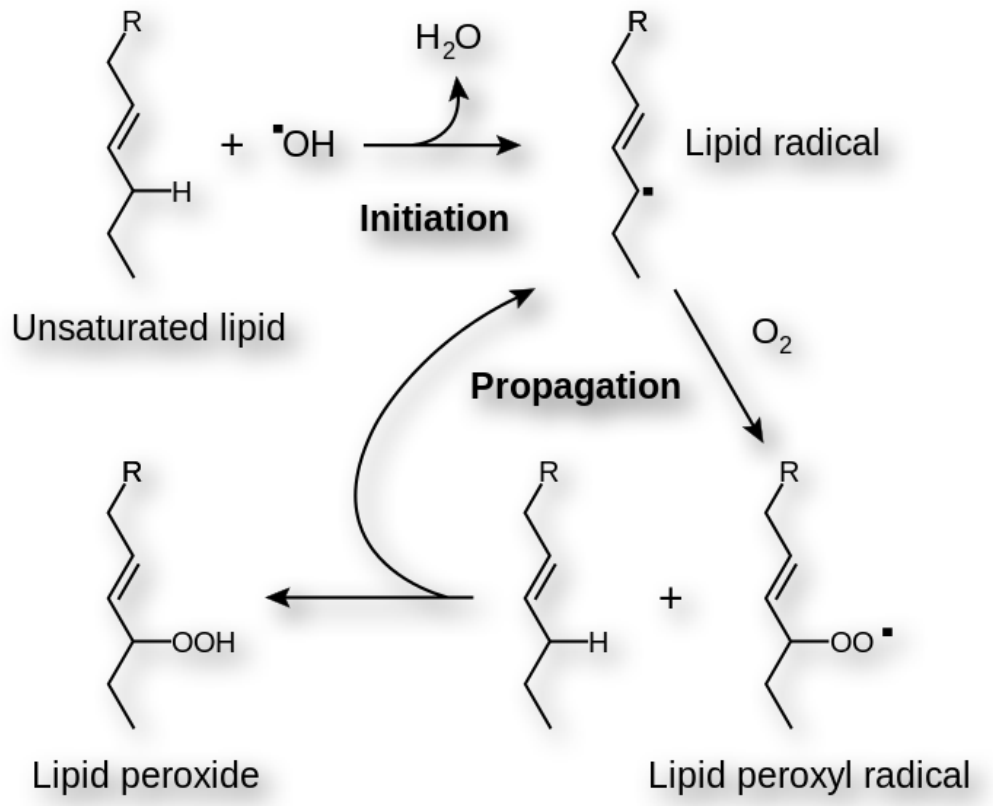
Drag related terms here

Index Find Term

Chapter 1 - Chemistry, Buffers, and Energy

Lipid Peroxidation

Lipid peroxidation is the oxidative degradation of lipids. It is the process in which free radicals "steal" electrons from the lipids in cell membranes, resulting in cell damage. This process proceeds by a free radical chain reaction mechanism. It most often affects polyunsaturated fatty acids, because they contain multiple double bonds in between which lie methylene bridges (-CH_2-) that possess especially reactive hydrogen atoms. As with any radical reaction, the reaction consists of three major steps: initiation, propagation, and termination. The chemical products of this oxidation are known as lipid peroxides or lipid oxidation products (LOPs).



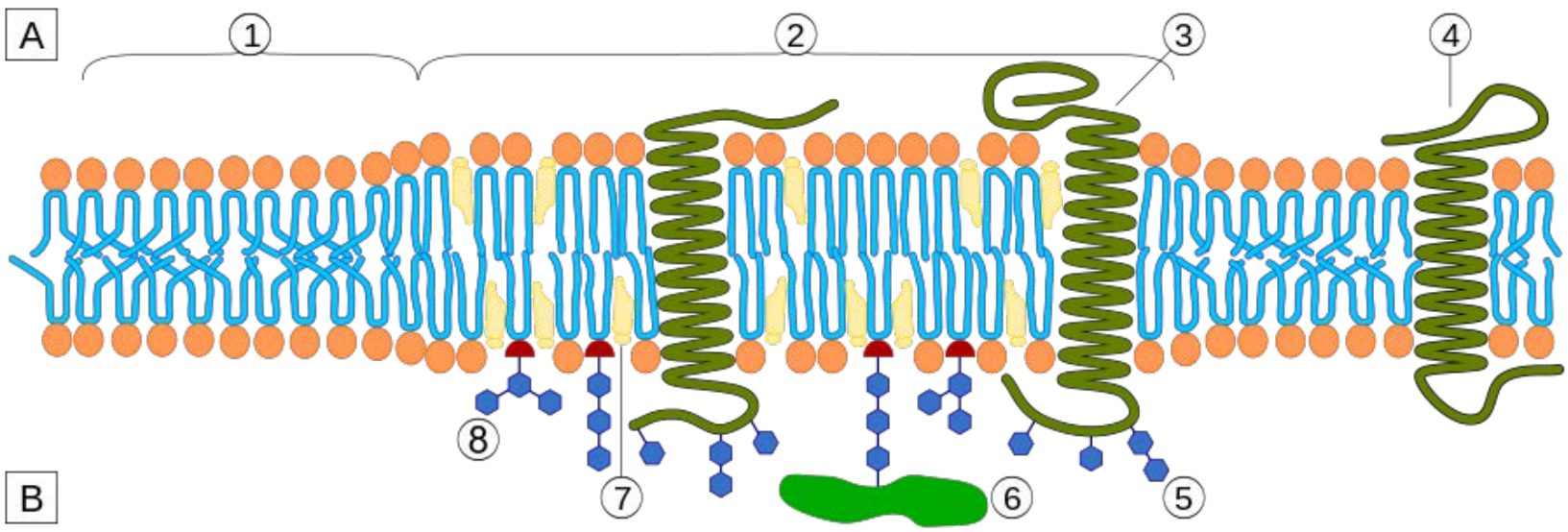
https://en.wikipedia.org/wiki/Lipid_peroxidation

Related Glossary Terms

Lipid Rafts

The plasma membranes of cells contain combinations of glycosphingolipids and protein receptors organized in glycolipoprotein microdomains termed lipid rafts.These specialized membrane microdomains compartmentalize cellular processes by serving as organizing centers for the assembly of signaling molecules, influencing membrane fluidity and membrane protein trafficking, and regulating neurotransmission and receptor trafficking. Lipid rafts are more ordered and tightly packed than the surrounding bilayer, but float freely in the membrane bilayer.

The lipid raft in the figure below is under #2



https://en.wikipedia.org/wiki/Lipid_raft

Related Glossary Terms

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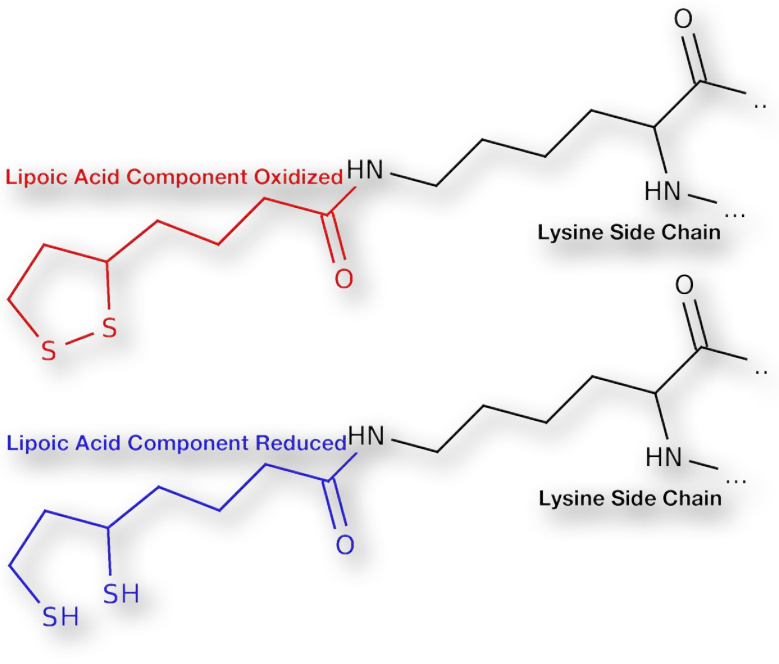
Lipoamide

Lipoamide is a trivial name for 6,8-dithiooctanoic amide. It is 6,8-dithiooctanoic acid's functional form where the carboxyl group is attached to protein (or any other amine) by an amide linkage (containing -NH_2). Sometimes lipoamide is used to refer to protein bound lipoic acid, but this can be misleading as this is technically incorrect. Lipoyl-protein or lipoyl-domain are better terms to refer to protein bound lipoic acid.

Lipamide is shown below in oxidized and reduced forms. The lipoic acid portions are shown in color.



https://en.wikipedia.org/wiki/Lipoamide

Related Glossary Terms

Drag related terms here

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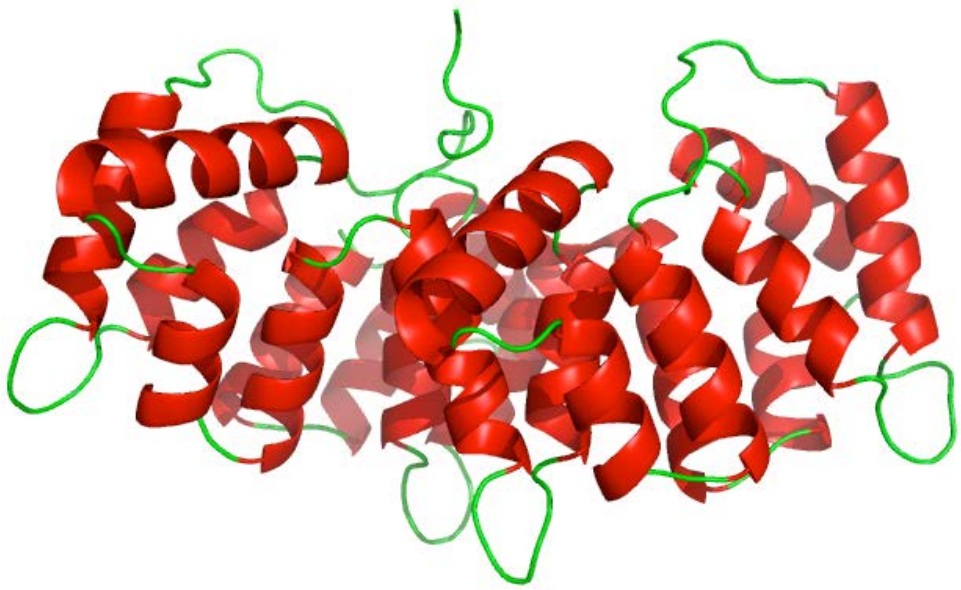
Lipocortin

Annexin is also known as lipocortin. Lipocortins suppress phospholipase A_2. In-
creased expression of the gene coding for annexin-1 is one of the mechanisms by
glucocorticoids (such as cortisol) inhibit inflammation.



https://en.wikipedia.org/wiki/Annexin

Related Glossary Terms

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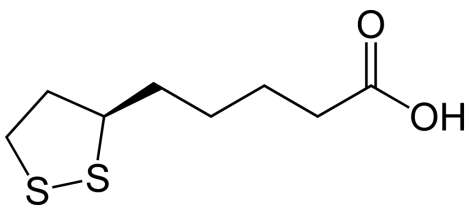
Lipoic Acid

Lipoic acid (LA), also known as α-lipoic acid and α lipoic acid (ALA) and thioctic acid is an organosulfur compound derived from octanoic acid. ALA is made in animals normally, and is essential for aerobic metabolism. It is also manufactured and is available as a dietary supplement in some countries where it is marketed as an antioxidant, and is available as a pharmaceutical drug in other countries.

The carbon atom at C6 is chiral and the molecule exists as two enantiomers (R)-(+)-lipoic acid (RLA) and (S)-(-)-lipoic acid (SLA) and as a racemic mixture (R/S)-lipoic acid (R/S-LA).

Most endogenously produced RLA is not "free" because octanoic acid, the precursor to RLA, is bound to the enzyme complexes prior to enzymatic insertion of the sulfur atoms. As a cofactor, RLA is covalently attached by an amide bond to a terminal lysine residue of the enzyme's lipoyl domains. One of the most studied roles of RLA is as a cofactor of the pyruvate dehydrogenase complex (PDC or PDHC), though it is a cofactor in other enzymatic systems as well (described below).

Only the (R)-(+)-enantiomer (RLA) exists in nature and is essential for aerobic metabolism because RLA is an essential cofactor of many enzyme complexes.



https://en.wikipedia.org/wiki/Lipoic_acid

Related Glossary Terms

Drag related terms here

Lipopolysaccharide Layer

A layer of lipopolysaccharides (LPS), also known as lipoglycans and endotox
are large molecules consisting of a lipid and a polysaccharide composed of O
outer core and inner core joined by a covalent bond are found in the outer m
of Gram-negative bacteria, and elicit strong immune responses in animals.

LPS is the major component of the outer membrane of Gram-negative bacte
uting greatly to the structural integrity of the bacteria, and protecting the me
from certain kinds of chemical attack. LPS also increases the negative charge
membrane and helps stabilize the overall membrane structure. It is of crucia
tance to gram-negative bacteria, whose death results if it is mutated or remo
induces a strong response from normal animal immune systems. It has also
cated in non-pathogenic aspects of bacterial ecology, including surface adhes
riophage sensitivity, and interactions with predators such as amoebae.

https://en.wikipedia.org/wiki/Lipopolysaccharide#Biosynthesis_and_trans

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Related Glossary Terms

Drag related terms here

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Chapter 3 - Membranes: Other Considerations

Chapter 9 - Point by Point: Membranes

Lipoprotein Complex

A lipoprotein complex is a biochemical assembly that contains both proteins a
ids, bound to the proteins, which allow fats to move through the water inside a
side cells. The proteins serve to emulsify the lipid molecules. Many enzymes, t
ers, structural proteins, antigens, adhesins, and toxins are lipoproteins. Examp
clude the plasma lipoprotein particles classified under high-density (HDL) and
density (LDL) lipoproteins, which enable fats to be carried in the blood stream
transmembrane proteins of the mitochondrion and the chloroplast, and bacter
proteins.

https://en.wikipedia.org/wiki/Lipoprotein

Related Glossary Terms

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Lipoprotein Complexes

A lipoprotein complex is a biochemical assembly that contains both protein
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transmembrane proteins of the mitochondrion and the chloroplast, and bac
proteins.

https://en.wikipedia.org/wiki/Lipoprotein

Related Glossary Terms

Drag related terms here

Lipoprotein Lipase

Lipoprotein lipase (LPL) (EC 3.1.1.34) is a member of the lipase gene family, w
cludes pancreatic lipase, hepatic lipase, and endothelial lipase. It is a water-solu
zyme that hydrolyzes triglycerides in lipoproteins, such as those found in chylo
and very low-density lipoproteins (VLDL), into three free fatty acids and one gl
molecule. It is also involved in promoting the cellular uptake of chylomicron re
cholesterol-rich lipoproteins, and free fatty acids. LPL requires ApoC-II as a co

LPL is attached to the luminal surface of endothelial cells in capillaries by the p
glycosylphosphatidylinositol HDL-binding protein 1 (GPIHBP1) and by heparan
fated proteoglycans. It is most widely distributed in adipose, heart, and skeletal
tissue, as well as in lactating mammary glands.

https://en.wikipedia.org/wiki/Lipoprotein_lipase

Related Glossary Terms

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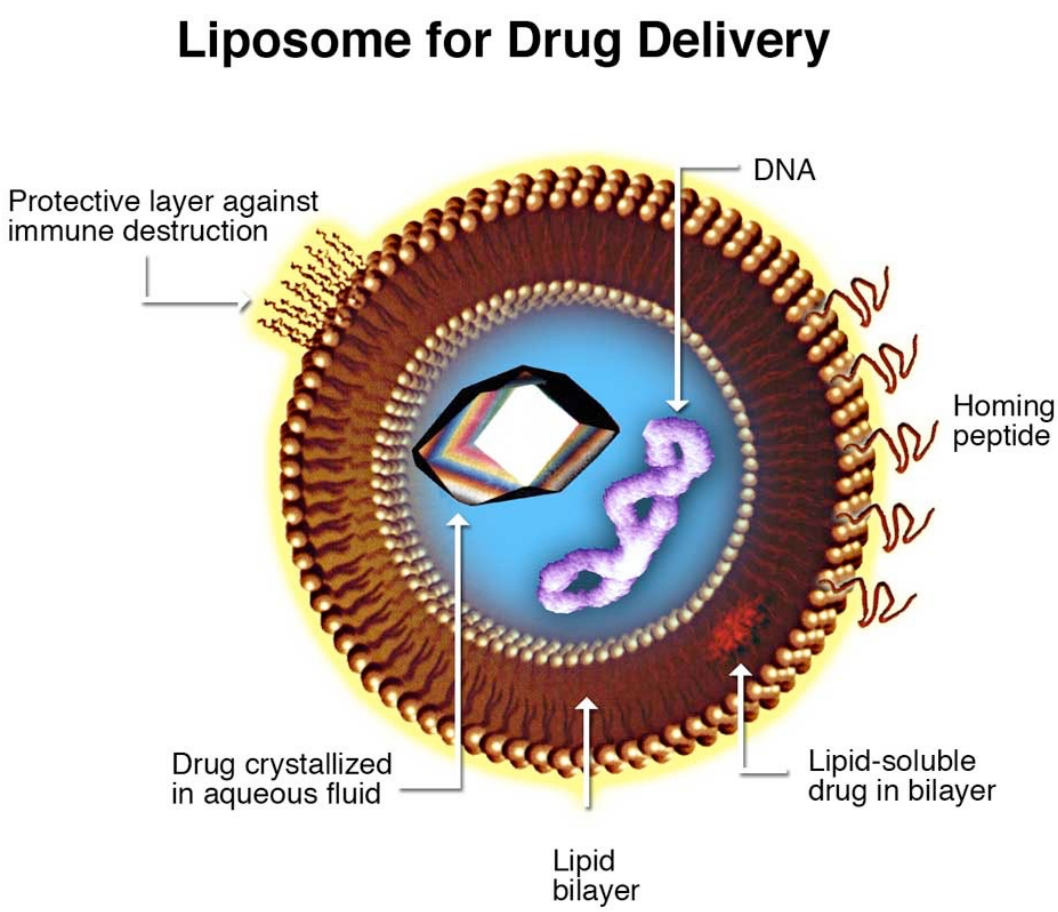
Index Find Term

Liposomes

A liposome is a spherical vesicle having at least one lipid bilayer. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs. Liposomes can be prepared by disrupting biological membranes (such as by sonication).



https://en.wikipedia.org/wiki/Liposome

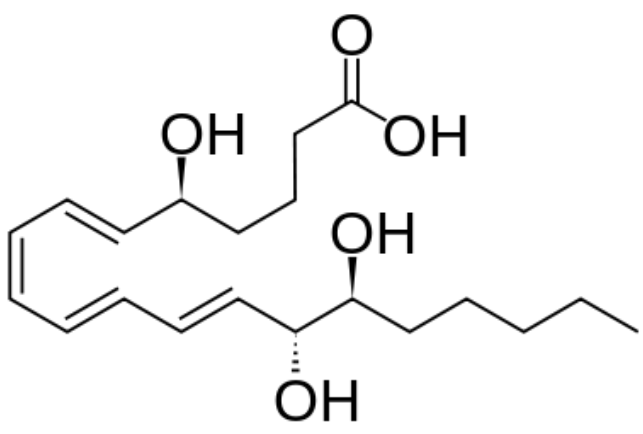
Related Glossary Terms

Drag related terms here

Lipoxins

Lipoxins are members of the family of bioactive products generated from arachidonic acid (AA). They have a number of immunomodulatory and anti-inflammatory actions. Lipoxins are short lived endogenously produced nonclassic eicosanoids whose appearance in inflammation signals the resolution of inflammation. They are abbreviated as LX, an acronym for lipoxygenase (LO) interaction products. At present two lipoxins have been identified - lipoxin A_4 (LXA_4) and lipoxin B_4 (LXB_4). LXB_4 is shown at the bottom.

Lipoxins are derived enzymatically from arachidonic acid, an ω-6 fatty acid. One important precursor to the lipoxins is 15-hydroxyicosatetraenoic acid (i.e. 15(S)-HETE) and its 15-hydroperoxy precusor. Transcellular biosynthetic mechanisms play a key role in their production. They are formed by platelets but they alone cannot synthesize them. Platelets depend upon neutrophils for LTA4, which is converted to LXA4 and LXB4 by the action of platelet 12-lipoxygenase. LTC4, LTD4, and LTE4 are also synthesized in platelets from LTA4. An analogous class, the resolvins, are derived from EPA and DHA, ω-3 fatty acids. Another analogous class, the epi-lipoxins, are formed by non-enzymatic peroxidation.



https://en.wikipedia.org/wiki/Lipoxin

Related Glossary Terms

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Index Find Term

Lnc RNAs

Long non-coding RNAs (long ncRNAs, lncRNA) are non-protein coding transcripts longer than 200 nucleotides. This somewhat arbitrary limit distinguishes long ncRNAs from small regulatory RNAs such as microRNAs (miRNAs), short interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and other short RNAs.

Many small RNAs, such as microRNAs or snoRNAs, exhibit strong conservation across diverse species. In contrast, long ncRNAs (such as Air and Xist) lack strong conservation, suggesting non-functionality or the effects of different selection pressures. Unlike mRNAs, which have to conserve the codon usage and prevent frameshift mutations in a single long ORF, selection may conserve only short regions of long ncRNAs that are constrained by structure or sequence-specific interactions. Therefore, we may see selection act only over small regions of the long ncRNA transcript. Thus, despite low conservation of long ncRNAs in general, it should be noted that many long ncRNAs still contain strongly conserved elements. For example, 19% of highly conserved phastCons elements occur in known introns, and another 32% in unannotated regions. Furthermore, a representative set of human long ncRNAs exhibit small, yet significant, reductions in substitution and insertion/deletion rates indicative of purifying selection that conserve the integrity of the transcript at the levels of sequence, promoter and splicing.

Large-scale sequencing of cDNA libraries and more recently transcriptomic sequencing by next generation sequencing indicate that long noncoding RNAs number in the order of tens of thousands in mammals. However, despite accumulating evidence suggesting that the majority of these are likely to be functional, only a relatively small proportion has been demonstrated to be biologically relevant. As of January 2016, 294 LncRNAs have been functionally annotated in LncRNAdb (a database of literature described LncRNAs), with the majority of these (183 LncRNAs) being described in humans. A further large-scale sequencing study provides evidence that many transcripts thought to be LncRNAs may, in fact, be translated into proteins

https://en.wikipedia.org/wiki/Long_non-coding_RNA

Related Glossary Terms

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Chapter 7 - Information Processing: Transcription

lncRNAs

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https://en.wikipedia.org/wiki/Long_non-coding_RNA

Related Glossary Terms

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Local Minima

In mathematical analysis, the maxima and minima (the respective plurals o
and minimum) of a function, known collectively as extrema (the plural of ex
are the largest and smallest value of the function, either within a given rang
or relative extrema) or on the entire domain of a function (the global or abs
trema).

https://en.wikipedia.org/wiki/Maxima_and_minima

Related Glossary Terms

Drag related terms here

Index

Find Term

Chapter 2 - Structure & Function: Proteins I

Lock and Key

To explain the observed specificity of enzymes, in 1894 Emil Fischer propos
both the enzyme and the substrate possess specific complementary geomet
that fit exactly into one another. This is often referred to as "the lock and ke
This early model explains enzyme specificity, but fails to explain the stabili
transition state that enzymes achieve.

https://en.wikipedia.org/wiki/Enzyme#.22Lock_and_key.22_model

Related Glossary Terms

Drag related terms here

Low Density Lipoprotein

Low-density lipoprotein (LDL) is one of the five major groups of lipoprotein. Th
groups, from least dense to most dense, are chylomicrons, very low-density lipo
(VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein and hi
density lipoprotein (HDL).

LDL particles pose a risk for cardiovascular disease when they invade the endot
and become oxidized, since the oxidized forms are more easily retained by the p
glycans. A complex set of biochemical reactions regulates the oxidation of LDL
cles, chiefly stimulated by presence of necrotic cell debris and free radicals in th
thelium. Increasing concentrations of LDL particles are strongly associated wit
creasing rates of accumulation of atherosclerosis within the walls of arteries ov
eventually resulting in sudden plaque ruptures and triggering clots within the a
opening, or a narrowing or closing of the opening, i.e. cardiovascular disease, st
and other vascular disease complications.

https://en.wikipedia.org/wiki/Low-density_lipoprotein

Related Glossary Terms

Drag related terms here

Low Density Lipoprotein Complexes

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opening, or a narrowing or closing of the opening, i.e. cardiovascular disease, st
and other vascular disease complications.

https://en.wikipedia.org/wiki/Low-density_lipoprotein

Related Glossary Terms

Drag related terms here

Lubricin

Proteoglycan 4 or lubricin is a proteoglycan that in humans is encoded by t
gene. This proteoglycan acts as a joint/boundary lubricant.

Lubricin is present in synovial fluid and on the surface (superficial layer) of
cartilage and therefore plays an important role in joint lubrication and syno
stasis.

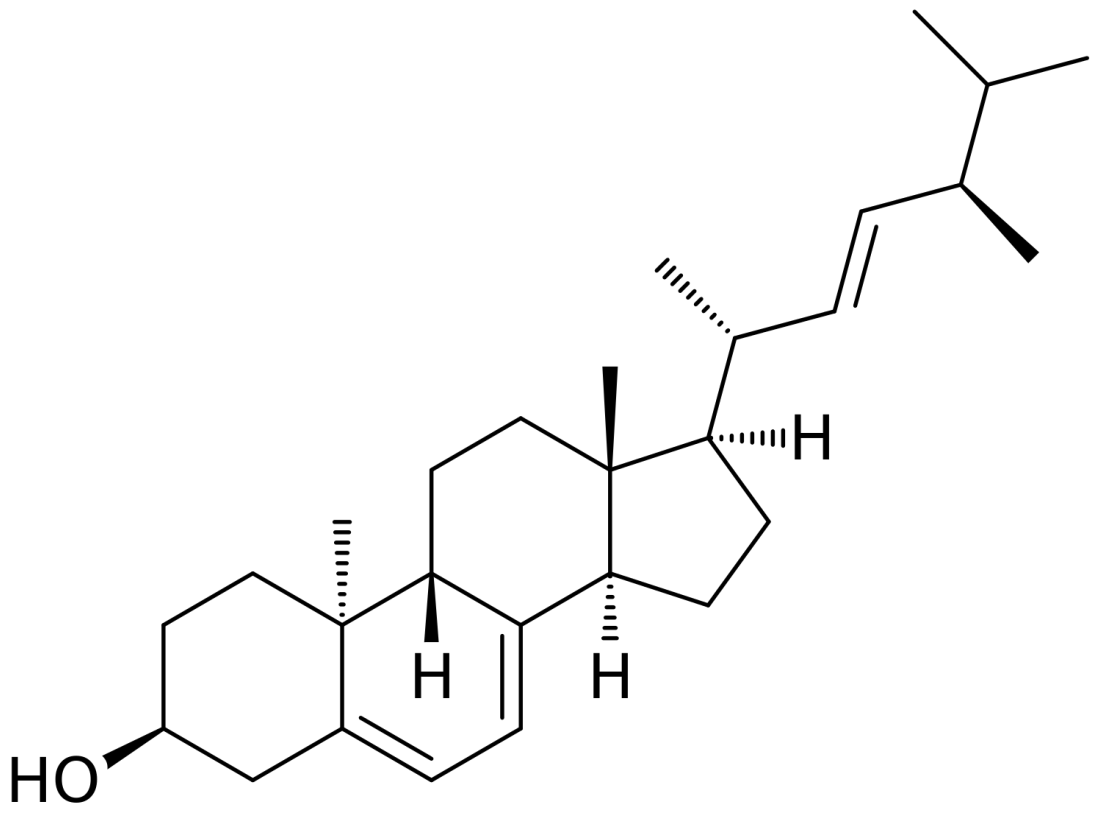
https://en.wikipedia.org/wiki/PRG4

Related Glossary Terms

Drag related terms here

Lumisterol

Lumisterol is a compound that is part of the vitamin D family of steroid compounds. It is the (9β,10α) stereoisomer of ergosterol and was produced as a photochemical by-product in the preparation of vitamin D_1, which was a mixture of vitamin D_2 and lumisterol. Vitamin D_2 can be formed from lumisterol by an electrocyclic ring opening and subsequent sigmatropic hydride shift.



https://en.wikipedia.org/wiki/Lumisterol

Related Glossary Terms

Luteinizing Hormone

Luteinizing hormone (LH, also known as lutropin and sometimes lutrophin
mone produced by gonadotropic cells in the anterior pituitary gland. In fem
acute rise of LH ("LH surge") triggers ovulation and development of the cor
teum. In males, where LH had also been called interstitial cell–stimulating
(ICSH), it stimulates Leydig cell production of testosterone. It acts synergis
FSH.

https://en.wikipedia.org/wiki/Luteinizing_hormone

Related Glossary Terms

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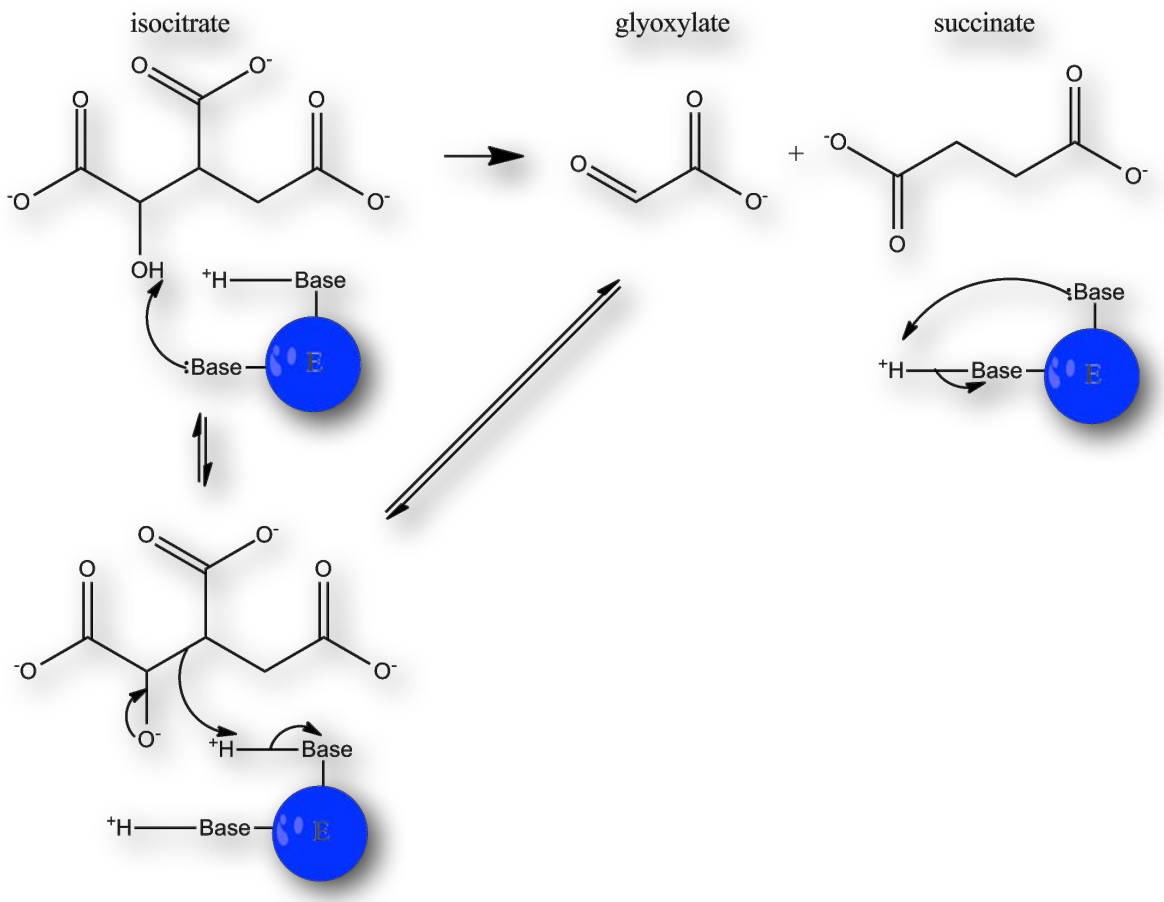
Chapter 2 - Structure & Function: Carbohydrates

Lyase

A lyase is an enzyme that catalyzes the breaking (an "elimination" reaction) of various chemical bonds by means other than hydrolysis (a "substitution" reaction) and oxidation, often forming a new double bond or a new ring structure. The reverse reaction is also possible (called a "Michael addition").

Isocitrate lyase is an example. It catalyzes the reaction below.



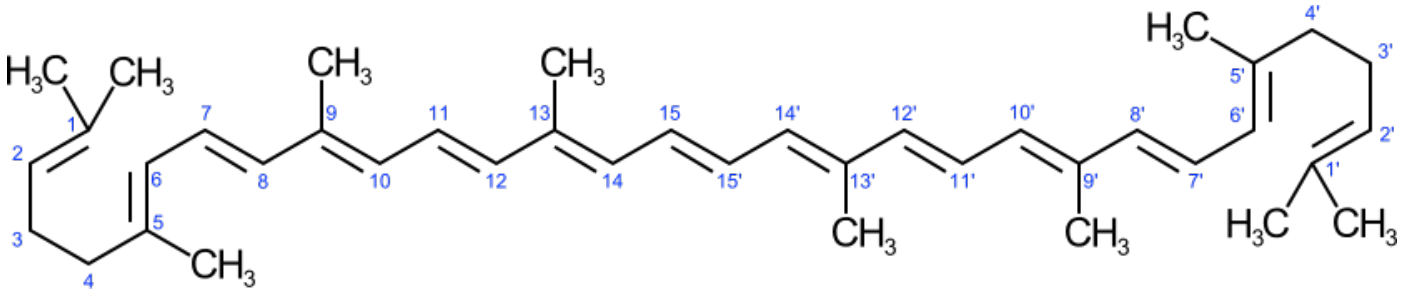
https://en.wikipedia.org/wiki/Lyase

Related Glossary Terms

Lycopene

Lycopene from the neo-Latin lycopersicum, the tomato species, is a bright red carotene and carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons, gac, and papayas, although not in strawberries, or cherries. Although lycopene is chemically a carotene, it has no vitamin A activity.

In plants, algae, and other photosynthetic organisms, lycopene is an important intermediate in the biosynthesis of many carotenoids, including β carotene, which is responsible for yellow, orange, or red pigmentation, photosynthesis, and photo-protection. Like all carotenoids, lycopene is a polyunsaturated hydrocarbon, i.e. an unsubstituted alkene. Structurally, lycopene is a tetraterpene and assembled from eight isoprene units that are composed entirely of carbon and hydrogen. It is insoluble in water. Lycopene's eleven conjugated double bonds give its deep red color and its antioxidant activity. Owing to the strong color, lycopene is a useful food coloring (registered as E160d) and is approved for usage in the USA, Australia and New Zealand (registered as 160d) and the EU.



https://en.wikipedia.org/wiki/Lycopene

Related Glossary Terms

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Lymph

Lymph is the fluid that circulates throughout the lymphatic system. The lyr
formed when the interstitial fluid (the fluid which lies in the interstices of a
sues) is collected through lymph capillaries. It is then transported through
sels to lymph nodes before emptying ultimately into the right or the left sub
vein, where it mixes back with blood.

https://en.wikipedia.org/wiki/Lymph

Related Glossary Terms

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Find Term

Chapter 1 - Chemistry, Buffers, and Energy

Lymphocytes

A lymphocyte is one of the subtypes of white blood cell in a vertebrate's im
tem. Lymphocytes include natural killer cells (NK cells) (which function in
mediated, cytotoxic innate immunity), T cells (for cell-mediated, cytotoxic a
munity), and B cells (for humoral, antibody-driven adaptive immunity). Th
main type of cell found in lymph, which prompted the name lymphocyte.

https://en.wikipedia.org/wiki/Lymphocyte

Related Glossary Terms

Drag related terms here

Lymphotactin

Chemokine (C motif) ligand (XCL1) is a small cytokine belonging to the XC family that is also known as lymphotactin. It is found in high levels in spl mus, intestine and peripheral blood leukocytes, and at lower levels in lung, gland and ovary. Cellular sources for XCL1 include activated thymic and pe blood $CD8^+$ T cells. This chemokine attracts T cells. In humans, XCL1 is clo to another chemokine called XCL2, whose gene is found at the same locus o some 1. XCL1 induces it chemotactic function by binding to a chemokine re called XCR1.

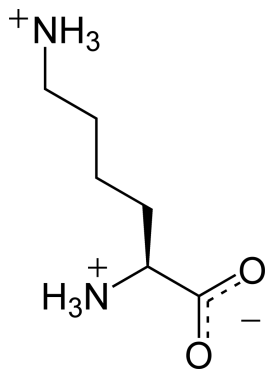
https://en.wikipedia.org/wiki/XCL1

Related Glossary Terms

Drag related terms here

Lysine

Lysine (abbreviated as Lys or K), encoded by the codons AAA and AAG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated –NH3+ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $–COO^-$ form under biological conditions), and a side chain lysyl ($(CH_2)_4NH_2$), classifying it as a charged (at physiological pH), aliphatic amino acid. It is essential in humans, meaning the body cannot synthesize it and thus it must be obtained from the diet.



https://en.wikipedia.org/wiki/Lysine

Related Glossary Terms

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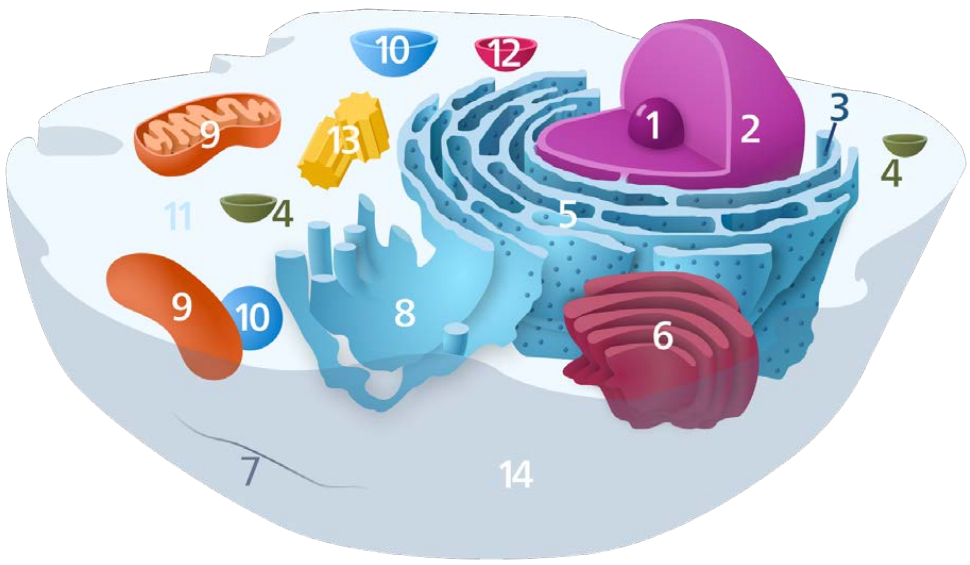
Lysosome

A lysosome (derived from the Greek words lysis, meaning "to loosen", and soma, "body") is a membrane-bound cell organelle found in most animal cells (they are absent in red blood cells). Structurally and chemically, they are spherical vesicles containing hydrolytic enzymes capable of breaking down virtually all kinds of biomolecules, including proteins, nucleic acids, carbohydrates, lipids, and cellular debris.

They are known to contain more than 50 different enzymes, which are all optimally active at an acidic environment of about pH 4.5 (about the pH of black coffee). Thus lysosomes act as the waste disposal system of the cell by digesting unwanted materials in the cytoplasm, both from outside of the cell and obsolete components inside the cell. For this function they are popularly referred to as "suicide bags" or "suicide sacs" of the cell. Furthermore, lysosomes are responsible for cellular homeostasis for their involvements in secretion, plasma membrane repair, cell signaling and energy metabolism, which are related to health and diseases.

The lysosome is depicted as structure #12 below



https://en.wikipedia.org/wiki/Lysosome

Related Glossary Terms

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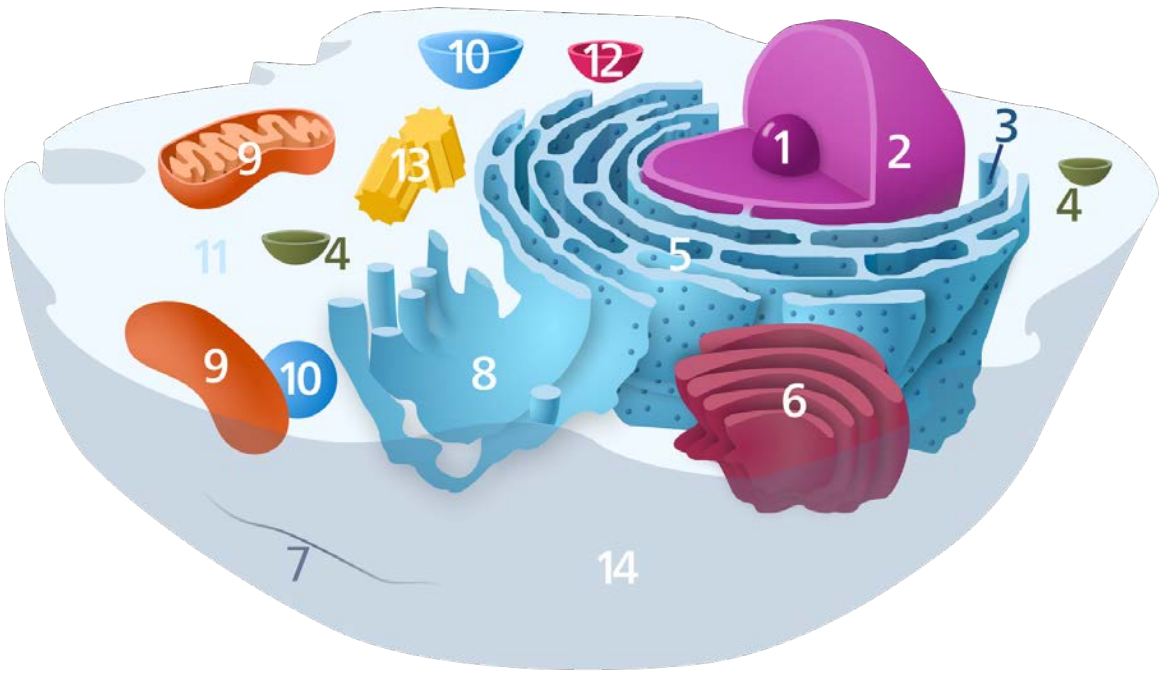

https://en.wikipedia.org/wiki/Lysosome

Related Glossary Terms

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Lysozyme

Lysozymes, also known as muramidase or N-acetylmuramide glycanhydrol
coside hydrolases. These are enzymes (EC 3.2.1.17) that damage bacterial c
catalyzing hydrolysis of 1,4-β-linkages between N-acetylmuramic acid and
glucosamine residues in a peptidoglycan and between N-acetyl-D-glucosam
dues in chitodextrins. Lysozyme is abundant in a number of secretions, suc
saliva, human milk, and mucus. It is also present in cytoplasmic granules o
phages and the polymorphonuclear neutrophils (PMNs). Large amounts of
can be found in egg white. C-type lysozymes are closely related to α-lactalb
quence and structure, making them part of the same family. In humans, th
enzyme is encoded by the LYZ gene.

https://en.wikipedia.org/wiki/Lysozyme

Related Glossary Terms

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Index Find Term

Lysyl-hydroxylase

Lysyl hydroxylase (or procollagen-lysine 5-dioxygenase) is an oxygenase en
catalyzes the hydroxylation of lysine to hydroxylysine. This reaction is nece
formation and stabilization of collagen. It takes place following protein syn
post-translational modification). The protein is a membrane-bound homoc
zyme that is localized to the cisternae (lumen) of the rough endoplasmic ret

It requires iron and vitamin C as cofactors.

https://en.wikipedia.org/wiki/Lysyl_hydroxylase

Related Glossary Terms

Drag related terms here

Macrophages

Macrophages (Greek: big eaters, from Greek μακρος (makros) = large, φαγειν (phagein) = to eat) are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, cancer cells, and anything else that does not have the types of proteins specific of healthy body cells on its surface in a process called phagocytosis. These large phagocytes are found in essentially all tissues, where they patrol for potential pathogens by amoeboid movement. They take various forms (with various names) throughout the body (e.g., histiocytes, Kupffer cells, alveolar macrophages, microglia, and others), but all are part of the mononuclear phagocyte system.

Besides phagocytosis, macrophages play a critical role in nonspecific defense (innate immunity) and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. For example, they are important as antigen presenters to T cells. In humans, dysfunctional macrophages cause severe diseases such as chronic granulomatous disease that result in frequent infections.

https://en.wikipedia.org/wiki/Macrophage

Related Glossary Terms

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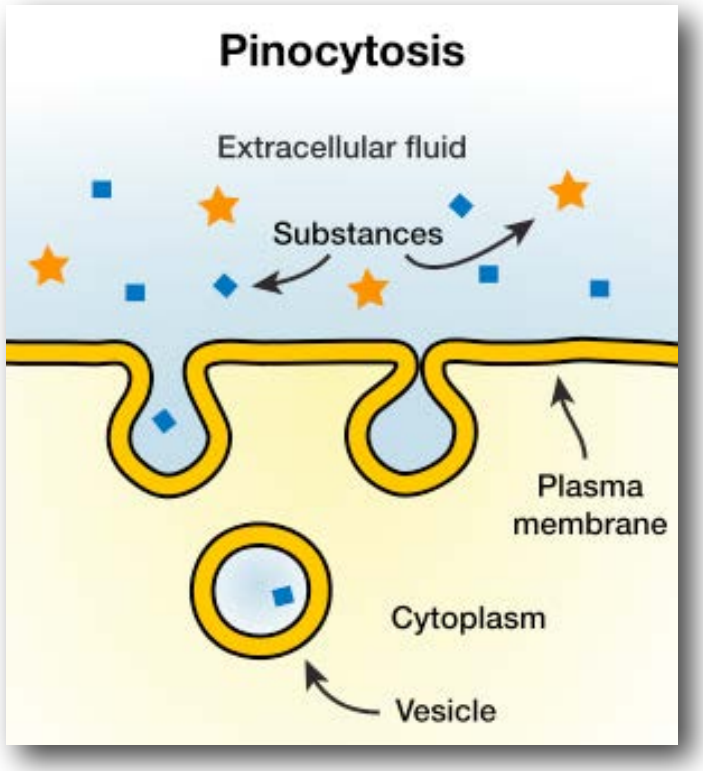
Macropinocytosis

In cellular biology, pinocytosis (pino- + cytosis), otherwise known as cell drinking, fluid endocytosis, and bulk-phase pinocytosis, is a mode of endocytosis in which small particles are brought into the cell, forming an invagination, and then suspended within small vesicles. These pinocytotic vesicles subsequently fuse with lysosomes to hydrolyze (break down) the particles. This process requires a lot of energy in the form of adenosine triphosphate (ATP), the chemical compound mostly used as energy in the majority of animal cells.



https://en.wikipedia.org/wiki/Pinocytosis

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Chapter 3 - Membranes: Other Considerations

Chapter 9 - Point by Point: Membranes

Chapter 9 - Point by Point: Membranes

Mad Cow disease

Bovine spongiform encephalopathy (BSE), commonly known as mad cow d
fatal neurodegenerative disease (encephalopathy) in cattle that causes a spo
eration of the brain and spinal cord. BSE has a long incubation period, abou
years, usually affecting adult cattle at a peak age onset of four to five years,
being equally susceptible. BSE is caused by a misfolded protein—a prion.

https://en.wikipedia.org/wiki/Bovine_spongiform_encephalopathy

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Chapter 9 - Point by Point: Structure and Function

Mad Cow Disease

Bovine spongiform encephalopathy (BSE), commonly known as mad cow d
fatal neurodegenerative disease (encephalopathy) in cattle that causes a spo
eration of the brain and spinal cord. BSE has a long incubation period, abou
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being equally susceptible. BSE is caused by a misfolded protein—a prion.

https://en.wikipedia.org/wiki/Bovine_spongiform_encephalopathy

Related Glossary Terms

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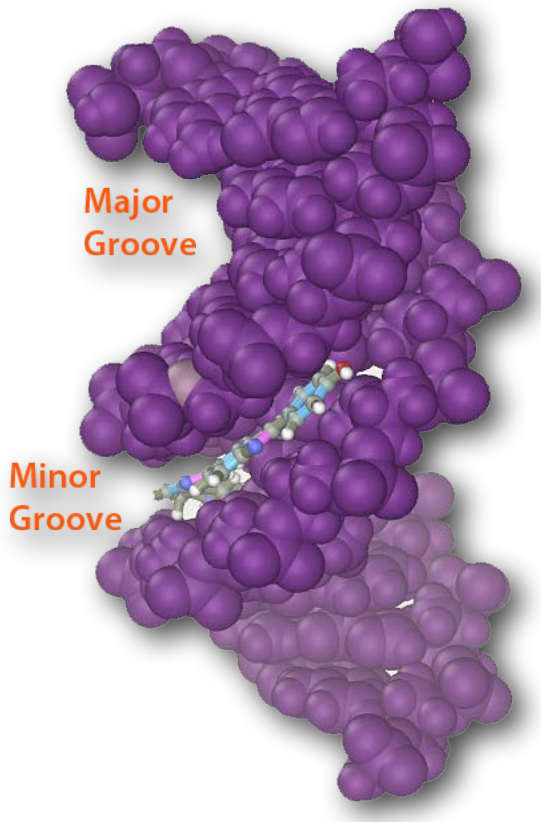
Major Groove

The double helix structure of DNA contains a major groove and minor groove. In B-DNA the major groove is wider than the minor groove. Given the difference in widths of the major groove and minor groove, many proteins which bind to B-DNA do so through the wider major groove.



https://en.wikipedia.org/wiki/Nucleic_acid_double_helix

Related Glossary Terms

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Major Histocompatibility Complex

The major histocompatibility complex (MHC) is a set of cell surface protein
for the acquired immune system to recognize foreign molecules in vertebra
in turn determines histocompatibility. The main function of MHC molecule
to peptide fragments derived from pathogens and display them on the cell s
recognition by the appropriate T-cells.

MHC molecules mediate interactions of leukocytes, also called white blood
(WBCs), which are immune cells, with other leukocytes or with body cells. T
determines compatibility of donors for organ transplant, as well as one's su
to an autoimmune disease via crossreacting immunization. In humans, the
also called the human leukocyte antigen (HLA).

https://en.wikipedia.org/wiki/Major_histocompatibility_complex

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Malaria

Malaria is a mosquito-borne infectious disease of humans and other anima
parasitic protozoans (a group of single-celled microorganisms) belonging t
modium type. Malaria causes symptoms that typically include fever, fatigue
and headaches. In severe cases it can cause yellow skin, seizures, coma, or d
toms usually begin ten to fifteen days after being bitten. If not properly trea
may have recurrences of the disease months later. In those who have recen
an infection, reinfection usually causes milder symptoms. This partial resis
pears over months to years if the person has no continuing exposure to mal

https://en.wikipedia.org/wiki/Malaria

Related Glossary Terms

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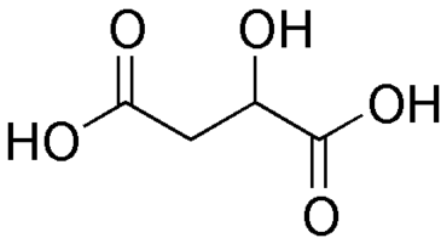
Malate

Malic acid is an organic compound with the molecular formula $C_4H_6O_5$. It is a dicarboxylic acid that is made by all living organisms, contributes to the pleasantly sour taste of fruits, and is used as a food additive. Malic acid has two stereoisomeric forms (L- and D-enantiomers), though only the L-isomer exists biologically. The salts and esters of malic acid are known as malates. The malate anion is an intermediate in the citric acid cycle.



https://en.wikipedia.org/wiki/Malic_acid

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Malate Dehydrogenase

Malate dehydrogenase (EC 1.1.1.37) (MDH) is an enzyme that reversibly catalyzes the oxidation of malate to oxaloacetate using the reduction of NAD^+ to NADH. This reaction is part of many metabolic pathways, including the citric acid cycle. Other malate dehydrogenases, which have other EC numbers and catalyze other reactions oxidizing malate, have qualified names like malate dehydrogenase ($NADP^+$).

Malate dehydrogenase is also involved in gluconeogenesis, the synthesis of glucose from smaller molecules. Pyruvate in the mitochondria is acted upon by pyruvate carboxylase to form oxaloacetate, a citric acid cycle intermediate. In order to get the oxaloacetate out of the mitochondria, malate dehydrogenase reduces it to malate, and it then traverses the inner mitochondrial membrane. Once in the cytosol, the malate is oxidized back to oxaloacetate by cytosolic malate dehydrogenase. Finally, phosphoenolpyruvate carboxykinase (PEPCK) converts oxaloacetate to phosphoenolpyruvate (PEP).

https://en.wikipedia.org/wiki/Malate_dehydrogenase

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Malate Synthase

Malate synthase (EC 2.3.3.9) is an enzyme that catalyzes the chemical reaction

Acetyl-CoA + H_2O + Glyoxylate <---> (L)-malate + CoASH

This enzyme participates in pyruvate metabolism and glyoxylate and dicarboxylate metabolism. Malate synthase works together with isocitrate lyase in the glyoxylate cycle to bypass two oxidative steps of citric acid cycle and permit carbon incorporation from acetate or fatty acids in many microorganisms. As a result, the cell would not need to lose 2 molecules of carbon dioxide when entering the glyoxylate cycle rather than the citric acid cycle. This pathway is especially important to *M. tuberculosis*, allowing long-term persistence of its infection. When the *M. tuberculosis* becomes phagocytosed, the bacterium upregulates genes encoding the glyoxylate shunt enzymes. Since this cycle is not found in humans and other mammals, malate synthase is perceived as a future drug target against tuberculosis and other microorganisms. Within germinating plants, the glyoxylate cycle allows the conversion of reserve lipids into carbohydrates within glyoxysomes.

https://en.wikipedia.org/wiki/Malate_synthase

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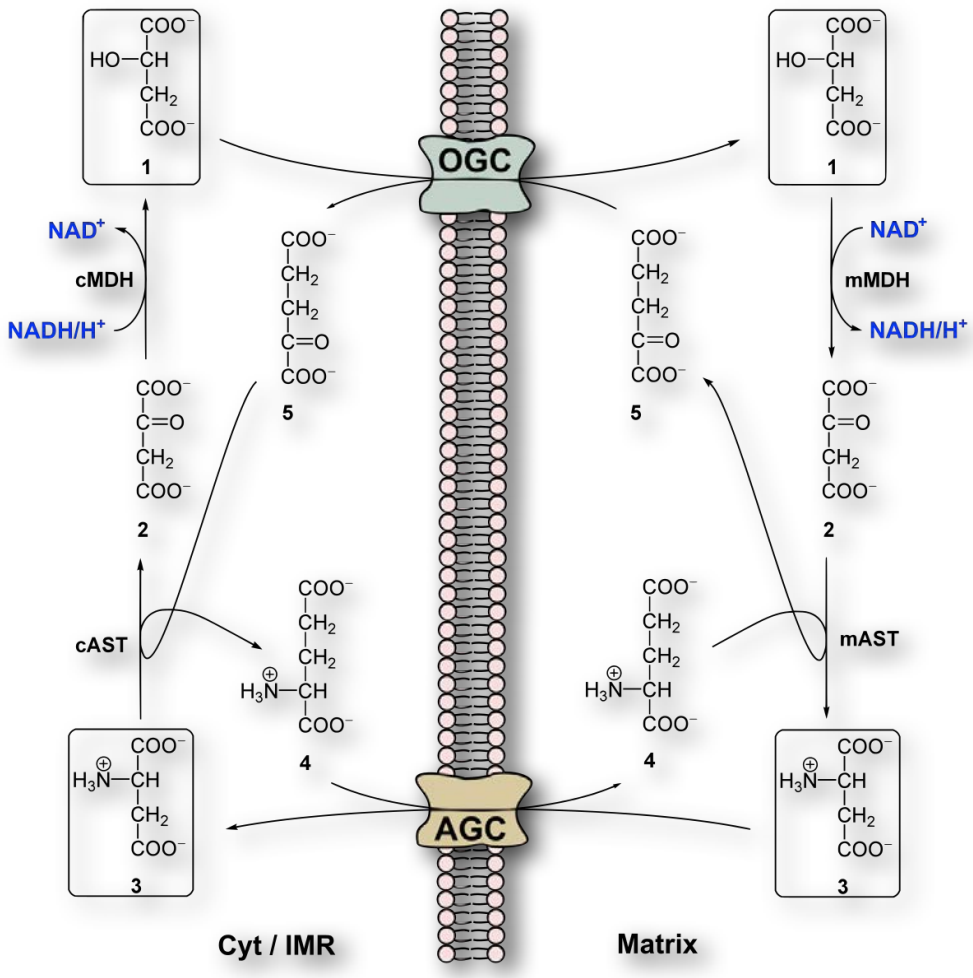
Malate-aspartate Shuttle

The malate-aspartate shuttle (sometimes also the malate shuttle) is a biochemical system for translocating electrons produced during glycolysis across the semipermeable inner membrane of the mitochondrion for oxidative phosphorylation in eukaryotes. These electrons enter the electron transport chain of the mitochondria via reduction equivalents to generate ATP. The shuttle system is required because the mitochondrial inner membrane is impermeable to NADH, the primary reducing equivalent of the electron transport chain. To circumvent this, malate carries the reducing equivalents across the membrane.



https://en.wikipedia.org/wiki/Malate-aspartate_shuttle

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MALDI-TOF

Matrix-assisted laser desorption/ionization (MALDI) is a soft ionization technique used in mass spectrometry, allowing the analysis of biomolecules (biopolymers such as DNA, proteins, peptides and sugars) and large organic molecules (such as polymers, dendrimers and other macromolecules), which tend to be fragile and fragment when ionized by more conventional ionization methods. It is similar in character to electrospray ionization (ESI) in that both techniques are relatively soft ways of obtaining ions of large molecules in the gas phase, though MALDI produces far fewer multiply charged ions.

MALDI methodology is a three-step process. First, the sample is mixed with a suitable matrix material and applied to a metal plate. Second, a pulsed laser irradiates the sample, triggering ablation and desorption of the sample and matrix material. Finally, the analyte molecules are ionized by being protonated or deprotonated in the hot plume of ablated gases, and can then be accelerated into whichever mass spectrometer is used to analyze them. The type of a mass spectrometer most widely used with MALDI is the TOF (time-of-flight mass spectrometer), mainly due to its large mass range. The TOF measurement procedure is also ideally suited to the MALDI ionization process since the pulsed laser takes individual 'shots' rather than working in continuous operation.

In proteomics, MALDI is used for the rapid identification of proteins isolated by using gel electrophoresis: SDS-PAGE, size exclusion chromatography, affinity chromatography, strong/weak ion exchange, isotope coded protein labelling (ICPL),and two-dimensional gel electrophoresis. Peptide mass fingerprinting is the most popular analytical application of MALDI-TOF mass spectrometers. MALDI TOF/TOF mass spectrometers are used to reveal amino acid sequence of peptides using post-source decay or high energy collision-induced dissociation (further use see mass spectrometry).
Loss of sialic acid has been identified in papers when DHB has been used as a matrix for MALDI MS analysis of glycosylated peptides. Using sinapinic acid, 4-HCCA and DHB as matrices, S. Martin studied loss of sialic acid in glycosylated peptides by metastable decay in MALDI/TOF in linear mode and reflector mode.

It has been reported that a reduction in loss of some post-translational modifications can be accomplished if IR MALDI is used instead of UV MALDI
In molecular biology, a mixture of 5-methoxysalicylic acid and spermine can be used as a matrix for oligonucleotides analysis in MALDI mass spectrometry, for instance after oligonucleotide synthesis.

https://en.wikipedia.org/wiki/Matrix-assisted_laser_desorption/ionization

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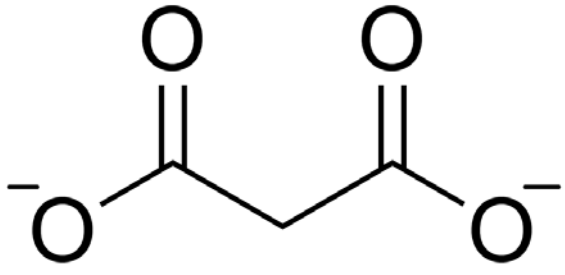
Malonate

The malonate or propanedioate ion is $CH_2(COO)_2^=$ (malonic acid minus two hydrogen ions). Malonate compounds include salts and esters of malonic acid, such as

diethyl malonate, $(C_2H_5)_2(C_3H_2O_4)$,
dimethyl malonate, $(CH_3)_2(C_3H_2O_4)$,
isodium malonate, $Na_2(C_3H_2O_4)$.

Malonate is a competitive inhibitor of the enzyme succinate dehydrogenase: malonate binds to the active site of the enzyme without reacting, and so competes with succinate, the usual substrate of the enzyme. The observation that malonate is a competitive inhibitor of succinate dehydrogenase was used to deduce the structure of the active site in that enzyme.The chemical malonate decreases cellular respiration. It resembles the substrate succinate, without a $-CH_2-CH_2$ group required for dehydrogenation.



https://en.wikipedia.org/wiki/Malonate

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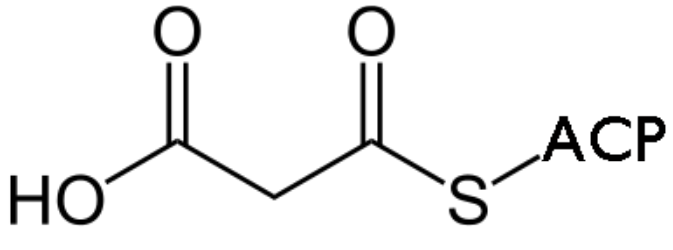
Malonyl-ACP

Malonyl-ACP is an intermediate in fatty acid biosynthesis. It is synthesized
malonyl-CoA by the enzyme malonyl coenzyme A:acyl carrier protein trans
(MCAT). Malonyl-ACP is a substrate for fatty acid synthase. It provides tw
bons in each round of synthesis of a fatty acid. The third carbon is released
dioxide in the process.



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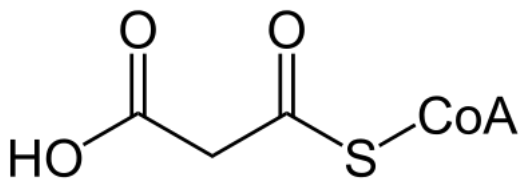
Malonyl-CoA

Malonyl-CoA is a coenzyme A thioester of malonic acid. It plays a key role in chain elongation in fatty acid biosynthesis and polyketide biosynthesis.

Malonyl-CoA is a highly-regulated molecule in fatty acid synthesis. As such, it inhibits the rate-limiting step in β-oxidation of fatty acids. Malonyl CoA inhibits fatty acids from associating with carnitine by regulating the enzyme carnitine acyltransferase, thereby preventing them from entering the mitochondria, where fatty acid oxidation and degradation occur.



https://en.wikipedia.org/wiki/Malonyl-CoA

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Malonyl-CoA : ACP transacylase

The systematic name of this enzyme class is malonyl-CoA:[acyl-carrier-pro
malonyltransferase. It catalyzes the chemical reaction

Malonyl-CoA + Acyl carrier protein (ACP) <----- > CoASH + Malonyl-[acy
protein (ACP)]

Thus, the two substrates of this enzyme are malonyl-CoA and acyl carrier p
whereas its two products are CoA and malonyl-acyl-carrier-protein. This er
longs to the family of transferases, specifically those acyltransferases transf
groups other than aminoacyl groups. This enzyme participates in fatty acid
sis.

https://en.wikipedia.org/wiki/(acyl-carrier-protein)_S-malonyltransferase

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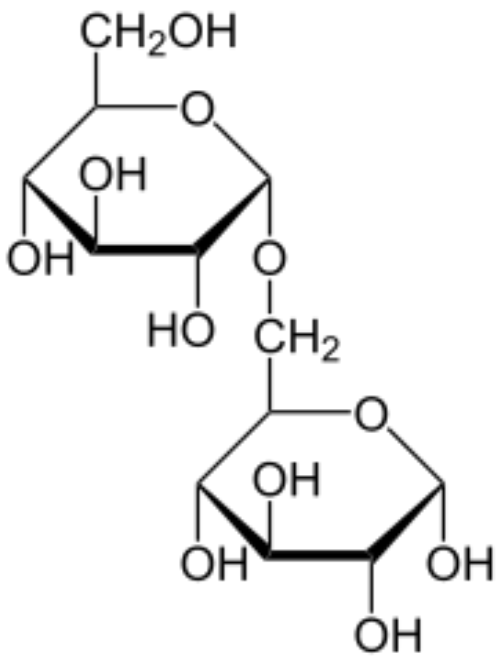
Chapter 6 - Metabolism: Fats and Fatty Acids

Maltose

Maltose, also known as maltobiose or malt sugar, is a disaccharide formed from two units of glucose joined with an α(1→4) bond, formed from a condensation reaction. The isomer isomaltose has two glucose molecules linked through an α(1→6) bond. Isomaltose is shown below.

Maltose is the second member of an important biochemical series of glucose chains. Maltose is the disaccharide produced when amylase breaks down starch. It is found in germinating seeds as they break down their starch stores to use for food, which is why it was named after malt. It is also produced when glucose is caramelized.



https://en.wikipedia.org/wiki/Maltose

Related Glossary Terms

Mannases

β-mannosidase (EC 3.2.1.25, mannanase, mannase, β-D-mannosidase, β-m
mannohydrolase, exo-β-D-mannanase, lysosomal β A mannosidase) is an e
systematic name β-D-mannoside mannohydrolase, which is in humans enc
MANBA gene. This enzyme catalyzes the hydrolysis of terminal, non-reduc
mannose residues in β-D-mannosides.

This gene encodes a member of the glycosyl hydrolase 2 family. The encode
localizes to the lysosome where it is the final exoglycosidase in the pathway
linked glycoprotein oligosaccharide catabolism. Mutations in this gene are
with β-mannosidosis, a lysosomal storage disease that has a wide spectrum
logical involvement.

https://en.wikipedia.org/wiki/Beta-mannosidase

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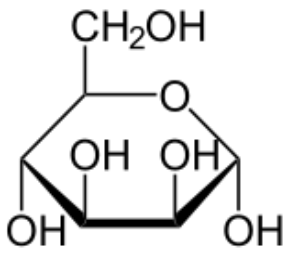
Mannose

Mannose is a sugar monomer of the aldohexose series of carbohydrates. Mannose is a C-2 epimer of glucose. Mannose is important in human metabolism, especially in the glycosylation of certain proteins. Several congenital disorders of glycosylation are associated with mutations in enzymes involved in mannose metabolism.

Mannose commonly exists as two different sized rings, the pyranose (six-membered) form and the furanose (five-membered) form. Each ring closure can have either an α or β configuration at the anomeric position. The chemical rapidly undergoes isomerization among these four forms. The α-D-mannopyranose form is shown below.



https://en.wikipedia.org/wiki/Mannose

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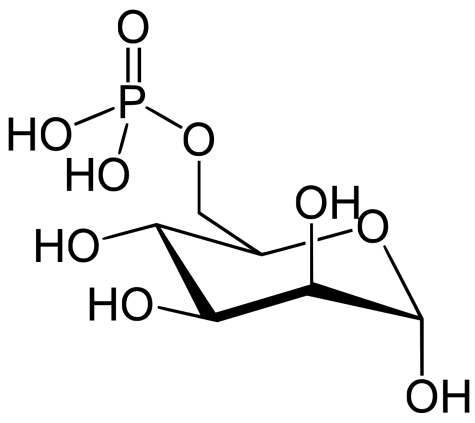
Mannose-6-phosphate

Mannose-6-phosphate (M6P) is a molecule bound by lectin in the immune system. M6P is converted to fructose 6-phosphate by mannose phosphate isomerase.

M6P is a key targeting signal for acid hydrolase precursor proteins that are destined for transport to lysosomes. The M6P tag is added to such proteins in the *cis*-Golgi apparatus. Specifically, in a reaction involving uridine diphosphate (UDP) and N-acetylglucosamine, the enzyme N-acetylglucosamine-1-phosphate transferase catalyzes the N-linked glycosylation of asparagine residues with M6P.

Once appropriately marked with the M6P targeting signal, these proteins are moved to the *trans*-Golgi network. There, the M6P moiety is recognized and bound by mannose 6-phosphate receptor (MPR) proteins at pH 6.5-6.7.
The M6P-tagged lysosomal enzymes are shipped to the late endosomes via vesicular transport. Enzyme replacement therapy (ERT) for several lysosomal storage diseases relies on this pathway to efficiently direct synthetic enzymes to the lysosome where each can metabolize its particular substrate. The pH in the late endosome can reach 6.0, which causes dissociation of M6P from its receptor. Upon release, the enzymes are ferried to their final destination in the lysosomes. The MPRs are packed into vesicles that bud off the late endosome and return to the "trans"-Golgi network. In this way, the MPRs can be recycled.



https://en.wikipedia.org/wiki/Mannose_6-phosphate

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MAP Kinases

Mitogen-activated protein kinases (MAPK) are protein kinases that are specific to the amino acids serine, threonine, and tyrosine. MAPKs belong to the CMGC (CDK/MAPK/GSK3/CLK) kinase group.

MAPKs are involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and proinflammatory cytokines. They regulate cell functions including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis. MAP kinases are found in eukaryotes only, but they are fairly diverse and encountered in all animals, fungi and plants, and even in an array of unicellular eukaryotes.

MAPKs typically form multi-tiered pathways, receiving input several levels above the actual MAP kinase. In contrast to the relatively simple, phosphorylation-dependent activation mechanism of MAPKs and MAP2Ks, MAP3Ks have stunningly complex regulation. Many of the better-known MAP3Ks, such as c-Raf, MEKK4 or MLK3 require multiple steps for their activation. These are typically allosterically-controlled enzymes, tighly locked into an inactive state by multiple mechanisms. The first step en route to their activation consist of relieving their autoinhibition by a smaller ligand (such as Ras for c-Raf, GADD45 for MEKK4 or Cdc42 for MLK3). This commonly (but not always) happens at the cell membrane, where most of their activators are bound (note that small G-proteins are constitutively membrane-associated due to prenylation). That step is followed by side-to-side homo- and heterodimerization of their now accessible kinase domains. Recently determined complex structures reveal that the dimers are formed in an orientation that leaves both their substrate-binding regions free. Importantly, this dimerization event also forces the MAP3 kinase domains to adopt a partially active conformation. Full activity is only achieved once these dimers transphosphorylate each other on their activation loops. The latter step can also be achieved or aided by auxiliary protein kinases (MAP4 kinases, members of the Ste20 family). Once a MAP3 kinase is fully active, it may phosphorylate its substrate MAP2 kinases, which in turn will phosphorylate their MAP kinase substrates.

https://en.wikipedia.org/wiki/Mitogen-activated_protein_kinase

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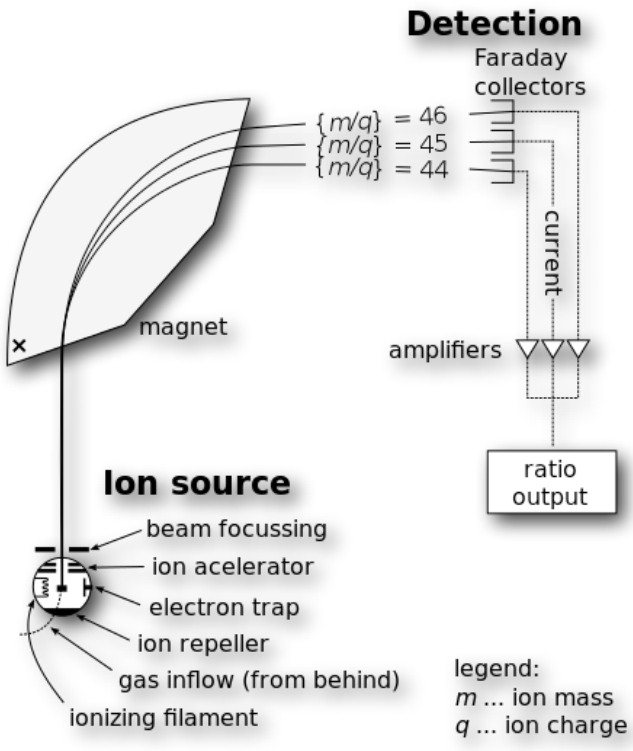
Mass Spectrometry

Mass spectrometry (MS) is an analytical technique that ionizes chemical species and sorts the ions based on their mass to charge ratio. In simpler terms, a mass spectrum measures the masses within a sample. Mass spectrometry is used in many different fields and is applied to pure samples as well as complex mixtures.

A mass spectrum is a plot of the ion signal as a function of the mass-to-charge ratio. These spectra are used to determine the elemental or isotopic signature of a sample, the masses of particles and of molecules, and to elucidate the chemical structures of molecules, such as peptides and other chemical compounds.
In a typical MS procedure, a sample, which may be solid, liquid, or gas, is ionized, for example by bombarding it with electrons. This may cause some of the sample's molecules to break into charged fragments. These ions are then separated according to their mass-to-charge ratio, typically by accelerating them and subjecting them to an electric or magnetic field: ions of the same mass-to-charge ratio will undergo the same amount of deflection.

The ions are detected by a mechanism capable of detecting charged particles, such as an electron multiplier. Results are displayed as spectra of the relative abundance of detected ions as a function of the mass-to-charge ratio. The atoms or molecules in the sample can be identified by correlating known masses to the identified masses or through a characteristic fragmentation pattern. MALDI-TOF is a popular type of mass spectrometry.



https://en.wikipedia.org/wiki/Mass_spectrometry

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Mast Cells

A mast cell (also known as a mastocyte or a labrocyte) is a type of white blo
cifically, it is a type of granulocyte derived from the myeloid stem cell that i
the immune and neuroimmune systems and contains many granules rich in
and heparin. Although best known for their role in allergy and anaphylaxis,
play an important protective role as well, being intimately involved in wour
angiogenesis, immune tolerance, defense against pathogens, and blood–bra
function.

https://en.wikipedia.org/wiki/Mast_cell

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Mature mRNA

Mature messenger RNA, often abbreviated as mature mRNA is a eukaryotic RNA tra
script that has been spliced and processed and is ready for translation in the course o
protein synthesis. Unlike the eukaryotic RNA immediately after transcription known
as precursor messenger RNA, it consists exclusively of exons, with all introns remove
Mature mRNA is also called "mature transcript", "mature RNA" or "mRNA".
The production of a mature mRNA molecule occurs in 3 steps:

1 During capping, a 7-methylguanosine residue is attached to the 5'-termina
end of the primary transcripts. This is otherwise known as the GTP or 5' Cap, and is
used for the stability and attachment point for ribosomes.

2 In polyadenylation, a poly-adenosine tail of about 200 adenylate residues
added by a nuclear polymerase post-transcriptionally. This is known as a Poly-A tail
and is used for stability and guidance, so that the mRNA can exit the nucleus and fin
the ribosome.

3 RNA splicing removes the non-coding RNA introns leaving behind the ex-
ons, which are then spliced and joined together to form the final mRNA.

https://en.wikipedia.org/wiki/Mature_messenger_RNA

Related Glossary Terms

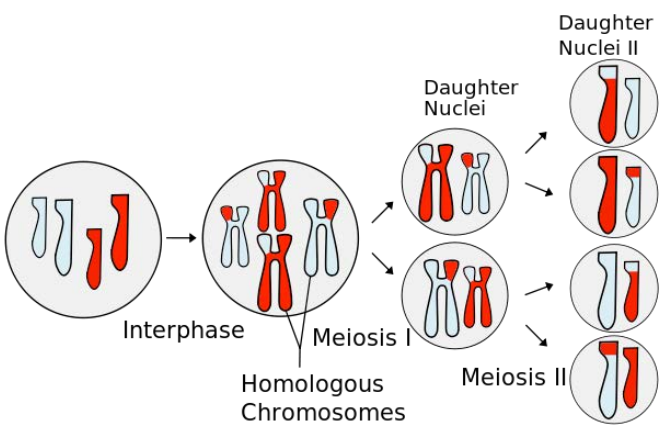
Drag related terms here

Meiosis

Meiosis is a specialized type of cell division that reduces the chromosome number by half. This process occurs in all sexually reproducing single-celled and multicellular eukaryotes, including animals, plants, and fungi. Errors in meiosis resulting in aneuploidy are the leading known cause of miscarriage and the most frequent genetic cause of developmental disabilities.

In meiosis, DNA replication is followed by two rounds of cell division to produce four potential daughter cells, each with half the number of chromosomes as the original parent cell. The two meiotic divisions are known as Meiosis I and Meiosis II. Before meiosis begins, during S phase of the cell cycle, the DNA of each chromosome is replicated so that it consists of two identical sister chromatids, which remain held together through sister chromatid cohesion. This S-phase can be referred to as "premeiotic S-phase" or "meiotic S-phase." Immediately following DNA replication, meiotic cells enter a prolonged G2-like stage known as meiotic prophase. During this time, homologous chromosomes pair with each other and undergo genetic recombination, a programmed process in which DNA is cut and then repaired, which allows them to exchange some of their genetic information. A subset of recombination events results in crossovers, which create physical links known as chiasmata (singular:chiasma, for the Greek letter Chi) between the homologous chromosomes. In most organisms, these links are essential to direct each pair of homologous chromosomes to segregate away from each other during Meiosis I, resulting in two haploid cells that half the number of chromosomes as the parent cell. During Meiosis II, the cohesion between sister chromatids is released and they segregate from one another, as during mitosis. In some cases all four of the meiotic products form gametes such as sperm, spores, or pollen. In female animals, three of the four meiotic products are typically eliminated by extrusion into polar bodies, and only one cell develops to produce an ovum.

Because the number of chromosomes is halved during meiosis, gametes can fuse (i.e. fertilization) to form a diploid zygote that contains two copies of each chromosome, one from each parent. Thus, alternating cycles of meiosis and fertilization enable sexual reproduction, with successive generations maintaining the same number of chromosomes. For example, diploid human cells contain 23 pairs of chromosomes (46 total), half of maternal origin and half of paternal origin. Meiosis produces haploid gametes (ova or sperm) that contain one set of 23 chromosomes. When two gametes (an egg and a sperm) fuse, the resulting zygote is once again diploid, with the mother and father each contributing 23 chromosomes. This same pattern, but not the same number of chromosomes, occurs in all organisms that utilize meiosis.



https://en.wikipedia.org/wiki/Meiosis

Melanin

Melanin is a broad term for a group of natural pigments found in most orga
(arachnids are one of the few groups in which it has not been detected). Me
duced by the oxidation of the amino acid tyrosine, followed by polymerizati
ment is produced in a specialized group of ligaments and tissues known as
cytes.

https://en.wikipedia.org/wiki/Melanin

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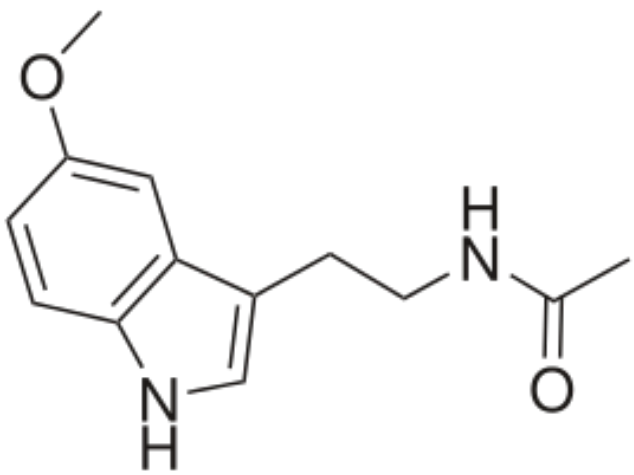
Melatonin

Melatonin, chemically N-acetyl-5-methoxy tryptamine, is a substance found in animals, plants, fungi, and bacteria. In animals, it is a hormone that anticipates the daily onset of darkness. However in other organisms, it may have different functions. Likewise, the synthesis of melatonin in animals differs from that in other organisms.

In animals, melatonin is involved in the entrainment (synchronization) of the circadian rhythms of physiological functions including sleep timing, blood pressure regulation, seasonal reproduction and many others. Many of melatonin's biological effects in animals are produced through activation of melatonin receptors, while others are due to its role as a pervasive and powerful antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA.



https://en.wikipedia.org/wiki/Melatonin

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Mellitin

Melittin is the principal active component of apitoxin (bee venom) and is a stimulator of phospholipase A_2. Melittin is a peptide consisting of 26 amino the sequence GIGAVLKVLTTGLPALISWIKRKRQQ.

Melittin inhibits protein kinase C, Ca^{++}/calmodulin-dependent protein kinase osin light chain kinase and Na^{+}/K^{+}-ATPase (synaptosomal membrane) and membrane lytic factor. Melittin is a small peptide with no disulphide bridge terminal part of the molecule is predominantly hydrophobic and the C-term hydrophilic and strongly basic.

https://en.wikipedia.org/wiki/Melittin

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Chapter 6 - Metabolism: Fats and Fatty Acids

Chapter 9 - Point by Point: Metabolism

Membrane

A membrane is a selective barrier. It allows some things to pass through, but stops others. Such things may be molecules, ions, or other small particles. Biological membranes include cell membranes (outer coverings of cells or organelles that allow passage of certain constituents); nuclear membranes, which cover a cell nucleus; and tissue membranes, such as mucosae and serosae. Synthetic membranes are made by humans for use in laboratories and industry (such as chemical plants). The influent of an artificial membrane is known as the feed-stream, the liquid that passes through the membrane is known as the permeate, and the liquid containing the retained constituents is the retentate or concentrate.

https://en.wikipedia.org/wiki/Membrane

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Membrane Flexibility

In biology, membrane fluidity refers to the viscosity of the lipid bilayer of a cell membrane or a synthetic lipid membrane. Lipid packing can influence the fluidity of the membrane. Viscosity of the membrane can affect the rotation and diffusion of proteins and other bio-molecules within the membrane, there-by affecting the functions of these molecules.

Membrane fluidity can be affected by a number of factors. One way to increase membrane fluidity is to heat up the membrane. Lipids acquire thermal energy when they are heated up. Energetic lipids move around more, arranging and rearranging randomly, making the membrane more fluid. At low temperatures, the lipids are laterally ordered and organized in the membrane, and the lipid chains are mostly in the all-trans configuration and pack well together. The composition of a membrane can also affect its fluidity. The membrane phospholipids incorporate fatty acids of varying length and saturation. Lipids with shorter chains are less stiff and less viscous because they are more susceptible to changes in kinetic energy due to their smaller molecular size and they have less surface area to undergo stabilizing van der Waals interactions with neighboring hydrophobic chains.

Lipid chains with double bonds are more fluid than lipids that are saturated with hydrogen and thus have only single bonds. On the molecular level, unsaturated double bonds make it harder for the lipids to pack together by putting kinks into the otherwise straightened hydrocarbon chain. Membranes made with such lipids have lower melting points: less thermal energy is required to achieve the same level of fluidity as membranes made with lipids with saturated chains. Incorporation of particular lipids, such as sphingomyelin, into synthetic lipid membranes is known to stiffen a membrane. Such membranes can be described as "a glass state, i.e., rigid but without crystalline order".

Cholesterol acts as a bidirectional regulator of membrane fluidity because at high temperatures, it stabilizes the membrane and raises its melting point, whereas at low temperatures it intercalates between the phospholipids and prevents them from clustering together and stiffening. Some drugs, e.g. Losartan, are also known to alter membrane viscosity. Another way to change membrane fluidity is to change the pressure. In the laboratory, supported lipid bilayers and monolayers can be made artificially. In such cases, one can still speak of membrane fluidity. These membranes are supported by a flat surface, e.g. the bottom of a box. The fluidity of these membranes can be controlled by the lateral pressure applied, e.g. by the side walls of a box.

https://en.wikipedia.org/wiki/Membrane_fluidity

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Chapter 2 - Structure & Function: Lipids

Membrane Fluidity

In biology, membrane fluidity refers to the viscosity of the lipid bilayer of a
brane or a synthetic lipid membrane. Lipid packing can influence the fluidi
membrane. Viscosity of the membrane can affect the rotation and diffusion
and other bio-molecules within the membrane, there-by affecting the funct
these molecules.

https://en.wikipedia.org/wiki/Membrane_fluidity

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Membrane Fusion

In membrane biology, fusion is the process by which two initially distinct li
merge their hydrophobic cores, resulting in one interconnected structure. I
proceeds completely through both leaflets of both bilayers, an aqueous brid
formed and the internal contents of the two structures can mix. Alternative
one leaflet from each bilayer is involved in the fusion process, the bilayers a
be hemifused. In hemifusion, the lipid constituents of the outer leaflet of th
ers can mix, but the inner leaflets remain distinct. The aqueous contents en
each bilayer also remain separated.

https://en.wikipedia.org/wiki/Lipid_bilayer_fusion

Related Glossary Terms

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Membrane Potential

Membrane potential (also transmembrane potential or membrane voltage) is the difference in electric potential between the interior and the exterior of a biological cell. With respect to the exterior of the cell, typical values of membrane potential range from –40 mV to –80 mV.

All animal cells are surrounded by a membrane composed of a lipid bilayer with proteins embedded in it. The membrane serves as both an insulator and a diffusion barrier to the movement of ions. Ion transporter/pump proteins actively push ions across the membrane and establish concentration gradients across the membrane, and ion channels allow ions to move across the membrane down those concentration gradients. Ion pumps and ion channels are electrically equivalent to a set of batteries and resistors inserted in the membrane, and therefore create a voltage difference between the two sides of the membrane.

Virtually all eukaryotic cells (including cells from animals, plants, and fungi) maintain a non-zero transmembrane potential,[citation needed] usually with a negative voltage in the cell interior as compared to the cell exterior ranging from –40 mV to –80 mV. The membrane potential has two basic functions. First, it allows a cell to function as a battery, providing power to operate a variety of "molecular devices" embedded in the membrane. Second, in electrically excitable cells such as neurons and muscle cells, it is used for transmitting signals between different parts of a cell. Signals are generated by opening or closing of ion channels at one point in the membrane, producing a local change in the membrane potential. This change in the electric field can be quickly affected by either adjacent or more distant ion channels in the membrane. Those ion channels can then open or close as a result of the potential change, reproducing the signal.

In non-excitable cells, and in excitable cells in their baseline states, the membrane potential is held at a relatively stable value, called the resting potential. For neurons, typical values of the resting potential range from –70 to –80 millivolts. That is, the interior of a cell has a negative baseline voltage of a bit less than one-tenth of a volt. The opening and closing of ion channels can induce a departure from the resting potential. This is called a depolarization if the interior voltage becomes less negative (say from –70 mV to –60 mV), or a hyperpolarization if the interior voltage becomes more negative (say from –70 mV to –80 mV). In excitable cells, a sufficiently large depolarization can evoke an action potential, in which the membrane potential changes rapidly and significantly for a short time (on the order of 1 to 100 milliseconds), often reversing its polarity. Action potentials are generated by the activation of certain voltage-gated ion channels.

https://en.wikipedia.org/wiki/Membrane_potential

Membrane Proteins

Membrane proteins are proteins that interact with, or are part of, biological membranes. They are one of the common types of protein along with soluble globular proteins, fibrous proteins, and disordered proteins. They are targets of over 50% of all modern medicinal drugs. It is estimated that 20–30% of all genes in most genomes encode membrane proteins.

Membrane proteins perform a variety of functions vital to the survival of organisms:

- Membrane receptor proteins relay signals between the cell's internal and external environments.
- Transport proteins move molecules and ions across the membrane. They can be categorized according to the Transporter Classification database.
- Membrane enzymes may have many activities, such as oxidoreductase, transferase or hydrolase.
- Cell adhesion molecules allow cells to identify each other and interact. For example, proteins involved in immune response.

https://en.wikipedia.org/wiki/Membrane_protein

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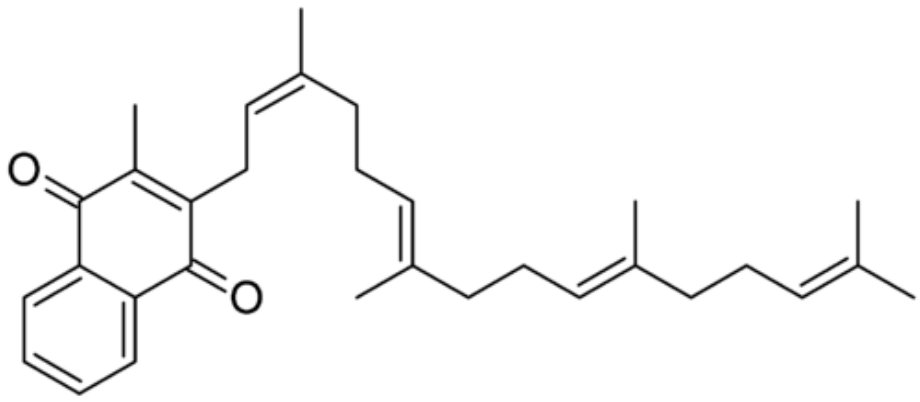
Menatetrenone

Menatetrenone (INN), also known as MK4, is a vitamin K compound used as a hemostatic agent, and also as adjunctive therapy for the pain of osteoporosis. Menatetrenone is one of the nine forms of vitamin K_2.

MK4 is produced via conversion of vitamin K_1 in the body, in the testes, pancreas and arterial walls. While major questions still surround the biochemical pathway for the transformation of vitamin K_1 to MK4, studies demonstrate the conversion is not dependent on gut bacteria, occurring in germ-free rats and in parenterally-administered K1 in rats. In fact, tissues that accumulate high amounts of MK4 have a remarkable capacity to convert up to 90% of the available K_1 into MK4.



https://en.wikipedia.org/wiki/Menatetrenone

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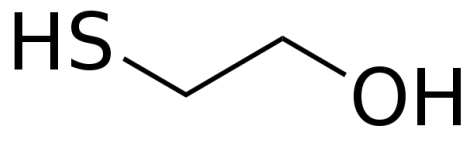
Chapter 4 - Catalysis: Blood Clotting

Mercaptoethanol

2-Mercaptoethanol (also β-mercaptoethanol, BME, 2BME, 2-ME or β-met) is the chemical compound with the formula $HOCH_2CH_2SH$. ME or βME, as it is commo abbreviated, is used to reduce disulfide bonds and can act as a biological antioxid by scavenging hydroxyl radicals (amongst others). It structure is below. Mercapt nol is widely used because the hydroxyl group confers solubility in water and lowe the volatility. Due to its diminished vapor pressure, its odor, while unpleasant, is objectionable than related thiols.



https://en.wikipedia.org/wiki/2-Mercaptoethanol

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Mercury

Mercury is a chemical element with symbol Hg and atomic number 80. It is
known as quicksilver and was formerly named hydrargyrum. A heavy, silve
element, mercury is the only metallic element that is liquid at standard con
temperature and pressure. The only other element that is liquid under thes
tions is bromine, though metals such as caesium, gallium, and rubidium m
above room temperature.

https://en.wikipedia.org/wiki/Mercury_(element)

Related Glossary Terms

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Metabolic Energy

Metabolism is the set of life-sustaining chemical transformations within th
ing organisms. The three main purposes of metabolism are the conversion
to energy to run cellular processes, the conversion of food/fuel to building
proteins, lipids, nucleic acids, and some carbohydrates, and the eliminatio
nous wastes. These enzyme-catalyzed reactions allow organisms to grow an
duce, maintain their structures, and respond to their environments. The wo
lism can also refer to the sum of all chemical reactions that occur in living
including digestion and the transport of substances into and between diffe
which case the set of reactions within the cells is called intermediary metab
termediate metabolism.

https://en.wikipedia.org/wiki/Metabolism

Related Glossary Terms

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Metabolic Pathway

In biochemistry, a metabolic pathway is a series of chemical reactions occurring within a cell. In a pathway, the initial chemical (metabolite) is modified by a sequence of chemical reactions. These reactions are catalyzed by enzymes, where the product of one enzyme acts as the substrate for the next. These enzymes often require dietary minerals, vitamins, and other cofactors to function.

Pathways are required for the maintenance of homeostasis within an organism and the flux of metabolites through a pathway is regulated depending on the needs of the cell and the availability of the substrate. The end product of a pathway may be used immediately, initiate another metabolic pathway or be stored for later use. The metabolism of a cell consists of an elaborate network of interconnected pathways that enable the synthesis and breakdown of molecules (anabolism and catabolism).

https://en.wikipedia.org/wiki/Metabolic_pathway

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Metabolic Pathways

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https://en.wikipedia.org/wiki/Metabolic_pathway

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Metabolism

Metabolism is the set of life-sustaining chemical transformations within the cells of living organisms. The three main purposes of metabolism are the conversion of food/fuel to energy to run cellular processes, the conversion of food/fuel to building blocks for proteins, lipids, nucleic acids, and some carbohydrates, and the elimination of nitrogenous wastes. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments.

The word metabolism can also refer to the sum of all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the set of reactions within the cells is called intermediary metabolism or intermediate metabolism.

Metabolism is usually divided into two categories: catabolism, the breaking down of organic matter, for example, by cellular respiration, and anabolism, the building up of components of cells such as proteins and nucleic acids. Usually, breaking down releases energy and building up consumes energy.

The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that require energy that will not occur by themselves, by coupling them to spontaneous reactions that release energy. Enzymes act as catalysts that allow the reactions to proceed more rapidly. Enzymes also allow the regulation of metabolic pathways in response to changes in the cell's environment or to signals from other cells.

The metabolic system of a particular organism determines which substances it will find nutritious and which poisonous. For example, some prokaryotes use hydrogen sulfide as a nutrient, yet this gas is poisonous to animals. The speed of metabolism, the metabolic rate, influences how much food an organism will require, and also affects how it is able to obtain that food.

A striking feature of metabolism is the similarity of the basic metabolic pathways and components between even vastly different species. For example, the set of carboxylic acids that are best known as the intermediates in the citric acid cycle are present in all known organisms, being found in species as diverse as the unicellular bacterium *Escherichia coli* and huge multicellular organisms like elephants. These striking similarities in metabolic pathways are likely due to their early appearance in evolutionary history, and their retention because of their efficacy.

https://en.wikipedia.org/wiki/Metabolism

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Metabolon

In biochemistry, a metabolon is a temporary structural-functional complex
tween sequential enzymes of a metabolic pathway, held together by non-co
actions, and structural elements of the cell such as integral membrane prot
proteins of the cytoskeleton.

The formation of metabolons allows passing (channelling) the intermediary
product from an enzyme directly as substrate into the active site of the cons
zyme of the metabolic pathway. The citric acid cycle is an example of a meta
which facilitates substrate channeling. During the functioning of metabolon
amount of water needed to hydrate the enzymes is reduced and enzyme act
creased.

https://en.wikipedia.org/wiki/Metabolon

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https://en.wikipedia.org/wiki/Metabolon

Related Glossary Terms

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Metalloproteases

A metalloproteinase, or metalloprotease, is any protease enzyme whose cat
mechanism involves a metal. An example of this would be meltrin which pl
cant role in the fusion of muscle cells during embryo development, in a pro
as myogenesis.

Most metalloproteases require zinc, but some use cobalt. The metal ion is c
to the protein via three ligands. The ligands co-ordinating the metal ion car
histidine, glutamate, aspartate, lysine, and arginine. The fourth coordinatio
is taken up by a labile water molecule.

https://en.wikipedia.org/wiki/Metalloproteinase

Related Glossary Terms

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Metamorphic Proteins

Metamorphic proteins are proteins that exist in an equilibrium of stable str
flip back and forth.

Related Glossary Terms

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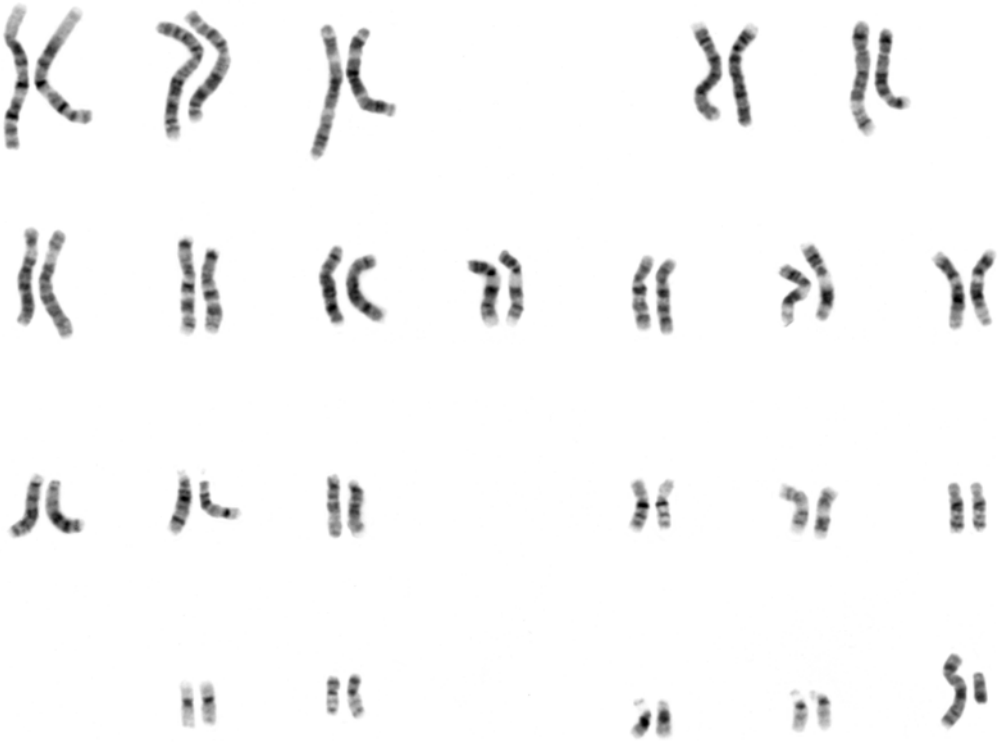
Metaphase

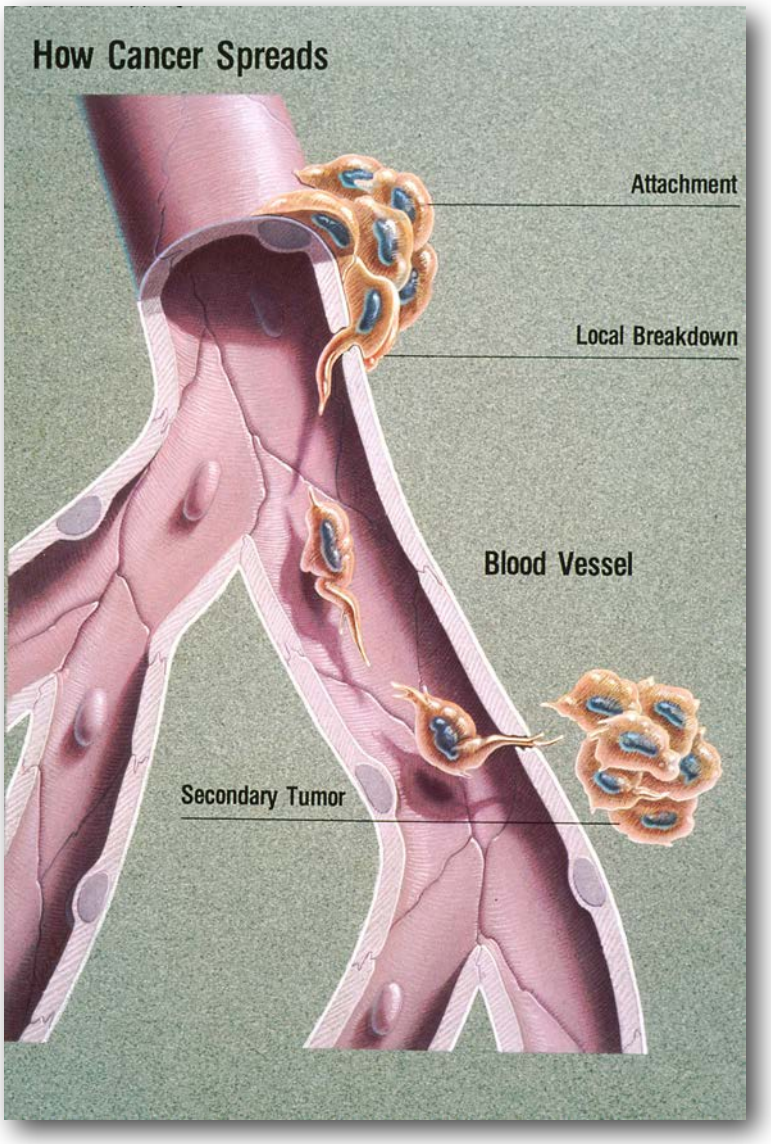
Metaphase is a stage of mitosis in the eukaryotic cell cycle in which chromosomes are at their second-most condensed and coiled stage (they are at their most condensed in anaphase). These chromosomes, carrying genetic information, align in the equator of the cell before being separated into each of the two daughter cells. Metaphase accounts for approximately 4% of the cell cycle's duration. Preceded by events in prometaphase and followed by anaphase, microtubules formed in prophase have already found and attached themselves to kinetochores in metaphase. Human metaphase chromosomes are shown below.



https://en.wikipedia.org/wiki/Metaphase

Metastatic

Metastasis, or metastatic disease, is the spread of a cancer or other disease from one organ or part of the body to another not directly connected with it. Cells that undergo metastasis or that are capable of it are metastatic.



https://en.wikipedia.org/wiki/Metastasis

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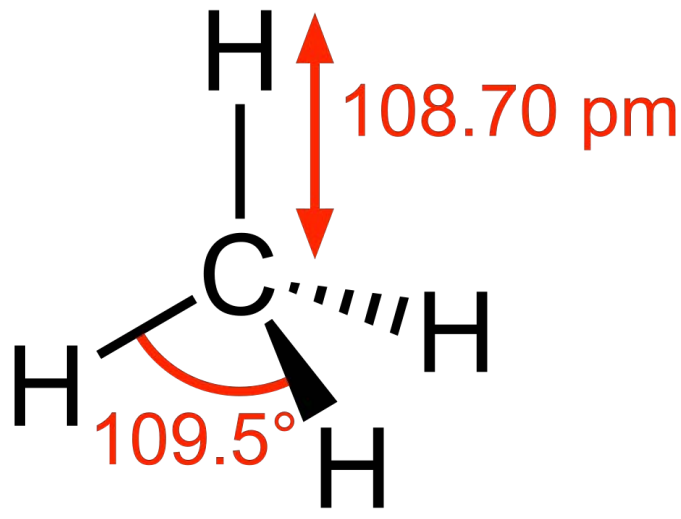
Methane

Methane is a chemical compound with the chemical formula CH_4 (one atom of carbon and four atoms of hydrogen). It is the simplest alkane and the main component of natural gas. The relative abundance of methane on Earth makes it an attractive fuel, though capturing and storing it poses challenges due to its gaseous state under normal conditions for temperature and pressure.



https://en.wikipedia.org/wiki/Methane

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Methanogenic

Methanogenesis or biomethanation is the formation of methane by microbe
methanogens. Organisms capable of producing methane have been identifi
from the domain *Archaea*, a group phylogenetically distinct from both euka
bacteria, although many live in close association with anaerobic bacteria. T
tion of methane is an important and widespread form of microbial metabol
most environments, it is the final step in the decomposition of biomass.

https://en.wikipedia.org/wiki/Methanogenesis

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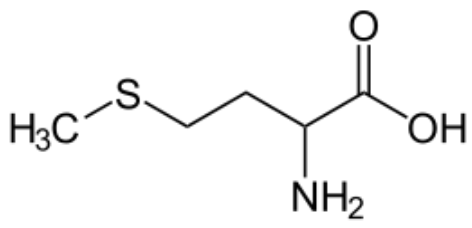
Chapter 2 - Structure & Function: Amino Acids

Methionine

Methionine (abbreviated as Met or M; encoded by the codon AUG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and an S-methyl thioether side chain, classifying it as a non-polar, aliphatic amino acid. It is essential in humans, meaning the body cannot synthesize it and thus it must be obtained from the diet.

Methionine is coded for by the initiation codon meaning it indicates the start of the coding region and is the first amino acid produced in a nascent polypeptide during mRNA translation and is coded by the initiation codon AUG, which also indicates mRNA's coding region where translation into protein begins.

https://en.wikipedia.org/wiki/Methionine



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Methionine Adenosyltransferase

S-adenosylmethionine synthetase (also known as methionine adenosyltran
(MAT)) is an enzyme that creates S-adenosylmethionine (AdoMet) by react
nine (a non-polar amino acid) and ATP (the basic currency of energy).

The S-adenosylmethionine synthetase enzyme is found in almost every orga
parasites which obtain AdoMet from their host. Isoenzymes are found in ba
ding yeast and even in mammalian mitochondria. Most MATs are homo-ol
the majority are tetramers. The monomers are organized into three domair
nonconsecutive stretches of the sequence, and the subunits interact throug
hydrophobic surface to form the dimers.

https://en.wikipedia.org/wiki/S-adenosylmethionine_synthetase_enzyme

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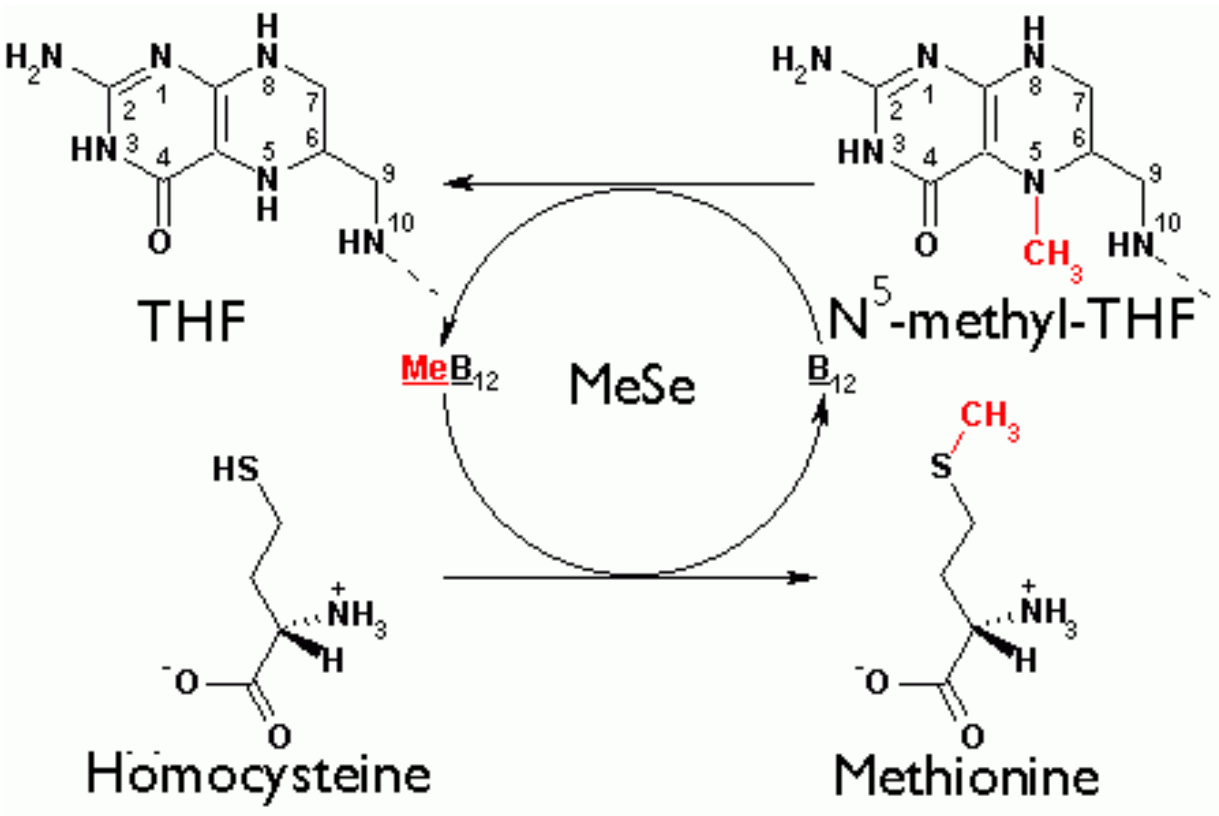
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Methionine Synthase

Methionine synthase also known as MS, MeSe, MetH is responsible for the regeneration of methionine from homocysteine. In humans it is encoded by the MTR gene (5-methyltetrahydrofolate-homocysteine methyltransferase). Methionine synthase forms part of the S-adenosylmethionine (SAMe) biosynthesis and regeneration cycle. In animals this enzyme requires Vitamin B_{12} (cobalamin) as a cofactor, whereas the form found in plants is cobalamin-independent. Microorganisms express both cobalamin-dependent and cobalamin-independent forms.



https://en.wikipedia.org/wiki/Methionine_synthase

Related Glossary Terms

Methionyl-tRNA Formyltransferase

Methionyl-tRNA formyltransferase (EC 2.1.2.9) is an enzyme that catalyzes
cal reaction

10-formyltetrahydrofolate + L-methionyl-tRNAfMet + H_2O <---> Tetrahyd
N-formylmethionyl-tRNAfMet

This enzyme participates in 3 metabolic pathways: methionine metabolism
bon pool by folate, and aminoacyl-tRNA biosynthesis. It is this enzyme in b
provides the fMet used for making the first amino acid in prokaryotic prote

https://en.wikipedia.org/wiki/Methionyl-tRNA_formyltransferase

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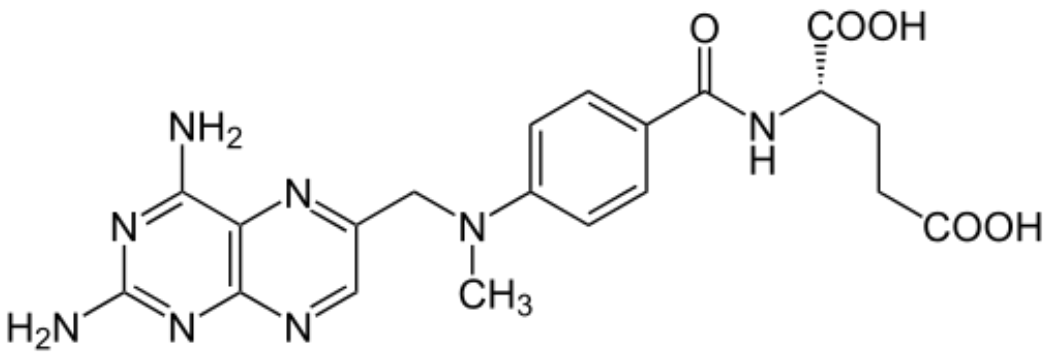
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 9 - Point by Point: Metabolism

Methotrexate

Methotrexate (MTX), formerly known as amethopterin, is an anti-metabolite and anti-folate drug.

It is used in treatment of cancer, autoimmune diseases, ectopic pregnancy, and for the induction of medical abortions. It acts by inhibiting the metabolism of folic acid via dihydrofolate reductase.



https://en.wikipedia.org/wiki/Methotrexate

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Methyl

A methyl group is an alkyl derived from methane, containing one carbon atom bo
to three hydrogen atoms — CH_3. In formulas, the group is often abbreviated Me. S
hydrocarbon groups occur in many organic compounds. It is a very stable group i
most molecules.

https://en.wikipedia.org/wiki/Methyl_group

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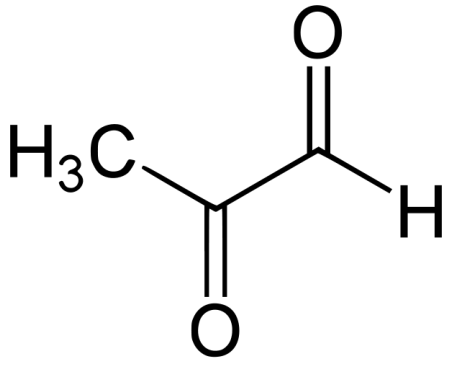
Methyl Glyoxal

Methylglyoxal, also called pyruvaldehyde or 2-oxopropanal, is the organic c
with the formula $CH_3C(O)CHO$. Gaseous methylglyoxal has two carbonyl g
dehyde and a ketone but in the presence of water, it exists as hydrates and c
It is a reduced derivative of pyruvic acid.



https://en.wikipedia.org/wiki/Methylglyoxal

Related Glossary Terms

Drag related terms here

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hydrocarbon groups occur in many organic compounds. It is a very stable g
most molecules.

https://en.wikipedia.org/wiki/Methyl_group

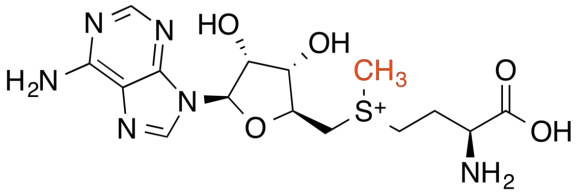
Related Glossary Terms

Drag related terms here

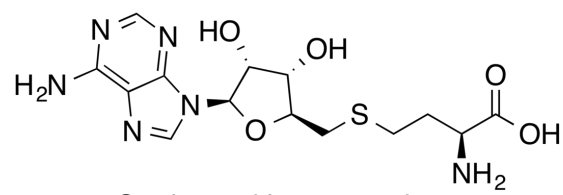
Methylase

Methyltransferases (methylases) are a large group of enzymes that all methylate their substrates but can be split into several subclasses based on their structural features. The most common class of methyltransferases is class I, all of which contain a Rossman fold for binding S-Adenosyl methionine (SAM). Class II methyltransferases contain a SET domain, which are exemplified by SET domain Histone methyltransferases, and class III methyltransferases, which are membrane associated. Methyltransferases can also be grouped as different types utilizing different substrates in methyl transfer reactions. These types include protein methyltransferases, DNA methyltransferases (important in restriction/modification systems), natural product methyltransferases, and non-SAM dependent methyltransferases.

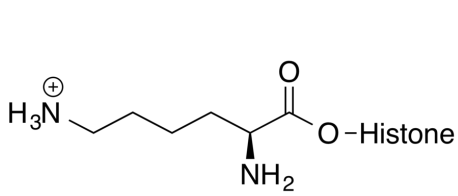
SAM is the classical methyl donor for methyltransferases, however, examples of other methyl donors are seen in nature. The general mechanism for methyl transfer is a SN2-like nucleophilic attack where the methionine sulfur serves as the nucleophile that transfers the methyl group to the enzyme substrate. SAM is converted to S-Adenosyl homocysteine (SAH) during this process. The breaking of the SAM-methyl bond and the formation of the substrate-methyl bond happen nearly simultaneously. These enzymatic reactions are found in many pathways and are implicated in genetic diseases, cancer, and metabolic diseases.



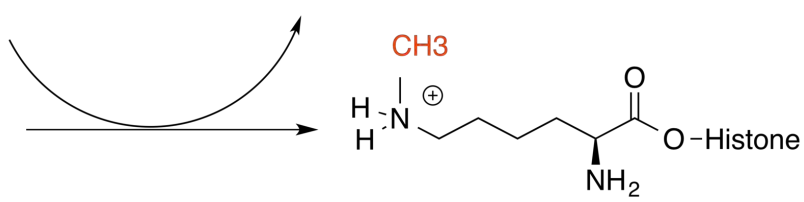
S-adenosyl methionine



S-adenosyl homocysteine



Lysine



Lysine

https://en.wikipedia.org/wiki/Methyltransferase

Methylation

In the chemical sciences, methylation denotes the addition of a methyl group on a substrate or the substitution of an atom or group by a methyl group. Methylation is a form of alkylation with a methyl group, rather than a larger carbon chain, replacing a hydrogen atom.

Biomolecules implicated in addition of methyl groups (one-carbon chemistry) include S-adenosylmethionine (SAM) and folates.

https://en.wikipedia.org/wiki/Methylation

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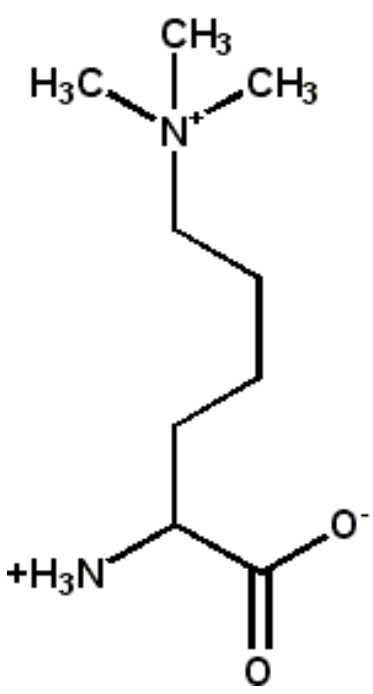
Methyllysine

In proteins, the amino acid residue lysine can be methylated once, twice or three times on its terminal side chain ammonium group.

Such methylated lysines play an important role in epigenetics; the methylation of specific lysines of certain histones in a nucleosome alters the binding of the surrounding DNA to those histones, which in turn affects the expression of genes on that DNA. The binding is affected because the effective radius of the positive charge is increased (methyl groups are larger than the hydrogen atoms they replace), reducing the strongest potential electrostatic attraction with the negatively charged DNA. Moreover, the methyl groups are themselves hydrophobic, and alter the structure of water in their vicinity, similar to tetramethyl ammonium.

Trimethyllysine is shown below.



https://en.wikipedia.org/wiki/Methyllysine

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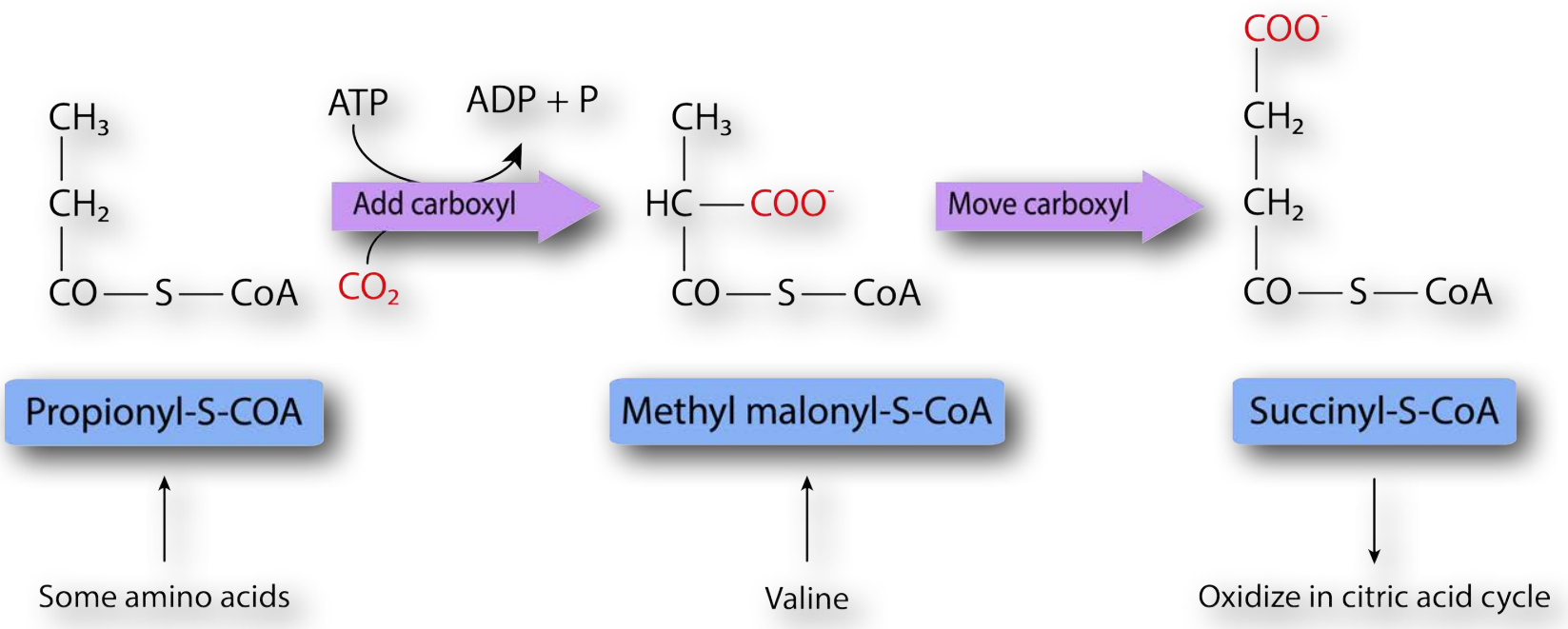
Chapter 2 - Structure & Function: Amino Acids

Methylmalonyl-CoA Mutase

Methylmalonyl coenzyme A mutase, also known as MCM is an enzyme that catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA and it is involved in key metabolic pathways. It requires a vitamin B_{12}-derived prosthetic group, adenosylcobalamin (commonly referred to as AdoCbl), to function.

The enzyme is important in the last step of the conversion of propionyl-CoA to succinyl-CoA and is shown in the figure below.



https://en.wikipedia.org/wiki/Methylmalonyl-CoA_mutase

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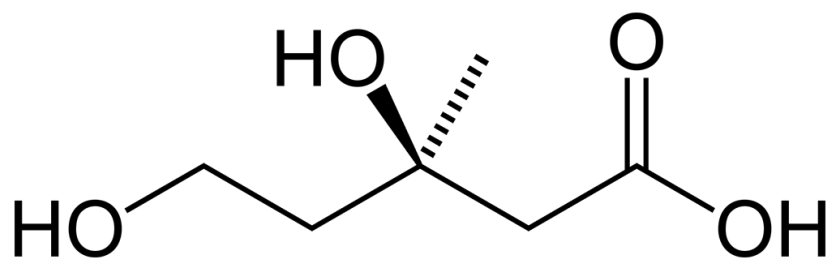
Mevalonate

Mevalonic acid (MVA) is a key organic compound in biochemistry. The name
traction of dihydroxymethylvalerolactone. The carboxylate anion of mevalonic
which is the predominant form in biological environments, is known as meval
and is of major pharmaceutical importance. Drugs such as the statins (which l
els of cholesterol) stop the production of mevalonate (and the rest of the chol
biosynthetic pathway) by inhibiting HMG-CoA reductase.



https://en.wikipedia.org/wiki/Mevalonic_acid

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MHC

The major histocompatibility complex (MHC) is a set of cell surface protein
for acquired immune system to recognize foreign molecules in vertebrates,
turn determines histocompatibility. The main function of MHC molecules i
peptide fragments derived from pathogens and display them on the cell sur
ognition by the appropriate T-cells. MHC molecules mediate interactions o
cytes, also called white blood cells (WBCs), which are immune cells, with ot
cytes or with body cells. The MHC determines compatibility of donors for o
plant, as well as one's susceptibility to an autoimmune disease via crossrea
nization. In humans, the MHC is also called the human leukocyte antigen (

https://en.wikipedia.org/wiki/Major_histocompatibility_complex

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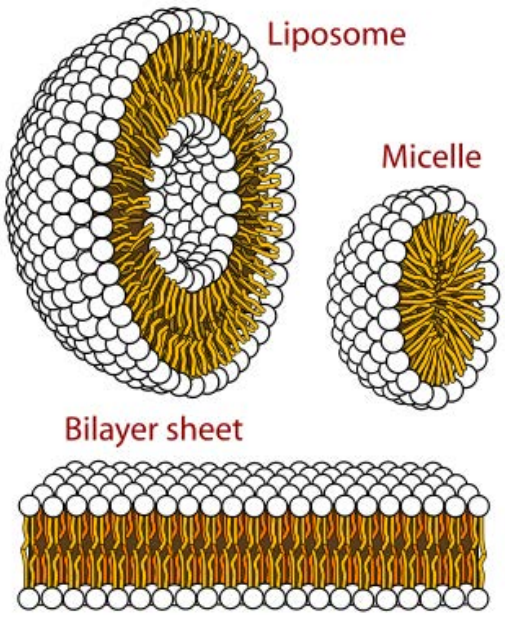
Micelles

A micelle is an aggregate (or supramolecular assembly) of surfactant molecules dispersed in a liquid colloid. A typical micelle in aqueous solution forms an aggregate with the hydrophilic "head" regions in contact with surrounding solvent, sequestering the hydrophobic single-tail regions in the micelle centre. This phase is caused by the packing behavior of single-tail lipids in a bilayer. The difficulty filling all the volume of the interior of a bilayer, while accommodating the area per head group forced on the molecule by the hydration of the lipid head group, leads to the formation of the micelle.

This type of micelle is known as a normal-phase micelle (oil-in-water micelle). Inverse micelles have the head groups at the center with the tails extending out (water-in-oil micelle). Micelles are approximately spherical in shape. Other phases, including shapes such as ellipsoids, cylinders, and bilayers, are also possible. The shape and size of a micelle are a function of the molecular geometry of its surfactant molecules and solution conditions such as surfactant concentration, temperature, pH, and ionic strength. The process of forming micelles is known as micellization and forms part of the phase behavior of many lipids according to their polymorphism.



https://en.wikipedia.org/wiki/Micelle

Michaelis-Menten Kinetics

In biochemistry, Michaelis–Menten kinetics is one of the best-known models of enzyme kinetics. It is named after German biochemist Leonor Michaelis and Canadian physician Maud Menten. The model takes the form of an equation describing the rate of enzymatic reactions, by relating reaction rate to , the concentration of a substrate S. Its formula is given by

$$v = \frac{d[P]}{dt} = \frac{V_{\max}[S]}{K_{\mathrm{M}} + [S]}.$$

This equation is called Michaelis–Menten equation. Here, V_{max} represents the maximum rate achieved by the system, at maximum saturation of the substrate concentration. The Michaelis constant K_M is the substrate concentration at which the reaction rate is half of . Biochemical reactions involving a single substrate are often assumed to follow Michaelis–Menten kinetics, without regard to the model's underlying assumptions.

https://en.wikipedia.org/wiki/Michaelis–Menten_kinetics

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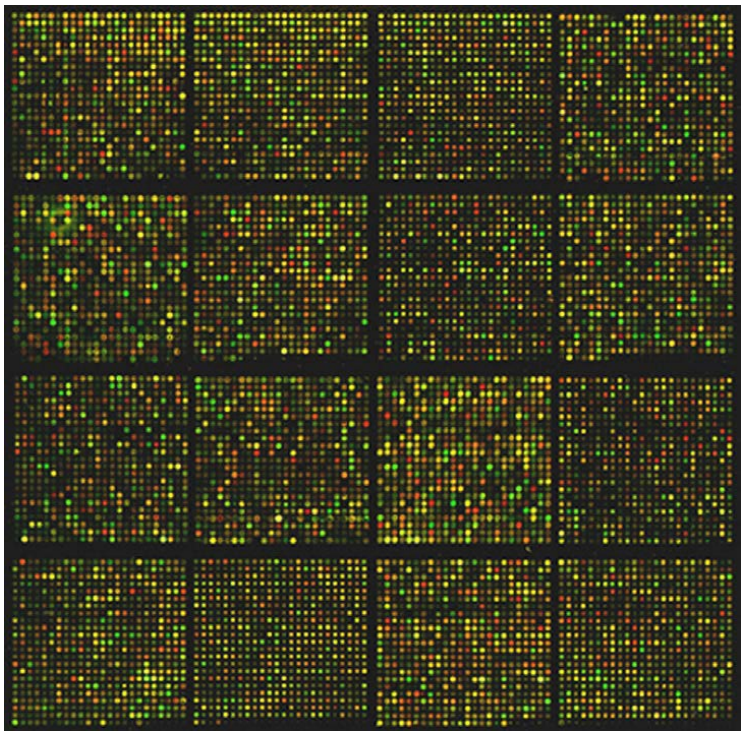
Microarrays

A microarray is a multiplex lab-on-a-chip. It is a 2D array on a solid substrate (usually a glass slide or silicon thin-film cell) that assays large amounts of biological material using high-throughput screening miniaturized, multiplexed and parallel processing and detection methods. The concept and methodology of microarrays was first introduced and illustrated in antibody microarrays (also referred to as antibody matrix) by Tse Wen Chang in 1983 in a scientific publication and a series of patents.

The "gene chip" industry started to grow significantly after the 1995 Science Paper by the Ron Davis and Pat Brown labs at Stanford University. With the establishment of companies, such as Affymetrix, Agilent, Applied Microarrays, Arrayit, Illumina, and others, the technology of DNA microarrays has become the most sophisticated and the most widely used, while the use of protein, peptide and carbohydrate microarrays is expanding.

Types of microarrays include:
• DNA microarrays, such as cDNA microarrays, oligonucleotide microarrays, BAC microarrays and SNP microarrays
• MMChips, for surveillance of microRNA populations
• Protein microarrays
• Peptide microarrays, for detailed analyses or optimization of protein–protein interactions
• Tissue microarrays
• Cellular microarrays (also called transfection microarrays)
• Chemical compound microarrays
• Antibody microarrays
• Carbohydrate arrays (glycoarrays)
• Phenotype microarrays
• Reverse Phase Protein Microarrays, microarrays of lysates or serum
interferometric reflectance imaging sensor (IRIS)

Pictured below is a cDNA microarray.



https://en.wikipedia.org/wiki/Microarray

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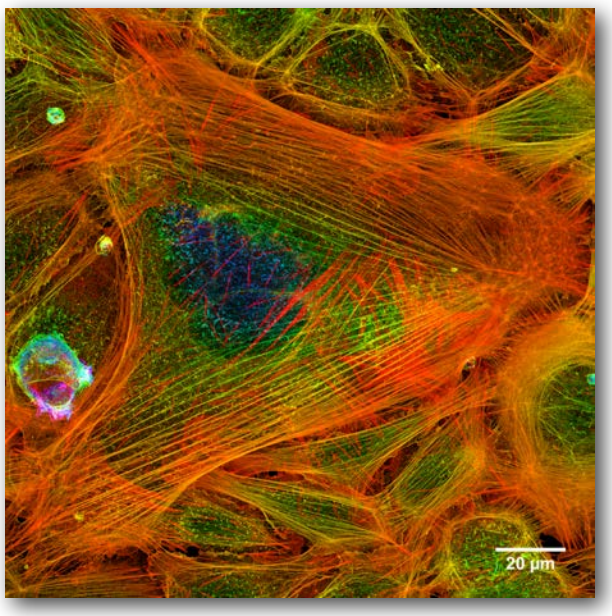
Microfilaments

Microfilaments or actin thin filaments are the thinnest filaments of the cytoskeleton, a structure found in the cytoplasm of eukaryotic cells. These linear polymers of actin subunits are flexible and relatively strong, resisting buckling by multi-piconewton compressive forces and filament fracture by nanonewton tensile forces. Microfilaments are highly versatile, functioning in cytokinesis, amoeboid movement, and changes in cell shape. In inducing this cell motility, one end of the actin filament elongates while the other end contracts, presumably by myosin II molecular motors.

Shown below are stained actin microfilaments



https://en.wikipedia.org/wiki/Microfilament

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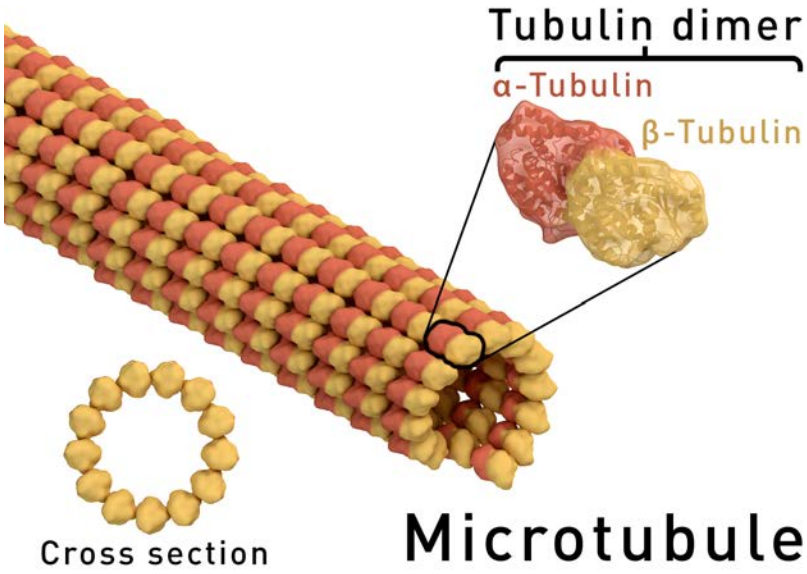
Microtubules

Microtubules are a component of the cytoskeleton, found throughout the cytoplasm. These tubular polymers of tubulin can grow as long as 50 micrometers and are highly dynamic. The outer diameter of a microtubule is about 24 nm while the inner diameter is about 12 nm. They are found in eukaryotic cells, as well as some bacteria, and are formed by the polymerization of a dimer of two globular proteins, α and β tubulin.



https://en.wikipedia.org/wiki/Microtubule

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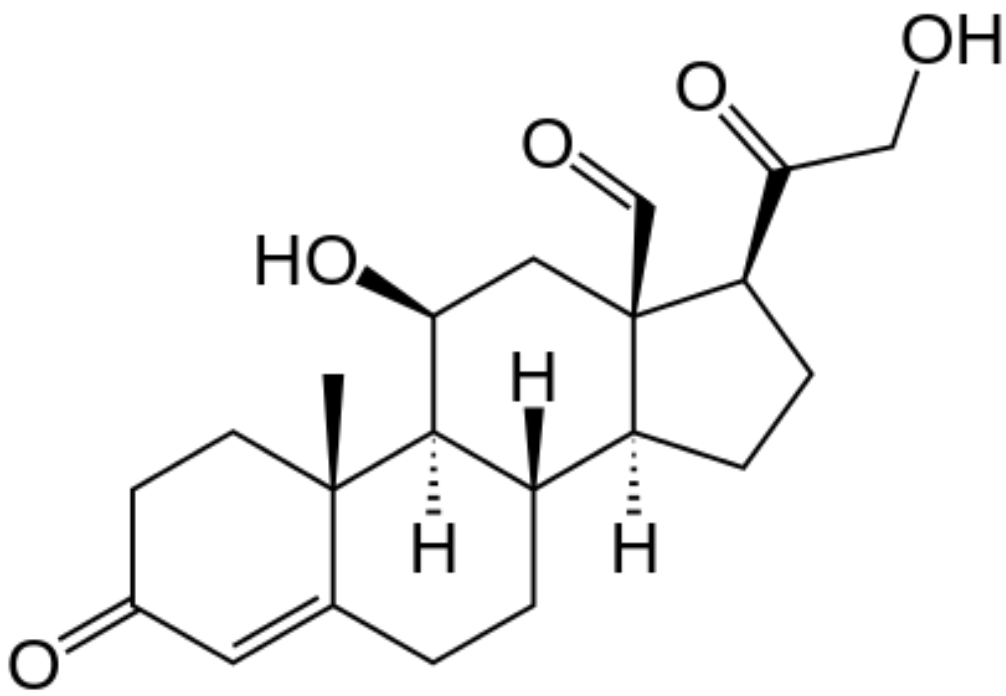
Mineralocorticoids

Mineralocorticoids are a class of corticosteroids, which are a class of steroid hormones. Mineralocorticoids are corticosteroids that influence salt and water balances (electrolyte balance and fluid balance). The primary mineralocorticoid is aldosterone, notable for a second keto group at the 18 position.

The name mineralocorticoid derives from early observations that these hormones were involved in the retention of sodium, a mineral. The mineralocorticoid known as aldosterone is shown below.



https://en.wikipedia.org/wiki/Mineralocorticoid

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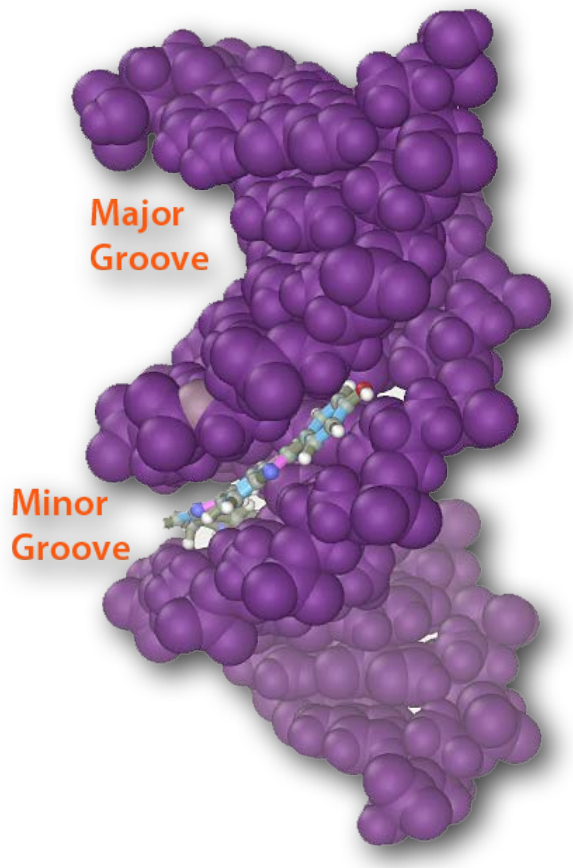
Minor Groove

The double helix structure of DNA contains a major groove and minor groove. In B-DNA the major groove is wider than the minor groove. Given the difference in widths of the major groove and minor groove, many proteins which bind to B-DNA do so through the wider major groove.



https://en.wikipedia.org/wiki/Nucleic_acid_double_helix

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Chapter 2 - Structure and Function: Nucleic Acids

Chapter 9 - Point by Point: Structure and Function

miRNAs

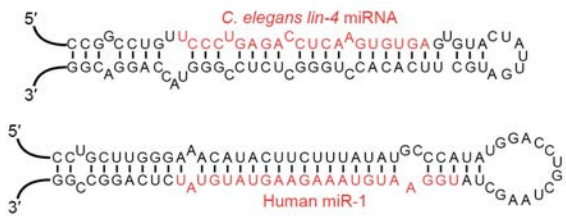
A microRNA (abbreviated miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals and some viruses, that functions in RNA silencing and post-transcriptional regulation of gene expression.
Encoded by eukaryotic nuclear DNA in plants and animals and by viral DNA in certain viruses whose genome is based on DNA, miRNAs function via base-pairing with complementary sequences within mRNA molecules.As a result, these mRNA molecules are silenced, by one or more of the following processes:

• Cleavage of the mRNA strand into two pieces,
• Destabilization of the mRNA through shortening of its poly(A) tail, and
• Less efficient translation of the mRNA into proteins by ribosomes.

miRNAs resemble the small interfering RNAs (siRNAs) of the RNA interference (RNAi) pathway, except miRNAs derive from regions of RNA transcripts that fold back on themselves to form short hairpins, whereas siRNAs derive from longer regions of double-stranded RNA. The human genome may encode over 1000 miRNAs, which are abundant in many mammalian cell types and appear to target about 60% of the genes of humans and other mammals.

miRNAs are well conserved in both plants and animals, and are thought to be a vital and evolutionarily ancient component of gene regulation.While core components of the microRNA pathway are conserved between plants and animals, miRNA repertoires in the two kingdoms appear to have emerged independently with different primary modes of action.

Plant miRNAs usually have near-perfect pairing with their mRNA targets, which induces gene repression through cleavage of the target transcripts. In contrast, animal miRNAs are able to recognize their target mRNAs by using as little as 6–8 nucleotides (the seed region) at the 5' end of the miRNA, which is not enough pairing to induce cleavage of the target mRNAs. Combinatorial regulation is a feature of miRNA regulation in animals. A given miRNA may have hundreds of different mRNA targets, and a given target might be regulated by multiple miRNAs.



https://en.wikipedia.org/wiki/MicroRNA

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Misfolding

Aggregated/misfolded proteins are associated with prion-related illnesses such as Creutzfeldt-Jakob disease, bovine spongiform encephalopathy (mad cow disease), amyloid-related illnesses such as Alzheimer's disease and familial amyloid cardiomyopathy or polyneuropathy, as well as intracytoplasmic aggregation diseases such as Huntington's and Parkinson's disease. These age onset degenerative diseases are associated with the aggregation of misfolded proteins into insoluble, extracellular aggregates and/or intracellular inclusions including cross-β sheet amyloid fibrils. It is not completely clear whether the aggregates are the cause or merely a reflection of the loss of protein homeostasis, the balance between synthesis, folding, aggregation and protein turnover.

Recently the European Medicines Agency approved the use of Tafamidis or Vyndaqel (a kinetic stabilizer of tetrameric transthyretin) for the treatment of transthyretin amyloid diseases. This suggests that the process of amyloid fibril formation (and not the fibrils themselves) causes the degeneration of post-mitotic tissue in human amyloid diseases. Misfolding and excessive degradation instead of folding and function leads to a number of proteopathy diseases such as antitrypsin-associated emphysema, cystic fibrosis and the lysosomal storage diseases, where loss of function is the origin of the disorder. While protein replacement therapy has historically been used to correct the latter disorders, an emerging approach is to use pharmaceutical chaperones to fold mutated proteins to render them functional.

https://en.wikipedia.org/wiki/Protein_folding#Incorrect_protein_folding_and_neurodegenerative_disease

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Mismatch Repair

DNA mismatch repair is a system for recognizing and repairing erroneous insertion, deletion, and mis-incorporation of bases that can arise during DNA replication and re-combination, as well as repairing some forms of DNA damage.

Mismatch repair is strand-specific. During DNA synthesis the newly synthesized (daughter) strand will commonly include errors. In order to begin repair, the mis-match repair machinery distinguishes the newly synthesized strand from the template (parental). In Gram-negative bacteria, transient hemimethylation distinguishes the strands (the parental is methylated and daughter is not). However, in other prokaryo-tes and eukaryotes, the exact mechanism is not clear. It is suspected that, in eukaryo-tes, newly synthesized lagging-strand DNA transiently contains nicks (before being sealed by DNA ligase) and provides a signal that directs mismatch proofreading sys-tems to the appropriate strand. This implies that these nicks must be present in the leading strand, and evidence for this has recently been found. Recent work has shown that nicks are sites for RFC-dependent loading of the replication sliding clamp PCNA, in an orientation-specific manner, such that one face of the donut-shape protein is jux-taposed toward the 3'-OH end at the nick. Oriented PCNA then directs the action of the MutLalpha endonuclease to one strand in the presence of a mismatch and MutSalpha or MutSbeta.

Any mutational event that disrupts the superhelical structure of DNA carries with it the potential to compromise the genetic stability of a cell. The fact that the damage de-tection and repair systems are as complex as the replication machinery itself highlights the importance evolution has attached to DNA fidelity.

Examples of mismatched bases include a G/T or A/C pairing (see DNA repair). Mis-matches are commonly due to tautomerization of bases during G2. The damage is re-paired by recognition of the deformity caused by the mismatch, determining the tem-plate and non-template strand, and excizing the wrongly incorporated base and replac-ing it with the correct nucleotide. The removal process involves more than just the mis-matched nucleotide itself. A few or up to thousands of base pairs of the newly synthe-sized DNA strand can be removed.

https://en.wikipedia.org/wiki/DNA_mismatch_repair

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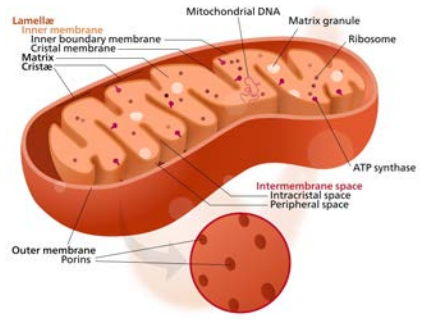
Mitochondria

The mitochondrion (plural mitochondria) is a double membrane-bound organelle found in most eukaryotic cells. Mitochondria have been described as "the powerhouse of the cell" because they generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy.

A mitochondrion contains outer and inner membranes composed of phospholipid bi-layers and proteins. The two membranes have different properties. Because of this double-membraned organization, there are five distinct parts to a mitochondrion. They are:

1. the outer mitochondrial membrane,
2. the intermembrane space (the space between the outer and inner membranes),
3. the inner mitochondrial membrane,
4. the cristae space (formed by infoldings of the inner membrane), and
5. the matrix (space within the inner membrane).



https://en.wikipedia.org/wiki/Mitochondrion

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Mitochondrial Matrix

In the mitochondrion, the matrix contains soluble enzymes that catalyze the oxidation of pyruvate and other small organic molecules. It is into the matrix that protons travel during oxidative phosphorylation and where DNA is released when made in the same process.

The mitochondrial matrix also contains the mitochondrial DNA and ribosomes. The word "matrix" stems from the fact that this space is viscous, compared to the relatively aqueous cytoplasm.

https://en.wikipedia.org/wiki/Mitochondrial_matrix

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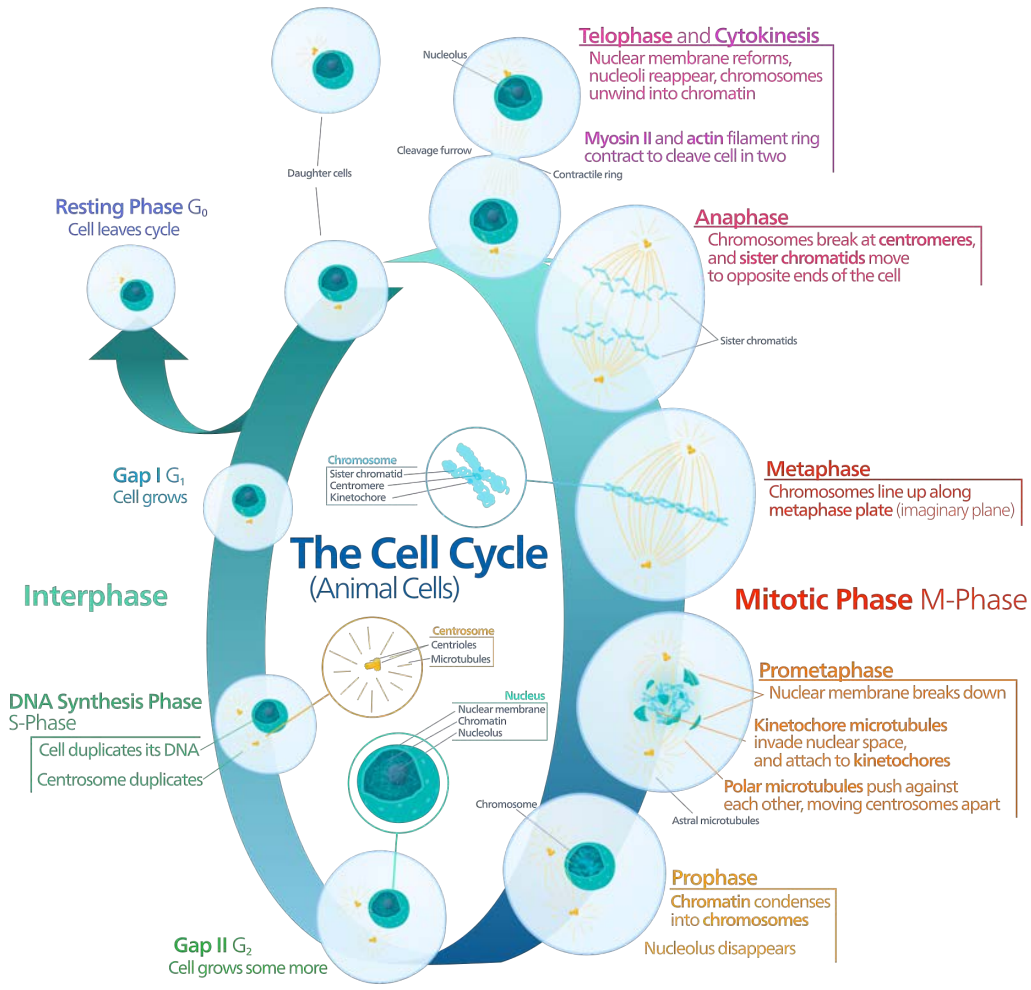
Mitosis

Mitosis is a part of the cell cycle in which chromosomes in a cell nucleus are separated into two identical sets of chromosomes, and each set ends up in its own nucleus. In general, mitosis (division of the nucleus) is often accompanied or followed by cytokinesis, which divides the cytoplasm, organelles and cell membrane into two new cells containing roughly equal shares of these cellular components. Mitosis and cytokinesis together define the mitotic (M) phase of an animal cell cycle—the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell.

The animal cell cycle is shown below.



https://en.wikipedia.org/wiki/Mitosis

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Mitosis Promoting Factor

Maturation-promoting factor (abbreviated MPF, also called mitosis-promo
or M-Phase-promoting factor) is the cyclin-Cdk complex that was discovere
frog eggs. It stimulates the mitotic and meiotic phases of the cell cycle. MPF
the entrance into mitosis (the M phase) from the G2 phase by phosphorylat
ple proteins needed during mitosis. MPF is activated at the end of G2 by a p
phatase, which removes an inhibitory phosphate group added earlier.

The MPF is also called the M phase kinase because of its ability to phospho
proteins at a specific point in the cell cycle and thus control their ability to f

https://en.wikipedia.org/wiki/Maturation_promoting_factor

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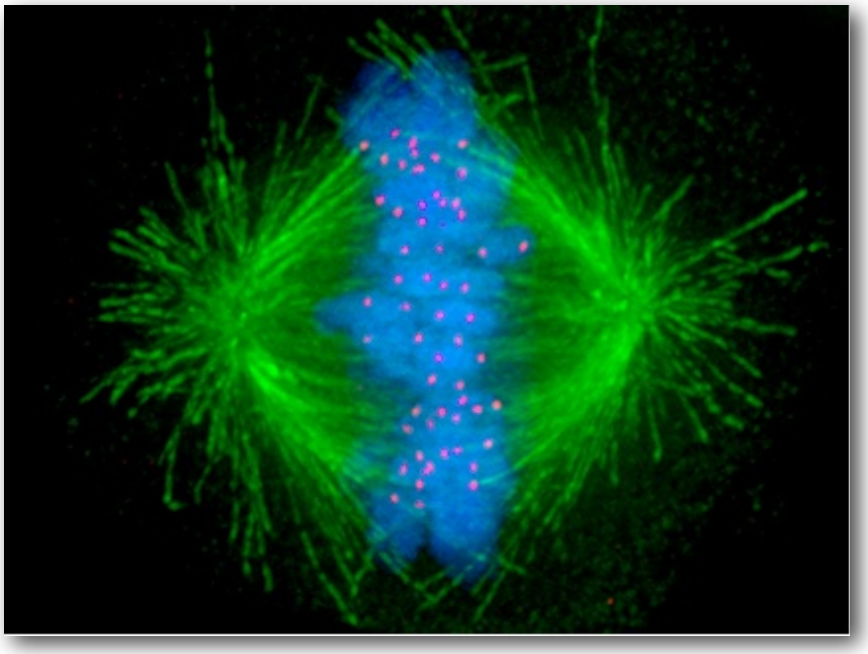
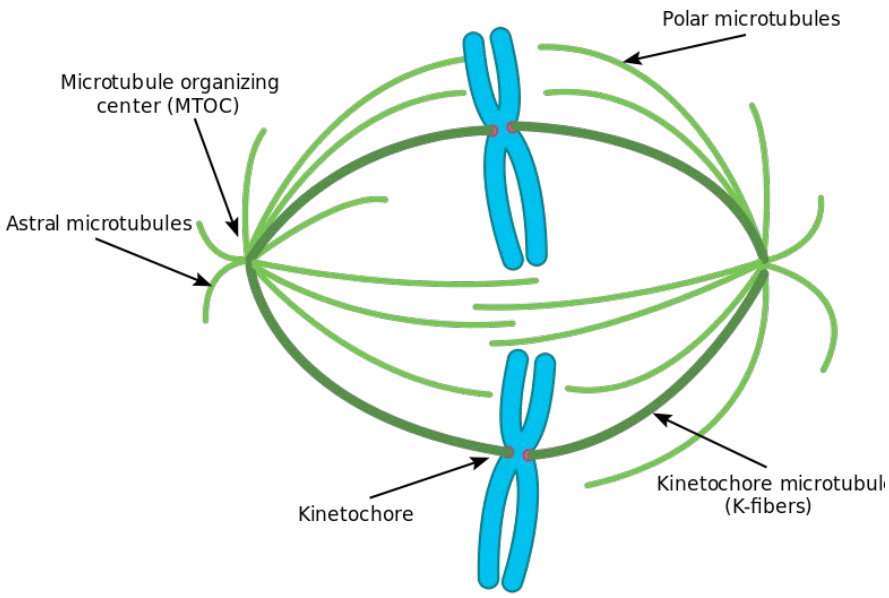
Mitotic Spindles

In cell biology, the spindle apparatus refers to the cytoskeletal structure of eukaryotic cells that forms during cell division to separate sister chromatids between daughter cells. It is referred to as the mitotic spindle during mitosis, a process that produces genetically identical daughter cells, or the meiotic spindle during meiosis, a process that produces gametes with half the number of chromosomes of the parent cell.





https://en.wikipedia.org/wiki/Spindle_apparatus

Mixed Function Oxidase

Mixed-function oxidase is the name of a family of oxidase enzymes that catalyze a reaction in which each of the two atoms of oxygen in O_2 is used for a different function in the reaction.

Oxidase is a general name for enzymes that catalyze oxidations in which molecular oxygen is the electron acceptor but oxygen atoms do not appear in the oxidized product. Often, oxygen is reduced to either water (cytochrome oxidase of the mitochondrial electron transfer chain) or hydrogen peroxide (dehydrogenation of fatty acyl-CoA in peroxisomes). Most of the oxidases are flavoproteins.

The name "mixed-function oxidase" indicates that the enzyme oxidizes two different substrate simultaneously. Desaturation of fatty acyl-CoA in vertebrates is an example of the mixed-function oxidase reaction. In the process, saturated fatty acyl-CoA and NADPH are oxidized by molecular oxygen (O_2) to produce monounsaturated fatty acyl-CoA, $NADP^+$ and 2 molecules of water.

The mixed-function oxidase reaction proceeds as follows:

$AH + BH_2 + O_2 \text{ --> } AOH + B + H_2O$

https://en.wikipedia.org/wiki/Mixed-function_oxidase

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Molecular Response

In the process of blood clotting, the mechanism by which the process works a step of activation (wounding) followed by 2) a cellular response (aggregat platelets) and 3) a molecular response (polymerization of the protein called create a meshwork that hardens). Factors released in the cellular response vate the molecular response.

https://en.wikipedia.org/wiki/Coagulation

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Molecularity

Molecularity in a reaction is the number of molecules that come together to
elementary reaction and is equal to the sum of stoicheometric coefficients o
in this elementary reaction. Depending on how many molecules come toget
tion can be unimolecular, bimolecular or termolecular.

https://en.wikipedia.org/wiki/Molecularity

Related Glossary Terms

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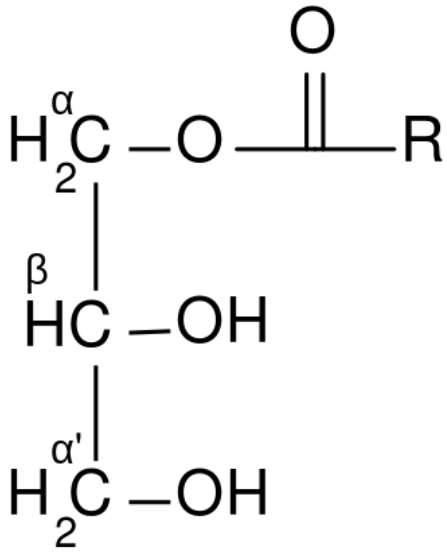
Monoacylglyceride

A monoglyceride (monoacylglyceride or monoacylglycerol) is a glyceride in which a glycerol molecule has formed an ester bond with exactly one fatty acid molecule. The more formally correct terms in modern convention are acylglycerol and monoacylglycerol.

In normal metabolic processes, monoacylglycerols are hydrolyzed by monoacylglycerol lipase to produce glycerol and a free fatty acid as required.



https://en.wikipedia.org/wiki/Monoglyceride

Related Glossary Terms

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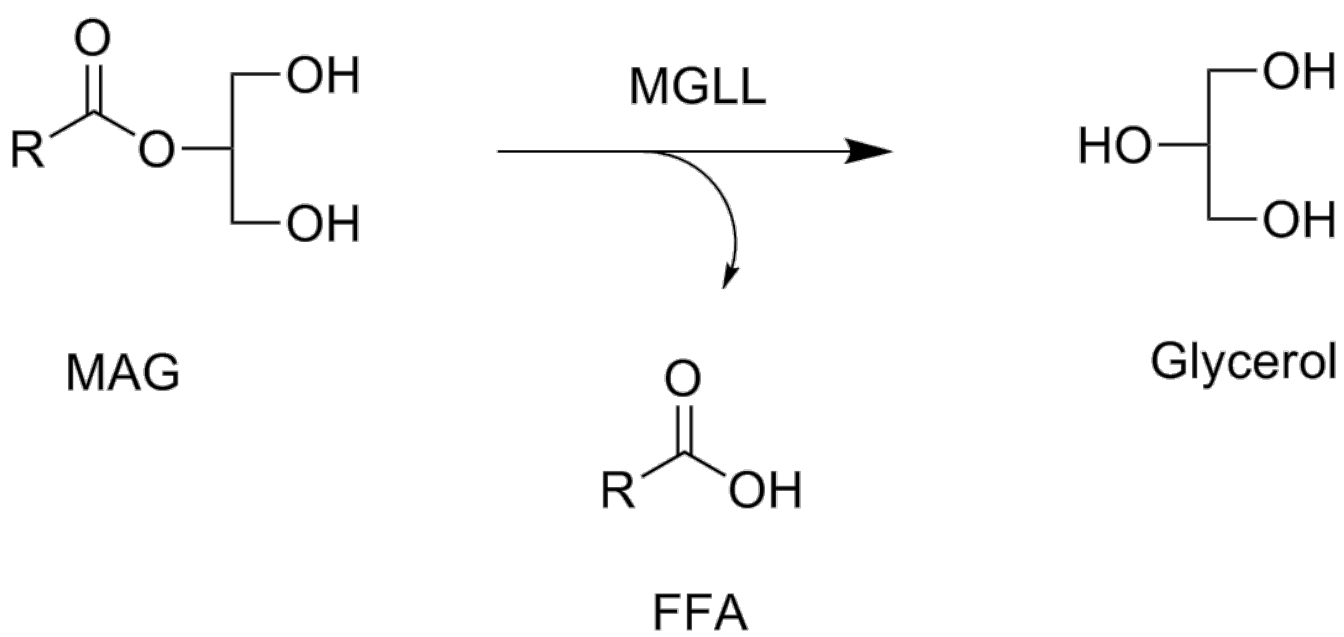
Monoacylglyceride Lipase

Monoacylglycerol lipase, also known as MAG lipase, MAGL, MGL or MGLL is a protein that, in humans, is encoded by the MGLL gene. MAGL is a 33-kDa, membrane-associated member of the serine hydrolase superfamily and contains the classical GXSXG consensus sequence common to most serine hydrolases. The catalytic triad has been identified as Ser122, His269, and Asp239.

Monoacylglycerol lipase is a key enzyme in the hydrolysis of the endocannabinoid 2-arachidonoylglycerol (2-AG). It converts monoacylglycerols to the free fatty acid and glycerol. This is shown in the reaction below.



https://en.wikipedia.org/wiki/Monoacylglycerol_lipase

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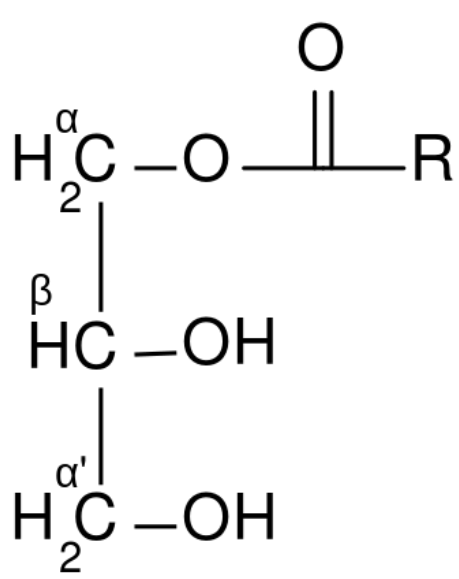
Monoacylglycerol

A monoglyceride (monoacylglyceride or monoacylglycerol) is a glyceride in which a glycerol molecule has formed an ester bond with exactly one fatty acid molecule. The more formally correct terms in modern convention are acylglycerol and monoacylglycerol.

In normal metabolic processes, monoacylglycerols are hydrolyzed by monoacylglycerol lipase to produce glycerol and a free fatty acid as required.



https://en.wikipedia.org/wiki/Monoglyceride

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Chapter 2 - Structure & Function: Lipids

Monoamine Oxidases

L-Monoamine oxidases (MAO) (EC 1.4.3.4) are a family of enzymes that catalyze the oxidation of monoamines. They are found bound to the outer membrane of mitochondria in most cell types in the body. The enzyme was originally discovered by Mary Bernheim in the liver and was named tyramine oxidase. They belong to the protein family of flavin-containing amine oxidoreductases.

Monoamine oxidases catalyze the oxidative deamination of monoamines. Oxygen is used to remove an amine group from a molecule, resulting in the corresponding aldehyde and ammonia.
Monoamine oxidases contain the covalently bound cofactor FAD and are, thus, classified as flavoproteins.

They are well known enzymes in pharmacology, since they are the substrate for the action of a number of monoamine oxidase inhibitor drugs. MAO-A is particularly important in the catabolism of monoamines ingested in food. Both MAOs are also vital to the inactivation of monoaminergic neurotransmitters, for which they display different specificities.

• Serotonin, melatonin, noradrenaline, and adrenaline are mainly broken down by MAO-A.
• Phenethylamine and benzylamine are mainly broken down by MAO-B.
• Both forms break down dopamine, tyramine, and tryptamine equally.
Specific reactions catalyzed by MAO include:
• Adrenaline or noradrenaline to 3,4-dihydroxymandelic acid
• Metanephrine or normetanephrine to vanillylmandelic acid (VMA)
• Dopamine to dihydroxyphenylacetic acid
• 3-Methoxytyramine to homovanillic acid

https://en.wikipedia.org/wiki/Monoamine_oxidase

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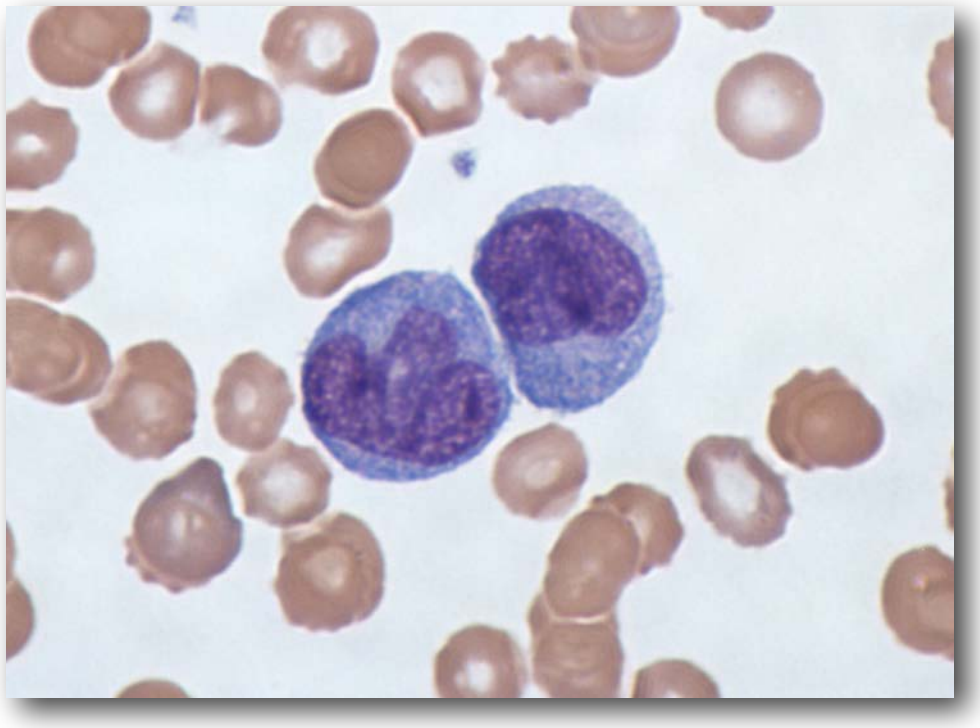
Monocyte

Monocytes are a type of white blood cell, or leukocyte. They are the largest type of leukocyte, and differentiate into: macrophages, dendritic cells, and foam cells. As a part of the vertebrate innate immune system monocytes also influence the process of adaptive immunity.

There are at least three types of monocyte in human blood. Two monocytes below (in blue) are shown surrounded by red blood cells.



https://en.wikipedia.org/wiki/Monocyte

Related Glossary Terms

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Monooxygenase

Monooxygenases are enzymes that incorporate one hydroxyl group into subst
many metabolic pathways. In this reaction, the two atoms of dioxygen are rec
one hydroxyl group and one H_2O molecule by the concomitant oxidation of N
One important subset of the monooxygenases, the Cytochrome P450 omega h
lases, is used by cells to metabolize arachidonic acid (i.e. eicosatetraenoic acid
cell signaling molecules, 20-Hydroxyeicosatetraenoic acid or to reduce or tota
vate the activate signaling molecules for example by hydoxylating leukotriene
20-hydroxy-leukotriene B5, 5-hydroxyeicosatetraenoic acid to 5,20-
dihydroxyeicosatetraenoic acid, 5-oxo-eicosatetraenoic acid to 5-oxo-20-
hydroxyeicosatetraenoic acid, 12-hydroxyeicosatetraenoic acid to 12,20-
dihydroxyeicosatetraenoic acid, and [epoxyeicosatrienoic acid]]s to 20-hydro
epoxyeicosatrienoic acids.

https://en.wikipedia.org/wiki/Monooxygenase

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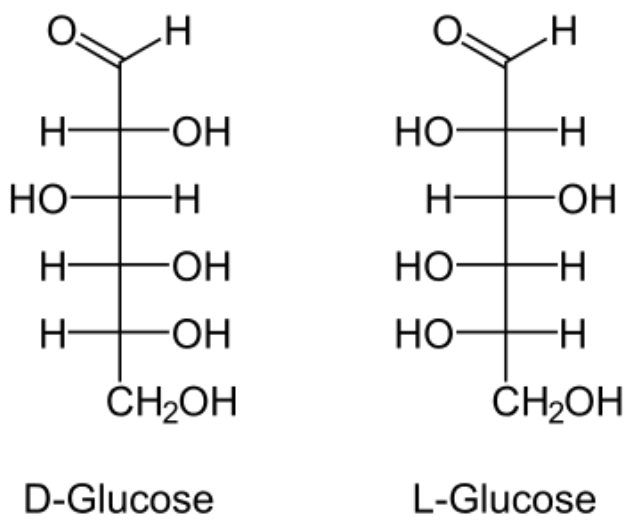
Monosaccharide

Monosaccharides (from Greek monos: single, sacchar: sugar), also called simple sugars, are the most basic units of carbohydrates. They are fundamental units of carbohydrates and cannot be further hydrolized to simpler compounds. The general formula is $C(n)H_2(n)O(n)$. They are the simplest form of sugar and are usually colorless, water-soluble, and crystalline solids. Some monosaccharides have a sweet taste. Examples of monosaccharides include glucose (dextrose), fructose (levulose) and galactose.

Monosaccharides are the building blocks of disaccharides (such as sucrose and lactose) and polysaccharides (such as cellulose and starch). Further, each carbon atom that supports a hydroxyl group (so, all of the carbons except for the primary and terminal carbon) is chiral, giving rise to a number of isomeric forms, all with the same chemical formula. For instance, galactose and glucose are both aldohexoses, but have different physical structures and chemical properties. D-glucose and L-glucose are shown below.



D-Glucose L-Glucose

https://en.wikipedia.org/wiki/Monosaccharide

Related Glossary Terms

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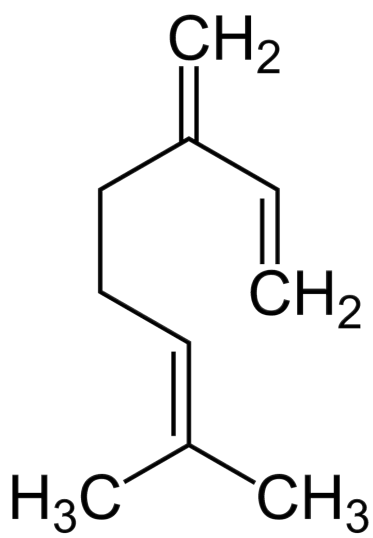
Monoterpenes

Monoterpenes are a class of terpenes that consist of two isoprene units and h
molecular formula $C_{10}H_{16}$. Monoterpenes may be linear (acyclic) or contain r
chemical modifications such as oxidation or rearrangement produce the relat
erpenoids. Depicted below is myrcene, a monoterpene.



https://en.wikipedia.org/wiki/Monoterpene

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Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

Morpheein Model

The morpheein model of allosteric regulation is a dissociative concerted model.
A morpheein is a homo-oligomeric structure that can exist as an ensemble of physiologically significant and functionally different alternate quaternary assemblies. Transitions between alternate morpheein assemblies involve oligomer dissociation, conformational change in the dissociated state, and reassembly to a different oligomer. The required oligomer disassembly step differentiates the morpheein model for allosteric regulation from the classic MWC and KNF models. Porphobilinogen synthase (PBGS) is the prototype morpheein.

The morpheein model is similar to the MWC model, but with an added step of dissociation of the subunits. The MWC model proposes that flipping between R and T states occurs by the complex as a whole and occurs on all units simultaneously.

The morpheein model instead proposes that the multi-subunit enzyme breaks down to individual units which can then flip in structure and re-form the complex. In the morpheein model, only identically shaped units (all R, for example) can come together in the complex, thus explaining the “all-R-” or “all-T-” state found in the MWC model.

A large number of enzymes, including prominent ones like citrate synthase, acetyl-CoA carboxylase, glutamate dehydrogenase, ribonucleotide reductase and lactate dehydrogenase have behavior consistent with the morpheein model.

https://en.wikipedia.org/wiki/Allosteric_regulation#Morpheein_model

Motor Neurons

A motor neuron (or motoneuron) is a nerve cell (neuron) whose cell body is located in the spinal cord and whose fiber (axon) projects outside the spinal cord to directly or indirectly control effector organs, mainly muscles and glands. Motor neurons' axons are efferent nerve fibers that carry signals from the spinal cord to the effectors to produce effects. Types of motor neurons are alpha motor neurons, beta motor neurons, and gamma motor neurons.

There are upper motor neurons and lower motor neurons, with the cell type described above being a lower motor neuron. Upper motor neurons are cortico-spinal interneurons that arise from the motor cortex and descend to the spinal cord where they activate the lower motor neurons through synapses. The term 'motor neuron' is usually restricted to the efferent neurons that actually innervate muscles (the lower motor neurons).

A single motor neuron may innervate many muscle fibers and a muscle fiber can undergo many action potentials in the time taken for a single muscle twitch. As a result, if an action potential arrives before a twitch has completed, the twitches can superimpose on one another, either through summation or a tetanic contraction. In summation, the muscle is stimulated repetitively such that additional action potentials coming from the somatic nervous system arrive before the end of the twitch. The twitches thus superimpose on one another, leading to a force greater than that of a single twitch. A tetanic contraction is caused by constant, very high frequency stimulation - the action potentials come at such a rapid rate that individual twitches are indistinguishable, and tension rises smoothly eventually reaching a plateau.

https://en.wikipedia.org/wiki/Motor_neuron

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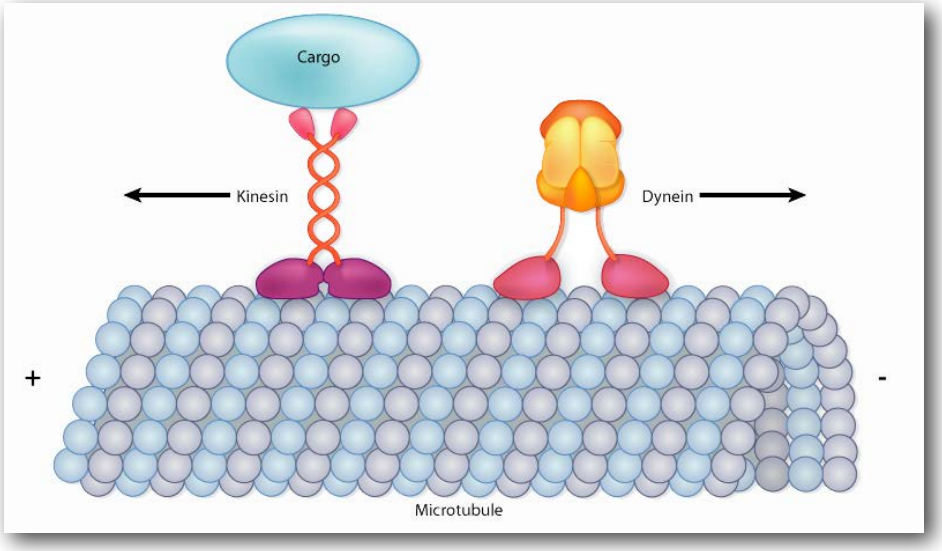
Motor Proteins

Motor proteins are a class of molecular motors that are able to move along the surface of a suitable substrate. They convert chemical energy into mechanical work by the hydrolysis of ATP. Flagellar rotation, however, is powered by a proton pump.

The best prominent example of a motor protein is the muscle protein myosin which "motors" the contraction of muscle fibers in animals. Motor proteins are the driving force behind most active transport of proteins and vesicles in the cytoplasm. Kinesins and cytoplasmic dyneins play essential roles in intracellular transport such as axonal transport and in the formation of the spindle apparatus and the separation of the chromosomes during mitosis and meiosis. Axonemal dynein, found in cilia and flagella, is crucial to cell motility, for example in spermatozoa, and fluid transport, for example in trachea.

Motor proteins utilizing the cytoskeleton for movement fall into two categories based on their substrates: Actin motors such as myosin move along microfilaments through interaction with actin. Microtubule motors such as dynein and kinesin move along microtubules through interaction with tubulin. There are two basic types of microtubule motors: plus-end motors and minus-end motors, depending on the direction in which they "walk" along the microtubule cables within the cell.



https://en.wikipedia.org/wiki/Motor_protein

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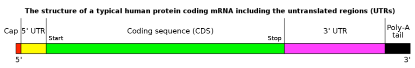
mRNA

Messenger RNA (mRNA) is a large family of RNA molecules that convey genetic information from DNA to the ribosome, where they specify the amino acid sequence of the protein products of gene expression. Following transcription of primary transcript mRNA (known as pre-mRNA) by RNA polymerase, processed, mature mRNA is translated into a polymer of amino acids: a protein, as summarized in the central dogma of molecular biology.

As in DNA, mRNA genetic information is in the sequence of nucleotides, which are arranged into codons consisting of three base pairs each. Each codon encodes for a specific amino acid, except the stop codons, which terminate protein synthesis. The structure of a eukaryotic mRNA is shown below.



https://en.wikipedia.org/wiki/Messenger_RNA

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mRNA cap

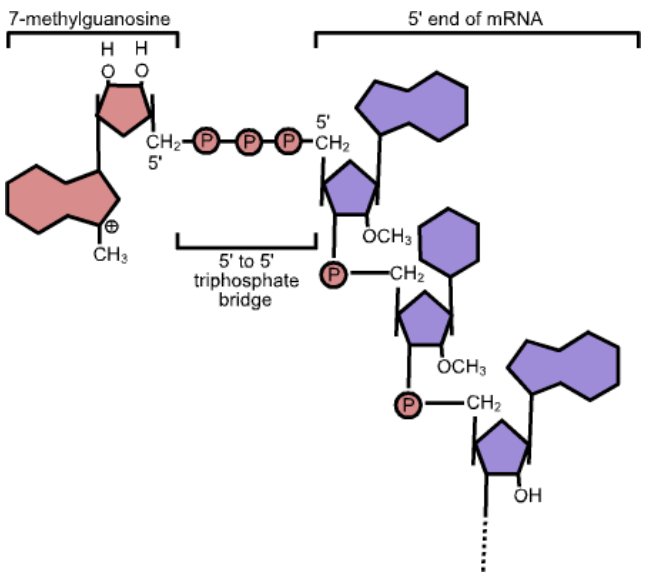
In molecular biology, the five-prime cap (5′ cap) is a specially altered nucleotide on the 5′ end of some eukaryotic primary transcripts such as precursor messenger RNA. This process, known as mRNA capping, is highly regulated and vital in the creation of stable and mature messenger RNA able to undergo translation during protein synthesis. Mitochondrial and chloroplast mRNA are not capped.

In eukaryotes, the 5′ cap (cap-0), found on the 5′ end of an mRNA molecule, consists of a guanine nucleotide connected to mRNA via an unusual 5′ to 5′ triphosphate linkage. This guanosine is methylated on the 7 position directly after capping in vivo by a methyltransferase. It is referred to as a 7-methylguanylate cap, abbreviated m7G.

The 5′ cap has four main functions:

1. Regulation of nuclear export
2. Prevention of degradation by exonucleases
3. Promotion of translation (see Ribosome and Translation (biology))
4. Promotion of 5′ proximal intron excision

Nuclear export of RNA is regulated by the cap binding complex (CBC), which binds exclusively to capped RNA. The CBC is then recognized by the nuclear pore complex and exported. Once in the cytoplasm after the pioneer round of translation, the CBC is replaced by the translation factors eIF4E and eIF4G of the eIF4F complex. This complex is then recognized by other translation initiation machinery including the ribosome.



https://en.wikipedia.org/wiki/Five-prime_cap

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mTOR

The mechanistic target of rapamycin, also known as mammalian target of r
(mTOR) or FK506-binding protein 12-rapamycin-associated protein 1 (FRA
protein that in humans is encoded by the MTOR gene. MTOR is a serine/th
tein kinase that regulates cell growth, cell proliferation, cell motility, cell su
tein synthesis, autophagy, transcription. MTOR belongs to the phosphatidy
kinase-related kinase protein family, and fibrosis.

https://en.wikipedia.org/wiki/Mechanistic_target_of_rapamycin

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Mucins

Mucins are a family of high molecular weight, heavily glycosylated proteins (glycocon jugates) produced by epithelial tissues in most organisms of Kingdom Animalia. Mucins' key characteristic is their ability to form gels. Therefore they are a key comp nent in most gel-like secretions, serving functions from lubrication to cell signaling to forming chemical barriers. They often take an inhibitory role. Some mucins are assoc ated with controlling mineralization, including nacre formation in mollusks, calcifica tion in echinoderms and bone formation in vertebrates. They bind to pathogens as pa of the immune system. Overexpression of the mucin proteins, especially MUC1, is ass ciated with many types of cancer.

Although some mucins are membrane-bound due to the presence of a hydrophobic membrane-spanning domain that favors retention in the plasma membrane, most mucins are secreted as principal components of mucus by mucous membranes or are secreted to become a component of saliva.

https://en.wikipedia.org/wiki/Mucin

Related Glossary Terms

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Muscle Tissue

Muscle is a soft tissue found in most animals. Muscle cells contain protein filaments of actin and myosin that slide past one another, producing a contraction that changes both the length and the shape of the cell. Muscles function to produce force and motion. They are primarily responsible for maintaining and changing posture, locomotion, as well as movement of internal organs, such as the contraction of the heart and the movement of food through the digestive system via peristalsis.

Muscle tissues are derived from the mesodermal layer of embryonic germ cells in a process known as myogenesis. There are three types of muscle, skeletal or striated, cardiac, and smooth. Muscle action can be classified as being either voluntary or involuntary. Cardiac and smooth muscles contract without conscious thought and are termed involuntary, whereas the skeletal muscles contract upon command. Skeletal muscles in turn can be divided into fast and slow twitch fibers.

Muscles are predominantly powered by the oxidation of fats and carbohydrates, but anaerobic chemical reactions are also used, particularly by fast twitch fibers. These chemical reactions produce adenosine triphosphate (ATP) molecules that are used to power the movement of the myosin heads.

The term muscle is derived from the Latin musculus meaning "little mouse" perhaps because of the shape of certain muscles or because contracting muscles look like mice moving under the skin.

https://en.wikipedia.org/wiki/Muscle

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Muscular Contraction

Muscle contraction is the activation of tension-generating sites within muscle fibers. In physiology, muscle contraction does not mean muscle shortening because muscle tension can be produced without changes in muscle length such as holding a heavy book or a dumbbell at the same position. The termination of muscle contraction is followed by muscle relaxation, which is a return of the muscle fibers to their low tension-generating state.

https://en.wikipedia.org/wiki/Muscle_contraction

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Mut Genes

Mismatch repair systems are present in essentially all cells to correct errors
not corrected by proofreading. These systems consist of at least two protein
tects the mismatch, and the other recruits an endonuclease that cleaves the
thesized DNA strand close to the region of damage. In *E. coli* , the proteins
are the Mut class proteins. This is followed by removal of damaged region b
clease, resynthesis by DNA polymerase, and nick sealing by DNA ligase.

https://en.wikipedia.org/wiki/DNA_repair

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Mutagenicity

A mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level. As many mutations can cause cancer, mutagens are therefore also likely to be carcinogens, although not always necessarily so. Not all mutations are caused by mutagens: so-called "spontaneous mutations" occur due to spontaneous hydrolysis, errors in DNA replication, repair and recombination.

Mutagens cause changes to the DNA that can affect the transcription and replication of the DNA, which in severe cases can lead to cell death. The mutagen produces mutations in the DNA, and deleterious mutation can result in aberrant, impaired or loss of function for a particular gene, and accumulation of mutations may lead to cancer. Mutagens may therefore be also carcinogens. However, some mutagens exert their mutagenic effect through their metabolites, and therefore whether such mutagens actually become carcinogenic may be dependent on the metabolic processes of an organisms, and a compound shown to be mutagenic in one organism may not necessarily be carcinogenic in another.
Different mutagens act on the DNA differently. Powerful mutagens may result in chromosomal instability, causing chromosomal breakages and rearrangement of the chromosomes such as translocation, deletion, and inversion. Such mutagens are called clastogens.

Mutagens may also modify the DNA sequence. The changes in nucleic acid sequences by mutations include substitution of nucleotide base-pairs and insertions and deletions of one or more nucleotides in DNA sequences. Although some of these mutations are lethal or cause serious disease, many have minor effects as they do not result in residue changes that have significant effect on the structure and function of the proteins. Many mutations are silent mutations, causing no visible effects at all, either because they occur in non-coding or non-functional sequences, or they do not change the amino-acid sequence due to the redundancy of codons.

Some mutagens can cause aneuploidy and change the number of chromosomes in the cell. In the Ames test, where the varying concentrations of the chemical are used in the test, the dose response curve obtained is nearly always linear, suggesting that there is no threshold for mutagenesis. Similar results are also obtained in studies with radiations, indicating that there may be no safe threshold for mutagens. However, some proposed that low level of some mutagens may stimulate the DNA repair processes and therefore may not necessarily be harmful.

https://en.wikipedia.org/wiki/Mutagen

Mutase

A mutase is an enzyme of the isomerase class that catalyzes the shifting of a
group from one position to another within the same molecule. Examples of
bisphosphoglycerate mutase, which appears in red blood cells and phospho
mutase, which acts in glycolysis. In glycolysis, it changes 3-phosphoglycera
phosphoglycerate. In particular it moves phosphate groups within a single
for instance: phosphoglycerate mutase.

https://en.wikipedia.org/wiki/Mutase

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Chapter 6 - Metabolism: Sugars

Mutation

A mutation is a permanent alteration of the nucleotide sequence of the genome of an organism, virus, or extrachromosomal DNA or other genetic elements. Mutations result from damage to DNA which is not repaired, errors in the process of replication, or from the insertion or deletion of segments of DNA by mobile genetic elements. Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both normal and abnormal biological processes including evolution, cancer, and the development of the immune system, including junctional diversity.

https://en.wikipedia.org/wiki/Mutation

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Mutations

A mutation is a permanent alteration of the nucleotide sequence of the gen
organism, virus, or extrachromosomal DNA or other genetic elements. Mut
sult from damage to DNA which is not repaired, errors in the process of rep
from the insertion or deletion of segments of DNA by mobile genetic eleme
tions may or may not produce discernible changes in the observable charac
(phenotype) of an organism. Mutations play a part in both normal and abn
logical processes including evolution, cancer, and the development of the i
tem, including junctional diversity.

https://en.wikipedia.org/wiki/Mutation

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MWC

The Monod-Wyman-Changeux model (MWC model, also known as the con
model or symmetry model) describes allosteric transitions of proteins mad
tical subunits. The concept of two distinct symmetric states is the central p
the MWC model. The main idea of the model is that regulated proteins, su
enzymes and receptors, exist in different interconvertible states in the abse
regulator. The ratio of the different conformational states is determined by
equilibrium.

https://en.wikipedia.org/wiki/Monod-Wyman-Changeux_model

Related Glossary Terms

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Myelin Sheath

Myelin is a fatty white substance that surrounds the axon of some nerve cel
an electrically insulating layer. It is essential for the proper functioning of t
system. It is an outgrowth of a type of glial cell. During infancy, myelinatio
quickly, leading to a child's fast development, including crawling and walki
first year. Myelination continues through the adolescent stage of life.

https://en.wikipedia.org/wiki/Myelin

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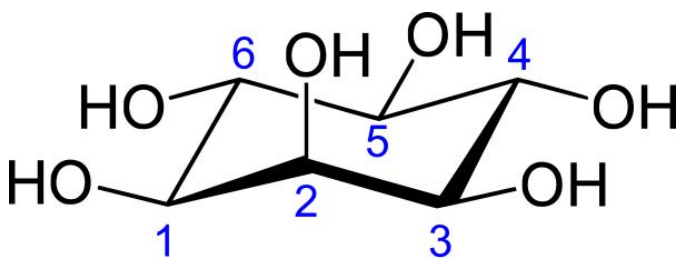
Myo-inositol

Inositol is a chemical compound with formula $C_6H_{12}O_6$, a six-fold alcohol (p
clohexane. It exists in nine possible stereoisomers, of which the most prom
widely occurring in nature, is myo-inositol

myo-Inositol plays an important role as the structural basis for a number o
messengers in eukaryotic cells, the various inositol phosphates.



https://en.wikipedia.org/wiki/Inositol

Related Glossary Terms

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Myogenesis

Myogenesis is the formation of muscular tissue, particularly during embryo
ment.

https://en.wikipedia.org/wiki/Myogenesis

Related Glossary Terms

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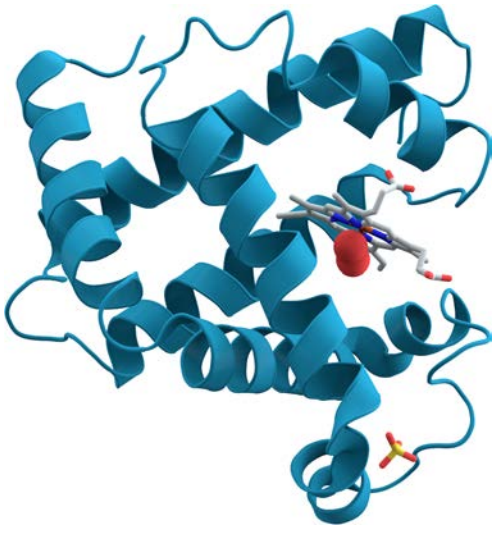
Myoglobin

Myoglobin is an iron- and oxygen-binding protein found in the muscle tissue of vertebrates in general and in almost all mammals. It is related to hemoglobin, which is the iron- and oxygen-binding protein in blood, specifically in the red blood cells. In humans, myoglobin is only found in the bloodstream after muscle injury. It is an abnormal finding, and can be diagnostically relevant when found in blood.
Myoglobin is the primary oxygen-carrying pigment of muscle tissues. High concentrations of myoglobin in muscle cells allow organisms to hold their breath for a longer period of time.



https://en.wikipedia.org/wiki/Myoglobin

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Myosin

Myosins comprise a family of ATP-dependent motor proteins and are best known for their role in muscle contraction and their involvement in a wide range of other motility processes in eukaryotes. They are responsible for actin-based motility. The term was originally used to describe a group of similar ATPases found in the cells of both striated muscle tissue and smooth muscle tissue. Following the discovery by Pollard and Korn (1973) of enzymes with myosin-like function in *Acanthamoeba castellanii*, a large number of divergent myosin genes have been discovered throughout eukaryotes. Thus, although myosin was originally thought to be restricted to muscle cells (hence myo-(s) + -in), there is no single "myosin" but rather a huge superfamily of genes whose protein products share the basic properties of actin binding, ATP hydrolysis (ATPase enzyme activity), and force transduction. Virtually all eukaryotic cells contain myosin isoforms. Some isoforms have specialized functions in certain cell types (such as muscle), while other isoforms are ubiquitous. The structure and function of myosin is strongly conserved across species, to the extent that rabbit muscle myosin II will bind to actin from an amoeba.

https://en.wikipedia.org/wiki/Myosin

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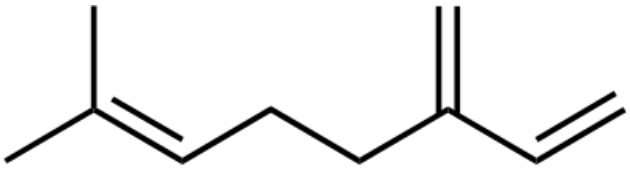
Myrcene

Myrcene, or β-myrcene, is an olefinic natural organic hydrocarbon. It is mo
classified as a monoterpene. Monoterpenes are dimers of isoprenoid precu
myrcene is one of the most important. It is a component of the essential oil
plants including bay, cannabis, ylang-ylang, wild thyme, parsley, and hops.
duced mainly semi-synthetically from myrcia, from which it gets its name.



https://en.wikipedia.org/wiki/Myrcene

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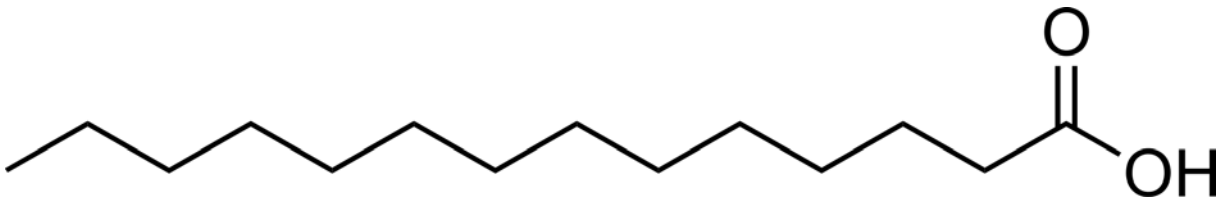
Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

Myristic Acid

Myristic acid, also called tetradecanoic acid, is a common saturated fatty ac
molecular formula $CH_3(CH_2)_{12}COOH$. A myristate is a salt or ester of myris
Myristic acid is named after the nutmeg *Myristica fragrans*.



https://en.wikipedia.org/wiki/Myristic_acid

Related Glossary Terms

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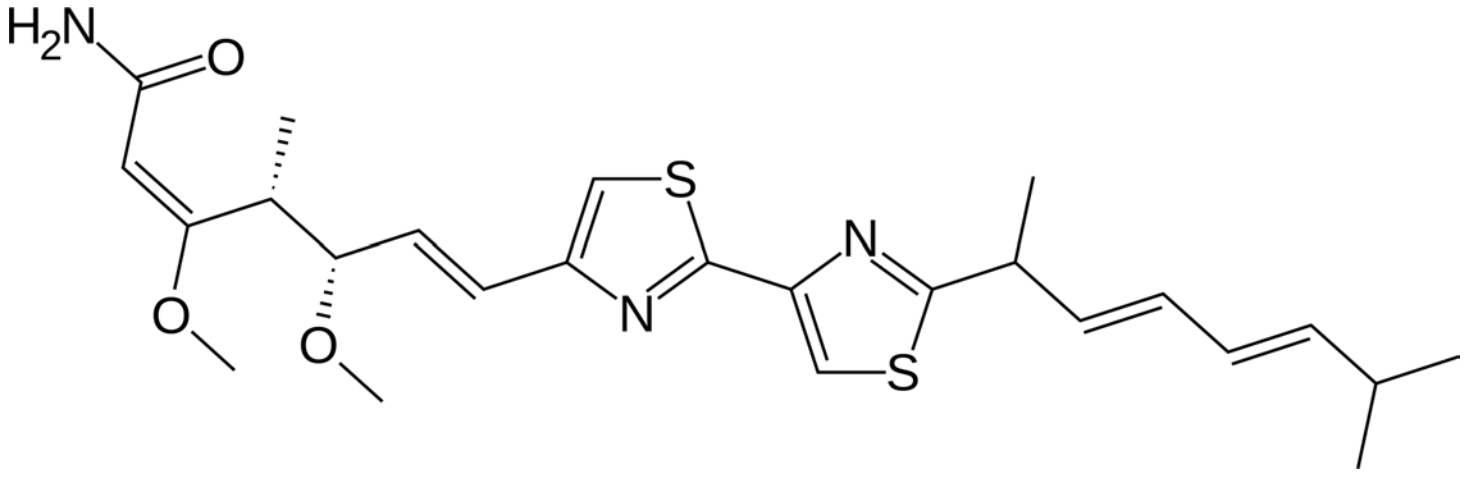
Myxothiazol

Myxothiazol (produced by the myxobacterium *Myxococcus fulvus*) is an inh
the mitochondrial cytochrome bc_1 complex (coenzyme Q - cytochrome c red



https://en.wikipedia.org/wiki/Myxothiazol

Related Glossary Terms

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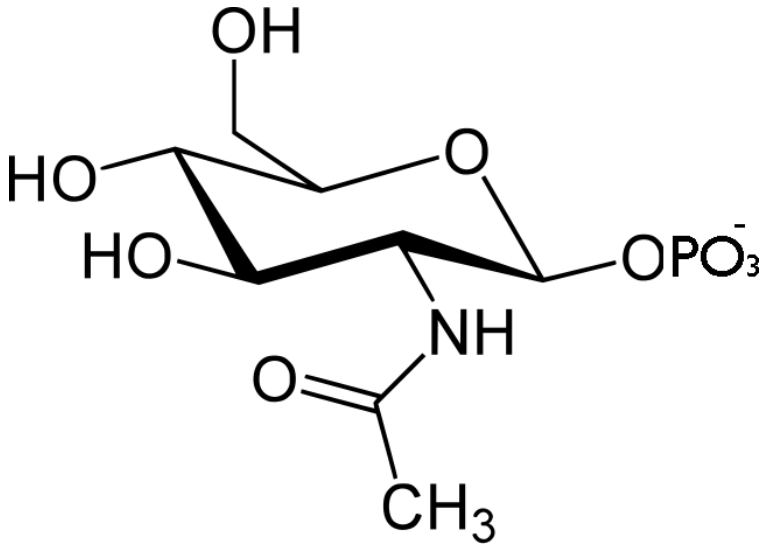
N-acetyl-glucosamine-1-phosphate

N-acetyl-glucosamine-1-phosphate is produced in step three of the peptido
thesis process by isomerization of N-acetyl-glucosamine-6-phosphate.



Related Glossary Terms

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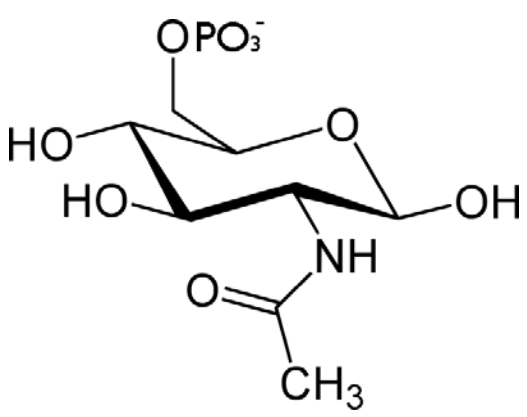
N-acetyl-glucosamine-6-phosphate

In the first step of peptidoglycan synthesis, the glutamine, which is an amino ac
nates an amino group to a sugar, fructose 6-phosphate. This turns fructose 6-
phosphate into glucosamine-6-phosphate. In step two, an acetyl group is transf
from acetyl CoA to the amino group on the glucosamine-6-phosphate creating I
acetyl-glucosamine-6-phosphate. In step three of the synthesis process, the N-a
glucosamine-6-phosphate is isomerized, which will change N-acetyl-glucosami
phosphate to N-acetyl-glucosamine-1-phosphate.



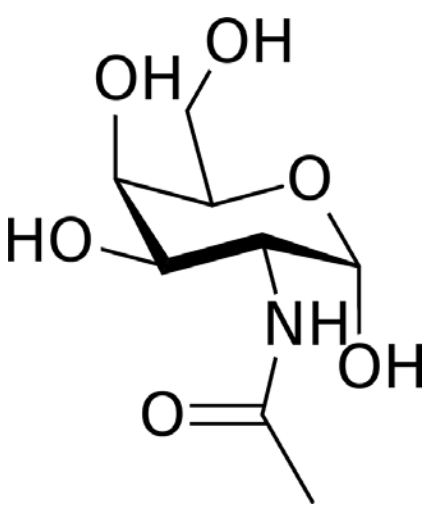
https://en.wikipedia.org/wiki/Peptidoglycan

Related Glossary Terms

Drag related terms here

N-acetylgalactosamine

N-Acetylgalactosamine (GalNAc), is an amino sugar derivative of galactose.
In humans it is the terminal carbohydrate forming the antigen of blood group A.
It is typically the first monosaccharide that connects serine or threonine in partic
forms of protein O-glycosylation. N-Acetylgalactosamine is necessary for intercel
communication, and is concentrated in sensory nerve structures of both humans
animals.



https://en.wikipedia.org/wiki/N-Acetylgalactosamine

Related Glossary Terms

Drag related terms here

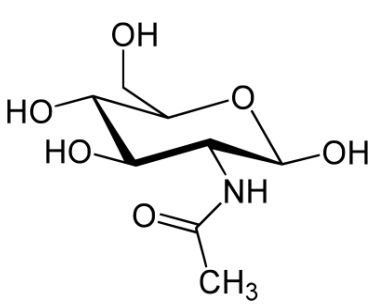
N-acetylglucosamine

N-acetylglucosamine (N-acetyl-D-glucosamine, or GlcNAc, or NAG) is a monosaccharide and a derivative of glucose. It is an amide between glucosamine and acetic acid. It has a molecular formula of $C_8H_{15}NO_6$, a molar mass of 221.21 g/mol, and it is significant in several biological systems.

It is part of a biopolymer in the bacterial cell wall, built from alternating units of GlcNAc and N-acetylmuramic acid (MurNAc), cross-linked with oligopeptides at the lactic acid residue of MurNAc. This layered structure is called peptidoglycan (formerly called murein).

GlcNAc is the monomeric unit of the polymer chitin, which forms the outer coverings of insects and crustaceans. It is the main component of the radulas of mollusks, the beaks of cephalopods, and a major component of the cell walls of most fungi. Polymerized with glucuronic acid, it forms hyaluronan.

GlcNAc has been reported to be an inhibitor of elastase release from human polymorphonulear leukocytes (range 8 - 17% inhibition), however this is much weaker than the inhibition seen with N-acetyl-galactosamine (range 92 - 100%).



https://en.wikipedia.org/wiki/N-Acetylglucosamine

Related Glossary Terms

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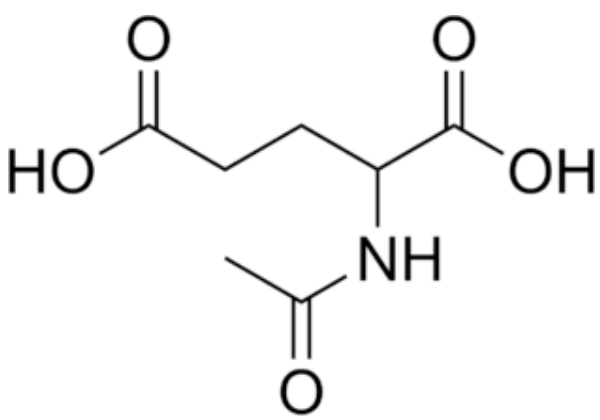
N-acetylglutamate

N-acetylglutamic acid (abbreviated NAcGlu) is biosynthesized from glutamic acid and acetyl-CoA by the enzyme N-acetylglutamate synthase. Arginine is the activator for thi reaction.

The reverse reaction, hydrolysis of the acetyl group, is catalyzed by a specific hydro-lase. NAcGlu activates carbamoyl phosphate synthetase in the urea cycle.



https://en.wikipedia.org/wiki/N-Acetylglutamic_acid

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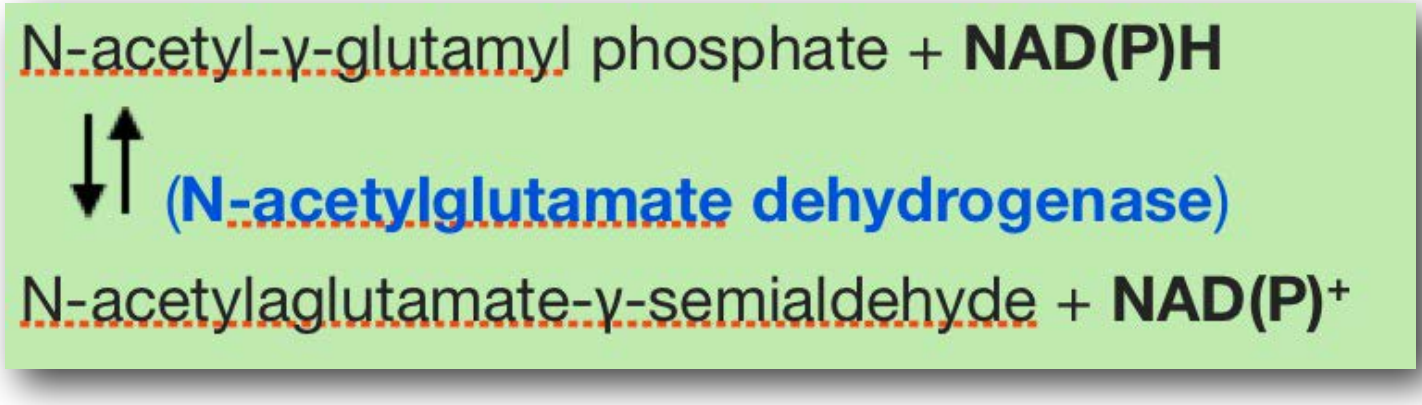
N-acetylglutamate Dehydrogenase

N-acetylglutamate dehydrogenase catalyzes conversion of N-acetyl-γ-glutar
phate to N-acetylglutamate-γ-semialdehyde in the third step of conversion
mate to serine.



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N-acetylglutamate Kinase

Acetylglutamate kinase is an enzyme that catalyzes the chemical reaction:

ATP + N-acetyl-L-glutamate <--> ADP + N-acetyl-L-glutamyl 5-phosphate

Thus, the two substrates of this enzyme are ATP and N-acetyl-L-glutamate, two products are ADP and N-acetyl-L-glutamyl 5-phosphate.
This enzyme belongs to the family of transferases, specifically those transfe phosphorus-containing groups (phosphotransferases) with a carboxy group tor. This enzyme participates in urea cycle and metabolism of amino groups

https://en.wikipedia.org/wiki/Acetylglutamate_kinase

Related Glossary Terms

Drag related terms here

N-acetylornithinase

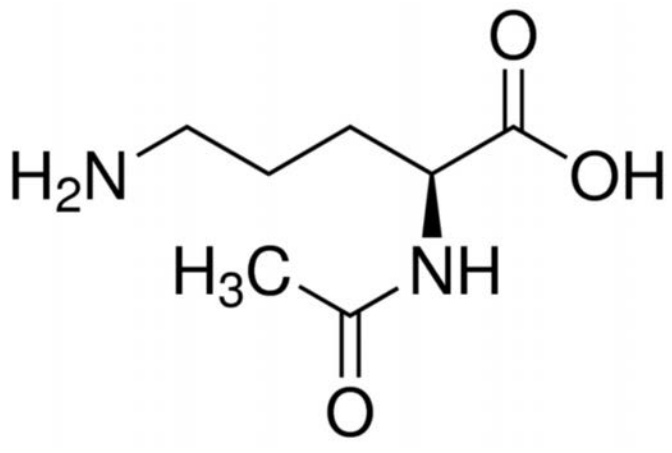
N-acetylornithinase catalyzes conversion of N-acetylornithine to ornithine step of conversion of glutamate to serine.

Related Glossary Terms

Drag related terms here

N-acetylornithine

N-acetylornithine is a precursor of ornithine in the biosynthetic pathway le
thesis of serine from glutamate.

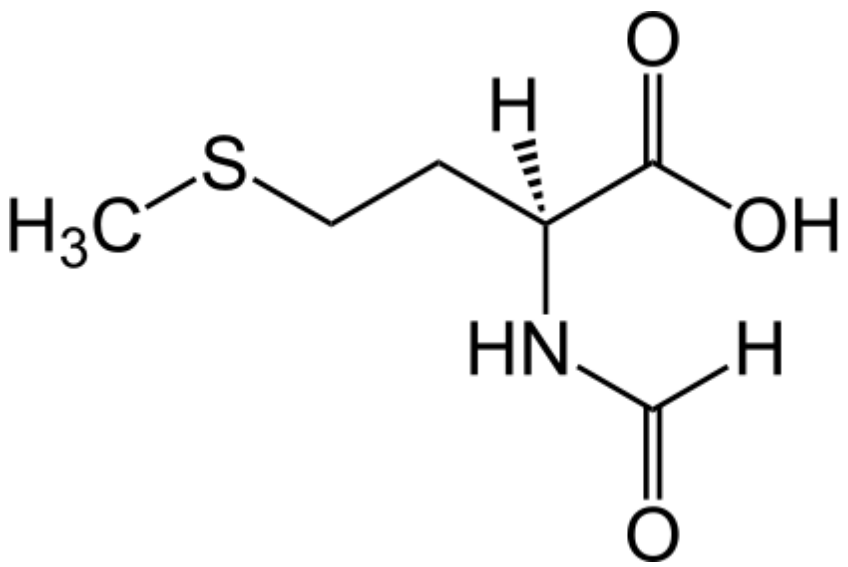


Related Glossary Terms

Drag related terms here

N-formyl-methionine

N-Formylmethionine (fMet) is a derivative of the amino acid methionine in
formyl group has been added to the amino group. It is specifically used for i
protein synthesis from bacterial and organellar genes, and may be removed
translationally.



https://en.wikipedia.org/wiki/N-Formylmethionine

Related Glossary Terms

Drag related terms here

N-glycosylation

N-linked glycosylation, is the attachment of the sugar molecule oligosaccha as glycan to a nitrogen atom (amide nitrogen of asparagine (Asn) residue o in a process called N-glycosylation. This type of linkage is important for bo ture and function of some eukaryotic proteins. The N-linked glycosylation p curs in eukaryotes and widely in archaea, but very rarely in eubacteria.

https://en.wikipedia.org/wiki/N-linked_glycosylation

Related Glossary Terms

Drag related terms here

N-linked

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as glycan to a nitrogen atom (amide nitrogen of asparagine (Asn) residue o
in a process called N-glycosylation, studied in biochemistry. This type of lin
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glycosylation process occurs in eukaryotes and widely in archaea, but very r
bacteria.

https://en.wikipedia.org/wiki/N-linked_glycosylation

Related Glossary Terms

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bacteria.

https://en.wikipedia.org/wiki/N-linked_glycosylation

Related Glossary Terms

Drag related terms here

N-terminal

The N-terminus (also known as the amino-terminus, NH_2-terminus, N-terminal end amine-terminus) refers to the start of a protein or polypeptide terminated by an amir acid with a free amine group (-NH_2). By convention, peptide sequences are written N terminus to C-terminus, left to right in LTR languages. This correlates the translation direction to the text direction (because when a protein is translated from messenger RNA, it is created from N-terminus to C-terminus - amino acids are added to the car- bonyl end).

https://en.wikipedia.org/wiki/N-terminus

Related Glossary Terms

Drag related terms here

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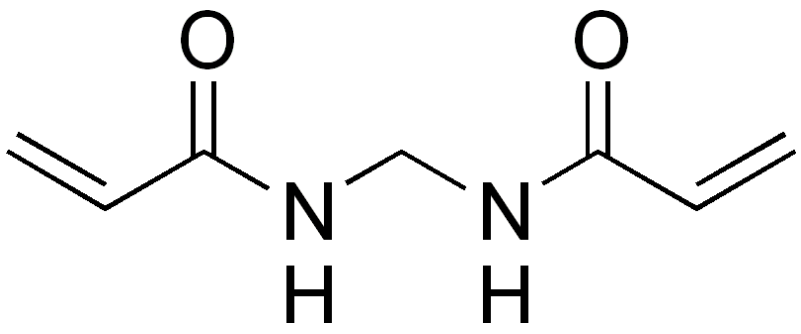
N,N’-Methylene-bisacrylamide

N,N'-Methylenebisacrylamide (MBAm or MBAA) is a cross-linking agent used
the formation of polymers such as polyacrylamide. Its molecular formula is C
Bisacrylamide and it is one of the compounds of the polyacrylamide gel (used
PAGE). Bisacrylamide polymerizes with acrylamide and is capable of creating
links between polyacrylamide chains, thus creating a network of polyacrylami
than unconnected linear chains of polyacrylamide.



https://en.wikipedia.org/wiki/N,N%27-Methylenebisacrylamide

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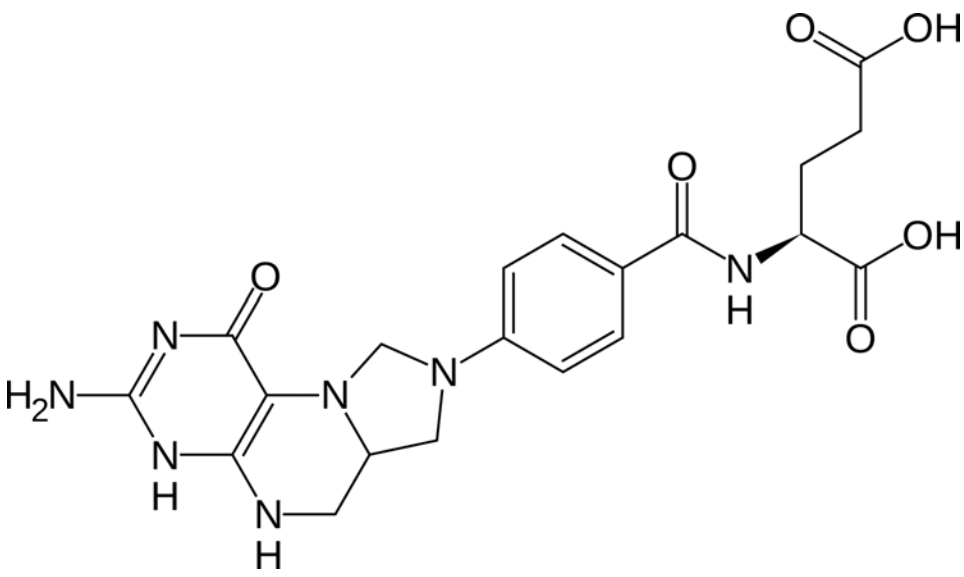
N_5,N_{10}-Methylene Tetrahydrofolate

N_5,N_{10}-Methylenetetrahydrofolate (5,10-CH_2-THF) is the substrate used by the enzyme methylenetetrahydrofolate reductase (MTHFR) to generate 5-methyltetrahydrofolate (5-MTHF, or levomefolic acid).

N_5,N_{10}-CH_2-THF can also be used as a coenzyme in the biosynthesis of thymidine. To be specific, it is the C_1-donor in the reactions catalyzed by thymidylate synthase and thymidylate synthase (FAD). It also acts as a cofactor in the synthesis of serine from glycine via the enzyme serine hydroxymethyl transferase.



https://en.wikipedia.org/wiki/5,10-Methylenetetrahydrofolate

Related Glossary Terms

Drag related terms here

N_{10}-formyl-tetrahydrofolate

10-Formyltetrahydrofolate (10-CHO-THF) is a form of tetrahydrofolate tha
donor of formyl groups in anabolism. In these reactions 10-CHO-THF is us
strate in formyltransferase reactions. This is important in purine biosynthe
10-CHO-THF is a substrate for phosphoribosylaminoimidazolecarboxamid
transferase, as well as in the formylation of the methionyl initiator tRNA (f
when 10-CHO-THF is a substrate for methionyl-tRNA formyltransferase.

https://en.wikipedia.org/wiki/10-Formyltetrahydrofolate

Related Glossary Terms

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Na^+/K^+ ATPase

The Na^+/K^+ ATPase (sodium-potassium adenosine triphosphatase, also kn
Na^+/K^+ pump or sodium-potassium pump) is an enzyme (EC 3.6.3.9) (an e
transmembrane ATPase) found in the plasma membrane of all animal cells
K^+ ATPase enzyme is a solute pump that pumps sodium out of cells while p
tassium into cells, both against their concentration gradients. This pumpin
(it uses energy from ATP) and is important for cell physiology. An example
is nerve conduction.

https://en.wikipedia.org/wiki/Na%2B/K%2B-ATPase

Related Glossary Terms

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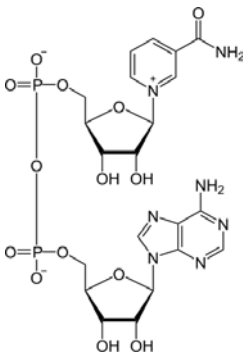
NAD+

Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme found in all living cells. The compound is a dinucleotide, because it consists of two nucleotides joined through their phosphate groups. One nucleotide contains an adenine base and the other nicotinamide. Nicotinamide adenine dinucleotide exists in two forms, an oxidized and reduced form abbreviated as NAD^+ and NADH respectively.

In metabolism, nicotinamide adenine dinucleotide is involved in redox reactions, carrying electrons from one reaction to another. The coenzyme is, therefore, found in two forms in cells: NAD^+ is an oxidizing agent – it accepts electrons from other molecules and becomes reduced. This reaction forms NADH, which can then be used as a reducing agent to donate electrons. These electron transfer reactions are the main function of NAD^+. However, it is also used in other cellular processes, the most notable one being a substrate of enzymes that add or remove chemical groups from proteins, in post-translational modifications. Because of the importance of these functions, the enzymes involved in NAD metabolism are targets for drug discovery.

In organisms, NAD^+ can be synthesized from simple building-blocks (de novo) from the amino acids tryptophan or aspartic acid. In an alternative fashion, more complex components of the coenzymes are taken up from food as the vitamin called niacin. Similar compounds are released by reactions that break down the structure of NAD^+. These preformed components then pass through a salvage pathway that recycles them back into the active form. Some NAD^+ is also converted into nicotinamide adenine dinucleotide phosphate ($NADP^+$). The chemistry of this related coenzyme is similar to that of NAD^+, but it has different roles in metabolism.



https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide

Related Glossary Terms

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NADH

Nicotinamide adenine dinucleotide (NAD⁺) is a coenzyme found in all living cells. The compound is a dinucleotide, because it consists of two nucleotides joined through their phosphate groups. One nucleotide contains an adenine base and the other nicotinamide. Nicotinamide adenine dinucleotide exists in two forms, an oxidized and reduced form abbreviated as NAD⁺ and NADH respectively.

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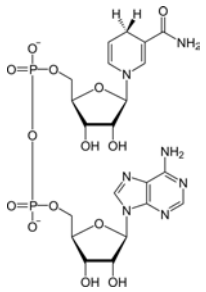

https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide

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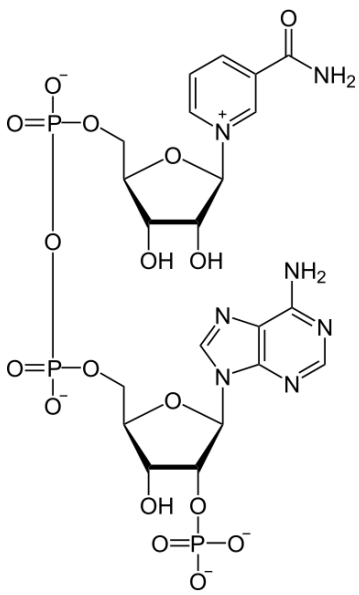
NADP+

NADP+ is a cofactor used in anabolic reactions, such as lipid and nucleic acid synthesis, which require NADPH as a reducing agent. NADPH is the reduced form of NADP+. NADP+ differs from NAD+ in the presence of an additional phosphate group on the 2' position of the ribose ring that carries the adenine moiety.

In photosynthetic organisms, NADPH is produced by ferredoxin-NADP+ reductase in the last step of the electron chain of the light reactions of photosynthesis. It is used as reducing power for the biosynthetic reactions in the Calvin cycle to assimilate carbon dioxide. It is used to help turn the carbon dioxide into glucose. It is also needed in the reduction of nitrate into ammonia for plant assimilation in nitrogen cycle.

The major source of NADPH in animals and other non-photosynthetic organisms is the pentose phosphate pathway. However, there are several other lesser-known mechanisms of generating NADPH, all of which depend on the presence of mitochondria. The key enzymes in these processes are: NADP-linked malic enzyme, NADP-linked isocitrate dehydrogenase, NADP+-linked glutamate dehydrogenase and nicotinamide nucleotide transhydrogenase. The isocitrate dehydrogenase mechanism appears to be the major source of NADPH in fat and possibly also liver cells. Also, in mitochondria, NADH kinase produces NADPH and ADP, using NADH and ATP as substrates.



https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide_phosphate

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NADPH

$NADP^+$ is a cofactor used in anabolic reactions, such as lipid and nucleic acid synthesis, which require NADPH as a reducing agent. NADPH is the reduced form of $NADP^+$. $NADP^+$ differs from NAD^+ in the presence of an additional phosphate group on the 2' position of the ribose ring that carries the adenine moiety.

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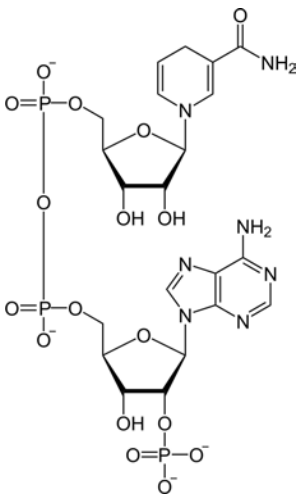

https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide_phosphate

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NADPH Oxidase

The NADPH oxidase (nicotinamide adenine dinucleotide phosphate-oxidase) is a membrane-bound enzyme complex that faces the extracellular space. It can be found in the plasma membrane as well as in the membranes of phagosomes used by neutrophil white blood cells to engulf microorganisms.

NADPH oxidase generates superoxide by transferring electrons from NADPH inside the cell across the membrane and coupling these to molecular oxygen to produce superoxide anion, a reactive free-radical.

Superoxide kills bacteria and fungi by mechanisms that are not yet fully understood, but may inactivate critical metabolic enzymes, initiate lipid peroxidation, and liberate redox-active iron, which allows the generation of indiscriminate oxidants such as the hydroxyl radical. It is presumed that superoxide kills bacteria directly, as the virulence of many pathogens is dramatically attenuated when their superoxide dismutase (SOD) genes are deleted. However, downstream products of superoxide also include hydrogen peroxide and hypochlorous acid, the reactive agent in bleach.

https://en.wikipedia.org/wiki/NADPH_oxidase

Related Glossary Terms

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NAG Synthetase

N-acetylglutamate synthase (NAGS) is an enzyme that catalyzes the produc
Acetylglutamate (NAG) from glutamate and acetyl-CoA.
Put simply NAGS catalyzes the following reaction:

Acetyl-CoA + L-glutamate → CoASH + N-acetyl-L-glutamate

NAGS, a member of the N-acetyltransferase family of enzymes, is present i
karyotes and eukaryotes, although its role and structure differ widely deper
species. NAG can be used in the production of ornithine and arginine, two i
amino acids, or as an allosteric cofactor for carbamoyl phosphate synthase
mammals, NAGS is expressed primarily in the liver and small intestine, and
ized to the mitochondrial matrix.

https://en.wikipedia.org/wiki/N-Acetylglutamate_synthase

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NaOH

Sodium hydroxide (NaOH), also known as lye and caustic soda, is an inorga
pound. It is a white solid and highly caustic metallic base and alkali salt of s
which is available in pellets, flakes, granules, and as prepared solutions at a
different concentrations. Sodium hydroxide forms an approximately 50% (
saturated solution with water.

https://en.wikipedia.org/wiki/Sodium_hydroxide

Related Glossary Terms

Drag related terms here

NDP Phosphatase

NDP phosphatase is an enzyme that converts CDP to CMP in pyrimidine sa
way synthesis.

Related Glossary Terms

Drag related terms here

NDPK

Nucleoside-diphosphate kinases (NDPKs, also NDP Kinase, (poly)nucleotide kinases and nucleoside diphosphokinases) are enzymes that catalyze the exchange of terminal phosphate between different nucleoside diphosphates (NDP) and triphosphates (NTP) in a reversible manner to produce nucleotide triphosphates. Many NDP serve as acceptor while NTP are donors of phosphate group. The general reaction via ping-pong mechanism is as follows:

XDP + YTP ⟷ XTP + YDP
(X and Y each represent different nitrogenous base).

NDPK activities maintain an equilibrium between the concentrations of different nucleoside triphosphates such as, for example, when guanosine triphosphate (GTP) produced in the citric acid cycle is converted to adenosine triphosphate (ATP). Other activities include cell proliferation, differentiation and development, signal transduction, G protein-coupled receptor, endocytosis, and gene expression.

https://en.wikipedia.org/wiki/Nucleoside-diphosphate_kinase

Related Glossary Terms

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Neddylated

Neddylation is the process by which the ubiquitin-like protein NEDD8 is co
its target proteins. This process is analogous to ubiquitination, although it r
own E1 and E2 enzymes. No NEDD8-specific E3 has yet been identified and
ble that the Neddylation system relies on E3 ligases with dual specificity.

https://en.wikipedia.org/wiki/Neddylation

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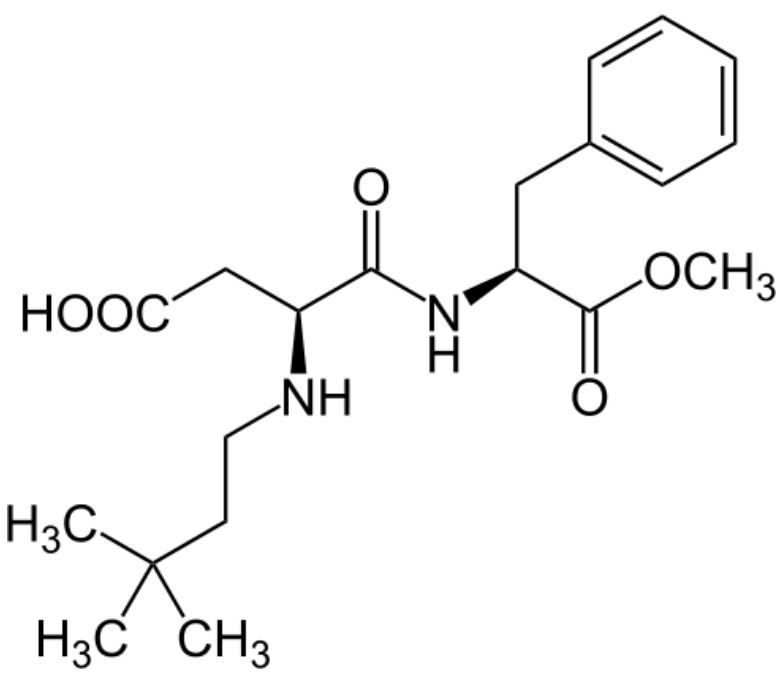
Neotame

Neotame is an artificial sweetener made by NutraSweet that is between 7,000 and 13,000 times sweeter than sucrose (table sugar). It is moderately heat-stable, extremely potent, rapidly metabolized, completely eliminated, and does not appear to accumulate in the body.

The major metabolic pathway is hydrolysis of the methyl ester by esterases that are present throughout the body, which yields de-esterified neotame and methanol. Because only trace amounts of neotame are needed to sweeten foods, the amount of methanol derived from neotame is much lower than that found in common foods.



https://en.wikipedia.org/wiki/Neotame

Related Glossary Terms

Nernst Equation

In electrochemistry, the Nernst equation is an equation that relates the reduction potential of a half-cell (or the total voltage, i.e. the electromotive force, of the full cell) at any point in time to the standard electrode potential, temperature, activity, and reaction quotient of the underlying reactions and species used. When the reaction quotier is equal to the equilibrium constant of the reaction for a given temperature, i.e. when the concentration of species are at their equilibrium values, the Nernst equation gives the equilibrium voltage of the half-cell (or the full cell), which is zero. At equilibrium, $Q = K$, $\Delta G = 0$, and therefore, $E = 0$. It is named after the German physical chemist who first formulated it, Walther Nernst.

$$E = E^\circ + (RT/nF)*\ln\left(\frac{[\text{reduced molecule}]}{[\text{oxidized molecule}]}\right)$$

https://en.wikipedia.org/wiki/Nernst_equation

Related Glossary Terms

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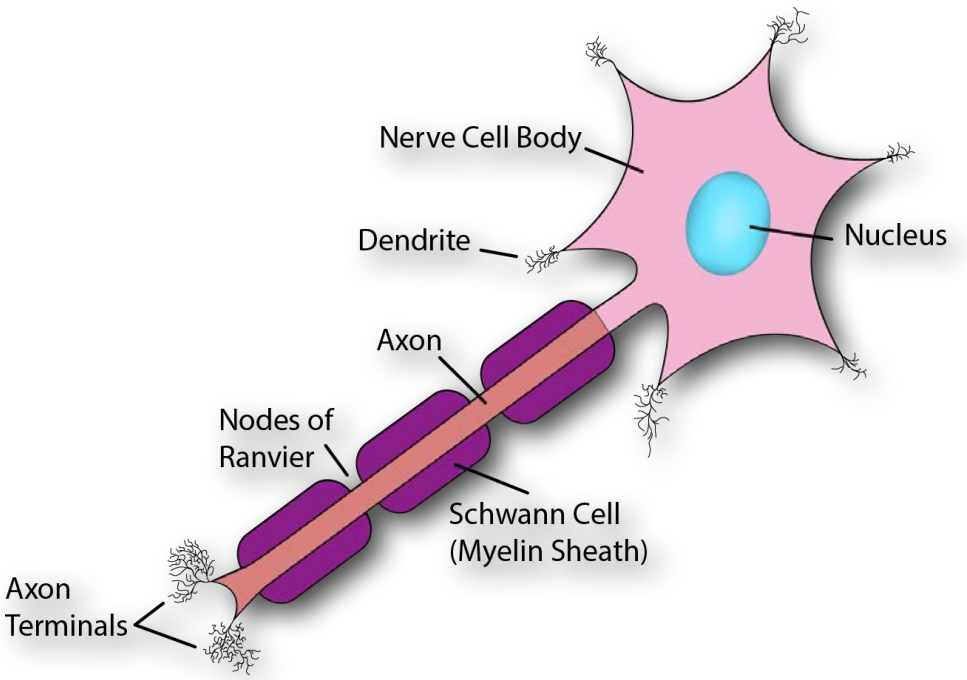
Chapter 5 - Energy: Basics

Nerve Tissue

Nervous tissue is the main component of the two parts of the nervous system. The brain and spinal cord of the central nervous system (CNS), and the branching peripheral nerves of the peripheral nervous system (PNS), which regulates and controls bodily functions and activity. It is composed of neurons, or nerve cells, which receive and transmit impulses, and neuroglia, also known as glial cells or more commonly as just glia (from the Greek, meaning glue), which assist the propagation of the nerve impulse as well as providing nutrients to the neuron.

Nervous tissue is made up of different types of nerve cells, all of which have an axon, the long stem-like part of the cell that sends action potential signals to the next cell. Functions of the nervous system are sensory input, integration, control of muscles and glands, homeostasis, and mental activity.



https://en.wikipedia.org/wiki/Nervous_tissue

Related Glossary Terms

Drag related terms here

Neuraminidase

Neuraminidase enzymes are glycoside hydrolase enzymes (EC 3.2.1.18) tha
glycosidic linkages of neuraminic acids. Neuraminidase enzymes are a large
found in a range of organisms. The best-known neuraminidase is the viral n
dase, a drug target for the prevention of the spread of influenza infection. T
raminidases are frequently used as antigenic determinants found on the su
Influenza virus. Some variants of the influenza neuraminidase confer more
to the virus than others. Other homologs are found in mammalian cells, wh
range of functions. At least four mammalian sialidase homologs have been
the human genome.

https://en.wikipedia.org/wiki/Neuraminidase

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Neurocan

Neurocan core protein is a protein that in humans is encoded by the NCAN gene. Ne
rocan is a member of the lectican / chondroitin sulfate proteoglycan protein families
and consists of neurocan core protein and chondroitin sulfate. It is thought to be in-
volved in the modulation of cell adhesion and migration.

Neurocan is a significant component of the extracellular matrix, and its levels are
modulated by a variety of factors, but mice in which the NCAN gene has been knocke
out show no easily observable defects in brain development or behavior. However, a
genome-wide association study published in 2011 identified Neurocan as a susceptib
ity factor for bipolar disorder. A more comprehensive study published in 2012 con-
firmed that association. The 2012 study examined correlations between NCAN allele
and various symptoms of bipolar disorder, and also examined the behavior of NCAN
knockout mice. In the human subjects, it was found that NCAN genotype was strong
associated with manic symptoms but not with depressive symptoms. In the mice, the
absence of functional Neurocan resulted in a variety of manic-like behaviors, which
could be normalized by administering lithium.

https://en.wikipedia.org/wiki/Neurocan

Related Glossary Terms

Drag related terms here

Neurons

A neuron is an electrically excitable cell that processes and transmits information through electrical and chemical signals. These signals between neurons occur via synapses, specialized connections with other cells. Neurons can connect to each other to form neural networks. Neurons are the core components of the brain and spinal cord of the central nervous system (CNS), and of the ganglia of the peripheral nervous system (PNS).

A typical neuron consists of a cell body (soma), dendrites, and an axon.

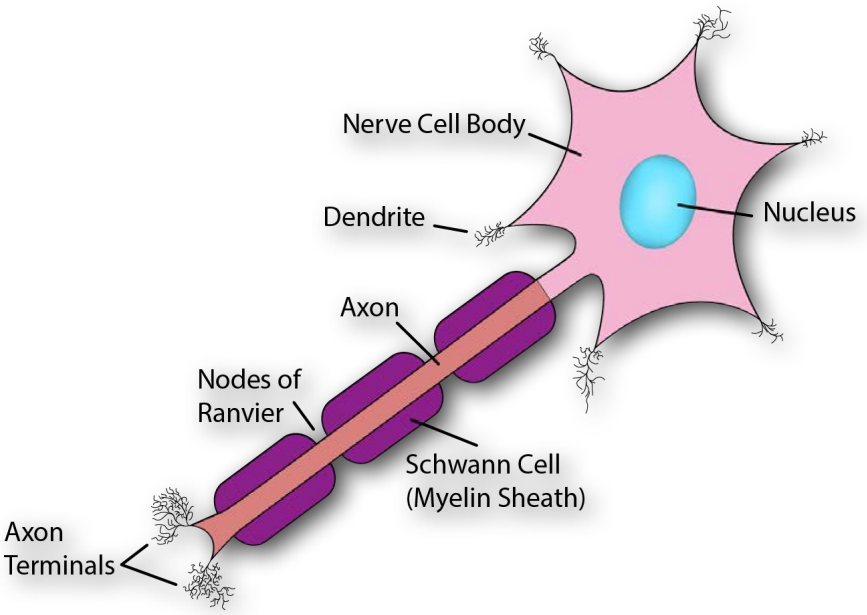

Image by Pehr Jacobson

https://en.wikipedia.org/wiki/Neuron

Related Glossary Terms

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Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino acid neuropeptide that acts as a neurot
in the brain and in the autonomic nervous system of humans. Slight variatio
peptide are found in many other animals. In the autonomic system it is prod
mainly by neurons of the sympathetic nervous system and serves as a strong
strictor and also causes growth of fat tissue. In the brain, it is produced in va
tions including the hypothalamus, and is thought to have several functions, i
increasing food intake and storage of energy as fat, reducing anxiety and stre
ing pain perception, affecting the circadian rhythm, reducing voluntary alcol
lowering blood pressure, and controlling epileptic seizures.

https://en.wikipedia.org/wiki/Neuropeptide_Y

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Neurotoxins

Neurotoxins are substances that are poisonous or destructive to nerve tissu
ins are an extensive class of exogenous chemical neurological insults that ca
affect function in both developing and mature nervous tissue. The term can
used to classify endogenous compounds, which, when abnormally contact,
neurologically toxic. Though neurotoxins are often neurologically destructi
ability to specifically target neural components is important in the study of
tems. Common examples of neurotoxins include lead, ethanol (drinking alc
ganese glutamate, nitric oxide (NO), botulinum toxin (e.g. Botox), tetanus t
tetrodotoxin. Some substances such as nitric oxide and glutamate are in fac
for proper function of the body and only exert neurotoxic effects at excessiv
tions.

https://en.wikipedia.org/wiki/Neurotoxin

Related Glossary Terms

Drag related terms here

Neurotransmission

Neurotransmission, also called synaptic transmission, is the process by which signaling molecules called neurotransmitters are released by a neuron (the presynaptic neuron), and bind to and activate the receptors of another neuron (the postsynaptic neuron). Neurotransmission is essential for the process of communication between two neurons. Synaptic transmission relies on: the availability of the neurotransmitter; the release of the neurotransmitter by exocytosis; the binding of the postsynaptic receptor by the neurotransmitter; the functional response of the postsynaptic cell; and the subsequent removal or deactivation of the neurotransmitter.

https://en.wikipedia.org/wiki/Neurotransmission

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Neurotransmitter

Neurotransmitters are endogenous chemicals that enable neurotransmission. They transmit signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by receptors on the target cells. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet and only require a small number of biosynthetic steps for conversion. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown, but more than 100 chemical messengers have been uniquely identified.

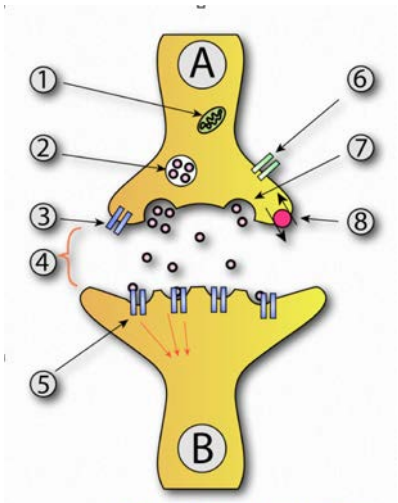

Figure 3.55 - Release of neurotransmitters (small circles) from presynaptic neuron A to postsynaptic neuron B. 1 = Mitochondrion / 2 = Synaptic vesicle with neurotransmitter / 3 = Autoreceptor / 4 = Synaptic cleft / 5 = Neurotransmitter receptor / 6 = Calcium channel / 7 = Fused vesicle releasing neurotransmitter / 8 = Neurotransmitter re-uptake pump

https://en.wikipedia.org/wiki/Neurotransmitter

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Neutrophils

Neutrophil (also known as neutrophils or occasionally neutrocytes) are the most abundant type of granulocytes and the most abundant (40% to 75%) type of white blood cells in most mammals. They form an essential part of the innate immune system.

They are formed from stem cells in the bone marrow. They are short-lived and highly motile, or mobile, as they can enter parts of tissue where other cells/molecules wouldn't be able to enter otherwise.

Neutrophils are a type of phagocyte and are normally found in the bloodstream. During the beginning (acute) phase of inflammation, particularly as a result of bacterial infection, environmental exposure, and some cancers, neutrophils are one of the first-responders of inflammatory cells to migrate towards the site of inflammation.

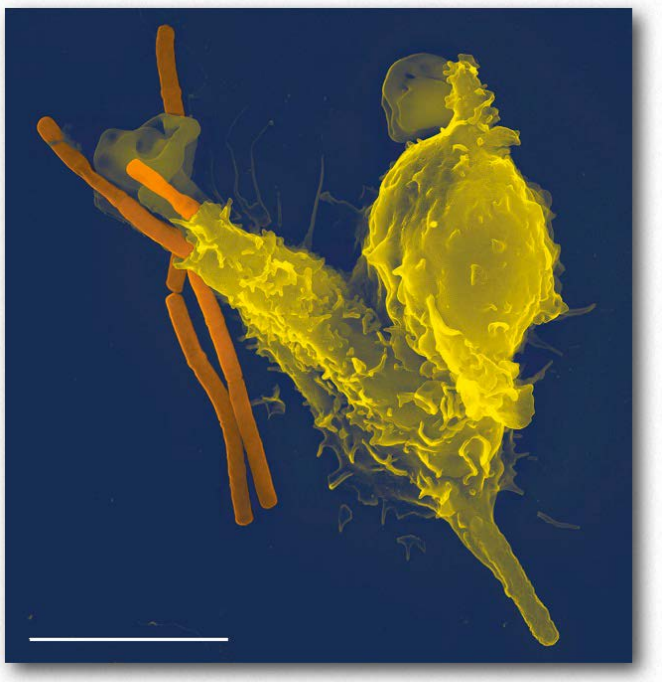

Figure 3.52 - Phagocytosis by a neutrophil (yellow) of an *Anthrax bacillus* (orange)

https://en.wikipedia.org/wiki/Neutrophil

Related Glossary Terms

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NH_4^+

The ammonium cation is a positively charged polyatomic ion with the chem
mula NH_4^+. It is formed by the protonation of ammonia (NH_3) in water.

Ammonium ions are a waste product of the metabolism of animals. In fish
invertebrates, it is excreted directly into the water. In mammals, sharks, an
ans, it is converted in the urea cycle to urea, because urea is less toxic and c
stored more efficiently. In birds, reptiles, and terrestrial snails, metabolic a
is converted into uric acid, which is solid and can therefore be excreted with
water loss.

https://en.wikipedia.org/wiki/Ammonium

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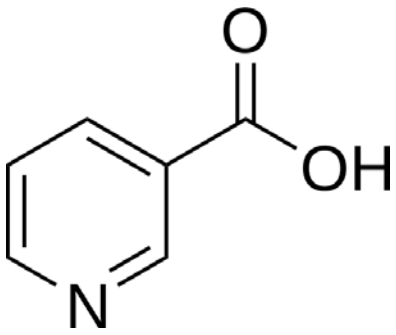
Niacin

Niacin, also known as vitamin B_3 and nicotinic acid, is an organic compound with the formula C6H5NO2 and, depending on the definition used, one of the 20 to 80 essential human nutrients. Pharmaceutical and supplemental niacin are primarily used to treat hypercholesterolemia (high cholesterol) and pellagra (niacin deficiency). Insufficient niacin in the diet can cause nausea, skin and mouth lesions, anemia, headaches, and tiredness.

This colorless, water-soluble solid is a derivative of pyridine, with a carboxyl group (COOH) at the 3-position. Other forms of vitamin B_3 include the corresponding amide and nicotinamide ("niacinamide"), where the carboxyl group has been replaced by a carboxamide group ($CONH_2$), as well as more complex amides and a variety of esters.

Niacin cannot be directly converted to nicotinamide, but both compounds are precursors of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) *in vivo*.



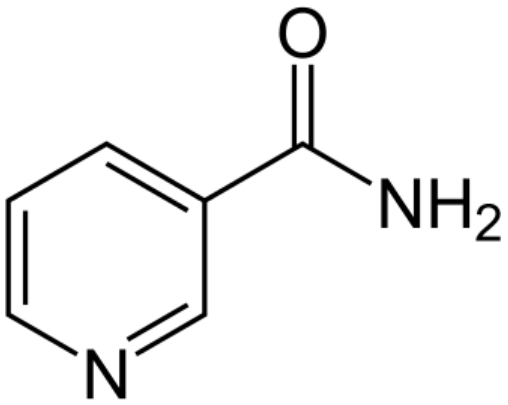
https://en.wikipedia.org/wiki/Niacin

Related Glossary Terms

Drag related terms here

Nicotinamide

Nicotinamide, also known as niacinamide, NAA, and nicotinic amide, is the amide of nicotinic acid (vitamin B_3 /niacin). Nicotinamide is a water-soluble vitamin and is par of the vitamin B group. Nicotinic acid, also known as niacin, is converted to nicotinamide *in vivo*, and, though the two are identical in their vitamin functions, nicotinamide does not have the same pharmacological and toxic effects of niacin, which occur incidental to niacin's conversion. Thus nicotinamide does not reduce cholesterol or cause flushing, although nicotinamide may be toxic to the liver at doses exceeding 3 g day for adults. In cells, niacin is incorporated into nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), although the pathways for nicotinic acid amide and nicotinic acid are very similar.



https://en.wikipedia.org/wiki/Nicotinamide

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Nitric oxide

Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat.

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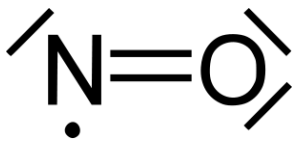
Nitric Oxide

Nitric oxide (nitrogen oxide, nitrogen monoxide) is a molecular, chemical compound with chemical formula of NO. One of several oxides of nitrogen, it is a colorless gas under standard conditions. Nitric oxide is a free radical—i.e., its bonding structure includes an unpaired electron—and it is in the class of heteronuclear diatomic molecules that are of historic theoretical interest (for the insights they gave in formulating early modern theories of bonding).

In mammals including humans, NO is an important cellular signaling molecule involved in many physiological and pathological processes. It is a powerful vasodilator with a short half-life of a few seconds in the blood.



https://en.wikipedia.org/wiki/Nitric_oxide

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Nitric Oxide Synthase

Nitric oxide synthases (NOSs) are a family of enzymes catalyzing the production of nitric oxide (NO) from L-arginine. NO is an important cellular signaling molecule. It helps modulate vascular tone, insulin secretion, airway tone, and peristalsis, and is involved in angiogenesis and neural development. It may function as a retrograde neurotransmitter. Nitric oxide is mediated in mammals by the calcium-calmodulin controlled isoenzymes eNOS (endothelial NOS) and nNOS (neuronal NOS). The inducible isoform, iNOS, is involved in immune response, binds calmodulin at physiologically relevant concentrations, and produces NO as an immune defense mechanism, as NO is a free radical with an unpaired electron. It is the proximate cause of septic shock and may function in autoimmune disease.

NOS catalyzes the reaction:

L-arginine + 3/2 NADPH + 1/2 H^+ + 2 O_2 <---> Citrulline + Nitric oxide + 2H_2O + 3/2 $NADP^+$

NOS isoforms catalyze other leak and side reactions, such as superoxide production at the expense of NADPH. As such, this stoichiometry is not generally observed, and reflects the three electrons supplied per NO by NADPH.

https://en.wikipedia.org/wiki/Nitric_oxide_synthase

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Nitrogenous Base

A nitrogenous base, or nitrogen-containing base, is an organic molecule wit
gen atom that has the chemical properties of a base. The main biological fu
nitrogenous base is to bond nucleic acids together. A nitrogenous base owes
properties to the lone pair of electrons of a nitrogen atom.

Nitrogenous bases are typically classified as the derivatives of two parent co
pyrimidine and purine. They are non-polar and due to their aromaticity, pl
pyrimidines and purines resemble pyridine and are thus weak bases and re
reactive towards electrophilic aromatic substitution.

https://en.wikipedia.org/wiki/Nitrogenous_base

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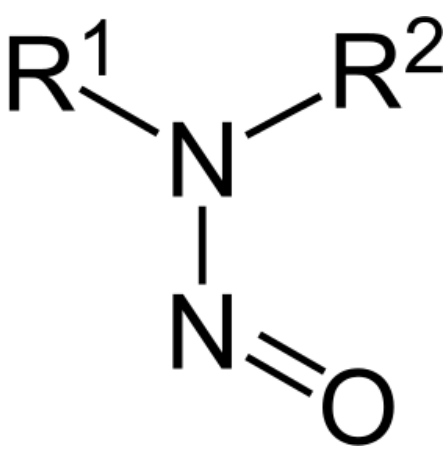
Chapter 2 - Structure and Function: Nucleic Acids

Nitrosamines

Nitrosamines are chemical compounds of the chemical structure R1N(–R2)–N=O, that is, a nitroso group bonded to an amine. Most nitrosamines are carcinogenic. Nitrosamines are used in the manufacture of some cosmetics, pesticides, and in most rubber products.

Nitrosamines can cause cancers in a wide variety of animal species, a feature that suggests that they may also be carcinogenic in humans. At present, available epidemiological evidence from case-control studies on nitrite and nitrosamine intake supports a positive association with gastric cancer risk. Regarding oesophageal cancer, available evidence supports a positive association between nitrite and nitrosamine intake and gastric cancer (GC), between meat and processed meat intake and GC and oesophageal cancer, and between preserved fish, vegetable and smoked food intake and GC, but is not conclusive.

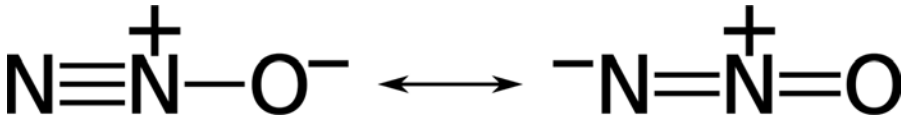


https://en.wikipedia.org/wiki/N-acetylglucosamine-1-phosphate_transferase

Nitrous Oxide

Nitrous oxide, commonly known as laughing gas, nitrous, nitro, or NOS is a ch
compound with the formula N_2O. It is an oxide of nitrogen. At room temperatu
a colorless, non-flammable gas, with a slightly sweet odor and taste. It is used
gery and dentistry for its anaesthetic and analgesic effects. It is known as "laug
gas" due to the euphoric effects of inhaling it, a property that has led to its recr
use as a dissociative anaesthetic.

Nitrous oxide gives rise to nitric oxide (NO) on reaction with oxygen atoms, an
NO in turn reacts with ozone. As a result, it is the main naturally occurring reg
stratospheric ozone.



https://en.wikipedia.org/wiki/Nitrous_oxide

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NMR

Nuclear magnetic resonance (NMR) is a physical phenomenon in which nu
magnetic field absorb and re-emit electromagnetic radiation. This energy is
cific resonance frequency which depends on the strength of the magnetic fi
magnetic properties of the isotope of the atoms. In practical applications, t
quency is similar to VHF and UHF television broadcasts (60–1000 MHz). N
the observation of specific quantum mechanical magnetic properties of the
cleus. Many scientific techniques exploit NMR phenomena to study molecu
crystals, and non-crystalline materials through nuclear magnetic resonance
copy. NMR is also routinely used in advanced medical imaging techniques,
magnetic resonance imaging (MRI).

https://en.wikipedia.org/wiki/Nuclear_magnetic_resonance

Related Glossary Terms

Drag related terms here

Non-competitive Inhibition

Non-competitive inhibition is a type of enzyme inhibition where the inhibitor reduces the activity of the enzyme and binds equally well to the enzyme whether or not it has already bound the substrate.

Non-competitive inhibition models a system where the inhibitor and the substrate may both be bound to the enzyme at any given time. When both the substrate and the inhibitor are bound, the enzyme-substrate-inhibitor complex cannot form product and can only be converted back to the enzyme-substrate complex or the enzyme-inhibitor complex. Non-competitive inhibition is distinguished from general mixed inhibition in that the inhibitor has an equal affinity for the enzyme and the enzyme-substrate complex.

The most common mechanism of non-competitive inhibition involves reversible binding of the inhibitor to an allosteric site, but it is possible for the inhibitor to operate via other means including direct binding to the active site. It differs from competitive inhibition in that the binding of the inhibitor does not prevent binding of substrate, and vice versa, it simply prevents product formation for a limited time.

This type of inhibition reduces the maximum rate of a chemical reaction without changing the apparent binding affinity of the catalyst for the substrate (K_{mapp} – see Michaelis-Menten kinetics).

https://en.wikipedia.org/wiki/Non-competitive_inhibition

Related Glossary Terms

Drag related terms here

Non-competitive Inhibitor

A non-competitive inhibitor of an enzymatic reaction is a molecule that competes with the substrate of an enzyme for binding the enzyme and it stops action of the active site. Non-competitive inhibitors typically resemble the substrate they compete with.

Non-competitive inhibition models a system where the inhibitor and the substrate may both be bound to the enzyme at any given time. When both the substrate and the inhibitor are bound, the enzyme-substrate-inhibitor complex cannot form product and can only be converted back to the enzyme-substrate complex or the enzyme-inhibitor complex. Non-competitive inhibition is distinguished from general mixed inhibition in that the inhibitor has an equal affinity for the enzyme and the enzyme-substrate complex. The most common mechanism of non-competitive inhibition involves reversible binding of the inhibitor to an allosteric site, but it is possible for the inhibitor to operate via other means including direct binding to the active site. It differs from competitive inhibition in that the binding of the inhibitor does not prevent binding of substrate, and vice versa, it simply prevents product formation for a limited time.

This type of inhibition reduces the maximum rate of a chemical reaction without changing the apparent binding affinity of the catalyst for the substrate.

https://en.wikipedia.org/wiki/Non-competitive_inhibition

Related Glossary Terms

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Chapter 4 - Catalysis: Control of Activity

Non-essential Amino Acids

A non-essential amino acid is one that can be synthesized by the body and need not be in the diet.

An essential amino acid or indispensable amino acid is an amino acid that cannot be synthesized *de novo* (from scratch) by the organism, and thus must be supplied in its diet. The nine amino acids humans cannot synthesize are phenylalanine, valine, threonine, tryptophan, methionine, leucine, isoleucine, lysine, and histidine.

Six other amino acids are considered conditionally essential in the human diet, meaning their synthesis can be limited under special pathophysiological conditions, such as prematurity in the infant or individuals in severe catabolic distress. These six are arginine, cysteine, glycine, glutamine, proline and tyrosine.

Five amino acids can be completely synthesized to meet the body's needs and are completely non-essential. These five are alanine, aspartic acid, asparagine, glutamic acid and serine.

https://en.wikipedia.org/wiki/Essential_amino_acid

Related Glossary Terms

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Non-homologous End Joining

Non-homologous end joining (NHEJ) is a pathway that repairs double-strand breaks in DNA. NHEJ is referred to as "non-homologous" because the break ends are directly ligated without the need for a homologous template, in contrast to homology directed repair, which requires a homologous sequence to guide repair. The term "non-homologous end joining" was coined in 1996 by Moore and Haber.

NHEJ typically utilizes short homologous DNA sequences called microhomologies to guide repair. These microhomologies are often present in single-stranded overhangs on the ends of double-strand breaks. When the overhangs are perfectly compatible, NHEJ usually repairs the break accurately. Imprecise repair leading to loss of nucleotides can also occur, but is much more common when the overhangs are not compatible. Inappropriate NHEJ can lead to translocations and telomere fusion, hallmarks of tumor cells.

NHEJ is evolutionarily conserved throughout all kingdoms of life and is the predominant double-strand break repair pathway in mammalian cells. In budding yeast (Saccharomyces cerevisiae), however, homologous recombination dominates when the organism is grown under common laboratory conditions.
When the NHEJ pathway is inactivated, double-strand breaks can be repaired by a more error-prone pathway called microhomology-mediated end joining (MMEJ). In this pathway, end resection reveals short microhomologies on either side of the break, which are then aligned to guide repair. This contrasts with classical NHEJ, which typically uses microhomologies already exposed in single-stranded overhangs on the DSB ends. Repair by MMEJ therefore leads to deletion of the DNA sequence between the microhomologies.

https://en.wikipedia.org/wiki/Non-homologous_end_joining

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Non-polar

A molecule may be non-polar either when there is an equal sharing of elect
tween the two atoms of a diatomic molecule or because of the symmetrical
ment of polar bonds in a more complex molecule. For example, methane (C
tetrahedral, 3-dimensional arrangement of four carbon-hydrogen bonds at
results in no overall dipole in the molecule.

https://en.wikipedia.org/wiki/Chemical_polarity#Nonpolar_molecules

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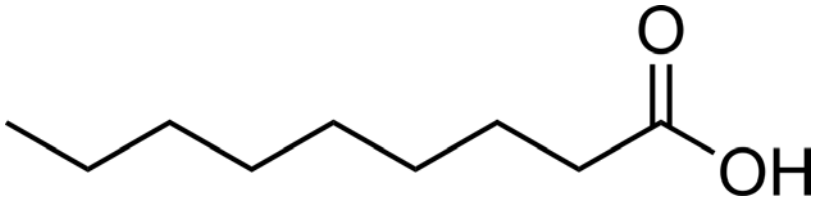
Nonanoic Acid

Nonanoic acid, also called pelargonic acid, is an organic compound compos
nine-carbon chain terminating in a carboxylic acid with structural formula
$CH_3(CH_2)_7COOH$. Nonanoic acid forms esters—nonanoates. It is a clear, oi
with an unpleasant, rancid odor. It is nearly insoluble in water, but very sol
roform, ether, and hexane.



https://en.wikipedia.org/wiki/Nonanoic_acid

Related Glossary Terms

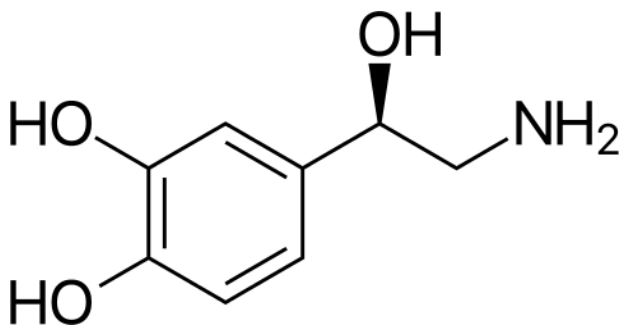
Drag related terms here

Noradrenalin

Norepinephrine (NE), also called noradrenaline (NA) or noradrenalin, is an organic chemical in the catecholamine family that functions in the human brain and body as a hormone and neurotransmitter.

Norepinephrine is synthesized and released by the central nervous system, and also by a division of the autonomic nervous system called the sympathetic nervous system. In the brain, norepinephrine is produced in closely packed brain cell neurons or nuclei that are small yet exert powerful effects on other brain areas.

The general function of norepinephrine is to mobilize the brain and body for action. Norepinephrine release is lowest during sleep, rises during wakefulness, and reaches much higher levels during situations of stress or danger, in the so-called fight-or-flight response.



https://en.wikipedia.org/wiki/Norepinephrine

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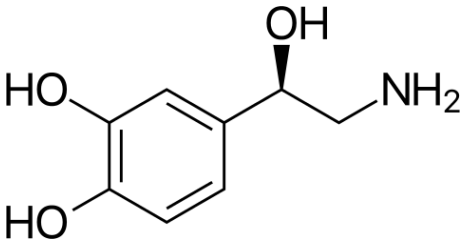

https://en.wikipedia.org/wiki/Norepinephrine

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Normal Phase Separation

In normal-phase chromatography, the stationary phase is polar and the mo
is non-polar. Typical stationary phases for normal-phase chromatography a
organic moieties with cyano and amino functional groups. In normal-phase
raphy, the least polar compounds elute first and the most polar compounds
The mobile phase consists of a non-polar solvent such as hexane or heptane
with a slightly more polar solvent such as isopropanol, ethyl acetate or chlo
tention increases as the amount of non-polar solvent in the mobile phase in

https://en.wikipedia.org/wiki/Aqueous_normal-phase_chromatography

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Northern Blot

The northern blot is a technique used in molecular biology research to stud
pression by detection of RNA (or isolated mRNA) in a sample.
With northern blotting it is possible to observe cellular control over structu
tion by determining the particular gene expression rates during differentiat
morphogenesis, as well as in abnormal or diseased conditions. Northern bl
volves the use of electrophoresis to separate RNA samples by size, and dete
hybridization probe complementary to part of or the entire target sequence

Northern blotting takes its name from its similarity to the first blotting tech
Southern blot, named for biologist Edwin Southern. The major difference is
rather than DNA, is analyzed in the northern blot.

https://en.wikipedia.org/wiki/Northern_blot

Related Glossary Terms

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NSAIDs

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs), als
nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroida
inflammatory medicines (NSAIMs), are a drug class that groups together d
provide analgesic (pain-killing) and antipyretic (fever-reducing) effects, an
doses, anti-inflammatory effects.

The term nonsteroidal distinguishes these drugs from steroids, which, amo
range of other effects, have a similar eicosanoid-depressing, anti-inflamma

The most prominent members of this group of drugs, aspirin, ibuprofen an
are all available over the counter in most countries.

https://en.wikipedia.org/wiki/Nonsteroidal_anti-inflammatory_drug

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Related Glossary Terms

Drag related terms here

NTP Phosphatase

NTP phosphatase is an enzyme in the pyrimidine salvage pathway that con
CDP and as such, is important also for providing substrate (CDP) for ribon
ductase to make dCDP.

Related Glossary Terms

Drag related terms here

Nuclear Hormone Receptor

In the field of molecular biology, nuclear receptors are a class of proteins found within cells that are responsible for sensing steroid and thyroid hormones and certain other molecules. In response, these receptors work with other proteins to regulate the expression of specific genes, thereby controlling the development, homeostasis, and metabolism of the organism.

Nuclear receptors have the ability to directly bind to DNA and regulate the expression of adjacent genes, hence these receptors are classified as transcription factors. The regulation of gene expression by nuclear receptors generally only happens when a ligand — a molecule that affects the receptor's behavior — is present. More specifically, ligand binding to a nuclear receptor results in a conformational change in the receptor, which, in turn, activates the receptor, resulting in up- or down-regulation of gene expression.

A unique property of nuclear receptors that differentiates them from other classes of receptors is their ability to directly interact with and control the expression of genomic DNA. As a consequence, nuclear receptors play key roles in both embryonic development and adult homeostasis.

https://en.wikipedia.org/wiki/Nuclear_receptor

Related Glossary Terms

Drag related terms here

Nuclear Magnetic Resonance

Nuclear magnetic resonance (NMR) is a physical phenomenon in which nu
magnetic field absorb and re-emit electromagnetic radiation. This energy is
cific resonance frequency which depends on the strength of the magnetic fi
magnetic properties of the isotope of the atoms. In practical applications, t
quency is similar to VHF and UHF television broadcasts (60–1000 MHz). N
the observation of specific quantum mechanical magnetic properties of the
cleus. Many scientific techniques exploit NMR phenomena to study molecu
crystals, and non-crystalline materials through nuclear magnetic resonance
copy. NMR is also routinely used in advanced medical imaging techniques,
magnetic resonance imaging (MRI).

https://en.wikipedia.org/wiki/Nuclear_magnetic_resonance

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Chapter 2 - Structure & Function: Proteins I

Nuclease

A nuclease is an enzyme capable of cleaving the phosphodiester bonds between the nucleotide subunits of nucleic acids. Older publications may use terms such as "polynucleotidase" or "nucleodepolymerase".

Nucleases are usually further divided into endonucleases and exonucleases, although some of the enzymes may fall in both categories. Well known nucleases are deoxyribonuclease and ribonuclease.

https://en.wikipedia.org/wiki/Nuclease

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Nucleation

Nucleation is the first step in the formation of either a new thermodynamic
new structure via self-assembly or self-organization. Nucleation is typically
be the process that determines how long an observer has to wait before the
or self-organized structure appears. Nucleation is often found to be very se
purities in the system.

https://en.wikipedia.org/wiki/Nucleation

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Chapter 2 - Structure & Function: Proteins I

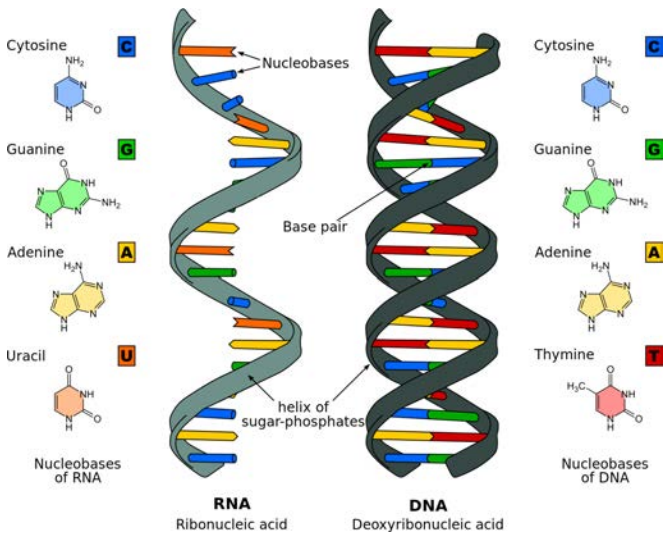
Chapter 9 - Point by Point: Structure and Function

Nucleic Acid

Nucleic acids are biopolymers, or large biomolecules, essential for all known forms of life. Nucleic acids, which include DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are made from monomers known as nucleotides. Each nucleotide has three components: a 5-carbon sugar, a phosphate group, and a nitrogenous base. If the sugar is deoxyribose, the polymer is DNA. If the sugar is ribose, the polymer is RNA. When all three components are combined, they form a nucleic acid. Nucleotides are also known as phosphate nucleotides.

Nucleic acids are among the most important biological macromolecules (others being amino acids/proteins, sugars/carbohydrates, and lipids/fats). They are found in abundance in all living things, where they function in encoding, transmitting and expressing genetic information—in other words, information is conveyed through the nucleic acid sequence, or the order of nucleotides within a DNA or RNA molecule. Strings of nucleotides strung together in a specific sequence are the mechanism for storing and transmitting hereditary, or genetic information via protein synthesis.

Nucleic acids were discovered by Friedrich Miescher in 1869. Experimental studies of nucleic acids constitute a major part of modern biological and medical research, and form a foundation for genome and forensic science, as well as the biotechnology and pharmaceutical industries.



https://en.wikipedia.org/wiki/Nucleic_acid

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Nucleoid

The nucleoid (meaning nucleus-like) is an irregularly shaped region within
prokaryote that contains all or most of the genetic material, called genopho
trast to the nucleus of a eukaryotic cell, it is not surrounded by a nuclear m
The genome of prokaryotic organisms generally is a circular, double-strand
DNA, of which multiple copies may exist at any time.

https://en.wikipedia.org/wiki/Nucleoid

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Nucleoid Associated Proteins

Proteins that carry out the dynamic spatial organization of the nucleic acid
as nucleoid proteins or nucleoid-associated proteins (NAPs) and are distinc
tones of eukaryotic nuclei. In contrast to histones, the DNA-binding protei
cleoid do not form nucleosomes, in which DNA is wrapped around a protei
stead, these proteins often use other mechanisms to promote compaction s
looping. The most studied NAPs are HU, H-NS, Fis, CbpA, Dps that organiz
nome by driving events such as DNA bending, bridging, and aggregation. T
teins can form clusters (like H-NS does) in order to locally compact specific
regions, or be scattered throughout the chromosome (HU, Fis) and they see
volved also in coordinating transcription events, spatially sequestering spec
and participating in their regulation.

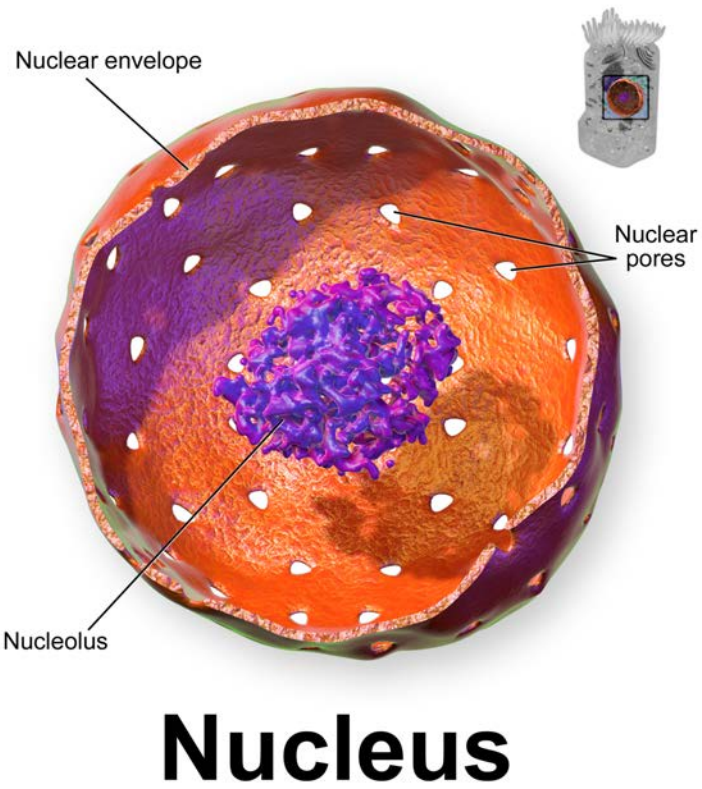
https://en.wikipedia.org/wiki/Nucleoid

Related Glossary Terms

Drag related terms here

Nucleolus

The nucleolus is the largest structure in the nucleus of eukaryotic cells, where it primarily serves as the site of ribosome synthesis and assembly. Nucleoli also have other important functions like assembly of signal recognition particles and playing a role in the cell's response to stress. Nucleoli are made of proteins and RNA and form around specific chromosomal regions. Malfunction of nucleoli can be the cause of several human diseases.



https://en.wikipedia.org/wiki/Nucleolus

Related Glossary Terms

Nucleophile

A nucleophile is a chemical species that donates an electron pair to an electrophile to form a chemical bond in relation to a reaction. All molecules or ions with a free pair of electrons or at least one Pi bond can act as nucleophiles. Because nucleophiles donate electrons, they are by definition Lewis bases.

Nucleophilic describes the affinity of a nucleophile to the nuclei. Nucleophilicity, some times referred to as nucleophile strength, refers to a substance's nucleophilic character and is often used to compare the affinity of atoms.

Neutral nucleophilic reactions with solvents such as alcohols and water are named solvolysis. Nucleophiles may take part in nucleophilic substitution, whereby a nucleophile becomes attracted to a full or partial positive charge.

https://en.wikipedia.org/wiki/Nucleophile

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Nucleophilic

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https://en.wikipedia.org/wiki/Nucleophile

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Nucleoporin

The nucleoporins are a family of proteins which are the constituent building blocks of the nuclear pore complex (NPC). The nuclear pore complex is a massive structure that extends across the nuclear envelope, forming a gateway that regulates the flow of macromolecules between the cell nucleus and the cytoplasm. Nuclear pores in turn allow the transport of water-soluble molecules across the nuclear envelope. Nucleoporins, a family of around 30 proteins, are the main components of the nuclear pore complex in eukaryotic cells. Nucleoporin 62 is the most abundant member of this family. Nucleoporins are able to transport molecules across the nuclear envelope at a very high rate. A single NPC is able to transport 60,000 protein molecules across the nuclear envelope every minute.

Nucleoporins mediate transport of macromolecules between the cell nucleus and cytoplasm in eukaryotes. Certain members of the nucleoporin family form the structural scaffolding of the nuclear pore complex. However, nucleoporins primarily function by interacting with transport molecules known as karyopherins, also known as Kaps. These karyopherins interact with nucleoporins that contain FG peptide repeats, that is, they contain repeating sequences of the amino acids phenylalanine (F) and glycine (G). In doing so, karyopherins are able to shuttle their cargo across the nuclear envelope. Nucleoporins are only required for the transport of large hydrophilic molecules above 40 kDa, as smaller molecules pass through nuclear pores via passive diffusion. Nucleoporins play an important role in the transport of mRNA from the nucleus to the cytoplasm after transcription. Depending on their function, certain nucleoporins are localized to a single side of the nuclear pore complex, either cytosolic or nucleoplasmic. Other nucleoporins may be found on both faces. Interestingly, it has been recently shown that FG nucleoporins have specific evolutionary conserved features encoded in their sequences that provide insight into how they regulate the transport of molecules through the nuclear pore complex (NPC).

https://en.wikipedia.org/wiki/Nucleoporin

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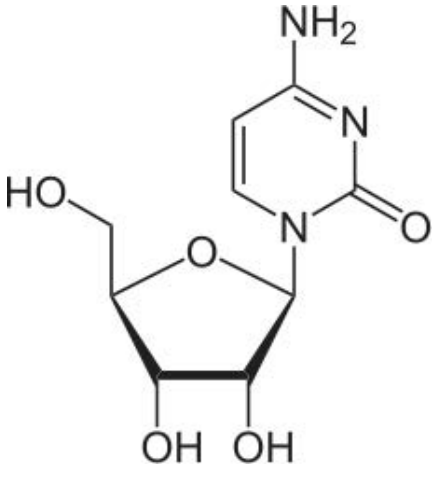
Chapter 4 - Catalysis: Mechanism

Nucleoside

Nucleosides are glycosylamines that can be thought of as nucleotides without a phosphate group. A nucleoside consists simply of a nucleobase (also termed a nitrogenous base) and a 5-carbon sugar (either ribose or deoxyribose), whereas a nucleotide is composed of a nucleobase, a five-carbon sugar, and one or more phosphate groups. In a nucleoside, the base is bound to either ribose or deoxyribose via a β-glycosidic linkage. Examples of nucleosides include cytidine (shown below), uridine, adenosine, guanosine, thymidine and inosine.



https://en.wikipedia.org/wiki/Nucleoside

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Nucleoside Diphosphokinase

Nucleoside-diphosphate kinases (NDPKs, also NDP Kinase, (poly)nucleotide kina
and nucleoside diphosphokinases) are enzymes that catalyze the exchange of term
phosphate between different nucleoside diphosphates (NDP) and triphosphates (N
in a reversible manner to produce nucleotide triphosphates. Many NDP serve as a
tor while NTP are donors of phosphate group. The general reaction via ping-pong
mechanism is as follows:

XDP + YTP ⟷ XTP + YDP
(X and Y each represent different nitrogenous base).

NDPK activities maintain an equilibrium between the concentrations of different n
cleoside triphosphates such as, for example, when guanosine triphosphate (GTP) p
duced in the citric acid (Krebs) cycle is converted to adenosine triphosphate (ATP)
Other activities include cell proliferation, differentiation and development, signal
duction, G protein-coupled receptor, endocytosis, and gene expression.

https://en.wikipedia.org/wiki/Nucleoside-diphosphate_kinase

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Nucleoside Monophosphate Kinase

A nucleoside-phosphate kinase is an enzyme that catalyzes the chemical rea

ATP + Nucleoside Phosphate <---> ADP + Nucleoside Diphosphate

This enzyme belongs to the family of transferases, specifically those transfe
phosphorus-containing groups (phosphotransferases) with a phosphate gro
tor. The systematic name of this enzyme class is ATP:nucleoside-phosphate
transferase. This enzyme is also called NMP-kinase, or nucleoside-monoph
nase.

https://en.wikipedia.org/wiki/Nucleoside-phosphate_kinase

Related Glossary Terms

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Nucleoside Monophosphates

A nucleoside monophosphate is a nucleoside with a single phosphate. This
cleotide. Nucleotides are organic molecules that serve as the monomers, or
of nucleic acids like DNA (deoxyribonucleic acid) and RNA (ribonucleic aci
building blocks of nucleic acids, nucleotides are composed of a nitrogenous
five-carbon sugar (ribose or deoxyribose), and at least one phosphate group
cleoside plus a phosphate group yields a nucleotide.

Nucleotides also function to carry packets of energy within the cell in the fo
nucleoside triphosphates (ATP, GTP, CTP and UTP), playing a central role
lism. In addition, nucleotides participate in cell signaling (cGMP and cAMP
incorporated into important cofactors of enzymatic reactions (e.g. coenzym
FMN, NAD^+, and $NADP^+$).

https://en.wikipedia.org/wiki/Nucleotide

Related Glossary Terms

Drag related terms here

Nucleoside Triphosphates

A nucleoside triphosphate (NTP) is a molecule containing a nucleoside bound to three phosphate groups. It is thus one type of nucleotide. Nucleotide derivatives are necessary for life, as they are the building blocks of nucleic acids and have thousands of other roles in cell metabolism and regulation. NTPs generally provide energy and phosphate groups for phosphorylation.

Natural nucleoside triphosphates include adenosine triphosphate (ATP), guanosine triphosphate (GTP), cytidine triphosphate (CTP), 5-methyluridine triphosphate (m5UTP), and uridine triphosphate (UTP). ATP is a major source of cellular energy. GTP is a very frequent cofactor of enzymes and proteins.

The terms ATP, GTP, CTP, and UTP refer to those nucleoside triphosphates that contain ribose. The nucleoside triphosphates containing deoxyribose are called dNTPs, and take the prefix deoxy- in their names and small d- in their abbreviations: deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dGTP), deoxycytidine triphosphate (dCTP), deoxythymidine triphosphate (dTTP) and deoxyuridine triphosphate (dUTP). The dNTPs are the building blocks for DNA (they lose two of the phosphate groups in the process of incorporation).

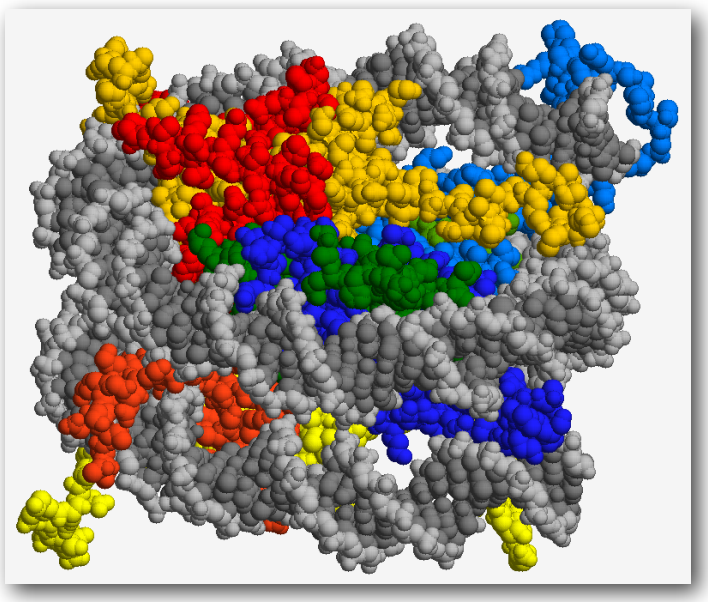
Apart from (d)ATP, (d)GTP, (d)CTP, (d)TTP and (d)UTP, there are other less abundant NTPs, such as intermediates of nucleotide metabolism, but also "rare" natural nucleotides or even artificial nucleotides. An example of rare NTPs are the tautomeric forms of some NTPs. They can cause mismatched base pairing during DNA replication. For example, a tautomeric form of cytosine is capable of forming 3 hydrogen bonds with adenine, and it will spontaneously tautomerize to its original cytosine form, causing a mismatch. By a similar token, the deamination of cytosine leads to uracil, whereas a deamination of a commonly encountered (in eukaryotes) 5-methylcytosine will lead to thymine. However, the 3' to 5' exonuclease activity of DNA polymerase III ensures that mismatched bases are excised during replication.

https://en.wikipedia.org/wiki/Nucleoside_triphosphate

Nucleosome

A nucleosome is a basic unit of DNA packaging in eukaryotes, consisting of a segment of DNA wound in sequence around eight histone protein cores. This structure is often compared to thread wrapped around a spool.

Nucleosomes form the fundamental repeating units of eukaryotic chromatin, which is used to pack the large eukaryotic genomes into the nucleus while still ensuring appropriate access to it (in mammalian cells approximately 2 m of linear DNA have to be packed into a nucleus of roughly 10 µm diameter). Nucleosomes are folded through a series of successively higher order structures to eventually form a chromosome. This both compacts DNA and creates an added layer of regulatory control, which ensures correct gene expression. Nucleosomes are thought to carry epigenetically inherited information in the form of covalent modifications of their core histones.



https://en.wikipedia.org/wiki/Nucleosome

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Nucleotidase

A nucleotidase is a hydrolytic enzyme that catalyzes the hydrolysis of a nucl
monophosphate into a nucleoside and phosphate(s).

Nucleoside monophosphate + H_2O = A nucleoside + Phosphate

For example, it converts adenosine monophosphate to adenosine, and guar
phosphate to guanosine. Nucleotidases have an important function in dige
they break down consumed nucleic acids to be reused in salvage reactions.

https://en.wikipedia.org/wiki/Nucleotidase

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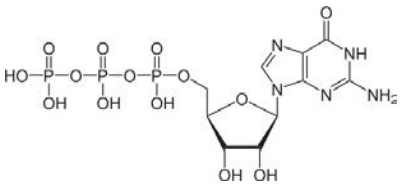
Nucleotide

Nucleotides are organic molecules that serve as the monomers, or subunits, of nucleic acids like DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). The building blocks of nucleic acids, nucleotides are composed of a nitrogenous base, a five-carbon sugar (ribose or deoxyribose), and at least one phosphate group. Thus a nucleoside plus a phosphate group yields a nucleotide.

Nucleotides also function to carry packets of energy within the cell in the form of the nucleoside triphosphates (ATP, GTP (shown below), CTP and UTP), playing a central role in metabolism. In addition, nucleotides participate in cell signaling (cGMP and cAMP), and are incorporated into important cofactors of enzymatic reactions (e.g. coenzyme A, FAD, FMN, NAD, and NADP$^+$).



https://en.wikipedia.org/wiki/Nucleotide

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Nucleotide Excision Repair

Nucleotide excision repair is a DNA repair mechanism. DNA damage occurs constantly because of chemicals (e.g. intercalating agents), radiation and other mutagens Three excision repair pathways exist to repair single stranded DNA damage: Nucleotide excision repair (NER), base excision repair (BER), and DNA mismatch repair (MMR). While the BER pathway can recognize specific non-bulky lesions in DNA, it can correct only damaged bases that are removed by specific glycosylases. Similarly, the MMR pathway only targets mismatched Watson-Crick base pairs.

Nucleotide excision repair (NER) is a particularly important excision mechanism tha removes DNA damage induced by ultraviolet light (UV). UV DNA damage results in bulky DNA adducts - these adducts are mostly thymine dimers and 6,4-photoproduct Recognition of the damage leads to removal of a short single-stranded DNA segment that contains the lesion. The undamaged single-stranded DNA remains and DNA polymerase uses it as a template to synthesize a short complementary sequence.

https://en.wikipedia.org/wiki/Nucleotide_excision_repair

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https://en.wikipedia.org/wiki/Nucleotide_excision_repair

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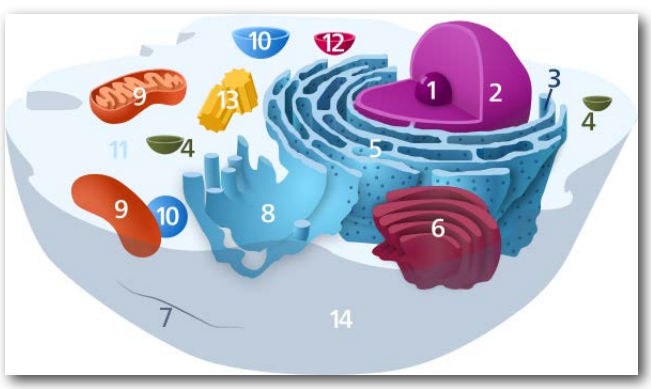
Nucleus

In cell biology, the nucleus (#2 in the figure below) is a membrane-enclosed organelle found in eukaryotic cells. Eukaryotes usually have a single nucleus, but a few cell types have no nuclei, and a few others have many.

Cell nuclei contain most of the cell's genetic material, organized as multiple long linear DNA molecules in complex with a large variety of proteins, such as histones, to form chromosomes. The genes within these chromosomes are the cell's nuclear genome. The function of the nucleus is to maintain the integrity of these genes and to control the activities of the cell by regulating gene expression—the nucleus is, therefore, the control center of the cell. The main structures making up the nucleus are the nuclear envelope, a double membrane that encloses the entire organelle and isolates its contents from the cellular cytoplasm, and the nucleoskeleton (which includes nuclear lamina), a network within the nucleus that adds mechanical support, much like the cytoskeleton, which supports the cell as a whole.



https://en.wikipedia.org/wiki/Cell_nucleus

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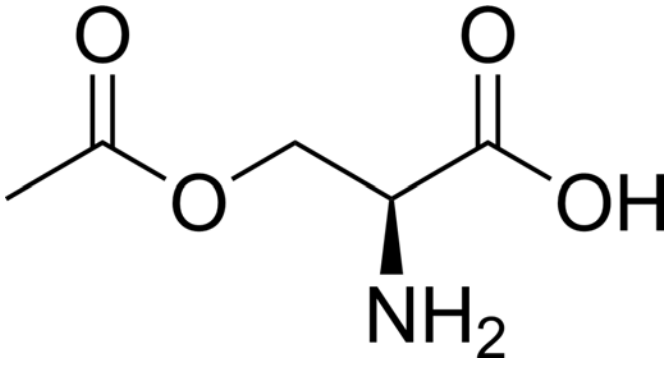
O-acetyl-L-serine

O-Acetylserine is the α-amino acid with the chemical formula HO2C-$CH(NH_2)CH_2OC(O)CH_3$. It is an intermediate in the biosynthesis of the cor amino acid cysteine in bacteria and plants. O-Acetylserine is biosynthesized tion of the serine by the enzyme serine transacetylase.



https://en.wikipedia.org/wiki/O-Acetylserine

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

O-glycosylation

O-linked glycosylation is the attachment of a sugar molecule to an oxygen atom in an amino acid residue in a protein. O-linked glycosylation is a form of glycosylation that occurs in the Golgi apparatus in eukaryotes. It also occurs in archaea and bacteria.

O-linked glycosylation occurs at a later stage during protein processing, probably in the Golgi apparatus. This is the addition of N-acetyl-galactosamine to serine or threonine residues by the enzyme UDP-N-acetyl-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase (EC number 2.4.1.41), followed by other carbohydrates (such as galactose and sialic acid). This process is important for certain types of proteins such as proteoglycans, which involves the addition of glycosaminoglycan chains to an initially unglycosylated "proteoglycan core protein." These additions are usually serine O-linked glycoproteins, which seem to have one of two main functions.

One function involves secretion to form components of the extracellular matrix, adhering one cell to another by interactions between the large sugar complexes of proteoglycans. The other main function is to act as a component of mucosal secretions, and it is the high concentration of carbohydrates that tends to give mucus its "slimy" feel. GlcNAc-β-Ser/Thr, which are found in nuclear and cytoskeletal proteins, were the first reported example of glycosylated proteins found in a location other than secretory channels.

https://en.wikipedia.org/wiki/O-linked_glycosylation

Related Glossary Terms

O-linked

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an amino acid residue in a protein. O-linked glycosylation is a form of glyco
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https://en.wikipedia.org/wiki/O-linked_glycosylation

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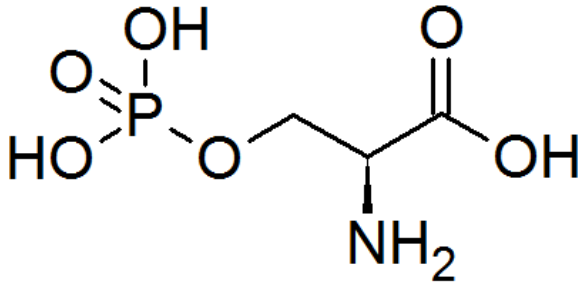
https://en.wikipedia.org/wiki/O-linked_glycosylation

Related Glossary Terms

O-phosphoserine

Phosphoserine (abbreviated as SEP or J) is an ester of serine and phosphoric acid. Phosphoserine is a component of many proteins as the result of posttranslational modifications. The phosphorylation of the alcohol functional group in serine to produce phosphoserine is catalyzed by various types of kinases. Through the use of technologies that utilize an expanded genetic code, phosphoserine can also be incorporated into proteins during translation.

Phosphoserine has three potential coordination sites (carboxyl, amine and phosphate group) Determination of the mode of coordination between phosphorylated ligands and metal ions occurring in an organism is a first step to explain the function of the phosphoserine in bioinorganic processes.



https://en.wikipedia.org/wiki/Phosphoserine

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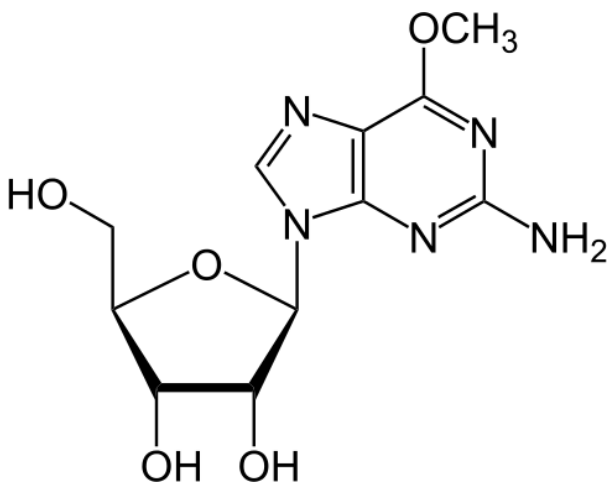
O^6-methylguanine Methyltransferase

O^6-alkylguanine DNA alkyltransferase (also known as AGT, MGMT or AGAT) is a protein that in humans is encoded by the O^6-methylguanine DNA methyltransferase (MGMT) gene. O^6-methylguanine DNA methyltransferase is crucial for genome stability. It repairs the naturally occurring mutagenic DNA lesion O^6-methylguanine back to guanine and prevents mismatch and errors during DNA replication and transcription. Accordingly, loss of MGMT increases the carcinogenic risk in mice after exposure to alkylating agents.

Shown below, O^6-methylguanine



https://en.wikipedia.org/wiki/O-6-methylguanine-DNA_methyltransferase

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Obligate Anaerobes

Obligate anaerobes are microorganisms that get killed by normal atmospheric concentrations of oxygen (20.95% O2). Oxygen tolerance varies between species, some capable of surviving in up to 8% oxygen, others losing viability unless the oxygen concentration is less than 0.5%.

The oxygen sensitivity of obligate anaerobes has been attributed to a combination of factors:

Because molecular oxygen contains two unpaired electrons in its outer orbital, it is readily reduced to superoxide (O_2^-) and hydrogen peroxide (H_2O_2) within cells. Aerobic organisms produce superoxide dismutase and catalase to detoxify these products, but obligate anaerobes produce these enzymes in very small quantities, or not at all. (The variability in oxygen tolerance of obligate anaerobes (<0.5 to 8% O2) is thought to reflect the quantity of superoxide dismutase and catalase being produced.)

Dissolved oxygen increases the redox potential of a solution, and high redox potential inhibits the growth of some obligate anaerobes. For example, methanogens grow at a redox potential lower than -0.3 V.

Sulfide is an essential component of some enzymes, and molecular oxygen oxidizes this to form disulfide, thus inactivating certain enzymes (e.g. nitrogenase). Organisms may not be able to grow with these essential enzymes deactivated. Growth may be inhibited due to a lack of reducing equivalents for biosynthesis, because electrons are exhausted in reducing oxygen.

https://en.wikipedia.org/wiki/Obligate_anaerobe

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Index Find Term

Octamer

The core histones all exist as dimers, which are similar in that they all posse
tone fold domain - three α helices linked by two loops. It is this helical struc
allows for interaction between distinct dimers, particularly in a head-tail fa
called the handshake motif). The resulting four distinct dimers then come t
form one octameric nucleosome core, approximately 63 Angstroms in diam
noid (DNA)-like particle). 147 base pairs of DNA wrap around this core par
times in a left-handed super-helical turn to give a particle of around 100 An
across.

https://en.wikipedia.org/wiki/Histone

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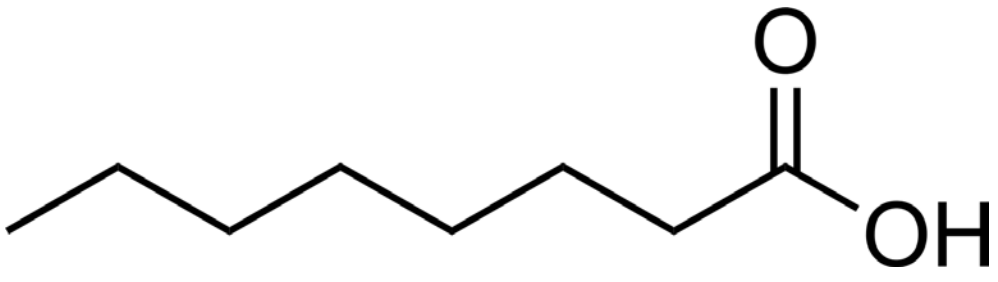
Chapter 2 - Structure and Function: Nucleic Acids

Octanoic acid

Caprylic acid is the common name for the eight-carbon saturated fatty acid
the systematic name octanoic acid. Its compounds are found naturally in th
various mammals, and as a minor constituent of coconut oil and palm kern
an oily liquid that is minimally soluble in water with a slightly unpleasant r
smell and taste.



https://en.wikipedia.org/wiki/Caprylic_acid

Related Glossary Terms

Drag related terms here

Oil

An oil is any neutral, nonpolar chemical substance that is a viscous liquid at ambient temperatures and is both hydrophobic (immiscible with water, literally "water fearing") and lipophilic (miscible with other oils, literally "fat loving"). Olive oil is shown below. Oils have a high carbon and hydrogen content and are usually flammable and slippery.

https://en.wikipedia.org/wiki/Oil

Related Glossary Terms

Drag related terms here

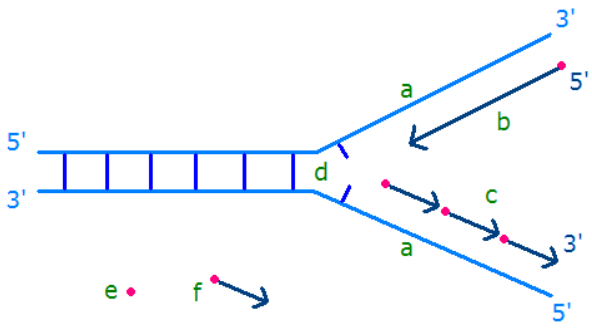
Okazaki Fragments

Okazaki fragments are short, newly synthesized DNA fragments that are formed on the lagging template strand during DNA replication. They are complementary to the lagging template strand, together forming short double-stranded DNA sections. Okazaki fragments are between 1000 and 2000 nucleotides long in *Escherichia coli* and are approximately 150 nucleotides long in eukaryotes. They are separated by ~120-nucleotide RNA primers and are unligated until RNA primers are removed, followed by enzyme ligase connecting (ligating) the two Okazaki fragments into one continuous newly synthesized complementary strand.

On the leading strand DNA replication proceeds continuously along the DNA molecule as the parent double-stranded DNA is unwound, but on the lagging strand the new DNA is made in installments, which are later joined together by a DNA ligase enzyme. This is because the enzymes that synthesize the new DNA can only work in one direction along the parent DNA molecule. On the leading strand this route is continuous, but on the lagging strand it is discontinuous.

DNA is synthesized from 5' to 3', so when copying the 3' to 5' strand, replication is continuous. Phosphodiester links form between the 3' to 5' and nucleotides can be added with the aid of the enzyme DNA polymerase for the continuous leading strand. However, in order to synthesize the lagging strand (the replication fork which is traveling in the opposite direction) synthesis occurs in small sections (100-200 nucleotides at a time in eukaryotes). These new stretches of DNA are called Okazaki fragments and each one requires its own RNA primer.

The image below shows Okazaki fragments being formed at a replication fork on the bottom strand. They are labeled ‘c’.



https://en.wikipedia.org/wiki/Okazaki_fragments

Related Glossary Terms

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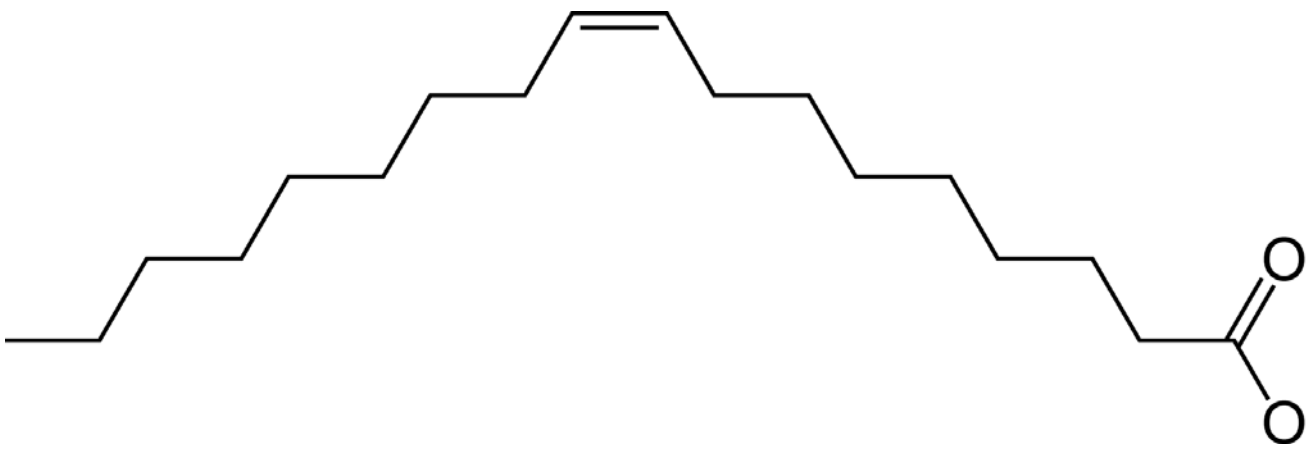
Oleate

Oleic acid (ionized form = oleate) is a fatty acid that occurs naturally in various animal and vegetable fats and oils. It is an odorless, colorless oil, although commercial samples may be yellowish. In chemical terms, oleic acid is classified as a monounsaturated ω-9 fatty acid, abbreviated with a lipid number of 18:1 *cis*-9. It has the formula $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$. The term "oleic" means related to, or derived from, oil of olive, the oil that is predominantly composed of oleic acid.

Oleic acid undergoes the reactions of carboxylic acids and alkenes. It is soluble in aqueous base to give soaps called oleates.



https://en.wikipedia.org/wiki/Oleic_acid

Related Glossary Terms

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Oligomerize

An oligomer is a molecular complex that consists of a few monomer units, i
to a polymer, where the number of monomers is, in principle, not limited. D
trimers, and tetramers are, for instance, oligomers composed of two, three
monomers, respectively. To oligomerize would be to assemble an oligomer

In the context of biochemistry, an oligomer usually refers to a macromolecu
plex formed by non-covalent bonding of a few macromolecules like protein
acids. In this sense, a homo-oligomer would be formed by few identical mo
by contrast, a hetero-oligomer would be made of more than one, different,
cules.

https://en.wikipedia.org/wiki/Oligomer

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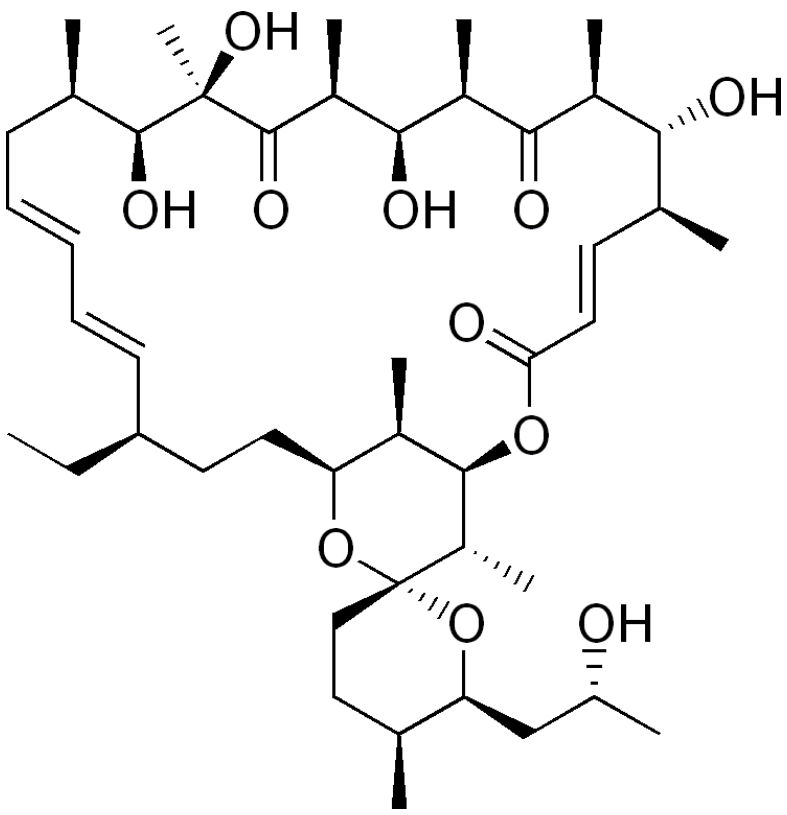
Chapter 3 - Membranes: Other Considerations

Oligomycin

Oligomycins are macrolides created by *Streptomyces* that can be poisonous to other organisms. They have use as antibiotics. Oligomycin A (shown below) is an inhibitor of ATP synthase. In oxidative phosphorylation research, it is used to prevent state 3 (phosphorylating) respiration. Oligomycin A inhibits ATP synthase by blocking its proton channel (F_o subunit), which is necessary for oxidative phosphorylation of ADP to ATP (energy production).



https://en.wikipedia.org/wiki/Oligomycin

Related Glossary Terms

Oligosaccharide

An oligosaccharide is a saccharide polymer containing a small number (typically three to ten) of simple sugars (monosaccharides). Oligosaccharides can have many functions including cell recognition and cell binding. For example, glycolipids have an important role in the immune response.

In general, oligosaccharides are found either N- or O-linked to compatible amino acid side-chains in proteins or to lipid moieties (see glycans). N-linked oligosaccharides are found attached to asparagine via a β linkage to the amine nitrogen of the side chain. Alternately, O-linked oligosaccharides are generally attached to threonine or serine on the alcohol group of the side chain.

https://en.wikipedia.org/wiki/Oligosaccharide

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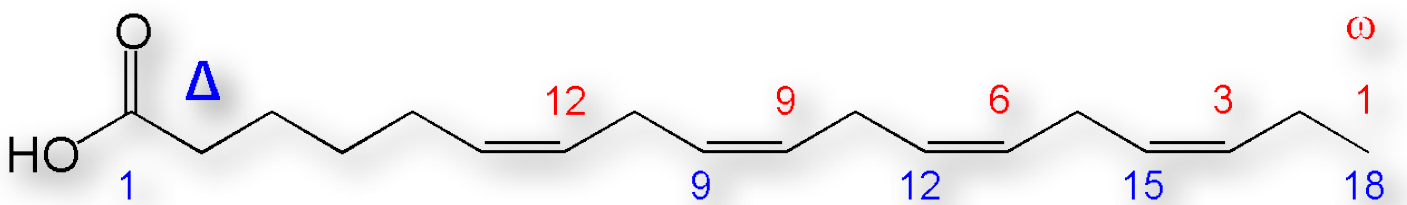
Omega Numbering

Omega-9 fatty acids (ω−9 fatty acids or n−9 fatty acids) are a family of unsaturated fatty acids which have in common a final carbon–carbon double bond in the ω−9 position - that is, the ninth bond from the methyl end of the fatty acid.

The position of the carbon-carbon double bonds in carboxylic acid chains in fats is designated by Greek letters. The carbon atom closest to the carboxyl group is the α carbon, the next carbon is the β carbon and so on. In fatty acids the carbon atom of the methyl group at the end of the hydrocarbon chain is called the ω carbon because ω is the last letter of the Greek alphabet. ω-3 fatty acids have a double bond three carbons away from the methyl carbon, whereas ω-6 fatty acids have a double bond six carbons away from the methyl carbon.



https://en.wikipedia.org/wiki/Omega-9_fatty_acid
https://en.wikipedia.org/wiki/Polyunsaturated_fat

Related Glossary Terms

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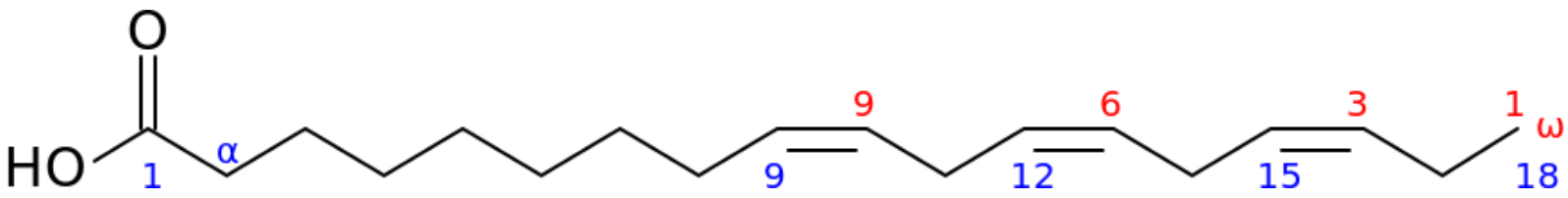
Omega-3 Fatty Acid

Omega-3 fatty acids — also called ω-3 fatty acids or n-3 fatty acids — are polyunsaturated fatty acids (PUFAs) with a double bond (C=C) at the third carbon atom from the end of the carbon chain. The fatty acids have two ends, the carboxylic acid (-COOH) end, which is considered the beginning of the chain, thus "α", and the methyl (CH_3) end, which is considered the "tail" of the chain, thus "ω". The way in which a fatty acid is named is determined by the location of the first double bond, counted from the methyl end, that is, the omega (ω-) or the n- end.

The three types of ω-3 fatty acids involved in human physiology are α-linolenic acid (ALA - shown below) (found in plant oils), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (both commonly found in marine oils). Marine algae and phytoplankton are primary sources of ω-3 fatty acids. Common sources of plant oils containing the ω-3 ALA fatty acid include walnut, edible seeds, clary sage seed oil, algal oil, flaxseed oil, Sacha Inchi oil, Echium oil, and hemp oil, while sources of animal omega-3 EPA and DHA fatty acids include fish oils, egg oil, squid oils, and krill oil. Dietary supplementation with ω-3 fatty acids does not appear to affect the risk of death, cancer or heart disease. Furthermore, fish oil supplement studies have failed to support claims of preventing heart attacks or strokes.



https://en.wikipedia.org/wiki/Omega-3_fatty_acid

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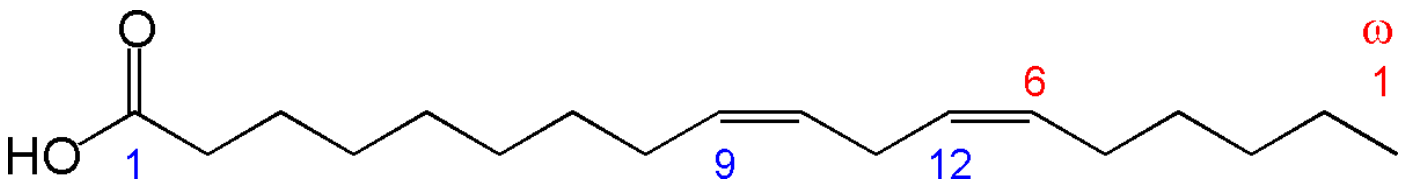
Omega-6

ω-6 fatty acids (also referred to as omega-6 fatty acids or n-6 fatty acids) are a family of pro-inflammatory and anti-inflammatory polyunsaturated fatty acids that have in common a final carbon-carbon double bond in the n-6 position, that is, the sixth bond, counting from the methyl end.

The biological effects of the ω-6 fatty acids are largely produced during & after physical activity for the purpose of promoting growth and during the inflammatory cascade to halt cell damage and promote cell repair by their conversion to ω-6 eicosanoids that bind to diverse receptors found in every tissue of the body.

Linoleic acid (18:2, n−6 - pictured below), the shortest-chained ω-6 fatty acid, is one of many essential fatty acids and is categorized as an essential fatty acid because the human body cannot synthesize it. Mammalian cells lack the enzyme ω-3 desaturase and therefore cannot convert omega-6 fatty acids to omega-3 fatty acids. Closely related ω-3 and ω-6 fatty acids act as competing substrates for the same enzymes. This outlines the importance of the proportion of ω-3 to ω-6 fatty acids in a diet.



https://en.wikipedia.org/wiki/Omega-6_fatty_acid

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Chapter 2 - Structure & Function: Lipids

Omega-oxidation

ω oxidation (omega-oxidation) is a process of fatty acid metabolism in som
animals. It is an alternative pathway to β oxidation that, instead of involvin
bon, involves the oxidation of the ω carbon (the carbon most distant from t
group of the fatty acid). The process is normally a minor catabolic pathway
medium-chain fatty acids (10-12 carbon atoms), but becomes more importa
oxidation is defective.

In vertebrates, the enzymes for ω oxidation are located in the smooth ER of
kidney cells, instead of in the mitochondria as with β oxidation.

https://en.wikipedia.org/wiki/Omega_oxidation

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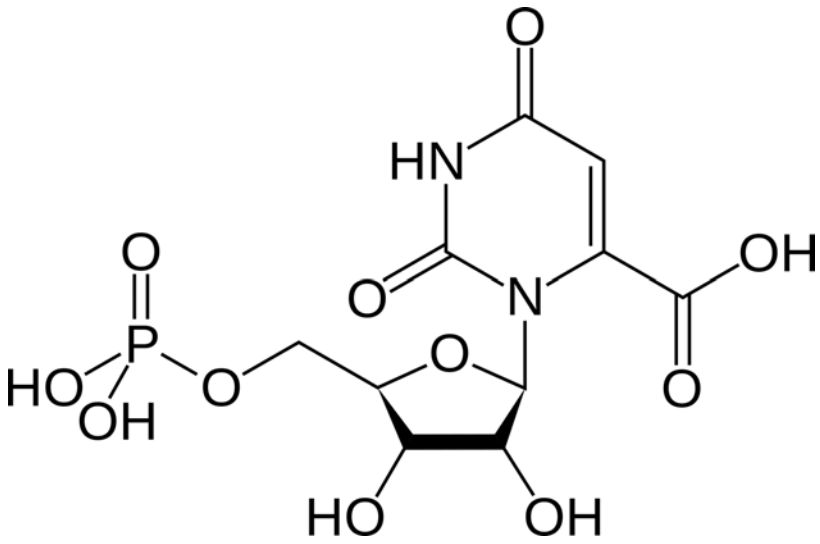
OMP

Orotidine 5'-monophosphate (OMP), also known as orotidylic acid, is a pyrimidine nucleotide which is the last intermediate in the biosynthesis of uridine monophosphate. OMP is formed from orotate and phosphoribosyl pyrophosphate by the enzyme Orotate phosphoribosyltransferase. In humans, the enzyme UMP synthase converts OMP into uridine 5'- monophosphate. If UMP synthase is defective, orotic aciduria can result.



https://en.wikipedia.org/wiki/Orotidine_5%27-monophosphate

Related Glossary Terms

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OMP Decarboxylase

Orotidine 5’-phosphate decarboxylase (OMP decarboxylase) or orotidylate decarboxylase is an enzyme involved in pyrimidine biosynthesis. It catalyzes the decarboxylation of orotidine monophosphate (OMP) to form uridine monophosphate (UMP). The function of this enzyme is essential to the *de novo* biosynthesis of the pyrimidine nucleotides uridine triphosphate, cytidine triphosphate, and thymidine triphosphate. OMP decarboxylase has been a frequent target for scientific investigation because of its demonstrated extreme catalytic efficiency and its usefulness as a selection marker for yeast strain engineering.

The exact mechanism by which OMP decarboxylase catalyzes its reaction has been a subject of rigorous scientific investigation. The driving force for the loss of the carboxyl linked to the C_6 of the pyrimidine ring comes from the close proximity of an aspartate residue carboxyl group in the enzyme's active site, which destabilizes the ground state relative to the transition state of the uncatalyzed reaction. There have been multiple hypotheses about what form the transition state takes before protonation of the C_6 carbon occurs to yield the final product. Many studies investigated the binding of a potent inhibitor of OMP decarboxylase, 6-hydroxy uridine monophosphate (BMP, a barbituric acid derivative), within the active site, to identify which essential amino acid residues are directly involved with stabilization of the transition state. Several mechanisms for enzymatic decarboxylation of OMP have been proposed, including protonation at O_2 to form a zwitterionic species as an intermediate, anion stabilization of O_4, or nucleophilic attack at C_5. Current consensus suggests that the mechanism proceeds through a stabilized carbanion at the C_6 after loss of carbon dioxide. This mechanism was suggested from studies investigating kinetic isotope effects in conjunction with competitive inhibition and active site mutagenesis. In this mechanism the short-lived carbanion species is stabilized by a nearby lysine residue, before it is quenched by a proton.

https://en.wikipedia.org/wiki/Orotidine_5%27-phosphate_decarboxylase

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Related Glossary Terms

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Oncogene

An oncogene is a gene that has the potential to cause cancer. In tumor cells often mutated or expressed at high levels.

Most normal cells will undergo a programmed form of rapid cell death (apo when critical functions are altered. Activated oncogenes can cause those cel nated for apoptosis to survive and proliferate instead. Most oncogenes requ tional step, such as mutations in another gene, or environmental factors, su infection, to cause cancer. Since the 1970s, dozens of oncogenes have been human cancer. Many cancer drugs target the proteins encoded by oncogene

https://en.wikipedia.org/wiki/Oncogene

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Chapter 3 - Membranes: Basic Concepts

Open Complex

The open complex is a structure formed on a DNA during the process of transcription in the initiation phase.

The following steps occur, in order, for transcription initiation:
• RNA polymerase (RNAP) binds to one of several specificity factors, σ, to form a holoenzyme. In this form, it can recognize and bind to specific promoter regions in the DNA. The -35 region and the -10 ("Pribnow box") region comprise the core prokaryotic promoter, and |T| stands for the terminator. The DNA on the template strand between the +1 site and the terminator is transcribed into RNA, which is then translated into protein. At this stage, the DNA is double-stranded ("closed"). This holoenzyme/wound-DNA structure is referred to as the closed complex.
• The DNA is unwound and becomes single-stranded ("open") in the vicinity of the initiation site (defined as +1). This holoenzyme/unwound-DNA structure is called the open complex.
• The RNA polymerase transcribes the DNA (the β subunit initiates the synthesis), but produces about 10 abortive (short, non-productive) transcripts which are unable to leave the RNA polymerase because the exit channel is blocked by the σ-factor.
• The σ-factor eventually dissociates from the core enzyme, and elongation proceeds.

https://en.wikipedia.org/wiki/Bacterial_transcription

Related Glossary Terms

Drag related terms here

Operator

In genetics, an operator is a segment of DNA to which a transcription factor binds t
regulate gene expression. The transcription factor is a repressor, which can bind to
operator to prevent transcription.

The main operator (O_2) in the classically defined lac operon is located slightly down
stream of the promoter. Two additional operators, O_1 and O_3 are located at -82 and
+412, respectively.

https://en.wikipedia.org/wiki/Operator_(biology)

Related Glossary Terms

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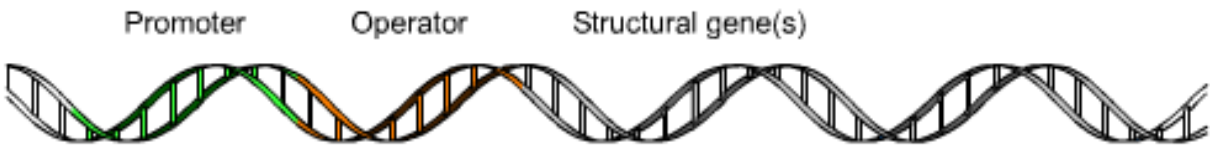
Operon

An operon is a functioning unit of genomic DNA containing a cluster of genes under the control of a single promoter. The genes are transcribed together into an mRNA strand and either translated together in the cytoplasm, or undergo trans-splicing to create monocistronic mRNAs that are translated separately, i.e. several strands of mRNA that each encode a single gene product. The result of this is that the genes contained in the operon are either expressed together or not at all. Several genes must be co-transcribed to define an operon.



https://en.wikipedia.org/wiki/Operon

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Ordered Binding

Ordered binding is a consideration for enzymes that bind more than one su

In these enzymes, both substrates bind to the enzyme to produce an EAB te
plex. The order of binding can either be random (in a random mechanism)
strates have to bind in a particular sequence (in an ordered mechanism).

https://en.wikipedia.org/wiki/Enzyme_kinetics

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Organelle

In cell biology, an organelle is a specialized subunit within a cell that has a specific function. Individual organelles are usually separately enclosed within their own lipid bilayers.

The name organelle comes from the idea that these structures are to cells what an organ is to the body (hence the name organelle, the suffix -elle being a diminutive). Organelles are identified by microscopy, and can also be purified by cell fractionation. There are many types of organelles, particularly in eukaryotic cells. While prokaryotes do not possess organelles *per se*, some do contain protein-based microcompartments, which are thought to act as primitive organelles.

Eukaryotic cells are structurally complex, and by definition are organized, in part, by interior compartments that are themselves enclosed by lipid membranes that resemble the outermost cell membrane. The larger organelles, such as the nucleus and vacuoles, are easily visible with the light microscope. They were among the first biological discoveries made after the invention of the microscope.

Not all eukaryotic cells have each of the organelles listed below. Exceptional organisms have cells that do not include some organelles that might otherwise be considered universal to eukaryotes (such as mitochondria). There are also occasional exceptions to the number of membranes surrounding organelles, listed in the tables below (e.g., some that are listed as double-membrane are sometimes found with single or triple membranes). In addition, the number of individual organelles of each type found in a given cell varies depending upon the function of that cell.

https://en.wikipedia.org/wiki/Organelle

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Organelles

In cell biology, an organelle is a specialized subunit within a cell that has a specific function. Individual organelles are usually separately enclosed within their own lipid bilayers.

The name organelle comes from the idea that these structures are to cells what an organ is to the body (hence the name organelle, the suffix -elle being a diminutive). Organelles are identified by microscopy, and can also be purified by cell fractionation. There are many types of organelles, particularly in eukaryotic cells. While prokaryotes do not possess organelles *per se*, some do contain protein-based microcompartments, which are thought to act as primitive organelles.

Eukaryotic cells are structurally complex, and by definition are organized, in part, by interior compartments that are themselves enclosed by lipid membranes that resemble the outermost cell membrane. The larger organelles, such as the nucleus and vacuoles, are easily visible with the light microscope. They were among the first biological discoveries made after the invention of the microscope.

Not all eukaryotic cells have each of the organelles listed below. Exceptional organisms have cells that do not include some organelles that might otherwise be considered universal to eukaryotes (such as mitochondria). There are also occasional exceptions to the number of membranes surrounding organelles, listed in the tables below (e.g., some that are listed as double-membrane are sometimes found with single or triple membranes). In addition, the number of individual organelles of each type found in a given cell varies depending upon the function of that cell.

https://en.wikipedia.org/wiki/Organelle

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Organic Compounds

An organic compound is any member of a large class of gaseous, liquid, or s
cal compounds whose molecules contain carbon. For historical reasons, a fe
carbon-containing compounds, such as carbides, carbonates, simple oxides
(such as CO and CO_2), and cyanides are considered inorganic. The distincti
organic and inorganic carbon compounds, while "useful in organizing the v
of chemistry... is somewhat arbitrary".

https://en.wikipedia.org/wiki/Organic_compound

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Origins of Replication

The origin of replication (also called the replication origin) is a particular sequence in a genome at which replication is initiated. This can either involve the replication of DNA in living organisms such as prokaryotes and eukaryotes, or that of DNA or RNA in viruses, such as double-stranded RNA viruses.

DNA replication may proceed from this point bidirectionally or unidirectionally. The specific structure of the origin of replication varies somewhat from species to species, but all share some common characteristics such as high AT content (repeats of adenine and thymine are easier to separate because their base stacking interactions are not as strong as those of guanine and cytosine). The origin of replication binds the pre-replication complex, a protein complex that recognizes, unwinds, and begins to copy DNA.

https://en.wikipedia.org/wiki/Origin_of_replication

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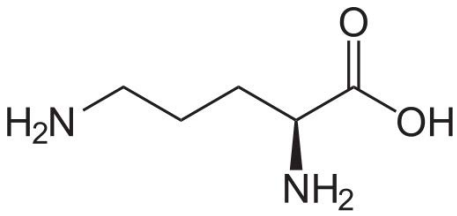
Ornithine

Ornithine is a non-proteinogenic amino acid that plays a role in the urea cycle.

Ornithine is not an amino acid coded for by DNA, that is, not proteinogenic. However, in mammalian non-hepatic tissues, the main use of the urea cycle is in arginine biosynthesis, so, as an intermediate in metabolic processes, ornithine is quite important.

L-Ornithine is one of the products of the action of the enzyme arginase on L-arginine, creating urea. Therefore, ornithine is a central part of the urea cycle, which allows for the disposal of excess nitrogen.



https://en.wikipedia.org/wiki/Ornithine

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Ornithine Acyltransferase

Ornithine N-benzoyltransferase (EC 2.3.1.127) is an enzyme that catalyzes t
reaction

2 benzoyl-CoA + L-ornithine <--> 2 CoASH + N_2,N_5-dibenzoyl-L-ornithine

Thus, the two substrates of this enzyme are benzoyl-CoA and L-ornithine, w
two products are CoASH and N_2,N_5-dibenzoyl-L-ornithine.

This enzyme belongs to the family of transferases, specifically those acyltra
transferring groups other than aminoacyl groups. The systematic name of t
class is benzoyl-CoA:L-ornithine N-benzoyltransferase. This enzyme is also
nithine N-acyltransferase.

https://en.wikipedia.org/wiki/Ornithine_N-benzoyltransferase

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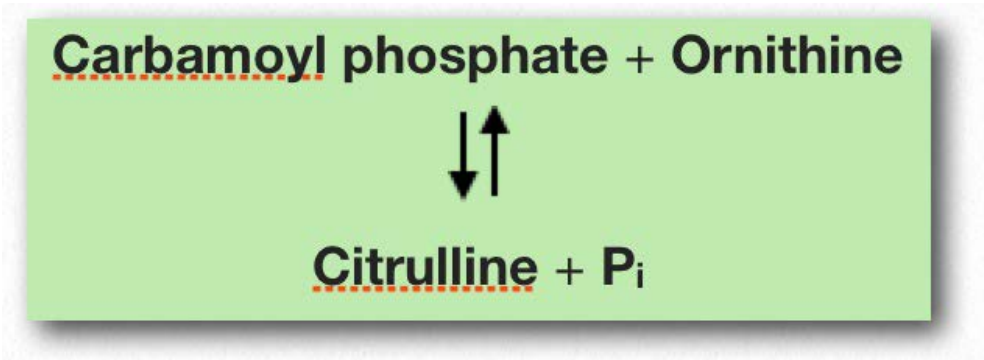
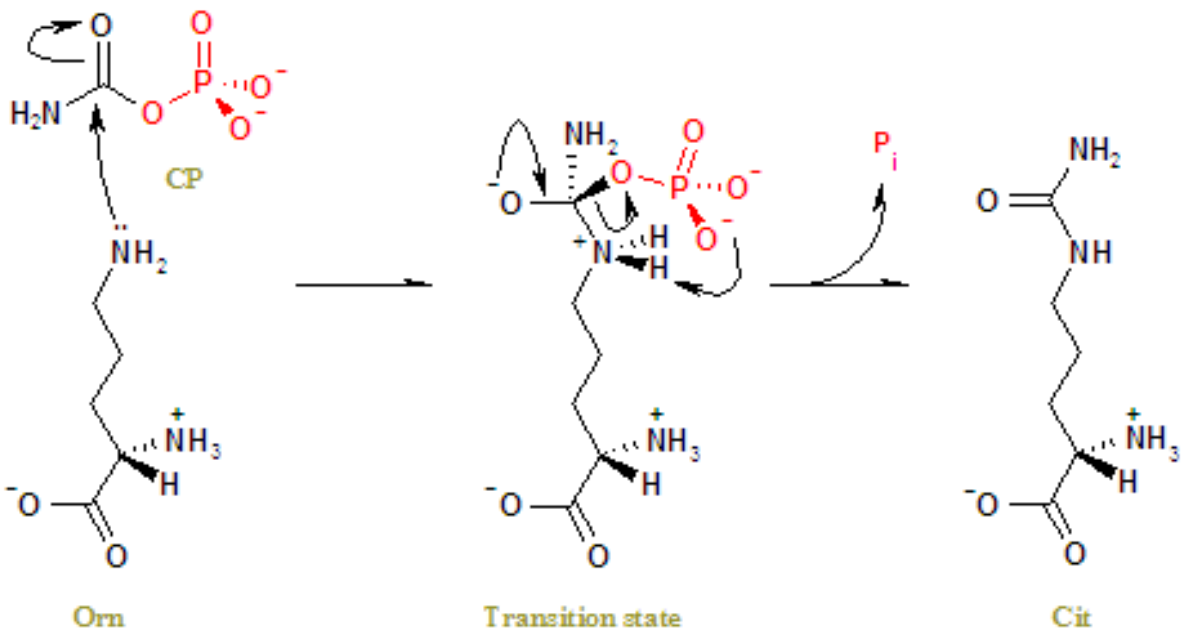
Chapter 4 - Catalysis: Mechanism

Ornithine Transcarbamoylase

Ornithine transcarbamylase (OTC) (also called ornithine carbamoyltransferase) is an enzyme that catalyzes the reaction between carbamoyl phosphate (CP) and ornithine (Orn) to form citrulline (Cit) and phosphate (P_i).



In plants and microbes, OTC is involved in arginine (Arg) biosynthesis, whereas in mammals it is located in the mitochondria and is part of the urea cycle.



https://en.wikipedia.org/wiki/Ornithine_transcarbamylase

Ornithine-citrulline Antiport

An antiporter (also called exchanger or counter-transporter) is a cotranspo
tegral membrane protein involved in secondary active transport of two or m
ent molecules or ions (i.e., solutes) across a phospholipid membrane such a
plasma membrane in opposite directions.

The ornithine-citrulline antiport is important in the urea cycle for transpor
nithine into the mitochondrion and citrulline out.

https://en.wikipedia.org/wiki/Antiporter

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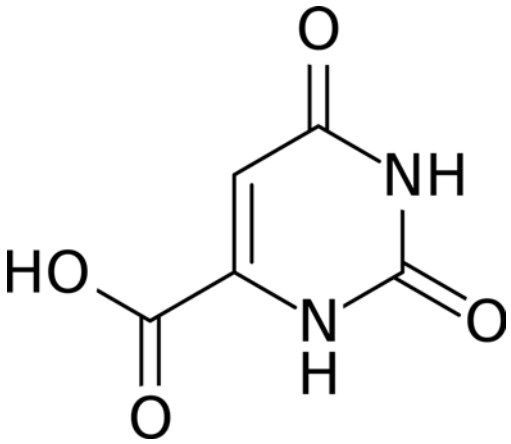
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Orotate

Orotic acid is a heterocyclic compound and an acid. It is also known as pyrimidinecarboxylic acid. Historically it was believed to be part of the vitamin B complex and was called vitamin B_{13}, but it is now known that it is not a vitamin.

The compound is manufactured in the body *via* a mitochondrial enzyme, dihydroorotate dehydrogenase. or a cytoplasmic enzyme of pyrimidine synthesis pathway. It is sometimes used as a mineral carrier in some dietary supplements (to increase their bioavailability), most commonly for lithium orotate.



https://en.wikipedia.org/wiki/Orotic_acid

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Orotate Phosphoribosyl Transferase

Orotate phosphoribosyltransferase (OPRTase) or Orotic acid phosphoribos
rase is an enzyme involved in pyrimidine biosynthesis. It catalyzes the form
orotidine 5'-monophosphate (OMP) from orotate and phosphoribosyl pyro
In yeast and bacteria, orotate phosphoribosyltransferase is an independent
with a unique gene coding for the protein, whereas in mammals and other
lar organisms, the catalytic function is carried out by a domain of the bifun
zyme UMP synthase.

https://en.wikipedia.org/wiki/Orotate_phosphoribosyltransferase

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Chapter 6 - Metabolism: Nucleotides

Chapter 6 - Metabolism: Nucleotides

Osmotic Pressure

Osmotic pressure is the minimum pressure which needs to be applied to a solution to prevent the inward flow of water across a semipermeable membrane. It is also defined as the measure of the tendency of a solution to take in water by osmosis. Potential osmotic pressure is the maximum osmotic pressure that could develop in a solution if it were separated from distilled water by a selectively permeable membrane. The phenomenon of osmosis arises from the propensity of a pure solvent to move through a semi-permeable membrane and into a solution containing a solute to which the membrane is impermeable. This process is of vital importance in biology as the cell's membrane is semipermeable.

https://en.wikipedia.org/wiki/Osmotic_pressure

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Osteocalcin

Osteocalcin, also known as bone γ-carboxyglutamic acid-containing protein
is a noncollagenous protein found in bone and dentin. Because it has gla do
synthesis is vitamin K dependent. In humans, the osteocalcin is encoded by
gene. Its receptor is GPRC6A.

Osteocalcin is secreted solely by osteoblasts and thought to play a role in th
metabolic regulation and is pro-osteoblastic, or bone-building, by nature.

https://en.wikipedia.org/wiki/Osteocalcin

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Outer Leaflet

The lipid bilayer consists of two layers- an outer leaflet and an inner leaflet. The co
nents of bilayers are distributed unequally between the two surfaces to create asyn
try between the outer and inner surfaces. This asymmetric organization is importa
for cell functions such as cell signaling. The asymmetry of the biological membran
flects the different functions of the two leaflets of the membrane. As seen in the flu
membrane model of the phospholipid bilayer, the outer leaflet and inner leaflet of
membrane are asymmetrical in their composition. Certain proteins and lipids rest
on one surface of the membrane and not the other.

https://en.wikipedia.org/wiki/Biological_membrane

In human red blood cells, the inner (cytoplasmic) leaflet is composed mostly of ph
phatidylethanolamine, phosphatidylserine and phosphatidylinositol and its phosp
lated derivatives. By contrast, the outer (extracellular) leaflet is based on phospha
choline, sphingomyelin and a variety of glycolipids,

https://en.wikipedia.org/wiki/Lipid_bilayer

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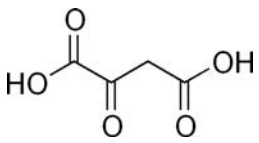
Oxaloacetate

Oxaloacetic acid (also known as oxalacetic acid) is a crystalline organic compound with the chemical formula $HO_2CC(O)CH_2CO_2H$. Oxaloacetic acid, in the form of its conjugate base oxaloacetate, is a metabolic intermediate in many processes that occur in animals. It takes part in the: gluconeogenesis, urea cycle, glyoxylate cycle, amino acid synthesis, fatty acid synthesis and citric acid cycle.

Oxaloacetate forms in several ways in nature. A principal route is upon oxidation of L-malate, catalyzed by malate dehydrogenase, in the citric acid cycle.



https://en.wikipedia.org/wiki/Oxaloacetic_acid

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Oxidation

Oxidation is the loss of electrons or an increase in oxidation state by a molecule, atom, or ion.

Redox reactions, or oxidation-reduction reactions, have a number of similarities to acid–base reactions. Like acid–base reactions, redox reactions are a matched set, that is, there cannot be an oxidation reaction without a reduction reaction happening simultaneously. The oxidation alone and the reduction alone are each called a half-reaction, because two half-reactions always occur together to form a whole reaction. When writing half-reactions, the gained or lost electrons are typically included explicitly in order that the half-reaction be balanced with respect to electric charge.

https://en.wikipedia.org/wiki/Redox

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Oxidative Phosphorylation

Oxidative phosphorylation (or OXPHOS in short) is the metabolic pathway in which cells use enzymes to oxidize nutrients, thereby releasing energy which is used to re-form ATP. In most eukaryotes, this takes place inside mitochondria. Almost all aerobic organisms carry out oxidative phosphorylation. This pathway is probably so pervasive because it is a highly efficient way of releasing energy, compared to alternative fermentation processes such as anaerobic glycolysis.

During oxidative phosphorylation, electrons are transferred from electron donors to electron acceptors such as oxygen, in redox reactions. These redox reactions release energy, which is used to form ATP.

https://en.wikipedia.org/wiki/Oxidative_phosphorylation

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Oxidative Stress

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g. O_2^- (superoxide radical), OH (hydroxyl radical) and H_2O_2 (hydrogen peroxide). Further, some reactive oxidative species act as cellular messengers in redox signaling. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling.

In humans, oxidative stress is thought to be involved in the development of Asperger syndrome, ADHD, cancer, Parkinson's disease, Lafora disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, fragile X syndrome, Sickle Cell Disease, lichen planus, vitiligo, autism, infection, Chronic fatigue syndrome, and Depression. However, reactive oxygen species can be beneficial, as they are used by the immune system as a way to attack and kill pathogens. Short-term oxidative stress may also be important in prevention of aging by induction of a process named mitohormesis.

https://en.wikipedia.org/wiki/Oxidative_stress

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Oxidized

Redox reactions include all chemical reactions in which atoms have their oxi
state changed. In general, redox reactions involve the transfer of electrons be
chemical species. The chemical species from which the electron is stripped is
have been oxidized.

https://en.wikipedia.org/wiki/Redox

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Oxygen

Oxygen is a chemical element with symbol O and atomic number 8. It is a member of the chalcogen group on the periodic table and is a highly reactive nonmetal and oxidizing agent that readily forms compounds (notably oxides) with most elements.

Many major classes of organic molecules in living organisms contain oxygen, such as proteins, nucleic acids, carbohydrates, and fats, as do the major constituent inorganic compounds of animal shells, teeth, and bone. Most of the mass of living organisms is oxygen as a component of water, the major constituent of lifeforms. Oxygen is used in cellular respiration and released by photosynthesis, which uses the energy of sunlight to produce oxygen from water and carbon dioxide.

https://en.wikipedia.org/wiki/Oxygen

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Oxygen Evolving Complex

The oxygen-evolving complex, (OEC) also known as the water-splitting com
water-oxidizing enzyme involved in the photooxidation of water during the
tions of photosynthesis. It is surrounded by 4 core proteins of photosystem
membrane-lumen interface. Based on a widely accepted theory from 1970 b
complex can exist in 5 states: S_0 to S_4. Photons trapped by photosystem II r
tem from state S_0 to S_4. S_4 is unstable and reacts with water producing free

https://en.wikipedia.org/wiki/Oxygen-evolving_complex

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Oxygen Transport

About 98.5% of the oxygen in a sample of arterial blood in a healthy human bre
air at sea-level pressure is chemically combined with the hemoglobin (Hgb). Ab
1.5% is physically dissolved in the other blood liquids and not connected to Hgb
hemoglobin molecule is the primary transporter of oxygen in mammals and ma
other species (for exceptions, see below). Hemoglobin has an oxygen binding ca
of between 1.36 and 1.40 ml O_2 per gram hemoglobin, which increases the total
oxygen capacity seventyfold, compared to if oxygen solely were carried by its so
of 0.03 ml O_2 per liter blood per mm Hg partial pressure of oxygen (approxima
100 mm Hg in arteries).

With the exception of pulmonary and umbilical arteries and their correspondin
arteries carry oxygenated blood away from the heart and deliver it to the body v
rioles and capillaries, where the oxygen is consumed. Afterwards, venules, and
carry deoxygenated blood back to the heart.

https://en.wikipedia.org/wiki/Blood#Oxygen_transport

Related Glossary Terms

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Oxygenase

An oxygenase is any enzyme that oxidizes a substrate by transferring the ox
molecular oxygen O_2 (as in air) to it. The oxygenases form a class of oxidore

There are two types of oxygenases:
• Monooxygenases, or mixed function oxidase, transfer one oxygen atom to
strate, and reduce the other oxygen atom to water.
• Dioxygenases, or oxygen transferases, incorporate both atoms of molecula
(O_2) into the product(s) of the reaction.

Among the most important monooxygenases are the cytochrome P_{450} oxida
sible for breaking down numerous chemicals in the body.

https://en.wikipedia.org/wiki/Oxygenase

Related Glossary Terms

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P-site

Ribosomes are the workplaces of protein biosynthesis, the process of translating mRNA into protein. The mRNA comprises a series of codons that dictate to the ribosome the sequence of the amino acids needed to make the protein. Using the mRNA as a template, the ribosome traverses each codon (3 nucleotides) of the mRNA, pairing it with the appropriate amino acid provided by an aminoacyl-tRNA. Aminoacyl-tRNA contains a complementary anticodon on one end and the appropriate amino acid on the other. For fast and accurate recognition of the appropriate tRNA, the ribosome utilizes large conformational changes (conformational proofreading) . The small ribosomal subunit, typically bound to an aminoacyl-tRNA containing the amino acid methionine, binds to an AUG codon on the mRNA and recruits the large ribosomal subunit. The ribosome contains three RNA binding sites, designated A, P and E. The A site binds an aminoacyl-tRNA. The P site binds a peptidyl-tRNA (a tRNA bound to the peptide being synthesized) and the E site binds a free tRNA before it exits the ribosome. Protein synthesis begins at a start codon AUG near the 5' end of the mRNA. mRNA binds to the P site of the ribosome first. The ribosome is able to identify the start codon by use of the Shine-Dalgarno sequence of the mRNA in prokaryotes and Kozak box in eukaryotes.

Although catalysis of the peptide bond involves the C_2 hydroxyl of RNA's P-site adenosine in a proton shuttle mechanism, other steps in protein synthesis (such as translocation) are caused by changes in protein conformations.

https://en.wikipedia.org/wiki/Ribosome

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PAICS

Phosphoribosylaminoimidazole carboxylase (or AIR carboxylase) is an enzy
volved in nucleotide biosynthesis and in particular in purine biosynthesis. I
the conversion of 5'-phosphoribosyl-5-aminoimidazole ("AIR") into 5'-phos
4-carboxy-5-aminoimidazole ("CAIR") as described in the reaction:

5-aminoimidazole ribonucleotide + CO_2 $\rightleftharpoons$ 5'-phosphoribosyl-4-carboxy-5-

aminoimidazole + 2 H^+

https://en.wikipedia.org/wiki/Phosphoribosylaminoimidazole_carboxylas

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Chapter 6 - Metabolism: Nucleotides

Palindrome

A palindromic sequence is a nucleic acid sequence on double-stranded DNA or RNA wherein reading 5' (five-prime) to 3' (three prime) forward on one strand matches the sequence reading backward 5' to 3' on the complementary strand with which it forms a double helix. This definition of palindrome thus depends on complementary strands being palindromic of each other.

The meaning of palindrome in the context of genetics is slightly different from the definition used for words and sentences. Since a double helix is formed by two paired strands of nucleotides that run in opposite directions in the 5'-to-3' sense, and the nucleotides always pair in the same way (Adenine (A) with Thymine (T) for DNA, with Uracil (U) for RNA, Cytosine (C) with Guanine (G)), a (single-stranded) nucleotide sequence is said to be a palindrome if it is equal to its reverse complement. For example, the DNA sequence ACCTAGGT is palindromic because its nucleotide-by-nucleotide complement is TGGATCCA, and reversing the order of the nucleotides in the complement gives the original sequence.

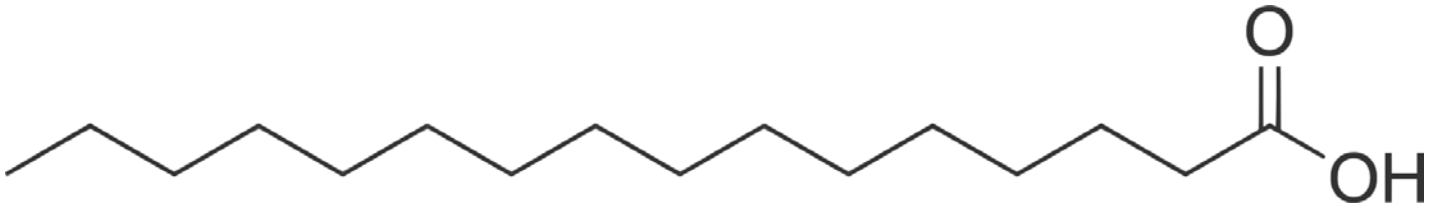
A palindromic nucleotide sequence can form a hairpin. Palindromic DNA motifs are found in most genomes or sets of genetic instructions. Palindromic motifs are made by the order of the nucleotides that specify the complex chemicals (proteins) which, as a result of those genetic instructions, the cell is to produce. They have been specially researched in bacterial chromosomes and in the so-called Bacterial Interspersed Mosaic Elements (BIMEs) scattered over them. Recently, a research genome sequencing project discovered that many of the bases on the Y chromosome are arranged as palindromes. A palindrome structure allows the Y chromosome to repair itself by bending over at the middle if one side is damaged.

Palindromes also appear to be found frequently in proteins, but their role in the protein function is not clearly known. It has recently been suggested that the existence of palindromes in peptides might be related to the prevalence of low-complexity regions in proteins, as palindromes are frequently associated with low-complexity sequences. Their prevalence might be also related to an α helical formation propensity of these sequences, or in formation of protein/protein complexes.

https://en.wikipedia.org/wiki/Palindromic_sequence

Palmitate

Palmitic acid, or hexadecanoic acid in IUPAC nomenclature, is the most co
acid (saturated) found in animals, plants and microorganisms. Its chemical
$CH_3(CH_2)_{14}COOH$. As its name indicates, it is a major component of the oil
trees (palm oil), but can also be found in meats, cheeses, butter, and dairy p
Palmitate is a term for the salts and esters of palmitic acid. The palmitate a
observed form of palmitic acid at physiologic pH (7.4).



https://en.wikipedia.org/wiki/Palmitic_acid

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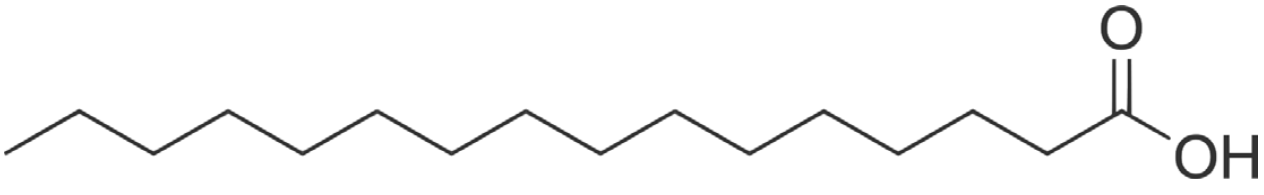
Chapter 2 - Structure & Function: Lipids

Chapter 2 - Structure & Function: Lipids

Palmitic Acid

Palmitic acid, or hexadecanoic acid in IUPAC nomenclature, is the most common fatty acid (saturated) found in animals, plants and microorganisms. Its chemical formula is $CH_3(CH_2)_{14}COOH$. As its name indicates, it is a major component of the oil from palm trees (palm oil), but can also be found in meats, cheeses, butter, and dairy products. Palmitate is a term for the salts and esters of palmitic acid. The palmitate anion is the observed form of palmitic acid at physiologic pH (7.4).



https://en.wikipedia.org/wiki/Palmitic_acid

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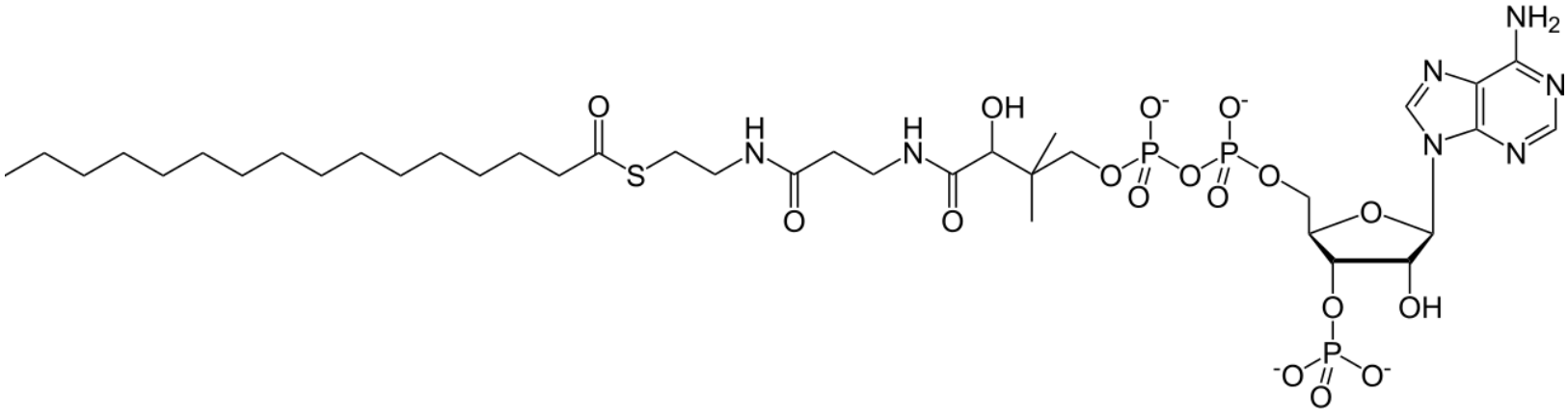
Palmitoyl-CoA

Palmitoyl-CoA is an acyl-CoA thioester used in the biosynthesis of sphingosine. It is also part of the carnitine shuttle system, which transports other fatty acyl-CoA molecules into the mitochondria for β-oxidation.



https://en.wikipedia.org/wiki/Palmitoyl-CoA

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Pancreatic Lipase

Pancreatic lipase, also known as pancreatic triacylglycerol lipase, is an enzyme s
creted from the pancreas. As the primary lipase enzyme that hydrolyzes (breaks
dietary fat molecules in the human digestive system, it is one of the main digesti
zymes, converting triglyceride substrates found in ingested oils to monoglyceri
free fatty acids.

Unlike some pancreatic enzymes that are activated by proteolytic cleavage (e.g.,
sinogen), pancreatic lipase is secreted in its final form. However, it becomes effi
only in the presence of colipase in the duodenum.

In humans, pancreatic lipase is encoded by the PNLIP gene.

Triacylglycerol + 2 H_2O ⇌2-monoacylglycerol + 2 Fatty Acid Anions

https://en.wikipedia.org/wiki/Pancreatic_lipase

Related Glossary Terms

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Index Find Term

Pancreatitis

Pancreatitis is inflammation of the pancreas. The pancreas is a large organ
stomach that produces digestive enzymes. There are two main types, acute
and chronic pancreatitis. Signs and symptoms of pancreatitis include pain i
abdomen, nausea and vomiting. The pain often goes into the back and is us
vere. In acute pancreatitis a fever may occur and symptoms typically resolv
days. In chronic pancreatitis weight loss, fatty stool, and diarrhea may occu
tions may include infection, bleeding, diabetes mellitus, or problems with c
gans.

https://en.wikipedia.org/wiki/Pancreatitis

Related Glossary Terms

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Papain

Papain, also known as papaya proteinase I, is a cysteine protease enzyme p
paya (*Carica papaya*) and mountain papaya (*Vasconcellea cundinamarce*
pain belongs to a family of related proteins with a wide variety of activities,
endopeptidases, aminopeptidases, dipeptidyl peptidases and enzymes with
and endo-peptidase activity. Papain-like cysteine proteinases are essentiall
sized as inactive proenzymes (zymogens) with N-terminal pro-peptide regi
tivation process of these enzymes includes the removal of pro-peptide regi
serve a variety of functions *in vivo* and *in vitro*.

https://en.wikipedia.org/wiki/Papain

Related Glossary Terms

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Paracrine

Paracrine signaling is a form of cell-cell communication in which a cell produ
nal to induce changes in nearby cells, altering the behavior or differentiation
cells. Signaling molecules known as paracrine factors diffuse over a relatively
tance (local action), as opposed to endocrine factors (hormones which travel
bly longer distances via the circulatory system), juxtacrine interactions, and
signaling. Cells that produce paracrine factors secrete them into the immedia
cellular environment. Factors then travel to nearby cells in which the gradien
received determines the outcome. These highly conserved receptors and path
be organized into four major families based on similar structures: Fibroblast
factor (FGF) family, Hedgehog family, Wnt family, and TGF-β superfamily. E
a paracrine factor to its respective receptor initiates signal transduction casc
ing different responses

https://en.wikipedia.org/wiki/Paracrine_signaling

Related Glossary Terms

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Parallel

The term parallel, as used in molecular biology relates to orientation, not to
The term is most commonly used to describe protein sequences aligned in t
rection, such as two strands adjacent to each other that have their amino ar
ends aligned with each other. Parallel contrasts with anti-parallel, which m
entations are opposite each other. DNA strands in a double helix are arran
anti-parallel fashion - the 3’ end of one strand is aligned with the 5’ end of t

Related Glossary Terms

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Parkin

Parkin is a protein which in humans is encoded by the PARK2 gene. The precise fun
tion of this protein is unknown. However, the protein is a component of a multiprote
E_3 ubiquitin ligase complex which in turn is part of the ubiquitin-proteasome system
that mediates the targeting of proteins for degradation. Mutations in this gene are
known to cause a familial form of Parkinson's disease known as autosomal recessive
venile Parkinson's disease (AR-JP). Moreover, Parkin is described to be necessary fo
mitophagy (autophagy of mitochondria).

However, how loss of function of the parkin protein leads to dopaminergic cell death
this disease is unclear. The prevailing hypothesis is that parkin helps degrade one or
more proteins toxic to dopaminergic neurons. Putative substrates of parkin include
synphilin-1, CDC-rel1, cyclin E, p38 tRNA synthase, Pael-R, synaptotagmin XI, sp22
and parkin itself (see also ubiquitin ligase). Additionally, Parkin contains a C-termin
motif that binds PDZ domains. Parkin has been shown to associate in a PDZ depend-
ent manner with the PDZ domain containing proteins CASK and PICK1.

https://en.wikipedia.org/wiki/Parkin_(ligase)

Related Glossary Terms

Drag related terms here

Parkinson Disease

Parkinson's disease (PD) is a degenerative disorder of the central nervous s
mainly affecting the motor system. Early in the course of the disease, the m
symptoms are movement-related. These include shaking, rigidity, slowness
ment and difficulty with walking and gait. Later, thinking and behavioral p
may arise, with dementia commonly occurring in the advanced stages of th
and depression being the most common psychiatric symptom. Other sympt
clude sensory, sleep, and emotional problems. The main motor symptoms a
tively called "parkinsonism", or a "parkinsonian syndrome".

https://en.wikipedia.org/wiki/Parkinson%27s_disease

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tively called "parkinsonism", or a "parkinsonian syndrome".

https://en.wikipedia.org/wiki/Parkinson%27s_disease

Related Glossary Terms

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PARP

Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in a nu
cellular processes involving mainly DNA repair and programmed cell death. P
composed of four domains of interest: a DNA-binding domain, a caspase-clea
main (see below), an auto-modification domain, and a catalytic domain. The D
binding domain is composed of two zinc finger motifs. In the presence of dam
DNA (base pair-excised), the DNA-binding domain will bind the DNA and inc
conformational shift. It has been shown that this binding occurs independent
other domains. This is integral in a programmed cell death model based on ca
cleavage inhibition of PARP. The auto-modification domain is responsible for
the protein from the DNA after catalysis. Also, it plays an integral role in cleav
induced inactivation.

https://en.wikipedia.org/wiki/Poly_ADP_ribose_polymerase

Related Glossary Terms

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Partial Hydrogenation

Hydrogenation – to treat with hydrogen – is a chemical reaction between m
drogen (H_2) and another compound or element, usually in the presence of a
such as nickel, palladium or platinum. The process is commonly employed
saturate organic compounds. Hydrogenation typically constitutes the addit
of hydrogen atoms to a molecule, generally an alkene. Catalysts are require
action to be usable. Non-catalytic hydrogenation takes place only at very h
tures. Hydrogenation reduces double and triple bonds in hydrocarbons. Co
drogenation of unsaturated fats produces saturated fats. In the case of part
genation, *trans* fats may be generated as well.

https://en.wikipedia.org/wiki/Hydrogenation

Related Glossary Terms

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Passenger RNA

The RNAi pathway is found in many eukaryotes, including animals, and is i
the enzyme Dicer, which cleaves long double-stranded RNA (dsRNA) mole
short double-stranded fragments of ~20 nucleotide siRNAs. Each siRNA is
into two single-stranded RNAs (ssRNAs), the passenger strand and the gui
The passenger strand is degraded and the guide strand is incorporated into
induced silencing complex (RISC).

https://en.wikipedia.org/wiki/RNA_interference

Related Glossary Terms

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Passive Transport

Passive transport is a movement of biochemicals and other atomic or molecular substances across cell membranes without need of energy input. Unlike active transport, it does not require an input of cellular energy because it is instead driven by the tendency of the system to grow in entropy. The rate of passive transport depends on the permeability of the cell membrane, which, in turn, depends on the organization and characteristics of the membrane lipids and proteins. The four main kinds of passive transport are simple diffusion, facilitated diffusion, filtration and osmosis.

Facilitated diffusion, also called carrier-mediated diffusion, is the movement of molecules across the cell membrane via special transport proteins that are embedded within the cellular membrane. Large, insoluble molecules, such as glucose, vesicles and proteins require a carrier molecule to move through the plasma membrane. Therefore, it will bind with its specific carrier proteins, and the complex will then be bonded to a receptor site and moved through the cellular membrane. Facilitated diffusion is a passive process: The solutes move down the concentration gradient and don't use extra cellular energy to move. Channel proteins are another type of facilitated diffusion that allow the selective transport of one type of hydrophilic molecule across the cell membrane. Aquaporins are channel proteins that allow the passage of water across the cell membrane.

Facilitated diffusion may be achieved as a consequence of charge gradients in addition to concentration gradients. Plant cells create an unequal distribution of charge across their plasma membrane by actively taking up or excluding ions. Active transport of protons by H^+ ATPases alters membrane potential allowing for facilitated passive transport of particular ions such as potassium down their charge gradient through high affinity transporters and channels.

https://en.wikipedia.org/wiki/Passive_transport

Pathway

A biological pathway is a series of actions among molecules in a cell that lea
tain product or a change in a cell. Such a pathway can trigger the assembly
cules, such as a fat or protein. Pathways can also turn genes on and off, or s
move. Some of the most common biological pathways are involved in metal
regulation of gene expression and the transmission of signals. Pathways pla
in advanced studies of genomics.

https://en.wikipedia.org/wiki/Biological_pathway

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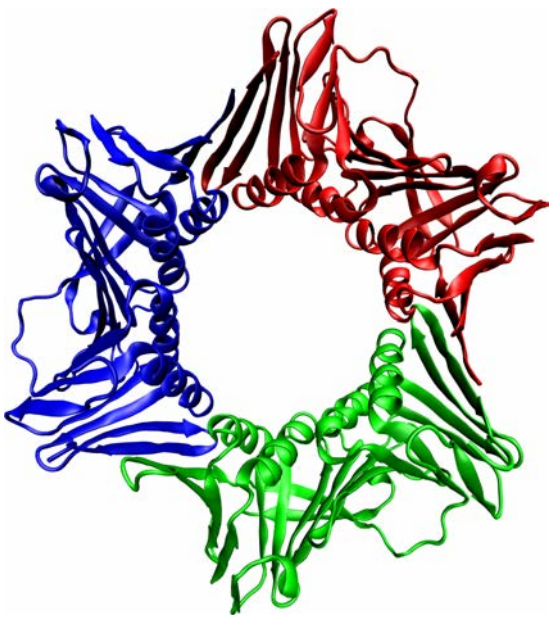
PCNA

Proliferating cell nuclear antigen (PCNA) is a DNA clamp that acts as a processivity factor for DNA polymerase δ in eukaryotic cells and is essential for replication. PCNA is a homotrimer and achieves its processivity by encircling the DNA, where it acts as a scaffold to recruit proteins involved in DNA replication, DNA repair, chromatin remodeling and epigenetics.

Many proteins interact with PCNA via the two known PCNA-interacting motifs PCNA-interacting peptide (PIP) box and AlkB homologue 2 PCNA interacting motif (APIM). Proteins binding to PCNA via the PIP-box are mainly involved in DNA replication whereas proteins binding to PCNA via APIM are mainly important in the context of genotoxic stress.

The protein encoded by this gene is found in the nucleus and is a cofactor of DNA polymerase delta. The encoded protein acts as a homotrimer and helps increase the processivity of leading strand synthesis during DNA replication. In response to DNA damage, this protein is ubiquitinated and is involved in the RAD6-dependent DNA repair pathway. Two transcript variants encoding the same protein have been found for this gene. Pseudogenes of this gene have been described on chromosome 4 and on the X chromosome.



https://en.wikipedia.org/wiki/Proliferating_cell_nuclear_antigen

PCR

The polymerase chain reaction (PCR) is a process used in molecular biology to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. In the first step, the two strands of the DNA double helix are physically separated at a high temperature in a process called DNA melting. In the second step, the temperature is lowered and the two DNA strands become templates for DNA polymerase to selectively amplify the target DNA. The selectivity of PCR results from the use of primers that are complementary to the DNA region targeted for amplification under specific thermal cycling conditions.

Developed in 1983 by Kary Mullis, PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications. These include DNA cloning for sequencing, DNA-based phylogeny, or functional analysis of genes, the diagnosis of hereditary diseases, the identification of genetic fingerprints (used in forensic sciences and DNA paternity testing), and the detection and diagnosis of infectious diseases. In 1993, Mullis was awarded the Nobel Prize in Chemistry along with Michael Smith for his work on PCR.

The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA fragments) containing sequences complementary to the target region along with a DNA polymerase, which the method is named after, are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the DNA template is exponentially amplified. PCR can be extensively modified to perform a wide array of genetic manipulations.

Almost all PCR applications employ a heat-stable DNA polymerase, such as Taq polymerase (an enzyme originally isolated from the bacterium *Thermus aquaticus*). This DNA polymerase enzymatically assembles a new DNA strand from DNA building-blocks, the nucleotides, by using single-stranded DNA as a template and DNA oligonucleotides (also called DNA primers), which are required for initiation of DNA synthesis. The vast majority of PCR methods use thermal cycling, i.e., alternately heating and cooling the PCR sample through a defined series of temperature steps.

https://en.wikipedia.org/wiki/Polymerase_chain_reaction

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PCTP

Phosphatidylcholine transfer protein (PCTP) also known as StAR-related li
domain protein 2 (STARD2) is a specific intracellular phospholipid bindin
that can transfer phosphatidylcholine between different membranes in the

In humans, phosphatidylcholine transfer protein is encoded by the PCTP g

https://en.wikipedia.org/wiki/Phosphatidylcholine_transfer_protein

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Chapter 2 - Structure & Function: Lipids

PDK1

The Pyruvate Dehydrogenase (PDH) complex must be tightly regulated due tral role in general metabolism. Within the complex, there are three serine the E1 component that are sites for phosphorylation. This phosphorylation the complex. In humans, there have been four isozymes of Pyruvate Dehyd nase that have been shown to phosphorylate these three sites: PDK1, PDK2 PDK4. PDK1 is the only enzyme capable of phosphorylating the 3rd serine s the TPP coenzyme is bound, the rates of phosphorylation by all four isozym tically affected. Specifically, the incorporation of phosphate groups by PDK 2 and 3 is significantly reduced.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase_lipoamide_kinas 1

Related Glossary Terms

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PDZ domain

The PDZ domain is a common structural domain of 80-90 amino-acids found in the signaling proteins of bacteria, yeast, plants, viruses and animals. Proteins containing PDZ domains play a key role in anchoring receptor proteins in the membrane to cytoskeletal components. PDZ is an acronym combining the first letters of three proteins — post synaptic density protein (PSD95), Drosophila disc large tumor suppressor (Dlg1), and zonula occludens-1 protein (zo-1) — which were first discovered to share the domain. PDZ domains have previously been referred to as DHR (Dlg homologous region) or GLGF (glycine-leucine-glycine-phenylalanine) domains. Proteins with these domains help hold together and organize signaling complexes at cellular membranes. Protein domains, connected by intrinsically disordered flexible linker regions, induce long-range allostery via protein domain dynamics. PDZ domains also play a highly significant role in the anchoring of cell surface receptors (such as CFTR[disambiguation needed] and FZD7) to the actin cytoskeleton via mediators like NHERF and ezrin.

In general PDZ domains bind to a short region of the C-terminus of other specific proteins. These short regions bind to the PDZ domain by β sheet augmentation. This means that the β sheet in the PDZ domain is extended by the addition of a further β strand from the tail of the binding partner protein.

https://en.wikipedia.org/wiki/PDZ_domain

Related Glossary Terms

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Pectin

Pectin is a structural heteropolysaccharide contained in the primary cell walls of terrestrial plants. It was first isolated and described in 1825 by Henri Braconnot. It is produced commercially as a white to light brown powder, mainly extracted from citrus fruits, and is used in food as a gelling agent, particularly in jams and jellies. It is also used in fillings, medicines, sweets, as a stabilizer in fruit juices and milk drinks, and as a source of dietary fiber.

In plant biology, pectin consists of a complex set of polysaccharides that are present in most primary cell walls and are particularly abundant in the non-woody parts of terrestrial plants. Pectin is a major component of the middle lamella, where it helps to bind cells together, but is also found in primary cell walls.

The amount, structure and chemical composition of pectin differs among plants, within a plant over time, and in various parts of a plant. Pectin is an important cell wall polysaccharide that allows primary cell wall extension and plant growth. During fruit ripening, pectin is broken down by the enzymes pectinase and pectinesterase, in which process the fruit becomes softer as the middle lamellae break down and cells become separated from each other. A similar process of cell separation caused by the breakdown of pectin occurs in the abscission zone of the petioles of deciduous plants at leaf fall.

https://en.wikipedia.org/wiki/Pectin

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https://en.wikipedia.org/wiki/Pectin

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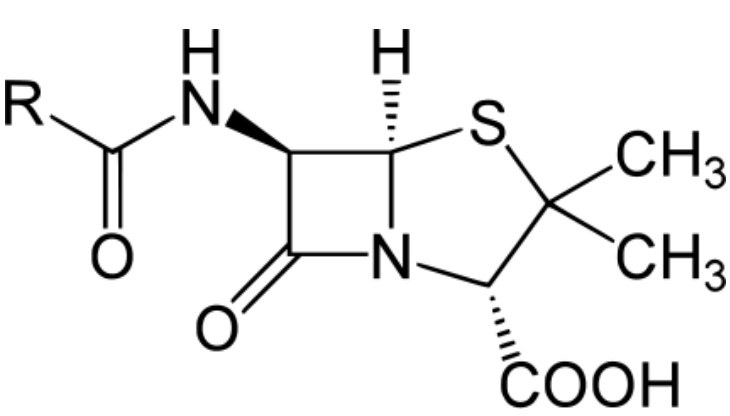
Penicillin

Penicillin (PCN or pen) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (oral use), procaine penicillin, and benzathine penicillin (intramuscular use). Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by *staphylococci* and *streptococci*. Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use.

About 10% of people report that they are allergic to penicillin, however, up to 90% of this group may not actually be allergic. Serious allergies only occur in about 0.03%. All penicillins are β-lactam antibiotics.

Penicillin was discovered in 1928 by Scottish scientist Alexander Fleming. People began using it to treat infections in 1942. There are several enhanced penicillin families which are effective against additional bacteria. These include the antistaphylococcal penicillins, aminopenicillins and the antipseudomonal penicillins. They are derived from *Penicillium* fungi.



https://en.wikipedia.org/wiki/Penicillin

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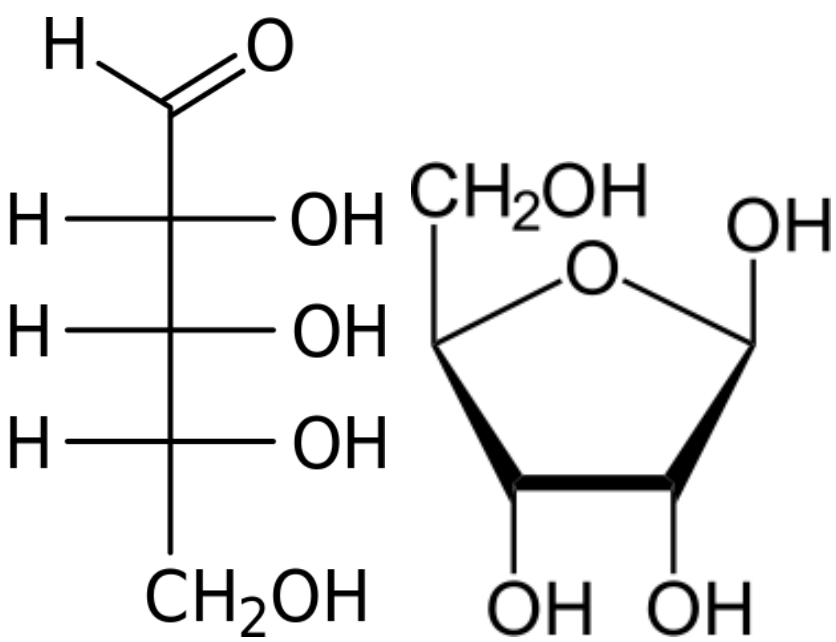
Pentose

A pentose is a monosaccharide with five carbon atoms. Pentoses are organ
two groups. Aldopentoses have an aldehyde functional group at position 1.
ses have a ketone functional group in position 2 or 3. Shown below is the p
bose in Fischer and Haworth forms.



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Pentose Phosphate Pathway

The pentose phosphate pathway (also called the phosphogluconate pathway and the hexose monophosphate shunt) is a metabolic pathway parallel to glycolysis that generates NADPH and pentoses (5-carbon sugars) as well as ribose 5-phosphate, a precursor for the synthesis of nucleotides. While it does involve oxidation of glucose, its primary role is anabolic rather than catabolic.

There are two distinct phases in the pathway. The first is the oxidative phase, in which NADPH is generated, and the second is the non-oxidative synthesis of 6-carbon sugars. For most organisms, the pentose phosphate pathway takes place in the cytosol. In plants, most steps take place in plastids.

The primary results of the pathway are:
• The generation of reducing equivalents, in the form of NADPH, used in reductive biosynthesis reactions within cells (e.g. fatty acid synthesis).
• Production of ribose 5-phosphate (R5P), used in the synthesis of nucleotides and nucleic acids.
• Production of erythrose 4-phosphate (E4P) used in the synthesis of aromatic amino acids.

Aromatic amino acids, in turn, are precursors for many biosynthetic pathways, including the lignin in wood. Dietary pentose sugars derived from the digestion of nucleic acids may be metabolized through the pentose phosphate pathway, and the carbon skeletons of dietary carbohydrates may be converted into glycolytic/gluconeogenic intermediates.

In mammals, the PPP occurs exclusively in the cytoplasm, and is found to be most active in the liver, mammary gland and adrenal cortex in the human. The PPP is one of the three main ways the body creates molecules with reducing power, accounting for approximately 60% of NADPH production in humans.

One of the uses of NADPH in the cell is to prevent oxidative stress. It reduces glutathione via glutathione reductase, which converts reactive H_2O_2 into H_2O by glutathione peroxidase. If absent, the H_2O_2 would be converted to hydroxyl free radicals by Fenton chemistry, which can attack the cell. Erythrocytes, for example, generate a large amount of NADPH through the pentose phosphate pathway to use in the reduction of glutathione. Hydrogen peroxide is also generated for phagocytes in a process often referred to as a respiratory burst.

https://en.wikipedia.org/wiki/Pentose_phosphate_pathway

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https://en.wikipedia.org/wiki/Pentose_phosphate_pathway

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PEPCK

Phosphoenolpyruvate carboxykinase (PEPCK) is an enzyme in the lyase family used in the metabolic pathway of gluconeogenesis. It converts oxaloacetate into phosphoenolpyruvate and carbon dioxide.

PEPCK-C catalyzes the rate-controlling step of gluconeogenesis, the process whereby glucose is synthesized. The enzyme has therefore been thought to be essential in glucose homeostasis, as evidenced by laboratory mice that contracted diabetes mellitus type 2 as a result of the overexpression of PEPCK-C.

The role that PEPCK-C plays in gluconeogenesis may be mediated by the citric acid cycle, the activity of which was found to be directly related to PEPCK-C abundance.

PEPCK-C levels alone were not highly correlated with gluconeogenesis in the mouse liver, as previous studies have suggested. While the mouse liver almost exclusively expresses PEPCK-C, humans equally present a mitochondrial isozyme (PEPCK-M). PEPCK-M has gluconeogenic potential per se. Therefore, the role of PEPCK-C and PEPCK-M in gluconeogenesis may be more complex and involve more factors than was previously believed.

It is found in two forms, cytosolic and mitochondrial.

https://en.wikipedia.org/wiki/Phosphoenolpyruvate_carboxykinase

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Pepsin

Pepsin is an enzyme that breaks down proteins into smaller peptides (that is
ase). It is produced in the stomach and is one of the main digestive enzymes
gestive systems of humans and many other animals, where it helps digest the
in food.

It is one of three principal proteases in the human digestive system, the othe
ing chymotrypsin and trypsin. During the process of digestion, these enzyme
which is specialized in severing links between particular types of amino acids
rate to break down dietary proteins into their components, i.e., peptides and
ids, which can be readily absorbed by the small intestine. Pepsin is most effic
cleaving peptide bonds between hydrophobic and preferably aromatic amino
such as phenylalanine, tryptophan, and tyrosine.

https://en.wikipedia.org/wiki/Pepsin

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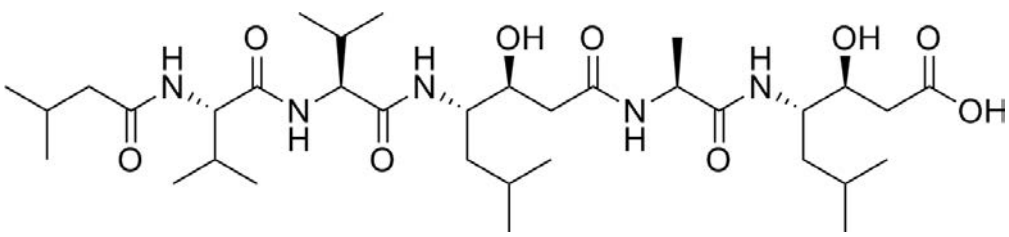
Pepstatin

Pepstatin is a potent inhibitor of aspartyl proteases. It is a hexa-peptide containing the unusual amino acid statine (Sta, (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid), having the sequence Isovaleryl-Val-Val-Sta-Ala-Sta (Iva-Val-Val-Sta-Ala-Sta). It was originally isolated from cultures of various species of *Actinomyces* due to its ability to inhibit pepsin at picomolar concentrations. Pepstatin A is well known to be an inhibitor of aspartic proteinases such as pepsin, cathepsins D and E. Except for its role as a proteinase inhibitor, however, the pharmacological action of pepstatin A upon cells remain unclear.

Pepstatin A suppresses receptor activator of NF-κB ligand (RANKL)–induced osteoclast differentiation. Pepstatin A suppresses the formation of multinuclear osteoclasts dose-dependently. This inhibition of the formation only affected osteoclast cells, i.e., not osteoblast-like cells. Furthermore, pepstatin A also suppresses differentiation from pre-osteoclast cells to mononuclear osteoclast cells dose-dependently. This inhibition seems to be independent of the activities of proteinases such as cathepsin D, because the formation of osteoclasts was not suppressed with the concentration that inhibited the activity of cathepsin D.

Cell signaling analysis indicated that the phosphorylation of ERK was inhibited in pepstatin A-treated cells, while the phosphorylation of IκB and Akt showed almost no change. Furthermore, pepstatin A decreased the expression of nuclear factor of activated T cells c1 (NFATc1). These results suggest that pepstatin A suppresses the differentiation of osteoclasts through the blockade of ERK signaling and the inhibition of NFATc1 expression.

Pepstatin is practically insoluble in water, chloroform, ether, and benzene, however it can be dissolved in methanol, ethanol, and DMSO with acetic acid, to between 1 and 5 mg/ml.



https://en.wikipedia.org/wiki/Pepstatin

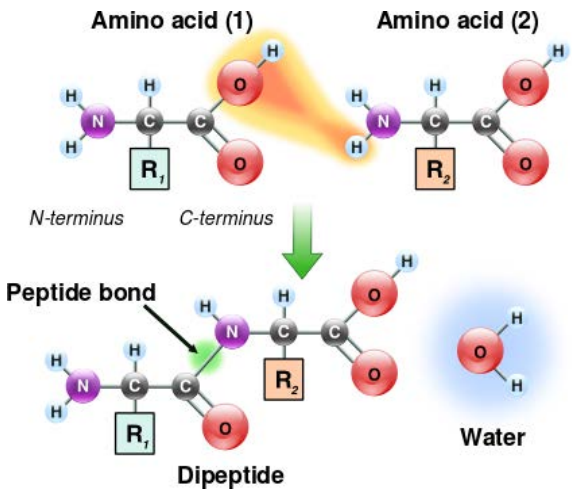
Peptide Bond

A peptide bond (amide bond) is a covalent chemical bond formed between two amino acid molecules.

When two amino acids form a dipeptide through a peptide bond it is called condensation. In condensation, two amino acids approach each other, with the acid moiety of one coming near the amino moiety of the other. One loses a hydrogen and oxygen from its carboxyl group (COOH) and the other loses a hydrogen from its amino group (NH_2). This reaction produces a molecule of water (H_2O) and two amino acids joined by a peptide bond (-CO-NH-). The two joined amino acids are called a dipeptide.

The peptide bond is synthesized when the carboxyl group of one amino acid molecule reacts with the amino group of the other amino acid molecule, causing the release of a molecule of water (H_2O), hence the process is a dehydration synthesis reaction (also known as a condensation reaction).

The formation of the peptide bond consumes energy, which, in living systems, is derived from ATP. Polypeptides and proteins are chains of amino acids held together by peptide bonds. Living organisms employ enzymes to produce polypeptides, and ribosomes to produce proteins. Peptides are synthesized by specific enzymes. For example, the tripeptide glutathione is synthesized in two steps from free amino acids, by two enzymes: γ-glutamylcysteine synthetase and glutathione synthetase.



https://en.wikipedia.org/wiki/Peptide_bond

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Peptide Hormone

Peptide hormones and protein hormones are hormones whose molecules are peptides or proteins, respectively. The latter have longer amino acid chain lengths than the former. These hormones have an effect on the endocrine system of animals, including humans. Most hormones can be classified as either amino acid–based hormones (amine, peptide, or protein) or steroid hormones. The former are water-soluble and act on the surface of target cells via second messengers - the latter, being lipid-soluble, move through the plasma membranes of target cells (both cytoplasmic and nuclear) to act within their nuclei.

Like all peptides and proteins, peptide hormones and protein hormones are synthesized in cells from amino acids according to mRNA transcripts, which are synthesized from DNA templates inside the cell nucleus. Preprohormones, peptide hormone precursors, are then processed in several stages, typically in the endoplasmic reticulum, including removal of the N-terminal signal sequence and sometimes glycosylation, resulting in prohormones. The prohormones are then packaged into membrane-bound secretory vesicles, which can be secreted from the cell by exocytosis in response to specific stimuli (e.g. --an increase in Ca^{2+} and cAMP concentration in cytoplasm).

https://en.wikipedia.org/wiki/Peptide_hormone

Related Glossary Terms

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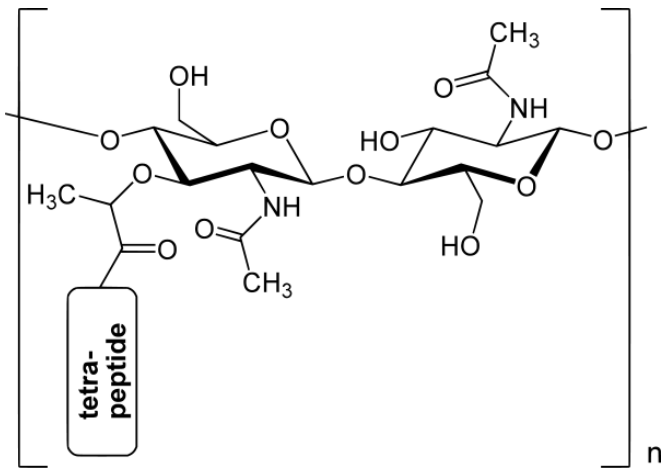
Peptidoglycan

Peptidoglycan, also known as murein, is a polymer consisting of sugars and amino acids that forms a mesh-like layer outside the plasma membrane of most bacteria, forming the cell wall. The sugar component consists of alternating residues of β-(1,4) linked N-acetylglucosamine and N-acetylmuramic acid. Attached to the N-acetylmuramic acid is a peptide chain of three to five amino acids. The peptide chain can be cross-linked to the peptide chain of another strand forming the 3D mesh-like layer. Peptidoglycan serves a structural role in the bacterial cell wall, giving structural strength, as well as counteracting the osmotic pressure of the cytoplasm. A common misconception is that peptidoglycan gives the cell its shape; however, whereas peptidoglycan helps maintain the structural strength of the cell, it is actually the MreB protein that facilitates cell shape. Peptidoglycan is also involved in binary fission during bacterial cell reproduction.

The peptidoglycan layer is substantially thicker in Gram-positive bacteria (20 to 80 nanometers) than in Gram-negative bacteria (7 to 8 nanometers), with the attachment of the S-layer. Peptidoglycan forms around 90% of the dry weight of Gram-positive bacteria but only 10% of Gram-negative strains. Thus, presence of high levels of peptidoglycan is the primary determinant of the characterization of bacteria as Gram-positive. In Gram-positive strains, it is important in attachment roles and serotyping purposes. For both Gram-positive and Gram-negative bacteria, particles of approximately 2 nm can pass through the peptidoglycan.



https://en.wikipedia.org/wiki/Peptidoglycan

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Peptidyl Transferase Center

The Peptidyl transferase is an aminoacyltransferase (EC 2.3.2.12) as well as the
mary enzymatic function of the ribosome, which forms peptide bonds between
cent amino acids using tRNAs during the translation process of protein biosynt
Peptidyl transferase activity is carried out by the ribosome. Peptidyl transferase
ity is not mediated by any ribosomal proteins but by ribosomal RNA (rRNA), a
zyme. Ribozymes are the only enzymes which are not made up of proteins, but
cleotides. All other enzymes are made up of proteins. This RNA relic is the mos
cant piece of evidence supporting the RNA World hypothesis.

• In prokaryotes, the 50S (23S component) ribosome subunit contains the pept
transferase component and acts as a ribozyme.
In eukaryotes, the 60S (28S component) ribosome subunit contains the peptidy
ferase component and acts as the ribozyme.

https://en.wikipedia.org/wiki/Peptidyl_transferase

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Perfect Enzymes

A diffusion limited enzyme (also called a perfect enzyme) is an enzyme whi
a reaction so efficiently that the rate limiting step is that of substrate diffusi
active site, or product diffusion out. This is also known as kinetic perfection
perfection. Since the rate of catalysis of such enzymes is set by the diffusion
reaction, it therefore represents an intrinsic, physical constraint on evolutio
mum peak height in the fitness landscape). Diffusion limited perfect enzym
rare. Most enzymes catalyze their reactions to a rate that is 1,000-10,000 ti
than this limit. This is due to both the chemical limitations of difficult react
the evolutionary limitations that such high reaction rates do not confer any
ness.

https://en.wikipedia.org/wiki/Diffusion_limited_enzyme

Related Glossary Terms

Drag related terms here

Perilipins

Perilipin is a protein that coats lipid droplets in adipocytes, the fat-storing cells in adi
pose tissue. Perilipin acts as a protective coating from the body's natural lipases, such
as hormone-sensitive lipase, which break triglycerides into glycerol and free fatty acid
for use in metabolism, a process called lipolysis. In humans, perilipin is expressed in
three different isoforms, A, B, and C, and perilipin A is the most abundant protein ass
ciated with the adipocyte lipid droplets.

Perilipin is hyperphosphorylated by PKA following β-adrenergic receptor activation.
Phosphorylated perilipin changes conformation, exposing the stored lipids to
hormone-sensitive lipase-mediated lipolysis. Although PKA also phosphorylates
hormone-sensitive lipase, which can increase its activity, the more than 50-fold in-
crease in fat mobilization (triggered by epinephrine) is primarily due to perilipin pho
phorylation. Perilipin is an important regulator of lipid storage.

https://en.wikipedia.org/wiki/Perilipin

Related Glossary Terms

Drag related terms here

Periostin

Periostin is a secreted extracellular matrix protein that was originally identifie
from the mesenchymal lineage (osteoblasts, osteoblast-derived cells, the perioc
ligament, and periosteum). It has been associated with the epithelial-mesenchy
transition in cancer and with the differentiation of mesenchyme in the developi
heart. This protein shares a homology with fasciclin I, a secreted cell adhesion r
cule found in insects. While periostin plays a wide variety of roles in tissue deve
ment along with disease, its function in tissue remodeling as a response to inju
common underlying role in these different mechanisms. Periostin is transientl
lated during cell fate changes, whether they are related to alterations in physiol
to pathological changes. It influences extracellular matrix restructuring, tissue
ing, and the epithelial-mesenchymal transition, all of which can be related to ti
healing, development, and disease. Thus, it functions as a mediator, balancing a
priate and inappropriate responses to tissue damage.

https://en.wikipedia.org/wiki/Periostin

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Peripheral Membrane Proteins

Peripheral Membrane Proteins are membrane proteins that adhere only temporarily to the biological membrane with which they are associated. These proteins attach to integral membrane proteins, or penetrate the peripheral regions of the lipid bilayer. The regulatory protein subunits of many ion channels and transmembrane receptors, for example, may be defined as peripheral membrane proteins. In contrast to integral membrane proteins, peripheral membrane proteins tend to collect in the water-soluble component, or fraction, of all the proteins extracted during a protein purification procedure. Proteins with GPI anchors are an exception to this rule and can have purification properties similar to those of integral membrane proteins.

The reversible attachment of proteins to biological membranes has shown to regulate cell signaling and many other important cellular events, through a variety of mechanisms. For example, the close association between many enzymes and biological membranes may bring them into close proximity with their lipid substrate(s). Membrane binding may also promote rearrangement, dissociation, or conformational changes within many protein structural domains, resulting in an activation of their biological activity. Additionally, the positioning of many proteins are localized to either the inner or outer surfaces or leaflets of their resident membrane. This facilitates the assembly of multi-protein complexes by increasing the probability of any appropriate protein–protein interactions.

https://en.wikipedia.org/wiki/Peripheral_membrane_protein

Related Glossary Terms

Drag related terms here

Peripheral Nervous System

The peripheral nervous system (PNS) is the part of the nervous system that consis
the nerves and ganglia on the outside of the brain and spinal cord. The main funct
of the PNS is to connect the central nervous system (CNS) to the limbs and organs
sentially serving as a communication relay going back and forth between the brain
spinal cord with the rest of the body. Unlike the CNS, the PNS is not protected by
bone of spine and skull, or by the blood–brain barrier, which leaves it exposed to t
ins and mechanical injuries. The peripheral nervous system is mainly divided into
somatic nervous system and the autonomic nervous system. In the somatic nervou
tem, the cranial nerves are part of the PNS with the exception of cranial nerve II, t
optic nerve, along with the retina. The second cranial nerve is not a true peripher
nerve but a tract of the diencephalon. Cranial nerve ganglia originate in the CNS.
ever, the remaining ten cranial nerve axons extend beyond the brain and are there
considered part of the PNS. The Autonomic nervous system is an involuntary cont
of smooth muscle. The connection between CNS and organs allows the system to b
two different functional states: sympathetic and parasympathetic.

https://en.wikipedia.org/wiki/Peripheral_nervous_system

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Peripherin

Peripherin is a type III Intermediate filament (IF) protein expressed mainly in neu
of the peripheral nervous system (PNS). It is also found in neurons of the central n
ous system (CNS) that have projections toward peripheral structures, such as spin
motor neurons. Its size, structure, and sequence/location of protein motifs is simi
other type III IF proteins such as desmin, vimentin and glial fibrillary acidic prote
(GFAP). Like these proteins, peripherin can self-assemble to form homopolymeric
mentous networks (networks formed from peripherin protein dimers), but it can a
heteropolymerize with neurofilaments in several neuronal types. This protein in h
mans is encoded by the PRPH gene. Peripherin is thought to play a role in neurite
gation during development and axonal regeneration after injury, but its exact func
is unknown. It is also associated with some of the major neuropathologies that cha
terize amyotropic lateral sclerosis (ALS), but despite extensive research into how n
filaments and peripherin contribute to ALS, their role in this disease is still unider
fied.

https://en.wikipedia.org/wiki/Peripherin

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Periplasmic Space

The periplasm is a concentrated gel-like matrix in the space between the inner cytoplasmic membrane and the bacterial outer membrane called the periplasmic space in gram-negative bacteria. It has been found using cryo-electron microscopy, that a much smaller periplasmic space is present in gram-positive bacteria.

The periplasm may constitute up to 40% of the total cell volume of gram-negative bacteria, and this is a much smaller percentage in gram-positive bacteria.

Although the bacteria are conventionally divided into two main groups — gram-positive and gram-negative, based upon their Gram-stain retention property — this classification system is ambiguous as it can refer to three distinct aspects (staining result, cell-envelope organization, taxonomic group), which do not necessarily coalesce for some bacterial species. However, although Gram-staining response of bacteria is an empirical criterion, its basis lies in the marked differences in the ultrastructure and chemical composition of the two main kinds of bacteria. These bacteria are distinguished from each other based on the presence or absence of an outer lipid membrane, which is a more reliable and fundamental characteristic of the bacterial cells.

https://en.wikipedia.org/wiki/Periplasm

Related Glossary Terms

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Peroxidase

Peroxidases are a large family of enzymes that typically catalyze a reaction o

$$ROOR' + \text{electron donor } (2\ e^-) + 2H^+ \rightarrow ROH + R'OH$$

For many of these enzymes the optimal substrate is hydrogen peroxide, but more active with organic hydroperoxides such as lipid peroxides. Peroxidas tain a heme cofactor in their active sites, or alternately redox-active cystein cysteine residues.

https://en.wikipedia.org/wiki/Peroxidase

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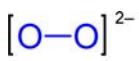
Peroxide

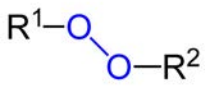
A peroxide is a compound containing an oxygen–oxygen single bond or the peroxide anion, $O^{=}$

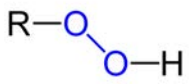
The O–O group is called the peroxide group or peroxo group. In contrast to oxide ions, the oxygen atoms in the peroxide ion have an oxidation state of –1.

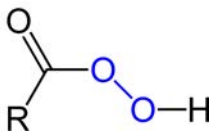
The simplest stable peroxide is hydrogen peroxide. Superoxides, dioxygenyls, ozones and ozonides are considered separately. Peroxide compounds can be roughly classified into organic and inorganic. Whereas the inorganic peroxides have an ionic, salt-like character, the organic peroxides are dominated by the covalent bonds. The oxygen–oxygen chemical bond of peroxide is unstable and easily split into reactive radicals via homolytic cleavage. For this reason, peroxides are found in nature only in small quantities, in water, atmosphere, plants, and animals. Peroxide ion formation has recently been highlighted as one of the main mechanisms by which oxides accommodate excess oxygen in ionic crystals and may have a large impact on a range of industrial applications including solid oxide fuel cells.

Peroxides have a bleaching effect on organic substances and therefore are added to some detergents and hair colorants. Other large-scale applications include medicine and chemical industry, where peroxides are used in various synthesis reactions or occur as intermediate products. With an annual production of over 2 million tonnes, hydrogen peroxide is the most economically important peroxide. Many peroxides are unstable and hazardous substances. They cannot be stored and therefore are synthesized *in situ* and used immediately. Different peroxide types are shown below.









https://en.wikipedia.org/wiki/Peroxide

Peroxiredoxins

Peroxiredoxins are a ubiquitous family of antioxidant enzymes that also co
cytokine-induced peroxide levels and thereby mediate signal transduction i
ian cells. The family members in humans are PRDX1, PRDX2, PRDX3, PRD
PRDX5, and PRDX6. The physiological importance of peroxiredoxins is illu
their relative abundance (one of the most abundant proteins in erythrocyte
moglobin is peroxiredoxin. Peroxiredoxins are proposed to play a role in ce
by regulating H_2O_2 levels.

https://en.wikipedia.org/wiki/Peroxiredoxin

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Peroxisomes

Peroxisomes are organelles found in virtually all eukaryotic cells. They are involved in the catabolism of very long chain fatty acids, branched chain fatty acids, D-amino acids, and polyamines, reduction of reactive oxygen species - specifically hydrogen peroxide - and biosynthesis of plasmalogens, i.e. ether phospholipids critical for the normal function of mammalian brains and lungs. They also contain approximately 10% of the total activity of two enzymes in the pentose phosphate pathway, which is important for energy metabolism. It is vigorously debated if peroxisomes are involved in isoprenoid and cholesterol synthesis in animals. Other known peroxisomal functions include the glyoxylate cycle in germinating seeds ("glyoxysomes"), photorespiration in leaves, glycolysis in trypanosomes ("glycosomes"), and methanol and/or amine oxidation and assimilation in some yeasts.

Peroxisomes were identified as organelles by the Belgian cytologist Christian de Duve in 1967 after they had been first described by a Swedish doctoral student, J. Rhodin in 1954.

https://en.wikipedia.org/wiki/Peroxisome

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Peroxynitrite

Peroxynitrite (sometimes called peroxonitrite) is an ion with the formula ONOO. It is an unstable structural isomer of nitrate, NO. Although its conjugate acid is highly reactive, peroxynitrite is stable in basic solutions. It is prepared by the reaction of hydrogen peroxide with nitrite. Peroxynitrite is an oxidant and nitrating agent. Because of its oxidizing properties, peroxynitrite can damage a wide array of molecules in cells, including DNA and proteins.

Peroxynitrite is prepared by the reaction of hydrogen peroxide with nitrite:

$H_2O_2 + NO_2^= \rightarrow ONOO^- + H_2O$

Peroxynitrite is an oxidant and nitrating agent. Because of its oxidizing properties, peroxynitrite can damage a wide array of molecules in cells, including DNA and proteins. Formation of peroxynitrite *in vivo* has been ascribed to the reaction of the free radical superoxide with the free radical nitric oxide:

$\bullet O_2^- + \bullet NO \rightarrow ONO_2^-$

The resultant pairing of these two free radicals results in peroxynitrite, a molecule that is itself not a free radical, but that is a powerful oxidant.

In the laboratory, a solution of peroxynitrite can be prepared by treating acidified hydrogen peroxide with a solution of sodium nitrite, followed by rapid addition of NaOH. Its concentration is indicated by the absorbance at 302 nm

https://en.wikipedia.org/wiki/Peroxynitrite

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PFK-1

Phosphofructokinase-1 (PFK-1) is one of the most important regulatory enzymes of glycolysis. It is an allosteric enzyme made of 4 subunits and controlled by many activators and inhibitors. PFK-1 catalyzes the important "committed" step of glycolysis, the conversion of fructose 6-phosphate and ATP to fructose 1,6-bisphosphate and ADP.

F6P + ATP <=> F1,6BP + ADP

Glycolysis is the foundation for respiration, both anaerobic and aerobic. Because phosphofructokinase (PFK) catalyzes the ATP-dependent phosphorylation to convert fructose-6-phosphate into fructose 1,6-bisphosphate and ADP, it is one of the key regulatory and rate limiting steps of glycolysis. PFK is able to regulate glycolysis through allosteric inhibition, and in this way, the cell can increase or decrease the rate of glycolysis in response to the cell's energy requirements. For example, a high ratio of ATP to ADP will inhibit PFK and glycolysis. The key difference between the regulation of PFK in eukaryotes and prokaryotes is that in eukaryotes PFK is activated by fructose 2,6-bisphosphate. The purpose of fructose 2,6-bisphosphate is to supersede ATP inhibition, thus allowing eukaryotes to have greater sensitivity to regulation by hormones like glucagon and insulin.

https://en.wikipedia.org/wiki/Phosphofructokinase_1

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PFK-2

Phosphofructokinase 2 (PFK2) or fructose bisphosphatase 2 (FBPase2), is a
responsible for regulating the rates of glycolysis and gluconeogenesis in the
body. It is a homodimer of 55 kDa subunits arranged in a head-to-head fash
each polypeptide chain consisting of independent kinase and phosphatase d
When Ser-32 of the bifunctional protein is phosphorylated, the negative cha
the conformation change of the enzyme to favor the FBPase2 activity. Othe
PFK2 activity is favored. The PFK2 domain is closely related to the superfa
mononucleotide binding proteins including adenylate cyclase, whereas that
is related to a family of proteins that include phosphoglycerate mutases.

https://en.wikipedia.org/wiki/Phosphofructokinase_2

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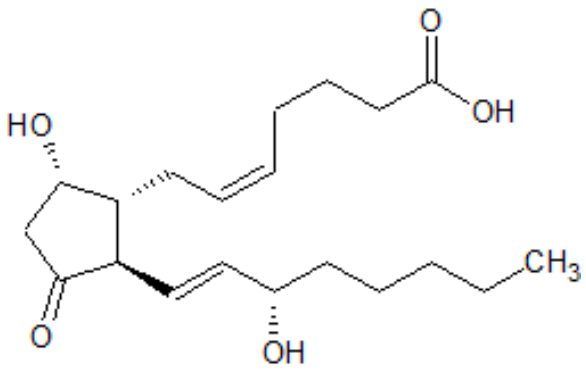
PGD_2

Prostaglandin D_2 (or PGD_2) is a prostaglandin that binds to the receptor PTGDR (DP1), as well as CRTH2 (DP2). It is a major prostaglandin produced by mast cells – recruits Th2 cells, eosinophils, and basophils. In mammalian organs, large amounts of PGD_2 are found only in the brain and in mast cells. It is critical to development of allergic diseases such as asthma.

Research carried out in 1989 found PGD_2 is the primary mediator of vasodilation (the "niacin flush") after ingestion of niacin (nicotinic acid).

A 2012 research paper indicates a causal link between elevated levels of localized PGD_2 and hair growth inhibition. Applied topically, the researchers found PGD_2 prevents hair growth, and mice that were genetically inclined to produce higher levels of PGD_2 had inhibited hair growth. The researchers also found PGD_2 levels were much higher in balding scalp tissue than nonbalding scalp tissue, through increased levels of prostaglandin D_2 synthase. The paper suggested that inhibition of hair growth involved binding of PGD_2 to a receptor called GPR44, and that GPR44 therefore would be a therapeutic target for androgenic alopecia in both men and women with hair loss and thinning. Because PGD_2's relation to asthma has been known for several years, several drugs that seek to reduce the effect of PGD_2 through blocking the GPR44 are already in clinical trials.

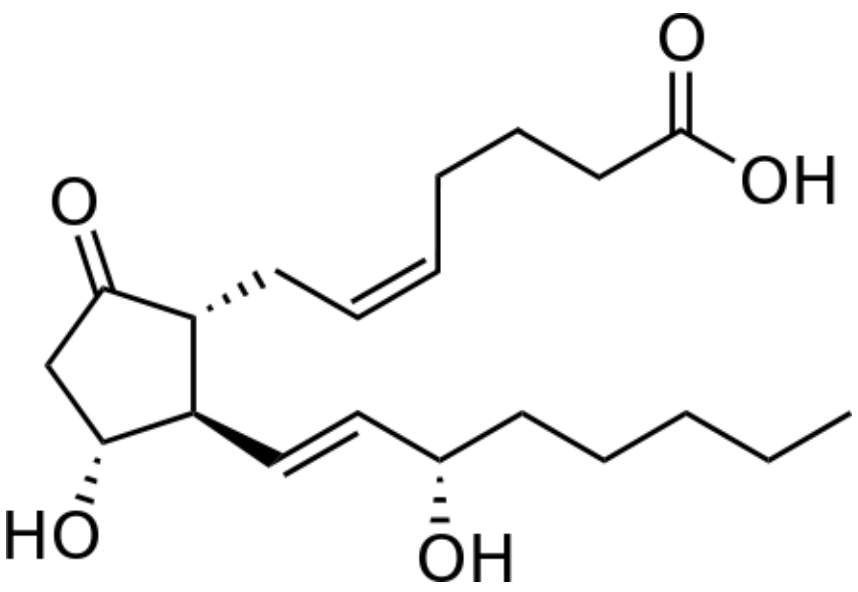


https://en.wikipedia.org/wiki/Prostaglandin_D_2

PGE_2

The naturally occurring prostaglandin E_2 (PGE_2) is known in medicine as dinoprostone. It has important effects in labor (softening the cervix and causing uterine contraction) and also stimulates osteoblasts to release factors that stimulate bone resorption by osteoclasts. PGE_2 is also the prostaglandin that ultimately induces fever.

PGE2 also suppresses T cell receptor signaling and may play a role in resolution of inflammation.



https://en.wikipedia.org/wiki/Prostaglandin_E2

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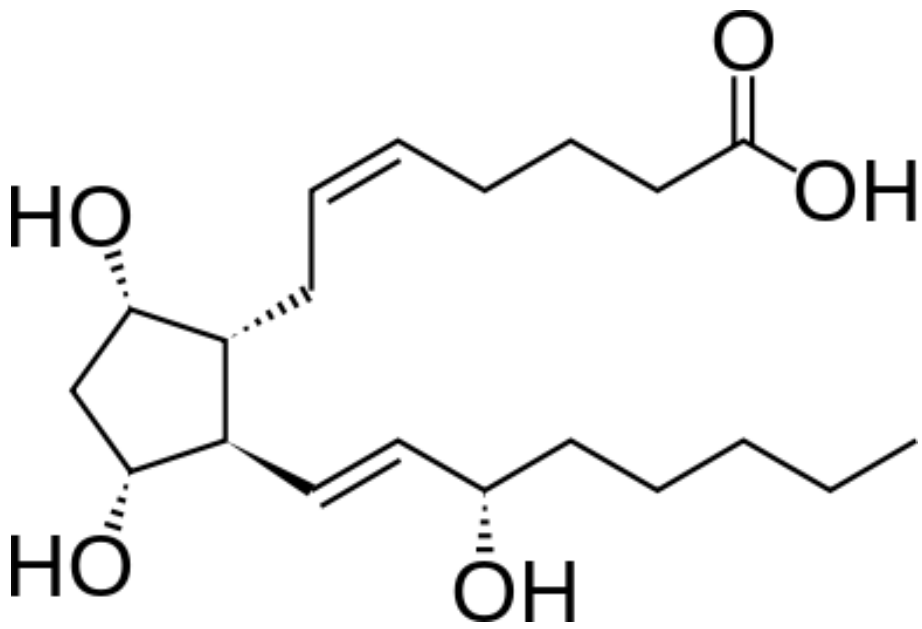
Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

$PGF_{2\alpha}$

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$ in prostanoid nomenclature), pharmaceutically termed dinoprost (INN), is a naturally occurring prostaglandin used in medicine to induce labor and as an abortifacient.

In domestic mammals, it is produced by the uterus when stimulated by oxytocin, in the event that there has been no implantation during the follicular phase. It acts on the corpus luteum to cause luteolysis, forming a corpus albicans and stopping the production of progesterone. Action of $PGF_{2\alpha}$ is dependent on the number of receptors on the corpus luteum membrane.



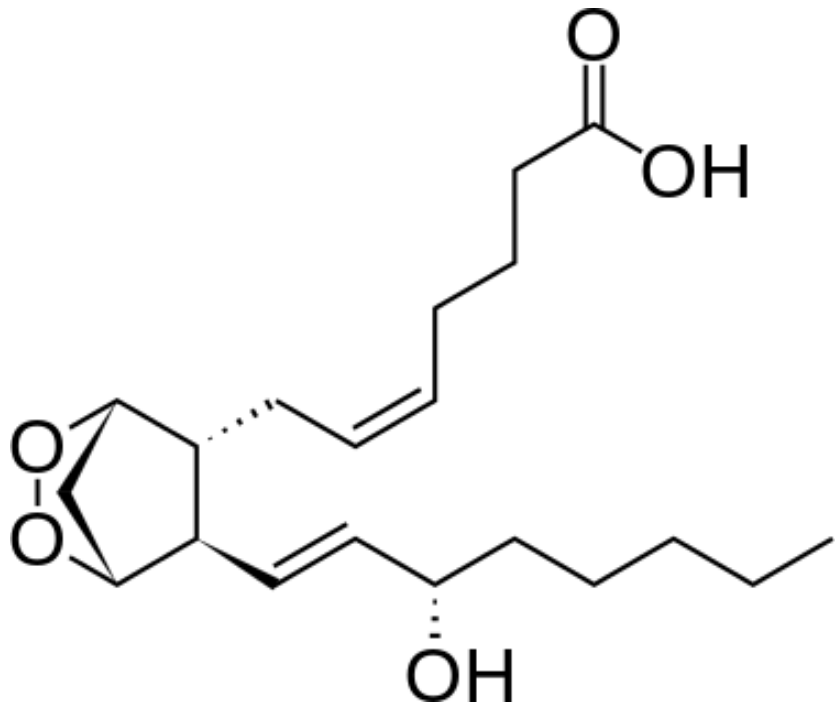
https://en.wikipedia.org/wiki/Prostaglandin_F2alpha

Related Glossary Terms

Drag related terms here

PGH_2

Prostaglandin H_2 is a type of prostaglandin and a precursor for many other biologicall
significant molecules. It is synthesized from arachidonic acid in a reaction catalyzed b
a cyclooxygenase enzyme.



https://en.wikipedia.org/wiki/Prostaglandin_H2

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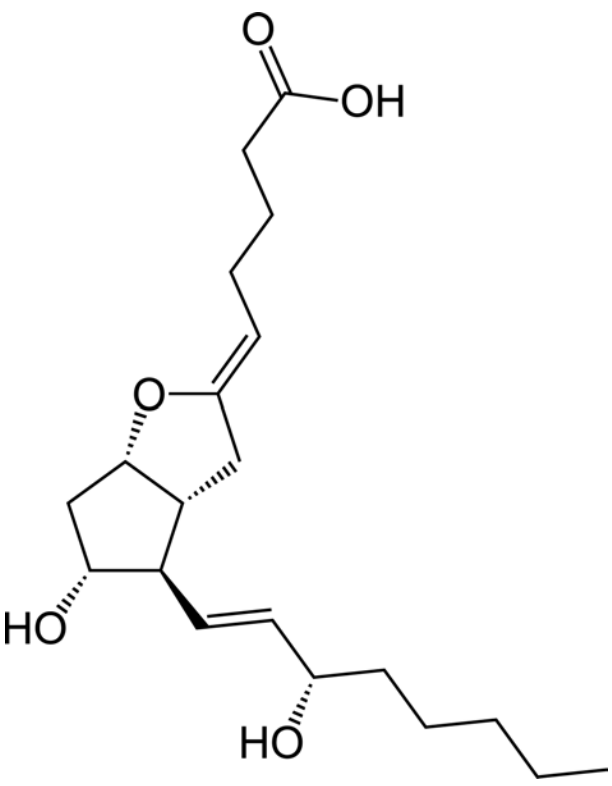
PGI_2

Prostacyclin (also called prostaglandin I_2 or PGI_2) is a prostaglandin member of the eicosanoid family of lipid molecules. It inhibits platelet activation and is also an effective vasodilator.

As a drug, it is also known as "epoprostenol".



https://en.wikipedia.org/wiki/Prostacyclin

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pH

pH is a numeric scale used to specify the acidity or basicity (alkalinity) of an aqueous solution. It is roughly the negative of the logarithm to base 10 of the molar concentration, measured in units of moles per liter, of hydrogen ions. More precisely it is the negative of the logarithm to base 10 of the activity of the hydrogen ion. Solutions with a pH less than 7 are acidic and solutions with a pH greater than 7 are basic. Pure water is neutral, being neither an acid nor a base. Contrary to popular belief, the pH value can be less than 0 or greater than 14 for very strong acids and bases respectively.

https://en.wikipedia.org/wiki/PH

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Phagocytes

Phagocytes are cells that protect the body by ingesting (phagocytosing) harmful foreign particles, bacteria, and dead or dying cells. During an infection, chemical signals attract phagocytes to places where the pathogen has invaded the body. These chemicals may come from bacteria or from other phagocytes already present. The phagocytes move by a method called chemotaxis. When phagocytes come into contact with bacteria, the receptors on the phagocyte's surface will bind to them. This binding will lead to the engulfing of the bacteria by the phagocyte. Some phagocytes kill the ingested pathogen with oxidants and nitric oxide.

After phagocytosis, macrophages and dendritic cells can also participate in antigen presentation, a process in which a phagocyte moves parts of the ingested material back to its surface. This material is then displayed to other cells of the immune system. Some phagocytes then travel to the body's lymph nodes and display the material to white blood cells called lymphocytes. This process is important in building immunity, and many pathogens have evolved methods to evade attacks by phagocytes.

https://en.wikipedia.org/wiki/Phagocyte

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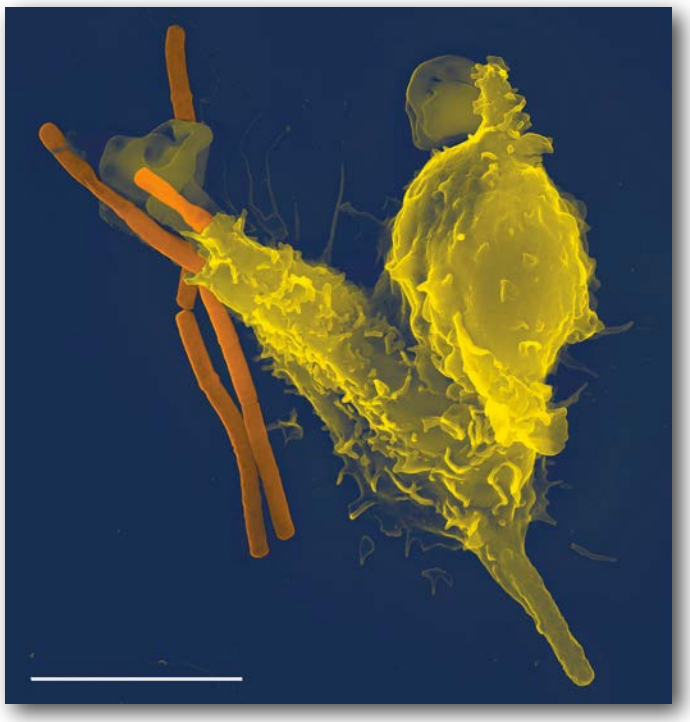
Phagocytosis

Phagocytosis is a specific form of endocytosis involving the vascular internalization of solids such as bacteria by an organism, and is therefore distinct from other forms of endocytosis such as the vesicular internalization of various liquids (pinocytosis). Phagocytosis is involved in the acquisition of nutrients for some cells. The process is homologous to eating at the level of single-celled organisms. In multicellular animals, the process has been adapted to eliminate debris and pathogens, as opposed to taking in fuel for cellular processes, except in the case of the animal *Trichoplax*. In an organism's immune system, phagocytosis is a major mechanism used to remove pathogens and cell debris.

For example, when a macrophage ingests a pathogenic microorganism, the pathogen becomes trapped in a phagosome which then fuses with a lysosome to form a phagolysosome. Within the phagolysosome, enzymes and toxic peroxides digest the pathogen. Bacteria, dead tissue cells, and small mineral particles are all examples of objects that may be phagocytized.



https://en.wikipedia.org/wiki/Phagocytosis

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Phagolysosome

A phagolysosome is a cytoplasmic body formed by the fusion of a phagoson
ing ingested particles, with a lysosome containing hydrolytic enzymes. Afte
food particles or pathogens contained within the phagosome are usually dig
the hydrolytic enzymes contained within the lysosome. Products of the dige
ther moved into the cytoplasm (useful materials) or exported by exocytosis
some formation follows phagocytosis. It is common in immunological funct
macrophages and forms the home of several infectious agents including *Le*

https://en.wikipedia.org/wiki/Phagolysosome

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Chapter 3 - Membranes: Other Considerations

Chapter 9 - Point by Point: Membranes

Phagosome

A phagosome is a vesicle formed around a particle absorbed by phagocytosis. T
ole is formed by the fusion of the cell membrane around the particle. A phagoso
cellular compartment in which pathogenic microorganisms can be killed and di
Phagosomes fuse with lysosomes in their maturation process, forming phagolys
somes.

Some bacterial pathogens that enter cells inside phagosomes either reproduce i
the formed phagolysosome (e.g. *Coxiella* spp.) or escape into the cytoplasm bef
phagosome fuses with the lysosome (e.g. Rickettsia spp.). Many mycobacteria,
ing *Mycobacterium tuberculosis* and *Mycobacteria avium paratuberculosis*, m
late the host macrophage to prevent nitrous acid-containing lysosomes from fu
with phagosomes and creating mature phagolysosomes. Such incomplete matu
of the phagosome maintains an environment favorable to the pathogens inside

https://en.wikipedia.org/wiki/Phagosome

Related Glossary Terms

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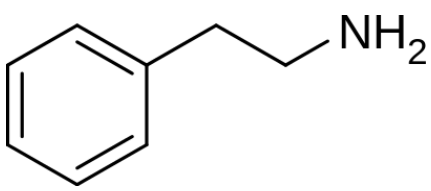
Phenethylamine

Phenethylamine (PEA), also known as β-phenylethylamine (β-PEA) and 2-phenylethylamine is an organic compound and a natural monoamine alkaloid, a trace amine, and also the name of a class of chemicals with many members that are well known for their psychoactive and stimulant effects.

Phenylethylamine functions as a monoaminergic neuromodulator and, to a lesser extent, a neurotransmitter in the human central nervous system. It is biosynthesized from the amino acid L-phenylalanine by enzymatic decarboxylation via the enzyme aromatic L-amino acid decarboxylase. In addition to its presence in mammals, phenethylamine is found in many other organisms and foods, such as chocolate, especially after microbial fermentation. It is sold as a dietary supplement for purported mood and weight loss-related therapeutic benefits. However, orally ingested phenethylamine experiences extensive first-pass metabolism by monoamine oxidase B (MAO-B) and then aldehyde dehydrogenase (ALDH), which metabolize it into phenylacetic acid. This prevents significant concentrations from reaching the brain when taken in low doses.



https://en.wikipedia.org/wiki/Phenethylamine

Related Glossary Terms

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Phenotypic

A phenotype (from Greek phainein, meaning "to show", and typos, meaning "type") is the composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties, phenology, behavior, and products of behavior (such as a bird's nest). A phenotype results from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two. When two or more clearly different phenotypes exist in the same population of a species, the species is called polymorph.

The genotype of an organism is the inherited instructions it carries within its genome.

This genotype-phenotype distinction was proposed by Wilhelm Johannsen in 1911 to make clear the difference between an organism's heredity and what that heredity produces. The distinction is similar to that proposed by August Weismann, who distinguished between germ plasm (heredity) and somatic cells (the body). The genotype-phenotype distinction should not be confused with Francis Crick's central dogma of molecular biology, which is a statement about the directionality of molecular sequential information flowing from DNA to protein, and not the reverse.

Richard Dawkins in 1978 and then again in his 1982 book *The Extended Phenotype* suggested that bird nests and other built structures such as caddis fly larvae cases and beaver dams can be considered as "extended phenotypes".

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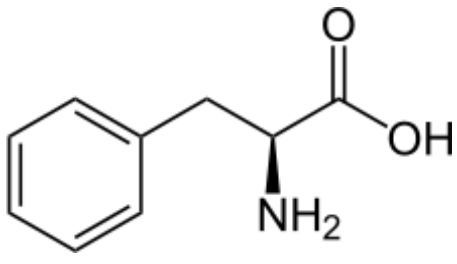
Chapter 7 - Genes and Genomes
Chapter 9 - Point by Point: Information Processing

Phenylalanine

Phenylalanine is an α-amino acid with the formula C6H5CH2CH(NH2)COOH. It can be viewed as a benzyl group substituted for the methyl group of alanine, or a phenyl group in place of a terminal hydrogen of alanine. This essential amino acid is classified as neutral, and nonpolar because of the inert and hydrophobic nature of the benzyl side chain. The L-isomer is used to biochemically form proteins, coded for by DNA. The codons for L-phenylalanine are UUU and UUC.

Phenylalanine is a precursor for tyrosine; the monoamine neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline); and the skin pigment melanin.

Phenylalanine is found naturally in the breast milk of mammals. It is used in the manufacture of food and drink products and sold as a nutritional supplement for its reputed analgesic and antidepressant effects. It is a direct precursor to the neuromodulator phenethylamine, a commonly used dietary supplement.



https://en.wikipedia.org/wiki/Phenylalanine

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Phenylalanine Hydroxylase

Phenylalanine hydroxylase (PheOH, alternatively PheH or PAH) is an enzy
lyzes the hydroxylation of the aromatic side-chain of phenylalanine to gene
sine. PheOH is one of three members of the biopterin-dependent aromatic
hydroxylases, a class of monooxygenase that uses tetrahydrobiopterin (BH_4
ridine cofactor) and a non-heme iron for catalysis. During the reaction, mo
gen is heterolytically cleaved with sequential incorporation of one oxygen a
BH_4 and phenylalanine substrate.

https://en.wikipedia.org/wiki/Phenylalanine_hydroxylase

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Phenylketonuria

Phenylketonuria (PKU) is an inborn error of metabolism involving impaired metabolism of the amino acid phenylalanine. Phenylketonuria is caused by absent or virtually absent phenylalanine hydroxylase (PAH) enzyme activity. The condition is also known as phenylalanine hydroxylase deficiency.

Protein-rich foods or the sweetener aspartame can act as poisons for people with phenylketonuria. The role of PAH is to break down excess phenylalanine from food. Phenylalanine is a necessary part of the human diet and is naturally present in all kinds of dietary protein. It is also used to make aspartame, known by the trade name Nutrasweet, which is used to sweeten low-calorie and sugar free soft drinks, yogurts, and desserts. In people without PKU, the PAH enzyme breaks down any excess phenylalanine from these sources beyond what is needed by the body. However, if there is not enough of the PAH enzyme or its cofactor, then phenylalanine can build up in the blood and brain to toxic levels, affecting brain development and function. PKU is rare, but important to identify, because if caught early it is very treatable. It is not contagious, and it is lifelong, but with early diagnosis and consistent treatment, the damaging effects can be minimal or non-existent.

Untreated PKU can lead to intellectual disability, seizures, and other serious medical problems. The best proven treatment for classical PKU patients is a strict phenylalanine-restricted diet supplemented by a medical formula containing amino acids and other nutrients. In the United States, the current recommendation is that the PKU diet should be maintained for life. Patients who are diagnosed early and maintain a strict diet can have a normal life span with normal mental development.

PKU is an inherited disease. When an infant is diagnosed with PKU, it is never the result of any action of the parents or any environmental factor. Rather, for a child to inherit PKU, both of his or her parents must have at least one mutated allele of the PAH gene. Most parents who are carriers of PKU genes are not aware that they have this mutation because being a carrier causes no medical problems. To be affected by PKU, a child must inherit two mutated alleles, one from each parent.

https://en.wikipedia.org/wiki/Phenylketonuria

Phenylpyruvate

Phenylpyruvic acid is the organic compound with the formula $C_6H_5CH_2C(C$ a keto-acid and is an immediate metabolic precursor of phenyalanine, requ transamination to produce the amino acid.

https://en.wikipedia.org/wiki/Phenylpyruvic_acid

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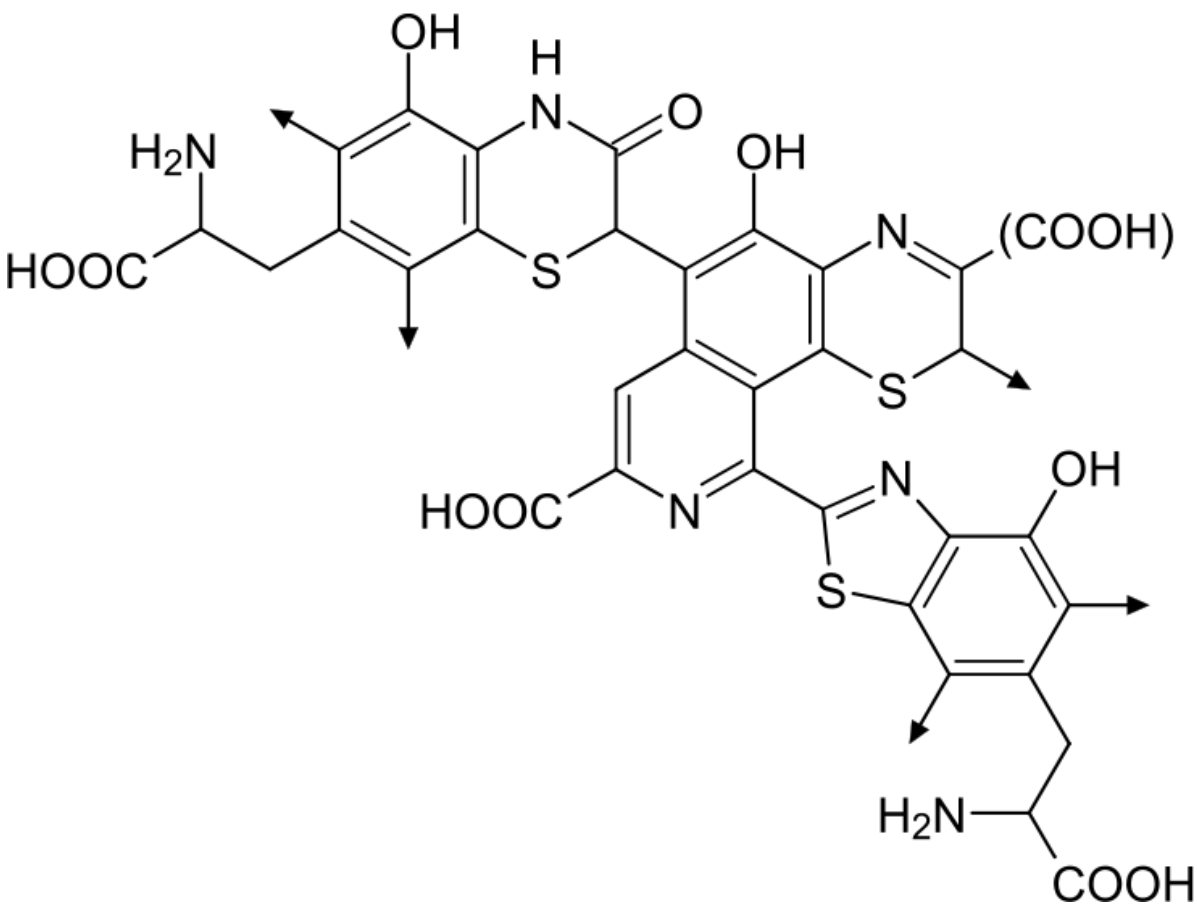
Pheomelanin

Pheomelanin is a cysteine-containing red polymer of benzothiazine units largely responsible for red hair, among other pigmentation. It is one of three types of melanin. Part of the structure of this polymer is shown below.



https://en.wikipedia.org/wiki/Melanin

Related Glossary Terms

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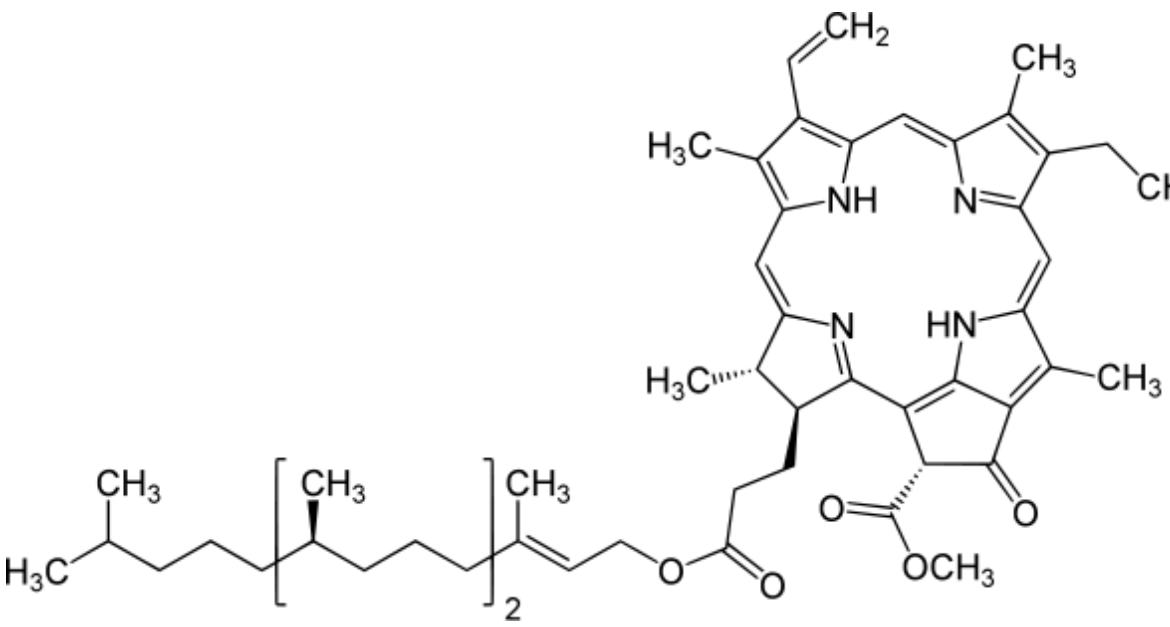
Pheophytin

Pheophytin or phaeophytin (abbreviated Pheo) is a chemical compound that serves as the first electron carrier intermediate in the electron transfer pathway of photosystem II (PS II) in plants, and the photosynthetic reaction center (RC P870) found in purple bacteria. In both PS II and RC P870, light drives electrons from the reaction center through pheophytin, which then passes the electrons to a quinone (QA) in RC P870 and RC P680. The overall mechanisms, roles, and purposes of the pheophytin molecules in the two transport chains are analogous to each other. The structure of pheophytin minus the magnesium ion it normally has in the porphyrin ring, is shown below.



https://en.wikipedia.org/wiki/Pheophytin

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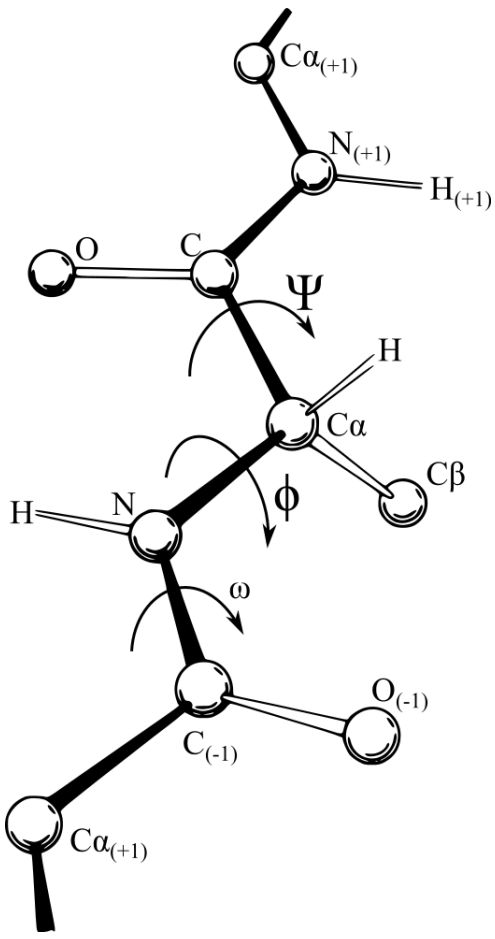
Phi and Psi angles

A Ramachandran plot (also known as a Ramachandran diagram or a [φ,ψ] plot), originally developed in 1963 by G. N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan, is a way to visualize energetically allowed regions for backbone dihedral angles ψ against φ of amino acid residues in protein structure.



https://en.wikipedia.org/wiki/Ramachandran_plot

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Phosphatase PTEN

Phosphatase and tensin homolog (PTEN) is a protein that, in humans, is encod
the PTEN gene. Mutations of this gene are a step in the development of many c
PTEN orthologs have been identified in most mammals for which complete ger
data are available.

This gene was identified as a tumor suppressor that is mutated in a large numb
cancers at high frequency. The protein encoded by this gene is a phosphatidylin
3,4,5-trisphosphate 3-phosphatase. It contains a tensin-like domain as well as a
lytic domain similar to that of the dual specificity protein tyrosine phosphatase
like most of the protein tyrosine phosphatases, this protein preferentially depho
lates phosphoinositide substrates. It negatively regulates intracellular levels of
phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor supp
by negatively regulating Akt/PKB signaling pathway.

https://en.wikipedia.org/wiki/PTEN_(gene)

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Phosphatases

A phosphatase is an enzyme that removes a phosphate group from its substrate by hydrolyzing phosphoric acid monoesters into a phosphate ion and a molecule with a free hydroxyl group (see dephosphorylation). This action is directly opposite to that of phosphorylases and kinases, which attach phosphate groups to their substrates by using energetic molecules like ATP. A common phosphatase in many organisms is alkaline phosphatase. Another large group of proteins present in archaea, bacteria, and eukaryotes exhibits deoxyribonucleotide and ribonucleotide phosphatase or pyrophosphatase activities that catalyze the decomposition of dNTP/NTP into dNDP/NDP and a free phosphate ion or dNMP/NMP and a free pyrophosphate ion. The other group of phosphatase is collectively called as protein phosphatase, which removes a phosphate group from the phosphorylated amino acid residue of the substrate protein. Protein phosphorylation is a common post-translational modification of protein catalyzed by protein kinases, and protein phosphatases reverse the effect.

https://en.wikipedia.org/wiki/Phosphatase

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Phosphate

A phosphate (PO_4^{-3} or abbreviated P_i) is an inorganic chemical and a salt of phosphoric acid. In organic chemistry, a phosphate, or organophosphate, is an ester of phosphoric acid. Of the various phosphoric acids and phosphates, organic phosphates are important in biochemistry and biogeochemistry (ecology), and inorganic phosphates are mined to obtain phosphorus for use in agriculture and industry. At elevated temperatures in the solid state, phosphates can condense to form pyrophosphates.

The addition and removal of phosphates from proteins in all cells is a pivotal strategy in the regulation of metabolic processes. Phosphorylation and dephosphorylation are important ways that energy is stored and released in living systems.

https://en.wikipedia.org/wiki/Phosphate

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Phosphate Translocase

Glucose-6-Phosphate Translocase is an enzyme that in humans is encoded
SLC37A4 gene. It consists of three subunits, each of which are vital compor
multi-enzyme Glucose-6-Phosphatase Complex (G6Pase). This important e
plex is located within the membrane of the endoplasmic reticulum, and cat
terminal reactions in both glycogenolysis and gluconeogenesis. The G6Pase
most abundant in liver tissue, but also present in kidney cells, small intesti
atic islets and at a lower concentration in the gallbladder. The G6Pase comp
highly involved in the regulation of homeostasis and blood glucose levels. V
framework of glucose regulation, the translocase components are responsib
porting the substrates and products across the endoplasmic reticulum mem
sulting in the release of free glucose into the bloodstream.

https://en.wikipedia.org/wiki/Glucose-6-phosphate_translocase

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Phosphates

A phosphate (PO_4^{-3} or abbreviated P_i) is an inorganic chemical and a salt of
acid. In organic chemistry, a phosphate, or organophosphate, is an ester of
acid. Of the various phosphoric acids and phosphates, organic phosphates a
tant in biochemistry and biogeochemistry (ecology), and inorganic phospha
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tures in the solid state, phosphates can condense to form pyrophosphates.

The addition and removal of phosphates from proteins in all cells is a pivot
in the regulation of metabolic processes. Phosphorylation and dephosphory
important ways that energy is stored and released in living systems.

https://en.wikipedia.org/wiki/Phosphate

Related Glossary Terms

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Phosphatidate Cytidylyltransferase

Phosphatidate cytidylyltransferase (also known as CDP- diacylglycerol synthase) (CDS) is the enzyme that catalyzes the synthesis of CDP-diacylglycerol from cytidine triphosphate and phosphatidate.

CTP + Phosphatidate ⇌ Diphosphate + CDP-diacylglycerol

Thus, the two substrates of this enzyme are cytidine triphosphate, or CTP, and phosphatidate, whereas its two products are diphosphate and CDP-diacylglycerol.

CDP-diacylglycerol is an important branch point intermediate in both prokaryotic and eukaryotic organisms. CDS is a membrane-bound enzyme.

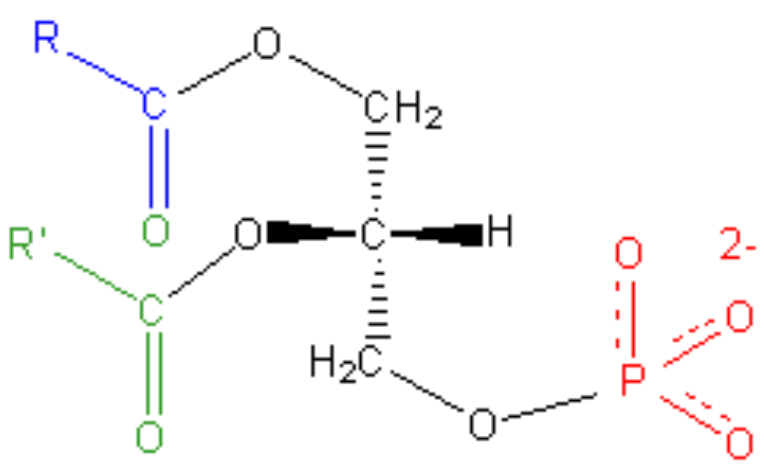
This enzyme belongs to the family of transferases, specifically those transferring phosphorus-containing nucleotide groups (nucleotidyltransferases). The systematic name of this enzyme class is CTP:phosphatidate cytidylyltransferase. Other names in common use include CDP diglyceride pyrophosphorylase, CDP-diacylglycerol synthase, CDP-diacylglyceride synthetase, cytidine diphosphoglyceride pyrophosphorylase, phosphatidate cytidyltransferase, phosphatidic acid cytidylyltransferase, CTP:1,2-diacylglycerophosphate-cytidyl transferase, CTP-diacylglycerol synthetase, DAG synthetase, and CDP-DG.

This enzyme participates in glycerophospholipid metabolism and phosphatidylinositol signaling system.

https://en.wikipedia.org/wiki/Phosphatidate_cytidylyltransferase

Phosphatide

Phosphatidic acids (PAs) (ionized form = phosphatidate) are the acid forms of phosph
tidates, a part of common phospholipids, major constituents of cell membranes. Phos
phatidic acids are the simplest diacyl-glycerophospholipids. Phosphatidic acid consist
of a glycerol backbone, with, in general, a saturated fatty acid bonded to carbon-1, an
unsaturated fatty acid bonded to carbon-2, and a phosphate group bonded to carbon-
3.



https://en.wikipedia.org/wiki/Phosphatidic_acid

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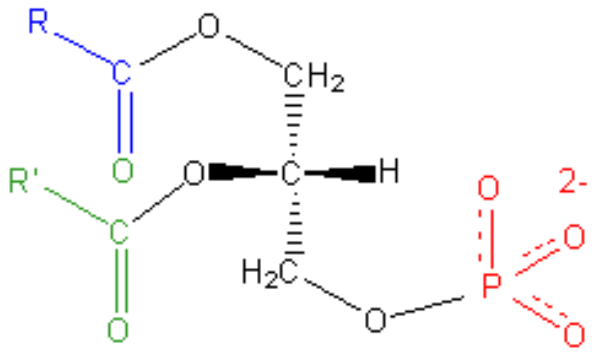
Phosphatidic Acid

Phosphatidic acids (PAs) (ionized form = phosphatidate) are the acid forms of phosphatidates, a part of common phospholipids, major constituents of cell membranes. Phosphatidic acids are the simplest diacyl-glycerophospholipids. Phosphatidic acid consists of a glycerol backbone, with, in general, a saturated fatty acid bonded to carbon-1, an unsaturated fatty acid bonded to carbon-2, and a phosphate group bonded to carbon-3.



https://en.wikipedia.org/wiki/Phosphatidic_acid

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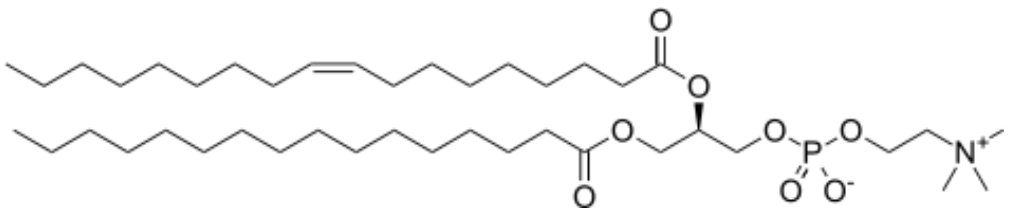
Phosphatidylcholine

Phosphatidylcholines (PC) are a class of phospholipids that incorporate choline as a headgroup. They are a major component of biological membranes and can be easily obtained from a variety of readily available sources, such as egg yolk or soybeans, from which they are mechanically or chemically extracted using hexane. They are also a member of the lecithin group of yellow-brownish fatty substances occurring in animal and plant tissues. Dipalmitoyl phosphatidylcholine (aka: lecithin) is a major component of pulmonary surfactant and is often used in the L/S ratio to calculate fetal lung maturity. While phosphatidylcholines are found in all plant and animal cells, they are absent in the membranes of most bacteria, including *Escherichia coli*. Purified phosphatidylcholine is produced commercially.

Phosphatidylcholine is a major constituent of cell membranes and pulmonary surfactant, and is more commonly found in the exoplasmic or outer leaflet of a cell membrane. It is thought to be transported between membranes within the cell by phosphatidylcholine transfer protein (PCTP).

Phosphatidylcholine also plays a role in membrane-mediated cell signaling and PCTP activation of other enzymes. One example of a phosphatidylcholine is shown below.



https://en.wikipedia.org/wiki/Phosphatidylcholine

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Phosphatidylcholine Transfer Protein

Phosphatidylcholine transfer protein (PCTP) also known as StAR-related li
domain protein 2 (STARD2) is a specific intracellular phospholipid bindin
that can transfer phosphatidylcholine between different membranes in the

In humans, phosphatidylcholine transfer protein is encoded by the PCTP g

https://en.wikipedia.org/wiki/Phosphatidylcholine_transfer_protein

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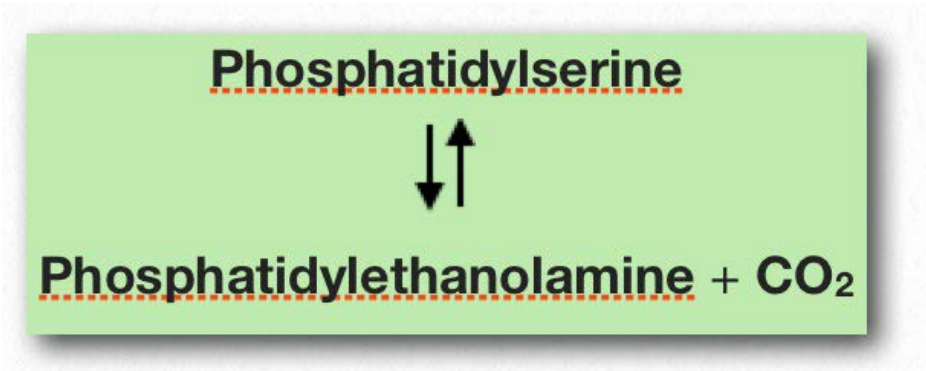
Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

Phosphatidylethanolamine

Phosphatidylethanolamines (sometimes abbreviated PE) are a class of phospholipids found in biological membranes. They are synthesized by the addition of CDP-ethanolamine to diglycerides, releasing CMP. S-Adenosyl methionine can subsequently methylate the amine of phosphatidylethanolamines to yield phosphatidylcholines. It can mainly be found in the inner (cytoplasmic) leaflet of the lipid bilayer. It is easily made by decarboxylation of serine.



https://en.wikipedia.org/wiki/Phosphatidylethanolamine

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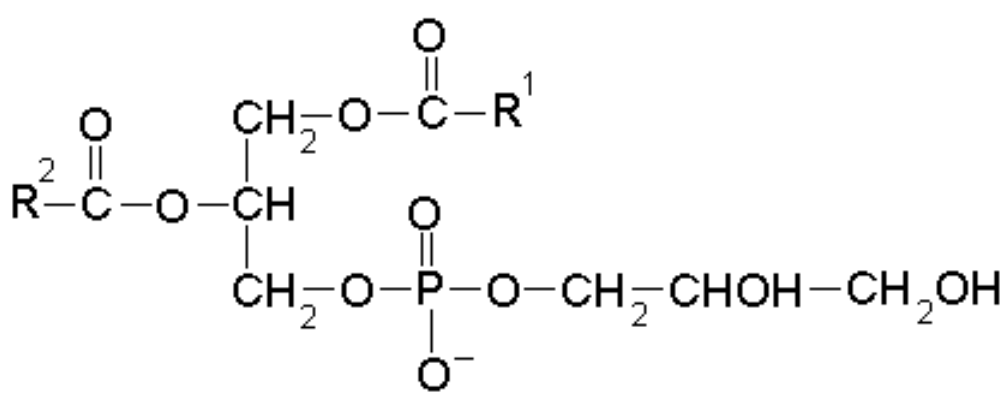
Phosphatidylglycerol

Phosphatidylglycerol is a glycerophospholipid found in pulmonary surfactant.
The general structure of phosphatidylglycerol consists of a L-glycerol 3-phosphate backbone ester-bonded to either saturated or unsaturated fatty acids on carbons 1 and 2. The head group substituent glycerol is bonded through a phosphomonoester. It is the precursor of surfactant and its presence (>0.3) in the amniotic fluid of the newborn indicates fetal lung maturity.

Approximately 98% of alveolar wall surface area is due to the presence of type I cells, with type II cells producing pulmonary surfactant covering around 2% of the alveolar walls. Once surfactant is secreted by the type II cells, it must be spread over the remaining type I cellular surface area. Phosphatidylglycerol is thought to be important in spreading of surfactant over the Type I cellular surface area. The major surfactant deficiency in premature infants relates to the lack of phosphatidylglycerol, even though it comprises less than 5% of pulmonary surfactant phospholipids. It is synthesized by head group exchange of a phosphatidylcholine enriched phospholipid using the enzyme phospholipase D.



https://en.wikipedia.org/wiki/Phosphatidylglycerol

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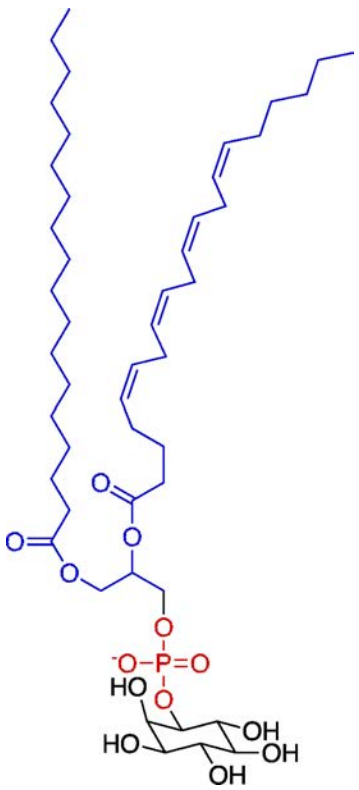
Phosphatidylinositol

Phosphatidylinositol consists of a family of lipids as illustrated on the right, a class of the phosphatidylglycerides. In such molecules the isomer of the inositol group is assumed to be the myo- conformer unless otherwise stated. Typically phosphatidylinositols form a minor component on the cytosolic side of eukaryotic cell membranes. The phosphate group gives the molecules a negative charge at physiological pH.

The form of phosphatidylinositol comprising the isomer muco-inositol acts as a sensory receptor in the taste function of the sensory system. In this context it is often referred to as PtdIns, but that does not imply any molecular difference from phosphatidylinositols comprising the myo- conformers of inositol.

The phosphatidylinositol can be phosphorylated to form phosphatidylinositol phosphate (PI-4-P, referred to as PIP in close context or informally), phosphatidylinositol bisphosphate (PIP2) and phosphatidylinositol trisphosphate (PIP3). All lipids based on phosphatidylinositol are known as inositides, or sometimes phosphoinositides.



https://en.wikipedia.org/wiki/Phosphatidylinositol

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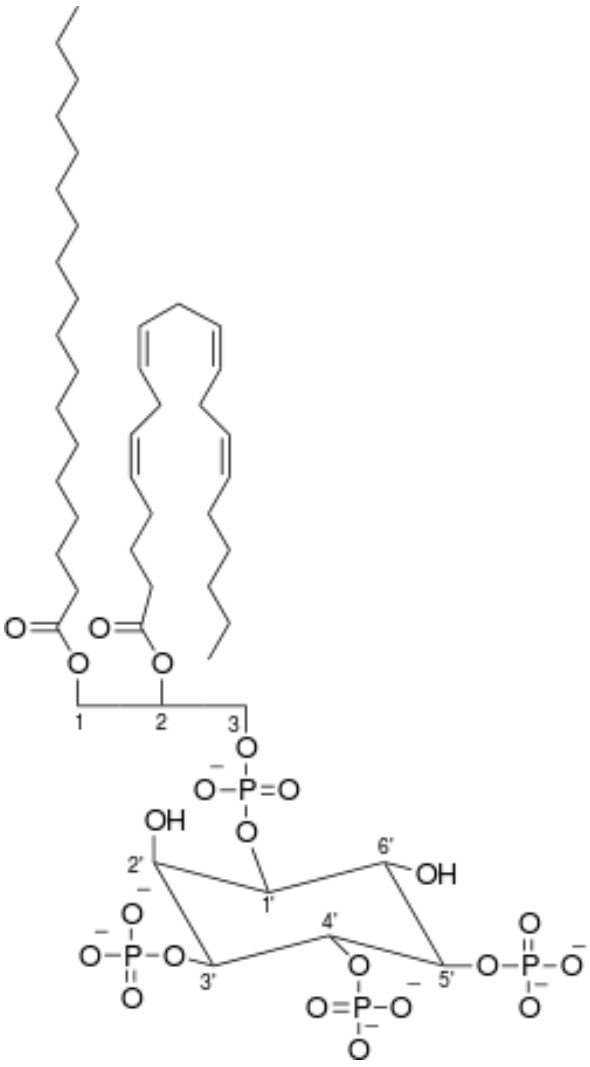
Phosphatidylinositol (3,4,5)-trisphosphate

Phosphatidylinositol (3,4,5)-trisphosphate, abbreviated PIP_3, is the product of the class I phosphoinositide 3-kinases (PI 3-kinases) phosphorylation of phosphatidylinositol (4,5)-bisphosphate (PIP_2). It is a phospholipid that resides on the plasma membrane. PIP_3 functions to activate downstream signaling components, the most notable one being the protein kinase AKT, which activates downstream anabolic signaling pathways required for cell growth and survival. Phospholipase C cleaves PIP_2 to produce inositol triphosphate IP_3, and diacylglycerol.



https://en.wikipedia.org/wiki/Phosphatidylinositol_(3,4,5)-trisphosphate

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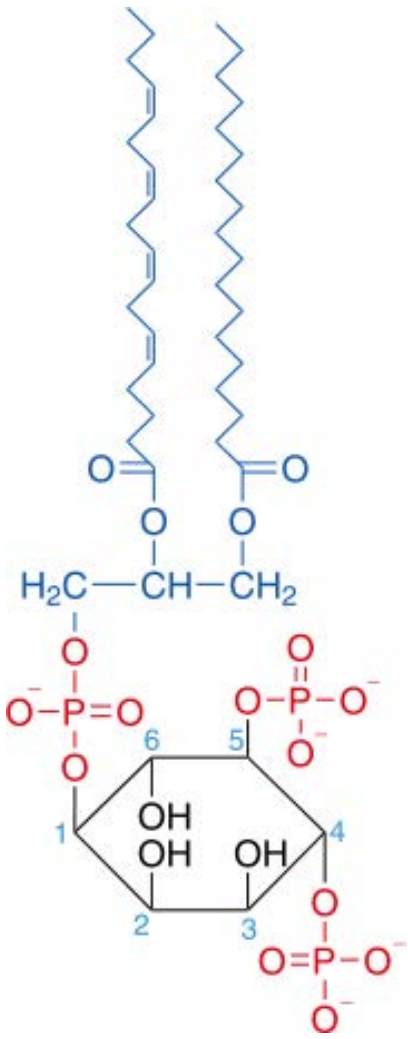
Chapter 2 - Structure & Function: Lipids

Phosphatidylinositol-4,5-bisphosphate

Phosphatidylinositol 4,5-bisphosphate or PtdIns(4,5)P_2, also known simply as PIP_2, is a minor phospholipid component of cell membranes. PtdIns(4,5)P_2 is enriched at the plasma membrane where it is a substrate for a number of important signaling proteins. PtdIns(4,5)P_2 is formed primarily by the type I phosphatidylinositol 4-phosphate 5-kinases from PI(4)P. In metazoans, PtdIns(4,5)P_2 can also be formed by type II phosphatidylinositol 5-phosphate 4-kinases from PI(5)P.

The fatty acids of PtdIns(4,5)P_2 are variable in different species and tissues, but studies show the most common fatty acids are stearic in position 1 and arachidonic in 2.



https://en.wikipedia.org/wiki/Phosphatidylinositol_4,5-bisphosphate

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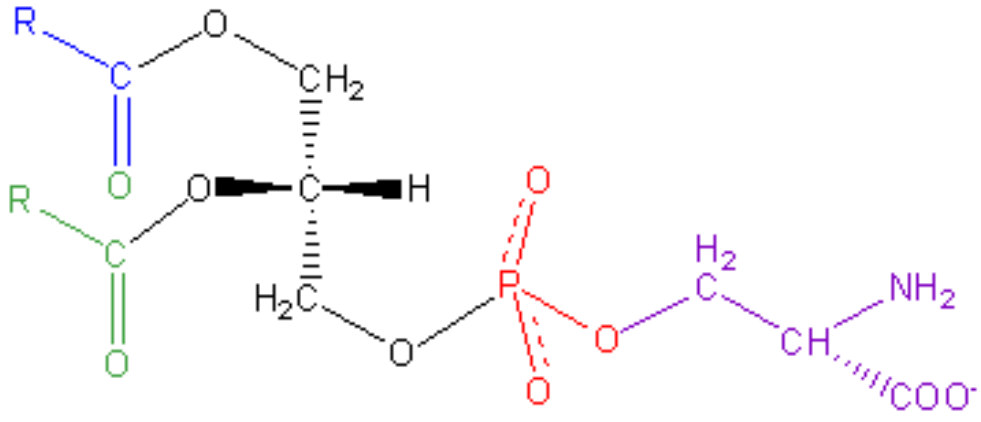
Chapter 2 - Structure & Function: Lipids

Phosphatidylserine

Phosphatidylserine (abbreviated Ptd-L-Ser or PS) is an important phospholipid membrane component (i.e. component of the cell membrane) which plays a key role in cell cycle signaling, specifically in relationship to apoptosis.



https://en.wikipedia.org/wiki/Phosphatidylserine

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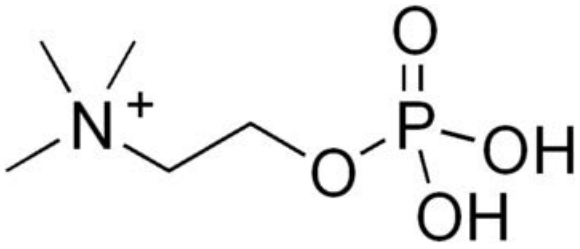
Phosphocholine

Phosphocholine is an intermediate in the synthesis of phosphatidylcholine in tissues. Phosphocholine is made in a reaction, catalyzed by choline kinase, that converts ATP and choline into phosphocholine and ADP. Phosphocholine is a molecule found, for example, in lecithin.

It is also used by nematodes and human placentas as a posttranslational modification to suppress an immune response by their hosts.

It is also one of the binding targets of C-reactive protein (CRP). Thus, when a cell is damaged, CRP binds to phosphocholine, beginning the recognition and phagocytotic immunologic response.

Phosphocholine is a natural constituent of hens' eggs (and many other eggs) often used in biomimetic membrane studies.



https://en.wikipedia.org/wiki/Phosphocholine

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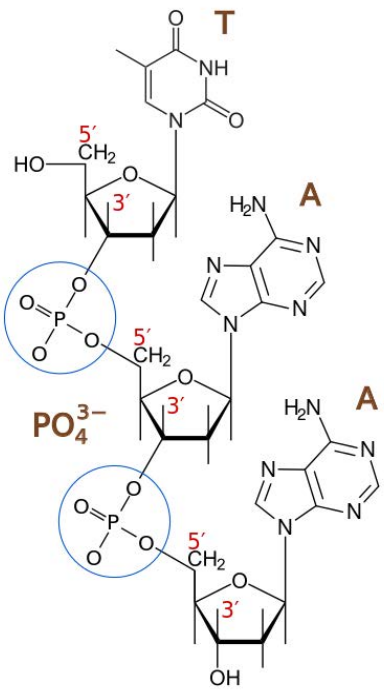
Phosphodiester

A phosphodiester bond occurs when exactly two of the hydroxyl groups in phosphoric acid react with hydroxyl groups on other molecules to form two ester bonds.

Phosphodiester bonds are central to all life on Earth, as they make up the backbone of the strands of nucleic acid. In DNA and RNA, the phosphodiester bond is the linkage between the 3' carbon atom of one sugar molecule and the 5' carbon atom of another, deoxyribose in DNA and ribose in RNA. Strong covalent bonds form between the phosphate group and two 5-carbon ring carbohydrates (pentoses) over two ester bonds.

The phosphate groups in the phosphodiester bond are negatively charged. Because the phosphate groups have a pKa near 0, they are negatively charged at pH 7. This repulsion forces the phosphates to take opposite sides of the DNA strands and is neutralized by proteins (histones), metal ions such as magnesium, and polyamines.

In order for the phosphodiester bond to be formed and the nucleotides to be joined, the tri-phosphate or di-phosphate forms of the nucleotide building blocks are broken apart to give off energy required to drive the enzyme-catalyzed reaction. When a single phosphate or two phosphates known as pyrophosphates break away and catalyze the reaction, the phosphodiester bond is formed.
Hydrolysis of phosphodiester bonds can be catalyzed by the action of phosphodiesterases which play an important role in repairing DNA sequences.
The phosphodiester linkage between two ribonucleotides can be broken by alkaline hydrolysis, whereas the linkage between two deoxyribonucleotides is more stable under these conditions. The relative ease of RNA hydrolysis is an effect of the presence of the 2' hydroxyl group.



https://en.wikipedia.org/wiki/Phosphodiester_bond

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Phosphodiesterase

A phosphodiesterase (PDE) is any enzyme that breaks a phosphodiester bond. Usually, phosphodiesterase refers to cyclic nucleotide phosphodiesterases, which have great clinical significance and are described below. However, there are many other families of phosphodiesterases, including phospholipases C and D, autotaxin, sphingomyelin phosphodiesterase, DNases, RNases, and restriction endonucleases (which all break the phosphodiester backbone of DNA or RNA), as well as numerous less-well-characterized small-molecule phosphodiesterases.

The cyclic nucleotide phosphodiesterases comprise a group of enzymes that degrade the phosphodiester bond in the second messenger molecules cAMP and cGMP. They regulate the localization, duration, and amplitude of cyclic nucleotide signaling within subcellular domains. PDEs are therefore important regulators of signal transduction mediated by these second messenger molecules.

https://en.wikipedia.org/wiki/Phosphodiesterase

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https://en.wikipedia.org/wiki/Phosphodiesterase

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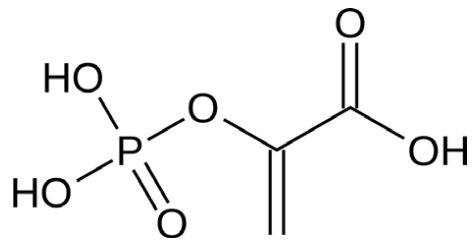
Phosphoenolpyruvate

Phosphoenolpyruvic acid (PEP), or phosphoenolpyruvate (2-phosphoenolpyruvate) as the anion, is an important chemical compound in biochemistry. It has the highest-energy phosphate bond found (-61.9 kJ/mol) in living organisms, and is involved in glycolysis and gluconeogenesis. In plants, it is also involved in the biosynthesis of various aromatic compounds, and in carbon fixation. In bacteria, it is also used as the source of energy for the phosphotransferase system. The acid form is shown below.



https://en.wikipedia.org/wiki/Phosphoenolpyruvic_acid

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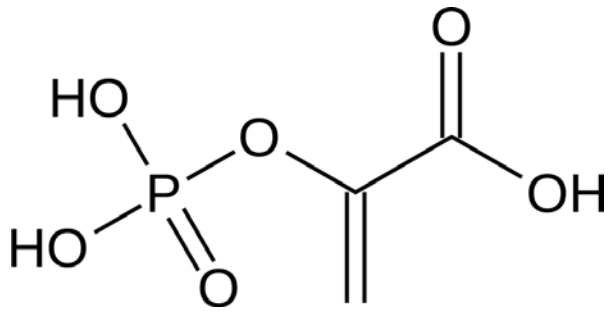

https://en.wikipedia.org/wiki/Phosphoenolpyruvic_acid

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Chapter 6 - Metabolism: Sugars

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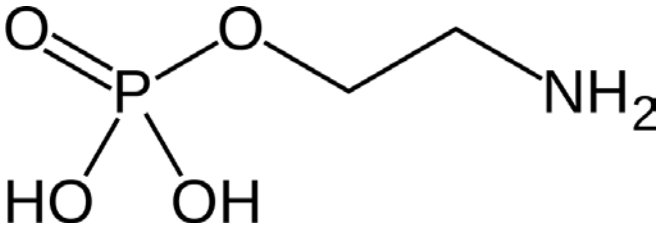
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Phosphoethanolamine

Phosphorylethanolamine or phosphoethanolamine is an ethanolamine deri
is used to construct sphingomyelins. This chemical possesses two pKa valu
10.39.



https://en.wikipedia.org/wiki/Phosphorylethanolamine

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Phosphofructokinase

Phosphofructokinase is a kinase enzyme that phosphorylates fructose 6-phosphate in glycolysis. The reaction catalyzed is

F6P + ATP <=> F1,6BP + ADP

The enzyme-catalyzed transfer of a phosphoryl group from ATP is an important reaction in a wide variety of biological processes. One enzyme that utilizes this reaction is phosphofructokinase (PFK), which catalyzes the phosphorylation of fructose-6-phosphate to fructose-1,6- bisphosphate, a key regulatory step in the glycolytic pathway. It is allosterically inhibited by ATP and allosterically activated by AMP, thus indicating the cell's energetic needs when it undergoes the glycolytic pathway. PFK exists as a homotetramer in bacteria and mammals (where each monomer possesses 2 similar domains) and as an octomer in yeast (where there are 4 α- (PFK1) and 4 β-chains (PFK2), the latter, like the mammalian monomers, possessing 2 similar domains). This protein may use the morpheein model of allosteric regulation.

PFK is about 300 amino acids in length, and structural studies of the bacterial enzyme have shown it comprises two similar (α/β) lobes: one involved in ATP binding and the other housing both the substrate-binding site and the allosteric site (a regulatory binding site distinct from the active site, but that affects enzyme activity). The identical tetramer subunits adopt 2 different conformations: in a 'closed' state, the bound magnesium ion bridges the phosphoryl groups of the enzyme products (ADP and fructose-1,6- bisphosphate). In an 'open' state, the magnesium ion binds only the ADP, as the 2 products are now further apart. These conformations are thought to be successive stages of a reaction pathway that requires subunit closure to bring the 2 molecules sufficiently close to react.

Deficiency in PFK leads to glycogenosis type VII (Tarui's disease), an autosomal recessive disorder characterized by severe nausea, vomiting, muscle cramps and myoglobinuria in response to bursts of intense or vigorous exercise. Sufferers are usually able to lead a reasonably ordinary life by learning to adjust activity levels.

https://en.wikipedia.org/wiki/Phosphofructokinase

Phosphoglucoisomerase

Glucose-6-phosphate isomerase (GPI), alternatively known as phosphoglucose isomerase (PGI), phosphoglucoisomerase, or phosphohexose isomerase (PHI), is an zyme that in humans is encoded by the GPI gene on chromosome 19. This gene en- codes a member of the glucose phosphate isomerase protein family. The encoded pro tein has been identified as a moonlighting protein based on its ability to perform mechanistically distinct functions. In the cytoplasm, the gene product functions as a glycolytic enzyme (glucose-6-phosphate isomerase) that interconverts glucose-6- phosphate (G6P) and fructose-6-phosphate (F6P). Extracellularly, the encoded prote (also referred to as neuroleukin) functions as a neurotrophic factor that promotes su vival of skeletal motor neurons and sensory neurons, and as a lymphokine that induc immunoglobulin secretion. The encoded protein is also referred to as autocrine moti ity factor (AMF) based on an additional function as a tumor-secreted cytokine and an ogenic factor. Defects in this gene are the cause of nonspherocytic hemolytic anemia and a severe enzyme deficiency can be associated with hydrops fetalis, immediate ne natal death and neurological impairment. Alternative splicing results in multiple tra script variants.

https://en.wikipedia.org/wiki/Glucose-6-phosphate_isomerase

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Phosphoglucomutase

Phosphoglucomutase is an enzyme that transfers a phosphate group on an
monomer from the 1' to the 6' position in the forward direction or the 6' to
tion in the reverse direction.

More precisely, it facilitates the interconversion of glucose 1-phosphate and
phosphate.

G1P <=> G6P

https://en.wikipedia.org/wiki/Phosphoglucomutase

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Phosphoglycerate Kinase

Phosphoglycerate kinase (PGK) is an enzyme that catalyzes the reversible transfer of a phosphate group from 1,3-bisphosphoglycerate (1,3-BPG) to ADP producing 3-phosphoglycerate (3-PG) and ATP.

1,3-BPG + ADP <=> 3-PG + ATP

Like all kinases, it is a transferase. PGK is a major enzyme used in glycolysis, in the first ATP-generating step of the glycolytic pathway. In gluconeogenesis, the reaction catalyzed by PGK proceeds in the opposite direction, generating ADP and 1,3-BPG.

In humans, two isozymes of PGK have been so far identified, PGK1 and PGK2. The isozymes have 87-88% identical amino acid sequence identity and though they are structurally and functionally similar, they have different localizations: PGK2, encoded by a autosomal gene, is unique to meiotic and postmeiotic spermatogenic cells, while PGK1 encoded on the X-chromosome, is ubiquitously expressed in all cells.

https://en.wikipedia.org/wiki/Phosphoglycerate_kinase

Related Glossary Terms

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Phosphoglycerate Mutase

Phosphoglycerate mutase (PGM) is an enzyme that catalyzes step 8 of glycol
catalyzes the internal transfer of a phosphate group from C-3 to C-2 which re
the conversion of 3-phosphoglycerate (3PG) to 2-phosphoglycerate (2PG) th
2,3-bisphosphoglycerate intermediate.

3-PG <=> 2-PG

These enzymes are categorized into the two distinct classes of either cofactor
dependent (dPGM) or cofactor-independent (iPGM). The dPGM enzyme (EC
is composed of approximately 250 amino acids and is found in all vertebrate
as in some invertebrates, fungi, and bacteria. The iPGM (EC 5.4.2.12) class is
all plants and algae as well as in some invertebrate, fungi, and Gram-positive
This class of PGM enzyme shares the same superfamily as alkaline phosphat

https://en.wikipedia.org/wiki/Phosphoglycerate_mutase

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Phosphoglycerolipid

The term glycerophospholipid (phosphoglycerolipid) signifies any derivative phosphoric acid that contains at least one O-acyl, or O-alkyl, or O-alk-1'- eny attached to the glycerol moiety.

The alcohol here is glycerol, to which two fatty acids and a phosphoric acid a tached as esters. This basic structure is a phosphatidate. Phosphatidate is an intermediate in the synthesis of many phosphoglycerides. The presence of ar tional group attached to the phosphate allows for many different phosphogly

By convention, structures of these compounds show the 3 glycerol carbon ato cally with the phosphate attached to carbon atom number three (at the botto malogens and phosphatidates are examples.

https://en.wikipedia.org/wiki/Glycerophospholipid

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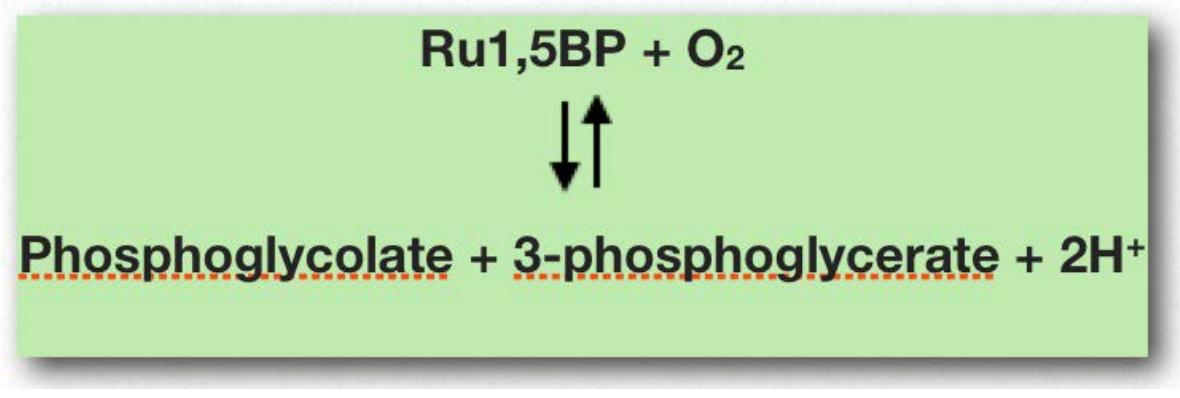
Phosphoglycolate

Phosphoglycolate is an intermediate in photorespiration - when O_2 binds to
instead of CO_2. It is produced in the following reaction



and is further metabolized to glyoxylate and then glycine.

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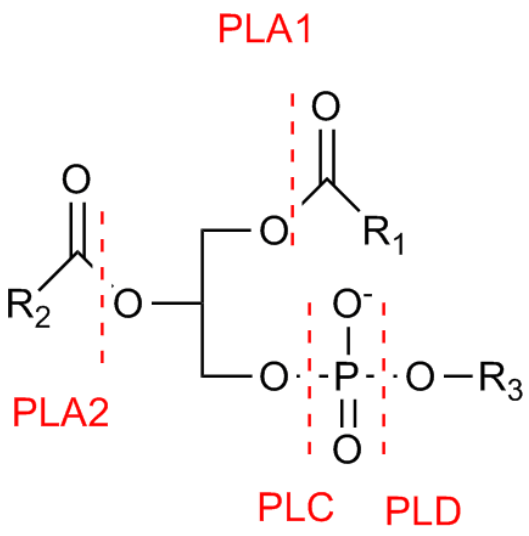
Phospholipase A_1

Phospholipase A_1 is a phospholipase enzyme which removes the 1-acyl group of a glycerolipid. It resides in a class of enzymes called phospholipase that hydrolyze phospholipids into fatty acids. There are 4 classes, which are separated by the type of reaction they catalyze. In particular, phospholipase A_1 (PLA_1) specifically catalyzes the cleavage at the SN-1 position of phospholipids, forming a fatty acid and a lysophospholipid.

PLA_1s are present in numerous species including humans, and have a variety of cellular functions that include regulation and facilitation of the production of lysophospholipid mediators, and acting as digestive enzymes. These enzymes are responsible for fast turnover rates of cellular phospholipids. In addition to this, the products of the reaction catalyzed by PLA_1 which are a fatty acid and a lysophospholipid are important in various biological functions such as platelet aggregation and smooth muscle contraction. In addition, lysophospholipids can be found as surfactants in food techniques and cosmetics, and can be used in drug delivery. Since PLA_1 is found in many species, it has been found that there are different classes of this one specific enzyme based on the organism being studied.

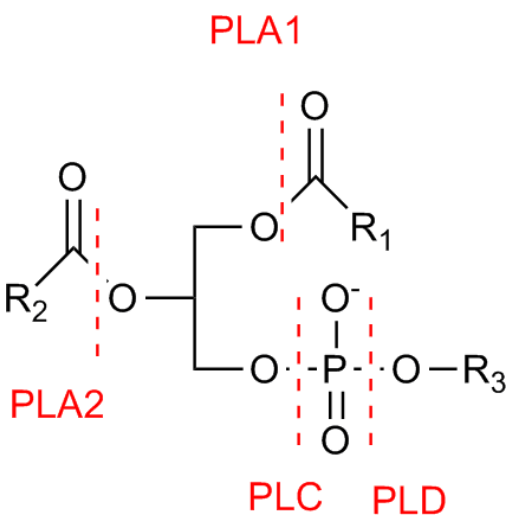


https://en.wikipedia.org/wiki/Phospholipase_A1

Phospholipase A_2

Phospholipases A_2 (PLA_2s) are enzymes that release fatty acids from the second carbon group of glycerolipids. This particular phospholipase specifically recognizes the sn-2 acyl bond of phospholipids and catalytically hydrolyzes the bond releasing arachidonic acid and lysophosphatidic acid. Upon downstream modification by cyclooxygenases, arachidonic acid is modified into active compounds called eicosanoids. Eicosanoids include prostaglandins and leukotrienes, which are categorized as anti-inflammatory and inflammatory mediators.

PLA_2 enzymes are commonly found in mammalian tissues as well as arachnid, insect and snake venom. Venom from both snakes and insects is largely composed of melittin, which is a stimulant of PLA_2. Due to the increased presence and activity of PLA_2 resulting from a snake or insect bite, arachidonic acid is released from the phospholipid membrane disproportionately. As a result, inflammation and pain occur at the site. There are also prokaryotic A_2 phospholipases.



https://en.wikipedia.org/wiki/Phospholipase_A2

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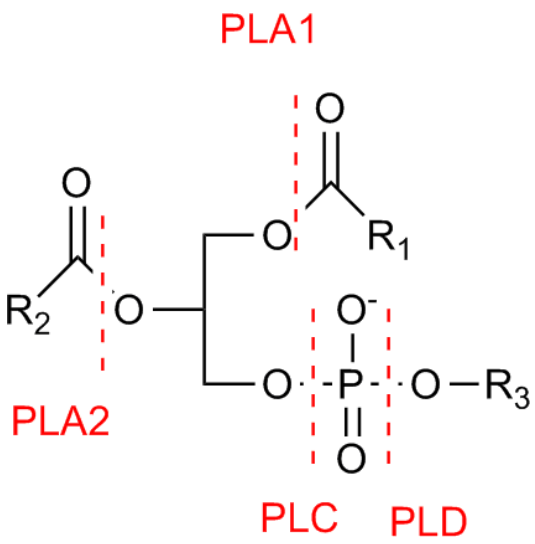
Phospholipase C

Phospholipase C (PLC) is a class of membrane-associated enzymes that cleave phospholipids just before the phosphate group of a glycerophospholipid (see figure). It is most commonly taken to be synonymous with the human forms of this enzyme, which play an important role in eukaryotic cell physiology, in particular signal transduction pathways. There are thirteen kinds of mammalian phospholipase C that are classified into six isotypes (β, γ, δ, ε, ζ, η) according to structure. Each PLC has unique and overlapping controls over expression and subcellular distribution. Activators of each PLC vary, but typically include heterotrimeric G protein subuntis, protein tyrosine kinases, small G proteins, Ca^{2+}, and phospholipids.



https://en.wikipedia.org/wiki/Phospholipase_C

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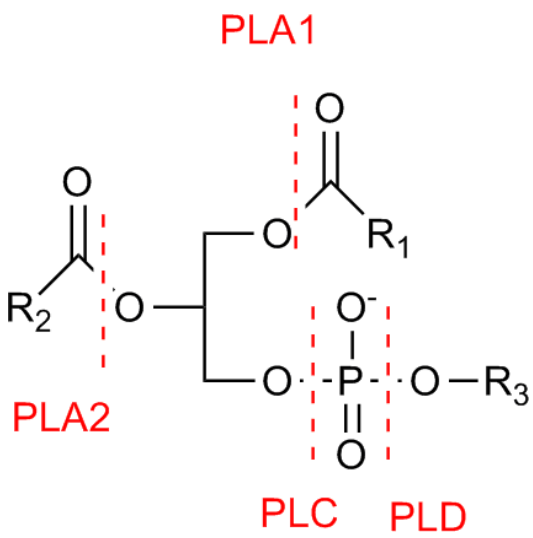
Phospholipases

A phospholipase is an enzyme that hydrolyzes glycerophospholipids into fatty acids and other lipophilic substances. There are four major classes, termed A, B, C and D, distinguished by the type of reaction which they catalyze:

Phospholipase A_1 - cleaves the SN-1 acyl chain.
Phospholipase A_2 - cleaves the SN-2 acyl chain, releasing arachidonic acid.
Phospholipase B - cleaves both SN-1 and SN-2 acyl chains. This enzyme is also known as a lysophospholipase.
Phospholipase C - cleaves before the phosphate, releasing diacylglycerol and a phosphate-containing head group. Phospholipase Cs play a central role in signal transduction, releasing the second messenger inositol triphosphate.
Phospholipase D - cleaves after the phosphate, releasing phosphatidic acid and an alcohol.



https://en.wikipedia.org/wiki/Phospholipase

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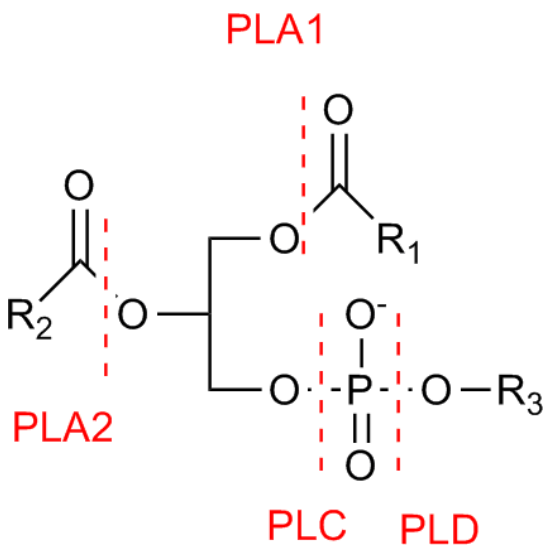
Phospholipiase D

Phospholipase D (EC 3.1.4.4, lipophosphodiesterase II, lecithinase D, choline phosphatase) (PLD) is an enzyme of the phospholipase superfamily. Phospholipases occur widely, and can be found in a wide range of organisms, including bacteria, yeast, plants, animals, and viruses. Phospholipase D's principal substrate is phosphatidylcholine, which it hydrolyzes to produce the signal molecule phosphatidic acid (PA), and soluble choline. Plants contain numerous genes that encode various PLD isoenzymes, with molecular weights ranging from 90-125 kDa. Mammalian cells encode two isoforms of phospholipase D: PLD_1 and PLD_2. Phospholipase D is an important player in many physiological processes, including membrane trafficking, cytoskeletal reorganization, receptor-mediated endocytosis, exocytosis, and cell migration. Through these processes, it has been further implicated in the pathophysiology of multiple diseases: in particular the progression of Parkinson's and Alzheimer's, as well as various cancers.



https://en.wikipedia.org/wiki/Phospholipase_D

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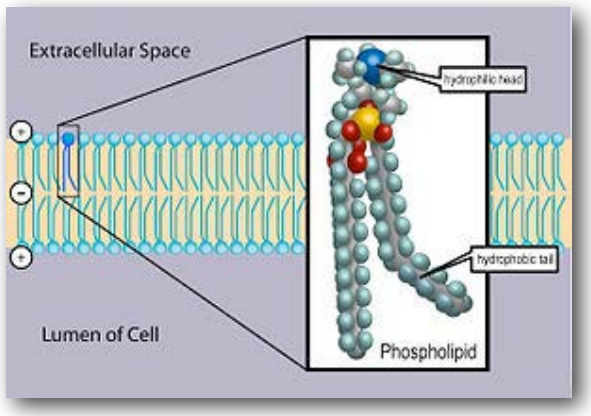
Phospholipid

Phospholipids are a class of lipids that are a major component of all cell membranes. They can form lipid bilayers because of their amphiphilic characteristic. They come in two classes - glycerophospholipids and phosphorylated sphingolipids, such as sphingomyelin. The structure of a glycerophospholipid molecule generally consists of two hydrophobic fatty acid "tails" and a hydrophilic phosphate "head", joined together by a glycerol molecule. The phosphate groups of glycerophospholipids can be modified with simple organic molecules such as choline.

The 'head' of a phospholipid is hydrophilic (attracted to water), while the hydrophobic 'tails' are repelled by water and are forced to aggregate. The hydrophilic head contains the negatively charged phosphate group and glycerol. The hydrophobic tail usually consists of 2 long fatty acid chains. When placed in water, phospholipids form a variety of structures depending on the specific properties of the phospholipid. These specific properties allow phospholipids to play an important role in the phospholipid bilayer. In biological systems, the phospholipids often occur with other molecules (e.g., proteins, glycolipids, sterols) in a bilayer such as a cell membrane. Lipid bilayers occur when hydrophobic tails line up against one another, forming a membrane of hydrophilic heads on both sides facing the water.
Such movement can be described by the fluid mosaic model, that describes the membrane as a mosaic of lipid molecules that act as a solvent for all the substances and proteins within it, so proteins and lipid molecules are then free to diffuse laterally through the lipid matrix and migrate over the membrane. Sterols contribute to membrane fluidity by hindering the packing together of phospholipids. However, this model has now been superseded, as through the study of lipid polymorphism it is now known that the behavior of lipids under physiological (and other) conditions is not simple.



https://en.wikipedia.org/wiki/Phospholipid

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Phosphomannoisomerase

Phosphomannoisomerase catalyzes the conversion of mannose-6-phosphat
fructose-6-phosphate.

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Phosphopentose Epimerase

Phosphopentose epimerase (also known as ribulose-phosphate 3-epimeras
lose 5-phosphate 3-epimerase) is a metalloprotein that catalyzes the interc
between D-ribulose 5-phosphate and D-xylulose 5-phosphate. This reversib
sion is required for carbon fixation in plants – through the Calvin cycle – a
nonoxidative phase of the pentose phosphate pathway. This enzyme has als
plicated in additional pentose and glucuronate interconversions.

https://en.wikipedia.org/wiki/Phosphopentose_epimerase

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Phosphopentose Isomerase

Ribose-5-phosphate isomerase (Rpi) is an enzyme that catalyzes the conver
tween ribose-5-phosphate (R5P) and ribulose-5-phosphate (Ru5P). It is a m
larger class of isomerases which catalyze the interconversion of chemical is
this case structural isomers of pentose). It plays a vital role in biochemical r
in both the pentose phosphate pathway and the Calvin cycle. The systemati
this enzyme class is D-ribose-5-phosphate aldose-ketose-isomerase.

https://en.wikipedia.org/wiki/Ribose-5-phosphate_isomerase

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Phosphoprotein Phosphatase

A protein phosphatase (phosphoprotein phosphatase) is an enzyme that removes a phosphate group from the phosphorylated amino acid residue of its substrate protein. Protein phosphorylation is one of the most common forms of reversible protein post-translational modification (PTM), with up to 30% of all proteins being phosphorylated at any given time. Protein kinases (PKs) are the effectors of phosphorylation and catalyze the transfer of a γ-phosphate from ATP to specific amino acids on proteins. Several hundred PKs exist in mammals and are classified into distinct super-families.

Proteins are phosphorylated predominantly on Ser, Thr and Tyr residues, which account for 86, 12 and 2% respectively of the phosphoproteome, at least in mammals. In contrast, protein phosphatases (PPs) are the primary effectors of dephosphorylation and can be grouped into three main classes based on sequence, structure and catalytic function. The largest class of PPs is the phosphoprotein phosphatase (PPP) family comprising PP1, PP2A, PP2B, PP4, PP5, PP6 and PP7, and the protein phosphatase Mg^{2+}- or Mn^{2+}-dependent (PPM) family, composed primarily of PP2C. The protein Tyr phosphatase (PTP) super-family forms the second group, and the aspartate-based protein phosphatases the third.

https://en.wikipedia.org/wiki/Protein_phosphatase

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Phosphoribosyl-AMP Cyclohydrolase

Phosphoribosyl-AMP cyclohydrolase is an enzyme that catalyzes the chemi

1-(5-phosphoribosyl)-AMP + H_2O ⇌1-(5-phosphoribosyl)-5-[(5-phosphoribosylamino)methylideneamino]imidazole-4-carboxamide

This enzyme belongs to the family of hydrolases, those acting on carbon-nit bonds other than peptide bonds, specifically in cyclic amidines. The system of this enzyme class is 1-(5-phospho-D-ribosyl)-AMP 1,6-hydrolase. Other r common use include PRAMP-cyclohydrolase, and phosphoribosyladenosin phosphate cyclohydrolase. This enzyme participates in histidine metabolism

https://en.wikipedia.org/wiki/Phosphoribosyl-AMP_cyclohydrolase

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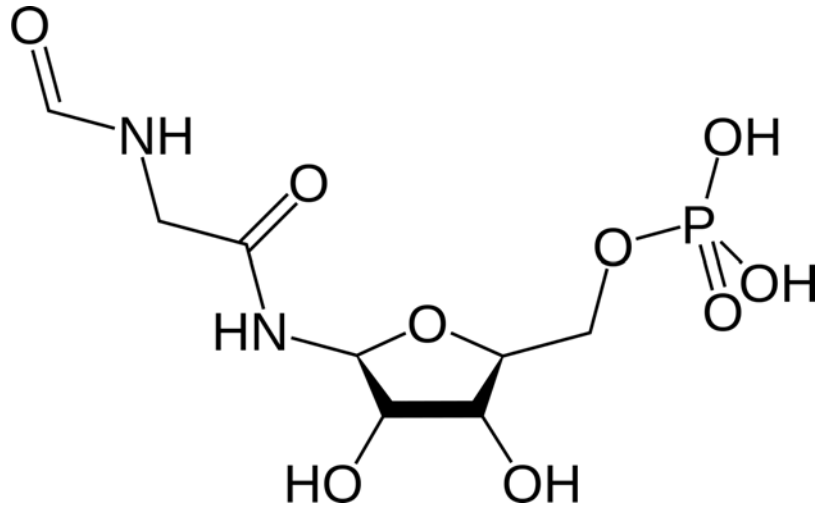
Phosphoribosyl-N-formylglycineamide

Phosphoribosyl-N-formylglycineamide (or FGAR) is a ribonucleotide deriv



https://en.wikipedia.org/wiki/Phosphoribosyl-N-formylglycineamide

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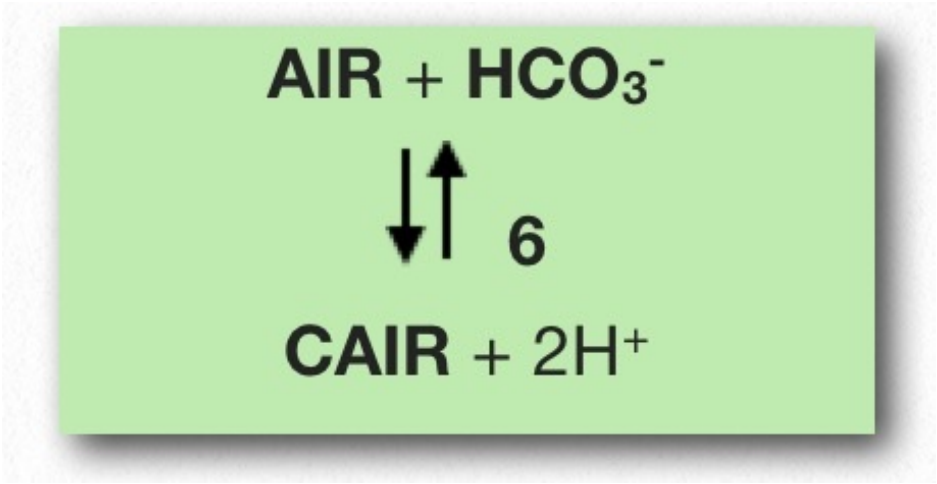
Phosphoribosylaminoimidazole carboxylase

Phosphoribosylaminoimidazole carboxylase (or AIR carboxylase) is an enzyme involved in purine nucleotide biosynthesis. It catalyzes the conversion of 5'-phosphoribosyl-5-aminoimidazole ("AIR") into 5'-phosphoribosyl-4-carboxy-5-aminoimidazole ("CAIR") as described in the reaction below. It is the sixth reaction in the pathway leading to synthesis of IMP.

5-aminoimidazole ribonucleotide (AIR) + HCO_3^- $\rightleftharpoons$5'-phosphoribosyl-4-carboxy-5-aminoimidazole (CAIR) + 2 H^+



https://en.wikipedia.org/wiki/Phosphoribosylaminoimidazole_carboxylase

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Related Glossary Terms

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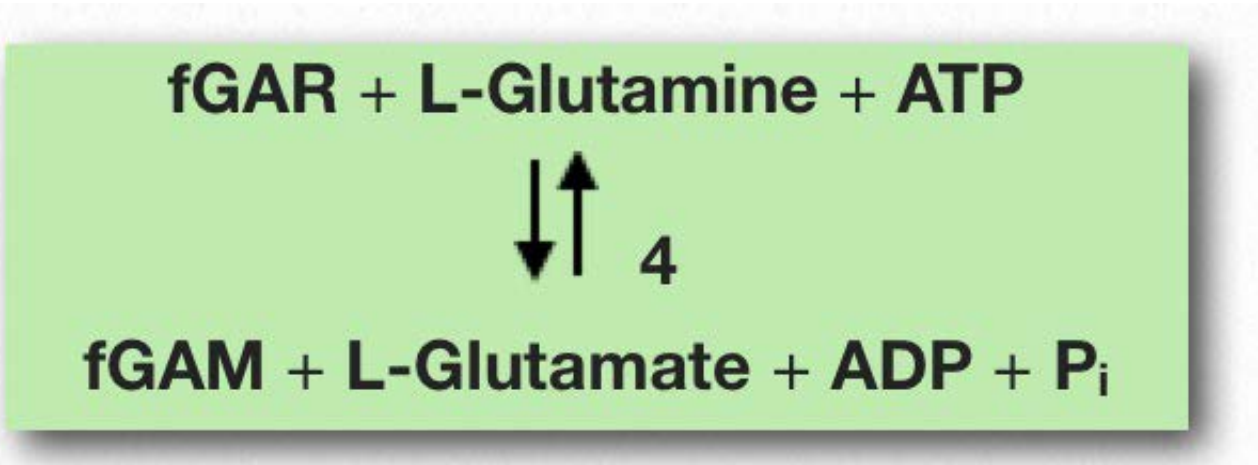
Phosphoribosylformylglycinamidine synthase

Phosphoribosylformylglycinamidine synthase is an enzyme that catalyzes the chemica reaction below. It is the fourth reaction in the synthesis pathway leading to IMP.

ATP + N_2-formyl-N_1-(5-phospho-D-ribosyl)glycinamide (fGAR) + L-glutamine + H_2O ⇌ ADP + P_i + 2-(formamido)-N1-(5-phospho-D-ribosyl)acetamidine (fGAM) + L-glutamate



This enzyme participates in purine metabolism.

https://en.wikipedia.org/wiki/Phosphoribosylformylglycinamidine_synthase

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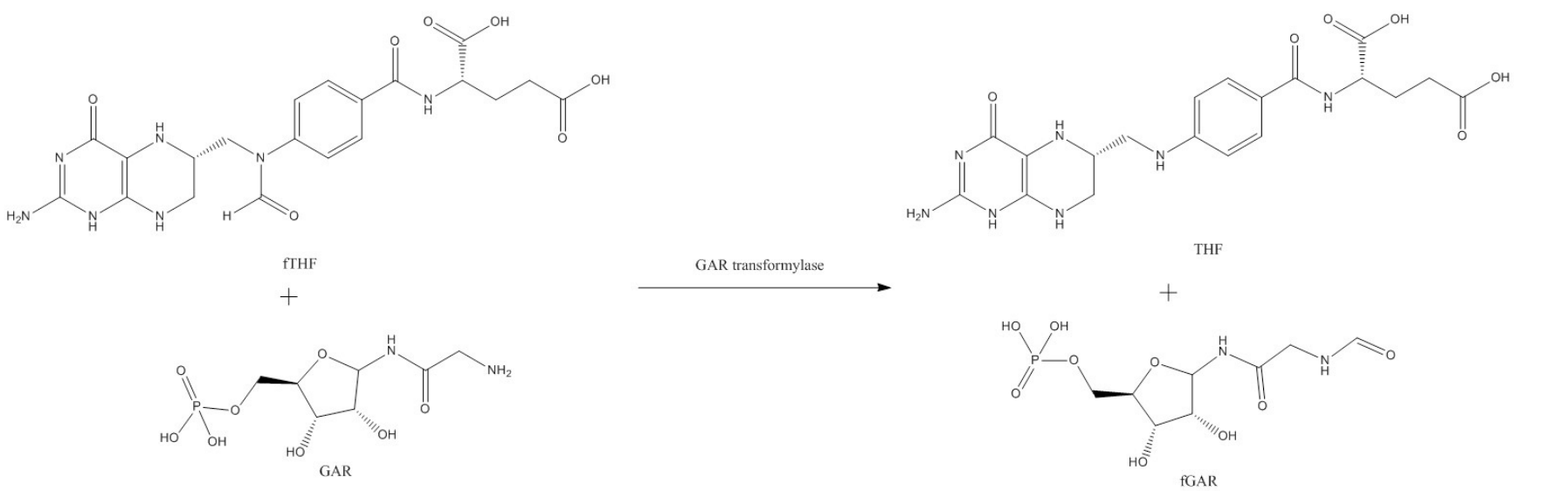
Phosphoribosylglycinamide Formyltransferase

Phosphoribosylglycinamide formyltransferase catalyzes the chemical reaction below.

10-formyltetrahydrofolate + N_1-(5-phospho-D-ribosyl)glycinamide ⇌ Tetrahydrofolate + N_2-formyl-N_1-(5-phospho-D-ribosyl)glycinamide

This reaction plays an important role in the formation of purines through the *de novo* purine biosynthesis pathway. This pathway creates inosine monophosphate (IMP), a precursor to adenosine monophosphate (AMP) and guanosine monophosphate (GMP).



https://en.wikipedia.org/wiki/Phosphoribosylglycinamide_formyltransferase

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Related Glossary Terms

Drag related terms here

Phosphoribulokinase

Phosphoribulokinase (EC 2.7.1.19) is an enzyme that catalyzes the chemical

ATP + D-ribulose 5-phosphate ⇌ ADP + D-ribulose 1,5-bisphosphate

This reaction is important in the dark reactions of photosynthesis (Calvin C generating the substrate (D-ribulose-1,5-bisphosphate) used by RUBISCO i of carbon dioxide. The enzyme belongs to the family of transferases, specif transferring phosphorus-containing groups (phosphotransferases) with an group as acceptor.

https://en.wikipedia.org/wiki/Phosphoribulokinase

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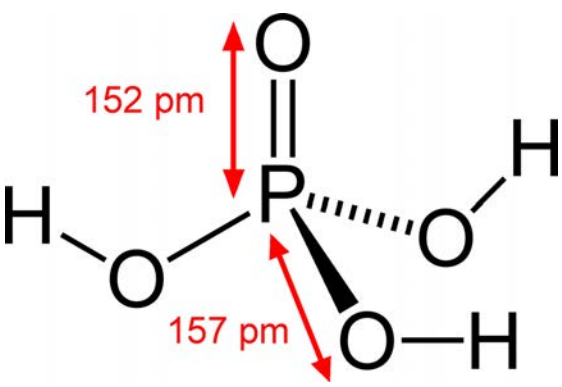
Phosphoric Acid

Phosphoric acid (also known as orthophosphoric acid or phosphoric(V) acid) is a mineral (inorganic) acid having the chemical formula H_3PO_4. Orthophosphoric acid refers to phosphoric acid, which is the IUPAC name for this compound. The prefix ortho is used to distinguish the acid from related phosphoric acids, called polyphosphoric acids. Orthophosphoric acid is a non-toxic acid, which, when pure, is a solid at room temperature and pressure. The conjugate base of phosphoric acid is the dihydrogen phosphate ion, which in turn has a conjugate base of hydrogen phosphate, which has a conjugate base of phosphate.



https://en.wikipedia.org/wiki/Phosphoric_acid

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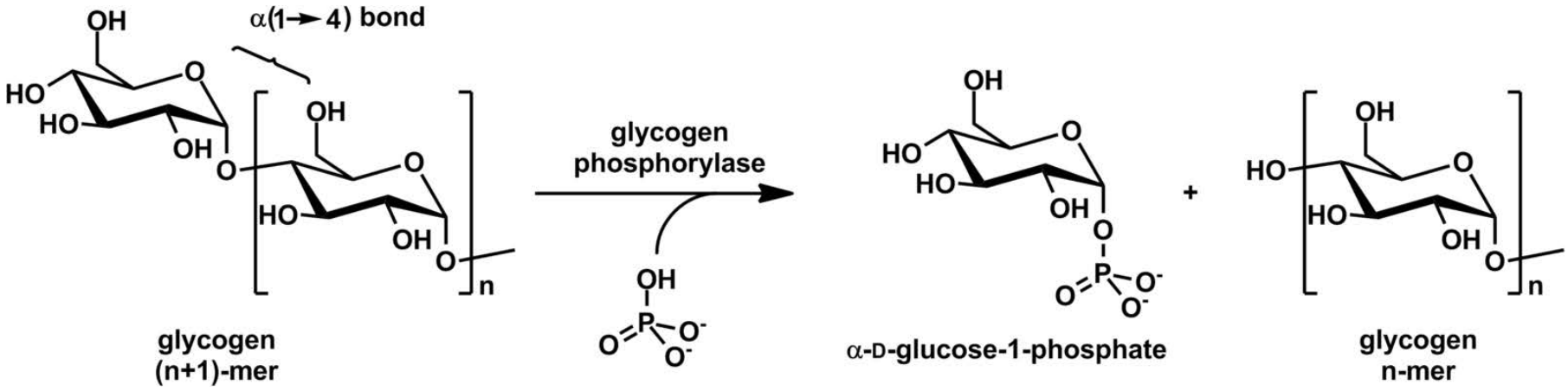
Phosphorolysis

Phosphorolysis is the cleavage of a compound in which inorganic phosphate is the attacking group. It is analogous to hydrolysis. An example of this is glycogen breakdown by glycogen phosphorylase, which catalyzes attack by inorganic phosphate on the terminal glycosyl residue at the nonreducing end of a glycogen molecule. If the glycogen chain has n glucose units, the products of a single phosphorolytic event are one molecule of glucose 1-phosphate and a glycogen chain of n-1 remaining glucose units.



https://en.wikipedia.org/wiki/Phosphorolysis

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Phosphorylase Kinase

Phosphorylase kinase (PhK) is a serine/threonine-specific protein kinase which activates glycogen phosphorylase to release glucose-1-phosphate from glycogen. PhK phosphorylates glycogen phosphorylase at two serine residues, triggering a conformational shift which favors the more active glycogen phosphorylase “a” form over the less active glycogen phosphorylase b.

The protein is a hexadecameric holoenzyme--that is, a homotetramer in which each subunit is itself a tetramer--arranged in an approximate “butterfly” shape. Each of the subunits is composed of an α, β, γ and δ subunit. The γ subunit is the site of the enzyme's catalytic activity while the other three subunits serve regulatory functions.

When unmodified, the α and β subunits inhibit the enzyme's catalysis, but phosphorylation of both these subunits by protein kinase A (PKA, or cAMP-dependent protein kinase) reduces their respective inhibitory activities. The δ subunit is the ubiquitous eukaryotic protein calmodulin which itself has 4 calcium ion binding sites. When cytosolic Ca^{++} levels rise-to as low as 10^{-7} M the δ subunit undergoes a large conformational change that activates the kinase's activity by binding to a complementary hydrophobic patch on the catalytic γ subunit.

https://en.wikipedia.org/wiki/Phosphorylase_kinase

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Phosphorylated Tyrosine

Tyrosine phosphorylation is the addition of a phosphate group to the amino acid tyro
sine on the protein. This transfer of phosphate group from ATP to the amino acid tyr
sine on the protein is made possible through enzymes called tyrosine kinases. Tyrosi
phosphorylation is considered to be one of the key steps in signal transduction and
regulation of enzymatic activity.

Two important classes of tyrosine kinase in tyrosine phosphorylation are receptor ty
sine kinase and nonreceptor tyrosine kinase. Receptor tyrosine kinases are type I tra
membrane proteins possessing an N-terminal extracellular domain, which can bind
tivating ligands, a single transmembrane domain, and a C-terminal cytoplasmic do-
main that includes the catalytic domain. Nonreceptor tyrosine kinases lack a trans-
membrane domain. Most are soluble intracellular proteins, but a subset associate wi
membranes via a membrane-targeting posttranslational modification, such as an N-
terminal myristoyl group, and can act as the catalytic subunit for receptors that lack
their own catalytic domain.

https://en.wikipedia.org/wiki/Tyrosine_phosphorylation

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Phosphorylation

Phosphorylation is the addition of a phosphoryl group ($PO_4^{=}$) to a molecule. Phosphorylation and its counterpart, dephosphorylation, turn many protein enzymes on and off, thereby altering their function and activity. Protein phosphorylation is one type of post-translational modification.
Protein phosphorylation in particular plays a significant role in a wide range of cellular processes. Its prominent role in biochemistry is the subject of a very large body of research.

Reversible phosphorylation of proteins is an important regulatory mechanism that occurs in both prokaryotic and eukaryotic organisms. Kinases phosphorylate proteins and phosphatases dephosphorylate proteins. Many enzymes and receptors are switched "on" or "off" by phosphorylation and dephosphorylation. Reversible phosphorylation results in a conformational change in the structure in many enzymes and receptors, causing them to become activated or deactivated. Phosphorylation usually occurs on serine, threonine, tyrosine and histidine residues in eukaryotic proteins. Histidine phosphorylation of eukaryotic proteins appears to be much more frequent than tyrosine phosphorylation. In prokaryotic proteins phosphorylation occurs on the serine, threonine, tyrosine, histidine or arginine or lysine residues. The addition of a phosphate molecule to a polar R group of an amino acid residue can turn a hydrophobic portion of a protein into a polar and extremely hydrophilic portion of molecule. In this way protein dynamics can induce a conformational change in the structure of the protein via long-range allostery with other hydrophobic and hydrophilic residues in the protein.

One such example of the regulatory role that phosphorylation plays is the p53 tumor suppressor protein. The p53 protein is heavily regulated and contains more than 18 different phosphorylation sites. Activation of p53 can lead to cell cycle arrest, which can be reversed under some circumstances, or apoptotic cell death. This activity occurs only in situations wherein the cell is damaged or physiology is disturbed in normal healthy individuals.

Upon the deactivating signal, the protein becomes dephosphorylated again and stops working. This is the mechanism in many forms of signal transduction, for example the way in which incoming light is processed in the light-sensitive cells of the retina.

https://en.wikipedia.org/wiki/Phosphorylation

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Phosphorylation of Tyrosine

Tyrosine phosphorylation is the addition of a phosphate group to the amino acid t
sine on the protein. This transfer of phosphate group from ATP to the amino acid
sine on the protein is made possible through enzymes called tyrosine kinases. Tyr
phosphorylation is considered to be one of the key steps in signal transduction an
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Two important classes of tyrosine kinase in tyrosine phosphorylation are receptor
sine kinase and nonreceptor tyrosine kinase. Receptor tyrosine kinases are type I
membrane proteins possessing an N-terminal extracellular domain, which can bi
tivating ligands, a single transmembrane domain, and a C-terminal cytoplasmic d
main that includes the catalytic domain. Nonreceptor tyrosine kinases lack a trans
membrane domain. Most are soluble intracellular proteins, but a subset associate
membranes via a membrane-targeting posttranslational modification, such as an
terminal myristoyl group, and can act as the catalytic subunit for receptors that la
their own catalytic domain.

https://en.wikipedia.org/wiki/Tyrosine_phosphorylation

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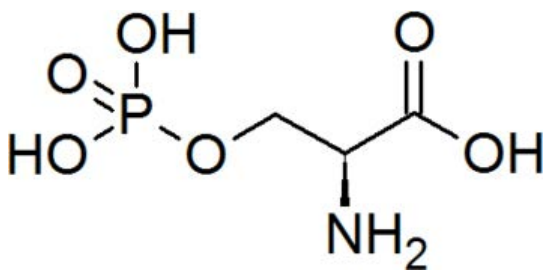
Phosphoserine

Phosphoserine is an ester of serine and phosphoric acid. Phosphoserine is a component of many proteins as the result of posttranslational modifications. The phosphorylation of the alcohol functional group in serine to produce phosphoserine is catalyzed by various types of kinases. Through the use of technologies that utilize an expanded genetic code, phosphoserine can also be incorporated into proteins during translation.

Phosphoserine is a normal metabolite found in human biofluids. Phosphoserine has three potential coordination sites (carboxyl, amine and phosphate group) Determination of the mode of coordination between phosphorylated ligands and metal ions occurring in an organism is a first step to explain the function of the phosphoserine in bioinorganic processes.



https://en.wikipedia.org/wiki/Phosphoserine

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Phosphoserine Aminotransferase

Phosphoserine transaminase catalyzes the chemical reactions below. The fi
is part of the biosynthetic pathway leading to serine.

O-phospho-L-serine + α-ketoglutarate ⇌ 3-phosphonooxypyruvate + L-glu

4-phosphonooxy-L-threonine + 2-oxoglutarate ⇌ (3R)-3-hydroxy-2-oxo-4
phosphonooxybutanoate + L-glutamate

This enzyme is a pyridoxal-phosphate protein.

https://en.wikipedia.org/wiki/Phosphoserine_transaminase

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Phosphoserine Phosphatase

Phosphoserine phosphatase is an enzyme that catalyzes the chemical reacti

O-phospho-L(or D)-serine + $H_2O \rightleftharpoons$L(or D)-serine + P_i

This enzyme belongs to the family of hydrolases, specifically those acting o
ric monoester bonds. This enzyme participates in glycine, serine and threo
lism.

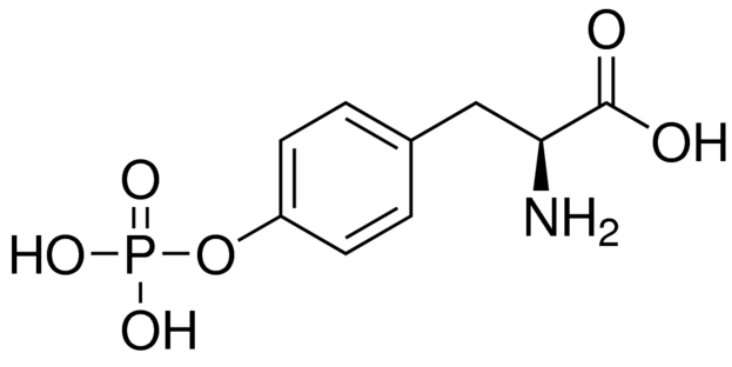
https://en.wikipedia.org/wiki/Phosphoserine_phosphatase

Related Glossary Terms

Drag related terms here

Phosphotyrosine

Aside from being a proteinogenic amino acid, tyrosine has a special role by virtu
the phenol functionality. It occurs in proteins that are part of signal transductio
esses. It functions as a receiver of phosphate groups that are transferred by way
tein kinases (so-called receptor tyrosine kinases). Phosphorylation of the hydro
group changes the activity of the target protein.



https://en.wikipedia.org/wiki/Tyrosine

Related Glossary Terms

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Photolyases

Photolyases (EC 4.1.99.3) are DNA repair enzymes that repair damage caused by exposure to ultraviolet light. This enzyme mechanism requires visible light, preferentially from the violet/blue end of the spectrum, and is known as photoreactivation.

Photolyase is a phylogenetically old enzyme which is present and functional in many species, from the bacteria to the fungi to plants and to the animals. Photolyase is particularly important in repairing UV induced damage in plants. The photolyase mechanism is no longer working in humans and other placental mammals who instead rely on the less efficient nucleotide excision repair mechanism.

Photolyases bind complementary DNA strands and break certain types of pyrimidine dimers that arise when a pair of thymine or cytosine bases on the same strand of DNA become covalently linked. These dimers result in a 'bulge' of the DNA structure, referred to as a lesion. The more common covalent linkage involves the formation of a cyclobutane bridge. Photolyases have a high affinity for these lesions and reversibly bind and convert them back to the original bases.

https://en.wikipedia.org/wiki/Photolyase

Related Glossary Terms

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Photophosphorylation

In the process of photosynthesis, the phosphorylation of ADP to form ATP using the energy of sunlight is called photophosphorylation. Only two sources of energy are available to living organisms: sunlight and reduction-oxidation (redox) reactions. All organisms produce ATP, which is the universal energy currency of life. This involves photolysis of water and a continuous unidirectional flow of electron from water to PSII.

In photophosphorylation, light energy is used to create a high-energy electron donor and a lower-energy electron acceptor. Electrons then move spontaneously from donor to acceptor through an electron transport chain.

https://en.wikipedia.org/wiki/Photophosphorylation

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Photorespiration

Photorespiration (also known as the oxidative photosynthetic carbon cycle, or C_2 photosynthesis) refers to a process in plant metabolism where the enzyme RuBisCO oxygenates RuBP, causing some of the energy produced by photosynthesis to be wasted. The desired reaction is the addition of carbon dioxide to RuBP (carboxylation), a key step in the Calvin–Benson cycle, however approximately 25% of reactions by RuBisCO instead add oxygen to RuBP (oxygenation), creating a product that cannot be used within the Calvin–Benson cycle. This process reduces the efficiency of photosynthesis, potentially reducing photosynthetic output by 25% in C_3 plants. Photorespiration involves a complex network of enzyme reactions that exchange metabolites between chloroplasts, leaf peroxisomes and mitochondria.

The oxygenation reaction of RuBisCO is a wasteful process because 3-phosphoglycerate is created at a reduced rate and higher metabolic cost compared with RuBP carboxylase activity. While photorespiratory carbon cycling results in the formation of G3P eventually, there is still a net loss of carbon (around 25% of carbon fixed by photosynthesis is re-released as CO2) and nitrogen, as ammonia. Ammonia must be detoxified at a substantial cost to the cell. Photorespiration also incurs a direct cost of one ATP and one NAD(P)H.

While it is common to refer to the entire process as photorespiration, technically the term refers only to the metabolic network which acts to rescue the products of the oxygenation reaction (phosphoglycolate).

https://en.wikipedia.org/wiki/Photorespiration

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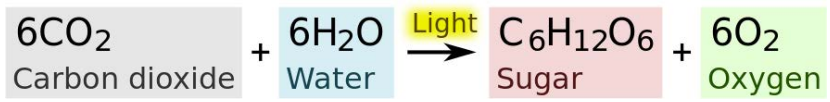
Photosynthesis

Photosynthesis is a process used by plants and other organisms to convert light energy, normally from the Sun, into chemical energy that can be later released to fuel the organisms' activities (energy transformation). This chemical energy is stored in carbohydrate molecules, such as sugars, which are synthesized from carbon dioxide and water – hence the name photosynthesis, from the Greek φώς, phōs, "light", and σύνθεσις, synthesis, "putting together". In most cases, oxygen is also released as a waste product. Most plants, most algae, and cyanobacteria perform photosynthesis. Such organisms are called photoautotrophs. Photosynthesis maintains atmospheric oxygen levels and supplies all of the organic compounds and most of the energy necessary for life on Earth.

Although photosynthesis is performed differently by different species, the process always begins when energy from light is absorbed by proteins called reaction centres that contain green chlorophyll pigments. In plants, these proteins are held inside organelles called chloroplasts, which are most abundant in leaf cells, while in bacteria they are embedded in the plasma membrane. In these light-dependent reactions, some energy is used to strip electrons from suitable substances, such as water, producing oxygen gas.

The hydrogen freed by water splitting is used in the creation of two further compounds: reduced nicotinamide adenine dinucleotide phosphate (NADPH) and adenosine triphosphate (ATP), the "energy currency" of cells. In plants, algae and cyanobacteria, sugars are produced by a subsequent sequence of light-independent reactions called the Calvin cycle, but some bacteria use different mechanisms, such as the reverse citric acid (Krebs) cycle. In the Calvin cycle, atmospheric carbon dioxide is incorporated into already existing organic carbon compounds, such as ribulose bisphosphate (RuBP). Using the ATP and NADPH produced by the light-dependent reactions, the resulting compounds are then reduced and removed to form further carbohydrates, such as glucose.

https://en.wikipedia.org/wiki/Photosynthesis



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Photosynthetic

A word used to describe a living organism that can perform photosynthesis
ess of photosynthesis itself.

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Photosystem I

Photosystem I (PSI) is an integral membrane protein complex that uses light energy to mediate electron transfer from plastocyanin to ferredoxin. Linear electron transport in PSI produces both ATP and NADPH, while cyclic electron transport drives the production of ATP but not the production NADPH. The PS I system comprises more than 110 co-factors, significantly more than photosystem II. These various components have a wide range of functions. The electron transfer components of the reaction center of PSI are a primary electron donor P-700 (chlorophyll dimer) and five electron acceptors: A_0 (chlorophyll), A_1 (a phylloquinone) and three Fe_4-S_4 iron-sulphur centres: F_x, F_a, and F_b.

Molecular data show that PS I likely evolved from the photosystems of green-sulfur bacteria. The photosystems of green sulfur bacteria and those of cyanobacteria, algae, and higher plants are not the same, however there are many analogous functions and similar structures. Three main features are similar between the different photosystems. First, redox potential is negative enough to reduce ferredoxin. Next, the electron-accepting reaction centers include iron-sulfur proteins. Last, redox centrers in complexes of both photosystems are constructed upon a protein subunit dimer. The photosystem of green sulfur bacteria even contains all of the same co-factors of the electron transport chain in PS I. The number and degree of similarities between the two photosystems strongly indicates that PS I is derived from the analogous photosystem of green-sulfur bacteria.

https://en.wikipedia.org/wiki/Photosystem_I

Related Glossary Terms

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Photosystem II

Photosystem II (or water-plastoquinone oxidoreductase) is the first protein complex in the light-dependent reactions of oxygenic photosynthesis. It is located in the thylakoid membrane of plants, algae, and cyanobacteria. Within the photosystem, enzymes capture photons of light to energize electrons that are then transferred through a variety of coenzymes and cofactors to reduce plastoquinone to plastoquinol. The energized electrons are replaced by oxidizing water to form hydrogen ions and molecular oxygen.

By replenishing lost electrons with electrons from the splitting of water, photosystem II provides the electrons for all of photosynthesis to occur. The hydrogen ions (protons) generated by the oxidation of water help to create a proton gradient that is used by ATP synthase to generate ATP. The energized electrons transferred to plastoquinone are ultimately used to reduce $NADP^+$ to NADPH or are used in cyclic photophosphorylation.

Photosynthetic water splitting (or oxygen evolution) is one of the most important reactions on the planet, since it is the source of nearly all the atmosphere's oxygen. Moreover, artificial photosynthetic water-splitting may contribute to the effective use of sunlight as an alternative energy-source.

The mechanism of water oxidation is still not fully elucidated, but we know many details about this process. The oxidation of water to molecular oxygen requires extraction of four electrons and four protons from two molecules of water. The experimental evidence that oxygen is released through cyclic reaction of oxygen evolving complex (OEC) within one PSII was provided by Pierre Joliot *et al*. They have shown that, if dark-adapted photosynthetic material (higher plants, algae, and cyanobacteria) is exposed to a series of single turnover flashes, oxygen evolution is detected with typical period-four damped oscillation with maxima on the third and the seventh flash and with minima on the first and the fifth flash . Based on this experiment, Bessel Kok and co-workers introduced a cycle of five flash-induced transitions of the so-called S-states, describing the four redox states of OEC: When four oxidizing equivalents have been stored (at the S_4-state), OEC returns to its basic and in the dark stable S_0-state. Finally, the intermediate S-states were proposed by Jablonsky and Lazar as a regulatory mechanism and link between S-states and tyrosine Z.

https://en.wikipedia.org/wiki/Photosystem_II

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Photosystems

Photosystems are functional and structural units of protein complexes involved in photosynthesis that together carry out the primary photochemistry of photosynthesis: the absorption of light and the transfer of energy and electrons. Photosystems are found in the thylakoid membranes of plants, algae and cyanobacteria (in plants and algae these are located in the chloroplasts), or in the cytoplasmic membrane of photosynthetic bacteria. There are two kinds of photosystems: II and I, respectively.

At the heart of a photosystem lies the reaction center, which is an enzyme that uses light to reduce molecules (provide with electrons). This reaction center is surrounded by light-harvesting complexes that enhance the absorption of light.

Two families of reaction centers in photosystems exist: type I reaction centers (such as photosystem I (P_{700}) in chloroplasts and in green-sulphur bacteria) and type II reaction centers (such as photosystem II (P_{680}) in chloroplasts and in non-sulphur purple bacteria).

Each photosystem can be identified by the wavelength of light to which it is most reactive (700 and 680 nanometers, respectively for PSI and PSII in chloroplasts), the amount and type of light-harvesting complexes present and the type of terminal electron acceptor used.

Type I photosystems use ferredoxin-like iron-sulfur cluster proteins as terminal electron acceptors, while type II photosystems ultimately shuttle electrons to a quinone terminal electron acceptor. Both reaction center types are present in chloroplasts and cyanobacteria, and work together to form a unique photosynthetic chain able to extract electrons from water, creating oxygen as a byproduct.

https://en.wikipedia.org/wiki/Photosystem

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Phototrophs

Phototrophs are organisms that carry out photon capture to acquire energy. They use the energy from light to carry out various cellular metabolic processes. It is a common misconception that phototrophs are obligatorily photosynthetic. Many, but not all, phototrophs often photosynthesize: they anabolically convert carbon dioxide into organic material to be utilized structurally, functionally, or as a source for later catabolic processes (e.g. in the form of starches, sugars and fats). All phototrophs either use electron transport chains or direct proton pumping to establish an electro-chemical gradient which is utilized by ATP synthase, to provide the molecular energy currency for the cell. Phototrophs can be either autotrophs or heterotrophs.

Most of the well-recognized phototrophs are autotrophic, also known as photoautotrophs, and can fix carbon. They can be contrasted with chemotrophs that obtain their energy by the oxidation of electron donors in their environments. Photoautotrophs are capable of synthesizing their own food from inorganic substances using light as an energy source. Green plants and photosynthetic bacteria are photoautotrophs. Photoautotrophic organisms are sometimes referred to as holophytic. Such organisms derive their energy for food synthesis from light and are capable of using carbon dioxide as their principal source of carbon.

Oxygenic photosynthetic organisms use chlorophyll for light-energy capture and oxidize water, "splitting" it into molecular oxygen. In contrast, anoxygenic photosynthetic bacteria have a substance called bacteriochlorophyll - which absorbs predominantly at non-optical wavelengths - for light-energy capture, live in aquatic environments, and will, using light, oxidize chemical substances such as hydrogen sulfide rather than water.

https://en.wikipedia.org/wiki/Phototroph

Related Glossary Terms

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Phycoerythrin

Phycoerythrin (PE) is a red protein-pigment complex from the light-harves
biliprotein family, present in red algae and cryptophytes, accessory to the m
phyll pigments responsible for photosynthesis.

Like all phycobiliproteins, it is composed of a protein part covalently bindi
phores called phycobilins. In the phycoerythrin family, the most known phy
are: phycoerythrobilin, the typical phycoerythrin acceptor chromophore, a
times phycourobilin. Phycoerythrins are composed of (αβ) monomers, usua
ized in a disk-shaped trimer (αβ)3 or hexamer (αβ)6 (second one is the fun
of the antenna rods). These typical complexes contain also third type of sub
chain.

https://en.wikipedia.org/wiki/Phycoerythrin

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Chapter 5 - Energy: Photophosphorylation

Phylloquinone

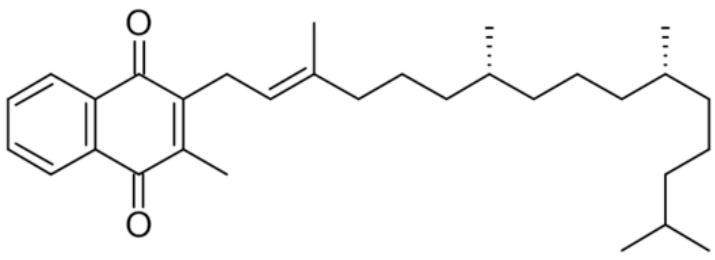
Phylloquinone, also Vitamin K_1, is a polycyclic aromatic ketone, based on 2-methyl-1,4-naphthoquinone, with a 3-phytyl substituent.

It is a fat-soluble vitamin that is stable to air and moisture but decomposes in sunlight. It is found naturally in a wide variety of green plants, particularly leaves, since it functions as an electron acceptor during photosynthesis, forming part of the electron transport chain of Photosystem I.

Phylloquinone is an electron acceptor during photosynthesis, forming part of the electron transport chain of Photosystem I.

Its best-known function in animals is as a cofactor in the formation of coagulation factors II (prothrombin), VII, IX, and X by the liver. It is also required for the formation of anticoagulant factors protein C and S. It is commonly used to treat warfarin toxicity, and as an antidote for coumatetralyl.

Vitamin K is required for bone protein formation.



https://en.wikipedia.org/wiki/Phylloquinone

Related Glossary Terms

Physiological pH

The pH of blood is usually slightly basic with a value of pH 7.365. This value is often referred to as physiological pH in biology and medicine. Plaque can create a local acidic environment that can result in tooth decay by demineralization. Enzymes and other proteins have an optimum pH range and can become inactivated or denatured outside this range.

pH in living systems

Compartment	pH
Gastric acid	1.5-3.5
Lysosomes	4.5
Granules of chromaffin cells	5.5
Human skin	5.5
Urine	6.0
Cytosol	7.2
Cerebrospinal fluid (CSF)	7.5
Blood (natural pH)	7.34–7.45
Mitochondrial matrix	7.5
Pancreas secretions	8.1

https://en.wikipedia.org/wiki/PH#pH_in_nature

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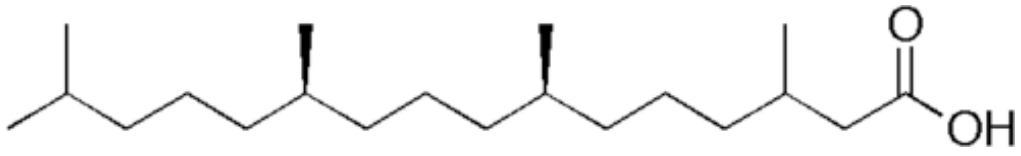
Phytanic Acid

Phytanic acid (or 3,7,11,15-tetramethyl hexadecanoic acid) is a branched chain acid that humans can obtain through the consumption of dairy products, rum mal fats, and certain fish. Western diets are estimated to provide 50–100 mg tanic acid per day. Unlike most fatty acids, phytanic acid cannot be metabolize oxidation. Instead, it undergoes α-oxidation in the peroxisome, where it is con into pristanic acid by the removal of one carbon. Pristanic acid can undergo se rounds of β-oxidation in the peroxisome to form medium chain fatty acids tha converted to carbon dioxide and water in mitochondria.



https://en.wikipedia.org/wiki/Phytanic_acid

Related Glossary Terms

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Phytic Acid

Phytic acid (known as inositol hexakisphosphate (IP6), inositol polyphosphate, or phytate when in salt form), discovered in 1903, a saturated cyclic acid, is the principal storage form of phosphorus in many plant tissues, especially bran and seeds.

Phosphorus and inositol in phytate form are not, in general, bioavailable to nonruminant animals because these animals lack the digestive enzyme phytase required to remove phosphate from the inositol in the phytate molecule. Ruminants are readily able to digest phytate because of the phytase produced by rumen microorganisms.

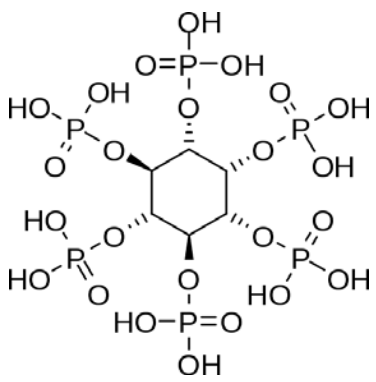
In most commercial agriculture, nonruminant livestock, such as swine, fowl, and fish, are fed mainly grains, such as maize, legumes, and soybeans. Because phytate from these grains and beans is unavailable for absorption, the unabsorbed phytate passes through the gastrointestinal tract, elevating the amount of phosphorus in the manure. Excess phosphorus excretion can lead to environmental problems, such as eutrophication.

The bioavailability of phytate phosphorus can be increased by supplementation of the diet with the enzyme phytase.

Also, viable low-phytic acid mutant lines have been developed in several crop species in which the seeds have drastically reduced levels of phytic acid and concomitant increases in inorganic phosphorus. However, reported germination problems have hindered the use of these cultivars thus far. Probability due to its critical role in both phosphorus and metal ion storage.

The use of sprouted grains will reduce the quantity of phytic acids in feed, with no significant reduction of nutritional value.

Phytate variants also have the potential to be used in soil remediation, to immobilize uranium, nickel and other inorganic contaminants.

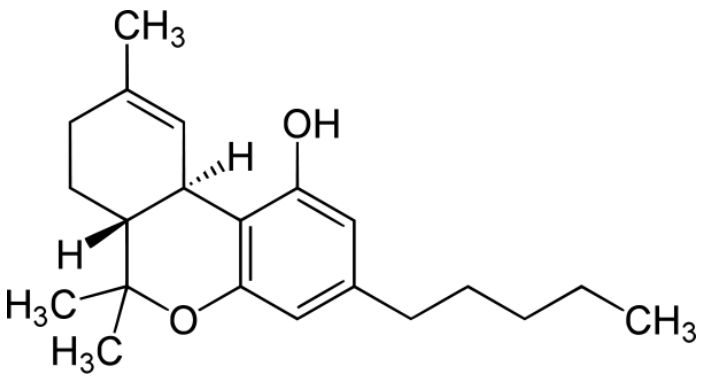


https://en.wikipedia.org/wiki/Phytic_acid

Phytocannabinoids

The classical cannabinoids are concentrated in a viscous resin produced in structures known as glandular trichomes. At least 113 different cannabinoids have been isolated from the *Cannabis* plant. To the right, the main classes of cannabinoids from *Cannabis* are shown. The best studied cannabinoids include tetrahydrocannabinol (THC - shown below), cannabidiol (CBD) and cannabinol (CBN).

Endocannabinoids serve as intercellular 'lipid messengers', signaling molecules that are released from one cell and activating the cannabinoid receptors present on other nearby cells. Although in this intercellular signaling role they are similar to the well-known monoamine neurotransmitters, such as acetylcholine and dopamine, endocannabinoids differ in numerous ways from them. For instance, they are used in retrograde signaling between neurons. Furthermore, endocannabinoids are lipophilic molecules that are not very soluble in water. They are not stored in vesicles, and exist as integral constituents of the membrane bilayers that make up cells. They are believed to be synthesized 'on-demand' rather than made and stored for later use. The mechanisms and enzymes underlying the biosynthesis of endocannabinoids remain elusive and continue to be an area of active research.



https://en.wikipedia.org/wiki/Cannabinoid

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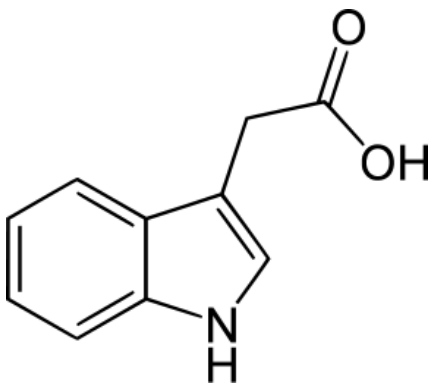
Phytohormone

Plant hormones (also known as phytohormones) are chemicals that regulate plant growth. Plant hormones are signal molecules produced within the plant, and occur in extremely low concentrations. Hormones regulate cellular processes in targeted cells locally and, moved to other locations, in other functional parts of the plant. Hormones also determine the formation of flowers, stems, leaves, the shedding of leaves, and the development and ripening of fruit. Plants, unlike animals, lack glands that produce and secrete hormones. Instead, each cell is capable of producing hormones.

Plant hormones shape the plant, affecting seed growth, time of flowering, the sex of flowers, senescence of leaves, and fruits. They affect which tissues grow upward and which grow downward, leaf formation and stem growth, fruit development and ripening, plant longevity, and even plant death. Hormones are vital to plant growth, and, lacking them, plants would be mostly a mass of undifferentiated cells. So they are also known as growth factors or growth hormones. Phytohormones are found not only in higher plants, but in algae too, showing similar functions, and in microorganisms, like fungi and bacteria, but, in this case, they play no hormonal or other immediate physiological role in the producing organism and can, thus, be regarded as secondary metabolites. Shown below is indole acetic acid, an auxin hormone.



https://en.wikipedia.org/wiki/Plant_hormone

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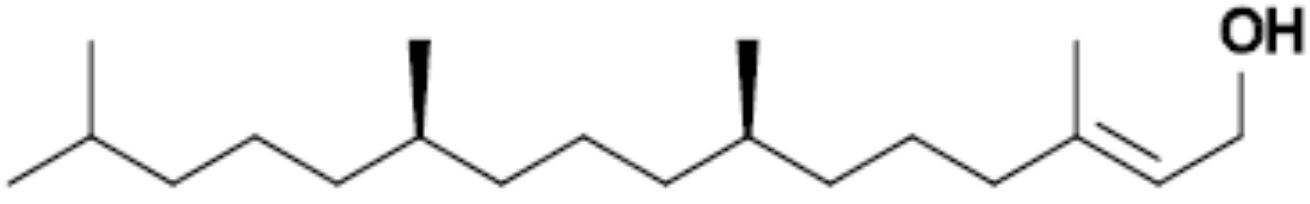
Chapter 2 - Structure & Function: Amino Acids

Phytol

Phytol is an acyclic diterpene alcohol that can be used as a precursor for the
ture of synthetic forms of vitamin E and vitamin K_1. In ruminants, the gut f
tion of ingested plant materials liberates phytol, a constituent of chlorophy
then converted to phytanic acid and stored in fats. In shark liver it yields pr



https://en.wikipedia.org/wiki/Phytol

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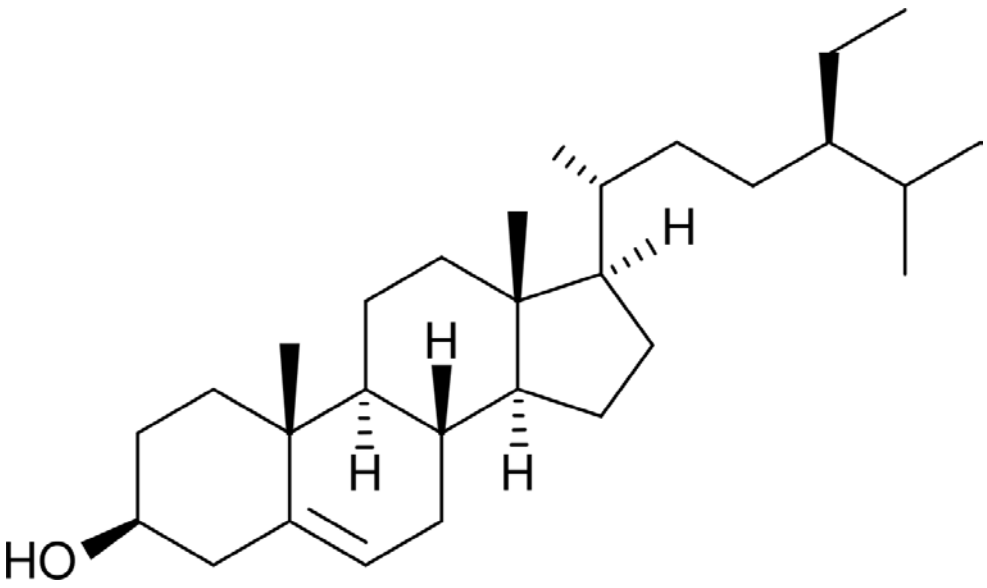
Chapter 2 - Structure & Function: Lipids

Phytosterols

Phytosterols, which encompass plant sterols and stanols, are steroid compounds similar to cholesterol which occur in plants and vary only in carbon side chains and/or presence or absence of a double bond. Stanols are saturated sterols, having no double bonds in the sterol ring structure. More than 200 sterols and related compounds have been identified. Free phytosterols extracted from oils are insoluble in water, relatively insoluble in oil, and soluble in alcohols. The most commonly occurring phytosterols in the human diet are β-sitosterol (shown below), campesterol and stigmasterol, which account for about 65%, 30% and 3% of diet contents, respectively.



https://en.wikipedia.org/wiki/Phytosterol

Related Glossary Terms

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P_i

P_i is a shortcut abbreviation for inorganic phosphate, such as released in dephosphorylation reactions catalyzed by phosphatases or released by hydrolytic cleavages (such as hydrolysis of ATP).

Related Glossary Terms

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Pi -turns

A turn is an element of secondary structure in proteins where the polypeptide chain reverses its overall direction.

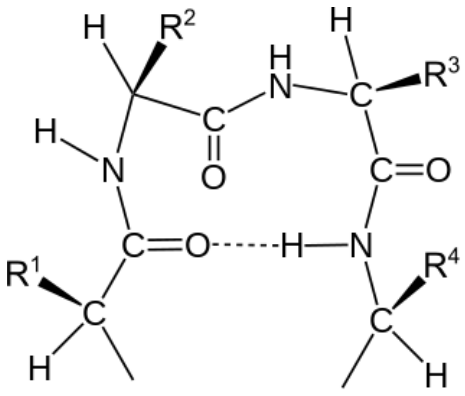
Turns are classified according to the separation between the two end residues:
In an α-turn the end residues are separated by four peptide bonds

(i --> i +/- 4).

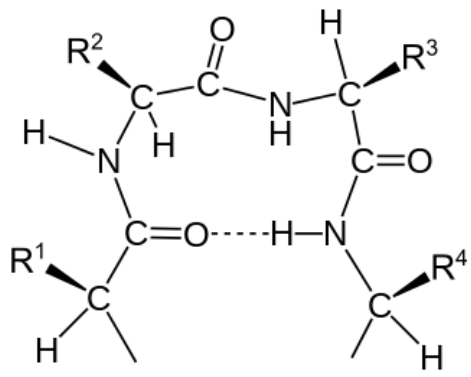
In a π-turn, by five bonds

(i --> i +/- 5)

Shown below is a β turn



ß turn: Type I



ß turn: Type II

https://en.wikipedia.org/wiki/Turn_(biochemistry)

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Chapter 2 - Structure & Function: Proteins I

PI-1

PI-1 in the phosphorylated form is an inhibitor of phosphoprotein phospha
phoprotein phosphatase removes phosphates added to proteins by kinases.
nases are active, PI-1 gets phosphorylated and actively inhibits phosphopro
phatase, thus stopping a futile cycle. When PI-1 gets dephosphorylated, ph
tein phosphatase becomes active and reverses actions of protein kinases.

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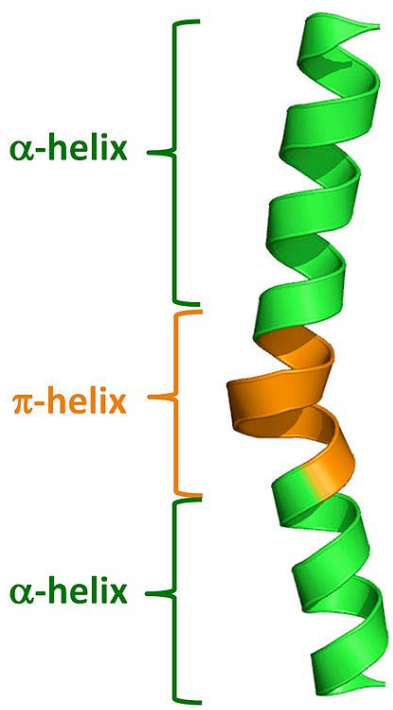
Pi-helix

A Pi helix (or π-helix) is a type of secondary structure found in proteins. Although once thought to be rare, short π-helices are found in 15% of known protein structures and are believed to be an evolutionary adaptation derived by the insertion of a single amino acid into an α-helix.

The amino acids in a standard π-helix are arranged in a right-handed helical structure. Each amino acid corresponds to an 87° turn in the helix (i.e., the helix has 4.1 residues per turn), and a translation of 1.15 Å (=0.115 nm) along the helical axis. Most importantly, the N-H group of an amino acid forms a hydrogen bond with the C=O group of the amino acid five residues earlier. This repeated i+5→i hydrogen bonding defines a π-helix.



https://en.wikipedia.org/wiki/Pi_helix

PI3-kinase

Phosphatidylinositol-4,5-bisphosphate 3-kinase (also called phosphatidylinositide 3-kinases, phosphatidylinositol-3-kinases, PI 3-kinases, PI(3)Ks, PI-3Ks or by the HUGO official stem symbol for the gene family, PI3K(s)) are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer.

PI3Ks are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns). The pathway, with oncogene PIK3CA and tumor suppressor PTEN, is implicated in insensitivity of cancer tumors to insulin and IGF1, and in calorie restriction.

PI 3-kinases have been linked to an extraordinarily diverse group of cellular functions, including cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. Many of these functions relate to the ability of class I PI 3-kinases to activate protein kinase B (PKB, aka Akt) as in the PI3K/AKT/mTOR pathway. The p110δ and p110γ isoforms regulate different aspects of immune responses. PI 3-kinases are also a key component of the insulin signaling pathway. Hence there is great interest in the role of PI 3-kinase signaling in diabetes mellitus.

https://en.wikipedia.org/wiki/Phosphoinositide_3-kinase

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Chapter 7 - Information Processing: Signaling

Chapter 9 - Point by Point: Information Processing

Pili

A pilus (Latin for 'hair'; plural : pili) is a hairlike appendage found on the su
many bacteria. The terms pilus and fimbria (Latin for 'fringe'; plural: fimbr
used interchangeably, although some researchers reserve the term pilus for
age required for bacterial conjugation. All pili are primarily composed of ol
pilin proteins.

Dozens of these structures can exist on the bacteria. Some bacterial viruses
phages attach to receptors on pili at the start of their reproductive cycle.

https://en.wikipedia.org/wiki/Pilus

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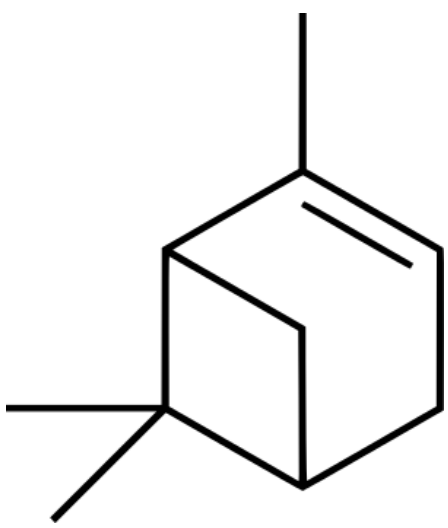
Pinene

Pinene ($C_{10}H_{16}$) is a bicyclic monoterpene chemical compound. There are two structural isomers of pinene found in nature: α-pinene and β-pinene. As the name suggests, both forms are important constituents of pine resin. They are also found in the resins of many other conifers, as well as in non-coniferous plants such as camphorweed (*Heterotheca*) and big sagebrush (*Artemisia tridentata*). Both isomers are used by many insects in their chemical communication system. The two isomers of pinene constitute the major component of turpentine.



https://en.wikipedia.org/wiki/Pinene

Related Glossary Terms

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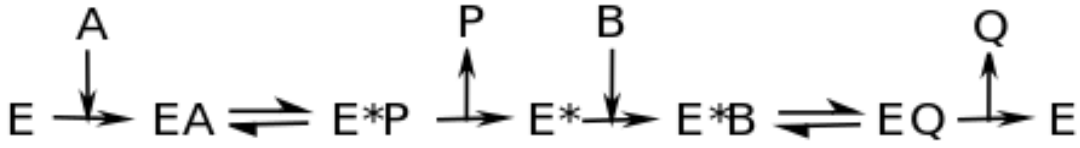
Ping-pong

Ping-pong is a term used to describe an enzymatic reaction in which the enzyme can exist in two different states that it switches between. These are called E and a chemically modified form of the enzyme called E*. This modified enzyme is known as an intermediate. In such mechanisms, substrate A binds, changes the enzyme to E* by, for example, transferring a chemical group to the active site, and is then released. Only after the first substrate is released can substrate B bind and react with the modified enzyme, regenerating the unmodified E form. When a set of v by [S] curves (fixed A, varying B) from an enzyme with a ping–pong mechanism are plotted in a Lineweaver–Burk plot, a set of parallel lines will be produced. This is called a secondary plot.

Enzymes with ping–pong mechanisms include some oxidoreductases such as thioredoxin peroxidase, transferases such as acylneuraminate cytidylyltransferase and serine proteases such as trypsin and chymotrypsin. Serine proteases are a very common and diverse family of enzymes, including digestive enzymes (trypsin, chymotrypsin, and elastase), several enzymes of the blood clotting cascade and many others. In these serine proteases, the E* intermediate is an acyl-enzyme species formed by the attack of an active site serine residue on a peptide bond in a protein substrate.



https://en.wikipedia.org/wiki/Enzyme_kinetics#Ping.E2.80.93pong_mechanisms

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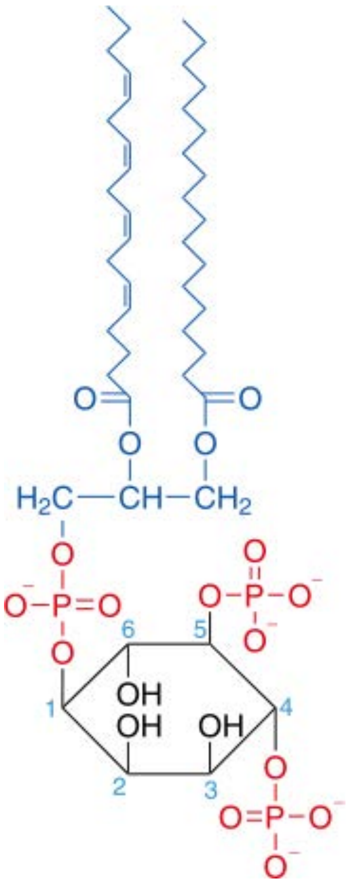
PIP_2

Phosphatidylinositol 4,5-bisphosphate or PtdIns(4,5)P_2, also known simply as PIP_2, is a minor phospholipid component of cell membranes. PtdIns(4,5)P_2 is enriched at the plasma membrane where it is a substrate for a number of important signaling proteins.

PtdIns(4,5)P_2 is formed primarily by the type I phosphatidylinositol 4-phosphate 5-kinases from PI(4)P. In metazoans, PtdIns(4,5)P2 can also be formed by type II phosphatidylinositol 5-phosphate 4-kinases from PI(5)P.

The fatty acids of PtdIns(4,5)P_2 are variable in different species and tissues, but studies show the most common fatty acids are stearic in position 1 and arachidonic in 2.



https://en.wikipedia.org/wiki/Phosphatidylinositol_4,5-bisphosphate

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PIP_3

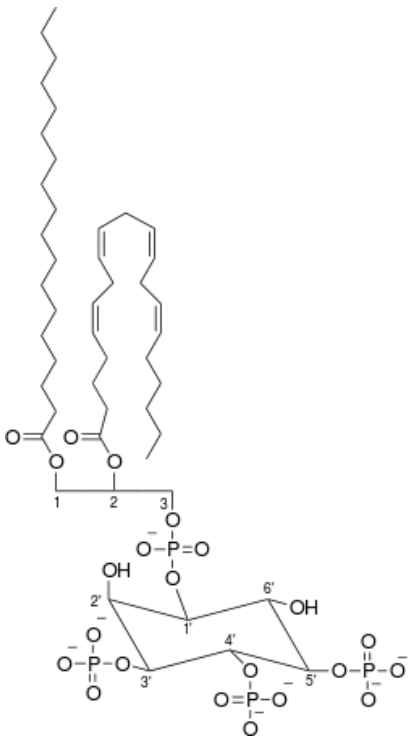
Phosphatidylinositol (3,4,5)-trisphosphate ($PtdIns(3,4,5)P_3$), abbreviated PIP_3, is the product of the class I phosphoinositide 3-kinases (PI 3-kinases) phosphorylation of phosphatidylinositol (4,5)-bisphosphate (PIP_2). It is a phospholipid that resides on the plasma membrane.

PIP_3 functions to activate downstream signaling components, the most notable one being the protein kinase AKT, which activates downstream anabolic signaling pathways required for cell growth and survival. Phospholipase C cleaves PIP_2 to produce inositol triphosphate IP_3, and diacylglycerol.

$PtdIns(3,4,5)P_3$ is dephosphorylated by the phosphatase PTEN on the 3 position, generating $PI(4,5)P_2$, and by SHIPs (SH2-containing inositol phosphatase) on the 5' position of the inositol ring, producing $PI(3,4)P_2$.

The PH domain in a number of proteins binds to $PtdIns(3,4,5)P_3$. Such proteins include Akt/PKB, PDK1, Btk1, and ARNO. The generation of $PtdIns(3,4,5)P_3$ at the plasma membrane upon the activation of class I PI 3-kinases causes these proteins to translocate to the plasma membrane and affects their activity accordingly.

The PH domain allows binding between $PtdIns(3,4,5)P_3$ and G protein-coupled receptor kinases (GRKs). This enhances the binding of the GRK to the plasma membrane.



https://en.wikipedia.org/wiki/Phosphatidylinositol_(3,4,5)-trisphosphate

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Pitch

In a helix, the pitch is the height of one complete helix turn, measured para
axis of the helix.

https://en.wikipedia.org/wiki/Helix#Types

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Chapter 2 - Structure & Function: Proteins I

Chapter 9 - Point by Point: Structure and Function

pK_a

The negative base 10 logarithm of the acid dissociation constant, K_a. The larger the value of pK_a, the smaller the extent of dissociation at any given pH (see Henderson–Hasselbalch equation)—that is, the weaker the acid. A weak acid has a pK_a value in the approximate range −2 to 12 in water. Acids with a pK_a value of less than about −2 are said to be strong acids. The dissociation of a strong acid is effectively complete such that concentration of the undissociated acid is too small to be measured. pK_a values for strong acids can, however, be estimated by theoretical means.

$$\mathrm{p}K_\mathrm{a} = -\log_{10} K_\mathrm{a}$$

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log \frac{[\mathrm{A}^-]}{[\mathrm{HA}]}$$

https://en.wikipedia.org/wiki/Acid_dissociation_constant

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Plankton

Plankton (singular plankter) are a diverse group of organisms that live in th
umn of large bodies of water and that cannot swim against a current. They
crucial source of food to many large aquatic organisms, such as fish and wh

These organisms include drifting or floating bacteria, archaea, algae, protoz
mals that inhabit, for example, the pelagic zone of oceans, seas, or bodies o
ter. Essentially, plankton are defined by their ecological niche rather than a
netic or taxonomic classification.

Though many planktonic species are microscopic in size, plankton includes
covering a wide range of sizes, including large organisms such as jellyfish.

https://en.wikipedia.org/wiki/Plankton

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Plant

Plants, also called green plants, are multicellular eukaryotes of the kingdom Pla
They form an unranked clade Viridiplantae that includes the flowering plants, c
and other gymnosperms, ferns, clubmosses, hornworts, liverworts, mosses and
green algae. Green plants exclude the red and brown algae, the fungi, archaea, b
and animals.

Green plants have cell walls with cellulose and obtain most of their energy from
light via photosynthesis by primary chloroplasts, derived from endosymbiosis w
nobacteria. Their chloroplasts contain chlorophylls a and b, which gives them t
green color. Some plants are parasitic and have lost the ability to produce norm
amounts of chlorophyll or to photosynthesize. Plants are also characterized by s
reproduction, modular and indeterminate growth, and an alternation of genera
although asexual reproduction is also common.

https://en.wikipedia.org/wiki/Plant

Related Glossary Terms

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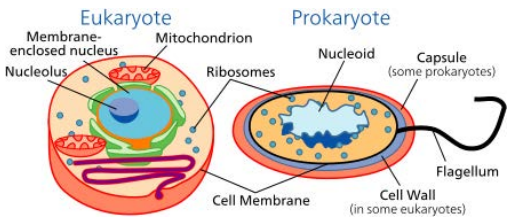
Plasma Membrane

The plasma membrane (also called a cell membrane) is a biological membrane that separates the interior of all cells from the outside environment. The cell membrane is selectively permeable to ions and organic molecules and controls the movement of substances in and out of cells. The basic function of the cell membrane is to protect the cell from its surroundings. It consists of the phospholipid bilayer with embedded proteins. Cell membranes are involved in a variety of cellular processes such as cell adhesion, ion conductivity and cell signaling and serve as the attachment surface for several extracellular structures, including the cell wall, glycocalyx, and intracellular cytoskeleton. They can also be artificially reassembled.



https://en.wikipedia.org/wiki/Cell_membrane

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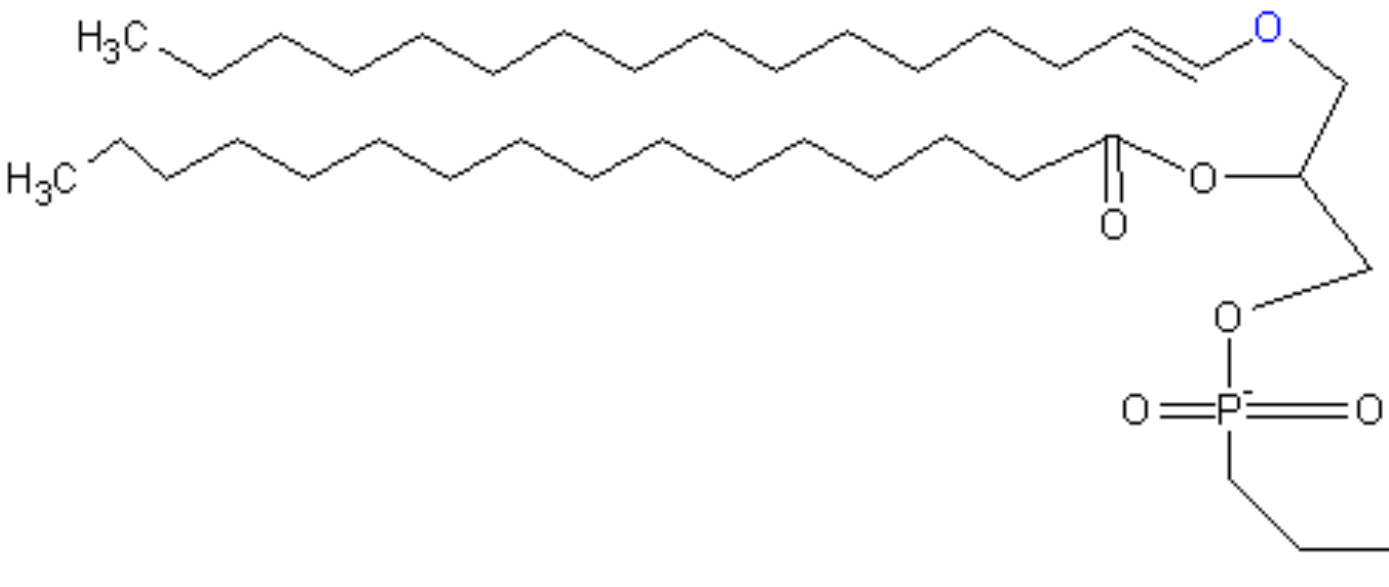
Plasmalogens

Plasmalogens are a type of ether phospholipid characterized by the presence of a vinyl ether linkage at the sn-1 position and an ester linkage at the sn-2 position. In mammals, the sn-1 position is typically derived from C16:0, C18:0, or C18:1 fatty alcohols while the sn-2 position is most commonly occupied by polyunsaturated fatty acids. The most common head groups present in mammalian plasmalogens are ethanolamine (designated plasmenylethalomines) or choline (designated plasmenylcholines).



https://en.wikipedia.org/wiki/Plasmalogen

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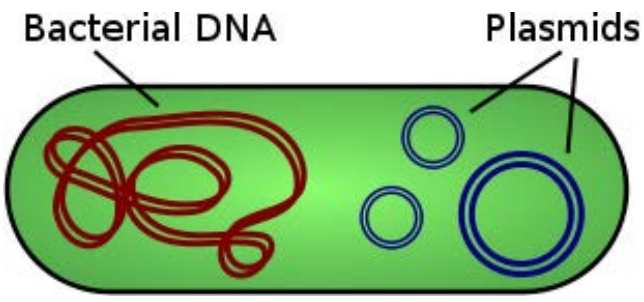
Chapter 2 - Structure & Function: Lipids
Chapter 9 - Point by Point: Structure and Function

Plasmids

A plasmid is a small DNA molecule within a cell that is physically separated from a chromosomal DNA and can replicate independently. They are most commonly found in bacteria as small circular, double-stranded DNA molecules. However, plasmids are sometimes present in archaea and eukaryotic organisms. In nature, plasmids often carry genes that may benefit the survival of the organism, for example antibiotic resistance. While the chromosomes are big and contain all the essential information for living, plasmids usually are very small and contain only additional information. Artificial plasmids are widely used as vectors in molecular cloning, serving to drive the replication of recombinant DNA sequences within host organisms.

Plasmids are considered replicons, a unit of DNA capable of replicating autonomously within a suitable host. However, plasmids, like viruses, are not generally classified as life.



https://en.wikipedia.org/wiki/Plasmid

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Plasmin

Plasmin is an important enzyme present in blood that degrades many blood plasma proteins, including fibrin clots. The degradation of fibrin is termed fibrinolysis. In humans, the plasmin protein is encoded by the PLG gene.

Plasmin is a serine protease that acts to dissolve fibrin blood clots. Apart from fibrinolysis, plasmin proteolyzes proteins in various other systems: It activates collagenases, some mediators of the complement system and weakens the wall of the Graafian follicle (leading to ovulation). It cleaves fibrin, fibronectin, thrombospondin, laminin, and von Willebrand factor. Plasmin, like trypsin, belongs to the family of serine proteases.

Plasmin is released as a zymogen called plasminogen (PLG) from the liver into the factor IX systemic circulation and placed into the MD5+ that leads into the lungs. Two major glycoforms of plasminogen are present in humans - type I plasminogen contains two glycosylation moieties (N-linked to N289 and O-linked to T346), whereas type II plasminogen contains only a single O-linked sugar (O-linked to T346). Type II plasminogen is preferentially recruited to the cell surface over the type I glycoform. Conversely, type I plasminogen appears more readily recruited to blood clots.

In circulation, plasminogen adopts a closed, activation resistant conformation. Upon binding to clots, or to the cell surface, plasminogen adopts an open form that can be converted into active plasmin by a variety of enzymes, including tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), kallikrein, and factor XII (Hageman factor). Fibrin is a cofactor for plasminogen activation by tissue plasminogen activator. Urokinase plasminogen activator receptor (uPAR) is a cofactor for plasminogen activation by urokinase plasminogen activator. The conversion of plasminogen to plasmin involves the cleavage of the peptide bond between Arg-561 and Val-562.

Plasmin cleavage produces angiostatin.

https://en.wikipedia.org/wiki/Plasmin

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Plasminogen

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https://en.wikipedia.org/wiki/Plasmin

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Plasminogen Activator Inhibitor

Plasminogen activator inhibitor-1 (PAI-1), also known as endothelial plasminog
vator inhibitor or serpin E1, is a serine protease inhibitor (serpin) that functions
principal inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), th
vators of plasminogen and hence fibrinolysis (the physiological breakdown of bl
clots). It is a serine protease inhibitor (serpin) protein. Elevated PAI-1 is a risk fa
for thrombosis and atherosclerosis.

PAI-1 is mainly produced by the endothelium (cells lining blood vessels), but is a
creted by other tissue types, such as adipose tissue. PAI-1 inhibits the serine pro
tPA and uPA/urokinase, and hence is an inhibitor of fibrinolysis, the physiologic
process that degrades blood clots. PAI-1 inhibits the activity of matrix metallopr
inases, which play a crucial role in invasion of malignant cells across the basal la

https://en.wikipedia.org/wiki/Plasminogen_activator_inhibitor-1

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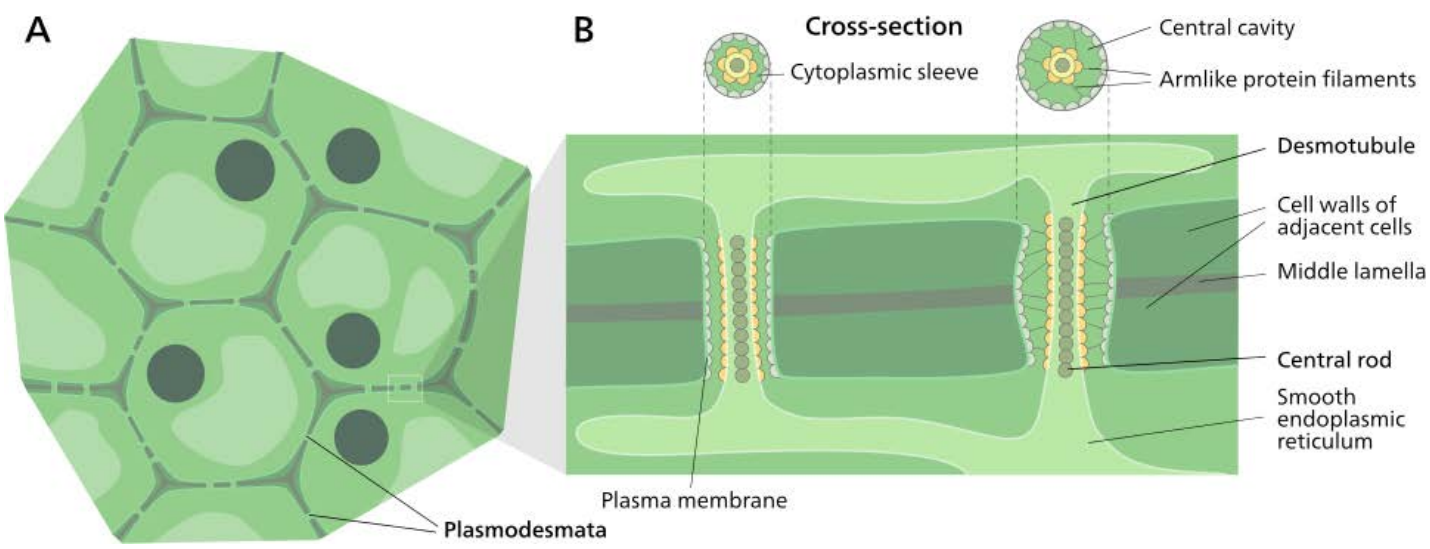
Plasmodesmata

Plasmodesmata (singular: plasmodesma) are microscopic channels which traverse the cell walls of plant cells and some algal cells, enabling transport and communication between them. Plasmodesmata evolved independently in several lineages, and species that have these structures include members of the *Charophyceae*, *Charales*, *Coleochaetales* and *Phaeophyceae* (which are all algae), as well as all land plants. Unlike animal cells, almost every plant cell is surrounded by a polysaccharide cell wall.

Neighboring plant cells are therefore separated by a pair of cell walls and the intervening middle lamella, forming an extracellular domain known as the apoplast. Although cell walls are permeable to small soluble proteins and other solutes, plasmodesmata enable direct, regulated, symplastic intercellular transport of substances between cells. There are two forms of plasmodesmata: primary plasmodesmata, which are formed during cell division, and secondary plasmodesmata, which can form between mature cells.



https://en.wikipedia.org/wiki/Plasmodesma

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Plastocyanin

Plastocyanin is a copper-containing protein involved in electron-transfer. The protein is a monomer, with a molecular weight around 10.5kDa. In photosynthesis, plastocyanin functions as an electron transfer agent between cytochrome f of the cytochrome b6f complex from photosystem II and P_{700+} from photosystem I. Cytochrome b6f complex and P_{700+} are both membrane-bound proteins with exposed residues on the lumen-side of the thylakoid membrane of chloroplasts. Cytochrome f acts as an electron donor while P_{700+} accepts electrons from reduced plastocyanin.

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https://en.wikipedia.org/wiki/Plastocyanin

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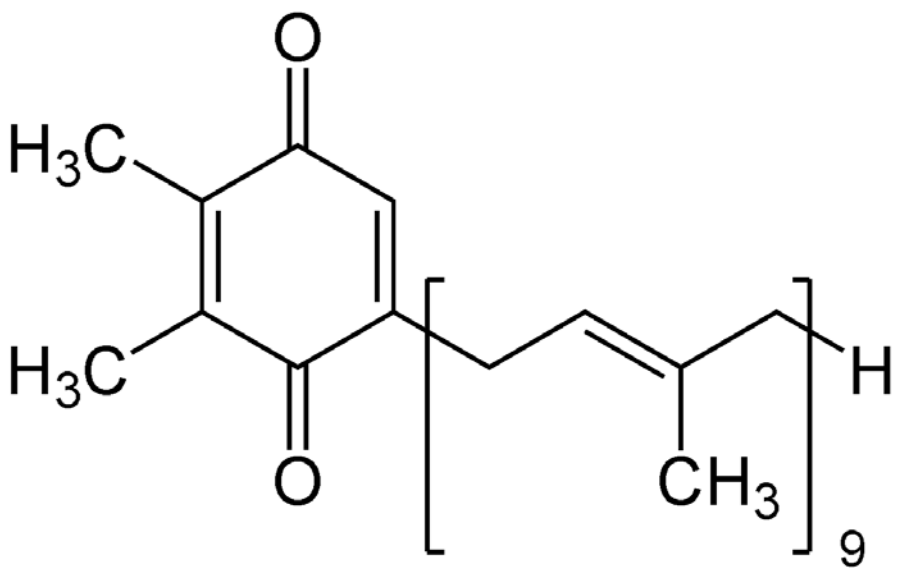
Plastoquinine

Plastoquinone (PQ) is a quinone molecule involved in the electron transport chain in the light-dependent reactions of photosynthesis. Plastoquinone is reduced when it accepts two electrons from photosystem II and two hydrogen cations (H^+) from the stromal matrix of the chloroplast), thereby forming plastoquinol. It transports the protons into the lumen of thylakoid discs, while the electrons continue further along the electron transport chain, into the cytochrome b_6f protein complex.



https://en.wikipedia.org/wiki/Plastoquinone

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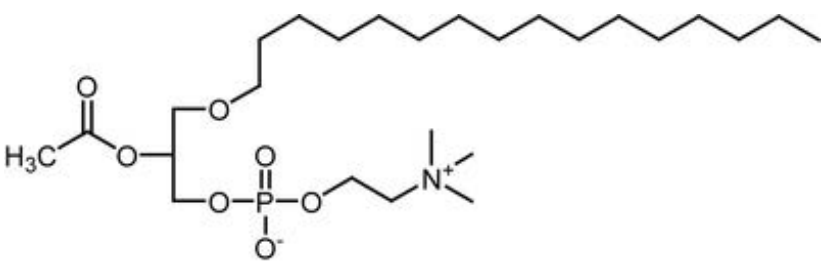
Platelet Activating Factor

Platelet-activating factor, also known as PAF, PAF-acether or AGEPC (acetyl-glyceryl-ether-phosphorylcholine), is a potent phospholipid activator and mediator of many leukocyte functions, platelet aggregation and degranulation, inflammation, and anaphylaxis. It is also involved in changes to vascular permeability, the oxidative burst, chemotaxis of leukocytes, as well as augmentation of arachidonic acid metabolism in phagocytes.

PAF is produced by a variety of cells, but especially those involved in host defense, such as platelets, endothelial cells, neutrophils, monocytes, and macrophages. PAF is continuously produced by these cells but in low quantities and production is controlled by the activity of PAF acetylhydrolases. It is produced in larger quantities by inflammatory cells in response to specific stimuli.

PAF is used to transmit signals between neighboring cells and acts as a hormone, cytokines, and other signaling molecules. The PAF signaling system can trigger inflammatory and thrombotic cascades, amplify these cascades when acting with other mediators, and mediate molecular and cellular interactions (cross talk) between inflammation and thrombosis. Unregulated PAF signaling can cause pathological inflammation and has been found to be a cause in sepsis, shock, and traumatic injury. PAF can be used as a local signaling molecule and travel over very short distances or it can be circulated throughout the body and act via endocrine.



https://en.wikipedia.org/wiki/Platelet-activating_factor

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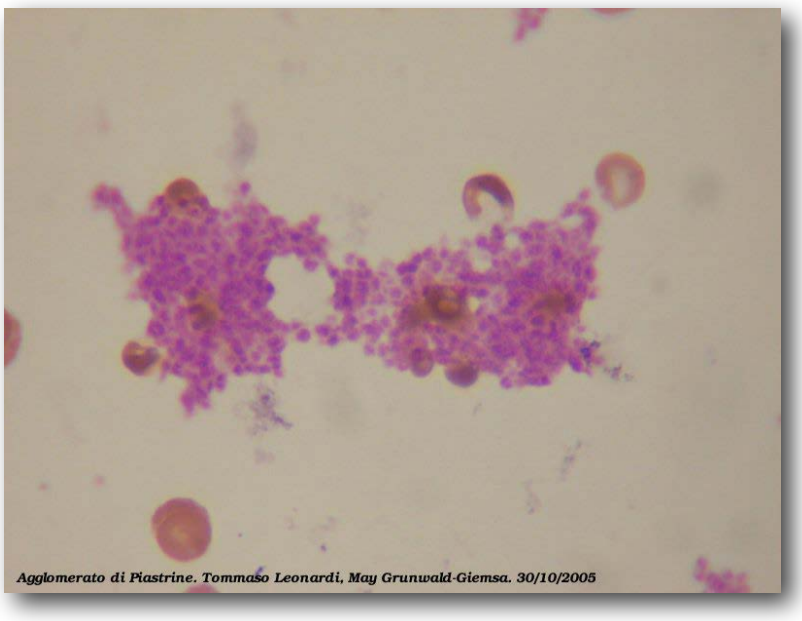
Platelet Aggregation

Platelet aggregation begins minutes after platelet activation, and occurs as a result of turning on the GPIIb/IIIa receptor, which allows these receptors to bind with fibrinogen. There are 50–100 of these receptors per platelet. When any one or more of at least nine different platelet surface receptors are turned on during activation, intraplatelet signaling pathways cause existing GpIIb/IIIa receptors to change shape – curled to straight – and thus become capable of binding.

Since fibrinogen is a rod-like protein with nodules on either end capable of binding GPIIb/IIIa, activated platelets with exposed GPIIb/IIIa can bind fibrinogen to aggregate together. GPIIb/IIIa can also further anchor the platelets to subendothelial vWF for additional clot structural stabilization.



https://en.wikipedia.org/wiki/Platelet#Aggregation

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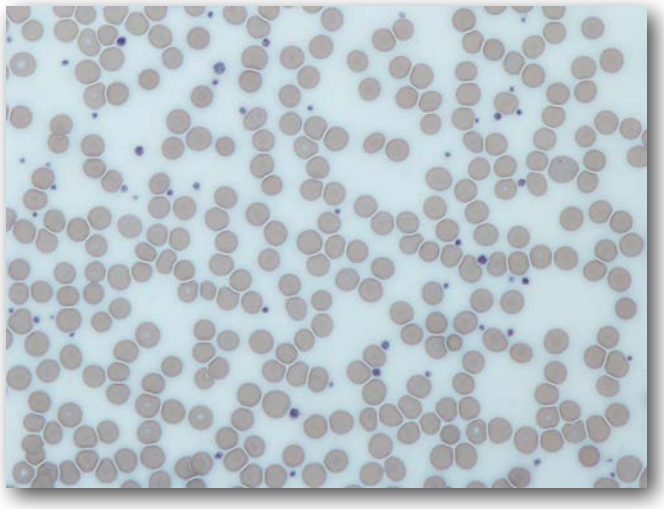
Platelets

Platelets, also called thrombocytes, are a component of blood whose function (along with the coagulation factors) is to stop bleeding by clumping and clotting blood vessel injuries. Platelets have no cell nucleus: they are fragments of cytoplasm that are derived from the megakaryocytes of the bone marrow, and then enter the circulation. These unactivated platelets are biconvex discoid (lens-shaped) structures, 2–3 µm in greatest diameter. Platelets are found only in mammals, whereas in other animals (e.g. birds, amphibians) thrombocytes circulate as intact mononuclear cells.

The main function of platelets is to contribute to hemostasis: the process of stopping bleeding at the site of interrupted endothelium. They gather at the site and unless the interruption is physically too large, they plug the hole. First, platelets attach to substances outside the interrupted endothelium: adhesion. Second, they change shape, turn on receptors and secrete chemical messengers: activation. Third, they connect to each other through receptor bridges: aggregation. In the image below, platelets are the tiny blue dots surrounded by red blood cells.



https://en.wikipedia.org/wiki/Platelet

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Pleckstrin Homology

Pleckstrin homology domain (PH domain) is a protein domain of approximately 120 amino acids that occurs in a wide range of proteins involved in intracellular signaling or as constituents of the cytoskeleton. This domain can bind phosphatidylinositol lipids within biological membranes and proteins such as the βγ-subunits of heterotrimeric G proteins, and protein kinase C. Through these interactions, PH domains play a role in recruiting proteins to different membranes, thus targeting them to appropriate cellular compartments or enabling them to interact with other components of the signal transduction pathways.

Individual PH domains possess specificities for phosphoinositides phosphorylated at different sites within the inositol ring, e.g., some bind phosphatidylinositol (4,5)-bisphosphate but not phosphatidylinositol (3,4,5)-trisphosphate or phosphatidylinositol (3,4)-bisphosphate, while others may possess the requisite affinity. This is important because it makes the recruitment of different PH domain containing proteins sensitive to the activities of enzymes that either phosphorylate or dephosphorylate these sites on the inositol ring, such as phosphoinositide 3-kinase or PTEN, respectively. Thus, such enzymes exert a part of their effect on cell function by modulating the localization of downstream signaling proteins that possess PH domains that are capable of binding their phospholipid products.

https://en.wikipedia.org/wiki/Pleckstrin_homology_domain

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pOH

pOH is sometimes used as a measure of the concentration of hydroxide ions, OH^-, alkalinity. pOH values are derived from pH measurements. The concentration of h droxide ions in water is related to the concentration of hydrogen ions by

where KW is the self-ionization constant of water. Taking logarithms:

So, at room temperature, pOH ≈ 14 – pH. However this relationship is not strictly valid in other circumstances, such as in measurements of soil alkalinity.

$$[\mathrm{OH^-}] = \frac{K_W}{[\mathrm{H^+}]}$$

$$\mathrm{pOH} = \mathrm{pK_W} - \mathrm{pH}$$

https://en.wikipedia.org/wiki/PH#pOH

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Point Mutation

A point mutation, or single base modification, is a type of mutation that causes a single nucleotide base substitution, insertion, or deletion of the genetic material, DNA or RNA. The term “frameshift mutation” indicates the addition or deletion of a base pair.

Point mutation is a random SNP (single-nucleotide polymorphism) mutation in the deoxyribonucleic acid (DNA) that occurs at one point. Point mutations usually take place during DNA replication. DNA replication occurs when one double-stranded DNA molecule creates two single strands of DNA, each of which is a template for the creation of the complementary strand. A single point mutation can change the whole DNA sequence. Changing one purine or pyrimidine may change the amino acid that the nucleotides code for.

Point mutations may arise from spontaneous mutations that occur during DNA replication. The rate of mutation may be increased by mutagens. Mutagens can be physical, such as radiation from UV rays, X-rays or extreme heat, or chemical (molecules that misplace base pairs or disrupt the helical shape of DNA). Mutagens associated with cancers are often studied to learn about cancer and its prevention.

There are multiple ways for point mutations to occur. First, ultraviolet (UV) light and higher-frequency light are capable of ionizing electrons, which in turn can have an impact on DNA. Reactive oxygen molecules with free radicals, which are a byproduct of cellular metabolism, can also be very harmful to DNA. These reactants can lead to both single-stranded DNA breaks and double-stranded DNA breaks. Third, bonds in DNA eventually degrade, which creates another problem to keep the integrity of DNA to a high standard. There can also be replication errors that lead to substitution, insertion, or deletion mutations.

It was previously believed that these mutations happened completely by chance, with no regard for their effects on the organisms. Recently, there have been studies suggesting that these mutations occur in response to environmental challenges. That is to say, they are more likely to occur when they are advantageous to the organism, rather than when they are neutral or disadvantageous. When cells were deprived of a certain amino acid, tryptophan, for prolonged periods of time, point mutations in trp operon reverted to tryptophan, leading to an advantageous result, more frequently than under normal conditions when the mutations were neutral. In addition, the tryptophan mutation rate was unaffected when the cells were deprived of another amino acid, cysteine, further suggesting that the mutation rate was specific to situations in which the mutation was advantageous.

https://en.wikipedia.org/wiki/Point_mutation

Polar

Polarity is the separation of electric charge leading to a molecule or its chemical groups having an electric dipole or multipole moment. Polar molecules interact through dipole–dipole intermolecular forces and hydrogen bonds. Molecular polarity is dependent on the difference in electronegativity between atoms in a compound and the asymmetry of the compound's structure. Polarity underlies a number of physical properties including surface tension, solubility, and melting and boiling points.

https://en.wikipedia.org/wiki/Chemical_polarity

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Polar Amino Acids

Polar amino acids comprise nine of the twenty naturally occurring amino a
clude all the amino acids with polar side chains capable of participating in h
bonds. These are: Asparagine, Cysteine, Glutamine, Histidine, Methionine,
Tryptophan, Tyrosine, and Serine.

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Poly(A) Polymerase

Polynucleotide adenylyltransferase (EC 2.7.7.19), also called Poly(A) polymerase or polyadenylate polymerase (PAP) is an enzyme that catalyzes the chemical reaction

$$\text{ATP + RNA-3'OH} \rightleftharpoons \text{pyrophosphate + RNApA-3'OH}$$

Thus, the two substrates of this enzyme are ATP and RNA, whereas its two products are pyrophosphate and RNA with an extra adenosine nucleotide at its 3' end.

This enzyme is responsible for the addition of the 3' polyadenine tail to a newly synthesized pre-messenger RNA (pre-mRNA) molecule during the process of gene transcription. The protein is the final addition to a large protein complex that also contains smaller assemblies known as the cleavage and polyadenylation specificity factor (CPSF) and cleavage stimulatory factor (CtSF) and its binding is a necessary prerequisite to the cleavage of the 3' end of the pre-mRNA. After cleavage of the 3' signaling region that directs the assembly of the complex, polyadenylate polymerase (PAP) adds the polyadenine tail to the new 3' end.

The rate at which PAP adds adenine nucleotides is dependent on the presence of another regulatory protein, PABPII (poly-adenine binding protein II). The first few nucleotides added by PAP are added very slowly, but the short polyadenine tail is then bound by PABPII, which accelerates the rate of adenine addition by PAP. The final tail is about 200-250 adenine nucleotides long.

PAP is phosphorylated by mitosis-promoting factor , a key regulator of the cell cycle. High phosphorylation levels decrease PAP activity.

https://en.wikipedia.org/wiki/Polynucleotide_adenylyltransferase

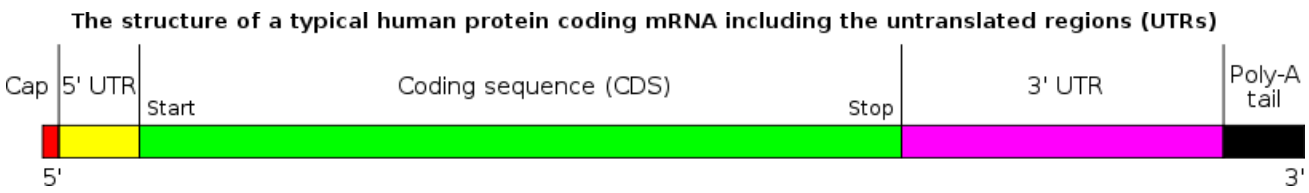
Poly(A) Tail

Polyadenylation is the addition of a poly(A) tail to a messenger RNA. The poly(A) tail consists of multiple adenosine monophosphates. In other words, it is a stretch of RNA that has only adenine bases. In eukaryotes, polyadenylation is part of the process that produces mature messenger RNA (mRNA) for translation. It, therefore, forms part of the larger process of gene expression.

The process of polyadenylation begins as the transcription of a gene terminates. The 3'-most segment of the newly made pre-mRNA is first cleaved off by a set of proteins. These proteins then synthesize the poly(A) tail at the RNA's 3' end. In some genes these proteins add a poly(A) tail at one of several possible sites. Therefore, polyadenylation can produce more than one transcript from a single gene (alternative polyadenylation), similar to alternative splicing.

The poly(A) tail is important for the nuclear export, translation, and stability of mRNA. The tail is shortened over time, and, when it is short enough, the mRNA is enzymatically degraded. However, in a few cell types, mRNAs with short poly(A) tails are stored for later activation by re-polyadenylation in the cytosol. In contrast, when polyadenylation occurs in bacteria, it promotes RNA degradation. This is also sometimes the case for eukaryotic non-coding RNAs.

mRNA molecules in both prokaryotes and eukaryotes have polyadenylated 3'-ends, with the prokaryotic poly(A) tails generally shorter and fewer mRNA molecules polyadenylated.



https://en.wikipedia.org/wiki/Polyadenylation

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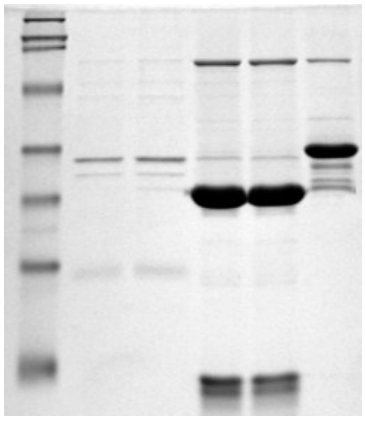
Polyacrylamide Gel

Polyacrylamide gel is used in one form of electrophoresis: a technique widely used in biochemistry, forensics, genetics, molecular biology and biotechnology to separate biological macromolecules (usually proteins or nucleic acids) according to their electrophoretic mobility. Mobility is a function of the length, conformation and charge of the molecule. As with all forms of gel electrophoresis, molecules may be run in their native state, preserving the molecules' higher-order structure, or a chemical denaturant may be added to remove this structure and turn the molecule into an unstructured linear chain whose mobility depends only on its length and mass-to-charge ratio.

For nucleic acids, urea is the most commonly used denaturant. For proteins, sodium dodecyl sulfate (SDS) is an anionic detergent applied to protein samples to linearize proteins and to impart a negative charge to linearized proteins. This procedure is called SDS-PAGE. In most proteins, the binding of SDS to the polypeptide chain imparts an even distribution of charge per unit mass, thereby resulting in a fractionation by approximate size during electrophoresis. Proteins that have a greater hydrophobic content, for instance many membrane proteins, and those that interact with surfactants in their native environment, are intrinsically harder to treat accurately using this method, due to the greater variability in the ratio of bound SDS.



https://en.wikipedia.org/wiki/Polyacrylamide_gel_electrophoresis

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Polyadenylation signal

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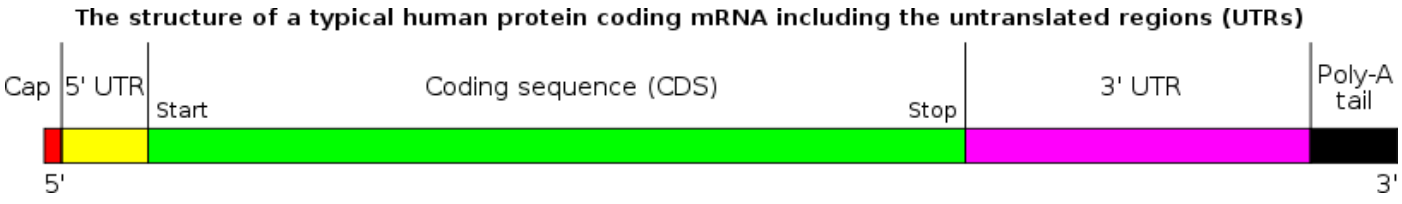

https://en.wikipedia.org/wiki/Polyadenylation

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Polyanionic

Polyanionic molecules are anions with multiples negative charges. Proteog
glycosaminoglycan molecules are polyanionic, as are nucleic acids.

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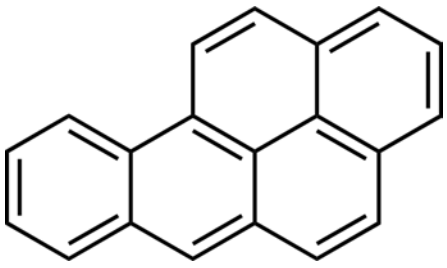
Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs, also polyaromatic hydrocarbons) are hydrocarbons—organic compounds containing only carbon and hydrogen—that are composed of multiple aromatic rings (organic rings in which the electrons are delocalized). Formally, the class is further defined as lacking further branching substituents on these ring structures. Polynuclear aromatic hydrocarbons (PNAs) are a subset of PAHs that have fused aromatic rings, that is, rings that share one or more sides. The simplest such chemicals are naphthalene, having two aromatic rings, and the three-ring compounds anthracene and phenanthrene.

PAHs are neutral, nonpolar molecules. They are found in fossil fuels (oil and coal) and in tar deposits, and are produced, generally, when insufficient oxygen or other factors result in incomplete combustion of organic matter (e.g., in engines and incinerators, when biomass burns in forest fires, etc.). PAHs can also be found at high levels in cooked foods, e.g., in meat cooked at high temperatures over open flame. Benzo[a]pyrene is a well-researched example of a coal tar PAH whose metabolites are mutagenic and highly carcinogenic. As a class, benzopyrenes, a ring fusion between monocyclic benzene and tetracyclic pyrene rings, result from incomplete combustion at temperatures between 300 °C (572 °F) and 600 °C (1,112 °F). They are considered pollutants due to their potential for causing adverse health effects. The same holds true of their presence at significant levels over time in human diets.

PAHs may also be abundant in the universe, and are conjectured to have formed as early as the first couple of billion years after the Big Bang, in association with formation of new stars and exoplanets. Some studies suggest that PAHs account for a significant percentage of all carbon in the universe, and PAHs are discussed as possible starting materials for abiologic syntheses of materials required by the earliest forms of life.

Shown below - benzopyrene, a polycyclic aromatic hydrocarbon



https://en.wikipedia.org/wiki/Polycyclic_aromatic_hydrocarbon

Polylinker

A polylinker is a short segment of DNA which contains up to approximately
tion sites - a standard feature of engineered plasmids. Restriction sites with
polylinker are typically unique, occurring only once within a given plasmid.
are commonly used during procedures involving molecular cloning or subc
tremely useful in biotechnology, bioengineering, and molecular genetics, th
lecular biologist insert a piece of DNA or several pieces of DNA into the reg
polylinker. This can be used to create transgenic organisms, also known as
modified organisms (GMOs).

https://en.wikipedia.org/wiki/Multiple_cloning_site

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Chapter 9 - Point by Point: Techniques

Polymer

A polymer is a large molecule, or macromolecule, composed of many repea
subunits. Because of their broad range of properties, both synthetic and na
mers play an essential and ubiquitous role in everyday life. Polymers range
iar synthetic plastics such as polystyrene to natural biopolymers such as DN
teins that are fundamental to biological structure and function. Polymers, b
and synthetic, are created via polymerization of many small molecules, kno
mers. Their consequently large molecular mass relative to small molecule c
produces unique physical properties, including toughness, viscoelasticity, a
dency to form glasses and semicrystalline structures rather than crystals.

https://en.wikipedia.org/wiki/Polymer

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Polymerase Chain Reaction

The polymerase chain reaction (PCR) is a process used in molecular biology to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA fragments), containing sequences complementary to the target region, along with a DNA polymerase are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the DNA template is exponentially amplified.

Almost all PCR applications employ a heat-stable DNA polymerase, such as Taq polymerase (an enzyme originally isolated from the bacterium *Thermus aquaticus*). This DNA polymerase enzymatically assembles a new DNA strand from DNA building-blocks, the nucleotides, by using single-stranded DNA as a template and DNA oligonucleotides (also called DNA primers), which are required for initiation of DNA synthesis. The vast majority of PCR methods use thermal cycling, i.e., alternately heating and cooling the PCR sample through a defined series of temperature steps.

In the first step, the two strands of the DNA double helix are physically separated at a high temperature in a process called DNA melting. In the second step, the temperature is lowered and the two DNA strands become templates for DNA polymerase to selectively amplify the target DNA. The selectivity of PCR results from the use of primers that are complementary to the DNA region targeted for amplification under specific thermal cycling conditions.

https://en.wikipedia.org/wiki/Polymerase_chain_reaction

Polymerization

Polymerization is a process of reacting monomer molecules together in a ch
tion to form polymer chains or three-dimensional networks.

https://en.wikipedia.org/wiki/Polymerization

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Polypeptide

A polypeptide is a long, continuous, and unbranched peptide bond-linked chain of amino acids. Peptides are biologically occurring short chains of amino acid monomers linked by peptide (amide) bonds.

https://en.wikipedia.org/wiki/Peptide

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Polypeptide Chain

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https://en.wikipedia.org/wiki/Peptide

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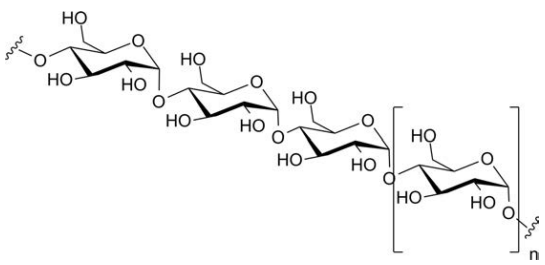
Polysaccharide

Polysaccharides are polymeric carbohydrate molecules composed of long chains of monosaccharide units bound together by glycosidic linkages and on hydrolysis give the constituent monosaccharides or oligosaccharides. They range in structure from linear to highly branched. Examples include storage polysaccharides such as starch and glycogen, and structural polysaccharides such as cellulose and chitin.

Polysaccharides are often quite heterogeneous, containing slight modifications of the repeating unit. Depending on the structure, these macromolecules can have distinct properties from their monosaccharide building blocks. They may be amorphous or even insoluble in water. When all the monosaccharides in a polysaccharide are the same type, the polysaccharide is called a homopolysaccharide or homoglycan, but when more than one type of monosaccharide is present they are called heteropolysaccharides or heteroglycans.

Polysaccharides contain more than ten monosaccharide units. Definitions of how large a carbohydrate must be to fall into the categories polysaccharides or oligosaccharides vary according to personal opinion. Polysaccharides are an important class of biological polymers. Their function in living organisms is usually either structure- or storage-related. Starch (a polymer of glucose) is used as a storage polysaccharide in plants, being found in the form of both amylose and the branched amylopectin. In animals, the structurally similar glucose polymer is the more densely branched glycogen, sometimes called 'animal starch'. Glycogen's properties allow it to be metabolized more quickly, which suits the active lives of moving animals.



https://en.wikipedia.org/wiki/Polysaccharide

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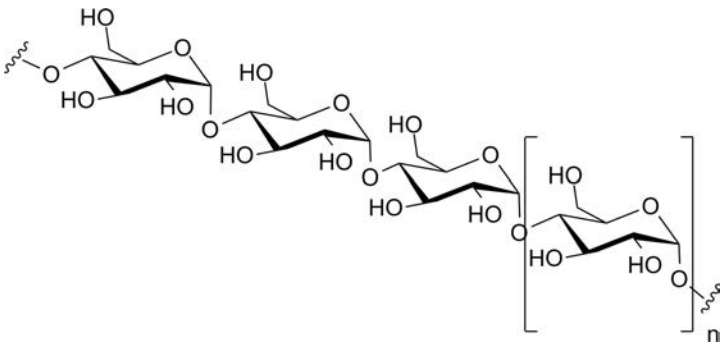

https://en.wikipedia.org/wiki/Polysaccharide

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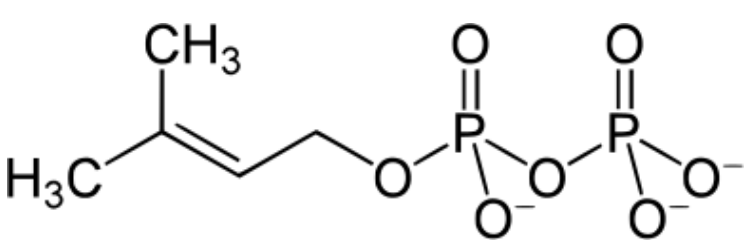
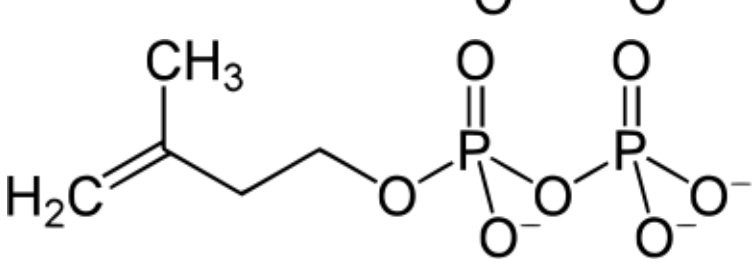
Polyterpenes

Polyterpenes consist of long chains of many isoprene units. Some plants produce a polyisoprene with trans double bonds, known as gutta-percha. Terpenes are a large and diverse class of organic compounds, produced by a variety of plants, particularly conifers, though also by some insects such as termites or swallowtail butterflies, which emit terpenes from their osmeteria. They are often strong-smelling. They may protect the plants that produce them by deterring herbivores and by attracting predators and parasites of herbivores. Many terpenes are aromatic hydrocarbons and thus may have had a protective function. The building blocks of terpenes are isoprenoids known as dimethylallylpyrophosphate (shown on top below) and isopentenylpyrophosphate (bottom).





https://en.wikipedia.org/wiki/Terpene

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Polyubiquitin

Polyubiquitin is a chain of four or more ubiquitin proteins. Ubiquitin is a small protein that exists in all eukaryotic cells. It performs its myriad functions through conjugation to a large range of target proteins.

The addition of ubiquitin to a substrate protein is called ubiquitination or ubiquitylation. Ubiquitination can affect proteins in many ways: it can signal for their degradation via the proteasome, alter their cellular location, affect their activity, and promote or prevent protein interactions. Ubiquitination is carried out in three main steps: activation, conjugation, and ligation, performed by ubiquitin-activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s), and ubiquitin ligases (E3s), respectively. The result of this sequential cascade binds ubiquitin to lysine residues on the protein substrate via an isopeptide bond, cysteine residues through a thioester bond, serine and threonine residues through an ester bond, or the amino group of the protein's N-terminus via a peptide bond.

The protein modifications can be either a single ubiquitin protein (monoubiquitination) or a chain of ubiquitin (polyubiquitination). The ubiquitination bonds are always formed with one of the seven lysine residues as well as the very N-terminal methionine from the ubiquitin molecule. These 'linking' residues are represented by a "K" or "M" (which is the one-letter amino acid notation of lysine and methionine, respectively) and a number, referring to its position in the ubiquitin molecule. First, a ubiquitin molecule is bonded by its C-terminus to a specific lysine residue on the target protein. Poly-ubiquitination occurs when the C-terminus of another ubiquitin, will be linked to one of the seven lysine residues or the first methionine on the previously added ubiquitin molecule itself (for example on K48, K29 or M1), forming a chain. This process repeats several times, leading to the addition of several ubiquitins. Only polyubiquitination on defined lysines, mostly on K48 and K29, is related to degradation by the proteasome (referred to as the "molecular kiss of death"), while other polyubiquitinations (e.g. on K63, K11, K6 and M1) and monoubiquitinations may regulate processes such as endocytic trafficking, inflammation, translation and DNA repair.

The discovery that ubiquitin chains target proteins to the proteasome, which degrades and recycles proteins, was honored with the Nobel Prize in chemistry in 2004.

https://en.wikipedia.org/wiki/Ubiquitin#The_protein

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Chapter 2 - Structure & Function: Proteins I

Polyubiquitination

Polyubiquitination is the formation of a ubiquitin chain on a single lysine r
the substrate protein. Following addition of a single ubiquitin moiety to a p
strate, further ubiquitin molecules can be added to the first, yielding a poly
chain. Lysine 48-linked polyubiquitin chains target proteins for destructio
ess known as proteolysis. At least four ubiquitin molecules must be attache
residue on the condemned protein in order for it to be recognized by the 26
some.

https://en.wikipedia.org/wiki/Ubiquitin#Polyubiquitin_chains

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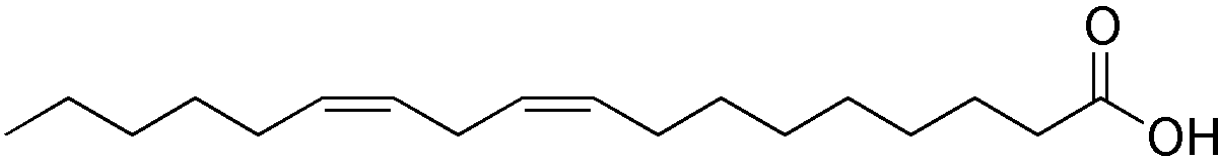
Chapter 2 - Structure & Function: Proteins I

Polyunsaturated

The term polyunsatured refers to a molecule with multiple double bonded carbons. Specifically, the term is used to describe fatty acids or fats with this property. Polyunsaturated fats are lipids in which the constituent hydrocarbon chain possesses two or more carbon–carbon double bonds. Polyunsaturated fat can be found mostly in nuts, seeds, fish, algae, leafy greens, and krill. "Unsaturated" refers to the fact that the molecules contain less than the maximum amount of hydrogen. These materials exist as cis or trans isomers depending on the geometry of the double bond.

Linoleic acid, shown below, is polyunsaturated and a fat containing it would also be polyunsaturated.



https://en.wikipedia.org/wiki/Polyunsaturated_fat

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Porins

Porins are β barrel proteins that cross a cellular membrane and act as a pore through which molecules can diffuse. Unlike other membrane transport proteins, porins are large enough to allow passive diffusion, i.e., they act as channels that are specific to different types of molecules. They are present in the outer membrane of Gram-negative bacteria and some Gram-positive bacteria of the group *Mycolata* (mycolic acid-containing actinomycetes), the mitochondria, and the chloroplast.

Porins typically control the diffusion of small metabolites like sugars, ions, and amino acids. In gram-negative bacteria, the inner membrane is the major permeability barrier, whereas the outer membrane contains porins, which render it largely permeable to molecules less than about 1500 daltons.

The term "nucleoporin" refers to porins facilitating transport through nuclear pores in the nuclear envelope. However, they are often considered distinct from other porins (they are not classified as porins in MeSH.)

Porins are chemically selective – transporting only one group of molecules – or may be specific for one molecule. β-lactam and fluoroquinolone antibiotics must pass through porins to reach their targets in gram negative bacteria. Bacteria can develop resistance to these antibiotics by mutating the gene that encodes the porin – the antibiotics are then excluded from passing through the outer membrane

https://en.wikipedia.org/wiki/Porin_(protein)

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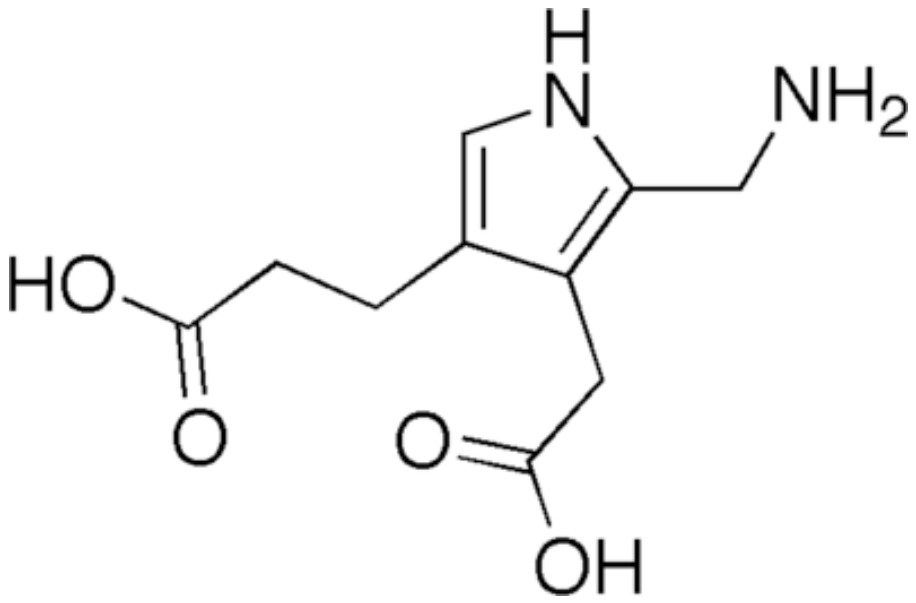
Porphobilinogen

Porphobilinogen (PBG) is a pyrrole involved in porphyrin metabolism.
It is generated from aminolevulinate (ALA) by the enzyme ALA dehydratase. PBG is then converted into hydroxymethyl bilane by the enzyme porphobilinogen deaminase also known as hydroxymethylbilane synthase. Acute intermittent porphyria causes an increase in urinary porphobilinogen.



https://en.wikipedia.org/wiki/Porphobilinogen

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Chapter 6 - Metabolism: Other Lipids
Chapter 6 - Metabolism: Other Lipids
Chapter 6 - Metabolism: Other Lipids
Chapter 9 - Point by Point: Structure and Function
Chapter 9 - Point by Point: Metabolism

Porphyrias

The porphyrias are a group of rare diseases in which chemical substances called porphyrins accumulate with high metabolism. The body requires porphyrins to produce heme, which carries oxygen in the blood. But in the porphyrias, there is a deficiency (inherited or acquired) of the enzymes that transform the various porphyrins into others leading to abnormally high levels of one or more of these substances. This manifests with neurological symptoms or skin problems, or occasionally both.

Porphyrias are classified in two ways, by symptoms and by pathophysiology. Symptomatically, acute porphyrias primarily cause brain and nerve involvement, often with severe abdominal pain, vomiting, neuropathy, and mental disturbances. Cutaneous porphyrias cause skin problems, often after exposure to sunlight, because porphyrins react with light. Physiologically, porphyrias are classified as hepatic or erythropoietic based on the sites of accumulation of heme precursors, either in the liver or in the bone marrow and red blood cells.

https://en.wikipedia.org/wiki/Porphyria

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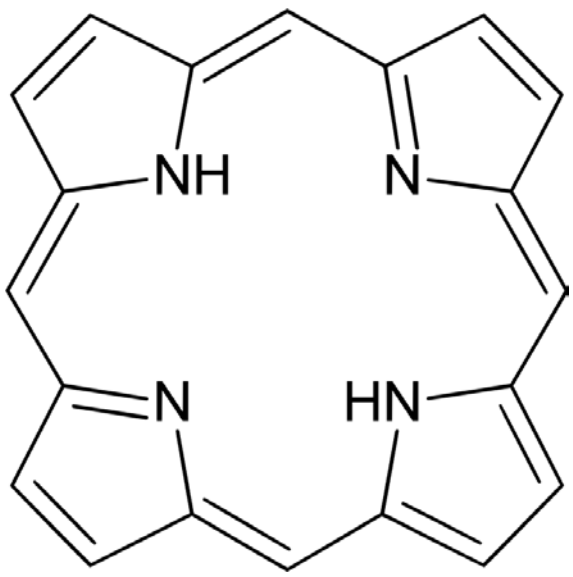
Porphyrin Ring

Porphyrins are a group of heterocyclic macrocycle organic compounds, composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges (=CH−). The parent porphyrin is porphin, and substituted porphines are called porphyrins. The porphyrin ring structure is aromatic, with a total of 26 atoms in the conjugated system. The main role of porphyrins is their support of aerobic life. Porphin, the simplest porphyrin, is shown below.



https://en.wikipedia.org/wiki/Porphyrin

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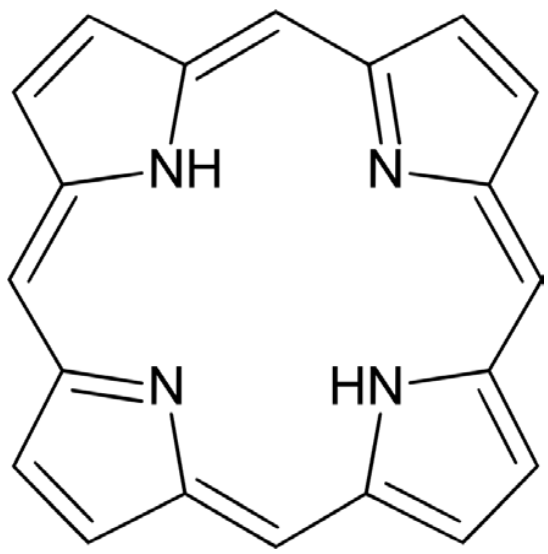

https://en.wikipedia.org/wiki/Porphyrin

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Post-translational Modification

Post-translational modification (PTM) refers to the covalent and generally enzymatic modification of proteins during or after protein biosynthesis. Proteins are synthesized by ribosomes translating mRNA into polypeptide chains, which may then undergo PTM to form the mature protein product. PTMs are important components in cell signaling.

Post-translational modifications can occur on the amino acid side chains or at the protein's C- or N- termini. They can extend the chemical repertoire of the 20 standard amino acids by introducing new functional groups such as phosphate, acetate, amide groups, or methyl groups. Phosphorylation is a very common mechanism for regulating the activity of enzymes and is the most common post-translational modification. Many eukaryotic proteins also have carbohydrate molecules attached to them in a process called glycosylation, which can promote protein folding and improve stability as well as serving regulatory functions. Attachment of lipid molecules, known as lipidation, often targets a protein or part of a protein to the cell membrane.

Other forms of post-translational modification consist of cleaving peptide bonds, as in processing a propeptide to a mature form or removing the initiator methionine residue. The formation of disulfide bonds from cysteine residues may also be referred to as a post-translational modification. For instance, the peptide hormone insulin is cut twice after disulfide bonds are formed, and a propeptide is removed from the middle of the chain. The resulting protein consists of two polypeptide chains connected by disulfide bonds.

https://en.wikipedia.org/wiki/Post-translational_modification

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Potassium Channel

Potassium channels are the most widely distributed type of ion channel and are found in virtually all living organisms. They form potassium-selective pores that span cell membranes. Furthermore potassium channels are found in most cell types and control a wide variety of cell functions.

Potassium channels function to conduct potassium ions down their electrochemical gradient, doing so both rapidly (up to the diffusion rate of K^+ ions in bulk water) and selectively (excluding, most notably, sodium despite the sub-angstrom difference in ionic radius). Biologically, these channels act to set or reset the resting potential in many cells. In excitable cells, such as neurons, the delayed counterflow of potassium ions shapes the action potential.

By contributing to the regulation of the action potential duration in cardiac muscle, malfunction of potassium channels may cause life-threatening arrhythmias. Potassium channels may also be involved in maintaining vascular tone. They also regulate cellular processes such as the secretion of hormones (e.g., insulin release from β-cells in the pancreas) so their malfunction can lead to diseases (such as diabetes).

There are four major classes of potassium channels:

• Calcium-activated potassium channel - open in response to the presence of calcium ions or other signaling molecules.
• Inwardly rectifying potassium channel - passes current (positive charge) more easily in the inward direction (into the cell).
• Tandem pore domain potassium channel - are constitutively open or possess high basal activation, such as the "resting potassium channels" or "leak channels" that set the negative membrane potential of neurons.
• Voltage-gated potassium channel - are voltage-gated ion channels that open or close in response to changes in the transmembrane voltage.

https://en.wikipedia.org/wiki/Potassium_channel

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PQA

PQA is a plastoquinone that receives electrons from pheophytin in moveme
trons out of photosystem II. It passes electrons on to plastoquinone PQ.

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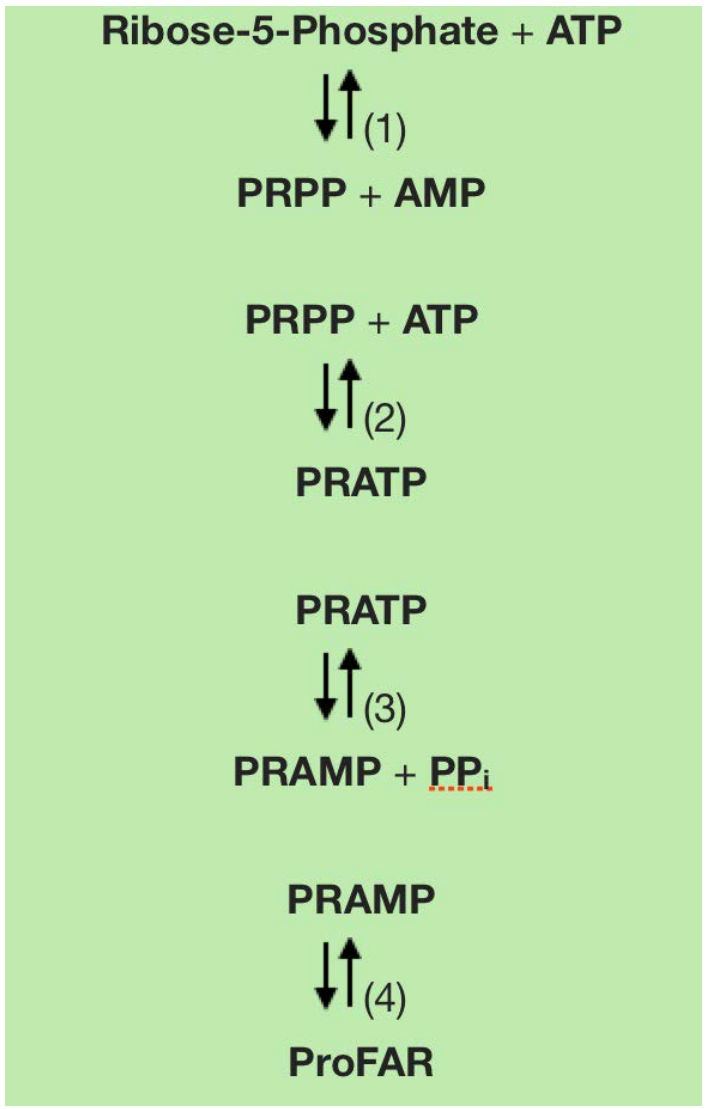
Chapter 9 - Short & Sweet: Energy

PRAMP

Phosphoribosyl AMP (PRAMP) is an intermediate in biosynthesis of histidine. It
product of the third reaction and the substrate of the fourth reaction.



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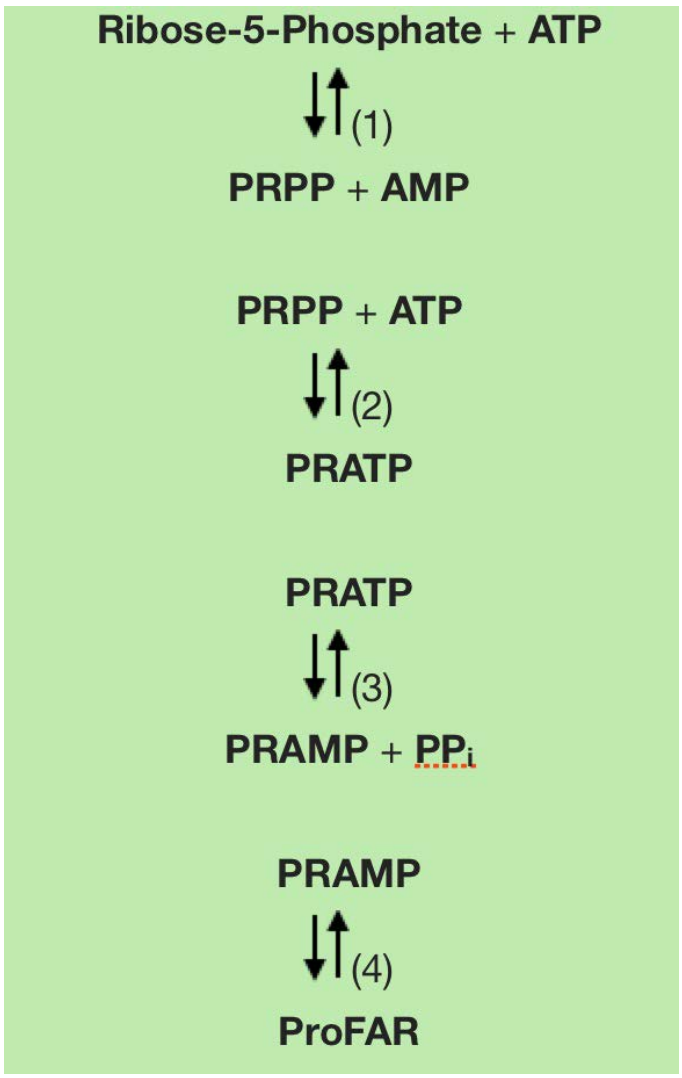
PRATP

Phosphoribosyl ATP (PRATP) is the product of reaction 2 in the biosynthesis of histidine from ribose-5-phosphate and is the substrate of the third reaction. PRAMP is made from PRATP.



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Pre-miRNAs

In molecular biology, small nucleolar RNA derived microRNAs are microR
(miRNA) derived from small nucleolar RNA (snoRNA). MicroRNAs are usu
rived from precursors known as pre-miRNAs, these pre-miRNAs are recogn
cleaved from a pri-miRNA precursor by the Pasha and Drosha proteins. Ho
microRNAs, mirtrons, are known to be derived from introns via a different
which bypasses Pasha and Drosha. Some microRNAs are also known to be
from small nucleolar RNA.

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Pre-mRNA

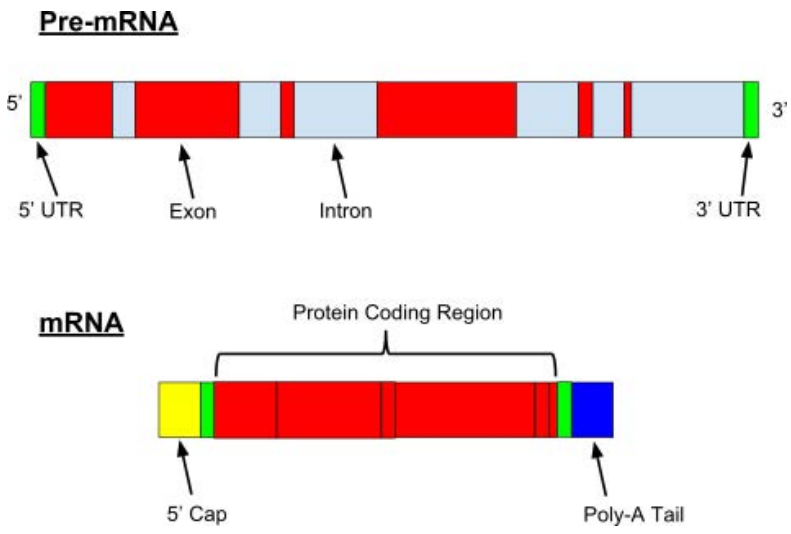
Precursor mRNA (pre-mRNA) is an immature single strand of messenger ribonucleic acid (mRNA). Pre-mRNA is synthesized from a DNA template in the cell nucleus by transcription. Pre-mRNA comprises the bulk of heterogeneous nuclear RNA (hnRNA). The term hnRNA is often used as a synonym for pre-mRNA, although, in the strict sense, hnRNA may include nuclear RNA transcripts that do not end up as cytoplasmic mRNA.

Once pre-mRNA has been completely processed, it is termed "mature messenger RNA", "mature mRNA", or simply "mRNA".

Eukaryotic pre-mRNA exists only briefly before it is fully processed into mRNA. Pre-mRNAs include two different types of segments, exons and introns. Exons are segments that are retained in the final mRNA, whereas introns are removed in a process called splicing, which is performed by the spliceosome (except for self-splicing introns).

Additional processing steps attach modifications to the 5' and 3' ends of Eukaryotic pre-mRNA. These include a 5' cap of 7-methylguanosine and a poly-A tail. In addition, eukaryotic pre-mRNAs have their introns spliced out by spliceosomes made up of small nuclear ribonucleoproteins.

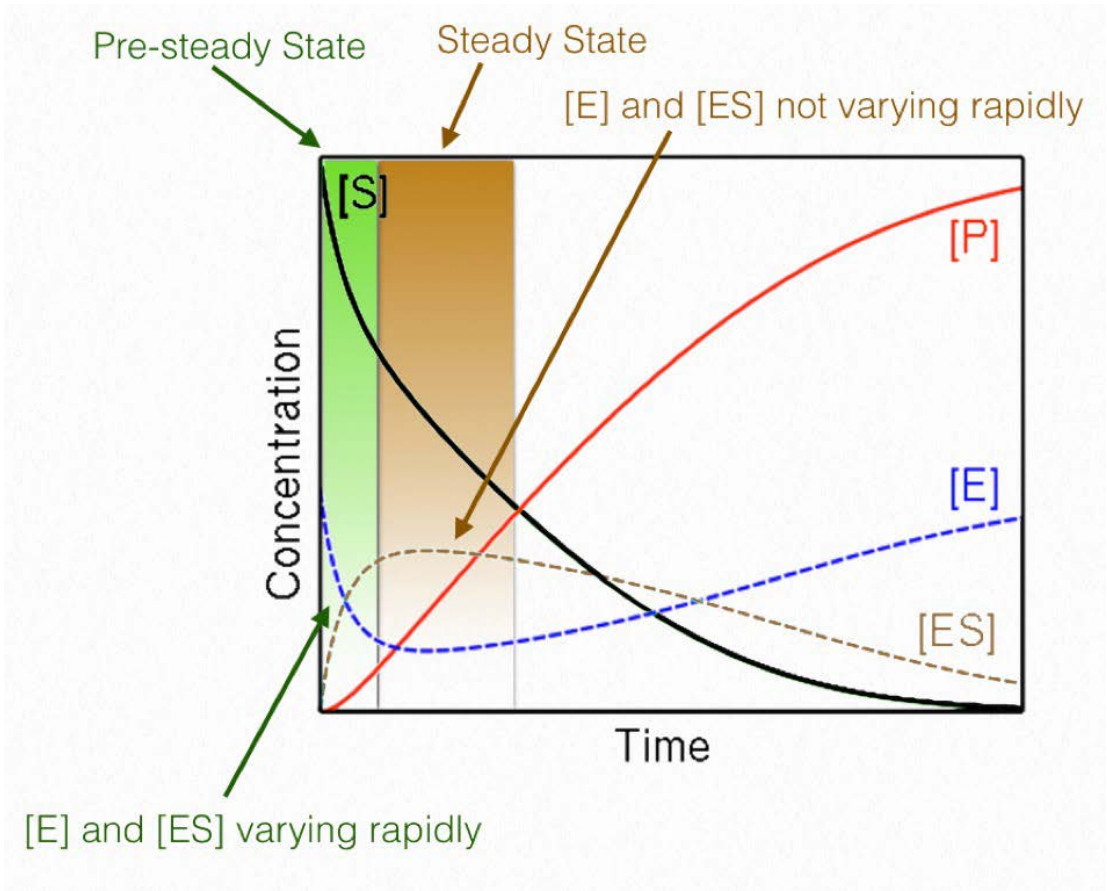
When a pre-mRNA strand has been properly processed to an mRNA sequence, it is exported out of the nucleus and eventually translated into a protein – a process accomplished in conjunction with ribosomes.



https://en.wikipedia.org/wiki/Precursor_mRNA

Pre-steady State

In the first moment after an enzyme is mixed with substrate, no product has been formed and no intermediates exist. The study of the next few milliseconds of the reaction is called Pre-steady-state kinetics also referred to as Burst kinetics. Pre-steady-state kinetics is therefore concerned with the formation and consumption of enzyme–substrate intermediates (such as ES or E*) until their steady-state concentrations are reached.



https://en.wikipedia.org/wiki/Enzyme_kinetics#Pre-steady-state_kinetics

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Chapter 4 - Catalysis: Basic Principles

Pre-tRNA

tRNAs are synthesized by RNA polymerase III, which makes precursor molecules called pre-tRNA that then undergo processing to generate mature tRNAs. The init transcripts contain additional RNA sequences at both the 5' and 3' ends. Some pre- tRNAs also contain introns. These additional sequences are removed from the tran script during processing.

The 5' leader sequence of the pre-tRNA (the additional nucleotides at the 5'-end) is moved by an unusual endonuclease called ribonuclease P (RNase P). RNase is a rib nucleoprotein complex composed of a catalytic RNA and numerous proteins. The 3 trailer sequence (extra nucleotides at the 3' end of the pre-tRNA) is later removed b different nucleases. All tRNAs must have a 3' CCA sequence that is necessary for th charging of the tRNAs with amino acids. In bacteria, this CCA sequence is encoded the tRNA gene, but in eukaryotes, the CCA sequence is added post-transcriptionall an enzyme called tRNA nucleotidyl transferase (tRNT).

https://en.wikipedia.org/wiki/Transfer_RNA

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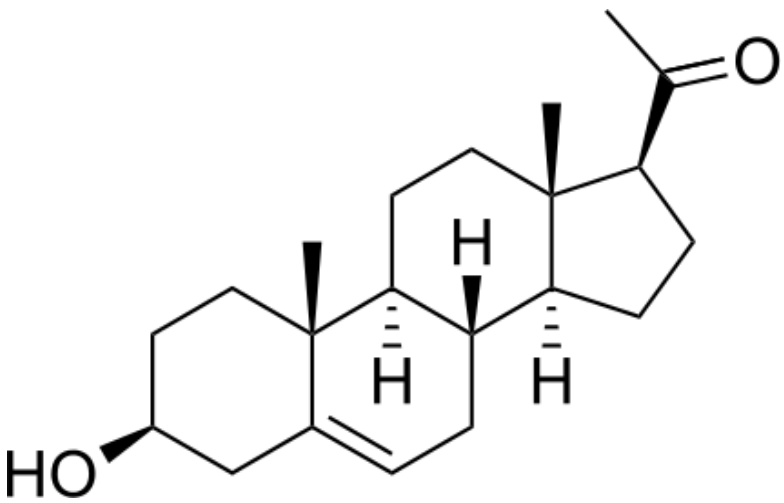
Pregnenolone

Pregnenolone, also known as P_5, is an endogenous steroid hormone. It is the precursor of the progestogens, mineralocorticoids, glucocorticoids, androgens, and estrogens, as well as the neuroactive steroids. In addition, pregnenolone is biologically active in its own right, acting as a neurosteroid.

Pregnenolone is synthesized from cholesterol. This conversion involves hydroxylation at the side-chain at C_{20} and C_{22} positions, with cleavage of the side-chain. The enzyme performing this task is cytochrome P_{450scc}, located in the mitochondria, and controlled by anterior pituitary tropic hormones, such as ACTH, FSH, LH.



https://en.wikipedia.org/wiki/Pregnenolone

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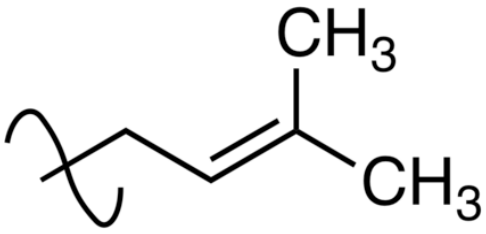
Prenylated

Prenylation (also known as isoprenylation or lipidation) is the addition of hydrophobic molecules to a protein or chemical compound. It is usually assumed that prenyl groups (3-methyl-but-2-en-1-yl) facilitate attachment to cell membranes, similar to lipid anchors like the GPI anchor, though direct evidence is missing. Prenyl groups have been shown to be important for protein–protein binding through specialized prenyl-binding domains.

Protein prenylation involves the transfer of either a farnesyl or a geranyl-geranyl moiety to C-terminal cysteine(s) of the target protein. There are three enzymes that carry out prenylation in the cell, farnesyl transferase, Caax protease and geranylgeranyl transferase I.

Farnesylation is a type of prenylation, a post-translational modification of proteins by which an isoprenyl group is added to a cysteine residue. It is an important process to mediate protein–protein interactions and protein–membrane interactions.



https://en.wikipedia.org/wiki/Prenylation

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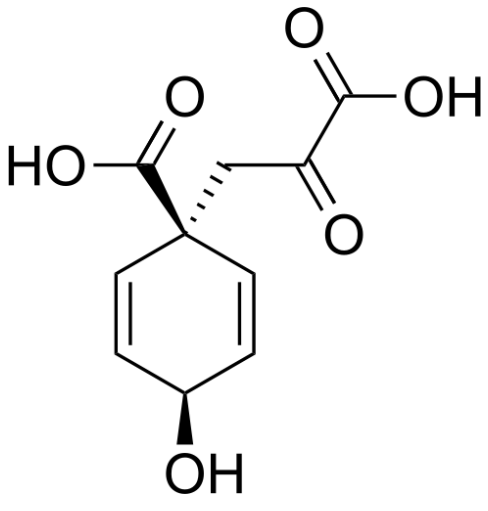
Prephenate

Prephenic acid, commonly also known by its anionic form prephenate, is an intermediate in the biosynthesis of the aromatic amino acids phenylalanine and tyrosine. It is synthesized by a [3,3]-sigmatropic Claisen rearrangement of chorismate.



https://en.wikipedia.org/wiki/Prephenic_acid

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Pri-miRNA

miR-30 microRNA precursor is a small non-coding RNA that regulates gene
sion. Animal microRNAs are transcribed as pri-miRNA (primary miRNA) of
length which in turns are processed in the nucleus by Drosha into ~70 nucle
stem-loop precursor called pre-miRNA (preliminary miRNA) and subsequen
essed by the Dicer enzyme to give a mature ~22 nucleotide product. In this c
ture sequence comes from both the 3' (miR-30) and 5' (mir-97-6) arms of th
sor. The products are thought to have regulatory roles through complementa
mRNA.

A screen of 17 miRNAs that have been predicted to regulate a number of brea
associated genes found variations in the microRNAs miR-17 and miR-30c-1,
tients were noncarriers of BRCA1 or BRCA2 mutations, lending the possibili
milial breast cancer may be caused by variation in these miRNAs.

https://en.wikipedia.org/wiki/Mir-30_microRNA_precursor

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Primary Structure

The primary structure of a peptide or protein is the linear sequence of its amino acid structural units, and partly comprises its overall biomolecular structure. By convention, the primary structure of a protein is reported starting from the amino-terminal (N) end to the carboxyl-terminal (C) end.

In general, polypeptides are unbranched polymers, so their primary structure can often be specified by the sequence of amino acids along their backbone. However, proteins can become cross-linked, most commonly by disulfide bonds, and the primary structure also requires specifying the cross-linking atoms, e.g., specifying the cysteines involved in the protein's disulfide bonds. Other crosslinks include desmosine.

The chiral centers of a polypeptide chain can undergo racemization. In particular, the L-amino acids normally found in proteins can spontaneously isomerize at the atom to form D-amino acids, which cannot be cleaved by most proteases. Finally, the protein can undergo a variety of post-translational modifications.

https://en.wikipedia.org/wiki/Protein_primary_structure

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Primary Transcript

A primary transcript is the single-stranded ribonucleic acid (RNA) product synthesized by transcription of DNA, and processed to yield various mature RNA products such as mRNAs, tRNAs, and rRNAs. The primary transcripts designated to be mRNAs are modified in preparation for translation. For example, a precursor messenger RNA (pre-mRNA) is a type of primary transcript that becomes a messenger RNA (mRNA) after processing.

There are several steps contributing to the production of primary transcripts. All these steps involve a series of interactions to initiate and complete the transcription of DNA in the nucleus of eukaryotes. Certain factors play key roles in the activation and inhibition of transcription, where they regulate primary transcript production. Transcription produces primary transcripts that are further modified by several processes. These processes include the 5' cap, 3'-polyadenylation, and alternative splicing. In particular, alternative splicing directly contributes to the diversity of mRNA found in cells. The modifications of primary transcripts have been further studied in research seeking greater knowledge of the role and significance of these transcripts. Experimental studies based on molecular changes to primary transcripts the processes before and after transcription have led to greater understanding of diseases involving primary transcripts.

https://en.wikipedia.org/wiki/Primary_transcript

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Chapter 7 - Information Processing: RNA Processing

Primase

DNA primase, also called as DNA primerase, is an enzyme involved in the replication of DNA and is a type of RNA polymerase. Primase catalyzes the synthesis of a short RNA (or DNA in some organisms) segment called a primer complementary to a ssDNA template. Primase is of key importance in DNA replication because no known DNA polymerases can initiate the synthesis of a DNA strand without an initial RNA or DNA primer (for temporary DNA elongation). After this elongation the RNA piece is removed by a 5' to 3' exonuclease and refilled with DNA.

In bacteria, primase binds to the DNA helicase forming a complex called the primosome. Primase is activated by DNA helicase where it then synthesizes a short RNA primer approximately 11 ±1 nucleotides long, to which new nucleotides can be added by DNA polymerase.

The RNA segments are first synthesized by primase and then elongated by DNA polymerase. Then the DNA polymerase forms a protein complex with two primase subunits to form the alpha DNA Polymerase primase complex. Primase is one of the most error prone and slow polymerases. Primases in organisms such as *E. coli*, synthesize around 2000 to 3000 primers at the rate of one primer per second. Primase also acts as a halting mechanism to prevent the leading strand from outpacing the lagging strand by halting the progression of the replication fork. The rate determining step in primase is when the first phosphodiester bond is formed between two molecules of RNA.

The replication mechanisms differ between different bacteria and viruses where the primase covalently link to helicase in viruses such as the T7 bacteriophage. In viruses such as herpes simplex virus (HSV-1), primase can form complexes with helicase. The primase-helicase complex is used to unwind dsDNA and synthesizes the lagging strand using RNA primers[The majority of primers synthesized by primase are two to three nucleotides long.

https://en.wikipedia.org/wiki/Primase

Related Glossary Terms

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Primer

A primer is a strand of short nucleic acid sequences (generally about 10 base pairs) that serves as a starting point for DNA synthesis. It is required for DNA replication because the enzymes that catalyze this process, DNA polymerases, can only add new nucleotides to an existing strand of DNA. The polymerase starts replication at the 3'-end of the primer, and copies the opposite strand.

In most cases of natural DNA replication, the primer for DNA synthesis and replication is a short strand of RNA (which can be made *de novo*). Many of the laboratory techniques of biochemistry and molecular biology that involve DNA polymerase, such as DNA sequencing and the polymerase chain reaction (PCR), require DNA primers. These primers are usually short, chemically synthesized oligonucleotides, with a length of about twenty bases. They are hybridized to a target DNA, which is then copied by the polymerase.

https://en.wikipedia.org/wiki/Primer_(molecular_biology)

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Prions

A prion is an infectious agent thought to be the cause of the transmissible spongiform encephalopathies (TSEs). It is composed entirely of protein material, called PrP (short for prion protein), that can fold in multiple, structurally distinct ways, at least one of which is transmissible to other prion proteins, leading to disease that is similar to viral infection. The word prion, coined in 1982 by Stanley B. Prusiner, is a portmanteau derived from protein and infection, hence prion, and is short for "proteinaceous infectious particle" in reference to its ability to self-propagate and transmit its conformation to other proteins.

A protein as a standalone infectious agent stands in contrast to all other known infectious agents such as viruses, bacteria, fungi, and parasites, all of which contain nucleic acids (DNA, RNA, or both). For this reason, a minority of researchers still consider the prion/TSE hypothesis unproven. All known prion diseases in mammals affect the structure of the brain or other neural tissue. All are currently untreatable and universally fatal.

Prions may propagate by transmitting their misfolded protein state: When a prion enters a healthy organism, it induces existing, properly folded proteins to convert into the misfolded prion form. In this way, the prion acts as a template to guide the misfolding of more proteins into prion form. In yeast, this refolding is assisted by chaperone proteins such as Hsp104p. These refolded prions can then go on to convert more proteins themselves, leading to a chain reaction resulting in large amounts of the prion form.

All known prions induce the formation of an amyloid fold, in which the protein polymerizes into an aggregate consisting of tightly packed β sheets. Amyloid aggregates are fibrils, growing at their ends, and replicate when breakage causes two growing ends to become four growing ends. The incubation period of prion diseases is determined by the exponential growth rate associated with prion replication, which is a balance between the linear growth and the breakage of aggregates. The propagation of the prion depends on the presence of normally folded protein in which the prion can induce misfolding. Animals that do not express the normal form of the prion protein can neither develop nor transmit the disease.

Prion aggregates are extremely stable and accumulate in infected tissue, causing tissue damage and cell death. This structural stability means that prions are resistant to denaturation by chemical and physical agents, making disposal and containment of these particles difficult. Prion structure varies slightly between species, but nonetheless prion replication is subject to occasional epimutation and natural selection just like other forms of replication.

https://en.wikipedia.org/wiki/Prion

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Processivity

Processivity is an enzyme's ability to catalyze "consecutive reactions without rele
its substrate".

For example, processivity is the average number of nucleotides added by a polyn
enzyme, such as DNA polymerase, per association event with the template stran
DNA polymerases associated with DNA replication tend to be highly processive,
those associated with DNA repair tend to have low processivity. Because the bin
the polymerase to the template is the rate-limiting step in DNA synthesis, the ov
rate of DNA replication during S phase of the cell cycle is dependent on the proc
ity of the DNA polymerases performing the replication. DNA clamp proteins are
gral components of the DNA replication machinery and serve to increase the pro
ity of their associated polymerases. Some polymerases add over 50,000 nucleoti
a growing DNA strand before dissociating from the template strand, giving a rep
tion rate of up to 1,000 nucleotides per second.

https://en.wikipedia.org/wiki/Processivity

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Product

Products are the species formed from chemical reactions. In biochemistry, enzymes act as biological catalysts to convert substrate to product. For example, the products of the enzyme lactase are galactose and glucose, which are produced from the substrate lactose.

https://en.wikipedia.org/wiki/Product_(chemistry)#Biochemistry

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Products

Products are the species formed from chemical reactions. In biochemistry, as biological catalysts to convert substrate to product. For example, the pro enzyme lactase are galactose and glucose, which are produced from the sub tose.

https://en.wikipedia.org/wiki/Product_(chemistry)#Biochemistry

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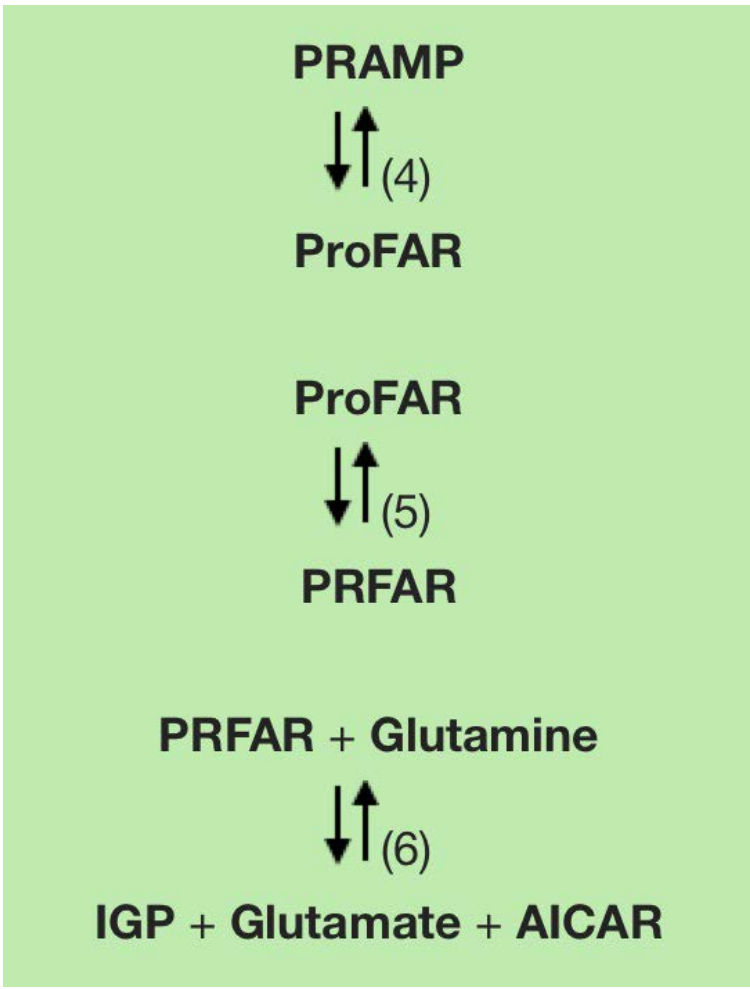
ProFAR

ProFAR-I (N′-[(5′-phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide) ribonucleotide) is an intermediate in the biosynthesis of histidine. It is the product of the fourth reaction from ribose-5-phosphate and the substrate for the fifth reaction.



Related Glossary Terms

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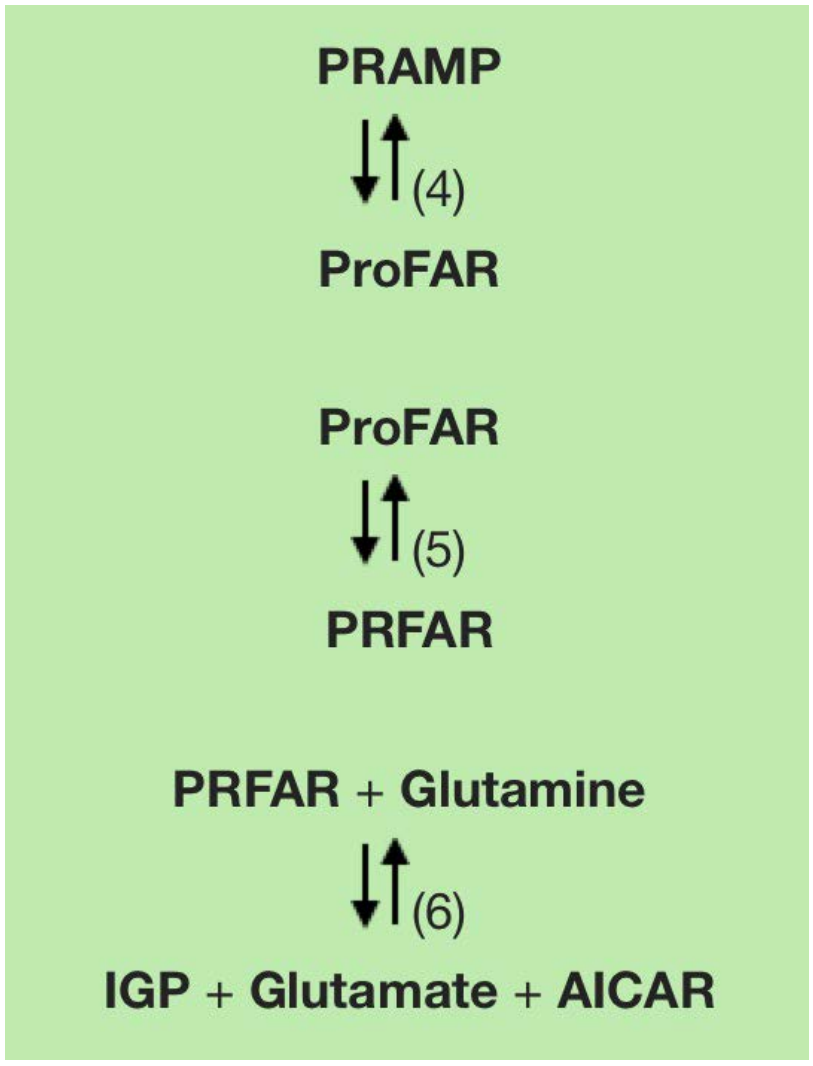
ProFAR-I

PROFAR-I N'-[(5'phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide r
nucleotide isomerase is an enzyme catalyzing the fifth reaction in the biosynthesis
histidine from ribose-5-phosphate.



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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Profilin

Profilin is an actin-binding protein involved in the dynamic turnover and res
of the actin cytoskeleton. It is found in all eukaryotic organisms in most cells
is important for spatially and temporally controlled growth of actin microfila
which is an essential process in cellular locomotion and cell shape changes. T
structuring of the actin cytoskeleton is essential for processes such as organ
ment, wound healing, and the hunting down of infectious intruders by cells o
mune system.

Profilin also binds sequences rich in the amino acid proline in diverse protei
most profilin in the cell is bound to actin, profilins have over 50 different bin
ners. Many of those are related to actin regulation, but profilin also seems to
volved in activities in the nucleus such as mRNA splicing.

https://en.wikipedia.org/wiki/Profilin

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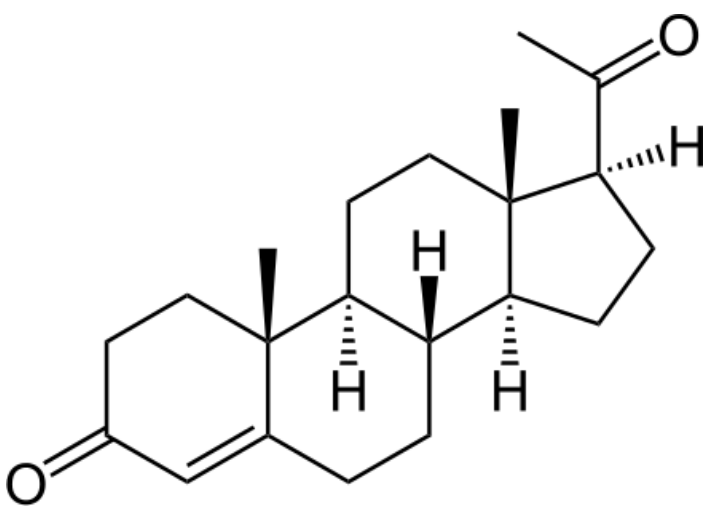
Progestagens

Progestogens (also sometimes spelled progestagens or gestagens) are a class of steroid hormones that bind to and activate the progesterone receptor (PR). The most important progestogen in the body is progesterone (P4 - shown below). Other endogenous progestogens include 17α-hydroxyprogesterone, 20α-dihydroprogesterone, 5α-dihydroprogesterone, 11-deoxycorticosterone, and 5α-dihydrodeoxycorticosterone. Synthetic progestogens are generally referred to as progestins. However, the terms progesterone, progestogen, and progestin are frequently used interchangeably both in the scientific literature and in clinical settings.



https://en.wikipedia.org/wiki/Progestogen

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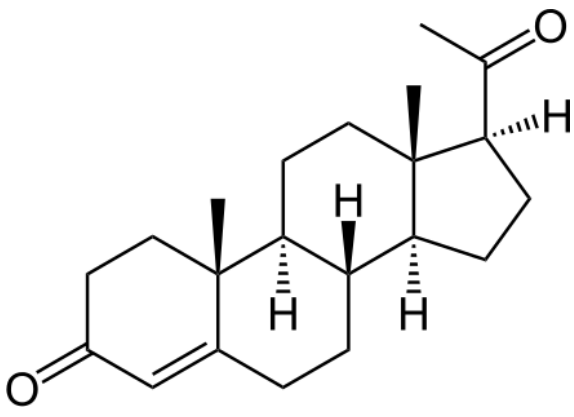
Progesterone

Progesterone (abbreviated as P4), also known as pregn-4-ene-3,20-dione, is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species. It belongs to a group of steroid hormones called the progestogens, and is the major progestogen in the body. Progesterone is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids, and plays an important role in brain function as a neurosteroid.

Progesterone is a potent agonist of the nuclear progesterone receptor (nPR) (with an affinity of KD = 1 nM). In addition, progesterone is an agonist of the more recently discovered membrane progesterone receptors (mPRs), as well as a ligand of the PGRMC1 (progesterone receptor membrane component 1 - formerly known as the σ2 receptor). Moreover, progesterone is also known to be an antagonist of the σ1 receptor, a negative allosteric modulator of the nACh receptors, and a potent antagonist of the mineralocorticoid receptor (MR). Progesterone prevents MR activation by binding to this receptor with an affinity exceeding even those of aldosterone and glucocorticoids such as cortisol and corticosterone, and produces antimineralocorticoid effects, such as natriuresis, at physiological concentrations. In addition, progesterone binds to and behaves as a partial agonist of the glucocorticoid receptor (GR), albeit with very low potency (EC50 >100-fold less relative to cortisol).



https://en.wikipedia.org/wiki/Progesterone

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Progesterone Receptor

The progesterone receptor (PR, also known as NR3C3 or nuclear receptor subfamily group C, member 3), is a protein found inside cells. It is activated by the steroid hormone progesterone.

In humans, PR is encoded by a single PGR gene residing on chromosome 11q22, it ha two main forms, A and B, that differ in their molecular weight. Progesterone is neces sary to induce the progesterone receptors. When no binding hormone is present the carboxyl terminal inhibits transcription. Binding to a hormone induces a structural change that removes the inhibitory action. Progesterone antagonists prevent the stru tural reconfiguration.

After progesterone binds to the receptor, restructuring with dimerization follows and the complex enters the nucleus and binds to DNA. There transcription takes place, re sulting in formation of messenger RNA that is translated by ribosomes to produce sp cific proteins.

https://en.wikipedia.org/wiki/Progesterone_receptor

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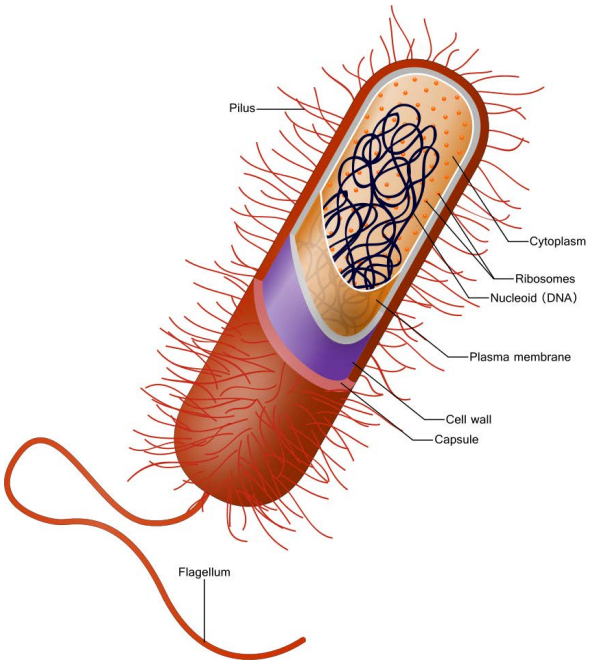
Prokaryotes

A prokaryote is a single-celled organism that lacks a membrane-bound nucleus (karyon), mitochondria, or any other membrane-bound organelle. In the prokaryotes all the intracellular water-soluble components (proteins, DNA and metabolites) are located together in the cytoplasm enclosed by the cell membrane, rather than in separate cellular compartments. Bacteria, however, do possess protein-based bacterial microcompartments, which are thought to act as primitive organelles enclosed in protein shells. Some prokaryotes, such as cyanobacteria may form large colonies. Others, such as myxobacteria, have multicellular stages in their life cycles.



https://en.wikipedia.org/wiki/Prokaryote

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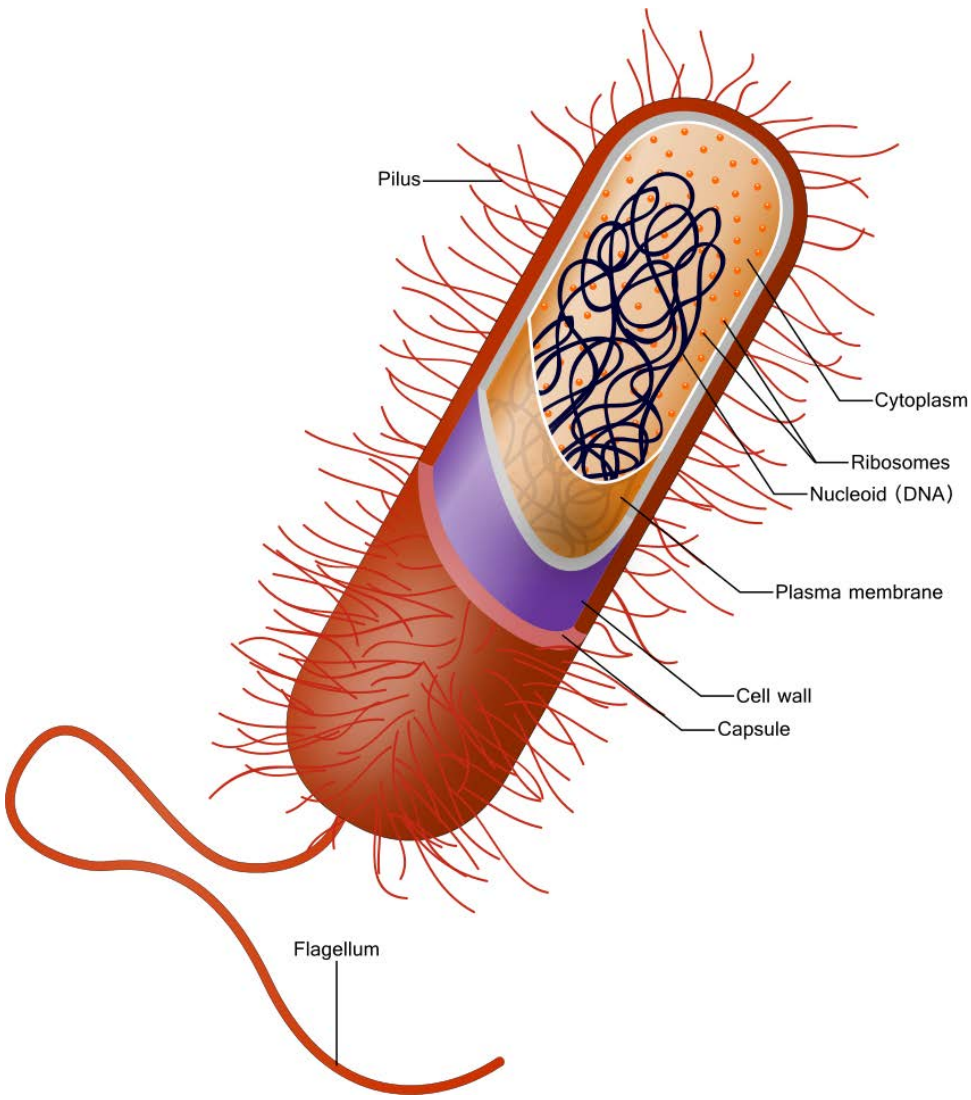
Prokaryotic

A prokaryote is a single-celled organism that lacks a membrane-bound nucleus (karyon), mitochondria, or any other membrane-bound organelle. In the prokaryotes all the intracellular water-soluble components (proteins, DNA and metabolites) are located together in the cytoplasm enclosed by the cell membrane, rather than in separate cellular compartments. Bacteria, however, do possess protein-based bacterial microcompartments, which are thought to act as primitive organelles enclosed in protein shells. Some prokaryotes, such as cyanobacteria may form large colonies. Others, such as myxobacteria, have multicellular stages in their life cycles.



https://en.wikipedia.org/wiki/Prokaryote

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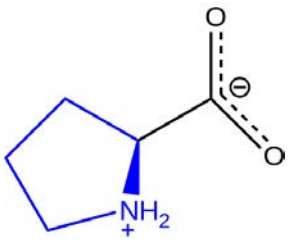
Proline

Proline (abbreviated as Pro or P; encoded by the codons CCU, CCC, CCA, and CCG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated -NH_2^+ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $–COO^–$ form under biological conditions), and a side chain pyrrolidine, classifying it as a nonpolar(at physiological pH), aliphatic amino acid. It is non-essential in humans, meaning the body can synthesize it from the non-essential amino acid L-glutamate.

Proline is the only amino acid with a secondary amine. Furthermore, it is unique in that the α-amino group is attached directly to the side chain, making the α carbon a direct substituent of the side chain.



https://en.wikipedia.org/wiki/Proline

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Prolyl Hydroxylase

Prolyl hydroxylase is a member of the class of enzymes known as 2-oxoglut
dependent dioxygenases. These enzymes catalyze the incorporation of oxyg
ganic substrates through a mechanism that requires 2-oxoglutarate, Fe^{++}, a
bate. This particular enzyme catalyzes the formation of (2S, 4R)-4-hydroxy
compound that represents the most prevalent post-translational modificati
man proteome.

https://en.wikipedia.org/wiki/Procollagen-proline_dioxygenase

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Prolyl-4-hydroxylase

Prolyl hydroxylase is a member of the class of enzymes known as 2-oxoglut
dependent dioxygenases. These enzymes catalyze the incorporation of oxyg
ganic substrates through a mechanism that requires 2-oxoglutarate, Fe^{++}, a
bate. This particular enzyme catalyzes the formation of (2S, 4R)-4-hydroxy
compound that represents the most prevalent post-translational modificati
man proteome.

https://en.wikipedia.org/wiki/Procollagen-proline_dioxygenase

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Promoter

For transcription to take place, the enzyme that synthesizes RNA, known as RNA polymerase, must attach to the DNA near a gene. Promoters contain specific DNA sequences such as response elements that provide a secure initial binding site for RNA polymerase and for proteins called transcription factors that recruit RNA polymerase. These transcription factors have specific activator or repressor sequences of corresponding nucleotides that attach to specific promoters and regulate gene expression.

Promoters are located near the transcription start sites of genes, on the same strand and upstream on the DNA (towards the 5' region of the sense strand). Promoters can be about 100–1000 base pairs long.

In bacteria:
The promoter is recognized by RNA polymerase and an associated sigma factor, which in turn are often brought to the promoter DNA by an activator protein's binding to its own DNA binding site nearby.

In eukaryotes:
The process is more complicated, and at least seven different factors are necessary for the binding of an RNA polymerase II to the promoter. Promoters represent critical elements that can work in concert with other regulatory regions (enhancers, silencers, boundary elements/insulators) to direct the level of transcription of a given gene.

https://en.wikipedia.org/wiki/Promoter_(genetics)

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Chapter 9 - Point by Point: Information Processing

Proofreading

The term proofreading is used in genetics to refer to the error-correcting processes, first proposed by John Hopfield and Jacques Ninio, involved in DNA replication, immune system specificity, enzyme-substrate recognition among many other processes that require enhanced specificity. The proofreading mechanisms of Hopfield and Ninio are non-equilibrium active processes that consume ATP to enhance specificity of various biochemical reactions.

In bacteria, all three DNA polymerases (I, II and III) have the ability to proofread, using 3’ → 5’ exonuclease activity. When an incorrect base pair is recognized, DNA polymerase reverses its direction by one base pair of DNA and excises the mismatched base. Following base excision, the polymerase can re-insert the correct base and replication can continue.

In eukaryotes only the polymerase that deal with the elongation (delta, and epsilon) have proofreading ability (3’ → 5’ exonuclease activity).

Proofreading also occurs in mRNA translation for protein synthesis. In this case, one mechanism is release of any incorrect aminoacyl-tRNA prior to peptide bond formation.

The extent of proofreading in DNA replication determines the mutation rate, and is different in different species. For example, loss of proof-reading due to mutations in the DNA polymerase epsilon gene results in a hyper-mutated genotype with >100 mutations per Mbase of DNA in human colorectal cancers.

https://en.wikipedia.org/wiki/Proofreading_(biology)

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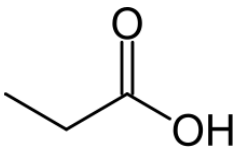
Propionic Acid

Propionic acid,also known as propanoic acid, is a naturally occurring carboxylic acid with chemical formula CH_3CH_2COOH. It is a clear liquid with a pungent and unpleasant smell somewhat resembling body odor. The anion $CH_3CH_2COO^-$ as well as the salts and esters of propionic acid are known as propionates (or propanoates).

Propionyl-CoA is a metabolic product of metabolism of amino acids with odd numbers of carbons. The metabolism of propionic acid begins with its conversion to propionyl coenzyme A (propionyl-CoA), the usual first step in the metabolism of carboxylic acids. Since propionic acid has three carbons, propionyl-CoA cannot directly enter either β oxidation or the citric acid cycle. In most vertebrates, propionyl-CoA is carboxylated to D-methylmalonyl-CoA, which is isomerized to L-methylmalonyl-CoA. A vitamin B_{12}-dependent enzyme catalyzes rearrangement of L-methylmalonyl-CoA to succinyl-CoA, which is an intermediate of the citric acid cycle and can be readily incorporated there.

In propionic acidemia, a rare inherited genetic disorder, propionate acts as a metabolic toxin in liver cells by accumulating in mitochondria as propionyl-CoA and its derivative, methylcitrate, two tricarboxylic acid cycle inhibitors. Propanoate is metabolized oxidatively by glia, which suggests astrocytic vulnerability in propionic acidemia when intramitochondrial propionyl-CoA may accumulate. Propionic acidemia may alter both neuronal and glial gene expression by affecting histone acetylation. When propionic acid is infused directly into rodents' brains, it produces reversible behavior (e.g., hyperactivity, dystonia, social impairment, perseveration) and brain changes (e.g., innate neuroinflammation, glutathione depletion) that may be used as a means to model autism in rats.

It also, being a three-carbon molecule, feeds into hepatic gluconeogenesis (that is, the creation of glucose molecules from simpler molecules in the liver).



https://en.wikipedia.org/wiki/Propionic_acid

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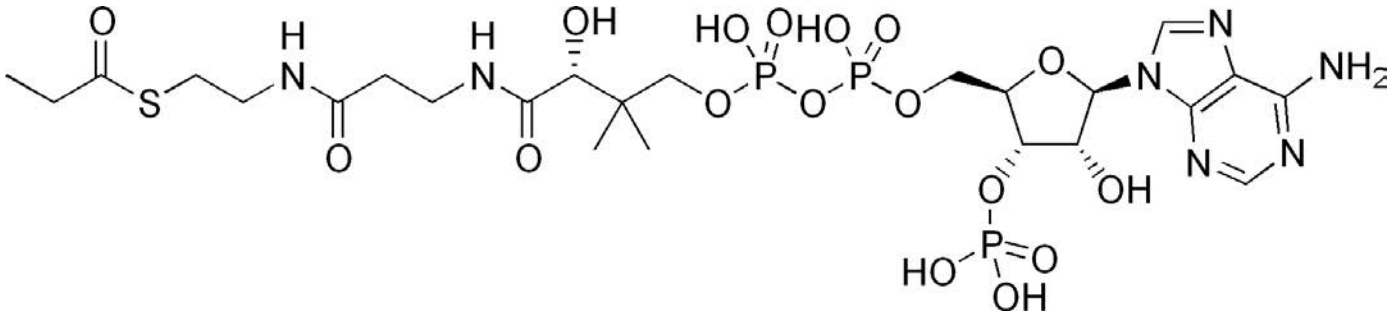
Propionyl-CoA

Propionyl-CoA is a coenzyme A derivative of propionic acid. There are several different ways in which it is formed: It is formed as a product of β-oxidation of odd-chain fatty acids. It is also a product of metabolism of isoleucine and valine. It is a product of α-ketobutyric acid, which in turn is a product of catabolism of threonine and methionine. It can also be formed as a by-product during the conversion of cholesterol to bile acids.



https://en.wikipedia.org/wiki/Propionyl-CoA

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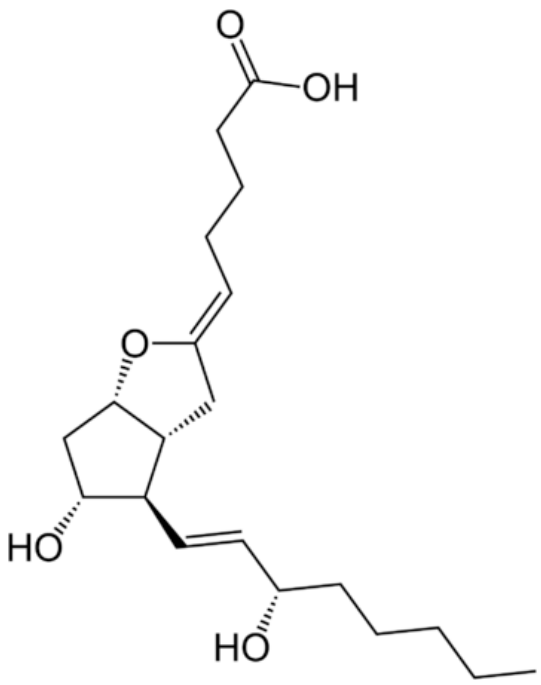
Prostacyclin

Prostacyclin (also called prostaglandin I_2 or PGI_2) chiefly prevents formation of the platelet plug involved in primary hemostasis (a part of blood clot formation). It does this by inhibiting platelet activation. It is also an effective vasodilator. Prostacyclin's interactions in contrast to thromboxane (TXA_2), another eicosanoid, strongly suggest a mechanism of cardiovascular homeostasis between the two hormones in relation to vascular damage.

As a drug, it is also known as "epoprostenol".



https://en.wikipedia.org/wiki/Prostacyclin

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Prostacyclin Synthase

Prostacyclin synthase is an enzyme involved in prostanoid biosynthesis that in human is encoded by the PTGIS gene. This gene encodes a member of the cytochrome P_{450} superfamily of enzymes. The cytochrome P_{450} proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. However, this protein is considered a member of the cytochrome P_{450} superfamily on the basis of sequence similarity rather than functional similarity. This endoplasmic reticulum membrane protein catalyzes the conversion of prostaglandin H_2 to prostacyclin (prostaglandin I_2), a potent vasodilator and inhibitor of platelet aggregation. An imbalance of prostacyclin and its physiological antagonist thromboxane A_2 contribute to the development of myocardial infarction, stroke, and atherosclerosis.

Unlike most P_{450} enzymes, PGIS does not require molecular oxygen (O_2). Instead it uses its heme cofactor to catalyze the isomerization of prostaglandin H_2 to prostacyclin. Prostaglandin H_2 is produced by cyclooxygenase in the first committed step of prostaglandin biosynthesis.

https://en.wikipedia.org/wiki/Prostacyclin_synthase

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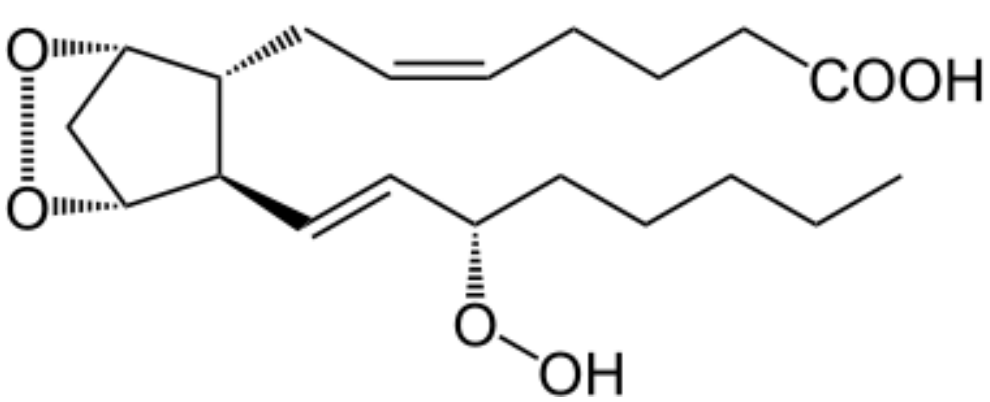
Prostaglandin G_2

Prostaglandin G_2 is an organic peroxide belonging to the family of prostagla
Vitro it is stable enough to be isolated pure, while *in vivo* it tends to quickly
into prostaglandin H_2 as a result of the catalytic enzyme COX. The molecule
portant intermediate reaction product of the metabolism of arachidonic aci
clooxygenase.



https://en.wikipedia.org/wiki/Prostaglandin_G2

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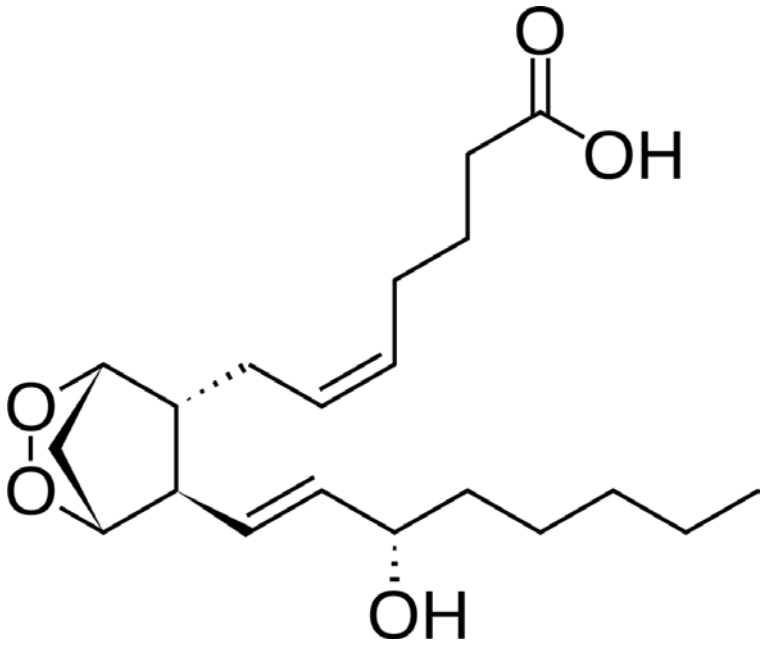
Prostaglandin H_2

Prostaglandin H_2 is a type of prostaglandin and a precursor for many other bio
significant molecules. It is synthesized from arachidonic acid in a reaction cata
a cyclooxygenase enzyme.



https://en.wikipedia.org/wiki/Prostaglandin_H2

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Prostaglandins

The prostaglandins (PG) are a group of physiologically active lipid compounds having diverse hormone-like effects in animals. Prostaglandins have been found in almost every tissue in humans and other animals. They are derived enzymatically from fatty acids. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. They are a subclass of eicosanoids and of the prostanoid class of fatty acid derivatives.

The structural differences between prostaglandins account for their different biological activities. A given prostaglandin may have different and even opposite effects in different tissues. The ability of the same prostaglandin to stimulate a reaction in one tissue and inhibit the same reaction in another tissue is determined by the type of receptor to which the prostaglandin binds. They act as autocrine or paracrine factors with their target cells present in the immediate vicinity of the site of their secretion. Prostaglandins differ from endocrine hormones in that they are not produced at a specific site but in many places throughout the human body.

https://en.wikipedia.org/wiki/Prostaglandin

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Prosthetic Group

A cofactor that is tightly or even covalently bound to a protein is termed a prosthetic group. A cofactor is a non-protein chemical compound that is required for the protein's biological activity to happen. These proteins are commonly enzymes, and cofactors can be considered "helper molecules" that assist in biochemical transformations.

Cofactors can be subdivided into either one or more inorganic ions, or a complex organic or metalloorganic molecule called a coenzyme, most of which are derived from vitamins and from required organic nutrients in small amounts. A cofactor that is tightly or even covalently bound is termed a prosthetic group. Additionally, some sources also limit the use of the term "cofactor" to inorganic substances. An inactive enzyme without the cofactor is called an apoenzyme, while the complete enzyme with cofactor is called a holoenzyme.

Some enzymes or enzyme complexes require several cofactors. For example, the multienzyme complex pyruvate dehydrogenase at the junction of glycolysis and the citric acid cycle requires five organic cofactors and one metal ion: loosely bound thiamine pyrophosphate (TPP), covalently bound lipoamide and flavin adenine dinucleotide (FAD), and the co-substrates nicotinamide adenine dinucleotide (NAD^+) and coenzyme A (CoA), and a metal ion (Mg^{++}).

Organic cofactors are often vitamins or are made from vitamins. Many contain the nucleotide adenosine monophosphate (AMP) as part of their structures, such as ATP, coenzyme A, FAD, and NAD^+. This common structure may reflect a common evolutionary origin as part of ribozymes in an ancient RNA world. It has been suggested that the AMP part of the molecule can be considered to be a kind of "handle" by which the enzyme can "grasp" the coenzyme to switch it between different catalytic centers.

https://en.wikipedia.org/wiki/Cofactor_(biochemistry)

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Protease

A protease (also called a peptidase or proteinase) is any enzyme that performs proteolysis, that is, begins protein catabolism by hydrolysis of the peptide bonds that link amino acids together in a polypeptide chain. Proteases have evolved multiple times, and different classes of protease can perform the same reaction by completely different catalytic mechanisms. Proteases can be found in animals, plants, bacteria, archaea and viruses.

Proteases are involved in digesting long protein chains into shorter fragments by splitting the peptide bonds that link amino acid residues. Some detach the terminal amino acids from the protein chain (exopeptidases, such as aminopeptidases, carboxypeptidase A). Others attack internal peptide bonds of a protein (endopeptidases, such as trypsin, chymotrypsin, pepsin, papain, elastase).

Catalysis is achieved by one of two mechanisms:

• Aspartic, glutamic and metallo- proteases activate a water molecule which performs a nucleophilic attack on the peptide bond to hydrolyze it.
• Serine, threonine and cysteine proteases use a nucleophilic residue in a (usually in a catalytic triad). That residue performs a nucleophilic attack to covalently link the protease to the substrate protein, releasing the first half of the product. This covalent acyl-enzyme intermediate is then hydrolyzed by activated water to complete catalysis by releasing the second half of the product and regenerating the free enzyme.

https://en.wikipedia.org/wiki/Protease

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Protease Inhibitors

In biology and biochemistry, protease inhibitors are molecules that inhibit the function of proteases. Many naturally occurring protease inhibitors are proteins. Protease inhibitors may be classified either by the type of protease they inhibit, or by their mechanism of action.

Protease inhibitors may be classified either by the type of protease they inhibit, or by their mechanism of action. In 2004 Rawlings and colleagues introduced a classification of protease inhibitors based on similarities detectable at the level of amino acid sequence. This classification initially identified 48 families of inhibitors that could be grouped into 26 related superfamily (or clans) by their structure. According to the MEROPS database there are now 85 families of inhibitors. These families are named with an I followed by a number, for example, I14 contains hirudin-like inhibitors.

https://en.wikipedia.org/wiki/Protease_inhibitor_(biology)

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Proteasome

Proteasomes are protein complexes inside all eukaryotes and archaea, and in some bacteria. The main function of the proteasome is to degrade unneeded or damaged proteins by proteolysis, a chemical reaction that breaks peptide bonds.

In eukaryotes, proteasomes are located in the nucleus and the cytoplasm. The main function of the proteasome is to degrade unneeded or damaged proteins by proteolysis, a chemical reaction that breaks peptide bonds. Enzymes that help such reactions are called proteases. Proteasomes are part of a major mechanism by which cells regulate the concentration of particular proteins and degrade misfolded proteins. The degradation process yields peptides of about seven to eight amino acids long, which can then be further degraded into shorter amino acid sequences and used in synthesizing new proteins. Proteins are tagged for degradation with a small protein called ubiquitin. The tagging reaction is catalyzed by enzymes called ubiquitin ligases. Once a protein is tagged with a single ubiquitin molecule, this is a signal to other ligases to attach additional ubiquitin molecules. The result is a polyubiquitin chain that is bound by the proteasome, allowing it to degrade the tagged protein. The proteasomal degradation pathway is essential for many cellular processes, including the cell cycle, the regulation of gene expression, and responses to oxidative stress.

https://en.wikipedia.org/wiki/Proteasome

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https://en.wikipedia.org/wiki/Proteasome

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Protein

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A linear chain of amino acid residues is called a polypeptide. A protein contains at least one long polypeptide. Short polypeptides, containing less than 20-30 residues, are rarely considered to be proteins and are commonly called peptides, or sometimes oligopeptides. The individual amino acid residues are bonded together by peptide bonds and adjacent amino acid residues. The sequence of amino acid residues in a protein is defined by the sequence of a gene, which is encoded in the genetic code. In general, the genetic code specifies 20 standard amino acids. However, in certain organisms the genetic code can include selenocysteine and—in certain archaea—pyrrolysine. Shortly after or even during synthesis, the residues in a protein are often chemically modified by posttranslational modification, which alters the physical and chemical properties, folding, stability, activity, and ultimately, the function of the proteins. Sometimes proteins have non-peptide groups attached, which can be called prosthetic groups or cofactors. Proteins can also work together to achieve a particular function, and they often associate to form stable protein complexes.

Once formed, proteins only exist for a certain period of time and are then degraded and recycled by the cell's machinery through the process of protein turnover. A protein's lifespan is measured in terms of its half-life and covers a wide range. They can exist for minutes or years with an average lifespan of 1–2 days in mammalian cells. Abnormal and or misfolded proteins are degraded more rapidly either due to being targeted for destruction or due to being unstable.
Like other biological macromolecules such as polysaccharides and nucleic acids, proteins are essential parts of organisms and participate in virtually every process within cells. Many proteins are enzymes that catalyze biochemical reactions and are vital to metabolism. Proteins also have structural or mechanical functions, such as actin and myosin in muscle and the proteins in the cytoskeleton, which form a system of scaffolding that maintains cell shape. Other proteins are important in cell signaling, immune responses, cell adhesion, and the cell cycle. Proteins are also necessary in animals' diets, since animals cannot synthesize all the amino acids they need and must obtain essential amino acids from food. Through the process of digestion, animals break down ingested protein into free amino acids that are then used in metabolism.

Proteins may be purified from other cellular components using a variety of techniques such as ultracentrifugation, precipitation, electrophoresis, and chromatography. The advent of genetic engineering has made possible a number of methods to facilitate purification. Methods commonly used to study protein structure and function include immunohistochemistry, site-directed mutagenesis, X-ray crystallography, nuclear magnetic resonance and mass spectrometry.

https://en.wikipedia.org/wiki/Protein

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Protein Disulfide Isomerase

Protein disulfide isomerase or PDI is an enzyme in the endoplasmic reticulum in eukaryotes that catalyzes the formation and breakage of disulfide bonds between cysteine residues within proteins as they fold. This allows proteins to quickly find the correct arrangement of disulfide bonds in their fully folded state, and therefore the enzyme acts to catalyze protein folding.

The reduced (dithiol) form of PDI is able to catalyze a reduction of mispaired thiol residues of a particular substrate, acting as an isomerase. Therefore, PDI is capable of catalyzing the post-translational modification disulfide exchange. Such exchange reactions can occur intramolecularly, leading to the rearrangement of disulfide bonds in a single protein.

Another major function of PDI relates to its activity as a chaperone, i.e., it aids wrongly folded proteins to reach a correctly folded state without the aid of enzymatic disulfide shuffling.

Oxidized PDI can catalyze the formation of a disulfide bridge. This reduces PDI, which is re-oxidized by a protein called Ero1.

https://en.wikipedia.org/wiki/Protein_disulfide-isomerase

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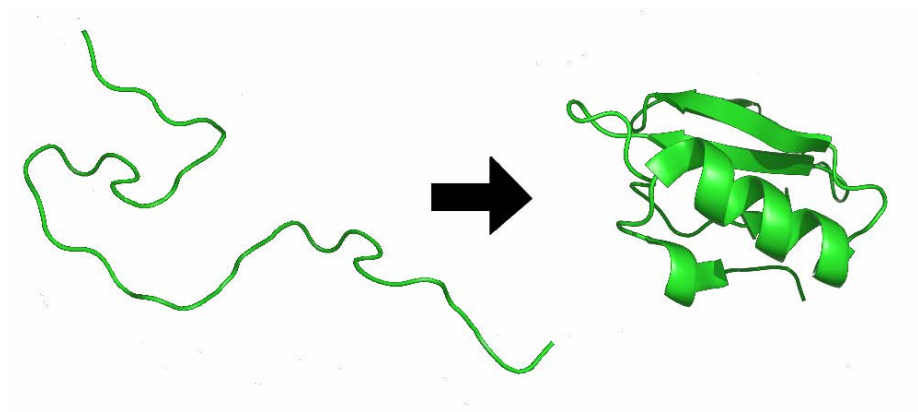
Protein Folding

Protein folding is the physical process by which a protein chain acquires its native 3-dimensional structure, a conformation that is usually biologically functional, in an expeditious and reproducible manner. It is the physical process by which a polypeptide folds into its characteristic and functional three-dimensional structure from random coil. Each protein exists as an unfolded polypeptide or random coil when translated from a sequence of mRNA to a linear chain of amino acids. This polypeptide lacks any stable (long-lasting) three-dimensional structure (the left hand side of the first figure). Amino acids interact with each other to produce a well-defined three-dimensional structure, the folded protein (the right hand side of the figure), known as the native state. The resulting three-dimensional structure is determined by the amino acid sequence (Anfinsen's dogma). Experiments beginning in the 1980s indicate the codon for an amino acid can also influence protein structure.

The correct three-dimensional structure is essential to function, although some parts of functional proteins may remain unfolded, so that protein dynamics is important. Failure to fold into native structure generally produces inactive proteins, but in some instances misfolded proteins have modified or toxic functionality. Several neurodegenerative and other diseases are believed to result from the accumulation of amyloid fibrils formed by misfolded proteins. Many allergies are caused by incorrect folding of some proteins, because the immune system does not produce antibodies for certain protein structures.



https://en.wikipedia.org/wiki/Protein_folding

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Protein Kinase A

In cell biology, protein kinase A (PKA) is a family of enzymes whose activity is dependent on cellular levels of cyclic AMP (cAMP). PKA is also known as cAMP-dependent protein kinase .Protein kinase A has several functions in the cell, including regulation of glycogen, sugar, and lipid metabolism. PKA phosphorylates proteins that have the motif Arginine-Arginine-X-Serine exposed, in turn (de)activating the proteins.

The PKA enzyme is also known as cAMP-dependent enzyme because it is activated only when cAMP is present. Hormones such as glucagon and epinephrine begin the activation cascade (that triggers protein kinase A) by binding to a G protein–coupled receptor (GPCR) on the target cell. When a GPCR is activated by its extracellular ligand, a conformational change is induced in the receptor that is transmitted to an attached intracellular heterotrimeric G protein complex by protein domain dynamics. The $G_{s\alpha}$ subunit of the stimulated G protein complex exchanges GDP for GTP and is released from the complex. The activated $G_{s\alpha}$ subunit binds to and activates an enzyme called adenylyl cyclase, which, in turn, catalyzes the conversion of ATP into cyclic adenosine monophosphate (cAMP) – increasing cAMP levels. Four cAMP molecules are required to activate a single PKA enzyme. This is done by two cAMP molecules binding to each of the two regulatory subunits on a PKA enzyme causing the subunits to detach exposing the two (now activated) catalytic subunits. Next the catalytic subunits can go on to phosphorylate other proteins.

Below is a list of the steps involved in PKA activation:
1 Cytosolic cAMP increases
2 Two cAMP molecules bind to each PKA regulatory subunit
3 The regulatory subunits move out of the active sites of the catalytic subunits and the R_2C_2 complex dissociates
4 The free catalytic subunits interact with proteins to phosphorylate Ser or Thr residues.

https://en.wikipedia.org/wiki/Protein_kinase_A

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Protein Kinase C

Protein kinase C also known as PKC (EC 2.7.11.13) is a family of protein kinase enzymes that are involved in controlling the function of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues on these proteins. PKC enzymes in turn are activated by signals such as increases in the concentration of diacylglycerol (DAG) or calcium ions (Ca2+). Hence PKC enzymes play important roles in several signal transduction cascades.

The PKC family consists of fifteen isozymes in humans. They are divided into three subfamilies, based on their second messenger requirements: conventional (or classical), novel, and atypical. Conventional (c)PKCs contain the isoforms α, βI, βII, and γ. These require Ca^{++}, DAG, and a phospholipid such as phosphatidylserine for activation. Novel (n)PKCs include the δ, ε, η, and θ isoforms, and require DAG, but do not require Ca^{++} for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. On the other hand, atypical (a)PKCs (including protein kinase Mζ and ι / λ isoforms) require neither Ca^{++} nor diacylglycerol for activation. The term "protein kinase C" usually refers to the entire family of isoforms. PKC is involved in receptor desensitization, in modulating membrane structure events, in regulating transcription, in mediating immune responses, in regulating cell growth, and in learning and memory. These functions are achieved by PKC-mediated phosphorylation of other proteins.

https://en.wikipedia.org/wiki/Protein_kinase_C

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Protein Kinases

A protein kinase is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). Phosphorylation usually results in a functional change of the target protein (substrate) by changing enzyme activity, cellular location, or association with other proteins. The human genome contains about 500 protein kinase genes and they constitute about 2% of all human genes. Up to 30% of all human proteins may be modified by kinase activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction. Protein kinases are also found in bacteria and plants.

Serine/threonine protein kinases (EC 2.7.11.1) phosphorylate the OH group of serine or threonine (which have similar side-chains). Activity of these protein kinases can be regulated by specific events (e.g., DNA damage), as well as numerous chemical signals, including cAMP/cGMP, diacylglycerol, and Ca^{++}/calmodulin. One very important group of protein kinases are the MAP kinases (acronym from: "mitogen-activated protein kinases"). Important subgroups are the kinases of the ERK subfamily, typically activated by mitogenic signals, and the stress-activated protein kinases JNK and p38.

While MAP kinases are serine/threonine-specific, they are activated by combined phosphorylation on serine/threonine and tyrosine residues. Activity of MAP kinases is restricted by a number of protein phosphatases, which remove the phosphate groups that are added to specific serine or threonine residues of the kinase and are required to maintain the kinase in an active conformation. Two major factors influence activity of MAP kinases: a) signals that activate transmembrane receptors (either natural ligands or crosslinking agents) and proteins associated with them (mutations that simulate active state) b) signals that inactivate the phosphatases that restrict a given MAP kinase. Such signals include oxidant stress.

https://en.wikipedia.org/wiki/Protein_kinase

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Protein Phosphatase 2A

Protein phosphatase 2 (PP2), also known as PP2A, is an enzyme that consists of a dimeric core enzyme composed of the structural A and catalytic C subunits, and a regulatory B subunit. The PP2A heterotrimeric protein phosphatase is a ubiquitous and conserved serine/threonine phosphatase with broad substrate specificity and diverse cellular functions. Among the targets of PP2A are proteins of oncogenic signaling cascades, such as Raf, MEK, and AKT.

PP2A consists of a dimeric core enzyme composed of the structural A and catalytic C subunits, and a regulatory B subunit. When the PP2A catalytic C subunit associates with the A and B subunits several species of holoenzymes are produced with distinct functions and characteristics. The A subunit, a founding member of the HEAT repeat protein family (huntington-elongation-A subunit-TOR), is the scaffold required for the formation of the heterotrimeric complex. When the A subunit binds it alters the enzymatic activity of the catalytic subunit, even if the B subunit is absent. While C and A subunit sequences show remarkable sequence conservation throughout eukaryotes, regulatory B subunits are more heterogeneous and are believed to play key roles in controlling the localization and specific activity of different holoenzymes. Multicellular eukaryotes express four classes of variable regulatory subunits: B (PR55), B′ (B56 or PR61), B″ (PR72), and B‴ (PR93/PR110), with at least 16 members in these subfamilies. In addition, accessory proteins and posttranslational modifications (such as methylation) control PP2A subunit associations and activities.

https://en.wikipedia.org/wiki/Protein_phosphatase_2

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Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

Protein Sorting

Protein targeting or protein sorting is the biological mechanism by which proteins are transported to the appropriate destinations in the cell or outside of it. Proteins can be targeted to the inner space of an organelle, different intracellular membranes, plasma membrane, or to exterior of the cell via secretion. This delivery process is carried out based on information contained in the protein itself. Correct sorting is crucial for the cell. Errors can lead to diseases.

Targeting signals are the pieces of information that enable the cellular transport machinery to correctly position a protein inside or outside the cell. This information is contained in the polypeptide chain or in the folded protein. The continuous stretch of amino acid residues in the chain that enables targeting are called signal peptides or targeting peptides. There are two types of targeting peptides, the presequences and the internal targeting peptides. The presequences of the targeting peptide are often found at the N-terminal extension and is composed of between 6-136 basic and hydrophobic amino acids. In case of peroxisomes the targeting sequence is on the C-terminal extension mostly. Other signals, known as signal patches, are composed of parts which are separate in the primary sequence. They become functional when folding brings them together on the protein surface. In addition, protein modifications like glycosylations can induce targeting.

https://en.wikipedia.org/wiki/Protein_targeting

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Protein Structure

Protein structure is the three-dimensional arrangement of atoms in a protein molecule. Proteins are polymers — specifically polypeptides — formed from sequences of monomer amino acids. By convention, a chain under 40 amino acids is often identified as a peptide, rather than a protein. To be able to perform their biological function, proteins fold into one or more specific spatial conformations driven by a number of non-covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals forces, and hydrophobic packing. To understand the functions of proteins at a molecular level, it is often necessary to determine their three-dimensional structure. This is the topic of the scientific field of structural biology, which employs techniques such as X-ray crystallography, NMR spectroscopy, and dual polarization interferometry to determine the structure of proteins.

Protein structures range in size from tens to several thousand amino acids. By physical size, proteins are classified as nanoparticles, between 1–100 nm. Very large aggregates can be formed from protein subunits. For example, many thousands of actin molecules assemble into a microfilament.

A protein may undergo reversible structural changes in performing its biological function. The alternative structures of the same protein are referred to as different conformations, and transitions between them are called conformational changes.

https://en.wikipedia.org/wiki/Protein_structure

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Protein Synthesis

Protein biosynthesis is the process whereby biological cells generate new proteins. It is balanced by the loss of cellular proteins via degradation or export. Translation, the assembly of amino acids by ribosomes, is an essential part of the biosynthetic pathway, along with generation of messenger RNA (mRNA), aminoacylation of transfer RNA (tRNA), co-translational transport, and post-translational modification. Protein biosynthesis is strictly regulated at multiple steps. They are principally during transcription (phenomena of RNA synthesis from DNA template) and translation (phenomena of amino acid assembly from RNA).

The cistron DNA is transcribed into a variety of RNA intermediates. The last version is used as a template in synthesis of a polypeptide chain. Protein will often be synthesized directly from genes by translating mRNA. When a protein must be available on short notice or in large quantities, a protein precursor is produced. A proprotein is an inactive protein containing one or more inhibitory peptides that can be activated when the inhibitory sequence is removed by proteolysis during posttranslational modification. A preprotein is a form that contains a signal sequence (an N-terminal signal peptide) that specifies its insertion into or through membranes, i.e., targets them for secretion. The signal peptide is cleaved off in the endoplasmic reticulum. Preproproteins have both sequences (inhibitory and signal) still present.

In protein synthesis, a succession of tRNA RNA molecules charged with appropriate amino acids are brought together with an mRNA molecule and matched up by base-pairing through the anti-codons of the tRNA with successive codons of the mRNA. The amino acids are then linked together to extend the growing protein chain, and the tRNAs, no longer carrying amino acids, are released. This whole complex of processes is carried out by the ribosome, formed of two main chains of RNA, called ribosomal RNA (rRNA), and more than 50 different proteins. The ribosome latches onto the end of an mRNA molecule and moves along it, capturing loaded tRNA molecules and joining together their amino acids to form a new protein chain.

Protein biosynthesis, although very similar, is different for prokaryotes and eukaryotes.

https://en.wikipedia.org/wiki/Protein_biosynthesis

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Proteins

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https://en.wikipedia.org/wiki/Protein

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Proteoglycans

Proteoglycans are proteins that are heavily glycosylated. The basic proteoglycan u
consists of a "core protein" with one or more covalently attached glycosaminoglyc
(GAG) chain(s). The point of attachment is a serine (Ser) residue to which the glyc
saminoglycan is joined through a tetrasaccharide bridge (e.g. chondroitin sulfate-
Gal-Gal-Xyl-PROTEIN). The Ser residue is generally in the sequence -Ser-Gly-X-G
(where X can be any amino acid residue but Proline), although not every protein w
this sequence has an attached glycosaminoglycan. The chains are long, linear carb
drate polymers that are negatively charged under physiological conditions due to
occurrence of sulfate and uronic acid groups. Proteoglycans occur in the connectiv
sue.

https://en.wikipedia.org/wiki/Proteoglycan

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Proteolysis

Proteolysis is the breakdown of proteins into smaller polypeptides or amino aci
catalyzed, the hydrolysis of peptide bonds is extremely slow, taking hundreds o
Proteolysis is typically catalyzed by cellular enzymes called proteases, but may a
cur by intra-molecular digestion. Low pH or high temperatures can also cause p
sis non-enzymatically.

Proteolysis in organisms serves many purposes. For example, digestive enzyme
down proteins in food to provide amino acids for the organism, while proteolyt
essing of a polypeptide chain after its synthesis may be necessary for the produc
an active protein. It is also important in the regulation of some physiological an
lar processes, as well as preventing the accumulation of unwanted or abnormal
teins in cells. Consequently, dis-regulation of proteolysis can cause diseases and
used in some venoms to damage prey.

https://en.wikipedia.org/wiki/Proteolysis

Related Glossary Terms

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Proteolytic Degradation

Protein degradation may take place intracellularly or extracellularly. In digestion of food, digestive enzymes may be released into the environment for extracellular digestion whereby proteolytic cleavage breaks down proteins into smaller peptides and amino acids so that they may be absorbed and used by an organism. In animals the food may be processed extracellularly in specialized digestive organs or guts, but in many bacteria the food may be internalized into the cell via phagocytosis. Microbial degradation of protein in the environment can be regulated by nutrient availability. For example, limitation for major elements in proteins (carbon, nitrogen, and sulfur) has been shown to induce proteolytic activity in the fungus *Neurospora crassa* as well as in whole communities of soil organisms.

Proteins in cells are also constantly being broken down into amino acids. This intracellular degradation of protein serves a number of functions: It removes damaged and abnormal protein and prevent their accumulation, and it also serves to regulate cellular processes by removing enzymes and regulatory proteins that are no longer needed. The amino acids may then be reused for protein synthesis.

https://en.wikipedia.org/wiki/Proteolysis#Protein_degradation

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Related Glossary Terms

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Proteome

The proteome is the entire set of proteins expressed by a genome, cell, tissue, o
ism at a certain time. More specifically, it is the set of expressed proteins in a gi
type of cell or organism, at a given time, under defined conditions. The term is
of proteins and genome. Proteomics is the study of the proteome.

The term proteome has been applied to several different types of biological syst
cellular proteome is the collection of proteins found in a particular cell type und
particular set of environmental conditions such as exposure to hormone stimul
can also be useful to consider an organism's complete proteome, which can be c
tualized as the complete set of proteins from all of the various cellular proteom
is very roughly the protein equivalent of the genome. The term "proteome" has
been used to refer to the collection of proteins in certain sub-cellular biological
tems. For example, all of the proteins in a virus can be called a viral proteome.

https://en.wikipedia.org/wiki/Proteome

Related Glossary Terms

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Proteomics

Proteomics is the large-scale study of proteins, particularly their structures and functions. While proteomics generally refers to the large-scale experimental analysis of proteins, it is often specifically used for protein purification and mass spectrometry.

Proteomics gives a different level of understanding than genomics for many reasons:

• the level of transcription of a gene gives only a rough estimate of its level of translation into a protein. An mRNA produced in abundance may be degraded rapidly or translated inefficiently, resulting in a small amount of protein.
• as mentioned above many proteins experience post-translational modifications that profoundly affect their activities. For example some proteins are not active until they become phosphorylated. Methods such as phosphoproteomics and glycoproteomics are used to study post-translational modifications.
• many transcripts give rise to more than one protein, through alternative splicing or alternative post-translational modifications.
• many proteins form complexes with other proteins or RNA molecules, and only function in the presence of these other molecules.
• protein degradation rate plays an important role in protein content.

One major factor affecting reproducibility in proteomics experiments is the simultaneous elution of many more peptides than can be measured by mass spectrometers. This causes stochastic differences between experiments due to data-dependant acquisition of tryptic peptides. Although early large-scale shotgun proteomics analyses showed considerable variability between laboratories, presumably due in part to technical and experimental differences between labs, reproducibility has been improved in more recent mass spectrometry analysis, particularly on the protein level and using Orbitrap mass spectrometers. Notably, targeted proteomics shows increased reproducibility and repeatability compared with shotgun methods, although at the expense of data density and effectiveness.

https://en.wikipedia.org/wiki/Proteomics

Related Glossary Terms

Drag related terms here

Proteopathy

In medicine, proteopathy refers to a class of diseases in which certain prote
structurally abnormal, and thereby disrupt the function of cells, tissues and
the body. Often the proteins fail to fold into their normal configuration. In
folded state, the proteins can become toxic in some way (a gain of toxic fun
they can lose their normal function. The proteopathies (also known as prote
protein conformational disorders, or protein misfolding diseases) include s
eases as Creutzfeldt–Jakob disease, Alzheimer's disease, Parkinson's diseas
ease, amyloidosis, and a wide range of other disorders.

https://en.wikipedia.org/wiki/Proteopathy

Related Glossary Terms

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Chapter 2 - Structure & Function: Proteins I

Prothrombin

Prothrombin is a coagulation factor that is proteolytically cleaved to form thrombin in the coagulation cascade, the clotting process. Thrombin in turn acts as a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions.

In the blood coagulation pathway, thrombin acts to convert factor XI to XIa, VIII to VIIIa, V to Va, fibrinogen to fibrin, and XIII to XIIIa. Factor XIIIa is a transglutaminase that catalyzes the formation of covalent bonds between lysine and glutamine residues in fibrin. The covalent bonds increase the stability of the fibrin clot. Thrombin interacts with thrombomodulin.

As part of its activity in the coagulation cascade, thrombin also promotes platelet activation and aggregation via activation of protease-activated receptors on the cell membrane of the platelet.

Negative feedback

Thrombin bound to thrombomodulin activates protein C, an inhibitor of the coagulation cascade. The activation of protein C is greatly enhanced following the binding of thrombin to thrombomodulin, an integral membrane protein expressed by endothelial cells. Activated protein C inactivates factors Va and VIIIa. Binding of activated protein C to protein S leads to a modest increase in its activity. Thrombin is also inactivated by antithrombin, a serine protease inhibitor.

https://en.wikipedia.org/wiki/Thrombin

Related Glossary Terms

Drag related terms here

Protists

Protists are the members of an informal grouping of diverse eukaryotic organisms that are not animals, plants or fungi. They do not form a natural group, or clade, but are often grouped together for convenience, like algae or invertebrates. In some systems of biological classification, such as the popular 5-kingdom scheme proposed by Robert Whittaker in 1969, the protists make up a kingdom called Protista, composed of "organisms which are unicellular or unicellular-colonial and which form no tissues."

Besides their relatively simple levels of organization, the protists do not have much in common. When used, the term “protists” is now considered to mean similar-appearing but diverse phyla that are not related through an exclusive common ancestor, and that have different life cycles, trophic levels, modes of locomotion, and cellular structures. In the classification system of Lynn Margulis, the term protist is reserved for microscopic organisms, while the more inclusive term Protoctista is applied to a biological kingdom which includes certain large multicellular eukaryotes, such as kelp, red algae and slime molds. Other workers use the term protist more broadly, to encompass both microbial eukaryotes and macroscopic organisms that do not fit into the other traditional kingdoms.

In cladistic systems, there are no equivalents to the taxa Protista or Protoctista, both terms referring to a paraphyletic group which spans the entire eukaryotic tree of life. In cladistic classification, the contents of Protista are distributed among various supergroups (SAR, Archaeplastida, Excavata, Opisthokonta, etc.) and "Protista", "Protoctista" and "Protozoa" are considered obsolete. However, there still remains some ambiguity about the position in the cladistic tree of some taxa - such as most excavata (metamonads, jakobids, Malawimonas and Collodictyon) and the term "protist" continues to be used informally as a catch-all term for Eukaryotic microorganisms - for example "protist pathogen" is used to denote any microbe which is not bacteria, virus, viroid or metazoa.

https://en.wikipedia.org/wiki/Protist

Related Glossary Terms

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Proton

A proton is a subatomic particle, symbol p, p+, or H^+, with a positive electric charge of +1e elementary charge and mass slightly less than that of a neutron. The number of protons in the nucleus is the defining property of an element, and is referred to as the atomic number (represented by the symbol Z). Since each element has a unique number of protons, each element has its own unique atomic number. Acids in solution are donors of protons.

https://en.wikipedia.org/wiki/Proton

Related Glossary Terms

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Proton Gradient

A proton gradient is a gradient of protons that can move across a membrane. The proton gradient can be used as intermediate energy storage for heat production and flagellar rotation. In addition, it is an interconvertible form of energy in active transport, electron potential generation, NADPH synthesis, and ATP synthesis/hydrolysis.

The electrochemical potential difference between the two sides of the membrane in mitochondria, chloroplasts, bacteria, and other membranous compartments that engage in active transport involving proton pumps, is at times called a chemiosmotic potential or proton motive force. In this context, protons are often considered separately using units of either concentration or pH.

https://en.wikipedia.org/wiki/Electrochemical_gradient

Related Glossary Terms

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Chapter 3 - Membranes: Transport

Protozoa

In some systems of biological classification, the protozoa are a diverse grou
lular eukaryotic organisms. Historically, protozoa were defined as single-ce
isms with animal-like behaviors, such as motility and predation. The group
garded as the zoological counterpart to the "protophyta", which were consi
plant-like, as they are capable of photosynthesis. The terms protozoa and p
are also used informally to designate single-celled, non-photosynthetic pro
as ciliates, amoebae and flagellates.

https://en.wikipedia.org/wiki/Protozoa

Related Glossary Terms

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PrP

The protein that prions are made of, PrP, is found throughout the body, eve
healthy people and animals. However, PrP found in infectious material has
structure and is resistant to proteases, the enzymes in the body that can no
break down proteins. The normal form of the protein is called PrPC, while t
tious form is called PrPSc — the C refers to 'cellular' PrP, while the Sc refers
pie', the prototypic prion disease, occurring in sheep. While PrPC is structu
defined, PrPSc is certainly polydisperse and defined at a relatively poor leve
be induced to fold into other more-or-less well-defined isoforms *in vitro*, a
tionship to the form(s) that are pathogenic *in vivo* is not yet clear.

https://en.wikipedia.org/wiki/Prion#Prion_Protein_.28PrP.29

Related Glossary Terms

Drag related terms here

PrP^c

PrP^c is a normal protein found on the membranes of cells. It has 209 amino a humans), one disulfide bond, a molecular mass of 35–36 kDa and a mainly c structure. Several topological forms exist - one cell surface form anchored via colipid and two transmembrane forms. The normal protein is not sedimenta ing that it cannot be separated by centrifuging techniques. Its function is a co sue that continues to be investigated. PrP^c binds copper (II) ions with high a significance of this finding is not clear, but it is presumed to relate to PrP str function. PrP^c is readily digested by proteinase K and can be liberated from t face *in vitro* by the enzyme phosphoinositide phospholipase C (PI-PLC), whi the glycophosphatidylinositol (GPI) glycolipid anchor. PrP has been reported important roles in cell-cell adhesion and intracellular signaling *in vivo*, and fore be involved in cell-cell communication in the brain.

https://en.wikipedia.org/wiki/Prion#PrPC

Related Glossary Terms

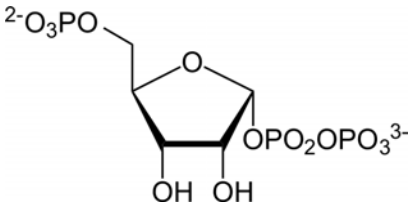
Drag related terms here

PRPP

Phosphoribosyl pyrophosphate (PRPP) is a pentosephosphate.It is formed from ribose 5-phosphate by the enzyme ribose-phosphate diphosphokinase. It plays a role in transferring phospho-ribose groups in several reactions. In *de novo* generation of purines, the enzyme amidophosphoribosyltransferase acts upon PRPP to create phosphoribosylamine.

Increased levels of PRPP is characterized by the overproduction and accumulation of uric acid leading to hyperuricemia and hyperuricosuria. It is one of the causes of gout.

Increased levels of PRPP are present in Lesch-Nyhan Syndrome. Decreased levels of hypoxanthine guanine phosphoribosyl transferase (HGPRT) causes this accumulation, as PRPP is a substrate used by HGPRT during purine salvage. Shown below is the α form of PRPP.



https://en.wikipedia.org/wiki/Phosphoribosyl_pyrophosphate

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PRPP Amidotransferase

Amidophosphoribosyltransferase (ATase), also known as glutamine phosphoribosylpyrophosphate amidotransferase (GPAT) or PRPP amidotransferase, is an enzyme responsible for catalyzing the conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) into 5-phosphoribosyl-1-amine (PRA), using the ammonia group from a glutamine side-chain. This is the committing step in *de novo* purine synthesis. In humans it is encoded by the PPAT (phosphoribosyl pyrophosphate amidotransferase) gene. ATase is a member of the purine/pyrimidine phosphoribosyltransferase family.

In an example of feedback inhibition, ATase is inhibited mainly by the end-products of the purine synthesis pathway, AMP, GMP, ADP, and GDP. Each enzyme subunit from the homotetramer has two binding sites for these inhibitors. The allosteric (A) site overlaps with the site for the ribose-5-phosphate of PRPP, while the catalytic (C) site overlaps with the site for the pyrophosphate of PRPP. The binding of specific nucleotide pairs to the two sites results in synergistic inhibition stronger than additive inhibition. Inhibition occurs via a structural change in the enzyme where the flexible glutamine loop gets locked in an open position, preventing the binding of PRPP.

https://en.wikipedia.org/wiki/Amidophosphoribosyltransferase

Related Glossary Terms

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PRPP Synthetase

PRPP synthetase is an enzyme that converts ribose 5-phosphate into phosphori
pyrophosphate (PRPP). The enzyme is involved in the synthesis of nucleotides
rines and pyrimidines), cofactors NAD^+ and $NADP^+$, and amino acids histidine
tryptophan, linking these biosynthetic processes to the pentose phosphate path
from which the substrate ribose 5-phosphate is derived. Ribose 5-phosphate is
duced by the HMP Shunt Pathway from Glucose-6-Phosphate. The product pho
bosyl pyrophosphate acts as an essential component of the purine salvage pathw
the *de novo* synthesis of purines. Dysfunction of the enzyme would thereby unc
purine metabolism.

Ribose-phosphate pyrophosphokinase exists in bacteria, plants, and animals, a
there are three isoforms of human ribose-phosphate pyrophosphokinase. In hu
the genes encoding the enzyme are located on the X chromosome.

https://en.wikipedia.org/wiki/Ribose-phosphate_diphosphokinase

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Related Glossary Terms

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Chapter 6 - Metabolism: Nucleotides

PrP^{res}

Protease-resistant PrP^{Sc}-like protein (PrP^{res}) is an isoform of PrP^{c} from whi
turally altered and converted into a misfolded proteinase K-resistant form
model conversion of PrP^{c} to PrP^{Sc} *in vitro*, Saborio et al. rapidly converted
PrP^{res} by a procedure involving cyclic amplification of protein misfolding. T
"PrP^{res}" has been made to distinguish between PrP^{Sc}, which is isolated from
tissue and associated with the transmissible spongiform encephalopathy ag
ample, unlike PrP^{sc}, PrP^{res} may not necessarily be infectious.

https://en.wikipedia.org/wiki/Prion#PrPres

Related Glossary Terms

Drag related terms here

PrP^{sc}

The infectious isoform of PrP, known as PrP^{Sc}, is able to convert normal PrP^{c} pr
into the infectious isoform by changing their conformation, or shape. This, in tu
ters the way the proteins interconnect. PrP^{Sc} always causes prion disease. Altho
exact 3D structure of PrP^{Sc} is not known, it has a higher proportion of β-sheet s
in place of the normal α-helix structure.

Aggregations of these abnormal isoforms form highly structured amyloid fibers
accumulate to form plaques. It is unclear as to whether these aggregates are the
of cell damage or are simply a side-effect of the underlying disease process. The
each fiber acts as a template onto which free protein molecules may attach, allo
the fiber to grow. Under most circumstances, only PrP molecules with an identi
amino acid sequence to the infectious PrP^{Sc} are incorporated into the growing f
However, rare cross-species transmission is also possible.

https://en.wikipedia.org/wiki/Prion#PrPSc

Related Glossary Terms

Drag related terms here

PrP^{Sc}

The infectious isoform of PrP, known as PrP^{Sc}, is able to convert normal PrP
into the infectious isoform by changing their conformation, or shape. This, i
ters the way the proteins interconnect. PrP^{Sc} always causes prion disease. Alt
exact 3D structure of PrP^{Sc} is not known, it has a higher proportion of β-shee
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the fiber to grow. Under most circumstances, only PrP molecules with an ide
amino acid sequence to the infectious PrP^{Sc} are incorporated into the growin
However, rare cross-species transmission is also possible.

https://en.wikipedia.org/wiki/Prion#PrPSc

Related Glossary Terms

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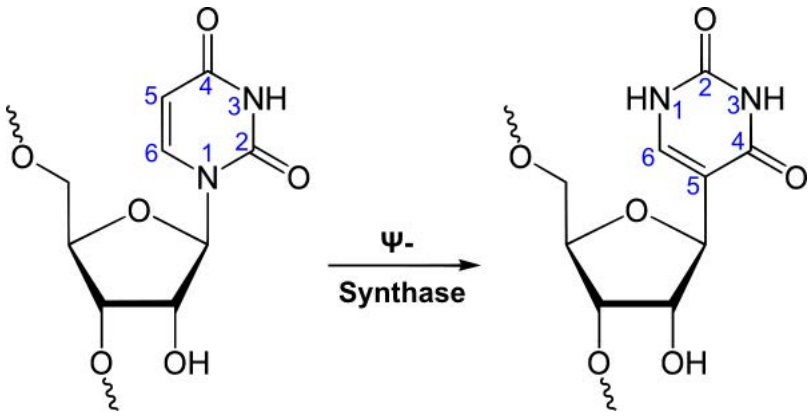
Pseudouridine

Pseudouridine (abbreviated by the Greek letter psi- Ψ) is an isomer of the nucleoside uridine in which the uracil is attached via a carbon-carbon instead of a nitrogen-carbon glycosidic bond. It is the most prevalent of the over one hundred different modified nucleosides found in RNA. Ψ is found in all species and in many classes of RNA. Ψ is formed by enzymes called Ψ synthases, which post-transcriptionally isomerize specific uridine residues in RNA in a process termed pseudouridylation.

It is commonly found in tRNA, associated with thymidine and cytosine in the TΨC arm and is one of the invariant regions of tRNA. The function of it is not very clear, but it is expected to play a role in association with aminoacyl transferases during their interaction with tRNA, and hence in the initiation of translation. Recent studies suggest it may offer protection from radiation.

Shown below is pseudouridine (right) synthesis from uridine (left)



https://en.wikipedia.org/wiki/Pseudouridine

Related Glossary Terms

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Pst I

PstI, is a Type II restriction endonuclease (or restriction enzyme) from *Pro*
artii. PstI recognition and cut site are as follows:

Recognition 5'CTGCAG 3' Cut 5'--CTGCA / G--3'
Recognition 3'GACGTC 5' Cut 3'--G / ACGTC—5'

https://en.wikipedia.org/wiki/PstI

Related Glossary Terms

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Pulling a Reaction

The phrase “pulling” a reaction refers to conditions in an enzymatic reactio
the concentration of product is reduced. It contrasts with “pushing” a react
which the amount of substrate is increased. Both have the effect of increasi
amount of forward reaction.

Related Glossary Terms

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Pupylated

Prokaryotic ubiquitin-like protein (Pup) is a functional analog of ubiquitin fou
prokaryote *Mycobacterium tuberculosis*. It serves the same function as ubiqu
though the enzymology of ubiquitylation and pupylation is different. In contra
three-step reaction of ubiquitylation, pupylation requires two steps, therefore
enzymes are involved in pupylation.

Similar to ubiquitin, Pup attaches to specific lysine residues of substrate prote
forming isopeptide bonds. It is then recognized by *Mycobacterium* proteasom
Pase (Mpa) by a binding-induced folding mechanism that forms a unique α-h
then delivers the Pup-substrate to the 20S proteasome by coupling of ATP hyd
for proteasomal degradation. The discovery of Pup indicates that like eukaryo
teria may use a small-protein modifier to control protein stability.

https://en.wikipedia.org/wiki/Prokaryotic_ubiquitin-like_protein

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Related Glossary Terms

Drag related terms here

Purine Nucleotide Phosphorylase

Purine nucleoside phosphorylase also known as PNP, PNPase or inosine phosphorylase is an enzyme that in humans is encoded by the NP gene.
The catalyzes the reaction

Purine nucleoside + Phosphate $\rightleftharpoons$ Purine base + α-D-ribose-1-phosphate

Purine nucleoside phosphorylase is an enzyme involved in purine metabolism. PNP metabolizes inosine into hypoxanthine and guanosine into guanine, in each case creating ribose phosphate. Note: adenosine is first metabolized to inosine via the enzyme adenosine deaminase.

Nucleoside phosphorylase is an enzyme which cleaves a nucleoside by phosphorylating the ribose to produce a nucleobase and ribose-1 phosphate. It is one enzyme of the nucleotide salvage pathways. These pathways allow the cell to produce nucleotide monophosphates when the *de novo* synthesis pathway has been interrupted or is nonexistent (as is the case in the brain). Often the *de novo* pathway is interrupted as a result of chemotherapy drugs such as methotrexate or aminopterin.

All salvage pathway enzymes require a high energy phosphate donor such as ATP or PRPP.

- Thymidine can be phosphorylated by thymidine kinase (TK).
- Uridine can be phosphorylated by uridine kinase (UK).
- Cytidine can be phosphorylated by cytidine kinase (CK).
- Deoxycytidine can be phosphorylated by deoxycytidine kinase (DCK).

Adenosine uses the enzyme adenosine kinase, which is a very important enzyme in the cell. Attempts are being made to develop an inhibitor for the enzyme for use in cancer chemotherapy.

https://en.wikipedia.org/wiki/Purine_nucleoside_phosphorylase

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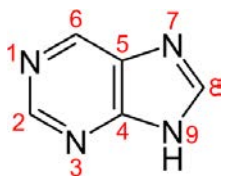
Purines

A purine is a heterocyclic aromatic organic compound. It consists of a pyrimidine ring fused to an imidazole ring. Purines, which include substituted purines and their tautomers, are the most widely occurring nitrogen-containing heterocycle in nature.

Purines and pyrimidines make up the two groups of nitrogenous bases, including the two groups of nucleotide bases. Two of the four deoxyribonucleotides and two of the four ribonucleotides, the respective building-blocks of DNA and RNA, are purines. In order to form DNA and RNA, both purines and pyrimidines are needed by the cell in approximately equal quantities. Both purine and pyrimidine are self-inhibiting and activating. When purines are formed, they inhibit the enzymes required for more purine formation. This self-inhibiting occurs as they also activate the enzymes needed for pyrimidine formation. Pyrimidine simultaneously self-inhibits and activates purine in similar manner. Because of this, there is nearly an equal amount of both substances in the cell at all times.



https://en.wikipedia.org/wiki/Purine

Related Glossary Terms

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Pushing a Reaction

The phrase “pushing” a reaction refers to conditions in an enzymatic reacti
the concentration of reactant is increased. It contrasts with “pulling” a rea
which the amount of product is reduced. Both have the effect of increasing
of forward reaction.

Related Glossary Terms

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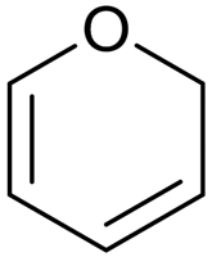
Pyran

In chemistry, pyran, or oxine, is a six-membered heterocyclic, non-aromatic ring, c
sisting of five carbon atoms and one oxygen atom and containing two double bonds
The molecular formula is C_5H_6O. There are two isomers of pyran that differ by the l
tion of the double bonds. In 2H-pyran (shown below), the saturated carbon is at po
tion 2, whereas, in 4H-pyran, the saturated carbon is at position 4.

Pyranoses are sugars in a ring structure with a six-membered ring, of which one of
members is an oxygen. They are named for pyran.



https://en.wikipedia.org/wiki/Pyran

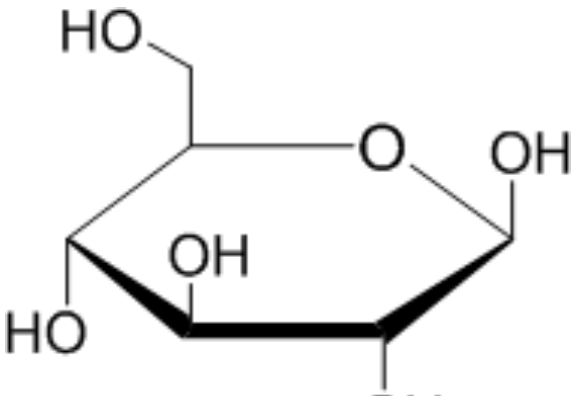
Related Glossary Terms

Drag related terms here

Pyranoses

Pyranose is a collective term for carbohydrates that have a chemical structure that includes a six-membered ring consisting of five carbon atoms and one oxygen atom. There may be other carbons external to the ring. The name derives from its similarity to the oxygen heterocycle pyran, but the pyranose ring does not have double bonds. A pyranose in which the anomeric OH at C(I) has been converted into an OR group is called a pyranoside.

Illustrations of pyranoses are said to be in the Haworth structures. The Haworth structure of glucose is shown below.



https://en.wikipedia.org/wiki/Pyranose

Related Glossary Terms

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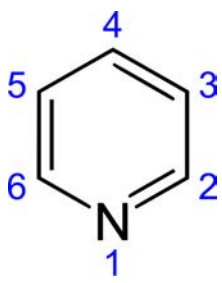
Pyridine

Pyridine is a basic heterocyclic organic compound with the chemical formula C_5H_5N. It is structurally related to benzene, with one methine group (=CH-) replaced by a nitrogen atom. The pyridine ring occurs in many important compounds, including azines and the vitamins niacin and pyridoxal.

Pyridine is used as a precursor to agrochemicals and pharmaceuticals and is also an important solvent and reagent. Pyridine is added to ethanol to make it unsuitable for drinking (see denatured alcohol). It is used in the *in vitro* synthesis of DNA, in the synthesis of sulfapyridine (a drug against bacterial and viral infections), antihistaminic drugs tripelennamine and mepyramine, as well as water repellents, bactericides, and herbicides. Some chemical compounds, although not synthesized from pyridine, contain its ring structure. They include B vitamins niacin and pyridoxal, the anti-tuberculosis drug isoniazid, nicotine and other nitrogen-containing plant products. Historically, pyridine was produced from coal tar and as a by-product of coal gasification. However, increased demand for pyridine resulted in the development of more economical methods of synthesis from acetaldehyde and ammonia, and more than 20,000 tons per year are manufactured worldwide.



https://en.wikipedia.org/wiki/Pyridine

Related Glossary Terms

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Pyrimidine

Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. One of the three diazines (six-membered heterocyclics with two nitrogen atoms in the ring), it has the nitrogen atoms at positions 1 and 3 in the ring. The other diazines are pyrazine (nitrogen atoms at the 1 and 4 positions) and pyridazine (nitrogen atoms at the 1 and 2 positions). In nucleic acids, three types of nucleobases are pyrimidine derivatives: cytosine (C), thymine (T), and uracil (U).

The pyrimidine ring system has wide occurrence in nature as substituted and ring fused compounds and derivatives, including the nucleotides, thiamine (vitamin B_1) and alloxan. It is also found in many synthetic compounds such as barbiturates and the HIV drug, zidovudine.

https://en.wikipedia.org/wiki/Pyrimidine

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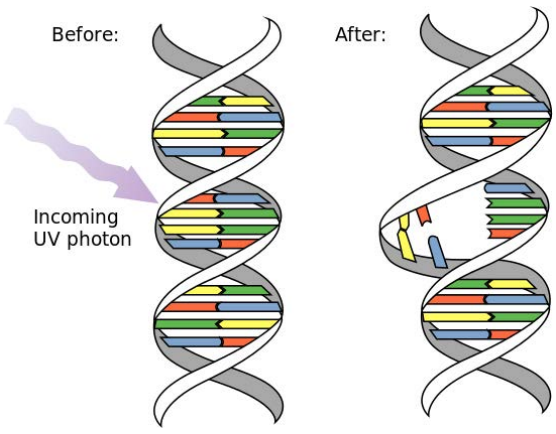
Pyrimidine Dimers

Pyrimidine dimers are molecular lesions formed from thymine or cytosine bases in DNA via photochemical reactions. Ultraviolet light induces the formation of covalent linkages by reactions localized on the C=C double bonds. In dsRNA (double-stranded RNA), uracil dimers may also accumulate as a result of UV radiation. Two common UV products are cyclobutane pyrimidine dimers (CPDs, including thymine dimers) and 6,4 photoproducts. These premutagenic lesions alter the structure of DNA and consequently inhibit polymerases and arrest replication. Dimers may be repaired by photoreactivation or nucleotide excision repair, but unrepaired dimers are mutagenic. Pyrimidine dimers are the primary cause of melanomas in humans.

Pyrimidine dimers introduce local conformational changes in the DNA structure, which allow recognition of the lesion by repair enzymes. In most organisms (excluding placental mammals such as humans) they can be repaired by photoreactivation. Photoreactivation is a repair process in which photolyase enzymes directly reverse CPDs via photochemical reactions. Lesions on the DNA strand are recognized by these enzymes, followed by the absorption of light wavelengths >300 nm (i.e. fluorescent and sunlight). This absorption enables the photochemical reactions to occur, which results in the elimination of the pyrimidine dimer, returning it to its original state.

Nucleotide excision repair is a more general mechanism for repair of lesions. This process excises the CPD and synthesizes new DNA to replace the surrounding region in the molecule. Xeroderma pigmentosum is a genetic disease in humans in which the nucleotide excision repair process is lacking, resulting in skin discoloration and multiple tumors on exposure to UV light. Unrepaired pyrimidine dimers in humans may lead to melanoma.



https://en.wikipedia.org/wiki/Pyrimidine_dimer

Related Glossary Terms

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Chapter 7 - DNA Repair

Pyrimidine-specific 5’ Nucleotidase

Pyrimidine-specific 5’ nucleotidase is an enzyme found in pyrimidine salva
ways. It catalyzes removal of phosphate from CMP and UMP to form cytos
cil, respectively.

Related Glossary Terms

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Find Term

Pyrophosphate

Pyrophosphate is a phosphorus oxyanion. Compounds such as salts and esters are also called pyrophosphates. The group is also called diphosphate or dipolyphosphate, although this should not be confused with two phosphates.

Pyrophosphates are very important in biochemistry. The anion $P_2O_7^{4-}$ is abbreviated PP_i and is formed by the hydrolysis of ATP into AMP in cells.

$ATP \rightarrow AMP + PP_i$

For example, when a nucleotide is incorporated into a growing DNA or RNA strand by a polymerase, pyrophosphate (PP_i) is released. Pyrophosphorolysis is the reverse of the polymerization reaction in which pyrophosphate reacts with the 3'-nucleosidemonophosphate (NMP or dNMP), which is removed from the oligonucleotide to release the corresponding triphosphate (dNTP from DNA, or NTP from RNA).

The pyrophosphate anion has the structure $P_2O_7^{4-}$, and is an acid anhydride of phosphate. It is unstable in aqueous solution and hydrolyzes into inorganic phosphate:

$P_2O_7^{4-} + H_2O \rightarrow 2\ HPO_4^{2-}$

or in biologists' shorthand notation:

$PP_i + H_2O \rightarrow 2\ P_i$

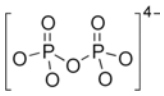
In the absence of enzymic catalysis, hydrolysis reactions of simple polyphosphates such as pyrophosphate, linear triphosphate, ADP, and ATP normally proceed extremely slowly in all but highly acidic media.
(The reverse of this reaction is a method of preparing pyrophosphates by heating phosphates.)

This hydrolysis to inorganic phosphate effectively renders the cleavage of ATP to AMP and PP_i irreversible, and biochemical reactions coupled to this hydrolysis are irreversible as well.

PP_i occurs in synovial fluid, blood plasma, and urine at levels sufficient to block calcification and may be a natural inhibitor of hydroxyapatite formation in extracellular fluid (ECF). Cells may channel intracellular PP_i into ECF. ANK is a nonenzymatic plasma-membrane PP_i channel that supports extracellular PP_i levels. Defective function of the membrane PP_i channel ANK is associated with low extracellular PP_i and elevated intracellular PP_i. Ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) may function to raise extracellular PP_i.

From the standpoint of high energy phosphate accounting, the hydrolysis of ATP to AMP and PP_i requires two high-energy phosphates, as to reconstitute AMP into ATP requires two phosphorylation reactions.

$AMP + ATP \rightarrow 2\ ADP$
$2\ ADP + 2\ P_i \rightarrow 2\ ATP$



https://en.wikipedia.org/wiki/Pyrophosphate

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Pyrroline-5-carboxylate Reductase

Pyrroline-5-carboxylate reductase is an enzyme that catalyzes the chemical

L-proline + $NAD(P)^+$ $\rightleftharpoons$1-pyrroline-5-carboxylate + $NAD(P)H + H^+$

This enzyme belongs to the family of oxidoreductases, specifically those act
CH-NH group of donors with NAD^+ or $NADP^+$ as acceptor. The systematic
this enzyme class is L-proline:$NAD(P)^+$ 5-oxidoreductase. Other names in c
include proline oxidase, L-proline oxidase, 1-pyrroline-5-carboxylate reduc
NADPH-L-Delta1-pyrroline carboxylic acid reductase, and L-proline-NAD(
oxidoreductase.

This enzyme participates in arginine and proline metabolism.

https://en.wikipedia.org/wiki/Pyrroline-5-carboxylate_reductase

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Pyrrolysine

Pyrrolysine (abbreviated as Pyl or O; encoded by the 'amber' stop codon UAG) is ar
amino acid that is used in the biosynthesis of proteins in some methanogenic archa
and bacterium. It is not present in humans. Pyrrolysine contains an α-amino group
(which is in the protonated $-NH_3^+$ form under biological conditions), a carboxylic a
group (which is in the deprotonated $-COO^-$ form under biological conditions). Its p
roline side-chain is similar to that of lysine in being basic and positively charged at
neutral pH.

https://en.wikipedia.org/wiki/Pyrrolysine

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Pyruvate

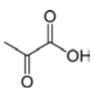
Pyruvic acid ($CH_3COCOOH$) is the simplest of the α-keto acids, with a carboxylic acid and a ketone functional group. Pyruvate, the conjugate base, CH_3COCOO^-, is a key intermediate in several metabolic pathways.

In glycolysis, one molecule of glucose breaks down into two molecules of pyruvate, which are then used to provide further energy, in one of two ways. Pyruvate is converted into acetyl-coenzyme A, which is the main input for a series of reactions known as the citric acid cycle. Pyruvate is also converted to oxaloacetate by an anaplerotic reaction, which replenishes citric acid cycle intermediates. Also, the oxaloacetate is used for gluconeogenesis.

If insufficient oxygen is available, the acid is broken down anaerobically, creating lactate in animals and ethanol in plants and microorganisms. Pyruvate from glycolysis is converted by fermentation to lactate using the enzyme lactate dehydrogenase and the coenzyme NADH in lactate fermentation, or to acetaldehyde and then to ethanol in alcoholic fermentation.

Pyruvate is a key intersection in the network of metabolic pathways. Pyruvate can be converted into carbohydrates via gluconeogenesis, to fatty acids or energy through acetyl-CoA, to the amino acid alanine, and to ethanol. Therefore, it unites several key metabolic processes.

Pyruvic acid supplies energy to cells through the citric acid cycle (also known as the Krebs or TCA cycle) when oxygen is present (aerobic respiration), and alternatively ferments to produce lactate (in mammals) when oxygen is lacking (fermentation).



https://en.wikipedia.org/wiki/Pyruvic_acid

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Pyruvate Carboxylase

Pyruvate carboxylase (PC) is an enzyme of the ligase class that catalyzes the (depending on the species) irreversible carboxylation of pyruvate to form oxaloacetate (OAA). The enzyme is a mitochondrial protein containing a biotin prosthetic group, requiring magnesium or manganese and acetyl CoA. It catalyzes the reaction that follows:

Pyruvate + Bicarbonate + ATP <=> Oxaloacetate + ADP

During gluconeogenesis, pyruvate carboxylase is involved in the synthesis of phosphoenolpyruvate (PEP) from pyruvate. Pyruvate is first converted by pyruvate carboxylase to oxaloacetate (OAA) in the mitochondrion requiring hydrolysis of one molecule of ATP. The OAA is then decarboxylated and simultaneously phosphorylated, which is catalyzed by one of two isoforms of phosphoenolpyruvate carboxykinase (PEPCK) either in the cytosol or in the mitochondria to produce PEP. Under ordinary gluconeogenic conditions, OAA is converted into PEP by mitochondrial PEPCK. The resultant PEP is then transported out of the mitochondrial matrix by an anion transporter carrier system, and converted into glucose by cytosolic gluconeogenic enzymes. However, during starvation when cytosolic NADH concentration is low and mitochrondrial NADH levels are high oxaloacetate can be used as a shuttle of reducing equivalents. As such OAA is converted into malate by mitochondrial Malate dehydrogenase (MDH). After export into the cytosol, malate is converted back into OAA, with concomitant reduction of NAD^+. OAA is subsequently converted to PEP which is available for gluconeogenesis in the cytosol along with the transported reducing equivalent NADH.

Very high levels of PC activity, together with high activities of other gluconeogenic enzymes including PEPCK, fructose-1,6-bisphosphatase and glucose-6-phosphatase in liver and kidney cortex, suggest that a primary role of PC is to participate in gluconeogenesis in these organs. During fasting or starvation when endogenous glucose is required for certain tissues (brain, white blood cells and kidney medulla), expression of PC and other gluconeogenic enzymes is elevated. Fasting promotes hepatic glucose production sustained by an increased pyruvate flux, and increases in PC activity and protein concentration. Diabetes similarly increases gluconeogenesis through enhanced uptake of substrate and increased flux through liver PC in mice and rats. Similarly to other gluconeogenic enzymes, PC is positively regulated by glucagon and glucocorticoids while negatively regulated by insulin. Further supporting the key role of PC in gluconeogenesis, in dairy cattle, which have hexose absorption ability at adequate nutrition levels, PC and the associated gluconeogenic enzyme PEPCK are markedly elevated during the transition to lactation in proposed support of lactose synthesis for milk production.

Aside from the role of PC in gluconeogenesis, PC serves an anaplerotic role (an enzyme catalyzed reaction that can replenish the supply of intermediates in the citric acid cycle) for the tricarboxylic acid cycle (essential to provide oxaloacetate), when intermediates are removed for different biosynthetic purposes.

Pyruvate carboxylase uses a covalently attached biotin cofactor which is used to catalyze the ATP– dependent carboxylation of pyruvate to oxaloacetate in two steps. Biotin is initially carboxylated by ATP and bicarbonate. The carboxyl group is subsequently transferred by carboxybiotin to a second active site where pyruvate is carboxylated to generate oxaloacetate. The BCCP domain transfers the tethered cofactor between the two remote active sites. The allosteric binding site in PC offers a target for modifiers of activity that may be useful in the treatment of obesity or type II diabetes, and the mechanistic insights gained from the complete structural description of RePC (R. etli) permit detailed investigations into the individual catalytic and regulatory sites of the enzyme.

https://en.wikipedia.org/wiki/Pyruvate_carboxylase

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Pyruvate Dehydrogenase

Pyruvate dehydrogenase is the first component enzyme of pyruvate dehydrogenase complex (PDC) that catalyzes the decarboxylation of pyruvate to produce acetyl-CoA and NADH. The pyruvate dehydrogenase complex contributes by a process called pyruvate decarboxylation . Acetyl-CoA may then be used in the citric acid cycle to carry out cellular respiration, so pyruvate dehydrogenase contributes to linking the glycolysis metabolic pathway to the citric acid cycle and releasing energy via NADH.

Pyruvate dehydrogenase (E1) performs the first two reactions within the pyruvate dehydrogenase complex (PDC): a decarboxylation of substrate 1 (pyruvate) and a reductive acetylation of substrate 2 (lipoic acid). Lipoic acid is covalently bound to dihydrolipoamide acetyltransferase (E2), which is the second catalytic component enzyme of PDC. The reaction catalyzed by pyruvate dehydrogenase (E1) is considered to be the rate-limiting step for the pyruvate dehydrogenase complex (PDHc).

Phosphorylation of E1 by pyruvate dehydrogenase kinase (PDK) inactivates E1 and subsequently the entire complex. PDK is inhibited by dichloroacetic acid and pyruvate, resulting in a higher quantity of active, unphosphorylated PDH. Phosphorylaton is reversed by pyruvate dehydrogenase phosphatase, which is stimulated by insulin, PEP, and AMP, but competitively inhibited by ATP, NADH, and Acetyl-CoA.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase

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Pyruvate Dehydrogenase Kinase

Pyruvate dehydrogenase kinase (also pyruvate dehydrogenase complex kinase nase, or PDK; EC 2.7.11.2) is a kinase enzyme which acts to inactivate the enzy vate dehydrogenase by phosphorylating it using ATP.

PDK thus participates in the regulation of the pyruvate dehydrogenase comple which pyruvate dehydrogenase is the first component. Both PDK and the pyru hydrogenase complex are located in the mitochondrial matrix of eukaryotes. T plex acts to convert pyruvate (a product of glycolysis in the cytosol) to acetyl-c which is then oxidized in the mitochondria to produce energy, in the citric aci

Pyruvate dehydrogenase kinase is activated by ATP, NADH and acetyl-CoA. It ited by ADP, NAD+, CoA-SH and pyruvate.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase_kinase

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Pyruvate Dehydrogenase Phosphatase

Pyruvate dehyrogenase phosphatase catalytic subunit 1 (PDPC 1), also known as protein phosphatase 2C, is an enzyme that in humans is encoded by the PDP1gene. PDPC 1 is an enzyme which serves to reverse the effects of pyruvate dehydrogenase kinase upon pyruvate dehydrogenase via catalyzing its dephosphorylation, thus activating it.

Pyruvate dehydrogenase (E1) is one of the three components (E1, E2, and E3) of the large pyruvate dehydrogenase complex. Pyruvate dehydrogenase kinases catalyze phosphorylation of serine residues of E1 to inactivate the E1 component and inhibit the complex. Pyruvate dehydrogenase phosphatases catalyze the dephosphorylation and activation of the E1 component to reverse the effects of pyruvate dehydrogenase kinases. Pyruvate dehydrogenase phosphatase is a heterodimer consisting of catalytic and regulatory subunits. Two catalytic subunits have been reported. One is predominantly expressed in skeletal muscle and another one is much more abundant in the liver. The catalytic subunit, encoded by this gene, is the former, and belongs to the protein phosphatase 2C (PP2C) superfamily. Along with the pyruvate dehydrogenase complex and pyruvate dehydrogenase kinases, this enzyme is located in the mitochondrial matrix.

https://en.wikipedia.org/wiki/Pyruvate_dehydrogenase_phosphatase

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Pyruvate Kinase

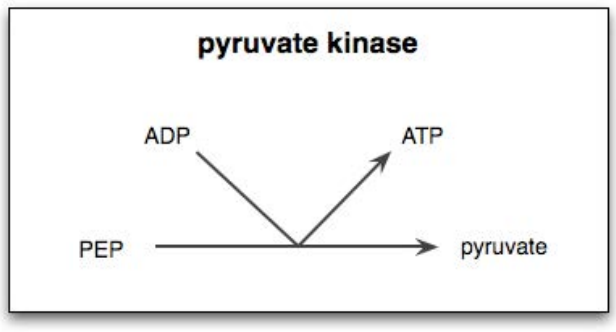
Pyruvate kinase is an enzyme involved in glycolysis. It catalyzes the transfer of a phosphate group from phosphoenolpyruvate (PEP) to ADP, yielding one molecule of pyruvate and one molecule of ATP.

Pyruvate kinase activity is regulated by
• Its own substrate PEP and fructose 1,6-bisphosphate, an intermediate in glycolysis, both of which enhance enzymatic activity. Thus, glycolysis is driven to operate faster when more substrate is present.
• ATP is a negative allosteric inhibitor. This accounts for parallel regulation with PFK 1.
• It is not known whether citrate plays a role in negative allosteric inhibition, however it is believed that acetyl-CoA does.
• Alanine, a negative allosteric modulator

This protein may use the morpheein model of allosteric regulation.
Like PFK, pyruvate kinase is regulated both by allosteric effectors and by covalent modification (phosphorylation). Pyruvate kinase is activated by F-1,6-BP in the liver, a second example of feedforward stimulation. ATP and alanine (a biosynthetic product of pyruvate) act as allosteric inhibitors of pyruvate kinase.

Liver pyruvate kinase is also regulated indirectly by epinephrine and glucagon, through protein kinase A. This protein kinase phosphorylates liver pyruvate kinase to deactivate it. Muscle pyruvate kinase is not inhibited by epinephrine activation of protein kinase A. Glucagon signals fasting (no glucose available). Thus, glycolysis is inhibited in the liver but unaffected in muscle when fasting. An increase in blood sugar leads to secretion of insulin, which activates phosphoprotein phosphatase I, leading to dephosphorylation and activation of pyruvate kinase. These controls prevent pyruvate kinase from being active at the same time as the enzymes that catalyze the reverse reaction (pyruvate carboxylase and phosphoenolpyruvate carboxykinase), preventing a futile cycle.

https://en.wikipedia.org/wiki/Pyruvate_kinase



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Q-cycle

The Q cycle (named for CoQ_{10}) describes a series of reactions that describe how the sequential oxidation and reduction of the lipophilic electron carrier, Coenzyme Q_{10} (CoQ_{10}), between the ubiquinol and ubiquinone forms, can result in the net pumping of protons across a lipid bilayer (in the case of the mitochondria, the inner mitochondrial membrane).

To summarize, the first reaction of Q cycle is:

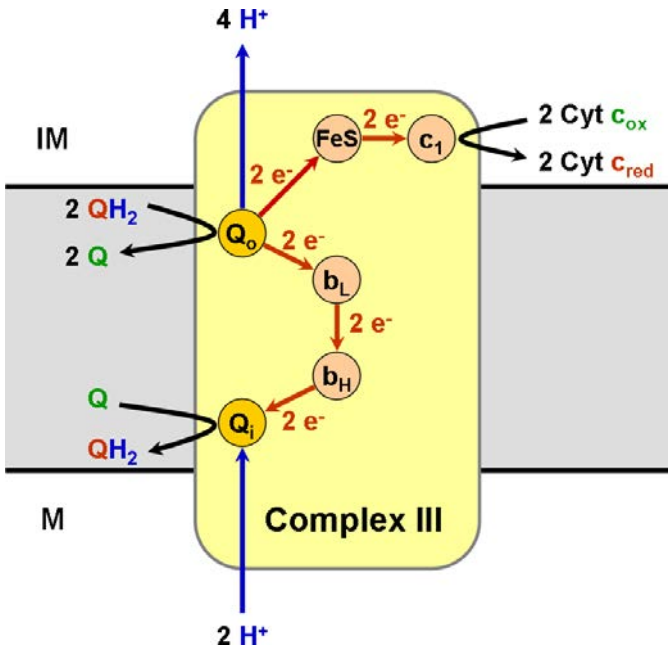
$CoQH_2$ + Cytochrome c_1 (Fe^{3+}) → $CoQ^{-\bullet}$ + Cytochrome c_1 (Fe^{2+}) + 2 H^+ (intermembrane)

Then the second reaction of the cycle involves the reduction of the transient semiquinone by another electron to give CoQH2:

$CoQH_2$ + $CoQ^{-\bullet}$ + cytochrome c_1 (Fe^{3+}) + 2 H^+ (matrix) → CoQ + $CoQH_2$ + cytochrome c_1 (Fe^{2+}) + 2 H^+ (intermembrane)

Combining the two equations, we have the overall reaction of Q cycle:

$CoQH_2$ + 2 cytochrome c_1 (Fe^{3+}) + 2 H^+ (matrix) → CoQ + 2 cytochrome c_1 (Fe^{2+}) + 4 H^+ (intermembrane).



https://en.wikipedia.org/wiki/Q_cycle

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Quaternary Structure

In biochemistry, quaternary structure is the number and arrangement of multiple folded protein subunits in a multi-subunit complex. It includes organizations from simple dimers to large homooligomers and complexes with defined or variable numbers of subunits.

The quaternary structure refers to the number and arrangement of the protein subunits with respect to one another. Examples of proteins with quaternary structure include hemoglobin, DNA polymerase, and ion channels.

Enzymes composed of subunits with diverse functions are sometimes called holoenzymes, in which some parts may be known as regulatory subunits and the functional core is known as the catalytic subunit. Other assemblies referred to instead as multiprotein complexes also possess quaternary structure. Examples include nucleosomes and microtubules. Changes in quaternary structure can occur through conformational changes within individual subunits or through reorientation of the subunits relative to each other. It is through such changes, which underlie cooperativity and allostery in "multimeric" enzymes, that many proteins undergo regulation and perform their physiological function.

The above definition follows a classical approach to biochemistry, established at times when the distinction between a protein and a functional, proteinaceous unit was difficult to elucidate. More recently, people refer to protein-protein interaction when discussing quaternary structure of proteins and consider all assemblies of proteins as protein complexes.

https://en.wikipedia.org/wiki/Protein_quaternary_structure

Related Glossary Terms

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Quorum Sensing

Quorum sensing is a system of stimuli and response correlated to population density. Many species of bacteria use quorum sensing to coordinate gene expression according to the density of their local population. In similar fashion, some social insects use quorum sensing to determine where to nest. In addition to its function in biological systems, quorum sensing has several useful applications for computing and robotics.

Quorum sensing can function as a decision-making process in any decentralized system, as long as individual components have: (a) a means of assessing the number of other components they interact with and (b) a standard response once a threshold number of components is detected.
Bacteria use quorum sensing to coordinate certain behaviors such as biofilm formation, virulence, and antibiotic resistance, based on the local density of the bacterial population.

Bacteria that use quorum sensing constitutively produce and secrete certain signaling molecules (called autoinducers or pheromones). These bacteria also have a receptor that can specifically detect the signaling molecule (inducer). When the inducer binds the receptor, it activates transcription of certain genes, including those for inducer synthesis. There is a low likelihood of a bacterium detecting its own secreted inducer. Thus, in order for gene transcription to be activated, the cell must encounter signaling molecules secreted by other cells in its environment.

https://en.wikipedia.org/wiki/Quorum_sensing

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R-group

An R-group is an atom or group of atoms substituted in place of a hydrogen atom
the parent chain of a hydrocarbon, becoming a moiety of the resultant new molec

https://en.wikipedia.org/wiki/Substituent

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R-state

Most allosteric effects can be explained by the concerted MWC model put forth by Monod, Wyman, and Changeux, or by the sequential model described by Koshland, Nemethy, and Filmer. Both postulate that enzyme subunits exist in one of two conformations, tensed (T) or relaxed (R), and that relaxed subunits bind substrate more readily than those in the tense state. The two models differ most in their assumptions about subunit interaction and the preexistence of both states.

https://en.wikipedia.org/wiki/Allosteric_regulation

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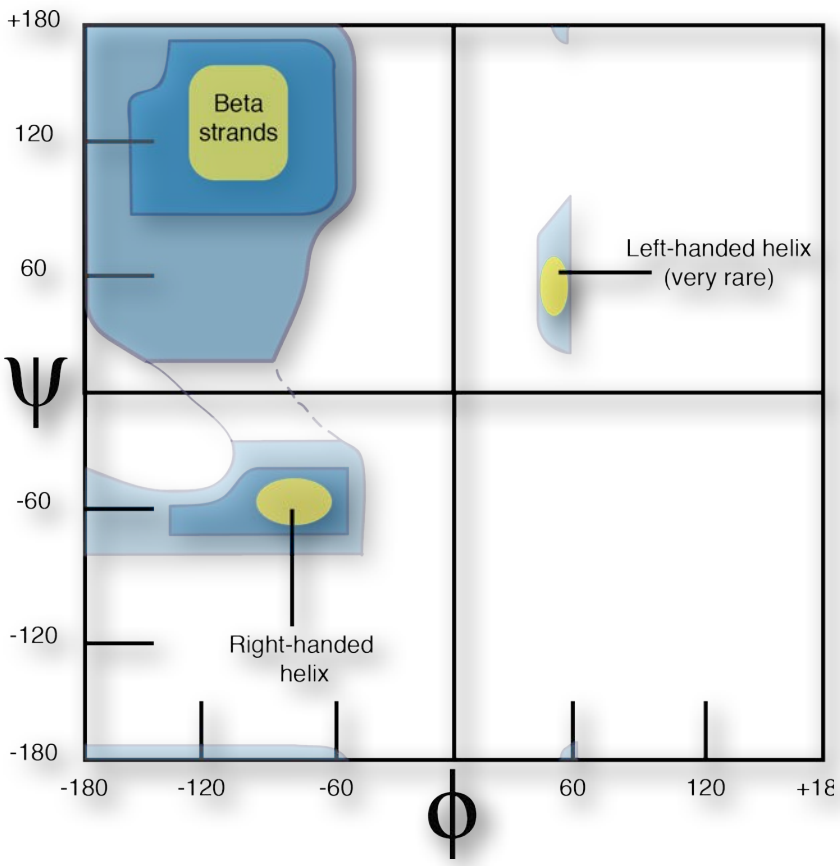
Ramachandran Plot

A Ramachandran plot (also known as a Ramachandran diagram or a [φ,ψ] plot), originally developed in 1963 by G. N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan, is a way to visualize energetically allowed regions for backbone dihedral angles ψ against φ of amino acid residues in protein structure. The ω angle at the peptide bond is 180°, since the partial-double-bond character keeps the peptide planar. The figure at below shows the allowed φ,ψ backbone conformational regions. Because dihedral angle values are circular and 0° is the same as 360°, the edges of the Ramachandran plot "wrap" right-to-left and bottom-to-top. For instance, the small strip of allowed values along the lower-left edge of the plot are a continuation of the large, extended-chain region at upper left.



https://en.wikipedia.org/wiki/Ramachandran_plot

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Chapter 2 - Structure & Function: Proteins I

Chapter 9 - Point by Point: Structure and Function

Random Binding

One of the mechanisms enzymes that bind multiple substrates use is called
displacement. There are two types of sequential displacement. The first is
dom binding. In it, the order of binding of the substrates to the enzyme has
on the ability of the enzyme to function. The other mechanism is called ord
ing and it requires substrates to bind to the enzyme in a specific order in or
enzyme to function.

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Random Coils

A random coil is a polymer conformation where the monomer subunits are orie
ed randomly while still being bonded to adjacent units. It is not one specific sha
a statistical distribution of shapes for all chains in a population of macromolecu

Segments of proteins, and polypeptides that lack secondary structure, are often
sumed to exhibit a random-coil conformation in which the only fixed relationsh
the joining of adjacent amino acid residues by a peptide bond. This is not actual
case, since the ensemble will be energy weighted due to interactions between an
acid side-chains, with lower-energy conformations being present more frequent
addition, even arbitrary sequences of amino acids tend to exhibit some hydroge
ing and secondary structure.

https://en.wikipedia.org/wiki/Random_coil

Related Glossary Terms

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RAS

RAS is a family of related proteins which is ubiquitously expressed in all cell lineages and organs. All RAS protein family members belong to a class of protein called small GTPase, and are involved in transmitting signals within cells (cellular signal transduction). RAS is the prototypical member of the RAS superfamily of proteins, which are all related in 3D structure and regulate diverse cell behaviors.

When RAS is 'switched on' by incoming signals, it subsequently switches on other proteins, which ultimately turn on genes involved in cell growth, differentiation and survival. As a result, mutations in RAS genes can lead to the production of permanently activated RAS proteins. This can cause unintended and overactive signaling inside the cell, even in the absence of incoming signals.

Because these signals result in cell growth and division, overactive RAS signaling can ultimately lead to cancer. The 3 RAS genes in humans (HRas, KRas, and NRas) are the most common oncogenes in human cancer. Mutations that permanently activate RAS are found in 20% to 25% of all human tumors and up to 90% in certain types of cancer (e.g., pancreatic cancer). For this reason, RAS inhibitors are being studied as a treatment for cancer, and other diseases with RAS overexpression.

https://en.wikipedia.org/wiki/Ras_subfamily

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Reactants

A reactant is a chemical substance that participates in a chemical reaction. T
tants react with each other and form the reaction products. For example, hy
oxygen are reactants and react with each other and form the final product o

Reactants are part of the stoichiometric equation in contrast to, for example
A catalyst participates in the reaction but does not occur in the stoichiometr
tion.

https://en.wikipedia.org/wiki/Reagent

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Reaction Center

A photosynthetic reaction center is a complex of several proteins, pigments and c
co-factors that together execute the primary energy conversion reactions of phot
thesis. Molecular excitations, either originating directly from sunlight or transfe
as excitation energy via light-harvesting antenna systems, give rise to electron tr
fer reactions along the path of a series of protein-bound co-factors. These co-fact
are light-absorbing molecules (also named chromophores or pigments) such as c
phyll and phaeophytin, as well as quinones.

The energy of the photon is used to excite an electron of a pigment. The free ener
ated is then used to reduce a chain of nearby electron acceptors, which have subs
quently higher redox-potentials. These electron transfer steps are the initial phas
series of energy conversion reactions, ultimately resulting in the conversion of th
ergy of photons to the storage of that energy by the production of chemical bond

https://en.wikipedia.org/wiki/Photosynthetic_reaction_centre

Related Glossary Terms

Drag related terms here

Reaction Centers

A photosynthetic reaction center is a complex of several proteins, pigments and co-factors that together execute the primary energy conversion reactions of photosynthesis. Molecular excitations, either originating directly from sunlight or transfered as excitation energy via light-harvesting antenna systems, give rise to electron transfer reactions along the path of a series of protein-bound co-factors. These co-factors are light-absorbing molecules (also named chromophores or pigments) such as chlorophyll and phaeophytin, as well as quinones.

The energy of the photon is used to excite an electron of a pigment. The free energy created is then used to reduce a chain of nearby electron acceptors, which have subsequently higher redox-potentials. These electron transfer steps are the initial photochemical series of energy conversion reactions, ultimately resulting in the conversion of the energy of photons to the storage of that energy by the production of chemical bonds.

https://en.wikipedia.org/wiki/Photosynthetic_reaction_centre

Related Glossary Terms

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Reactive Oxygen Species

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. Examples include peroxides, superoxide, hydroxyl radical, and singlet oxygen. In a biological context, ROS are formed as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis. However, during times of environmental stress (e.g., UV or heat exposure), ROS levels can increase dramatically. This may result in significant damage to cell structures. Cumulatively, this is known as oxidative stress. ROS are also generated by exogenous sources such as ionizing radiation.

Effects of ROS on cell metabolism are well documented in a variety of species. These include not only roles in apoptosis (programmed cell death) but also positive effects such as the induction of host defense genes and mobilization of ion transport systems. This implicates them in control of cellular function. In particular, platelets involved in wound repair and blood homeostasis release ROS to recruit additional platelets to sites of injury. These also provide a link to the adaptive immune system via the recruitment of leukocytes.

Reactive oxygen species are implicated in cellular activity to a variety of inflammatory responses including cardiovascular disease. They may also be involved in hearing impairment via cochlear damage induced by elevated sound levels, in ototoxicity of drugs such as cisplatin, and in congenital deafness in both animals and humans. ROS are also implicated in mediation of apoptosis or programmed cell death and ischaemic injury. Specific examples include stroke and heart attack.

In general, harmful effects of reactive oxygen species on the cell are most often:

1. damage of DNA
2. oxidations of polyunsaturated fatty acids in lipids (lipid peroxidation)
3. oxidations of amino acids in proteins
4. oxidative deactivation of specific enzymes by oxidation of co-factors

https://en.wikipedia.org/wiki/Reactive_oxygen_species

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RecA

RecA is a 38 kilodalton protein essential for the repair and maintenance of DNA. A RecA structural and functional homolog has been found in every species in which one has been seriously sought and serves as an archetype for this class of homologous DNA repair proteins. The homologous protein is called RAD51 in eukaryotes and RadA in archaea.

RecA has multiple activities, all related to DNA repair. In the bacterial SOS response, it has a co-protease function in the autocatalytic cleavage of the LexA repressor and the λ repressor.

RecA's association with DNA major is based on its central role in homologous recombination. The RecA protein binds strongly and in long clusters to ssDNA to form a nucleoprotein filament. The protein has more than one DNA binding site, and thus can hold a single strand and double strand together. This feature makes it possible to catalyze a DNA synapsis reaction between a DNA double helix and a complementary region of single stranded DNA. The RecA-ssDNA filament searches for sequence similarity along the dsDNA. The search process induces stretching of the DNA duplex, which enhances sequence complimentarity recognition (a mechanism termed conformational proofreading). The reaction initiates the exchange of strands between two recombining DNA double helices. After the synapsis event, in the heteroduplex region a process called branch migration begins. In branch migration an unpaired region of one of the single strands displaces a paired region of the other single strand, moving the branch point without changing the total number of base pairs. Spontaneous branch migration can occur, however as it generally proceeds equally in both directions it is unlikely to complete recombination efficiently. The RecA protein catalyzes unidirectional branch migration and by doing so makes it possible to complete recombination, producing a region of heteroduplex DNA that is thousands of base pairs long.

Since it is a DNA-dependent ATPase, RecA contains an additional site for binding and hydrolyzing ATP. RecA associates more tightly with DNA when it has ATP bound than when it has ADP bound.

https://en.wikipedia.org/wiki/RecA

Related Glossary Terms

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Receptor Mediated Endocytosis

Receptor-mediated endocytosis (RME), also called clathrin-mediated endocytosis, is a process by which cells absorb metabolites, hormones, other proteins - and in some cases viruses - (endocytosis) by the inward budding of plasma membrane vesicles containing proteins with receptor sites specific to the molecules being absorbed.

Clathrin-mediated endocytosis of many receptor types begins with ligand binding and receptor activation. The ligand and receptor (often bound to an adaptor protein) then diffuse through the plasma membrane until captured by a preformed or forming clathrin-coated pit. A mature pit will pinch off from the plasma membrane forming a clathrin-coated vesicle that then uncoats and typically fuses to an early endosome. Once fused the endocytosed cargo (receptor and/or ligand) can then be sorted to lysosomal, recycling, or other trafficking pathways.

The functions of receptor-mediated endocytosis are diverse. The process is widely used for the specific uptake of certain substances required by the cell (examples include LDL via the LDL receptor or iron via transferrin). The role of receptor-mediated endocytosis is also well recognized in the downregulation of transmembrane signal transduction. The activated receptor becomes internalized and is transported to late endosomes and lysosomes for degradation. However, receptor-mediated endocytosis is also actively implicated in transducing signals from the cell periphery to the nucleus. This became apparent when it was found that the association and formation of specific signaling complexes is required for the effective signaling of hormones (e.g. EGF). Additionally it has been proposed that the directed transport of active signaling complexes to the nucleus might be required to enable signaling as random diffusion is too slow and mechanisms permanently down-regulating incoming signals are strong enough to shut down signaling completely without additional signal-transducing mechanisms.

https://en.wikipedia.org/wiki/Receptor-mediated_endocytosis

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Receptor Protein

In biochemistry and pharmacology, a receptor is a protein-molecule that receives chemical-signals from outside a cell. When such chemical-signals bind to a receptor, they cause some form of cellular/tissue-response, e.g. a change in the electrical-activity of a cell. In this sense, a receptor is a protein-molecule that recognizes and responds to endogenous-chemical signals, e.g. an acetylcholine-receptor recognizes and responds to its endogenous-ligand, acetylcholine. However, sometimes in pharmacology, the term is also used to include other proteins that are drug-targets, such as enzymes, transporters and ion-channels.

Receptor-proteins are embedded in all cells' plasmatic-membranes, facing extracellular-(cell surface receptors), cytoplasmic (cytoplasmic-receptors), or in the nucleus (nuclear receptors). A molecule that binds to a receptor is called a ligand, and can be a peptide (short-protein) or another small molecule such as a neurotransmitter, hormone, pharmaceutical-drug, toxin, or parts of the outside of a virus or microbe. The endogenously designated-molecule for a particular receptor is referred to as its endogenous-ligand. For example, the endogenous-ligand for the nicotinic-acetylcholine receptor is acetylcholine but the receptor can also be activated by nicotine and blocked by curare.

Each receptor is linked to a specific cellular-biochemical pathway. While numerous receptors are found in most cells, each receptor will only bind with ligands of a particular structure, much like how locks will only accept specifically shaped-keys. When a ligand binds to its corresponding receptor, it activates or inhibits the receptor's associated-biochemical pathway.

https://en.wikipedia.org/wiki/Receptor_(biochemistry)

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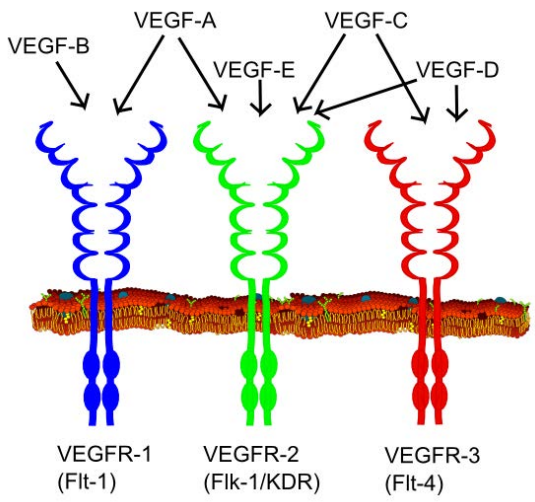
Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs or Tyrosine Kinase Receptors) are the high-affinity cell surface receptors for many polypeptide growth factors, cytokines, and hormones. Of the 90 unique tyrosine kinase genes identified in the human genome, 58 encode receptor tyrosine kinase proteins. Receptor tyrosine kinases have been shown not only to be key regulators of normal cellular processes but also to have a critical role in the development and progression of many types of cancer. Receptor tyrosine kinases are part of the larger family of protein tyrosine kinases, encompassing the receptor tyrosine kinase proteins which contain a transmembrane domain, as well as the non receptor tyrosine kinases which do not possess transmembrane domains.



https://en.wikipedia.org/wiki/Receptor_tyrosine_kinase

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https://en.wikipedia.org/wiki/Receptor-mediated_endocytosis

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Chapter 2 - Structure & Function: Lipids

Recessive Trait

Dominance in genetics is a relationship between alleles of one gene, in which the effect on phenotype of one allele masks the contribution of a second allele at the same locus. The first allele is dominant and the second allele is recessive. For genes on an autosome (any chromosome other than a sex chromosome), the alleles and their associated traits are autosomal dominant or autosomal recessive. Dominance is a key concept in Mendelian inheritance and classical genetics. Often the dominant allele codes for a functional protein whereas the recessive allele does not.

A classic example of dominance is the inheritance of seed shape in peas. Peas may be round, associated with allele R or wrinkled, associated with allele r. In this case, three combinations of alleles (genotypes) are possible: RR, Rr, and rr. The RR individuals have round peas and the rr individuals have wrinkled peas. In Rr individuals the R allele masks the presence of the r allele, so these individuals also have round peas. Thus, allele R is dominant to allele r, and allele r is recessive to allele R. This use of upper case letters for dominant alleles and lower case ones for recessive alleles is a widely followed convention.

More generally, where a gene exists in two allelic versions (designated A and a), three combinations of alleles are possible: AA, Aa, and aa. If AA and aa individuals (homozygotes) show different forms of some trait (phenotypes), and Aa individuals (heterozygotes) show the same phenotype as AA individuals, then allele A is said to dominate or be dominant to or show dominance to allele a, and a is said to be recessive to A.

Dominance is not inherent to an allele. It is a relationship between alleles; one allele can be dominant over a second allele, recessive to a third allele, and codominant to a fourth. Also, an allele may be dominant for a particular aspect of phenotype but not for other aspects influenced by the same gene. Dominance differs from epistasis, a relationship in which an allele of one gene affects the expression of another allele at a different gene.

https://en.wikipedia.org/wiki/Dominance_(genetics)

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Chapter 2 - Structure and Function: Proteins

Reciprocal Regulation

Reciprocal regulation is a coordinated means of simultaneously controlling metabolic pathways that do opposite things. In reciprocal regulation, a single molecule (allosteric regulation) or a single covalent modification (phosphorylation/ dephosphorylation, for example) has opposite effects on the different pathways.

For example, in glycolysis, the enzyme known as phosphofructokinase (PFK-1) is allosterically activated by AMP and a molecule known as F2,6BP. The corresponding enzyme from gluconeogenesis catalyzing a reversal of the glycolysis reaction is known as F1,6BPase. F1,6BPase is inhibited by both AMP and F2,6BP.

In glycogen metabolism, the enzymes phosphorylase kinase and glycogen phosphorylase catalyze reactions important for the breakdown of glycogen. The enzyme glycogen synthase catalyzes the synthesis of glycogen. Each of these enzymes is at least partly regulated by attachment and removal of phosphate.

Phosphorylation of phosphorylase kinase and glycogen phosphorylase has the effect of making them more active, whereas phosphorylation of glycogen synthase makes it less active. Conversely, dephosphorylation has the reverse effects on these enzymes - phosphorylase kinase and glycogen phosphorylase become less active and glycogen synthase becomes more active.

The advantage of reciprocal regulation schemes is that they are very efficient. It doesn't require separate molecules or separate treatments to control two pathways simultaneously. Further, its simplicity ensures that when one pathway is turned on, the other is turned off.

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Recombinant DNA

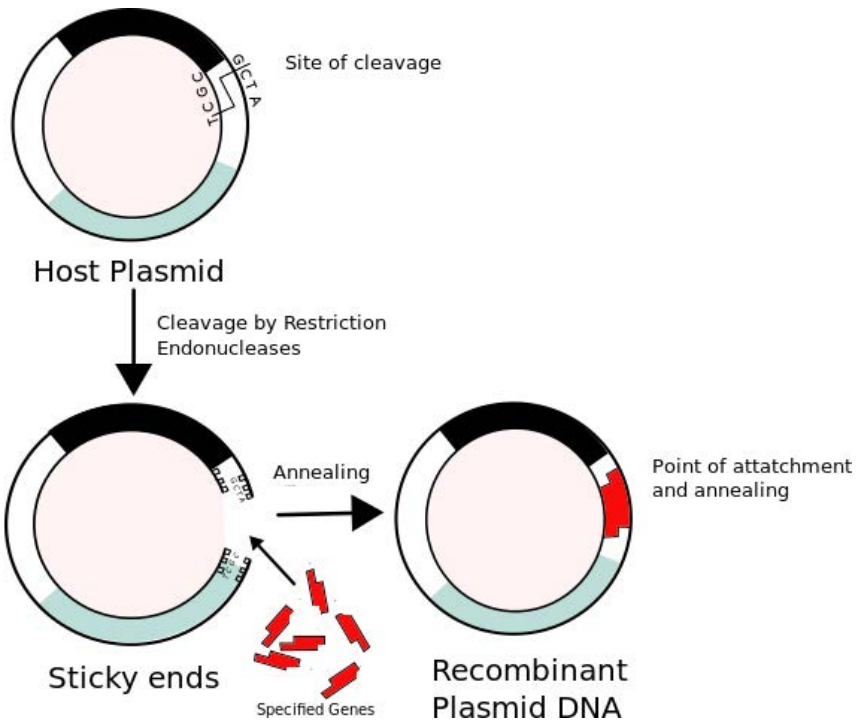
Recombinant DNA (rDNA) molecules are DNA molecules formed by laboratory methods of genetic recombination (such as molecular cloning) to bring together genetic material from multiple sources, creating sequences that would not otherwise be found in the genome. Recombinant DNA is possible because DNA molecules from all organisms share the same chemical structure. They differ only in the nucleotide sequence within that identical overall structure.

Recombinant DNA is the general name for a piece of DNA that has been created by the combination of at least two strands. Recombinant DNA molecules are sometimes called chimeric DNA, because they can be made of material from two different species, like the mythical chimera. R-DNA technology uses palindromic sequences and leads to the production of sticky and blunt ends.

The DNA sequences used in the construction of recombinant DNA molecules can originate from any species. For example, plant DNA may be joined to bacterial DNA, or human DNA may be joined with fungal DNA. In addition, DNA sequences that do not occur anywhere in nature may be created by the chemical synthesis of DNA, and incorporated into recombinant molecules. Using recombinant DNA technology and synthetic DNA, literally any DNA sequence may be created and introduced into any of a very wide range of living organisms.

Proteins that can result from the expression of recombinant DNA within living cells are termed recombinant proteins. When recombinant DNA encoding a protein is introduced into a host organism, the recombinant protein is not necessarily produced. Expression of foreign proteins requires the use of specialized expression vectors and often necessitates significant restructuring by foreign coding sequences.

Recombinant DNA differs from genetic recombination in that the former results from artificial methods in the test tube, while the latter is a normal biological process that results in the remixing of existing DNA sequences in essentially all organisms.



https://en.wikipedia.org/wiki/Recombinant_DNA

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Chapter 9 - Point by Point: Techniques

Recombinant Protein

A protein that can result from the expression of recombinant DNA within living

Following transplantation into the host organism, a foreign DNA contained wit
combinant DNA construct may or may not be expressed. That is, the DNA may
be replicated without expression, or it may be transcribed and translated at a re
nant protein is produced. Generally speaking, expression of a foreign gene requ
structuring the gene to include sequences that are required for producing an m
molecule that can be used by the host's translational apparatus (e.g. promoter,
tional initiation signal, and transcriptional terminator). Specific changes to the
organism may be made to improve expression of the ectopic gene. In addition,
may be needed to the coding sequences as well, to optimize translation, make th
tein soluble, direct the recombinant protein to the proper cellular or extracellul
tion, and stabilize the protein from degradation.

https://en.wikipedia.org/wiki/Recombinant_DNA

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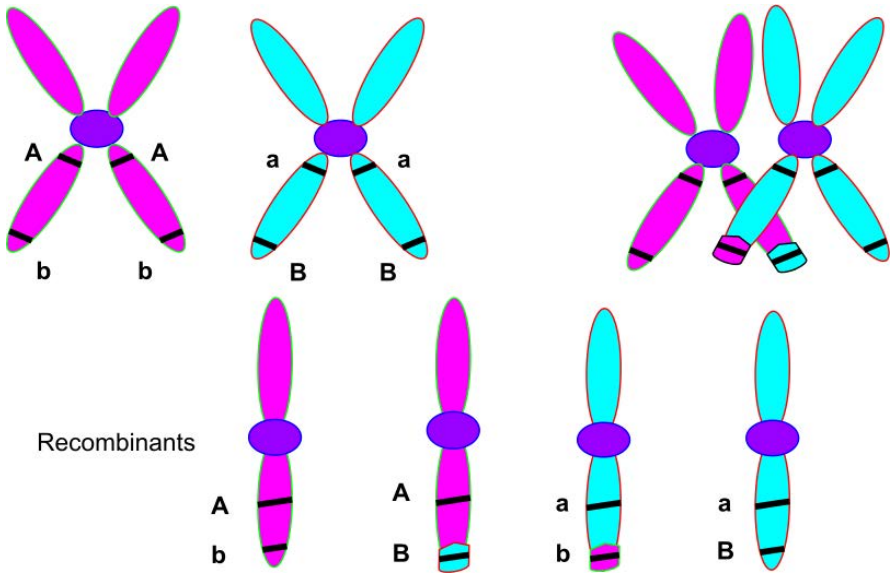
Chapter 8 - Basic Techniques

Recombination

Genetic recombination is the production of offspring with combinations of traits that differ from those found in either parent. In eukaryotes, genetic recombination during meiosis can lead to a novel set of genetic information that can be passed on from the parents to the offspring. Most recombination is naturally occurring. During meiosis in eukaryotes, genetic recombination involves the pairing of homologous chromosomes. This may be followed by information exchange between the chromosomes.

Recombination may also occur during mitosis in eukaryotes where it ordinarily involves the two sister chromosomes formed after chromosomal replication. In this case, new combinations of alleles are not produced since the sister chromosomes are usually identical. In meiosis and mitosis, recombination occurs between similar molecules of DNA (homologs). In meiosis, non-sister homologous chromosomes pair with each other so that recombination characteristically occurs between non-sister homologues. In both meiotic and mitotic cells, recombination between homologous chromosomes is a common mechanism used in DNA repair.

Genetic recombination and recombinational DNA repair also occurs in bacteria and archaea, which use asexual reproduction.



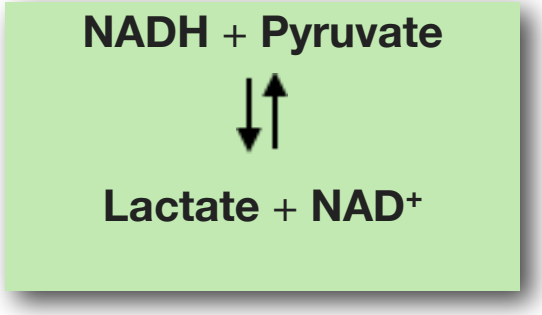
https://en.wikipedia.org/wiki/Genetic_recombination

Reduced

A term that refers to a chemical species that has gained electrons in a redox reaction.

Reduction is the part of a chemical reaction that involves the gaining of electrons. It refers to the side that accepts electrons. When iron reacts with oxygen it forms a chemical called rust. In that example, the iron is oxidized and the oxygen is reduced.

Biochemistry oxidation - reduction (redox) reactions usually involve electron carriers. For example, in the reaction catalyzed by lactate dehydrogenase,



pyruvate gets reduced by electrons and protons from NADH and NADH gets oxidized as it give up its electrons and proton. Reduction is the opposite of oxidation. A reduction reaction always comes together with an oxidation reaction.
https://simple.wikipedia.org/wiki/Reduction_(chemistry)

Related Glossary Terms

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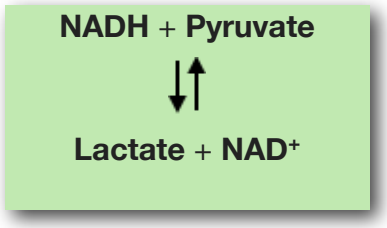

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https://simple.wikipedia.org/wiki/Reduction_(chemistry)

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Reduction Potential

A measure of the tendency of a chemical species to acquire electrons and thereby be reduced. Reduction potential is measured in volts (V), or millivolts (mV). Each species has its own intrinsic reduction potential. The more positive the potential, the greater the species' affinity for electrons and tendency to be reduced.

In aqueous solutions, reduction potential is a measure of the tendency of the solution to either gain or lose electrons when it is subject to change by introduction of a new species. A solution with a higher (more positive) reduction potential than the new species will have a tendency to gain electrons from the new species (i.e. to be reduced by oxidizing the new species) and a solution with a lower (more negative) reduction potential will have a tendency to lose electrons to the new species (i.e. to be oxidized by reducing the new species). Because the absolute potentials are difficult to accurately measure, reduction potentials are defined relative to a reference electrode. Reduction potentials of aqueous solutions are determined by measuring the potential difference between an inert sensing electrode in contact with the solution and a stable reference electrode connected to the solution by a salt bridge.

The sensing electrode acts as a platform for electron transfer to or from the reference half cell. It is typically platinum, although gold and graphite can be used either. The reference half cell consists of a redox standard of known potential. The standard hydrogen electrode (SHE) is the reference from which all standard redox potentials are determined and has been assigned an arbitrary half cell potential of 0.0 mV. However, it is fragile and impractical for routine laboratory use. Therefore, other more stable reference electrodes such as silver chloride and saturated calomel (SCE) are commonly used because of their more reliable performance.

Although measurement of the reduction potential in aqueous solutions is relatively straightforward, many factors limit its interpretation, such as effects of solution temperature and pH, irreversible reactions, slow electrode kinetics, non-equilibrium, presence of multiple redox couples, electrode poisoning, small exchange currents and inert redox couples. Consequently, practical measurements seldom correlate with calculated values. Nevertheless, reduction potential measurement has proven useful as an analytical tool in monitoring changes in a system rather than determining their absolute value (e.g. process control and titrations).

https://en.wikipedia.org/wiki/Reduction_potential

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Regulatory Sequences

A regulatory sequence is a segment of a nucleic acid molecule which is capable of increasing or decreasing the expression of specific genes within an organism. Regulation of gene expression is an essential feature of all living organisms and viruses.

In DNA, regulation of gene expression normally happens at the level of RNA biosynthesis (transcription), and is accomplished through the sequence-specific binding of proteins (transcription factors) that activate or inhibit transcription. Transcription factors may act as activators, repressors, or both. Repressors often act by preventing RNA polymerase from forming a productive complex with the transcriptional initiation region (promoter), while activators facilitate formation of a productive complex. Furthermore, DNA motifs have been shown to be predictive of epigenomic modifications, suggesting that transcription factors play a role in regulating the epigenome.

In RNA, regulation may occur at the level of protein biosynthesis (translation), RNA cleavage, RNA splicing, or transcriptional termination. Regulatory sequences are frequently associated with messenger RNA (mRNA) molecules, where they are used to control mRNA biogenesis or translation. A variety of biological molecules may bind to the RNA to accomplish this regulation, including proteins (e.g. translational repressors and splicing factors), other RNA molecules (e.g. miRNA) and small molecules, in the case of riboswitches.

https://en.wikipedia.org/wiki/Regulatory_sequence

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Regulatory Subunits

A single protein molecule that assembles (or "coassembles") with other pro
cules to facilitate or inhibit their activity. The enzyme ATCase, for example
six catalytic subunits and six regulatory subunits. The regulatory subunits
ATP or CTP. If they bind ATP, the regulatory subunits convert the enzyme
state, activating it. If they bind CTP, the regulatory subunits convert the en
the T-state, inactivating it.

https://en.wikipedia.org/wiki/Protein_subunit

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Release Factor

A release factor is a protein that allows for the termination of translation by recognizing the termination codon or stop codon in an mRNA sequence.
During translation of mRNA, most codons are recognized by "charged" tRNA molecules, called aminoacyl-tRNAs because they are adhered to specific amino acids corresponding to each tRNA's anticodon.

In the standard genetic code, there are three mRNA stop codons: UAG ("amber"), UAA ("ochre"), and UGA ("opal" or "umber").

Although these stop codons are triplets just like ordinary codons, they are not decoded by tRNAs. It was discovered by Mario Capecchi in 1967 that, instead, tRNAs do not ordinarily recognize stop codons at all, and that what he named "release factor" was not a tRNA molecule but a protein. Later, it was demonstrated that different release factors recognize different stop codons.
Prokaryotic translation termination is mediated by three prokaryotic release factors: RF1, RF2, and RF3.

• RF1 recognizes the termination codons UAA and UAG
RF2 recognizes UAA and UGA
RF3 is a GTP-binding protein that leads to the dissociation of RF1/RF2 after peptide release

Likewise, eukaryotic translation termination involves two eukaryotic release factors: eRF1 and eRF3.

• eRF1 recognizes all three termination codons
• eRF3 is a ribosome-dependent GTPase that helps eRF1 release the completed polypeptide

https://en.wikipedia.org/wiki/Release_factor

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https://en.wikipedia.org/wiki/Release_factor

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Chapter 7 - Information Processing: Translation

Renaturation

Denaturation is a process in which proteins or nucleic acids lose the quater
ture, tertiary structure and secondary structure which is present in their na
by application of some external stress or compound such as a strong acid o
centrated inorganic salt, an organic solvent (e.g., alcohol or chloroform), ra
heat. Renaturation is the reversal of the process of denaturation.

https://en.wikipedia.org/wiki/Denaturation_(biochemistry)

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Repetitive Sequences

Repeated sequences (aka. repetitive elements, or repeats) are patterns of nucleic acids (DNA or RNA) that occur in multiple copies throughout the genome. Repetitive DNA was first detected because of its rapid reassociation kinetics.

In many organisms, a significant fraction of the genomic DNA is highly repetitive, with over two-thirds of the sequence consisting of repetitive elements in human.

Debates regarding the potential in vivo functions of these elements have been long standing. Controversial references to ‘junk’ or ‘selfish’ DNA were put forward early on, implying that repetitive DNA segments are remainders from past evolution or autonomous self-replicating sequences hacking the cell machinery to proliferate. Repetitive elements found in eukaryotic genomes fall into different classes, depending on their mode of multiplication and/or structure. The disposition of repetitive elements consists either in arrays of tandemly repeated sequences, or in repeats dispersed throughout the genome. Originally discovered by Barbara McClintock, dispersed repeats have been increasingly recognized as a potential source of genetic variation and regulation. Together with these regulatory roles, a structural role of repeated DNA in shaping the 3D folding of genomes has also been proposed. This hypothesis is only supported by a limited set of experimental evidence. For instance in human, mouse and fly, several classes of repetitive elements present a high tendency for co-localization within the nuclear space, suggesting that DNA repeats positions can be used by the cell as a genome folding map.

https://en.wikipedia.org/wiki/Repeated_sequence_(DNA)

Replication Fork

The replication fork is a structure that forms within the nucleus during DNA replication. It is created by helicases, which break the hydrogen bonds holding the two DNA strands together. The resulting structure has two branching "prongs", each one made up of a single strand of DNA. These two strands serve as the template for the leading and lagging strands, which will be created as DNA polymerase matches complementary nucleotides to the templates. The templates may be properly referred to as the leading strand template and the lagging strand template.

DNA is always synthesized in the 5' to 3' direction. Since the leading and lagging strand templates are oriented in opposite directions at the replication fork, a major issue is how to achieve synthesis of nascent (new) lagging strand DNA, whose direction of synthesis is opposite to the direction of the growing replication fork.

Leading Strand

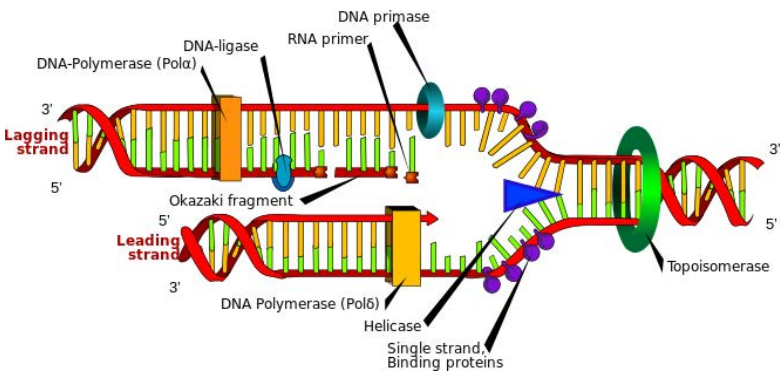
The leading strand is the strand of nascent DNA which is being synthesized in the same direction as the growing replication fork. A polymerase "reads" the leading strand template and adds complementary nucleotides to the nascent leading strand on a continuous basis. The polymerase involved in leading strand synthesis is DNA polymerase III (DNA Pol III) in prokaryotes. In eukaryotes, leading strand synthesis is thought to be conducted by Pol ε, however this view has been recently challenged, suggesting a role for Pol δ.

Lagging Strand

The lagging strand is the strand of nascent DNA whose direction of synthesis is opposite to the direction of the growing replication fork. Because of its orientation, replication of the lagging strand is more complicated as compared to that of the leading strand.The lagging strand is synthesized in short, separated segments. On the lagging strand template, a primase "reads" the template DNA and initiates synthesis of a short complementary RNA primer. A DNA polymerase extends the primed segments, forming Okazaki fragments. The RNA primers are then removed and replaced with DNA, and the fragments of DNA are joined together by DNA ligase.

Dynamics at the Replication Fork

As helicase unwinds DNA at the replication fork, the DNA ahead is forced to rotate. This process results in a build-up of twists in the DNA ahead. This build-up forms a torsional resistance that would eventually halt the progress of the replication fork. Topoisomerases are enzymes that temporarily break the strands of DNA, relieving the tension caused by unwinding the two strands of the DNA helix. Topoisomerases (including DNA gyrase) achieve this by adding negative supercoils to the DNA helix. Bare single-stranded DNA tends to fold back on itself forming secondary structures. These structures can interfere with the movement of DNA polymerase. To prevent this, single-strand binding proteins bind to the DNA until a second strand is synthesized, preventing secondary structure formation.



https://en.wikipedia.org/wiki/DNA_replication#Replication_fork

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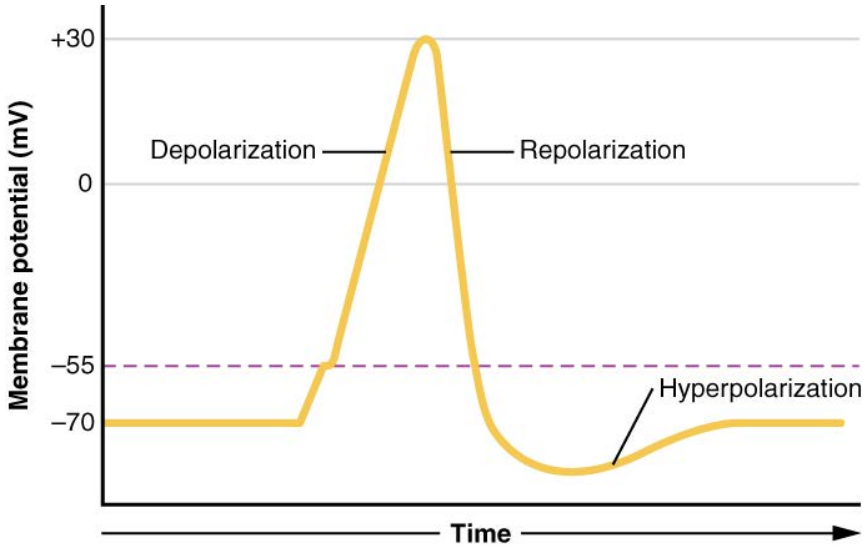
Repolarization

Repolarization refers to a cell’s response after its ion gradient has been altered - a process called depolarizatio. Depolarization, in biology, refers to a sudden change within a cell, during which the cell undergoes a dramatic electrical change. Most cells, especially those that compose the tissues of highly organized animals, typically maintain an internal environment that is negatively charged compared to the cell's surrounding environment. This difference in charge is called the cell's membrane potential. In the process of depolarization, the negative internal charge of the cell becomes positive for a very brief time. This shift from a negative to a positive internal cellular environment allows for the transmission of electrical impulses both within a cell and, in certain instances, between cells. This communicative function of depolarization is essential to the function of many cells, communication between cells, and the overall function of an organism.

After a cell has been depolarized, it undergoes one final change in internal charge. Following depolarization, the voltage gated sodium ion channels that had been open while the cell was undergoing depolarization close again. The increased positive charge within the cell now causes the potassium channels to open. Potassium ions (K+) begin to move down the electrochemical gradient (in favor of the concentration gradient and the newly established electrical gradient). As potassium moves out of the cell the potential within the cell plummets and approaches its resting potential once more. The sodium potassium pump works continuously throughout this process.



https://en.wikipedia.org/wiki/Depolarization

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Chapter 3 - Membranes: Transport

Repressors

In molecular genetics, a repressor is a DNA- or RNA-binding protein that inhibits the expression of one or more genes by binding to the operator or associated silencers. A DNA-binding repressor blocks the attachment of RNA polymerase to the promoter, thus preventing transcription of the genes into messenger RNA. An RNA-binding repressor binds to the mRNA and prevents translation of the mRNA into protein. This blocking of expression is called repression.

If an inducer, a molecule that initiates the gene expression, is present, then it can interact with the repressor protein and detach it from the operator. RNA polymerase then can transcribe the message (expressing the gene). A corepressor is a molecule that can bind to repressor and make it bind to the operator tightly, which decreases transcription. A repressor that binds with a corepressor is termed an aporepressor or inactive repressor. One type of aporepressor is the trp repressor, an important metabolic protein in bacteria.

The above mechanism of repression is a type of a feedback mechanism because it only allows transcription to occur if a certain condition is present: the presence of specific inducer(s). Within the Eukaryotic genome are regions of DNA known as silencers. These DNA sequences bind to repressors to partially or fully repress the expression of a gene. Silencers can be located several bases upstream or downstream from the actual promoter of the gene. Repressors can also have two binding sites: one for the silencer region and one for the promoter. This causes chromosome looping, allowing the promoter region and the silencer region to come to close proximity.

https://en.wikipedia.org/wiki/Repressor

Related Glossary Terms

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Resistin

Resistin also known as adipose tissue-specific secretory factor (ADSF) or C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein (XCP1) is a cysteine-rich adipose-derived peptide hormone that in humans is encoded by the RETN gene.

Resistin is an adipose-derived hormone (similar to a cytokine) whose physiologic role has been the subject of much controversy regarding its involvement with obesity and type II diabetes mellitus (T2DM). Resistin has been shown to cause "high levels of 'bad' cholesterol (low-density lipoprotein or LDL), increasing the risk of heart disease [...] resistin increases the production of LDL in human liver cells and also degrades LDL receptors in the liver. As a result, the liver is less able to clear 'bad' cholesterol from the body. Resistin accelerates the accumulation of LDL in arteries, increasing the risk of heart disease. [...] resistin adversely impacts the effects of statins, the main cholesterol-reducing drug used in the treatment and prevention of cardiovascular disease."

https://en.wikipedia.org/wiki/Resistin

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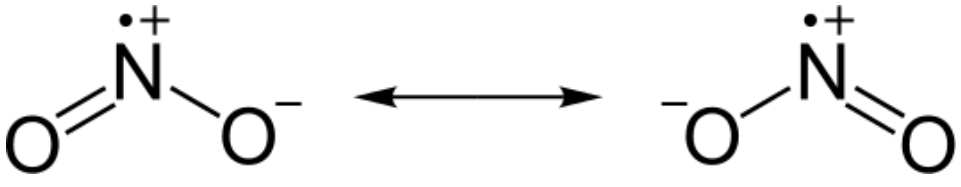
Resonant Structure

In chemistry, resonance or mesomerism is a way of describing delocalized ele
within certain molecules or polyatomic ions where the bonding cannot be exp
one single Lewis structure. A molecule or ion with such delocalized electrons
sented by several contributing structures (also called resonance structures or
structures).



https://en.wikipedia.org/wiki/Resonance_(chemistry)

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Chapter 2 - Structure & Function: Proteins I

Resonant Structures

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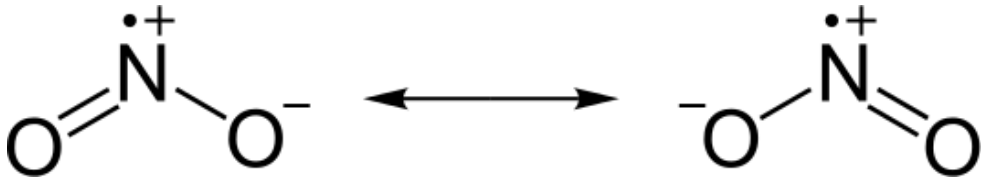

https://en.wikipedia.org/wiki/Resonance_(chemistry)

Related Glossary Terms

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Respirasome

Modern biological research has revealed strong evidence that the enzymes of the mitochondrial respiratory chain assemble into larger, supramolecular structures called respirasomes or supercomplexes, instead of the traditional fluid model of discrete enzymes dispersed in the inner mitochondrial membrane. These supercomplexes are functionally active and necessary for forming stable respiratory complexes.

The most common supercomplexes observed are Complex I/III, Complex I/III/IV, and Complex III/IV. Most of Complex II is found in a free-floating form in both plant and animal mitochondria. Complex V can be found co-migrating as a dimer with other supercomplexes, but scarcely as part of the supercomplex unit.

Supercomplex assembly appears to be dynamic and respiratory enzymes are able to alternate between participating in large respirasomes and existing in a free state. It is not known what triggers changes in complex assembly, but research has revealed that the formation of supercomplexes is heavily dependent upon the lipid composition of the mitochondrial membrane, and in particular requires the presence of cardiolipin, a unique mitochondrial lipid. In yeast mitochondria lacking cardiolipin, the number of enzymes forming respiratory supercomplexes was significantly reduced.

Another hypothesis for respirasome formation is that membrane potential may initiate changes in the electrostatic/hydrophobic interactions mediating the assembly/disassembly of supercomplexes.

https://en.wikipedia.org/wiki/Respirasome

Respiration

In physiology, respiration is defined as the movement of oxygen from the o
the cells within tissues, and the transport of carbon dioxide in the opposite

The physiological definition of respiration should not be confused with the
definition of respiration, which refers to cellular respiration: the metabolic
which an organism obtains energy by reacting oxygen with glucose to give w
bon dioxide and 38 ATP (energy). Although physiologic respiration is neces
tain cellular respiration and thus life in animals, the processes are distinct:
piration takes place in individual cells of the organism, while physiologic re
concerns the bulk flow and transport of metabolites between the organism
ternal environment.

https://en.wikipedia.org/wiki/Respiration_(physiology)

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Respiratory Control

Control of ventilation refers to the physiological mechanisms involved in the control of physiologic ventilation, which refers to the movement of air into and out of the lungs. Ventilation facilitates respiration. Respiration refers to the uptake of oxygen and the removal of carbon dioxide. Under most conditions, the partial pressure of carbon dioxide controls the rate of respiration.

At the molecular level, respiratory control relates to the interlinks between the electron transport system and oxidative phosphorylation. Normally these systems are tightly coupled, meaning that each depends on the other and stopping one stops both. Because of this interdependence, when ATP is not being used, oxidative phosphorylation slows, causing electron transport to slow. Since electron transport is linked to oxygen consumption, the breathing rate slows. When exercise begins, ATP is used, speeding up oxidative phosphorylation and electron transport. This causes oxygen consumption to increase and you start to breath more rapidly and deeply.

https://en.wikipedia.org/wiki/Control_of_ventilation

Related Glossary Terms

Drag related terms here

Resting Membrane Potential

The relatively static membrane potential of quiescent cells is called the resting membrane potential (or resting voltage), as opposed to the specific dynamic electrochemical changes (for example in firing of a nerve cell) called action potential and graded membrane potential.

Apart from the latter two, which occur in excitable cells (neurons, muscles, and some secretory cells in glands), membrane voltage in the majority of non-excitable cells can also undergo changes in response to environmental or intracellular stimuli. In principle, there is no difference between resting membrane potential and dynamic voltage changes like action potential from a biophysical point of view: all these phenomena are caused by specific changes in membrane permeabilities for potassium, sodium, calcium, and chloride ions, which in turn result from concerted changes in functional activity of various ion channels, ion transporters, and exchangers. Conventionally, resting membrane potential can be defined as a relatively stable, ground value of transmembrane voltage in animal and plant cells.

In the case of the resting membrane potential across an animal cell's plasma membrane, potassium (and sodium) gradients are established by the Na+/K+-ATPase (sodium-potassium pump) which transports 2 potassium ions inside and 3 sodium ions outside at the cost of 1 ATP molecule. In other cases, for example, a membrane potential may be established by acidification of the inside of a membranous compartment (such as the proton pump that generates membrane potential across synaptic vesicle membranes).

https://en.wikipedia.org/wiki/Resting_potential

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Resting Potential

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Any voltage is a difference in electric potential between two points—for example, the separation of positive and negative electric charges on opposite sides of a resistive barrier. The typical resting membrane potential of a cell arises from the separation of potassium ions from intracellular, relatively immobile anions across the membrane of the cell. Because the membrane permeability for potassium is much higher than that for other ions (disregarding voltage-gated channels at this stage), and because of the strong chemical gradient for potassium, potassium ions flow from the cytosol into the extracellular space carrying out positive charge, until their movement is balanced by build-up of negative charge on the inner surface of the membrane. Again, because of the high relative permeability for potassium, the resulting membrane potential is almost always close to the potassium reversal potential. But in order for this process to occur, a concentration gradient of potassium ions must first be set up. This work is done by the ion pumps/transporters and/or exchangers and generally is powered by ATP.

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https://en.wikipedia.org/wiki/Resting_potential

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Restriction Enzyme

A restriction enzyme or restriction endonuclease is an enzyme that cuts DNA at or near specific recognition nucleotide sequences known as restriction sites. Restriction enzymes are commonly classified into three types, which differ in their structure and whether they cut their DNA substrate at their recognition site, or if the recognition and cleavage sites are separate from one another. To cut DNA, all restriction enzymes make two incisions, once through each sugar-phosphate backbone (i.e. each strand) of the DNA double helix.

These enzymes are found in bacteria and archaea and provide a defense mechanism against invading viruses. Inside a prokaryote, the restriction enzymes selectively cut up foreign DNA in a process called restriction. Meanwhile, host DNA is protected by a modification enzyme (a methyltransferase) that modifies the prokaryotic DNA and blocks cleavage. Together, these two processes form the restriction modification system.

Restriction enzymes recognize a specific sequence of nucleotides and produce a double-stranded cut in the DNA. The recognition sequences can also be classified by the number of bases in its recognition site, usually between 4 and 8 bases, and the amount of bases in the sequence will determine how often the site will appear by chance in any given genome, e.g., a 4-base pair sequence would theoretically occur once every 4^4 or 256bp, 6 bases, 4^6 or 4,096bp, and 8 bases would be 4^8 or 65,536bp.

https://en.wikipedia.org/wiki/Restriction_enzyme

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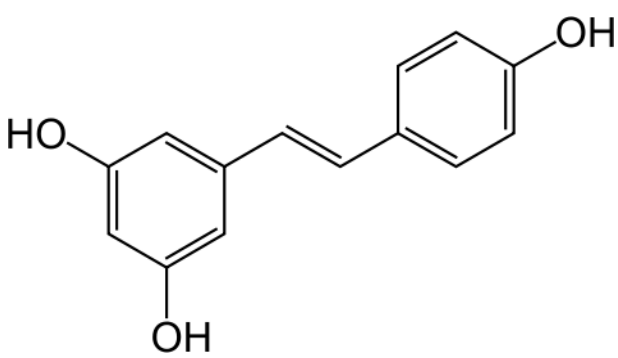
Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced naturally by several plants in response to injury or when the plant is under attack by pathogens such as bacteria or fungi. Food sources of resveratrol include the skin of grapes, blueberries, raspberries, and mulberries.

Although *in vitro* studies indicate resveratrol activates sirtuin 1 and PGC-1α, and affects functioning of mitochondria, other research disputes this effect. In cells treated with resveratrol, an increase is observed in the action of MnSOD (SOD2) which reduces superoxide, implying resistance to mitochondrial dysfunction, permeability transition, and apoptotic death in various diseases. Resveratrol has also been found to act as an agonist of the GPER (GPR30).



https://en.wikipedia.org/wiki/Resveratrol

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Retinal

Retinal is also known as retinaldehyde. It was originally called retinene, and renamed afterwards it was discovered to be vitamin A aldehyde. Retinal is one of the many forms of vitamin A (the number of which varies from species to species). Retinal is a polyene chromophore, bound to proteins called opsins, and is the chemical basis of animal vision. Retinal allows certain microorganisms to convert light into metabolic energy.

Structurally, all retinoids also possess a β-ionone ring and a polyunsaturated side chain, with either an alcohol, aldehyde, a carboxylic acid group or an ester group. The side chain is composed of four isoprenoid units, with a series of conjugated double bonds which may exist in *trans*- or *cis*-configuration.

Vision begins with the photoisomerization of retinal. When the 11-cis-retinal chromophore absorbs a photon it isomerizes from the 11-cis state to the all-*trans* state. The absorbance spectrum of the chromophore depends on its interactions with the opsin protein to which it is bound. Different opsins produce different absorbance spectra.

Vertebrate animals ingest retinal directly from meat, or they produce retinal from carotenoids, either from one of two carotenes (α-carotene, β-carotene) or from β-cryptoxanthin, a type of xanthophyll. These carotenoids must be obtained from plants or other photosynthetic organisms. No other carotenoids can be converted by animals to retinal, and some carnivores cannot convert any carotenoids at all. The other main forms of vitamin A, retinol, and a partially active form, retinoic acid, may both be produced from retinal.

Living organisms produce retinal (RAL) by irreversible oxidative cleavage of carotenoids. For example

β-carotene + O_2 → 2 Retinal

catalyzed by a β-carotene 15,15'-monooxygenase or a β-carotene 15,15'-dioxygenase. Just as carotenoids are the precursors of retinal, retinal is the precursor of the other forms of vitamin A. Retinal is interconvertible with retinol (ROL), the transport and storage form of vitamin A

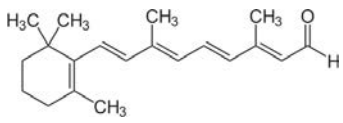
Retinal + NADPH + H+ ⇌ Retinol + $NADP^+$

Retinol + NAD^+ ⇌ Retinal + NADH + H^+

catalyzed by retinol dehydrogenases (RDHs) and alcohol dehydrogenases (ADHs). Retinol is called vitamin A alcohol, or more often, simply vitamin A. Retinal can also be oxidized to retinoic acid (RA)

retinal + NAD^+ + H_2O → Retinoic acid + NADH + H+ (catalyzed by RALDH)
retinal + O_2 + H_2O → Retinoic acid + H_2O_2 (catalyzed by retinal oxidase)

Retinoic acid, sometimes called vitamin A acid, is an important signaling molecule and hormone in vertebrate animals.



https://en.wikipedia.org/wiki/Retinal

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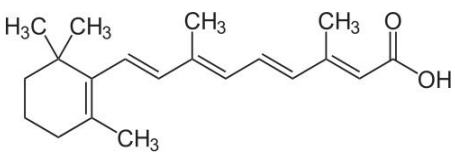
Retinoic Acid

Retinoic acid is a metabolite of vitamin A (retinol) that mediates the functions of vitamin A required for growth and development. Retinoic acid is required in chordate animals, which includes all higher animals from fish to humans. During early embryonic development, retinoic acid generated in a specific region of the embryo helps determine position along the embryonic anterior/posterior axis by serving as an intercellular signaling molecule that guides development of the posterior portion of the embryo. It acts through Hox genes, which ultimately control anterior/posterior patterning in early developmental stages.

The key role of retinoic acid in embryonic development mediates the high teratogenicity of retinoid pharmaceuticals, such as isotretinoin used for treatment of cancer and acne. Oral megadoses of pre-formed vitamin A (retinyl palmitate), and retinoic acid itself, also have teratogenic potential by this same mechanism.

Retinoic acid acts by binding to the retinoic acid receptor (RAR), which is bound to DNA as a heterodimer with the retinoid X receptor (RXR) in regions called retinoic acid response elements (RAREs). Binding of the retinoic acid ligand to RAR alters the conformation of the RAR, which affects the binding of other proteins that either induce or repress transcription of a nearby gene (including Hox genes and several other target genes). Retinoic acid receptors mediate transcription of different sets of genes controlling differentiation of a variety of cell types, thus the target genes regulated depend upon the target cells. In some cells, one of the target genes is the gene for the retinoic acid receptor itself (RAR-beta in mammals), which amplifies the response. Control of retinoic acid levels is maintained by a suite of proteins that control synthesis and degradation of retinoic acid.

The molecular basis for the interaction between retinoic acid and the Hox genes has been studied by using deletion analysis in transgenic mice carrying constructs of GFP reporter genes. Such studies have identified functional RAREs within flanking sequences of some of the most 3' Hox genes (including Hoxa1, Hoxb1, Hoxb4, Hoxd4), suggesting a direct interaction between the genes and retinoic acid. These types of studies strongly support the normal roles of retinoids in patterning vertebrate embryogenesis through the Hox genes.



https://en.wikipedia.org/wiki/Retinoic_acid

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Retinoic Acid Receptor

The retinoic acid receptor (RAR) is a type of nuclear receptor which can also a
transcription factor that is activated by both all-*trans* retinoic acid and 9-*cis* r
acid. There are three retinoic acid receptors (RAR), RAR-α, RAR-β, and RAR-
coded by the RARA, RARB, RARG genes, respectively. Each receptor isoform
eral splice variants: four- for α, four- for β, and two- for γ.

As with other type II nuclear receptors, RAR heterodimerizes with RXR and i
sence of ligand, the RAR/RXR dimer binds to hormone response elements kn
retinoic acid response elements (RAREs) complexed with corepressor protein
of agonist ligands to RAR results in dissociation of co-repressor and recruitme
activator protein that, in turn, promotes transcription of the downstream targ
into mRNA and eventually protein.

https://en.wikipedia.org/wiki/Retinoic_acid_receptor

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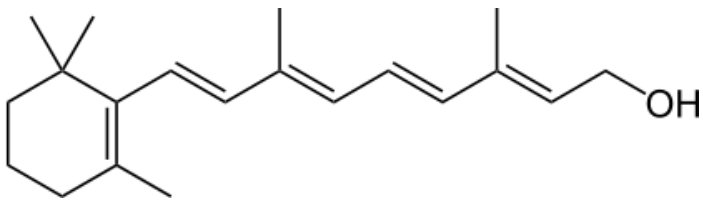
Retinol

Retinol is one of the animal forms of vitamin A. It is a diterpenoid and an alcohol and is convertible to other forms of vitamin A. The retinyl ester derivative of the alcohol serves as the storage form of the vitamin in animals.

When converted to the retinal (retinaldehyde) form, vitamin A is essential for vision, and when converted to retinoic acid is essential for skin health, teeth remineralization and bone growth. These chemical compounds are collectively known as retinoids, and possess the structural motif of all-*trans* retinol as a common feature in their structure.

Structurally, all retinoids also possess a β-ionone ring and a polyunsaturated side chain, with either an alcohol, aldehyde, a carboxylic acid group or an ester group. The side chain is composed of four isoprenoid units, with a series of conjugated double bonds which may exist in *trans*- or *cis*-configuration.

Retinol is produced in the body from the hydrolysis of retinyl esters, and from the reduction of retinal. Retinol in turn is ingested in a precursor form. Animal sources (liver and eggs) contain retinyl esters, whereas plants (carrots, spinach) contain provitamin A carotenoids (these may also be considered simply vitamin A). Hydrolysis of retinyl esters results in retinol, while provitamin A carotenoids can be cleaved to produce retinal by carotene dioxygenase in the intestinal mucosa. Retinal, also known as retinaldehyde, can be reversibly reduced to produce retinol or it can be irreversibly oxidized to produce retinoic acid, which then cannot function as the vitamin in the eye.



https://en.wikipedia.org/wiki/Retinol

Related Glossary Terms

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Retinol Dehydrogenase

Retinol Dehydrogenase is an enzyme that catalyzes the chemical reaction

$$\text{Retinol} + NAD^+ \rightleftharpoons \text{Retinal} + NADH + H^+$$

Sometimes, in addition to or along with NAD^+ , $NADP^+$ can act as a cofactor in the reaction as well. The substrate of the enzyme can be all-*trans*- or -*cis*- retinol. There are at least over 20 different isolated enzymes with RDH activity to date.

Retinoid dehydrogenases/reductases (oxidoreductases), including retinol dehydrogenase, catalyze the key oxidation-reduction reactions in the visual cycle, converting vitamin A to 11-cis retinal, which is the chromophore of the rod and cone photoreceptors. It is believed that RDHs at rod and cone are different, but related and can catalyze the same reaction. RDH12 is the primary enzyme that reduces all-*trans* retinal released from bleached photopigments during recovery phase in the visual cycle. The RDH12 enzyme can use either cis or trans retinoid isomers as substrates and can also function as both dehydrogenase (i.e. retinol to retinal) and reductase (i.e. retinal to retinol).

The conversion of retinol to retinal is the rate-limiting step in the retinoic acid biosynthesis. In vertebrates, the retinoic acid is the ligand that controls nuclear receptor signaling pathway, which is responsible for growth and development as well as epithelial maintenance, therefore can be used for cancer and acne treatment. In human, ADH4 can exhibit at least 10 fold higher V_{max}/K_m than other ADH.

https://en.wikipedia.org/wiki/Retinol_dehydrogenase

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Chapter 6 - Metabolism: Other Lipids

Retrotransposition

Transposable elements represent one of several types of mobile genetic elements. TEs are assigned to one of two classes according to their mechanism of transposition, which can be described as either copy and paste (Class I TEs) or cut and paste (Class II TEs).

Class I (retrotransposons)

Class I TEs are copied in two stages: first, they are transcribed from DNA to RNA, and the RNA produced is then reverse transcribed to DNA. This copied DNA is then inserted back into the genome at a new position. The reverse transcription step is catalyzed by a reverse transcriptase, which is often encoded by the TE itself. The characteristics of retrotransposons are similar to retroviruses, such as HIV.
Retrotransposons are commonly grouped into three main orders:

- TEs with long terminal repeats (LTRs), which encode reverse transcriptase, similar to retroviruses
- Long interspersed nuclear elements (LINEs, LINE-1s, or L1s), which encode reverse transcriptase but lack LTRs, and are transcribed by RNA polymerase II
- Short interspersed nuclear elements do not encode reverse transcriptase and are transcribed by RNA polymerase III

Retroviruses can also be considered TEs. For example, after conversion of retroviral RNA into DNA inside a host cell, the newly produced retroviral DNA is integrated into the genome of the host cell. These integrated DNAs are termed proviruses. The provirus is a specialized form of eukaryotic retrotransposon, which can produce RNA intermediates that may leave the host cell and infect other cells. The transposition cycle of retroviruses has similarities to that of prokaryotic TEs, suggesting a distant relationship between the two.

Class II (DNA transposons)

The cut-and-paste transposition mechanism of class II TEs does not involve an RNA intermediate. The transpositions are catalyzed by several transposase enzymes. Some transposases non-specifically bind to any target site in DNA, whereas others bind to specific target sequences. The transposase makes a staggered cut at the target site resulting in single-strand 5' or 3' DNA overhangs, so-called "sticky ends". This step cuts out the DNA transposon, which is then ligated into a new target site. The process involves activity of a DNA polymerase that fills in gaps and of a DNA ligase that closes the sugar-phosphate backbone. This results in duplication of the target site. The insertion sites of DNA transposons may be identified by short direct repeats (created by the staggered cut in the target DNA and filling in by DNA polymerase) followed by a series of inverted repeats important for the TE excision by transposase. Cut-and-paste TEs may be duplicated if their transposition takes place during S phase of the cell cycle, when a donor site has already been replicated but a target site has not yet been replicated. Such duplications at the target site can result in gene duplication, which plays an important role in genomic evolution. Not all DNA transposons transpose through the cut-and-paste mechanism. In some cases, a replicative transposition is observed in which a transposon replicates itself to a new target site (e.g. helitron (biology)). Class II TEs comprise less than 2% of the human genome, making the rest Class I.

https://en.wikipedia.org/wiki/Transposable_element

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Chapter 7 - Genes and Genomes
Chapter 9 - Point by Point: Information Processing

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https://en.wikipedia.org/wiki/Transposable_element

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Chapter 7 - Genes and Genomes
Chapter 9 - Point by Point: Information Processing

Retroviruses

Retroviridae is a family of enveloped viruses that replicate in a host cell through the process of reverse transcription. A retrovirus is a single-stranded positive-sense RNA virus with a DNA intermediate and, as an obligate parasite, targets a host cell. Once inside the host cell cytoplasm, the virus uses its own reverse transcriptase enzyme to produce DNA from its RNA genome — the reverse of the usual pattern, thus retro (backwards). This new DNA is then incorporated into the host cell genome by an integrase enzyme, at which point the retroviral DNA is referred to as a provirus. The host cell then treats the viral DNA as part of its own genome, translating and transcribing the viral genes along with the cell's own genes, producing the proteins required to assemble new copies of the virus.

In most systems, DNA is transcribed into RNA, and then RNA is translated into protein. However, retroviruses function differently – their RNA is reverse-transcribed into DNA, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translational processes to express the genes carried by the virus. So, the information contained in a retroviral gene is used to generate the corresponding protein via the sequence: RNA → DNA → RNA → polypeptide. This extends the fundamental process identified by Francis Crick (one gene-one peptide) in which the sequence is: DNA → RNA → peptide (proteins are made of one or more polypeptide chain, e.g. hemoglobin is a four-chain peptide).

Retroviruses are valuable research tools in molecular biology, and have been used successfully in gene delivery systems.

https://en.wikipedia.org/wiki/Retrovirus

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Chapter 8 - Basic Techniques

Reverse Phase Separation

Reversed-phase chromatography (also called RPC, reverse-phase chromatography, or hydrophobic chromatography) includes any chromatographic method that uses a hydrophobic stationary phase. RPC refers to liquid (rather than gas) chromatography.

In the 1970s, most liquid chromatography was performed using a solid support stationary phase (also called a "column") containing unmodified silica or alumina resins. This method is now called "normal phase chromatography". In normal phase chromatography, the stationary phase is hydrophilic and therefore has a strong affinity for hydrophilic molecules in the mobile phase. Thus, the hydrophilic molecules in the mobile phase tend to bind (or "adsorb") to the column, while the hydrophobic molecules pass through the column and are eluted first. In normal phase chromatography, hydrophilic molecules can be eluted from the column by increasing the polarity of the solution in the mobile phase.

The introduction of a technique using alkyl chains covalently bonded to the solid support created a hydrophobic stationary phase, which has a stronger affinity for hydrophobic compounds. The use of a hydrophobic stationary phase can be considered the opposite, or "reverse", of normal phase chromatography - hence the term "reversed-phase chromatography". Reversed-phase chromatography employs a polar (aqueous) mobile phase. As a result, hydrophobic molecules in the polar mobile phase tend to adsorb to the hydrophobic stationary phase, and hydrophilic molecules in the mobile phase will pass through the column and are eluted first. Hydrophobic molecules can be eluted from the column by decreasing the polarity of the mobile phase using an organic (non-polar) solvent, which reduces hydrophobic interactions. The more hydrophobic the molecule, the more strongly it will bind to the stationary phase, and the higher the concentration of organic solvent that will be required to elute the molecule.

https://en.wikipedia.org/wiki/Reversed-phase_chromatography

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Reverse Transcriptase

A reverse transcriptase (RT) is an enzyme used to generate complementary DNA (cDNA) from an RNA template, a process termed reverse transcription. It is mainly associated with retroviruses. However, non-retroviruses also use RT (for example, the hepatitis B virus, a member of the *Hepadnaviridae*, which are dsDNA-RT viruses, while retroviruses are ssRNA viruses). RT inhibitors are widely used as antiretroviral drugs. RT activities are also associated with the replication of chromosome ends (telomerase) and some mobile genetic elements (retrotransposons).

Retroviral RT has three sequential biochemical activities:

- (a) RNA-dependent DNA polymerase activity,
- (b) ribonuclease H, and
- (c) DNA-dependent DNA polymerase activity.

These activities are used by the retrovirus to convert single-stranded genomic RNA into double-stranded cDNA which can integrate into the host genome, potentially generating a long-term infection that can be very difficult to eradicate. The same sequence of reactions is widely used in the laboratory to convert RNA to DNA for use in molecular cloning, RNA sequencing, polymerase chain reaction (PCR), or genome analysis.

https://en.wikipedia.org/wiki/Reverse_transcriptase

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Reverse Transcription

Reverse transcription is the act of making a DNA from an RNA template us
transcriptase. A reverse transcriptase (RT) is an enzyme used to generate c
tary DNA (cDNA) from an RNA template, a process termed reverse transcr
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viral drugs. RT activities are also associated with the replication of chromos
(telomerase) and some mobile genetic elements (retrotransposons).

https://en.wikipedia.org/wiki/Reverse_transcriptase

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Chapter 9 - Point by Point: Information Processing

Reverse Transport Pathway

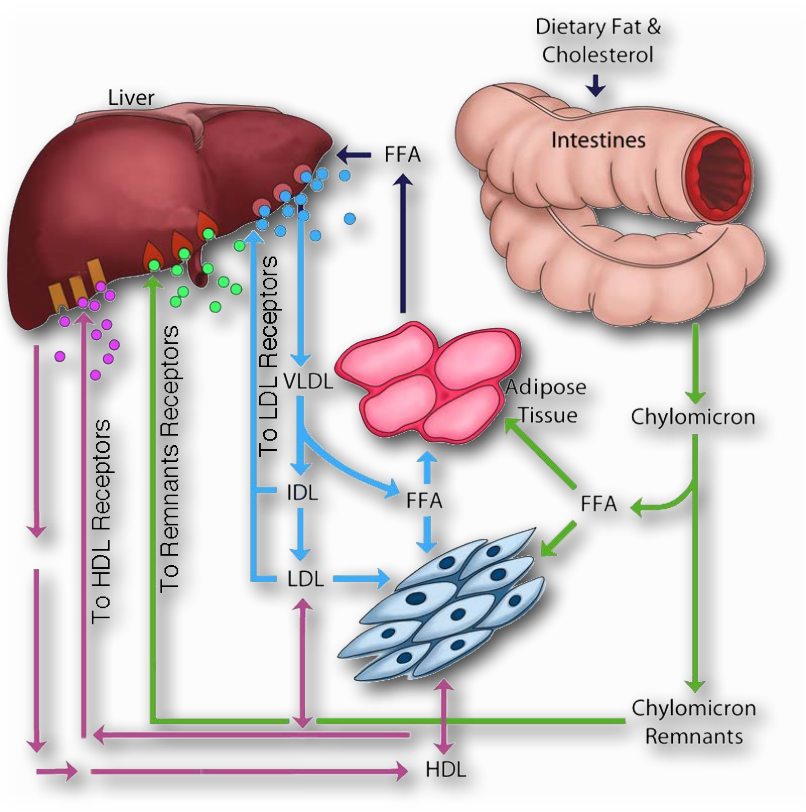
The exogenous pathway is one of three major pathways taken by lipids in the body. (The others are the endogenous pathway and the exogenous pathway.)

The reverse transport pathway is a method of moving lipids involving lipoprotein complexes known as the High Density Lipoproteins (HDLs). In contrast to the LDLs, which are commonly referred to as “bad cholesterol” (see below also), the HDLs are known as “good cholesterol.”

HDLs are synthesized in the liver and small intestine. They contain little or no lipid when made (called depleted HDLs), but serve the role of “scavenger” for cholesterol in the blood and from remnants of other (damaged) lipoprotein complexes in the blood. To perform its task, HDLs carry the enzyme known as lecithin-cholesterol acyl transferase (LCAT), which they use to form cholesteryl esters using fatty acids from lecithin (phosphatidylcholine) and then they internalize them.

The cholesterol used for this purpose comes from the bloodstream, from macrophages, and from foam cells (macrophage-LDL complexes). Addition of cholesteryl esters causes the HDL to swell and when it is mature, it returns its load of cholesterol back to the liver or, alternatively, to LDL molecules for endocytosis. HDLs have the effect of lowering levels of cholesterol and it is for that reason they are described as “good cholesterol.”

The reverse transport pathway is shown in the lower left (purple) of the figure below.

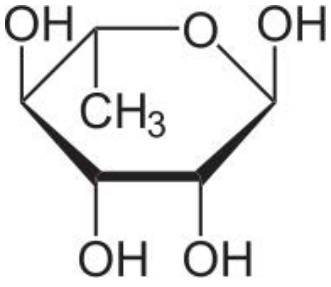


Rhamnose

Rhamnose (Rha, Rham) is a naturally occurring deoxy sugar. It can be classified as either a methyl-pentose or a 6-deoxy-hexose. Rhamnose occurs in nature in its L-form as L-rhamnose (6-deoxy-L-mannose). This is unusual, since most of the naturally occurring sugars are in D-form. Exceptions are the methyl pentoses L-fucose and L-rhamnose and the pentose L-arabinose.

Rhamnose can be isolated from Buckthorn (*Rhamnus*), poison sumac, and plants in the genus *Uncaria*. Rhamnose is also produced by microalgae belonging to class *Bacillariophyceae* (diatoms).

Rhamnose is commonly bound to other sugars in nature. It is a common glycone component of glycosides from many plants. Rhamnose is also a component of the outer cell membrane of acid-fast bacteria in the *Mycobacterium* genus, which includes the organism that causes tuberculosis.



https://en.wikipedia.org/wiki/Rhamnose

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Chapter 2 - Structure & Function: Carbohydrates

Rho Factor

A ρ factor (Rho factor) is a prokaryotic protein involved in the termination of transcription. Rho factor binds to the transcription terminator pause site, an exposed region of single stranded RNA (a stretch of 72 nucleotides) after the open reading frame at C-rich, G-poor sequences that lack obvious secondary structure.

Rho factor is an essential transcription protein in prokaryotes. In Escherichia coli, it is a ~274.6 kD hexamer of identical subunits. Each subunit has an RNA-binding domain and an ATP-hydrolysis domain. Rho is a member of the family of ATP-dependent hexameric helicases that function by wrapping nucleic acids around a single cleft extending around the entire hexamer. Rho functions as an ancillary factor for RNA polymerase.

There are two types of transcriptional termination in prokaryotes, rho-dependent termination and intrinsic termination (also called Rho-independent termination). Rho-dependent terminators account for about half of the *E. coli* factor-dependent terminators. Other termination factors discovered in *E. coli* include Tau and nusA. Rho-dependent terminators were first discovered in bacteriophage genomes.

A Rho factor acts on an RNA substrate. Rho's key function is its helicase activity, for which energy is provided by an RNA-dependent ATP hydrolysis. The initial binding site for Rho is an extended (~70 nucleotides, sometimes 80–100 nucleotides) single-stranded region, rich in cytosine and poor in guanine, called the rho utilization site (rut), in the RNA being synthesized, upstream of the actual terminator sequence. Several rho binding sequences have been discovered. No consensus is found among these, but the different sequences each seem specific, as small mutations in the sequence disrupts its function. Rho binds to RNA and then uses its ATPase activity to provide the energy to translocate along the RNA until it reaches the RNA–DNA helical region, where it unwinds the hybrid duplex structure. RNA polymerase pauses at the termination sequence, which is because there is a specific site around 100 nt away from the Rho binding site called the Rho-sensitive pause site. So, even though the RNA polymerase is about 40 nt per second faster than Rho, it does not pose a problem for the Rho termination mechanism as the RNA polymerase allows Rho factor to catch up.

In short, Rho factor acts as an ATP-dependent unwinding enzyme, moving along the newly forming RNA molecule towards its 3′ end and unwinding it from the DNA template as it proceeds.

https://en.wikipedia.org/wiki/Rho_factor

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Rho-dependent terminators

Termination is part of the process of transcribing RNA. In eukaryotes, a termination factor is required to release the newly made (nascent) RNA from the transcription complex. Prokaryote mRNAs often do not require a termination factor: an inverted repeat followed by a string of Us (uracils) in the mRNA template strand forms a stem-loop structure which destabilizes binding by the RNA polymerase and causes Rho-independent transcription termination.

The most extensively studied transcriptional termination factor is the Rho protein of *E. coli.* The Rho protein recognizes a cytosine-rich region of the elongating mRNA, but the exact features of the recognized sequences remain unknown. Rho forms a ring-shaped hexamer and advances along the mRNA, hydrolyzing ATP, toward RNA polymerase (5' to 3' with respect to the mRNA). When the Rho protein reaches the RNA polymerase complex, transcription is terminated by dissociation of the RNA polymerase from the DNA. The structure, as well as the activity, of the Rho protein is similar to that of the F1 subunit of ATP synthase, supporting the theory that the two share an evolutionary link. The antibiotic bicyclomycin works by inhibiting Rho.

https://en.wikipedia.org/wiki/Termination_factor

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Rhodopsin

Rhodopsin (also known as visual purple) is a light-sensitive receptor protein involved in visual phototransduction. Rhodopsin is a biological pigment found in the rods of the retina and is an essential G-protein-coupled receptor (GPCR) in phototransduction. Rhodopsin is extremely sensitive to light, and thus enables vision in low-light conditions. When rhodopsin is exposed to light, it immediately photobleaches. In humans, it is regenerated fully in about 45 minutes.

In rhodopsin, the aldehyde group of retinal is covalently linked to the amino group of a lysine residue on the protein in a protonated Schiff base ($-NH^+=CH^-$). When rhodopsin absorbs light, its retinal cofactor isomerizes from the 11-*cis* to the all-*trans* configuration, and the protein subsequently undergoes a series of relaxations to accommodate the altered shape of the isomerized cofactor. The intermediates formed during this process were first investigated in the laboratory of George Wald, who received the Nobel prize for this research in 1967.

In subsequent intermediates lumirhodopsin and metarhodopsin I, the Schiff's base linkage to all-*trans* retinal remains protonated, and the protein retains its reddish color. The critical change that initiates the neuronal excitation involves the conversion of metarhodopsin I to metarhodopsin II, which is associated with deprotonation of the Schiff's base and change in color from red to yellow. Metarhodopsin II activates the G protein transducin (Gt) to activate the visual phototransduction pathway. When transducin's α subunit is bound to GTP, it activates cGMP phosphodiesterase. cGMP phosphodiesterase hydrolyzes cGMP (breaks it down). cGMP can no longer activate cation channels. This leads to the hyperpolarization of photoreceptor cells and a change in the rate of transmitter release by these photoreceptor cells.

https://en.wikipedia.org/wiki/Rhodopsin

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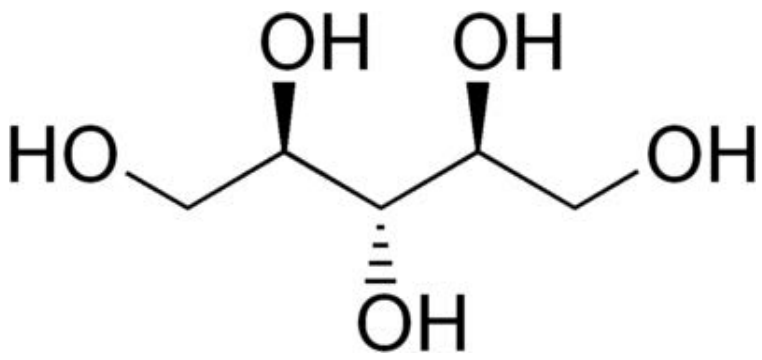
Ribitol

Ribitol or adonitol is a crystalline pentose alcohol ($C_5H_{12}O_5$) formed by the
ribose. It occurs naturally in the plant *Adonis vernalis*, as well as in the cell
Gram positive bacteria (specifically, as ribitol phosphate, in teichoic acids).
tributes to the chemical structure of riboflavin and flavin mononucleotide (
which is a nucleotide coenzyme, present in the enzyme glycolate oxidase.



https://en.wikipedia.org/wiki/Ribitol

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Ribonuclease

Ribonuclease (commonly abbreviated RNase) is a type of nuclease that catalyzes the degradation of RNA into smaller components. Ribonucleases can be divided into endoribonucleases and exoribonucleases, and comprise several sub-classes within the EC 2.7 (for the phosphorolytic enzymes) and 3.1 (for the hydrolytic enzymes) classes of enzymes.

All organisms studied contain many RNases of many different classes, showing that RNA degradation is a very ancient and important process. As well as cleaning of cellular RNA that is no longer required, RNases play key roles in the maturation of all RNA molecules, both messenger RNAs that carry genetic material for making proteins, and non-coding RNAs that function in varied cellular processes. In addition, active RNA degradation systems are a first defense against RNA viruses, and provide the underlying machinery for more advanced cellular immune strategies such as RNAi.

Some cells also secrete copious quantities of non-specific RNases such as A and T1. RNases are, therefore, extremely common, resulting in very short lifespans for any RNA that is not in a protected environment. Intracellular RNAs may be protected from RNase activity by a number of strategies including 5' end capping, 3' end polyadenylation, and folding within an RNA protein complex (ribonucleoprotein particle or RNP).

Another mechanism of protection is ribonuclease inhibitor (RI), which comprises a relatively large fraction of cellular protein (~0.1%) in some cell types, and which binds to certain ribonucleases with the highest affinity of any protein-protein interaction; the dissociation constant for the RI-RNase A complex is ~20 fM under physiological conditions. RI is used in most laboratories that study RNA to protect their samples against degradation from environmental RNases.

Similar to restriction enzymes, which cleave highly specific sequences of double-stranded DNA, a variety of endoribonucleases that recognize and cleave specific sequences of single-stranded RNA have been recently classified.

RNases play a critical role in many biological processes, including angiogenesis and self-incompatibility in flowering plants (angiosperms). Many stress-response toxins of prokaryotic toxin-antitoxin systems have been shown to have RNase activity and homology.

https://en.wikipedia.org/wiki/Ribonuclease

Ribonuclease P

Ribonuclease P (EC 3.1.26.5, RNase P) is a type of ribonuclease which cleaves RNA. RNase P is unique from other RNases in that it is a ribozyme – a ribonucleic acid that acts as a catalyst in the same way that a protein based enzyme would. Its function is to cleave off an extra, or precursor, sequence of RNA on tRNA molecules.

Ribonuclease P (RNase P) is a ubiquitous endoribonuclease, found in archaea, bacteria and eukarya as well as chloroplasts and mitochondria. Its best characterized activity is the generation of mature 5'-ends of tRNAs by cleaving the 5'-leader elements of precursor-tRNAs. Cellular RNase Ps are ribonucleoproteins (RNP). RNA from bacterial RNase Ps retains its catalytic activity in the absence of the protein subunit, i.e. it is a ribozyme. Isolated eukaryotic and archaeal RNase P RNA has not been shown to retain its catalytic function, but is still essential for the catalytic activity of the holoenzyme. Although the archaeal and eukaryotic holoenzymes have a much greater protein content than the bacterial ones, the RNA cores from all the three lineages are homologous—helices corresponding to P1, P2, P3, P4, and P10/11 are common to all cellular RNase P RNAs. Yet, there is considerable sequence variation, particularly among the eukaryotic RNAs.

https://en.wikipedia.org/wiki/Ribonuclease_P

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Ribonucleoside Diphosphates

Ribonucleoside diphosphates include ADP, GDP, CDP, and UDP. These m
made *de novo* from nucleoside monophosphates (AMP, GMP, CMP, and uD
tion of nucleoside monophosphate kinases. Each of the ribonucleoside dip
can be substrates of two important enzymes - ribonucleotide reductase (for
of deoxyribonucleotides) or NDPK (for synthesis of ribonucleoside triphosp

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Ribonucleoside Triphosphates

A nucleoside triphosphate (NTP) is a molecule containing a nucleoside bound to three phosphate groups. It is thus one type of nucleotide. Nucleotide derivatives are necessary for life, as they are the building blocks of nucleic acids and have thousands of other roles in cell metabolism and regulation. NTPs generally provide energy and phosphate groups for phosphorylation.

Natural nucleoside triphosphates include adenosine triphosphate (ATP), guanosine triphosphate (GTP), cytidine triphosphate (CTP), 5-methyluridine triphosphate (m5UTP), and uridine triphosphate (UTP). ATP is a major source of cellular energy. GTP is a very frequent cofactor of enzymes and proteins.

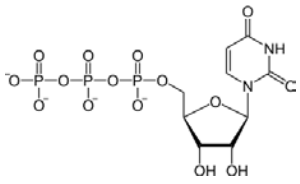
The terms ATP, GTP, CTP, and UTP refer to those nucleoside triphosphates that contain ribose. The nucleoside triphosphates containing deoxyribose are called dNTPs, and take the prefix deoxy- in their names and small d- in their abbreviations: deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dGTP), deoxycytidine triphosphate (dCTP), deoxythymidine triphosphate (dTTP) and deoxyuridine triphosphate (dUTP). The dNTPs are the building blocks for DNA (they lose two of the phosphate groups in the process of incorporation).

Apart from (d)ATP, (d)GTP, (d)CTP, (d)TTP and (d)UTP, there are other less abundant NTPs, such as intermediates of nucleotide metabolism, but also "rare" natural nucleotides or even artificial nucleotides. An example of rare NTPs are the tautomeric forms of some NTPs. They can cause mismatched base pairing during DNA replication. For example, a tautomeric form of cytosine is capable of forming 3 hydrogen bonds with adenine, and it will spontaneously tautomerize to its original cytosine form, causing a mismatch. By a similar token, the deamination of cytosine leads to uracil, whereas a deamination of a commonly encountered (in eukaryotes) 5-methylcytosine will lead to thymine. However, the 3' to 5' exonuclease activity of DNA polymerase III ensures that mismatched bases are excised during replication.

Generally nucleotides are nucleosides (a ribose/deoxyribose sugar covalently bonded to a nitrogenous base, such as adenine) that have 5' phosphate(s). However, for the sake of technical terminology, nucleotides are given classifications as nucleosides with a suffix describing the number of phosphates present in a specific unit. For example, if a nucleotide has one phosphate, it is a nucleoside monophosphate (NMP). If the nucleotide has two phosphates, then it is called a nucleoside diphosphate (NDP), and for three, it is a nucleoside triphosphate (NTP). The nucleotides that contain a ribose sugar are the monomers of RNA and those that contain a deoxyribose sugar compose DNA.

NTPs, NDPs and NMPs are ubiquitous in the cell cytoplasm, nucleus and organelles. Given their multifarious functions, their levels are under fairly tight metabolic control. Shifts in the ratio of available nucleotides can cause shifts in their incorporation, which, if not corrected, can lead to mutations. Most of the discussion on mutual ratios of nucleotides should belong under entry nucleotide, but concentrating strictly on the abundance of the triphosphorylated versions, we find that ATP spending is replenished by oxidative phosphorylation, while phosphorylation status of other nucleotides is regulated by NDP kinases (EC 2.7.4.6) and NMP kinases (EC 2.7.4.4) that use ATP pool as their cross-phosphorylation source.

Shown below - UTP



https://en.wikipedia.org/wiki/Nucleoside_triphosphate

Ribonucleotide Reductase

Ribonucleotide reductase (RNR), also known as ribonucleoside diphosphate reductase, is an enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides. Deoxyribonucleotides in turn are used in the synthesis of DNA. The reaction catalyzed by RNR is strictly conserved in all living organisms. Furthermore, RNR plays a critical role in regulating the total rate of DNA synthesis so that DNA to cell mass is maintained at a constant ratio during cell division and DNA repair.

A somewhat unusual feature of the RNR enzyme is that it catalyzes a reaction that proceeds via a free radical mechanism of action. The substrates for RNR are ADP, GDP, CDP and UDP. dTDP (deoxythymidine diphosphate) is synthesized by another enzyme (thymidylate kinase) from dTMP (deoxythymidine monophosphate).

The enzyme ribonucleotide reductase (RNR) catalyzes the *de novo* synthesis of dNDPs. Catalysis of ribonucleoside 5'-diphosphates (NDPs) involves a reduction at the 2'-carbon of ribose 5-phosphate to form the 2'-deoxy derivative-reduced 2'-deoxyribonucleoside 5'-diphosphates (dNDPs). This reduction is initiated with the generation of a free radical. Following a single reduction, RNR requires electrons donated from the dithiol groups of the protein thioredoxin. Regeneration of thioredoxin occurs when nicotinamide adenine dinucleotide phosphate (NADPH) provides two hydrogen atoms that are used to reduce the disulfide groups of thioredoxin.

Regulation of RNR is designed to maintain balanced quantities of dNTPs. Binding of effector molecules either increases or decreases RNR activity. When ATP binds to the allosteric activity site, it activates RNR. In contrast, when dATP binds to this site, it deactivates RNR. In addition to controlling activity, the allosteric mechanism also regulates the substrate specificity and ensures the enzyme produces an equal amount of each dNTP for DNA synthesis. In all classes, binding of ATP or dATP to the allosteric site induces reduction of cytidine 5'-diphosphate (CDP) and uridine 5'-diphosphate (UDP); 2'-deoxyguanosine 5'-triphosphate (dGTP) induces reduction of adenosine 5'-diphosphate (ADP); and 2'-deoxythymidine 5'-triphosphate (dTTP) induces reduction of guanosine 5'-diphosphate (GDP).

https://en.wikipedia.org/wiki/Ribonucleotide_reductase

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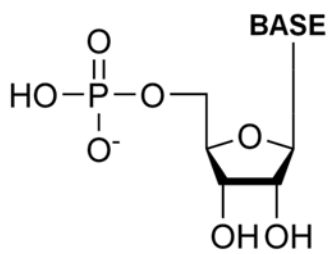
Ribonucleotides

In biochemistry, a ribonucleotide or ribotide is a nucleotide containing ribose as its pentose component. It is a molecular precursor of nucleic acids. Nucleotides are the basic building blocks of DNA and RNA. The monomer itself from ribonucleotides forms the basic building blocks for RNA. However, the reduction of ribonucleotides, by enzyme ribonucleotide reductase (RNR), forms deoxyribonucleotides, which are the essential building block for DNA. Successive nucleotides are linked together via phosphodiester bonds by 3'-5'.

Ribonucleotides are also utilized in other cellular functions. These special monomers are utilized in both cell regulation and cell signaling as seen in adenosine-monophosphate (AMP). Furthermore, ribonucleotides can be converted to adenosine triphosphate (ATP), the energy currency in organisms. Ribonucleotides can be converted to cyclic adenosine monophosphate (cyclic AMP) to regulate hormones in organisms as well. In living organisms, the most common bases for ribonucleotides are adenine (A), guanine (G), cytosine (C), or uracil (U). The nitrogenous bases are classified into two parent compounds, purine and pyrimidine.



https://en.wikipedia.org/wiki/Ribonucleotide

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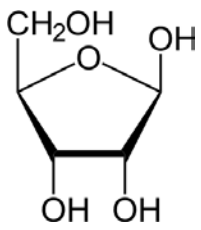
Ribose

Ribose is a carbohydrate with the formula C5H10O5; specifically, it is a pentose monosaccharide (simple sugar) with linear form H−(C=O)−(CHOH)4−H, which has all the hydroxyl groups on the same side in the Fischer projection.
The term may refer to either of two enantiomers. The term usually indicates D-ribose, which occurs widely in nature and is discussed here. Its synthetic mirror image, L-ribose, is not found in nature.

The ribose β-D-ribofuranose (shown below) forms part of the backbone of RNA. It is related to deoxyribose, which is found in DNA. Phosphorylated derivatives of ribose such as ATP and NADH play central roles in metabolism. cAMP and cGMP, formed from ATP and GTP, serve as secondary messengers in some signalling pathways.

Ribose is an aldopentose (a monosaccharide containing five carbon atoms) that, in its open chain form, has an aldehyde functional group at one end. In the conventional numbering scheme for monosaccharides, the carbon atoms are numbered from C_1' (in the aldehyde group) to C_5'. The deoxyribose derivative found in DNA differs from ribose by having a hydrogen atom in place of the hydroxyl group at C_2'. This hydroxyl group performs a function in RNA splicing.



https://en.wikipedia.org/wiki/Ribose

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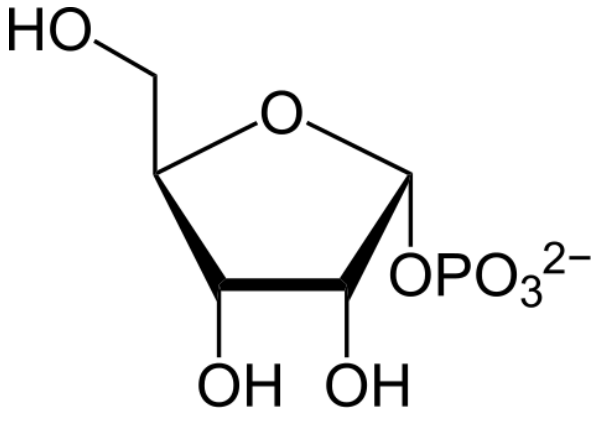
Ribose-1-phosphate

Ribose-1-phosphate is a product of action of the enzyme pyrimidine-nucleo
phorylase, which catalyzes the following pyrimidine salvage reaction:

Pyrimidine Nucleoside + P_i <=> Pyrimidine base + α-D-ribose 1-phosphate



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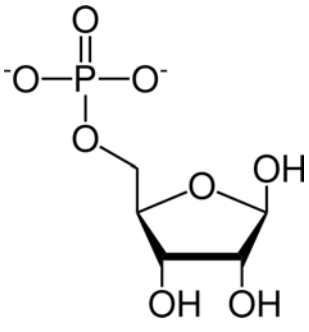
Ribose-5-phosphate

Ribose 5-phosphate is both a product and an intermediate of the pentose phosphate pathway. The last step of the oxidative reactions in the pentose phosphate pathway is the production of ribulose 5-phosphate. Depending on the body's state, ribulose 5-phosphate can reversibly isomerize to ribose 5-phosphate. Ribulose 5-phosphate can alternatively undergo a series of isomerizations as well as transaldolations and transketolations that result in the production of other pentose phosphates as well as fructose 6-phosphate and glyceraldehyde 3-phosphate (both intermediates in glycolysis).

Ribose-5-phosphate can also be used to make nucleotides. The first step in the process is formation of phosphoribosyl pyrophosphate, catalyzed by ribose-phosphate diphosphokinase.



https://en.wikipedia.org/wiki/Ribose_5-phosphate

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Ribose-5-phosphate Isomerase

Ribose-5-phosphate isomerase (Rpi) is an enzyme that catalyzes the conver
tween ribose-5-phosphate (R5P) and ribulose-5-phosphate (Ru5P). It is a m
larger class of isomerases which catalyze the interconversion of chemical is
this case structural isomers of pentose). It plays a vital role in biochemical r
in both the pentose phosphate pathway and the Calvin cycle.

The protein encoded by RPIA gene (Rpi) is an enzyme, which catalyzes the
conversion between ribose-5-phosphate and ribulose-5-phosphate in the pe
phosphate pathway and the Calvin cycle. This gene is highly conserved in m
isms. The enzyme plays an essential role in the carbohydrate metabolism.

https://en.wikipedia.org/wiki/Ribose-5-phosphate_isomerase

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Ribose-phosphate Diphosphokinase

Ribose-phosphate diphosphokinase (or phosphoribosyl pyrophosphate synthetase or ribose-phosphate pyrophosphokinase) is an enzyme that converts ribose 5-phosphate into phosphoribosyl pyrophosphate (PRPP).

Ribose-5-P + ATP <=> AMP + PRPP

The enzyme is involved in the synthesis of nucleotides (purines and pyrimidines), cofactors NAD^+ and $NADP^+$, and amino acids histidine and tryptophan, linking these biosynthetic processes to the pentose phosphate pathway, from which the substrate ribose 5-phosphate is derived.

The product of this reaction, phosphoribosyl pyrophosphate (PRPP), is used in numerous biosynthesis (*de novo* and salvage) pathways. PRPP provides the ribose sugar in *de novo* synthesis of purines and pyrimidines, used in the nucleotide bases that form RNA and DNA. PRPP reacts with orotate to form orotidylate, which can be converted to uridylate (UMP). UMP can then be converted to the nucleotide cytidine triphosphate (CTP).

The reaction of PRPP, glutamine, and ammonia forms 5-phosphoribosyl-1-amine, a precursor to inosinate (IMP), which can ultimately be converted to adenosine triphosphate (ATP) or guanosine triphosphate (GTP). PRPP plays a role in purine salvage pathways by reacting with free purine bases to form adenylate, guanylate, and inosinate. PRPP is also used in the synthesis of NAD. The reaction of PRPP with nicotinic acid yields the intermediate nicotinic acid mononucleotide.

https://en.wikipedia.org/wiki/Ribose-phosphate_diphosphokinase

Ribosomal RNAs

In molecular biology, ribosomal ribonucleic acid (rRNA) is the RNA component of the ribosome, and is essential for protein synthesis in all living organisms. It constitutes the predominant material within the ribosome, which is approximately 60% rRNA and 40% protein by weight. Ribosomes contain two major rRNAs and 50 or more proteins. The ribosomal RNAs form two subunits, the large subunit (LSU) and small subunit (SSU). The LSU rRNA acts as a ribozyme, catalyzing peptide bond formation.

Ribosomal RNA characteristics are important in evolution, thus taxonomy, and medicine.

- rRNA is one of only a few gene products present in all cells. For this reason, genes that encode the rRNA (rDNA) are sequenced to identify an organism's taxonomic group, calculate related groups, and estimate rates of species divergence. As a result, many thousands of rRNA sequences are known and stored in specialized databases such as RDP-II and SILVA.
- rRNA is the target of numerous clinically relevant antibiotics: chloramphenicol, erythromycin, kasugamycin, micrococcin, paromomycin, ricin, sarcin, spectinomycin, streptomycin, and thiostrepton.
- rRNA have been shown to be the origin of species-specific microRNAs, like miR-663 in humans and miR-712 in mouse. These miRNAs originate from the Internal Transcribed Spacers of the rRNA.

In prokaryotes a small 30S ribosomal subunit contains the 16S ribosomal RNA. The large 50S ribosomal subunit contains two rRNA species (the 5S and 23S ribosomal RNAs). Bacterial 16S ribosomal RNA, 23S ribosomal RNA, and 5S rRNA genes are typically organized as a co-transcribed operon. The 3' end of the 16S ribosomal RNA (in a ribosome) binds to a sequence on the 5' end of mRNA called the Shine-Dalgarno sequence.

Mammalian cells have 2 mitochondrial (12S and 16S) rRNA molecules and 4 types of cytoplasmic rRNA (the 28S, 5.8S, 18S, and 5S subunits). The 18S rRNA in most eukaryotes is in the small ribosomal subunit, and the large subunit contains three rRNA species (the 5S, 5.8S and 28S in mammals, 25S in plants, rRNAs).

https://en.wikipedia.org/wiki/Ribosomal_RNA

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Ribosome

The ribosome is a complex molecular machine found within all living cells, that serves as the site of biological protein synthesis (translation). Ribosomes link amino acids together in the order specified by messenger RNA (mRNA) molecules. Ribosomes consist of two major components: the small ribosomal subunit, which reads the RNA, and the large subunit, which joins amino acids to form a polypeptide chain. Each subunit is composed of one or more ribosomal RNA (rRNA) molecule and a variety of proteins. The ribosomes and associated molecules are also known as the translational apparatus.

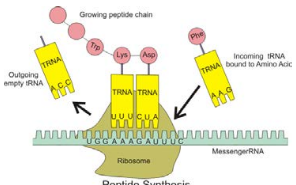
The sequence of DNA, which encodes the sequence of the amino acids in a protein, is copied into a messenger RNA chain. It may be copied many times into RNA chains. Ribosomes can bind to a messenger RNA chain and use its sequence for determining the correct sequence of amino acids. Amino acids are selected, collected, and carried to the ribosome by transfer RNA (tRNA) molecules, which enter one part of the ribosome and bind to the messenger RNA chain. It is during this binding that the correct translation of nucleic acid sequence to amino acid sequence occurs. For each coding triplet in the messenger RNA there is a distinct transfer RNA that matches and which carries the correct amino acid for that coding triplet. The attached amino acids are then linked together by another part of the ribosome. Once the protein is produced, it can then fold to produce a specific functional three-dimensional structure although during synthesis some proteins start folding into their correct form.

A ribosome is made from complexes of RNAs and proteins and is therefore a ribonucleoprotein. Each ribosome is divided into two subunits: 1. a smaller subunit which binds to a larger subunit and the mRNA pattern, and 2. a larger subunit which binds to the tRNA, the amino acids, and the smaller subunit. When a ribosome finishes reading an mRNA molecule, these two subunits split apart. Ribosomes are ribozymes, because the catalytic peptidyl transferase activity that links amino acids together is performed by the ribosomal RNA. Ribosomes are often embedded in the intracellular membranes that make up the rough endoplasmic reticulum.

Ribosomes from bacteria, archaea and eukaryotes (the three domains of life on Earth) resemble each other to a remarkable degree, evidence of a common origin. They differ in their size, sequence, structure, and the ratio of protein to RNA. The differences in structure allow some antibiotics to kill bacteria by inhibiting their ribosomes, while leaving human ribosomes unaffected. In bacteria and archaea, more than one ribosome may move along a single mRNA chain at one time, each "reading" its sequence and producing a corresponding protein molecule.

Prokaryotes have 70S ribosomes, each consisting of a small (30S) and a large (50S) subunit. Their small subunit has a 16S RNA subunit (consisting of 1540 nucleotides) bound to 21 proteins. The large subunit is composed of a 5S RNA subunit (120 nucleotides), a 23S RNA subunit (2900 nucleotides) and 31 proteins.

Eukaryotes have 80S ribosomes, each consisting of a small (40S) and large (60S) subunit. Their 40S subunit has an 18S RNA (1900 nucleotides) and 33 proteins. The large subunit is composed of a 5S RNA (120 nucleotides), 28S RNA (4700 nucleotides), a 5.8S RNA (160 nucleotides) subunits and 46 proteins.



Peptide Synthesis

https://en.wikipedia.org/wiki/Ribosome

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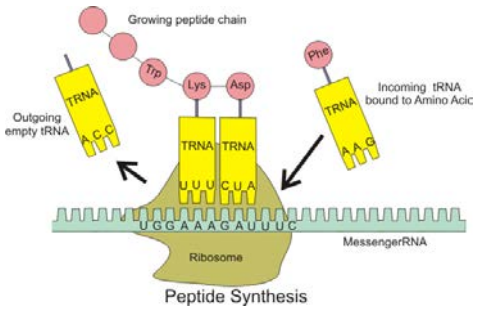

https://en.wikipedia.org/wiki/Ribosome

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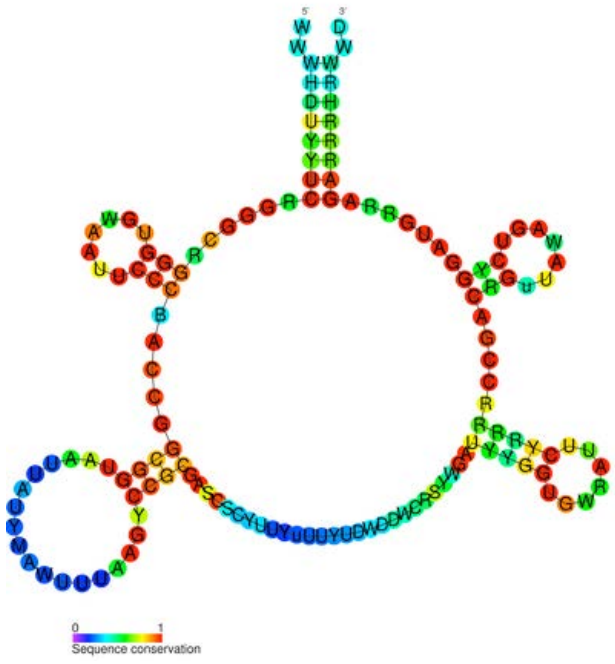
Riboswitch

In molecular biology, a riboswitch is a regulatory segment of a messenger RNA molecule that binds a small molecule, resulting in a change in production of the proteins encoded by the mRNA. Thus, a mRNA that contains a riboswitch is directly involved in regulating its own activity, in response to the concentrations of its effector molecule. The discovery that modern organisms use RNA to bind small molecules, and discriminate against closely related analogs, expanded the known natural capabilities of RNA beyond its ability to code for proteins, catalyze reactions, or to bind other RNA or protein macromolecules.

The original definition of the term "riboswitch" specified that they directly sense small-molecule metabolite concentrations. Although this definition remains in common use, some biologists have used a broader definition that includes other cis-regulatory RNAs. However, this article will discuss only metabolite-binding riboswitches.

Most known riboswitches occur in bacteria, but functional riboswitches of one type (the TPP riboswitch) have been discovered in plants and certain fungi. TPP riboswitches have also been predicted in archaea, but have not been experimentally tested.

Below - an FMN riboswitch



https://en.wikipedia.org/wiki/Riboswitch

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Ribosylpyrimidine Nucleosidase

Ribosylpyrimidine nucleosidase is an enzyme that catalyzes the chemical re
low involved in salvage synthesis of pyrimidine nucleotides:

Pyrimidine Nucleoside + H_2O $\rightleftharpoons$D-ribose + Pyrimidine Base

This enzyme belongs to the family of hydrolases, specifically those glycosyla
drolyse N-glycosyl compounds. The systematic name of this enzyme class is
pyrimidine-nucleoside ribohydrolase. Other names in common use include
ribosylpyrimidine nucleosidase, pyrimidine nucleosidase, N-ribosylpyrimic
drolase, pyrimidine nucleoside hydrolase, RihB, YeiK, and nucleoside riboh
This enzyme participates in purine metabolism and pyrimidine metabolism

https://en.wikipedia.org/wiki/Ribosylpyrimidine_nucleosidase

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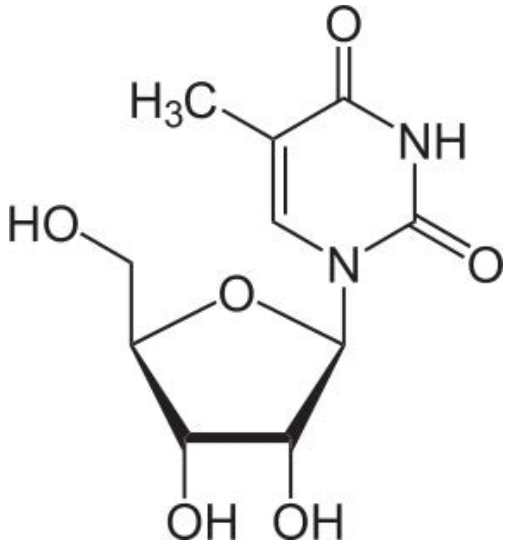
Ribothymidine

The chemical compound 5-methyluridine, also called ribothymidine, is a pyrir
nucleoside. It is the ribonucleoside counterpart to the deoxyribonucleoside thy
which lacks a hydroxyl group at the 2' position. 5-Methyluridine contains a thy
base joined to a ribose pentose sugar.



https://en.wikipedia.org/wiki/5-Methyluridine

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Ribozymes

Ribozymes (ribonucleic acid enzymes) are RNA molecules that are capable of catalyzing specific biochemical reactions, similar to the action of protein enzymes. The most common activities of natural or in vitro-evolved ribozymes are the cleavage or ligation of RNA and DNA and peptide bond formation.

Within the ribosome, ribozymes function as part of the large subunit ribosomal RNA to link amino acids during protein synthesis. They also participate in a variety of RNA processing reactions, including RNA splicing, viral replication, and transfer RNA biosynthesis. Examples of ribozymes include the hammerhead ribozyme, the VS ribozyme, Leadzyme and the hairpin ribozyme.

Although most ribozymes are quite rare in the cell, their roles are sometimes essential to life. For example, the functional part of the ribosome, the molecular machine that translates RNA into proteins, is fundamentally a ribozyme, composed of RNA tertiary structural motifs that are often coordinated to metal ions such as Mg^{++} as cofactors. In a model system, there is no requirement for divalent cations in a five-nucleotide RNA catalyzing *trans*-phenylalanation of a four-nucleotide substrate with 3 base pairs complementary with the catalyst, where the catalyst/substrate were devised by truncation of the C3 ribozyme. RNA may catalyze folding of the pathological protein conformation of a prion in a manner similar to that of a chaperonin, and may be involved in the viral concatemer cleavage that precedes the packing of viral genetic material into some virons.

RNA can also act as a hereditary molecule, which encouraged Walter Gilbert to propose that in the distant past, the cell used RNA as both the genetic material and the structural and catalytic molecule rather than dividing these functions between DNA and protein as they are today; this hypothesis is known as the "RNA world hypothesis" of the origin of life. Evidence that ribozymes were the first molecular machines used by early life suggests that they are in effect "molecular fossils".

https://en.wikipedia.org/wiki/Ribozyme

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Ribulose 1,5-bisphosphate

Ribulose-1,5-bisphosphate (RuBP) is an organic substance that is involved in photosynthesis. The enzyme ribulose bisphosphate carboxylase oxygenase (RuBisCO) catalyzes the reaction between RuBP and carbon dioxide. The product is the highly unstable 6-carbon intermediate known as 3-keto-2-carboxyarabinitol 1,5-bisphosphate. This six-carbon intermediate decays virtually instantaneously into two molecules of 3-phosphoglycerate (3-PG). RuBisCO also catalyzes RuBP with oxygen (O_2) in a process called photorespiration, a process that is more prevalent at high temperatures. During photorespiration RuBP combines with O_2 to become 3-PG + phosphoglycolic acid. In the Calvin Cycle, RuBP is a product of the phosphorylation of ribulose-5-phosphate by ATP.

https://en.wikipedia.org/wiki/Ribulose-1,5-bisphosphate

Related Glossary Terms

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Ribulose 5-phosphate Epimerase

L-ribulose-5-phosphate epimerase is an enzyme that catalyzes the intercon
ribulose 5-phosphate and xylulose 5-phosphate in the oxidative phase of th
phosphate pathway.

L-ribulose 5-phosphate ⇌ D-xylulose 5-phosphate

This enzyme participates in pentose and glucuronate interconversions and
and aldarate metabolism. It belongs to the family of isomerases, specificall
mases and epimerases acting on carbohydrates and derivatives. The system
of this enzyme class is L-ribulose-5-phosphate 4-epimerase. Other names i
use include phosphoribulose isomerase, ribulose phosphate 4-epimerase, L
phosphate 4-epimerase, L-ribulose 5-phosphate 4-epimerase, AraD, and L-

https://en.wikipedia.org/wiki/L-ribulose-5-phosphate_4-epimerase

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Ribulose 5-phosphate Kinase

Ribose 5-bisphosphate phosphokinase is an enzyme that catalyzes the chem
tion:

ATP + D-ribulose 5-phosphate ADP + D-ribulose 1,5-bisphosphate

This enzyme catalyzes the re-synthesis of ribulose 1,5-bisphosphate necessa
carboxylation reaction catalyzed by RUBISCO. It is also known as phospho
lokinase.

https://en.wikipedia.org/wiki/Phosphoribulokinase

Related Glossary Terms

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Ribulose-1,5-bisphosphate Carboxylase

Ribulose-1,5-bisphosphate carboxylase/oxygenase, commonly known by the abbreviation RuBisCO, is an enzyme involved in the first major step of carbon fixation, a process by which atmospheric carbon dioxide is converted by plants and other photosynthetic organisms to energy-rich molecules such as glucose. In chemical terms, it catalyzes the carboxylation of ribulose-1,5-bisphosphate (also known as RuBP). It is probably the most abundant enzyme on Earth.

Ribulose-1,5-bisphosphate + CO_2 + H_2O <=> 2 3-PG

RuBisCO is important biologically because it catalyzes the primary chemical reaction by which inorganic carbon enters the biosphere. While many autotrophic bacteria and archaea fix carbon via the reductive acetyl CoA pathway, the 3-hydroxypropionate cycle, or the reverse citric acid cycle, these pathways are relatively smaller contributors to global carbon fixation than that catalyzed by RuBisCO. Phosphoenolpyruvate carboxylase, unlike RuBisCO, only temporarily fixes carbon. Reflecting its importance, RuBisCO is the most abundant protein in leaves, accounting for 50% of soluble leaf protein in C3 plants (20–30% of total leaf nitrogen) and 30% of soluble leaf protein in C4 plants (5–9% of total leaf nitrogen).

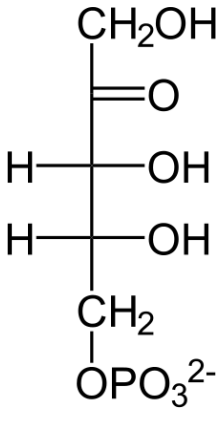
When carbon dioxide is the substrate, the product of the carboxylase reaction is a highly unstable six-carbon phosphorylated intermediate known as 3-keto-2-carboxyarabinitol-1,5-bisphosphate, which decays virtually instantaneously into two molecules of glycerate-3-phosphate. The extremely unstable molecule created by the initial carboxylation was unknown until 1988, when it was isolated. The 3-phosphoglycerate can be used to produce larger molecules such as glucose. Also, Rubisco side activities can lead to useless or inhibitory by-products. One such product is xylulose-1,5-bisphosphate, which inhibits Rubisco activity. When molecular oxygen is the substrate, the products of the oxygenase reaction are phosphoglycolate and 3-phosphoglycerate. Phosphoglycolate is recycled through a sequence of reactions called photorespiration, which involves enzymes and cytochromes located in the mitochondria and peroxisomes (this is a case of metabolite repair). In this process, two molecules of phosphoglycolate are converted to one molecule of carbon dioxide and one molecule of 3-phosphoglycerate, which can reenter the Calvin cycle.

Some of the phosphoglycolate entering this pathway can be retained by plants to produce other molecules such as glycine. At ambient levels of carbon dioxide and oxygen, the ratio of the reactions is about 4 to 1, which results in a net carbon dioxide fixation of only 3.5. Thus, the inability of the enzyme to prevent the reaction with oxygen greatly reduces the photosynthetic capacity of many plants. Some plants, many algae, and photosynthetic bacteria have overcome this limitation by devising means to increase the concentration of carbon dioxide around the enzyme, including C_4 carbon fixation, crassulacean acid metabolism, and the use of pyrenoid.

https://en.wikipedia.org/wiki/RuBisCO

Ribulose-5-phosphate

Ribulose 5-phosphate is one of the end-products of the pentose phosphate pathway. It is also an intermediate in the Calvin cycle. The molecule is formed by phosphogluconate dehydrogenase, and it can be acted upon by phosphopentose isomerase and phosphopentose epimerase. It is a metabolic precursor of ribulose-1,5-bisphosphate.



https://en.wikipedia.org/wiki/Ribulose_5-phosphate

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Right Handed

When describing a helix, if when looking down the line of sight along the he
clockwise screwing motion moves the helix away from the observer, then it
right-handed helix. Otherwise, it is a left-handed helix.

https://en.wikipedia.org/wiki/Helix

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Right-handed

When describing a helix, if when looking down the line of sight along the he
clockwise screwing motion moves the helix away from the observer, then it
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https://en.wikipedia.org/wiki/Helix

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RISC

The RNA-induced silencing complex, or RISC, is a multiprotein complex, specifically a ribonucleoprotein, which incorporates one strand of a single-stranded RNA (ssRNA) fragment, such as microRNA (miRNA), or double stranded small interfering RNA (siRNA). The single strand acts as a template for RISC to recognize complementary messenger RNA (mRNA) transcript. Once found, one of the proteins in RISC, called Argonaute, activates and cleaves the mRNA. This process is called RNA interference (RNAi) and it is found in many eukaryotes. It is a key process in gene silencing and defense against viral infections.

The RNase III Dicer aids RISC in RNA interference by cleaving dsRNA into 21-23 nucleotide long fragments with a two-nucleotide 3' overhang. These dsRNA fragments are loaded into RISC and each strand has a different fate based on the asymmetry rule phenomenon.

• The strand with the less stable 5' end is selected by the RNase Argonaute and integrated into RISC. This strand is known as the guide strand.
The other strand, known as the passenger strand, is degraded by RISC

RISC uses the bound guide strand to target complementary 3'-untranslated regions (3'UTR) of mRNA transcripts via Watson-Crick base pairing. RISC can now regulate gene expression of the mRNA transcript in a number of ways.

The most understood function of RISC is degrading target mRNA which reduces the levels of transcript available to be translated by ribosomes. There are two main requirements for mRNA degradation to take place:
• a near-perfect complementary match between the guide strand and target mRNA sequence, and,
• a catalytically active Argonaute protein, called a 'slicer', to cleave the target mRNA.

mRNA degradation is localized in cytoplasmic bodies called P-bodies.

https://en.wikipedia.org/wiki/RNA-induced_silencing_complex

Rise

Rise is a term used to define a helix. It corresponds to the distance betwee
steps or elements of a helix.

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RNA

Ribonucleic acid (RNA) is a polymeric molecule implicated in various biological roles in coding, decoding, regulation, and expression of genes. RNA and DNA are nucleic acids, and, along with proteins and carbohydrates, constitute the three major macromolecules essential for all known forms of life. Like DNA, RNA is assembled as a chain of nucleotides, but unlike DNA it is more often found in nature as a single-strand folded onto itself, rather than a paired double-strand. Cellular organisms use messenger RNA (mRNA) to convey genetic information (using the letters G, U, A, and C to denote the nitrogenous bases guanine, uracil, adenine, and cytosine) that directs synthesis of specific proteins. Many viruses encode their genetic information using an RNA genome.

Some RNA molecules play an active role within cells by catalyzing biological reactions, controlling gene expression, or sensing and communicating responses to cellular signals. One of these active processes is protein synthesis, a universal function wherein mRNA molecules direct the assembly of proteins on ribosomes. This process uses transfer RNA (tRNA) molecules to deliver amino acids to the ribosome, where ribosomal RNA (rRNA) then links amino acids together to form proteins.

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Synthesis of RNA is usually catalyzed by an enzyme—RNA polymerase—using DNA as a template, a process known as transcription. Initiation of transcription begins with the binding of the enzyme to a promoter sequence in the DNA (usually found "upstream" of a gene). The DNA double helix is unwound by the helicase activity of the enzyme. The enzyme then progresses reading the template strand in the 3' to 5' direction, synthesizing a complementary RNA in the 5' to 3' direction. The DNA sequence also dictates where termination of RNA synthesis will occur.

Messenger RNA (mRNA) carries information about a protein sequence to the ribosomes, the protein synthesis factories in the cell. It is coded so that every three nucleotides (a codon) correspond to one amino acid. In eukaryotic cells, once precursor mRNA (pre-mRNA) has been transcribed from DNA, it is processed to mature mRNA. This removes its introns—non-coding sections of the pre-mRNA. The mRNA is then exported from the nucleus to the cytoplasm, where it is bound to ribosomes and translated into its corresponding protein form with the help of tRNA. In prokaryotic cells, which do not have nucleus and cytoplasm compartments, mRNA can bind to ribosomes while it is being transcribed from DNA. After a certain amount of time the message degrades into its component nucleotides with the assistance of ribonucleases.

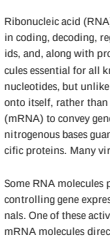
Transfer RNA (tRNA) is a small RNA chain of about 80 nucleotides that transfers a specific amino acid to a growing polypeptide chain at the ribosomal site of protein synthesis during translation. It has sites for amino acid attachment and an anticodon region for codon recognition that binds to a specific sequence on the messenger RNA chain through hydrogen bonding.

Ribosomal RNA (rRNA) is the catalytic component of the ribosomes. Eukaryotic ribosomes contain four different rRNA molecules: 18S, 5.8S, 28S and 5S rRNA. Three of the rRNA molecules are synthesized in the nucleolus, and one is synthesized elsewhere. In the cytoplasm, ribosomal RNA and protein combine to form a nucleoprotein called a ribosome. The ribosome binds mRNA and carries out protein synthesis. Several ribosomes may be attached to a single mRNA at any time. Nearly all the RNA found in a typical eukaryotic cell is rRNA.

Several types of RNA can down-regulate gene expression by being complementary to a part of an mRNA or a gene's DNA. MicroRNAs (miRNA; 21-22 nt) are found in eukaryotes and act through RNA interference (RNAi), where an effector complex of miRNA and enzymes can cleave complementary mRNA, block the mRNA from being translated, or accelerate its degradation.

While small interfering RNAs (siRNA; 20-25 nt) are often produced by breakdown of viral RNA, there are also endogenous sources of siRNAs. siRNAs act through RNA interference in a fashion similar to miRNAs. Some miRNAs and siRNAs can cause genes they target to be methylated, thereby decreasing or increasing transcription of those genes. Animals have Piwi-interacting RNAs (piRNA; 29-30 nt) that are active in germline cells and are thought to be a defense against transposons and play a role in gametogenesis.

Many RNAs are involved in modifying other RNAs. Introns are spliced out of pre-mRNA by spliceosomes, which contain several small nuclear RNAs (snRNA), or the introns can be ribozymes that are spliced by themselves. RNA can also be altered by having its nucleotides modified to other nucleotides than A, C, G and U. In eukaryotes, modifications of RNA nucleotides are in general directed by small nucleolar RNAs (snoRNA; 60-300 nt), found in the nucleolus and cajal bodies. snoRNAs associate with enzymes and guide them to a spot on an RNA by basepairing to that RNA. These enzymes then perform the nucleotide modification. rRNAs and tRNAs are extensively modified, but snRNAs and mRNAs can also be the target of base modification. RNA can also be methylated.



RNA Molecule

https://en.wikipedia.org/wiki/RNA

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RNA Editing

RNA editing is a molecular process through which some cells can make discrete changes to specific nucleotide sequences within a RNA molecule after it has been generated by RNA polymerase. RNA editing is relatively rare, and common forms of RNA processing (e.g. splicing, 5'-capping and 3'-polyadenylation) are not usually included as editing. Editing events may include the insertion, deletion, and base substitution of nucleotides within the edited RNA molecule.
RNA editing has been observed in some tRNA, rRNA, mRNA or miRNA molecules of eukaryotes and their viruses, archaea and prokaryotes. RNA editing occurs in the cell nucleus and cytosol, as well as within mitochondria and plastids. In vertebrates, editing is rare and usually consists of a small number of changes to the sequence of affected molecules. In other organisms, extensive editing (pan-editing) can occur. In some cases the majority of nucleotides in a mRNA sequence may result from editing.

RNA-editing processes show great molecular diversity, and some appear to be evolutionarily recent acquisitions that arose independently. The diversity of RNA editing phenomena includes nucleobase modifications such as cytidine (C) to uridine (U) and adenosine (A) to inosine (I) deaminations, as well as non-templated nucleotide additions and insertions. RNA editing in mRNAs effectively alters the amino acid sequence of the encoded protein so that it differs from that predicted by the genomic DNA sequence.

https://en.wikipedia.org/wiki/RNA_editing

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RNA Polymerase

RNA polymerase (RNAP or RNApol) (Ribonucleic acid), also known as DNA-dependent RNA polymerase, is an enzyme that produces primary transcript RNA. In cells, RNAP is necessary for constructing RNA chains using DNA genes as templates, a process called transcription. RNA polymerase enzymes are essential to life and are found in all organisms and many viruses. In chemical terms, RNAP is a nucleotidyl transferase that polymerizes ribonucleotides at the 3' end of an RNA transcript.

RNAP can initiate transcription at specific DNA sequences known as promoters. It then produces an RNA chain, which is complementary to the template DNA strand. The process of adding nucleotides to the RNA strand is known as elongation. In eukaryotes, RNAP can build chains as long as 2.4 million nucleotides (the full length of the dystrophin gene). RNAP will preferentially release its RNA transcript at specific DNA sequences encoded at the end of genes, which are known as terminators.

Products of RNAP include:
- Messenger RNA (mRNA)—template for the synthesis of proteins by ribosomes.
- Non-coding RNA or "RNA genes"—a broad class of genes that encode RNA that is not translated into protein. The most prominent examples of RNA genes are transfer RNA (tRNA) and ribosomal RNA (rRNA), both of which are involved in the process of translation. However, since the late 1990s, many new RNA genes have been found, and thus RNA genes may play a much more significant role than previously thought.
- Transfer RNA (tRNA)—transfers specific amino acids to growing polypeptide chains at the ribosomal site of protein synthesis during translation
- Ribosomal RNA (rRNA)—a component of ribosomes
- Micro RNA—regulates gene activity
- Catalytic RNA (Ribozyme)—enzymatically active RNA molecules

RNAP accomplishes de novo synthesis. It is able to do this because specific interactions with the initiating nucleotide hold RNAP rigidly in place, facilitating chemical attack on the incoming nucleotide. Such specific interactions explain why RNAP prefers to start transcripts with ATP (followed by GTP, UTP, and then CTP). In contrast to DNA polymerase, RNAP includes helicase activity, therefore no separate enzyme is needed to unwind DNA.

https://en.wikipedia.org/wiki/RNA_polymerase

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RNA Polymerase I

RNA polymerase 1 (also known as Pol I) is, in higher eukaryotes, the polymerase that only transcribes ribosomal RNA (but not 5S rRNA, which is synthesized by RNA polymerase III), a type of RNA that accounts for over 50% of the total RNA synthesized in a cell.

Pol I is a 590 kDa enzyme that consists of 14 protein subunits (polypeptides), and its crystal structure in the yeast *Saccharomyces cerevisiae* was solved at 2.8Å resolution in 2013. Twelve of its subunits have identical or related counterparts in RNA polymerase II (Pol II) and RNA polymerase III (Pol III). The other two subunits are related to Pol II initiation factors and have structural homologues in Pol III.

Ribosomal DNA transcription is confined to the nucleolus, where about 400 copies of the 32-kb rDNA gene are present, arranged as tandem repeats in nucleolus organizer regions. Each copy contains a ~13.3 kb sequence encoding the 18S, the 5.8S, and the 28S RNA molecules, interlaced with two internal transcribed spacers, ITS1 and ITS2, and flanked upstream by a 5' external transcribed spacer and a downstream 3' external transcribed spacer. These components are transcribed together to form the 45S pre-rRNA. The 45S pre-rRNA is then post-transcriptionally cleaved by C/D box and H/ACA box snoRNAs, removing the two spacers and resulting in the three rRNAs by a complex series of steps. The 5S ribosomal RNA is transcribed by Pol III. Because of the simplicity of Pol I transcription, it is the fastest-acting polymerase and contributes up to 60% of cellular transcription levels in exponentially growing cells.

https://en.wikipedia.org/wiki/RNA_polymerase_I

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RNA polymerase II

RNA polymerase II (RNAP II and Pol II) is an enzyme found in eukaryotic cells. It catalyzes the transcription of DNA to synthesize precursors of mRNA and most snRNA and microRNA. A 550 kDa complex of 12 subunits, RNAP II is the most studied type of RNA polymerase. A wide range of transcription factors are required for it to bind to upstream gene promoters and begin transcription.

The eukaryotic core RNA polymerase II was first purified using transcription assays. The purified enzyme has typically 10-12 subunits (12 in humans and yeast) and is incapable of specific promoter recognition. Many subunit-subunit interactions are known.

- DNA-directed RNA polymerase II subunit RPB1 - an enzyme that in humans is encoded by the POLR2A gene and in yeast is encoded by RPO21. RPB1 is the largest subunit of RNA polymerase II. It contains a carboxy terminal domain (CTD) composed of up to 52 heptapeptide repeats (YSPTSPS) that are essential for polymerase activity. The CTD was first discovered in the laboratory of C.J. Ingles at the University of Toronto and by JL Corden at Johns Hopkins University. In combination with several other polymerase subunits, the RPB1 subunit forms the DNA binding domain of the polymerase, a groove in which the DNA template is transcribed into RNA. It strongly interacts with RPB8.
- RPB2 (POLR2B) - the second-largest subunit that in combination with at least two other polymerase subunits forms a structure within the polymerase that maintains contact in the active site of the enzyme between the DNA template and the newly synthesized RNA.
- RPB3 (POLR2C) - the third-largest subunit. Exists as a heterodimer with another polymerase subunit, POLR2J forming a core subassembly. RPB3 strongly interacts with RPB1-5, 7, 10-12.
- RNA polymerase II subunit B4 (RPB4) - encoded by the POLR2D gene is the fourth-largest subunit and may have a stress protective role.
- RPB5 - In humans is encoded by the POLR2E gene. Two molecules of this subunit are present in each RNA polymerase II. RPB5 strongly interacts with RPB1, RPB3, and RPB6.
- RPB6 (POLR2F) - forms a structure with at least two other subunits that stabilizes the transcribing polymerase on the DNA template.
- RPB7 - encoded by POLR2G and may play a role in regulating polymerase function. RPB7 interacts strongly with RPB1 and RPB5.
- RPB8 (POLR2H) - interacts with subunits RPB1-3, 5, and 7.
- RPB9 - The groove in which the DNA template is transcribed into RNA is composed of RPB9 (POLR2I) and RPB1.
- RPB10 - the product of gene POLR2L. It interacts with RPB1-3 and 5, and strongly with RPB3.
- RPB11 - the RPB11 subunit is itself composed of three subunits in humans: POLR2J (RPB11-a), POLR2J2 (RPB11-b), and POLR2J3 (RPB11-c).
- RPB12 - Also interacting with RPB3 is RPB12 (POLR2K)

https://en.wikipedia.org/wiki/RNA_polymerase_II

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RNA Polymerase III

In eukaryote cells, RNA polymerase III (also called Pol III) transcribes DNA to synthesize ribosomal 5S rRNA, tRNA and other small RNAs. This enzyme complex has a more limited role than the Pol III in prokaryote cells.

The genes transcribed by RNA Pol III fall in the category of "housekeeping" genes whose expression is required in all cell types and most environmental conditions. Therefore, the regulation of Pol III transcription is primarily tied to the regulation of cell growth and the cell cycle, thus requiring fewer regulatory proteins than RNA polymerase II. Under stress conditions however, the protein Maf1 represses Pol III activity.

The types of RNAs transcribed from RNA polymerase III include:

- Transfer RNAs
- 5S ribosomal RNA
- U6 spliceosomal RNA
- RNase P and RNase MRP RNA
- 7SL RNA (the RNA component of the signal recognition particle)
- Vault RNAs
- Y RNA
- SINEs (short interspersed repetitive elements)
- 7SK RNA
- Several microRNAs
- Several small nucleolar RNAs
- Several gene regulatory antisense RNAs

https://en.wikipedia.org/wiki/RNA_polymerase_III

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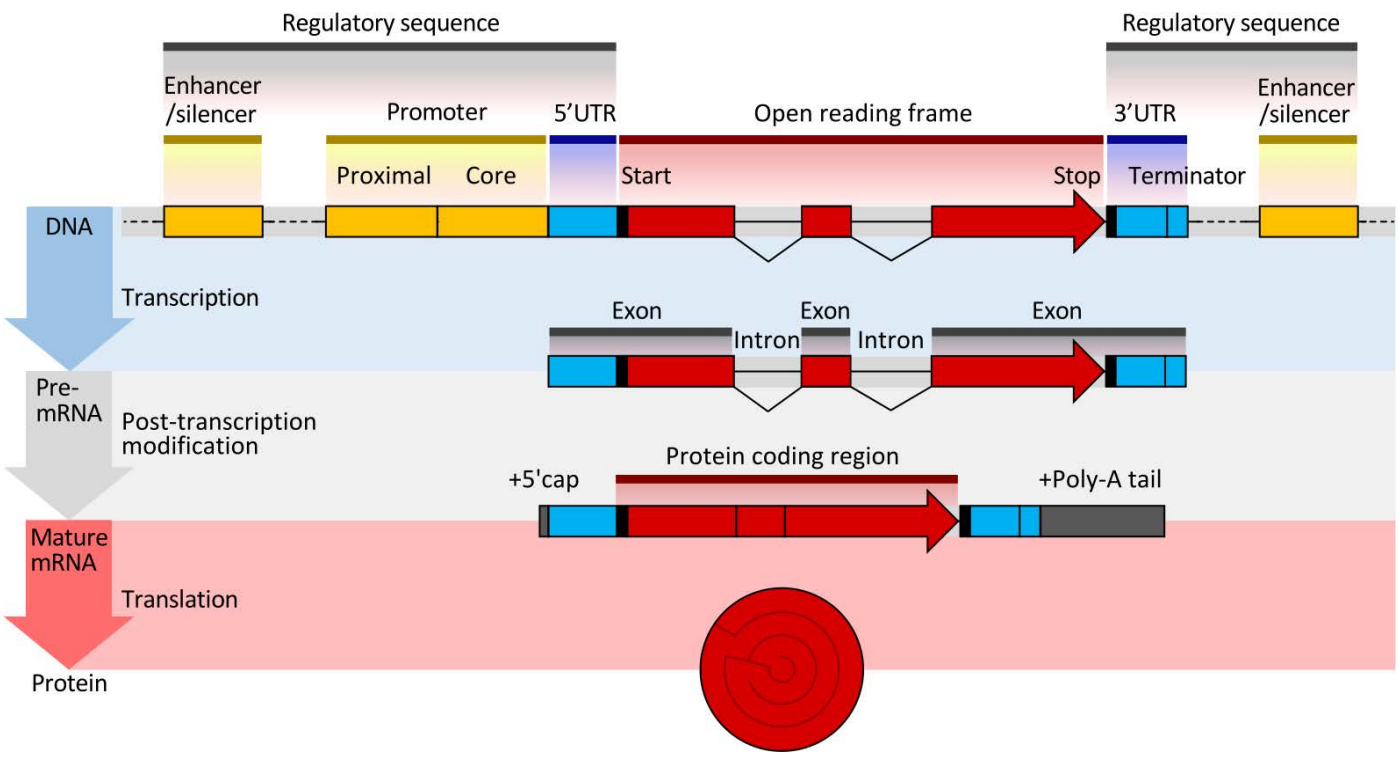
RNA Processing

Post-transcriptional modification or co-transcriptional modification is a process in cell biology by which, in eukaryotic cells, primary transcript RNA is converted into mature RNA. A notable example is the conversion of precursor messenger RNA into mature messenger RNA (mRNA), which includes splicing and occurs prior to protein synthesis. This process is vital for the correct translation of the genomes of eukaryotes, including humans, because the primary RNA transcript that is produced, as a result of transcription, contains both exons, which are either coding sections of the transcript or are important sequences involved in translation, and introns, which are the non-coding sections of the primary RNA transcript.

The pre-mRNA molecule undergoes three main modifications. These modifications are 5' capping, 3' polyadenylation, and RNA splicing, which occur in the cell nucleus before the RNA is translated.



https://en.wikipedia.org/wiki/RNA_polymerase_III

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RNase

Ribonuclease (commonly abbreviated RNase) is a type of nuclease that catalyzes the degradation of RNA into smaller components. Ribonucleases can be divided into endoribonucleases and exoribonucleases, and comprise several sub-classes within the EC 2.7 (for the phosphorolytic enzymes) and 3.1 (for the hydrolytic enzymes) classes of enzymes.

All organisms studied contain many RNases of many different classes, showing that RNA degradation is a very ancient and important process. As well as cleaning of cellular RNA that is no longer required, RNases play key roles in the maturation of all RNA molecules, both messenger RNAs that carry genetic material for making proteins, and non-coding RNAs that function in varied cellular processes. In addition, active RNA degradation systems are a first defense against RNA viruses, and provide the underlying machinery for more advanced cellular immune strategies such as RNAi.

Some cells also secrete copious quantities of non-specific RNases such as A and T1. RNases are, therefore, extremely common, resulting in very short lifespans for any RNA that is not in a protected environment. Intracellular RNAs may be protected from RNase activity by a number of strategies including 5' end capping, 3' end polyadenylation, and folding within an RNA protein complex (ribonucleoprotein particle or RNP).

Another mechanism of protection is ribonuclease inhibitor (RI), which comprises a relatively large fraction of cellular protein (~0.1%) in some cell types, and which binds to certain ribonucleases with the highest affinity of any protein-protein interaction; the dissociation constant for the RI-RNase A complex is ~20 fM under physiological conditions. RI is used in most laboratories that study RNA to protect their samples against degradation from environmental RNases.

Similar to restriction enzymes, which cleave highly specific sequences of double-stranded DNA, a variety of endoribonucleases that recognize and cleave specific sequences of single-stranded RNA have been recently classified.

RNases play a critical role in many biological processes, including angiogenesis and self-incompatibility in flowering plants (angiosperms). Many stress-response toxins of prokaryotic toxin-antitoxin systems have been shown to have RNase activity and homology.

https://en.wikipedia.org/wiki/Ribonuclease

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RNR

Ribonucleotide reductase (RNR), also known as ribonucleoside diphosphate reductase, is an enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides. Deoxyribonucleotides in turn are used in the synthesis of DNA. The reaction catalyzed by RNR is strictly conserved in all living organisms. Furthermore, RNR plays a critical role in regulating the total rate of DNA synthesis so that DNA to cell mass is maintained at a constant ratio during cell division and DNA repair.

A somewhat unusual feature of the RNR enzyme is that it catalyzes a reaction that proceeds via a free radical mechanism of action. The substrates for RNR are ADP, GDP, CDP and UDP. dTDP (deoxythymidine diphosphate) is synthesized by another enzyme (thymidylate kinase) from dTMP (deoxythymidine monophosphate).

The enzyme ribonucleotide reductase (RNR) catalyzes the *de novo* synthesis of dNDPs. Catalysis of ribonucleoside 5'-diphosphates (NDPs) involves a reduction at the 2'-carbon of ribose 5-phosphate to form the 2'-deoxy derivative-reduced 2'-deoxyribonucleoside 5'-diphosphates (dNDPs). This reduction is initiated with the generation of a free radical. Following a single reduction, RNR requires electrons donated from the dithiol groups of the protein thioredoxin. Regeneration of thioredoxin occurs when nicotinamide adenine dinucleotide phosphate (NADPH) provides two hydrogen atoms that are used to reduce the disulfide groups of thioredoxin.

Regulation of RNR is designed to maintain balanced quantities of dNTPs. Binding of effector molecules either increases or decreases RNR activity. When ATP binds to the allosteric activity site, it activates RNR. In contrast, when dATP binds to this site, it deactivates RNR. In addition to controlling activity, the allosteric mechanism also regulates the substrate specificity and ensures the enzyme produces an equal amount of each dNTP for DNA synthesis. In all classes, binding of ATP or dATP to the allosteric site induces reduction of cytidine 5'-diphosphate (CDP) and uridine 5'-diphosphate (UDP); 2'-deoxyguanosine 5'-triphosphate (dGTP) induces reduction of adenosine 5'-diphosphate (ADP); and 2'-deoxythymidine 5'-triphosphate (dTTP) induces reduction of guanosine 5'-diphosphate (GDP).

https://en.wikipedia.org/wiki/Ribonucleotide_reductase

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Rosalind Franklin

Rosalind Elsie Franklin (25 July 1920 – 16 April 1958) was an English chemist and X-ray crystallographer who made contributions to the understanding of the molecular structures of DNA (deoxyribonucleic acid), RNA (ribonucleic acid), viruses, coal, and graphite.

Franklin is best known for her work on the X-ray diffraction images of DNA while at King's College, London, which led to the discovery of the DNA double helix for which James Watson, Francis Crick and Maurice Wilkins shared the Nobel Prize in Physiology or Medicine in 1962.

https://en.wikipedia.org/wiki/Rosalind_Franklin

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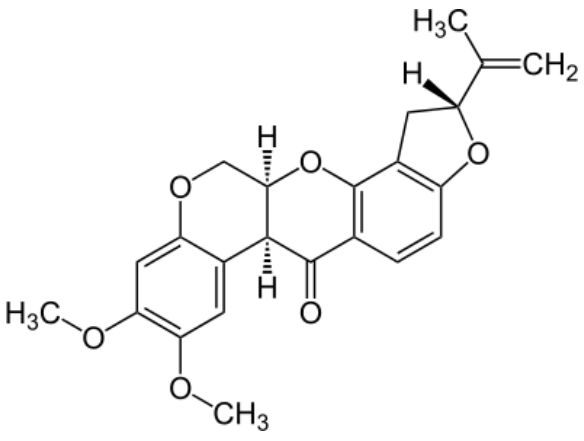
Rotenone

Rotenone is an odorless, colorless, crystalline isoflavone used as a broad-spectrum insecticide, piscicide, and pesticide. It occurs naturally in the seeds and stems of several plants, such as the jicama vine plant, and the roots of several members of Fabaceae. It was the first described member of the family of chemical compounds known as rotenoids.

Rotenone is used as a pesticide, insecticide, and as a nonselective piscicide (fish killer). It works by interfering with the electron transport chain in mitochondria. To be specific, it inhibits the transfer of electrons from iron-sulfur centers in complex I to ubiquinone. This interferes with NADH during the creation of usable cellular energy (ATP). Complex I is unable to pass off its electron to CoQ, creating a back-up of electrons within the mitochondrial matrix. Cellular oxygen is reduced to the radical, creating a reactive oxygen species, which can damage DNA and other components of the mitochondria.



https://en.wikipedia.org/wiki/Rotenone

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rRNAs

In molecular biology, ribosomal ribonucleic acid (rRNA) is the RNA component of the ribosome, and is essential for protein synthesis in all living organisms. It constitutes the predominant material within the ribosome, which is approximately 60% rRNA and 40% protein by weight. Ribosomes contain two major rRNAs and 50 or more proteins. The ribosomal RNAs form two subunits, the large subunit (LSU) and small subunit (SSU). The LSU rRNA acts as a ribozyme, catalyzing peptide bond formation.

Ribosomal RNA characteristics are important in evolution, thus taxonomy, and medicine.

- rRNA is one of only a few gene products present in all cells. For this reason, genes that encode the rRNA (rDNA) are sequenced to identify an organism's taxonomic group, calculate related groups, and estimate rates of species divergence. As a result, many thousands of rRNA sequences are known and stored in specialized databases such as RDP-II and SILVA.
- rRNA is the target of numerous clinically relevant antibiotics: chloramphenicol, erythromycin, kasugamycin, micrococcin, paromomycin, ricin, sarcin, spectinomycin, streptomycin, and thiostrepton.
- rRNA have been shown to be the origin of species-specific microRNAs, like miR-663 in humans and miR-712 in mouse. These miRNAs originate from the Internal Transcribed Spacers of the rRNA.

In prokaryotes a small 30S ribosomal subunit contains the 16S ribosomal RNA. The large 50S ribosomal subunit contains two rRNA species (the 5S and 23S ribosomal RNAs). Bacterial 16S ribosomal RNA, 23S ribosomal RNA, and 5S rRNA genes are typically organized as a co-transcribed operon. The 3' end of the 16S ribosomal RNA (in a ribosome) binds to a sequence on the 5' end of mRNA called the Shine-Dalgarno sequence.

Mammalian cells have 2 mitochondrial (12S and 16S) rRNA molecules and 4 types of cytoplasmic rRNA (the 28S, 5.8S, 18S, and 5S subunits). The 18S rRNA in most eukaryotes is in the small ribosomal subunit, and the large subunit contains three rRNA species (the 5S, 5.8S and 28S in mammals, 25S in plants, rRNAs).

https://en.wikipedia.org/wiki/Ribosomal_RNA

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Rubber

Natural rubber, also called India rubber or caoutchouc, as initially produced, cons
of polymers of the organic compound isoprene, with minor impurities of other org
compounds plus water. Malaysia is one of the leading producers of rubber. Forms
polyisoprene that are used as natural rubbers are classified as elastomers.

Currently, rubber is harvested mainly in the form of the latex from the para rubbe
or others. Latex is the polymer *cis*-1,4-polyisoprene – with a molecular weight of
100,000 to 1,000,000 daltons. Typically, a small percentage (up to 5% of dry mas
other materials, such as proteins, fatty acids, resins, and inorganic materials (salts
found in natural rubber. Polyisoprene can also be created synthetically, producing
what is sometimes referred to as "synthetic natural rubber", but the synthetic and
ral routes are completely different. Some natural rubber sources, such as gutta-pe
are composed of *trans*-1,4-polyisoprene, a structural isomer that has similar, but
identical, properties.

https://en.wikipedia.org/wiki/Natural_rubber

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Chapter 2 - Structure & Function: Lipids

Rumen

The rumen, also known as a paunch, forms the larger part of the reticuloru
is the first chamber in the alimentary canal of ruminant animals. It serves a
mary site for microbial fermentation of ingested feed. The smaller part of th
rumen is the reticulum, which is fully continuous with the rumen, but diffe
with regard to the texture of its lining.

https://en.wikipedia.org/wiki/Rumen

Related Glossary Terms

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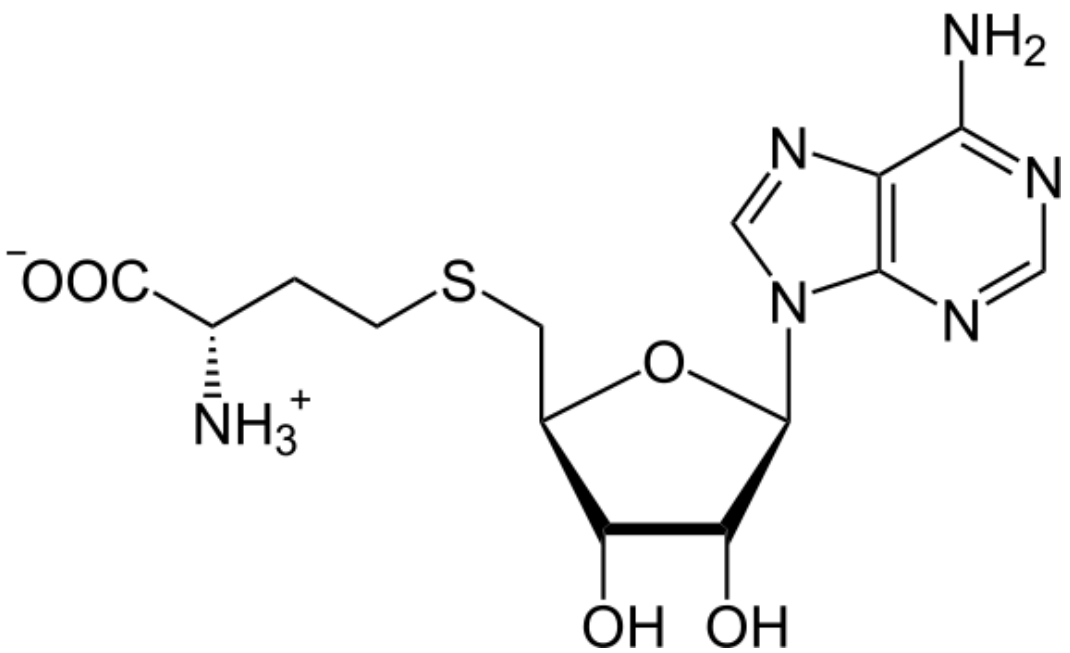
S-Adenosyl Homocysteine

S-Adenosyl-L-homocysteine (SAH) is an amino acid derivative used in sever
bolic pathways in most organisms. It is an intermediate in the synthesis of cy
adenosine and is formed by the demethylation of S-adenosyl-L-methionine (



https://en.wikipedia.org/wiki/S-Adenosyl-L-homocysteine

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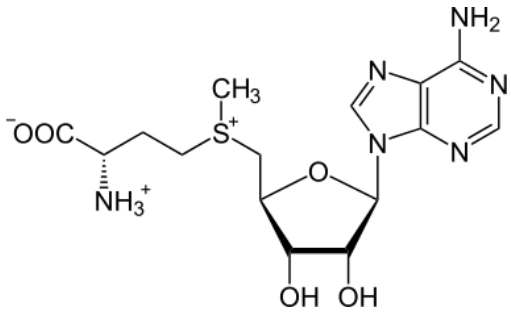
S-Adenosyl Methioinine

S-Adenosyl methionine (SAM-e) is a common co-substrate involved in methyl group transfers, transsulfuration, and aminopropylation. Although these anabolic reactions occur throughout the body, most SAM-e is produced and consumed in the liver. More than 40 methyl transfers from SAM-e are known, to various substrates such as nucleic acids, proteins, lipids and secondary metabolites. It is made from ATP and methionine by methionine adenosyltransferase.

The reactions that produce, consume, and regenerate SAM-e are called the SAM-e cycle. In the first step of this cycle, the SAM-dependent methylases (EC 2.1.1) that use SAM-e as a substrate produce S-adenosyl homocysteine as a product. This is hydrolyzed to homocysteine and adenosine by S-adenosylhomocysteine hydrolase EC 3.3.1.1 and the homocysteine recycled back to methionine through transfer of a methyl group from 5-methyltetrahydrofolate, by one of the two classes of methionine synthases (i.e. cobalamin-dependent (EC 2.1.1.13) or cobalamin-independent (EC 2.1.1.14)). This methionine can then be converted back to SAM-e, completing the cycle. In the rate-limiting step of the SAM cycle, MTHFR (methylenetetrahydrofolate reductase) irreversibly reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.

High levels of homocysteine have been associated with atherosclerosis (hardening and narrowing of the arteries), as well as an increased risk of heart attacks, strokes, liver damage, and possibly Alzheimer's disease. Therefore, vitamin B supplements are often taken along with SAM. These vitamins help metabolize the homocysteine into other useful compounds.



https://en.wikipedia.org/wiki/S-Adenosyl_methionine

Related Glossary Terms

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S-adenosylhomocysteine Hydrolase

S-adenosyl-L-homocysteine hydrolase (AdoHcyase) is an enzyme of the act
methyl cycle, responsible for the reversible hydration of S-adenosyl-L-hom
into adenosine and homocysteine.

AdoHcyase is a ubiquitous enzyme which binds and requires NAD^+ as a cof
cyase is a highly conserved protein of about 430 to 470 amino acids. The fa
tains a glycine-rich region in the central part of AdoHcyase a region though
volved in NAD-binding.

This protein may use the morpheein model of allosteric regulation.

https://en.wikipedia.org/wiki/S-adenosyl-L-homocysteine_hydrolase

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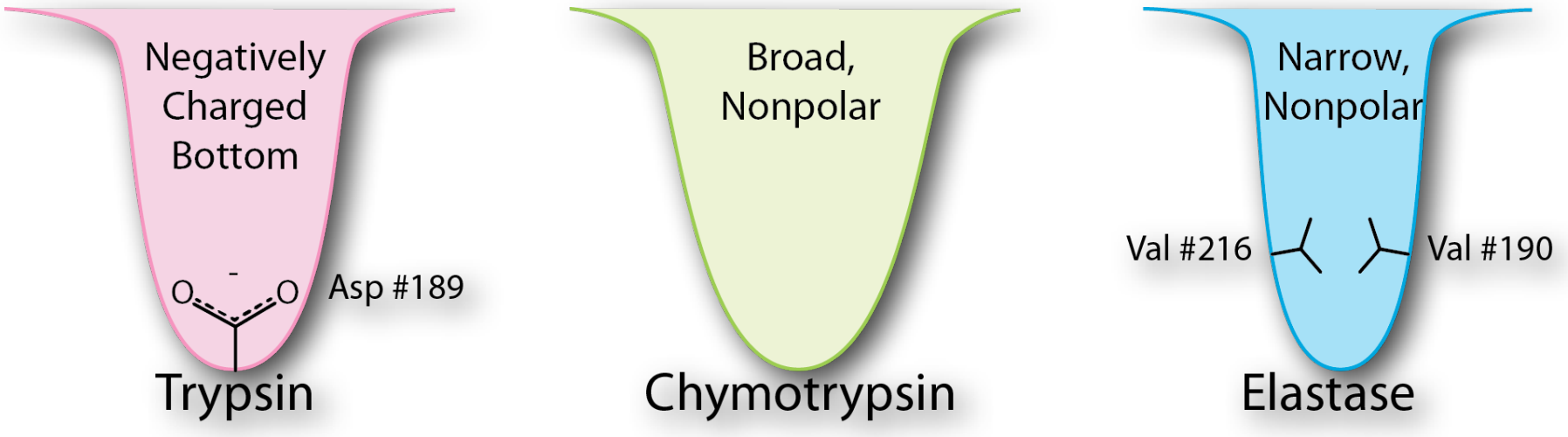
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

S1 Pocket

The S1 pocket is the part of a serine protease where the substrate recognition and bi
ing occurs. The S1 pocket determines a serine protease's specificity. Show below are
schematic reprsesentations of the S1 pockets of three serine proteases.



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Saccharide

A carbohydrate/saccharide is a biological molecule consisting of carbon (C), hydrogen (H) and oxygen (O) atoms, usually with a hydrogen–oxygen atom ratio of 2:1 (as in water). In other words, it has the empirical formula $C_n(H_2O)_n$. Carbohydrates are technically hydrates of carbon. Some exceptions exist. For example, deoxyribose, a sugar component of DNA, has the empirical formula $C_5H_{10}O_4$. Structurally it is more accurate to view them as polyhydroxy aldehydes and ketones.

The term is most common in biochemistry, where it is a synonym of saccharide, a group that includes sugars, starch, and cellulose. The saccharides are divided into four chemical groups: monosaccharides, disaccharides, oligosaccharides, and polysaccharides. In general, the monosaccharides and disaccharides, which are smaller (lower molecular weight) carbohydrates, are commonly referred to as sugars. The word saccharide comes from the Greek word σάκχαρον (sákkharon), meaning "sugar." While the scientific nomenclature of carbohydrates is complex, the names of the monosaccharides and disaccharides very often end in the suffix -ose. For example, grape sugar is the monosaccharide glucose, cane sugar is the disaccharide sucrose, and milk sugar is the disaccharide lactose.

Carbohydrates perform numerous roles in living organisms. Polysaccharides serve for the storage of energy (e.g. starch and glycogen) and as structural components (e.g. cellulose in plants and chitin in arthropods). The 5-carbon monosaccharide ribose is an important component of coenzymes (e.g. ATP, FAD and NAD^+) and the backbone of the genetic molecule known as RNA. The related deoxyribose is a component of DNA. Saccharides and their derivatives include many other important biomolecules that play key roles in the immune system, fertilization, preventing pathogenesis, blood clotting, and development.

https://en.wikipedia.org/wiki/Carbohydrate

Related Glossary Terms

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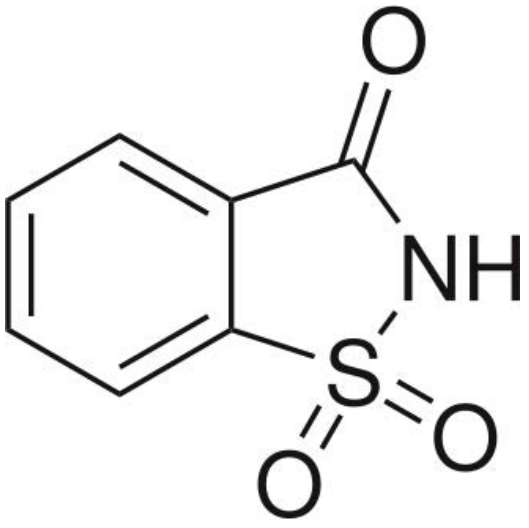
Saccharin

Saccharin is an artificial sweetener with effectively no food energy which is
400 times as sweet as sucrose or table sugar, but has a bitter or metallic aft
pecially at high concentrations. It is used to sweeten products such as drink
cookies, medicines, and toothpaste.



https://en.wikipedia.org/wiki/Saccharin

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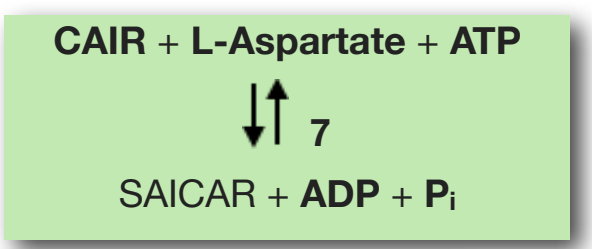
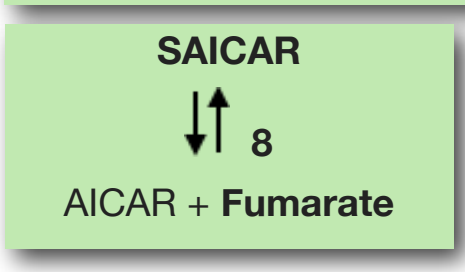
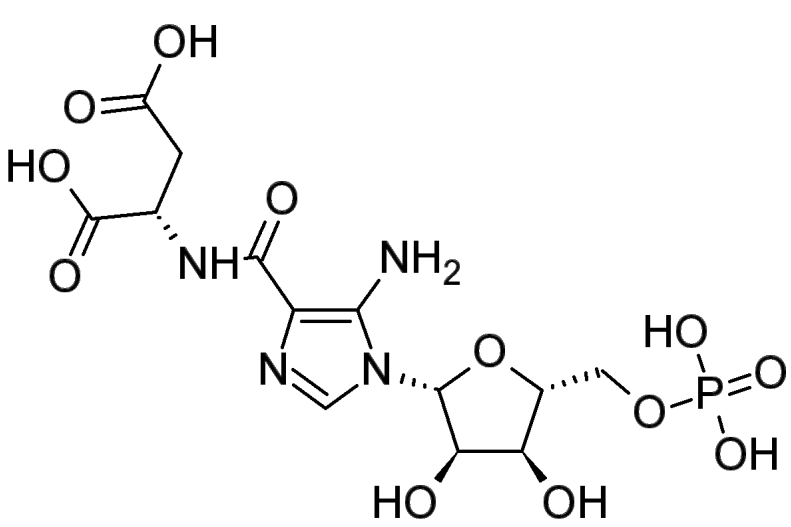
SAICAR

SAICAR (or phosphoribosylaminoimidazolesuccinocarboxamide) is an intermediate in the formation of purines. The conversion of ATP, L-aspartate, and 5-aminoimidazole-4-carboxyribonucleotide (CAIR) to 5-aminoimidazole-4-(N-succinylcarboxamide) ribonucleotide, ADP, and phosphate by phosphoribosylaminoimidazolesuccinocarboxamide synthetase (SAICAR synthetase) represents the eighth step (bottom image below) of *de novo* purine nucleotide biosynthesis.







https://en.wikipedia.org/wiki/Phosphoribosylaminoimidazolesuccinocarboxamide

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Related Glossary Terms

Salvage Pathways

A salvage pathway is a pathway in which nucleotides (purine and pyrimidin
thesized from intermediates in the degradative pathway for nucleotides.
Salvage pathways are used to recover bases and nucleosides that are formed
degradation of RNA and DNA. This is important in some organs because so
cannot undergo *de novo* synthesis.

The salvaged bases and nucleosides can then be converted back into nucleo

https://en.wikipedia.org/wiki/Nucleotide_salvage

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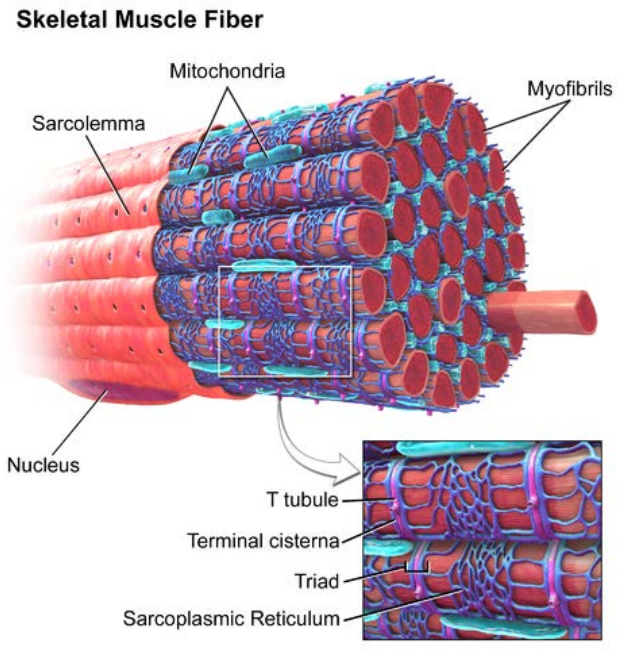
Sarcolemma

The sarcolemma also called the myolemma, is the cell membrane of a striated muscle fiber cell. It consists of a plasma membrane, which is a lipid bilayer, and an outer coat consisting of a thin layer of polysaccharide material (glycocalyx) that contacts the basement membrane, which contains numerous thin collagen fibrils and specialized proteins such as laminin that provide a scaffold for the muscle fiber to adhere to. Through transmembrane proteins residing in the plasma membrane, the actin skeleton inside the cell is connected to the basement membrane and the cell's exterior. At each end of the muscle fiber, the surface layer of the sarcolemma fuses with a tendon fiber, and the tendon fibers in turn collect into bundles to form the muscle tendons that then adhere onto bones.

The sarcolemma generally maintains the same function in muscle cells as the plasma membrane does in other eukaryote cells. It acts as a barrier between the extracellular and intracellular compartments, defining the individual muscle fiber from its surroundings. The lipid nature of the membrane allows it to separate the fluids of the intra- and extracellular compartments, since it is only selectively permeable to water through aquaporin channels. As in other cells this allows for the compositions of the compartments to be controlled by selective transport through the membrane. Membrane proteins, such as ion pumps, may create ion gradients with the consumption of ATP, that may later be used to drive transport of other substances through the membrane (Co-transport) or generate electrical impulses such as Action potentials.

A special feature of the sarcolemma is that it invaginates into the cytoplasm of the muscle cell, forming membranous tubules radially and longitudinally within the fiber called transverse tubules (T-tubules). On either side of the transverse tubules are terminal cisterna enlargements of smooth endoplasmic reticulum termed sarcoplasmatic reticulum (SR) in muscle. A transverse tubule surrounded by two SR cisterna are known as triads, and the contact between these structures is located at the junction of the A and I bands.



https://en.wikipedia.org/wiki/Sarcolemma

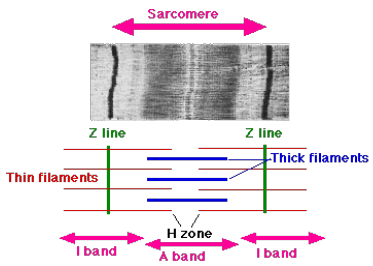
Sarcomeres

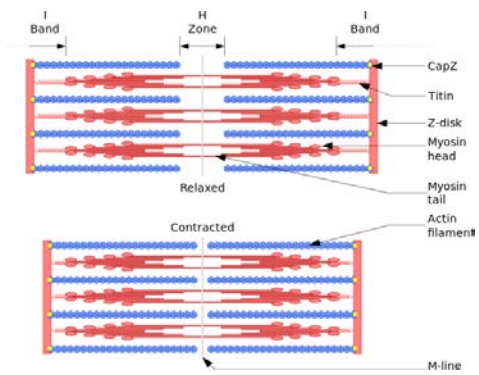
A sarcomere (Greek sarx "flesh", meros "part") is the basic unit of striated muscle tissue. Skeletal muscles are composed of tubular muscle cells (myocytes called muscle fibers) which are formed in a process known as myogenesis. Muscle fibers are composed of tubular myofibrils. Myofibrils are composed of repeating sections of sarcomeres, which appear under the microscope as dark and light bands. Sarcomeres are composed of long, fibrous proteins as filaments that slide past each other when a muscle contracts or relaxes.

Two of the important proteins are myosin, which forms the thick filament, and actin, which forms the thin filament. Myosin has a long, fibrous tail and a globular head, which binds to actin. The myosin head also binds to ATP, which is the source of energy for muscle movement. Myosin can only bind to actin when the binding sites on actin are exposed by calcium ions.

The sarcomeres are what give skeletal and cardiac muscles their striated appearance.
• A sarcomere is defined as the segment between two neighboring Z-lines (or Z-discs, or Z bodies). In electron micrographs of cross-striated muscle, the Z-line (from the German "Zwischenscheibe", the disc in between the I bands) appears as a series of dark lines.
• Surrounding the Z-line is the region of the I-band (for isotropic). I-band is the zone of thin filaments that is not superimposed by thick filaments.
• Following the I-band is the A-band (for anisotropic). Named for their properties under a polarizing microscope. An A-band contains the entire length of a single thick filament.
• Within the A-band is a paler region called the H-zone (from the German "heller", brighter). Named for their lighter appearance under a polarization microscope. H-band is the zone of the thick filaments that is not superimposed by the thin filaments.
• Within the H-zone is a thin M-line (from the German "Mittelscheibe", the disc in the middle of the sarcomere) formed of cross-connecting elements of the cytoskeleton.

The relationship between the proteins and the regions of the sarcomere are as follows:
• Actin filaments, the thin filaments, are the major component of the I-band and extend into the A-band.
• Myosin filaments, the thick filaments, are bipolar and extend throughout the A-band. They are cross-linked at the center by the M-band.
• The giant protein titin (connectin) extends from the Z-line of the sarcomere, where it binds to the thick filament (myosin) system, to the M-band, where it is thought to interact with the thick filaments. Titin (and its splice isoforms) is the biggest single highly elasticated protein found in nature. It provides binding sites for numerous proteins and is thought to play an important role as sarcomeric ruler and as blueprint for the assembly of the sarcomere.
• Another giant protein, nebulin, is hypothesized to extend along the thin filaments and the entire I-Band. Similar to titin, it is thought to act as a molecular ruler along for thin filament assembly.
• Several proteins important for the stability of the sarcomeric structure are found in the Z-line as well as in the M-band of the sarcomere.
• Actin filaments and titin molecules are cross-linked in the Z-disc via the Z-line protein α-actinin.
• The M-band proteins myomesin as well as C-protein crosslink the thick filament system (myosins) and the M-band part of titin (the elastic filaments).
• The interaction between actin and myosin filaments in the A-band of the sarcomere is responsible for the muscle contraction (sliding filament model).





https://en.wikipedia.org/wiki/Sarcomere

Related Glossary Terms

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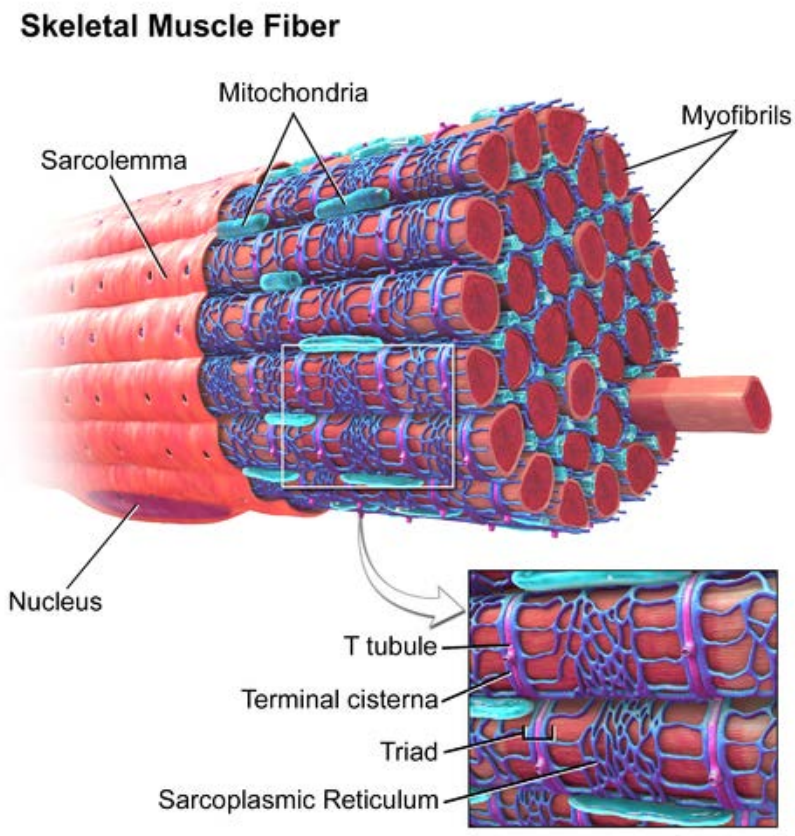
Sarcoplasmic Reticulum

The sarcoplasmic reticulum (SR) is smooth ER found in myocytes. The only structural difference between this organelle and the smooth endoplasmic reticulum is the medley of proteins they have, both bound to their membranes and drifting within the confines of their lumens. This fundamental difference is indicative of their functions: The endoplasmic reticulum synthesizes molecules, while the sarcoplasmic reticulum stores calcium ions and pumps them out into the sarcoplasm when the muscle fiber is stimulated. After their release from the sarcoplasmic reticulum, calcium ions interact with contractile proteins that utilize ATP to shorten the muscle fiber. The sarcoplasmic reticulum plays a major role in excitation-contraction coupling.



https://en.wikipedia.org/wiki/Endoplasmic_reticulum#Sarcoplasmic_reticulum

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Saturated

A saturated compound has no double or triple bonds. In the case of saturat
each carbon centre has four single bonds as is characteristic of other satura
carbons, alkanes. In contrast, in ethylene (C_2H_4), each carbon center is eng
single and one double bond. The term is often used to describe fats or the f
them that lack double bonds.

https://en.wikipedia.org/wiki/Saturation_(chemistry)

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Saturated Fat

A saturated fat is a fat in which the fatty acids all have single bonds. Fats are made of two kinds of smaller molecules: monoglyceride and fatty acids. Fats are made of long chains of carbon (C) atoms. Some carbon atoms are linked by single bonds (-C-C-) and others are linked by double bonds (-C=C-). Double bonds can react with hydrogen to form single bonds. They are called saturated, because the second bond is broken up and each half of the bond is attached to (saturated with) a hydrogen atom. Most animal fats are saturated. The fats of plants and fish are generally unsaturated. Saturated fats tend to have higher melting points than their corresponding unsaturated fats, leading to the popular understanding that saturated fats tend to be solids at body temperatures, while unsaturated fats tend to be liquid oils.

Various fats contain different proportions of saturated and unsaturated fat. Examples of foods containing a high proportion of saturated fat include animal fat products such as cream, cheese, butter, other whole milk dairy products and fatty meats which also contain dietary cholesterol. Certain vegetable products have high saturated fat content, such as coconut oil and palm kernel oil. Many prepared foods are high in saturated fat content, such as pizza, dairy desserts, and sausage.

The effect of saturated fat on risk of disease is controversial. Many reviews recommend a diet low in saturated fat and argue it will lower risks of cardiovascular diseases, diabetes, or death. However, other reviews have rejected those arguments.

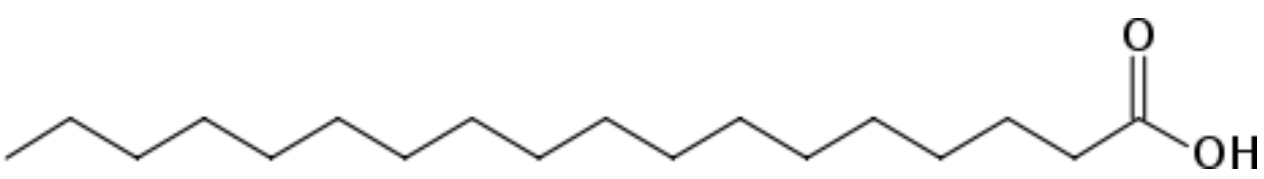
https://en.wikipedia.org/wiki/Saturated_fat

Related Glossary Terms

Saturated Fatty Acids

A fatty acid is a carboxylic acid with a long aliphatic chain, which is either saturated (containing no double bonds) or unsaturated (having at least one double bond). Most naturally occurring fatty acids have an unbranched chain of an even number of carbo atoms, from 4 to 28. Fatty acids are usually derived from triglycerides or phospholip-ids. Fatty acids are important sources of fuel because, when metabolized, they yield large quantities of ATP. Many cell types can use either glucose or fatty acids for this purpose. Long-chain fatty acids cannot cross the blood–brain barrier and so cannot b used as fuel by the cells of the central nervous system. However, medium-chain fatty acids octanoic acid and heptanoic acid can be used, in addition to glucose and ketone bodies.

Pictured below is a saturated fatty acid, stearic acid



https://en.wikipedia.org/wiki/Fatty_acid

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Saturation

The term saturation is used to refer to the relative amount of single bonds i
cule. Something that is highly saturated has relatively few double bonds, w
compound that is highly unsaturated has many double bonds.

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Schiff Base Reactions

Schiff bases are common enzymatic intermediates where an amine, such as
nal group of a lysine residue, reversibly reacts with an aldehyde or ketone o
or substrate. The common enzyme cofactor PLP forms a Schiff base with a l
due and is transaldiminated to the substrate(s). Similarly, the cofactor retin
Schiff base in rhodopsins, including human rhodopsin (via Lysine 296), wh
the photoreception mechanism.

An example where the substrate forms a Schiff base to the enzyme is in the
1,6-bisphosphate aldolase catalyzed reaction during glycolysis and in the m
of amino acids.

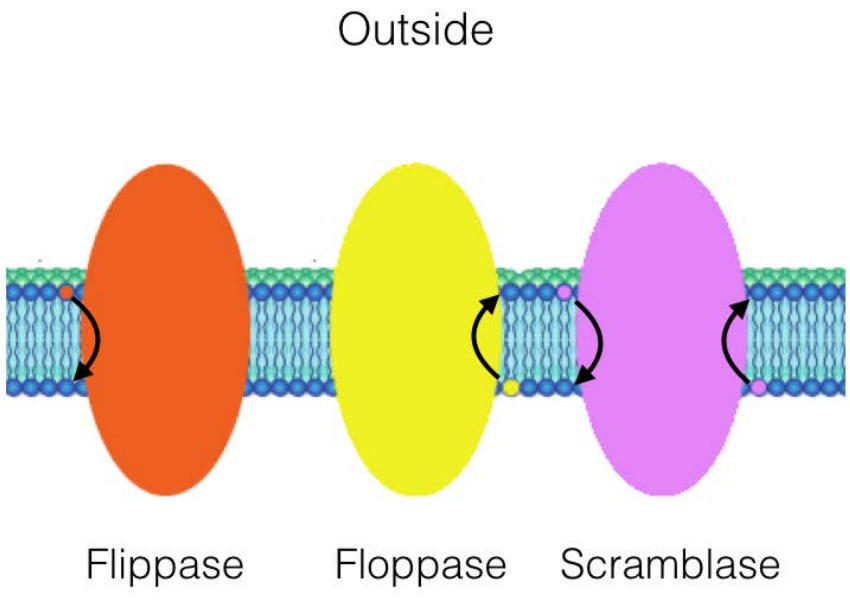
https://en.wikipedia.org/wiki/Schiff_base#Biochemistry

Related Glossary Terms

Drag related terms here

Scramblase

Scramblase is a protein responsible for the translocation of phospholipids between t
two monolayers of a lipid bilayer of a cell membrane.



https://en.wikipedia.org/wiki/Phospholipid_scramblase

Related Glossary Terms

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Scrapie

Scrapie is a fatal, degenerative disease that affects the nervous systems of sheep and goats. It is one of several transmissible spongiform encephalopathies (TSEs), which are related to bovine spongiform encephalopathy (BSE or "mad cow disease") and chronic wasting disease of deer. Like other spongiform encephalopathies, scrapie is caused by a prion.

The name scrapie is derived from one of the clinical signs of the condition, wherein affected animals will compulsively scrape off their fleeces against rocks, trees, or fences. The disease apparently causes an itching sensation in the animals. Other clinical signs include excessive lip smacking, altered gaits, and convulsive collapse.

Scrapie is infectious and transmissible among conspecifics, so one of the most common ways to contain it (since it is incurable) is to quarantine and destroy those affected. However, scrapie tends to persist in flocks and can also arise apparently spontaneously in flocks that have not previously had cases of the disease. The mechanism of transmission between animals and other aspects of the biology of the disease are only poorly understood, and these are active areas of research. Recent studies suggest prions may be spread through urine and persist in the environment for decades.

Scrapie usually affects sheep around three to five years of age. The potential for transmission at birth and from contact with placental tissues is apparent. No evidence indicates scrapie is infectious to humans.

https://en.wikipedia.org/wiki/Scrapie

Related Glossary Terms

Drag related terms here

Scurvy

Scurvy is a disease resulting from a deficiency of vitamin C. Typical sympto
scurvy are initially fatigue, followed by formation of spots on the skin, spon
and bleeding from the mucous membranes. Spots are most abundant on th
legs, and a person may look pale, feel depressed, and be partially immobiliz
scurvy advances, there can be open, suppurating wounds, loss of teeth, yell
ver, neuropathy and finally death from bleeding.

https://en.wikipedia.org/wiki/Scurvy

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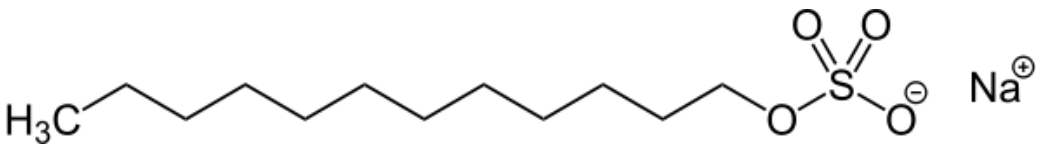
Chapter 2 - Structure and Function: Proteins

Chapter 9 - Point by Point: Structure and Function

SDS

Sodium dodecyl sulfate, synonymously sodium lauryl sulfate (or laurilsulfate - SDS or SLS, respectively), is a synthetic organic compound with the formula $CH_3(CH_2)_{11}SO_4Na$. The compound is commonly used in to aid lysing cells during DNA extraction, and for denaturing proteins in preparation for electrophoresis in the SDS-PAGE technique.

It is an anionic surfactant used in many cleaning and hygiene products. The sodium salt is of an organosulfate class of organics. It consists of a 12-carbon tail attached to a sulfate group, i.e., it is the sodium salt of dodecyl hydrogen sulfate, the ester of dodecyl alcohol and sulfuric acid. Its hydrocarbon tail combined with a polar "headgroup" give the compound amphiphilic properties and so make it useful as a detergent. Also derived as a component of mixtures produced from inexpensive coconut and palm oils, SDS is a common component of many domestic cleaning, personal hygiene and cosmetic, pharmaceutical, and food products, as well as of industrial and commercial cleaning and product formulations.



https://en.wikipedia.org/wiki/Sodium_dodecyl_sulfate#Laboratory_applications

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Related Glossary Terms

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SDS-PAGE

A gel electrophoresis technique that uses SDS to linearize proteins and to impart a negative charge to linearized proteins in order to determine their molecular weight irrespective of their shape.

When a protein mixture is heated to 100 °C in presence of SDS, the detergent wraps around the polypeptide backbone. It binds to polypeptides in a constant weight ratio of 1.4 g SDS/g of polypeptide. In this process, the intrinsic charges of polypeptides become negligible when compared to the negative charges contributed by SDS. Thus polypeptides after treatment become rod-like structures possessing a uniform charge density, that is same net negative charge per unit weight. The electrophoretic mobilities of these proteins is a linear function of the logarithms of their molecular weights. Without SDS, different proteins with similar molecular weights would migrate differently due to differences in mass-charge ratio, as each protein has an isoelectric point and molecular weight particular to its primary structure. This is known as native PAGE. Adding SDS solves this problem, as it binds to and unfolds the protein, giving a near uniform negative charge along the length of the polypeptide.

https://en.wikipedia.org/wiki/Polyacrylamide_gel_electrophoresis

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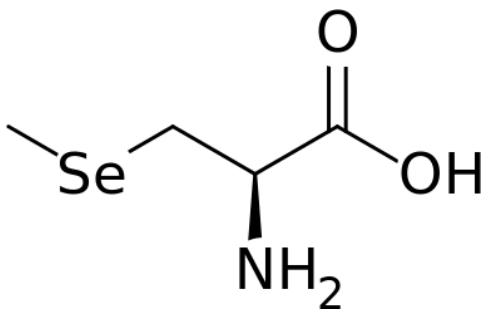
Se-methylselenocysteine

Se-methylselenocysteine (also known as methylselenocysteine), is an analog of S-methylcysteine in which the sulfur atom is replaced with a selenium atom. It is an inhibitor of DMBA-induced mammary tumors and a chemopreventive agent that blocks cell cycle progression and proliferation of premalignant mammary lesions and induces apoptosis of cancer cell lines in culture.

Apoptosis has been proposed as the most plausible mechanism for the chemopreventive activities of selenocompounds. Se-Methylselenocysteine was more efficient at inducing apoptosis than selenite, but was less toxic." The "selenite-induced cell death could be derived from necrosis rather than apoptosis, since selenite did not significantly induce several apoptotic phenomena, including the activation of caspase-3."

In the Nutritional Prevention of Cancer Trial, selenized yeast resulted in "a reduction in the incidence of prostate cancer and in total cancer incidence." Subsequent anticancer studies using selenomethionine did not show any benefit against cancer, but selenized yeast contains both selenomethionine and methylselenocysteine.



https://en.wikipedia.org/wiki/Methylselenocysteine

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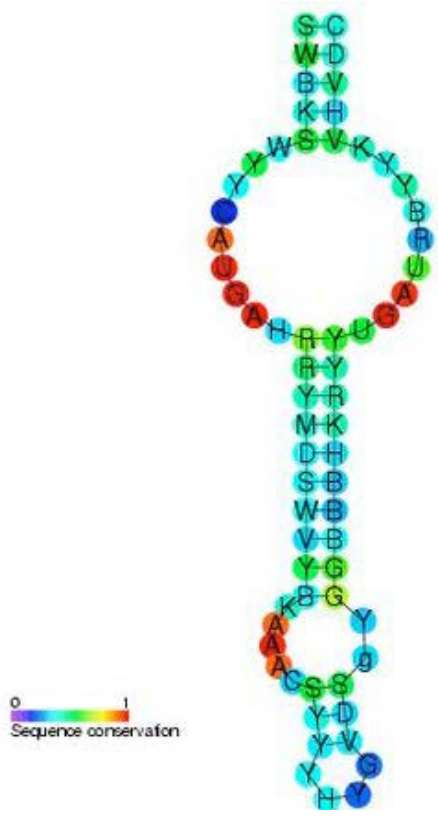
Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

SECIS

The SECIS element (SECIS: selenocysteine insertion sequence) is an RNA element around 60 nucleotides in length that adopts a stem-loop structure. This structural motif (pattern of nucleotides) directs the cell to translate UGA codons as selenocysteines. (UGA is normally a stop codon.) SECIS elements are thus a fundamental aspect of messenger RNAs encoding selenoproteins, proteins that include one or more selenocysteine residues.

In bacteria the SECIS element appears soon after the UGA codon it affects. In archaea and eukaryotes, it occurs in the 3' UTR of an mRNA, and can cause multiple UGA codons within the mRNA to code for selenocysteine. One archaeal SECIS element, in Methanococcus, is located in the 5' UTR.

The SECIS element appears defined by sequence characteristics, i.e. particular nucleotides tend to be at particular positions in it, and a characteristic secondary structure. The secondary structure is the result of base-pairing of complementary RNA nucleotides, and causes a hairpin-like structure. The eukaryotic SECIS element includes non-canonical A-G base pairs, which are uncommon in nature, but are critically important for correct SECIS element function. Although the eukaryotic, archaeal and bacterial SECIS elements each share a general hairpin structure, they are not alignable, e.g. an alignment-based scheme to recognize eukaryotic SECIS elements will not be able to recognize archaeal SECIS elements.



https://en.wikipedia.org/wiki/SECIS_element

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Chapter 2 - Structure & Function: Amino Acids

Second Law of Thermodynamics

The second law of thermodynamics states that the total entropy of an isolat
always increases over time, or remains constant in ideal cases where the sy
steady state or undergoing a reversible process. The increase in entropy acc
the irreversibility of natural processes, and the asymmetry between future a

https://en.wikipedia.org/wiki/Second_law_of_thermodynamics

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Chapter 5 - Energy: Basics

Second Messengers

Second messengers are intracellular signaling molecules released by the cell to trigger physiological changes such as proliferation, differentiation, migration, survival, and apoptosis. Secondary messengers are therefore one of the initiating components of intracellular signal transduction cascades. Examples of second messenger molecules include cyclic AMP, cyclic GMP, inositol trisphosphate, diacylglycerol, and calcium. The cell releases second messenger molecules in response to exposure to extracellular signaling molecules—the first messengers.

First messengers are extracellular factors, often hormones or neurotransmitters, such as epinephrine, growth hormone, and serotonin. Because peptide hormones and neurotransmitters typically are biochemically hydrophilic molecules, these first messengers may not physically cross the phospholipid bilayer cell membrane to initiate changes within the cell directly—unlike steroid hormones, which usually do. This functional limitation necessitates the cell to devise signal transduction mechanisms to transduce first messenger into second messengers, so that the extracellular signal may be propagated intracellularly.

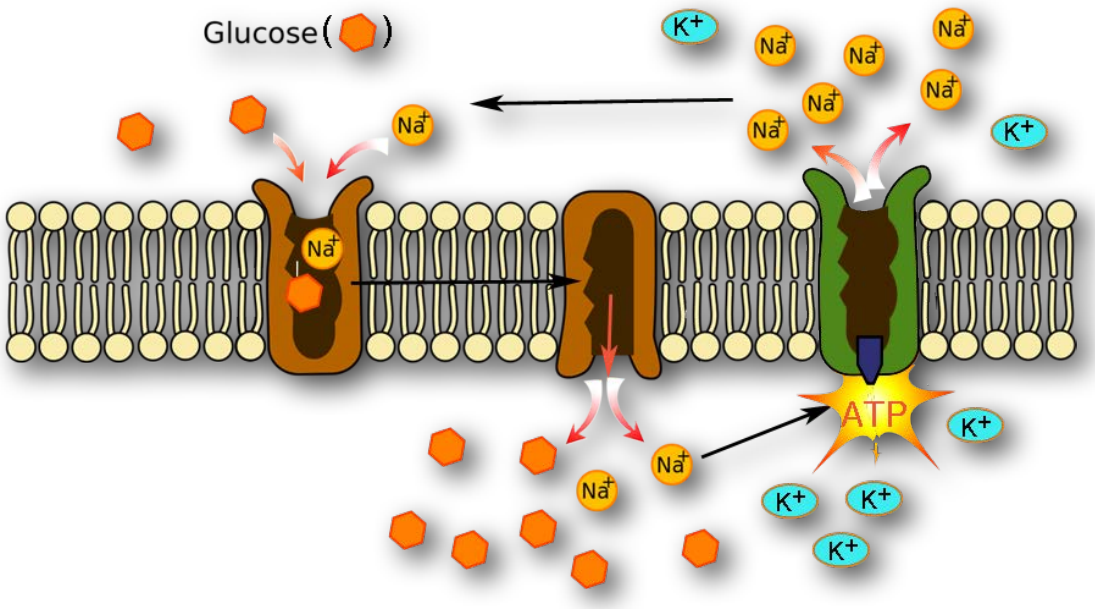
An important feature of the second messenger signaling system is that second messengers may be coupled downstream to multi-cyclic kinase cascades to greatly amplify the strength of the original first messenger signal. For example, Ras.GTP signals link with the Mitogen Activated Protein Kinase (MAPK) cascade to amplify the allosteric activation of proliferative transcription factors such as Myc and CREB.

https://en.wikipedia.org/wiki/Second_messenger_system

Related Glossary Terms

Secondary Active Transport

In secondary active transport, also known as coupled transport or co-transport, energy is used to transport molecules across a membrane. However, in contrast to primary active transport, there is no direct coupling of ATP. Instead it relies upon the electrochemical potential difference created by pumping ions in/out of the cell. Permitting one ion or molecule to move down an electrochemical gradient, but possibly against the concentration gradient where it is more concentrated to that where it is less concentrated increases entropy and can serve as a source of energy for metabolism (e.g. in ATP synthase).



https://en.wikipedia.org/wiki/Active_transport#Secondary_active_transport

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Secondary Amine

An aliphatic amine has no aromatic ring attached directly to the nitrogen atom. Aromatic amines have the nitrogen atom connected to an aromatic ring as in the various anilines. The aromatic ring decreases the alkalinity of the amine, depending on its substituents. The presence of an amine group strongly increases the reactivity of the aromatic ring, due to an electron-donating effect.

Amines are organized into four subcategories:

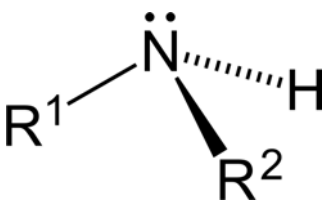
• Primary amines — Primary amines arise when one of three hydrogen atoms in ammonia is replaced by an alkyl or aromatic. Important primary alkyl amines include methylamine, ethanolamine (2-aminoethanol), and the buffering agent tris, while primary aromatic amines include aniline.

• Secondary amines — Secondary amines have two organic substituents (alkyl, aryl or both) bound to N together with one hydrogen (or no hydrogen if one of the substituent bonds is double). Important representatives include dimethylamine and methylethanolamine, while an example of an aromatic amine would be diphenylamine.

• Tertiary amines — In tertiary amines, all three hydrogen atoms are replaced by organic substituents. Examples include trimethylamine, which has a distinctively fishy smell, or triphenylamine.

• Cyclic amines — Cyclic amines are either secondary or tertiary amines. Examples of cyclic amines include the 3-membered ring aziridine and the six-membered ring piperidine. N-methylpiperidine and N-phenylpiperidine are examples of cyclic tertiary amines.

It is also possible to have four organic substituents on the nitrogen. These species are not amines but are quaternary ammonium cations and have a charged nitrogen center. Quaternary ammonium salts exist with many kinds of anions.



https://en.wikipedia.org/wiki/Amine

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Chapter 2 - Structure & Function: Amino Acids

Secondary Structure

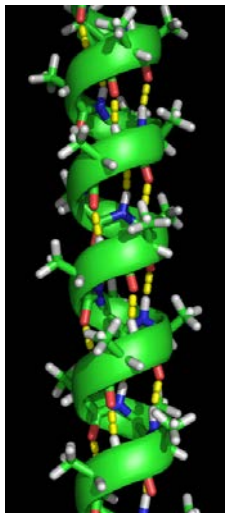
Protein secondary structure is the general three-dimensional form of local segments of proteins. Secondary structure can be formally defined by the pattern of hydrogen bonds of the protein (such as alpha helices and beta sheets) that are observed in an atomic-resolution structure. More specifically, the secondary structure is defined by the patterns of hydrogen bonds formed between amine hydrogen and carbonyl oxygen atoms contained in the backbone peptide bonds of the protein. The secondary structure may alternatively be defined based on the regular pattern of backbone dihedral angles in a particular region of the Ramachandran plot; thus, a segment of residues with such dihedral angles may be called a helix, regardless of whether it has the correct hydrogen bonds. The secondary structure may be provided by crystallographers in the corresponding PDB file.

Secondary structure does not describe the specific identity of amino acids in the protein which are defined as the primary structure, nor the global atomic positions in three-dimensional space, which are considered to be tertiary structure. Other types of biopolymers such as nucleic acids also possess characteristic secondary structures.

The most common secondary structures are α helices and β sheets. Other helices, such as the 3_{10} helix and π helix, are calculated to have energetically favorable hydrogen-bonding patterns but are rarely observed in natural proteins except at the ends of α helices due to unfavorable backbone packing in the center of the helix. Other extended structures such as the polyproline helix and α sheet are rare in native state proteins but are often hypothesized as important protein folding intermediates. Tight turns and loose, flexible loops link the more "regular" secondary structure elements. The random coil is not a true secondary structure, but is the class of conformations that indicate an absence of regular secondary structure.

Amino acids vary in their ability to form the various secondary structure elements. Proline and glycine are sometimes known as "helix breakers" because they disrupt the regularity of the α helical backbone conformation. However, both have unusual conformational abilities and are commonly found in turns. Amino acids that prefer to adopt helical conformations in proteins include methionine, alanine, leucine, glutamate and lysine ("MALEK" in amino-acid 1-letter codes). By contrast, the large aromatic residues (tryptophan, tyrosine and phenylalanine) and Cβ-branched amino acids (isoleucine, valine, and threonine) prefer to adopt β-strand conformations. However, these preferences are not strong enough to produce a reliable method of predicting secondary structure from sequence alone.

Show below - an a-helix stabilized by H-bonds (yellow)



https://en.wikipedia.org/wiki/Protein_secondary_structure

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Secretory Vesicles

Secretory vesicles contain materials that are to be excreted from the cell. Cells have many reasons to excrete materials. One reason is to dispose of wastes. Another reason is tied to the function of the cell. Within a larger organism, some cells are specialized to produce certain chemicals. These chemicals are stored in secretory vesicles and released when needed.

Types of secretory vesicles

• Synaptic vesicles are located at presynaptic terminals in neurons and store neurotransmitters. When a signal comes down an axon, the synaptic vesicles fuse with the cell membrane releasing the neurotransmitter so that it can be detected by receptor molecules on the next nerve cell.

• In animals endocrine tissues release hormones into the bloodstream. These hormones are stored within secretory vesicles. A good example is the endocrine tissue found in the islets of Langerhans in the pancreas. This tissue contains many cell types that are defined by which hormones they produce.

• Secretory vesicles hold the enzymes that are used to make the cell walls of plants, protists, fungi, bacteria, and Archaea cells as well as the extracellular matrix of animal cells.

• Bacteria, *Archaea*, fungi, and parasites release membrane vesicles (MVs) containing varied but specialized toxic compounds and biochemical signal molecules, which are transported to target cells to initiate processes in favor of the microbe, which include invasion of host cells and killing of competing microbes in the same niche.

Shown below - lipid vesicles

https://en.wikipedia.org/wiki/Vesicle_(biology_and_chemistry)#Secretory_vesicles

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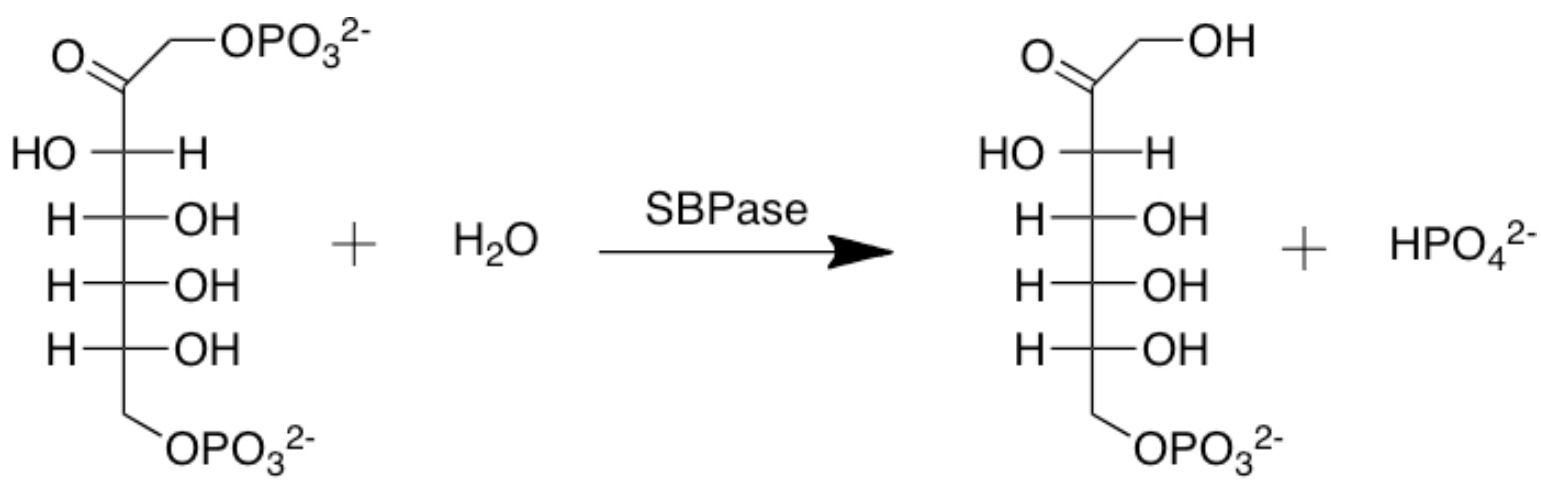
Sedoheptulose 1,7-bisphosphatase

Sedoheptulose-bisphosphatase is an enzyme that catalyzes the removal of a p
group from sedoheptulose 1,7-bisphosphate to produce sedoheptulose 7-phos
SBPase is an example of a phosphatase, or, more generally, a hydrolase. This
participates in the Calvin cycle.



sedoheptulose-1,7-bisphosphate

sedoheptulose-7-bisphosphate

https://en.wikipedia.org/wiki/Sedoheptulose-bisphosphatase

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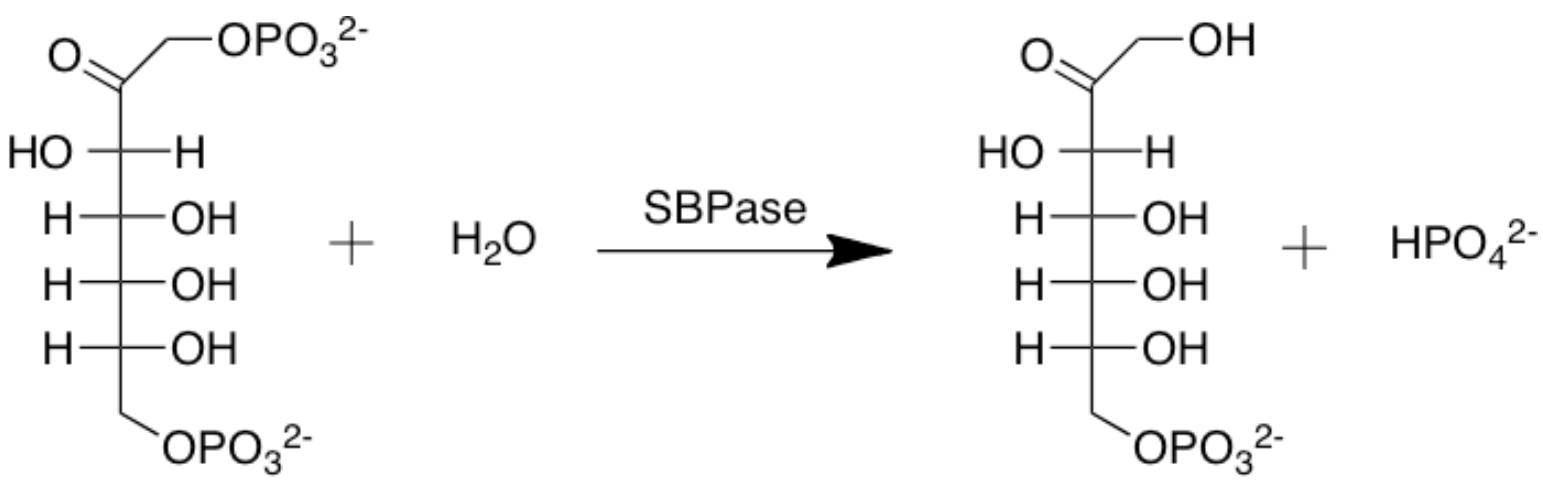
Sedoheptulose-1,7 bisphosphatase

Sedoheptulose-bisphosphatase is an enzyme that catalyzes the removal of a p
group from sedoheptulose 1,7-bisphosphate to produce sedoheptulose 7-pho
SBPase is an example of a phosphatase, or, more generally, a hydrolase. This
participates in the Calvin cycle.



sedoheptulose-1,7-bisphosphate

sedoheptulose-7-bisphosphate

https://en.wikipedia.org/wiki/Sedoheptulose-bisphosphatase

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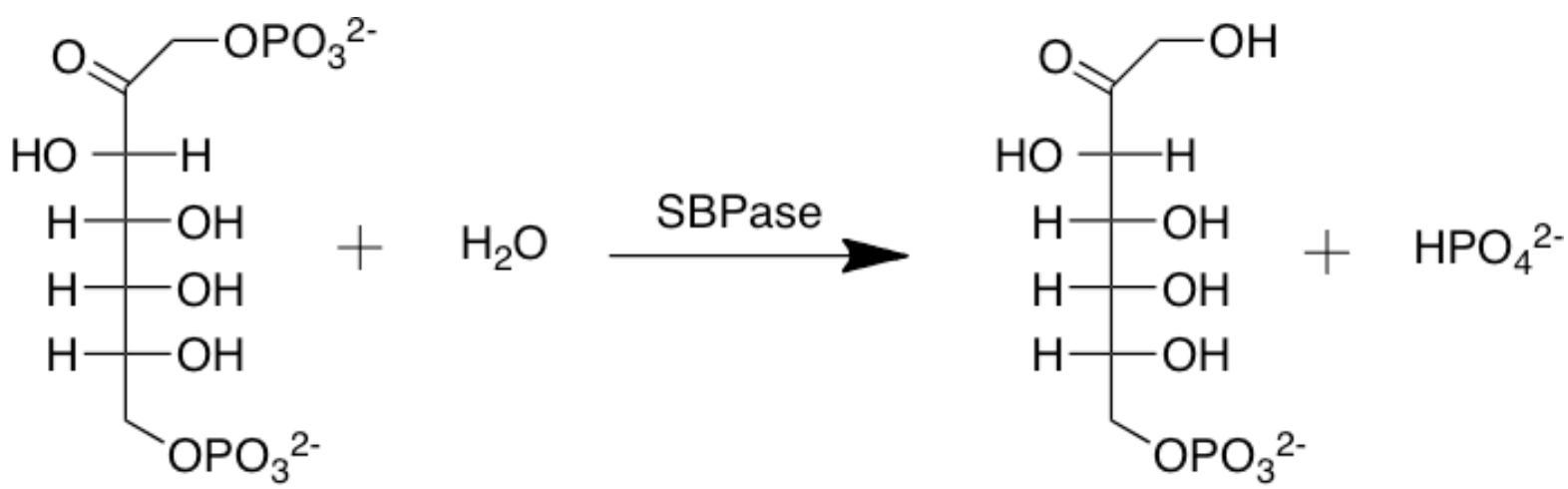
Sedoheptulose-1,7 bisphosphate

Sedoheptulose-1,7 bisphosphate is an intermediate of the Calvin cycle form
erythrose-4-phosphate and dihydroxyacetone phosphate (DHAP). It loses
to become sedoheptulose-7-phosphate in a reaction catalyzed by sedoheptu
bisphosphatase.



sedoheptulose-1,7-bisphosphate

sedoheptulose-7-bisphosphate

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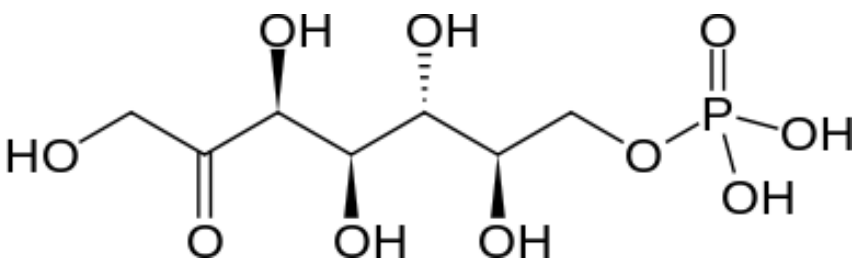
Sedoheptulose-7-phosphate

Sedoheptulose 7-phosphate is an intermediate in the pentose phosphate pathway.
It is formed by transketolase and acted upon by transaldolase.

Sedoheptulokinase is an enzyme that uses sedoheptulose and ATP to produce ADP and sedoheptulose 7-phosphate.

Sedoheptulose-bisphosphatase is an enzyme that uses sedoheptulose 1,7-bisphosphate and H_2O to produce sedoheptulose 7-phosphate and phosphate.



https://en.wikipedia.org/wiki/Sedoheptulose_7-phosphate

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Selectins

The selectins (cluster of differentiation 62 or CD62) are a family of cell adhesion molecules (or CAMs). All selectins are single-chain transmembrane glycoproteins that share similar properties to C-type lectins due to a related amino terminus and calcium-dependent binding. Selectins bind to sugar moieties and so are considered to be a type of lectin, cell adhesion proteins that bind sugar polymers.

Selectins are involved in constitutive lymphocyte homing, and in chronic and acute inflammation processes, including post-ischemic inflammation in muscle, kidney and heart, skin inflammation, atherosclerosis, glomerulonephritis and lupus erythematosus and cancer metastasis.

During an inflammatory response, stimuli such as histamine and thrombin cause endothelial cells to mobilize P-selectin from stores inside the cell to the cell surface. In addition, cytokines such as TNF-alpha stimulate the expression of E-selectin and additional P-selectin a few hours later.

As the leukocyte rolls along the blood vessel wall, the distal lectin-like domain of the selectin binds to certain carbohydrate groups presented on proteins (such as PSGL-1) on the leukocyte, which slows the cell and allows it to leave the blood vessel and enter the site of infection. The low-affinity nature of selectins is what allows the characteristic "rolling" action attributed to leukocytes during the leukocyte adhesion cascade.

Each selectin has a carbohydrate recognition domain that mediates binding to specific glycans on apposing cells. They have remarkably similar protein folds and carbohydrate binding residues, leading to overlap in the glycans to which they bind.

Selectins bind to the sialyl Lewis X (SLex) determinant “NeuAcα2-3Galβ1-4(Fucα1-3)GlcNAc.” However, SLex, per se, does not constitute an effective selectin receptor. Instead, SLex and related sialylated, fucosylated glycans are components of more extensive binding determinants.

The best-characterized ligand for the three selectins is P-selectin glycoprotein ligand-1 (PSGL-1), which is a mucin-type glycoprotein expressed on all white blood cells.

https://en.wikipedia.org/wiki/Selectin

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Chapter 2 - Structure and Function: Proteins

Chapter 9 - Point by Point: Structure and Function

Selection

Selection generally refers to the pressures on crops and organisms to evolve. These pressures include natural selection, and, in eukaryotic cells that reproduce sexually, sexual selection. Certain phenotypic traits (characteristics of an organism)—or, on a genetic level, alleles of genes—segregate within a population, where individuals with adaptive advantages or traits tend to succeeded more than their peers when they reproduce, and so contribute more offspring to the succeeding generation.

Whether or not selection takes place depends on the conditions in which the individuals of a species find themselves. Adults, juveniles, embryos, and gamete eggs and sperm all undergo selection. Factors fostering natural selection include sexual selection, primarily caused by mate choice in the mating phase of sexual reproduction, limits on resources (nourishment, habitat space, mates) and the existence of threats (predators, disease, adverse weather). Biologists often refer to such factors as selective or evolutionary pressures.

Natural selection has, since the 1930s, included sexual selection because biologists at the time did not think it was of great importance though it has become to be seen as more important in the 21st Century. Other subcategories of natural selection include ecological selection, stabilizing selection, disruptive selection and directional selection. Selective breeding can be seen in the breeding of dogs, and the domestication of farm animals and crops, now commonly known as selective breeding.

https://en.wikipedia.org/wiki/Selection_(biology)

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Selenium

Selenium is a chemical element with symbol Se and atomic number 34. Sel
are toxic in large amounts, but trace amounts are necessary for cellular fun
many organisms, including all animals. Selenium is an ingredient in many
mins and other dietary supplements, including infant formula. It is a comp
antioxidant enzymes glutathione peroxidase and thioredoxin reductase (wh
rectly reduce certain oxidized molecules in animals and some plants). It is a
in three deiodinase enzymes, which convert one thyroid hormone to anothe
requirements in plants differ by species, with some plants requiring relative
amounts, and others apparently requiring none.

https://en.wikipedia.org/wiki/Selenium

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Selenocysteine

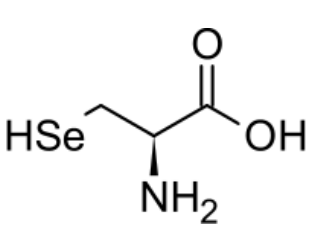
Selenocysteine (abbreviated as Sec or U, in older publications also as Se-Cys) is the 21st proteinogenic amino acid.

Selenocysteine exists naturally in three domains of life, but not in every lineage, as a building block of selenoproteins. Selenocysteine is a cysteine analogue with a selenium-containing selenol group in place of the sulfur-containing thiol group.

Unlike other amino acids present in biological proteins, selenocysteine is not coded for directly in the genetic code. Instead, it is encoded in a special way by a UGA codon, which is normally a stop codon. Such a mechanism is called translational recoding and its efficiency depends on the selenoprotein being synthesized and on translation initiation factors. When cells are grown in the absence of selenium, translation of selenoproteins terminates at the UGA codon, resulting in a truncated, nonfunctional enzyme. The UGA codon is made to encode selenocysteine by the presence of a selenocysteine insertion sequence (SECIS) in the mRNA. The SECIS element is defined by characteristic nucleotide sequences and secondary structure base-pairing patterns. In bacteria, the SECIS element is typically located immediately following the UGA codon within the reading frame for the selenoprotein. In Archaea and in eukaryotes, the SECIS element is in the 3' untranslated region (3' UTR) of the mRNA, and can direct multiple UGA codons to encode selenocysteine residues.

No free pool of selenocysteine exists in the cell. Its high reactivity would cause damage to cells. Instead, cells store selenium in the less reactive selenide form (H_2Se). Selenocysteine synthesis occurs on a specialized tRNA, which also functions to incorporate it into nascent polypeptides.

Selenocysteine is present in several enzymes (for example glutathione peroxidases, tetraiodothyronine 5' deiodinases, thioredoxin reductases, formate dehydrogenases, glycine reductases, selenophosphate synthetase 2, methionine-R-sulfoxide reductase B1 (SEPX1), and some hydrogenases).



https://en.wikipedia.org/wiki/Selenocysteine

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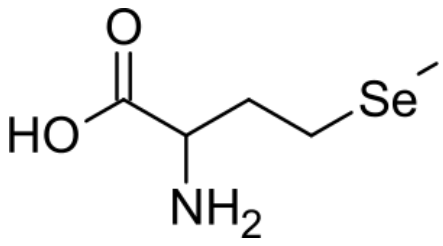
Selenomethionine

Selenomethionine is a naturally occurring amino acid. The L-selenomethionine enantiomer is the main form of selenium found in Brazil nuts, cereal grains, soybeans, and grassland legumes. *In vivo*, selenomethionine is randomly incorporated instead of methionine. Selenomethionine is readily oxidized.

Selenomethionine's antioxidant activity arises from its ability to deplete reactive oxygen species. Selenium and sulfur are chalcogens that share many chemical properties so the substitution of methionine with selenomethionine may have only a limited effect on protein structure and function. However, the incorporation of selenomethionine into tissue proteins and keratin in horses causes alkali disease.

Alkali disease is characterized by emaciation, loss of hair, deformation and shedding of hooves, loss of vitality, and erosion of the joints of long bones.



https://en.wikipedia.org/wiki/Selenomethionine

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Selenoprotein P

In molecular biology, the protein domain SelP stands for selenoprotein P which
only known eukaryotic selenoprotein that contains multiple selenocysteine (Sec
dues. It is a secreted glycoprotein, often found in the plasma. It's precise functi
mains to be elucidated, however it is thought to have antioxidant properties. Th
ticular protein contains two domains: a C terminal and an N terminal domain.
terminal domain is larger than the C terminal and the N-terminal is thought to
cosylated.

SelP may have antioxidant properties. It can attach to epithelial cells, and may
vascular endothelial cells against peroxynitrite toxicity. The high selenium cont
SelP suggests that it may be involved in selenium intercellular transport or stor
The promoter structure of bovine SelP suggests that it may be involved in coun
heavy metal intoxication, and may also have a developmental function.

https://en.wikipedia.org/wiki/Selenoprotein_P

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Selenoproteins

A selenoprotein is any protein that includes a selenocysteine (Sec, U, Se-Cys) amino acid residue. Selenoproteins exist in all major forms of life, eukaryotes, bacteria and archaea. Among eukaryotes, selenoproteins appear to be common in animals, but rare or absent in other phyla (one has been identified in the green alga *Chlamydomonas*, but almost none in other plants or in fungi). Selenium occurs in proteins as unspecifically incorporated selenomethionine, which replaces methionine residues. Proteins containing such unspecifically incorporated selenomethionine residues are not regarded as selenoproteins.

Human selenoproteins include:

- Iodothyronine deiodinases: DIO1, DIO2, DIO3
- Glutathione peroxidases: GPX1, GPX2, GPX3, GPX4, GPX6
- Selenoproteins: SelH (C11orf31), SelI (EPT1), SelK, SelM, SelN (SEPN1), SelO, SelP (SEPP1), SelR (MSRB1), SelS, SelT, SelV, SelW (SEPW1), Sel15
- Selenophosphate synthetase: (SEPHS2, SPS2)
- Thioredoxin reductases: TXNRD1, TXNRD2, TXNRD3

https://en.wikipedia.org/wiki/Selenoprotein

Related Glossary Terms

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Self-splicing RNA

Self-splicing occurs for rare introns that form a ribozyme, performing the fu
the spliceosome by RNA alone. There are three kinds of self-splicing intron
Group II and Group III. Group I and II introns perform splicing similar to t
some without requiring any protein. This similarity suggests that Group I a
trons may be evolutionarily related to the spliceosome. Self-splicing may al
ancient, and may have existed in an RNA world present before protein. Ab
all bacterial genomes sequenced to date contain at least one Group II intron

https://en.wikipedia.org/wiki/RNA_splicing#Self-splicing

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Chapter 4 - Catalysis: Basic Principles

Semi-conservative DNA Replication

Semiconservative replication describes the mechanism by which DNA is replicated in all known cells. This mechanism of replication was one of three models originally proposed for DNA replication:

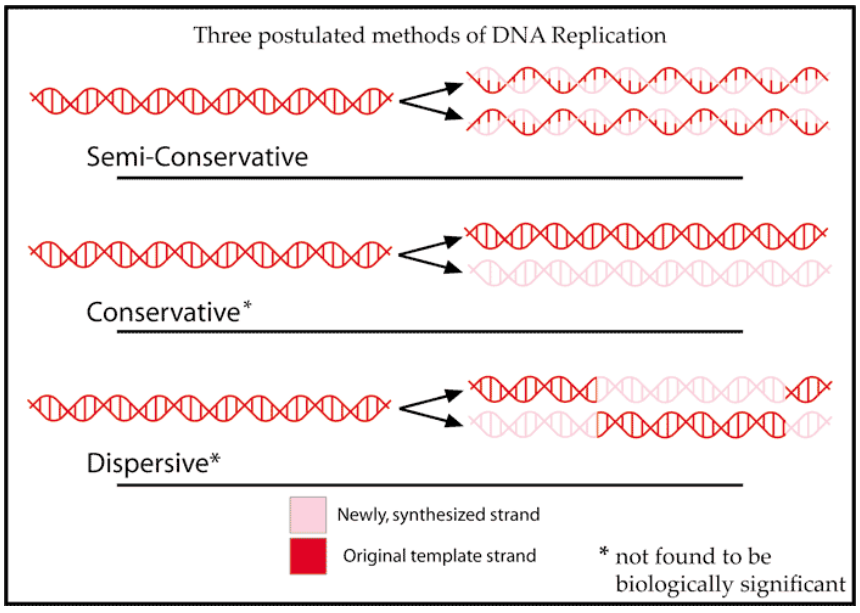
• Semiconservative replication would produce two copies that each contained one of the original strands and one new strand.

• Conservative replication would leave the two original template DNA strands together in a double helix and would produce a copy composed of two new strands containing all of the new DNA base pairs.

Dispersive replication would produce two copies of the DNA, both containing distinct regions of DNA composed of either both original strands or both new strands.

The deciphering of the structure of DNA by Watson and Crick in 1953 suggested that each strand of the double helix would serve as a template for synthesis of a new strand. However, there was no way of knowing how the newly synthesized strands might combine with the template strands to form two double helical DNA molecules. The semiconservative model seemed most reasonable since it would allow each daughter strand to remain associated with its template strand. The semiconservative model was supported by the Meselson-Stahl experiment and other even more revealing experiments that allowed for autoradiographic visualization of the distribution of old and new strands within replicated chromosomes.

Experimental evidence confirmed that two lines were observed, therefore offering compelling evidence for the semi-conservative theory.



https://en.wikipedia.org/wiki/Semiconservative_replication

Sensory Neurons

Sensory neurons are nerve cells that transmit sensory information (sight, s
ing, etc.). They are activated by sensory input, and send projections to othe
of the nervous system, ultimately conveying sensory information to the bra
cord. In complex organisms, when stimulation of a peripheral sensory neur
order sensory neuron) receptor exceeds a set level of intensity, an electrical
travels down the nerve fiber to the central nervous system, where it may ac
tor neuron or another sensory neuron (a second- or third-order neuron), o
less complex organisms, such as the hydra, sensory neurons transmit data
neurons or ganglia. Different types of receptor respond to different kinds o

https://en.wikipedia.org/wiki/Sensory_neuron

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Sequential Model

The sequential model is a theory that describes cooperativity of protein subun
losterism of enzymes. This model for allosteric regulation suggests that the su
multimeric proteins have two conformational states, R and T. In the sequenti
the binding of the ligand causes conformational change, whereas in the Conce
(MWC) model, it does not. Although the subunits go through conformational
independently the switch of one subunit makes the other subunits more likely
change, by reducing the energy needed for subsequent subunits to undergo th
conformational change. In elaboration, the binding of a ligand to one subunit
the protein's shape, thereby making it more thermodynamically favorable for
subunits to switch conformation to the high affinity state. It is named KNF af
Koshland, Némethy and Filmer.

https://en.wikipedia.org/wiki/Sequential_model

Related Glossary Terms

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Serine

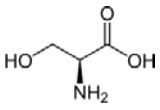
Serine (abbreviated as Ser or S) encoded by the codons UCU, UCC, UCA, UCG, AGU and AGC is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated form under biological conditions), a carboxyl group (which is in the deprotonated form in physiological conditions), and a side chain consisting of a hydroxymethyl group, classifying it as a polar amino acid. It can be synthesized in the human body under normal physiological circumstances, making it a nonessential amino acid.

Serine plays an important role in the catalytic function of many enzymes. It has been shown to occur in the active sites of chymotrypsin, trypsin, and many other enzymes. The so-called nerve gases and many substances used in insecticides have been shown to act by combining with a residue of serine in the active site of acetylcholine esterase, inhibiting the enzyme completely.

Serine sidechains are often hydrogen bonded; the commonest small motifs formed are ST turns, ST motifs (often at the beginning of alpha helices) and ST staples (usually at the middle of alpha helices).

As a constituent (residue) of proteins, its side chain can undergo O-linked glycosylation, which may be functionally related to diabetes. It is one of three amino acid residues that are commonly phosphorylated by kinases during cell signaling in eukaryotes. Phosphorylated serine residues are often referred to as phosphoserine.

Serine proteases are a common type of protease.



https://en.wikipedia.org/wiki/Serine

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Serine Hydroxymethyltransferase

Serine hydroxymethyltransferase (SHMT) is a PLP dependent enzyme whic
important role in cellular one-carbon pathways by catalyzing the reversible
ous conversions of L-serine to glycine and tetrahydrofolate (THF)to 5,10-
methylenetetrahydrofolate. This reaction provides the largest part of the or
units available to the cell.

As well as its primary role in folate metabolism, SHMT also catalyzes other
that may be biologically significant, including the conversion of 5,10-
methenyltetrahydrofolate to 10-formyltetrahydrofolate. When coupled with
tetrahydrofolate synthase and tetrahydropteroate, cSHMT also catalyzes th
sion of formate to serine.

https://en.wikipedia.org/wiki/Serine_hydroxymethyltransferase

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Serine Protease

Serine proteases (or serine endopeptidases) are enzymes that cleave peptide bonds in proteins, in which serine serves as the nucleophilic amino acid at the (enzyme's) active site. They are found ubiquitously in both eukaryotes and prokaryotes. Serine proteases fall into two broad categories based on their structure: chymotrypsin-like (trypsin-like) or subtilisin-like. In humans, they are responsible for co-ordinating various physiological functions, including digestion, immune response, blood coagulation and reproduction.

The main player in the catalytic mechanism in the chymotrypsin and subtillisin-related enzymes mentioned above is the catalytic triad. The triad is located in the active site of the enzyme, where catalysis occurs, and is preserved in all serine protease enzymes. The triad is a coordinated structure consisting of three amino acids: His 57, Ser 195 (hence the name "serine protease") and Asp 102. These three key amino acids each play an essential role in the cleaving ability of the proteases. While the amino acid members of the triad are located far from one another on the sequence of the protein, due to folding, they will be very close to one another in the heart of the enzyme. The particular geometry of the triad members are highly characteristic to their specific function: it was shown that the position of just four points of the triad characterize the function of the containing enzyme.

In the event of catalysis, an ordered mechanism occurs in which several intermediates are generated. The catalysis of the peptide cleavage can be seen as a ping-pong catalysis, in which a substrate binds (in this case, the polypeptide being cleaved), a product is released (the N-terminus "half" of the peptide), another substrate binds (in this case, water), and another product is released (the C-terminus "half" of the peptide).

Each amino acid in the triad performs a specific task in this process:
• The serine has an -OH group that is able to act as a nucleophile, attacking the carbonyl carbon of the scissile peptide bond of the substrate.
• A pair of electrons on the histidine nitrogen has the ability to accept the hydrogen from the serine -OH group, thus coordinating the attack of the peptide bond.
• The carboxyl group on the aspartic acid in turn hydrogen bonds with the histidine, making the nitrogen atom mentioned above much more electronegative.

Additional amino acids of the protease, Gly 193 and Ser 195, are involved in creating what is called an oxyanion hole. Both Gly 193 and Ser 195 can donate backbone hydrogens for hydrogen bonding. When the tetrahedral intermediate of step 1 and step 3 are generated, the negative oxygen ion, having accepted the electrons from the carbonyl double bond fits perfectly into the oxyanion hole. In effect, serine proteases preferentially bind the transition state and the overall structure is favored, lowering the activation energy of the reaction. This "preferential binding" is responsible for much of the catalytic efficiency of the enzyme.

https://en.wikipedia.org/wiki/Serine_protease

Related Glossary Terms

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https://en.wikipedia.org/wiki/Serine_protease

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Serine/Threonine Protein Kinases

A serine/threonine protein kinase is a kinase enzyme that phosphorylates the OH group of serine or threonine (which have similar sidechains). At least 125 of the 500+ human protein kinases are serine/threonine kinases (STK).

The term non-specific serine/threonine protein kinase describes a class of enzymes that belong to the family of transferases, specifically protein-serine/threonine kinases. These enzymes transfer phosphates to the oxygen atom of a serine or threonine side-chain in proteins. This process is called phosphorylation. Protein phosphorylation in particular plays a significant role in a wide range of cellular processes and is a very important posttranslational modification.

The chemical reaction performed by these enzymes can be written as

ATP + a protein $\rightleftharpoons$ ADP + a phosphoprotein

While serine/threonine kinases all phosphorylate serine or threonine residues in their substrates, they select specific residues to phosphorylate on the basis of residues that flank the phosphoacceptor site, which together comprise the consensus sequence. Since the consensus sequence residues of a target substrate only make contact with several key amino acids within the catalytic cleft of the kinase (usually through hydrophobic forces and ionic bonds), a kinase is usually not specific to a single substrate, but instead can phosphorylate a whole "substrate family" which share common recognition sequences. While the catalytic domain of these kinases is highly conserved, the sequence variation that is observed in the kinome (the subset of genes in the genome that encode kinases) provides for recognition of distinct substrates. Most kinases are inhibited by a pseudosubstrate that binds to the kinase like a real substrate but lacks the amino acid to be phosphorylated. When the pseudosubstrate is removed, the kinase can perform its normal function.

https://en.wikipedia.org/wiki/Serine/threonine-specific_protein_kinase

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Chapter 2 - Structure and Function: Proteins

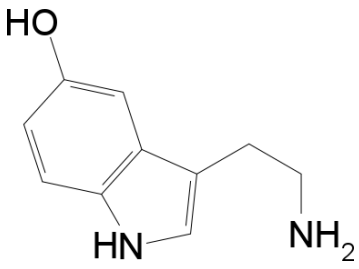
Serotonin

Serotonin is a monoamine neurotransmitter. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal tract (GI tract), blood platelets, and the central nervous system (CNS) of animals, including humans. It is popularly thought to be a contributor to feelings of well-being and happiness.

Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the GI tract, where it is used to regulate intestinal movements. The serotonin is secreted luminally and basolaterally which leads to increased serotonin uptake by circulating platelets and activation after stimulation, which gives increased stimulation of myenteric neurons and gastrointestinal motility. The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions. These include the regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning. Modulation of serotonin at synapses is thought to be a major action of several classes of pharmacological antidepressants.

Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they release serotonin, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting. Serotonin also is a growth factor for some types of cells, which may give it a role in wound healing. There are various serotonin receptors.

Serotonin is metabolized mainly to 5-HIAA, chiefly by the liver. Metabolism involves first oxidation by monoamine oxidase to the corresponding aldehyde. This is followed by oxidation by aldehyde dehydrogenase to 5-HIAA, the indole acetic acid derivative. The latter is then excreted by the kidneys.



https://en.wikipedia.org/wiki/Serotonin

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Serpins

Serpins are a superfamily of proteins with similar structures that were first identified for their protease inhibition activity and are found in all kingdoms of life. The acronym serpin was originally coined because the first serpins to be identified act on chymotrypsin-like serine proteases (serine protease inhibitors). They are notable for their unusual mechanism of action, in which they irreversibly inhibit their target protease by undergoing a large conformational change to disrupt its active site. This contrasts with the more common competitive mechanism for protease inhibitors that bind to and block access to the protease active site.

Protease inhibition by serpins controls an array of biological processes, including coagulation and inflammation, and consequently these proteins are the target of medical research. Their unique conformational change also makes them of interest to the structural biology and protein folding research communities. The conformational-change mechanism confers certain advantages, but it also has drawbacks: serpins are vulnerable to mutations that can result in serpinopathies such as protein misfolding and the formation of inactive long-chain polymers. Serpin polymerization not only reduces the amount of active inhibitor, but also leads to accumulation of the polymers, causing cell death and organ failure.

Although most serpins control proteolytic cascades, some proteins with a serpin structure are not enzyme inhibitors, but instead perform diverse functions such as storage (as in egg white—ovalbumin), transport as in hormone carriage proteins (thyroxine-binding globulin, cortisol-binding globulin) and molecular chaperoning (HSP47). The term serpin is used to describe these members as well, despite their non-inhibitory function, since they are evolutionarily related.

https://en.wikipedia.org/wiki/Serpin

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Serum Albumin

Serum albumin, often referred to simply as blood albumin, is an albumin (a type of globular protein) found in vertebrate blood. Human serum albumin is encoded by the ALB gene. Other mammalian forms, such as bovine serum albumin, are chemically similar.

Serum albumin is produced by the liver, occurs dissolved in blood plasma and is the most abundant blood protein in mammals. Albumin is essential for maintaining the oncotic pressure needed for proper distribution of body fluids between blood vessels and body tissues. Without albumin, the high pressure in the blood vessels would force more fluids out into the tissues. It also acts as a plasma carrier by non-specifically binding several hydrophobic steroid hormones and as a transport protein for hemin and fatty acids. Too much or too little circulating serum albumin may be harmful. Albumin in the urine usually denotes the presence of kidney disease. Occasionally albumin appears in the urine of normal persons following long standing (postural albuminuria).

Albumin functions primarily as a carrier protein for steroids, fatty acids, and thyroid hormones in the blood and plays a major role in stabilizing extracellular fluid volume by contributing to oncotic pressure (known also as colloid osmotic pressure) of plasma.

Because smaller animals (for example rats) function at a lower blood pressure, they need less oncotic pressure to balance this, and thus need less albumin to maintain proper fluid distribution.

https://en.wikipedia.org/wiki/Serum_albumin

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Serum Amyloid A

Serum amyloid A (SAA) proteins are a family of apolipoproteins associated with high-density lipoprotein (HDL) in plasma. Different isoforms of SAA are expressed constitutively (constitutive SAAs) at different levels or in response to inflammatory stimuli (acute phase SAAs). These proteins are produced predominantly by the liver. The conservation of these proteins throughout invertebrates and vertebrates suggests that SAAs play a highly essential role in all animals.

Acute-phase serum amyloid A proteins (A-SAAs) are secreted during the acute phase of inflammation. These proteins have several roles, including the transport of cholesterol to the liver for secretion into the bile, the recruitment of immune cells to inflammatory sites, and the induction of enzymes that degrade extracellular matrix. A-SAAs are implicated in several chronic inflammatory diseases, such as amyloidosis, atherosclerosis, and rheumatoid arthritis.

Three acute-phase SAA isoforms have been reported in mice, called SAA1, SAA2, and SAA3. During inflammation, SAA1 and SAA2 are expressed and induced principally in the liver, whereas SAA3 is induced in many distinct tissues. SAA1 and SAA2 genes are regulated in liver cells by the proinflammatory cytokines IL-1, IL-6, and TNF-α. Both SAA1 and SAA2 are induced up to a 1000-fold in mice under acute inflammatory conditions following exposure to bacterial lipopolysaccharide (LPS). Three A-SAA genes have also been identified in humans, although the third gene, SAA3, is believed to represent a pseudogene that does not generate messenger RNA or protein. Molecular weights of the human proteins are estimated at 11.7 kDa for SAA1 and 12.8 kDa for SAA4.

https://en.wikipedia.org/wiki/Serum_amyloid_A

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Sesquarterpenes

Terpenes are lipid molecules that may be classified by the number of isopre
they contain. A prefix in the name indicates the number of terpene units ne
semble the molecule.

Sesquarterpenes are composed of seven isoprene units and have the molecu
$C_{35}H_{56}$. Sesquarterpenes are typically microbial in their origin. Examples of
penoids are ferrugicadiol and tetraprenylcurcumene.

https://en.wikipedia.org/wiki/Terpene

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Sesquiterpenes

Sesquiterpenes are a class of terpenes that consist of three isoprene units a
empirical formula $C_{15}H_{24}$. Like monoterpenes, sesquiterpenes may be acycl
tain rings, including many unique combinations. Biochemical modification
oxidation or rearrangement produce the related sesquiterpenoids.

https://en.wikipedia.org/wiki/Sesquiterpene

Related Glossary Terms

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Sesterterpenes

Terpenes are lipid molecules that may be classified by the number of isopre
they contain. A prefix in the name indicates the number of terpene units ne
semble the molecule.

Sesterterpenes, having 25 carbons and five isoprene units, are rare relative
sizes. (The sester- prefix means half to three, i.e. two and a half.) An examp
terterpenoid is geranylfarnesol.

https://en.wikipedia.org/wiki/Terpene

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SH_2 domain

The SH_2 (Src Homology 2) domain is a structurally conserved protein domain contained within the Src oncoprotein and in many other intracellular signal-transducing proteins. SH_2 domains allow proteins containing those domains to dock to phosphorylated tyrosine residues on other proteins. SH_2 domains are commonly found in adapter proteins that aid in the signal transduction of receptor tyrosine kinase pathways.

SH_2 domains typically bind a phosphorylated tyrosine residue in the context of a longer peptide motif within a target protein, and SH2 domains represent the largest class of known pTyr-recognition domains.

Phosphorylation of tyrosine residues in a protein occurs during signal transduction and is carried out by tyrosine kinases. In this way, phosphorylation of a substrate by tyrosine kinases acts as a switch to trigger binding to an SH_2 domain-containing protein. Many tyrosine containing short linear motifs that bind to SH_2 domains are conserved across a wide variety of higher Eukaryotes. The intimate relationship between tyrosine kinases and SH_2 domains is supported by their coordinate emergence during eukaryotic evolution.

The function of SH_2 domains is to specifically recognize the phosphorylated state of tyrosine residues, thereby allowing SH_2 domain-containing proteins to localize to tyrosine-phosphorylated sites. This process constitutes the fundamental event of signal transduction through a membrane, in which a signal in the extracellular compartment is "sensed" by a receptor and is converted in the intracellular compartment to a different chemical form, i.e. that of a phosphorylated tyrosine. Tyrosine phosphorylation leads to activation of a cascade of protein-protein interactions whereby SH_2 domain-containing proteins are recruited to tyrosine-phosphorylated sites. This process initiates a series of events which eventually result in altered patterns of gene expression or other cellular responses. The SH_2 domain, which was first identified in the oncoproteins Src and Fps, is about 100 amino-acid residues long. It functions as a regulatory module of intracellular signaling cascades by interacting with high affinity to phosphotyrosine-containing target peptides in a sequence-specific and strictly phosphorylation-dependent manner.

https://en.wikipedia.org/wiki/SH2_domain

Sheets

The β-sheet (also β-pleated sheet) is a form of regular (super)secondary str
proteins. β sheets consist of β strands (also β-strand) connected laterally by
two or three backbone hydrogen bonds, forming a generally twisted, pleate
β-strand is a stretch of polypeptide chain typically 3 to 10 amino acids long
bone in an extended conformation. The higher-level association of β-sheets
implicated in formation of the protein aggregates and fibrils observed in ma
diseases, notably the amyloidoses such as Alzheimer's disease.

https://en.wikipedia.org/wiki/Beta_sheet

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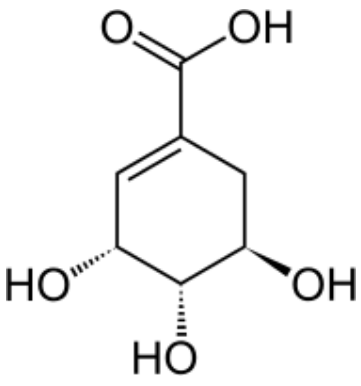
Chapter 2 - Structure & Function: Proteins I

Shikimic Acid

Shikimic acid, more commonly known as its anionic form shikimate, is a cyclohexene, a cyclitol and a cyclohexanecarboxylic acid. It is an important biochemical metabolite in plants and microorganisms. Shikimic acid is also the glycoside part of some hydrolysable tannins.

In the pharmaceutical industry, shikimic acid from the Chinese star anise (*Illicium verum*) is used as a base material for production of oseltamivir (Tamiflu). Although shikimic acid is present in most autotrophic organisms, it is a biosynthetic intermediate and in general found in very low concentrations. The low isolation yield of shikimic acid from the Chinese star anise is blamed for the 2005 shortage of oseltamivir.

Shikimic acid can also be extracted from the seeds of the sweetgum (*Liquidambar styraciflua*) fruit, which is abundant in North America, in yields of around 1.5%. For example, 4 kg of sweetgum seeds is needed for fourteen packages of Tamiflu. By comparison, star anise has been reported to yield 3 to 7% shikimic acid. Biosynthetic pathways in *E. coli* have recently been enhanced to allow the organism to accumulate enough material to be used commercially.



https://en.wikipedia.org/wiki/Shikimic_acid

Shine Dalgarno Sequence

The Shine-Dalgarno (SD) sequence is a ribosomal binding site in prokaryotic messenger RNA, generally located around 8 bases upstream of the start codon AUG. The RNA sequence helps recruit the ribosome to the messenger RNA (mRNA) to initiate protein synthesis by aligning the ribosome with the start codon. The Shine-Dalgarno sequence exists both in bacteria and archaea. It is also present in some chloroplast and mitochondrial transcripts. The six-base consensus sequence is AGGAGG. In *Escherichia coli*, for example, the sequence is AGGAGGU, while subsequence GAGG dominates in *E. coli* virus T4 early genes.

Using a method developed by Hunt, Shine and Dalgarno showed that the nucleotide tract at the 3' terminus of *E. coli* 16S ribosomal RNA (rRNA) is pyrimidine-rich and has the sequence -PyACCUCCUUA 3' OH. They proposed that these ribosomal nucleotides recognize the complementary purine-rich sequence AGGAGGU, which is found upstream of the start codon AUG in a number mRNAs found in viruses that affect E. coli. Many studies have confirmed that base pairing between the Shine-Dalgarno sequence in mRNA and the 3' end of 16S rRNA is of prime importance for initiation of translation by bacterial ribosomes.

Given the complementary relationship between rRNA and the Shine-Dalgarno sequence in mRNA, it was proposed that the sequence at the 3'-end of the rRNA determines the capacity of the prokaryotic ribosome to translate a particular gene in a mRNA. Base pairing between the 3'-end of the rRNA and the Shine-Dalgarno sequence in mRNA is a mechanism by which the cell can distinguish between initiator AUGs and internal and/or out-of-frame AUG sequences. The degree of base pairing also plays a role in determining the rate of initiation at different AUG initiator codons.

https://en.wikipedia.org/wiki/Shine-Dalgarno_sequence

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Sialic Acid

Sialic acid is a generic term for the N- or O-substituted derivatives of neuraminic acid, a monosaccharide with a nine-carbon backbone. It is also the name for the most common member of this group, N-acetylneuraminic acid (Neu5Ac or NANA). Sialic acids are found widely distributed in animal tissues and to a lesser extent in other organisms, ranging from plants and fungi to yeasts and bacteria, mostly in glycoproteins and gangliosides (they occur at the end of sugar chains connected to the surfaces of cells and soluble proteins). That is because it seems to have appeared late in evolution. However, it has been observed in *Drosophila* embryos and other insects and in the capsular polysaccharides of certain strains of bacteria.

The sialic acid family includes 43 derivatives of the nine-carbon sugar neuraminic acid, but these acids unusually appear free in nature. Normally they can be found as components of oligosaccharide chains of mucins, glycoproteins and glycolipids occupying terminal, nonreducing positions of complex carbohydrates on both external and internal membrane areas where they are very exposed and develop important functions.

In humans, the brain has the highest sialic acid concentration, where these acids play an important role in neural transmission and ganglioside structure in synaptogenesis. In general, the amino group bears either an acetyl or a glycolyl group, but other modifications have been described. These modifications along with linkages have shown to be tissue specific and developmentally regulated expressions, so some of them are only found on certain types of glycoconjugates in specific cells. The hydroxyl substituents may vary considerably. Acetyl, lactyl, methyl, sulfate, and phosphate groups have been found.

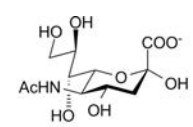
Sialic acid-rich glycoproteins (sialoglycoproteins) bind selectin in humans and other organisms. Metastatic cancer cells often express a high density of sialic acid-rich glycoproteins. This overexpression of sialic acid on surfaces creates a negative charge on cell membranes. This creates repulsion between cells (cell opposition) and helps these late-stage cancer cells enter the blood stream.

Many bacteria also use sialic acid in their biology, although this is usually limited to bacteria that live in association with higher animals (deuterostomes). Many of these incorporate sialic acid into cell surface features like their lipopolysaccharide and capsule, which helps them evade the innate immune response of the host. Other bacteria simply use sialic acid as a good nutrient source, as it contains both carbon and nitrogen and can be converted to fructose-6-phosphate, which can then enter central metabolism.

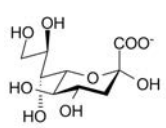
Sialic acid-rich oligosaccharides on the glycoconjugates (glycolipids, glycoproteins, proteoglycans) found on surface membranes help keep water at the surface of cells. The sialic acid-rich regions contribute to creating a negative charge on the cells' surfaces. Since water is a polar molecule with partial positive charges on both hydrogen atoms, it is attracted to cell surfaces and membranes. This also contributes to cellular fluid uptake.

Sialic acid can "hide" mannose antigens on the surface of host cellsThis prevents activation of complement. Sialic acid in the form of polysialic acid is an unusual posttranslational modification that occurs on the neural cell adhesion molecules (NCAMs). In the synapse, the strong negative charge of the polysialic acid prevents NCAM cross-linking of cells.

Two forms of sialic acid are shown below



N-Acetylneuraminic acid
Neu5Ac



2-Keto-3-deoxynonic acid
Kdn

https://en.wikipedia.org/wiki/Sialic_acid

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Sickle Cell Anemia

Sickle-cell disease (SCD) is a group of genetically passed down blood disorders in which red blood cells take on a sickle-like shape under certain circumstances. Problems in sickle cell disease typically begin around 5 to 6 months of age. A number of health problems may develop, such as attacks of pain ("sickle-cell crisis"), anemia, bacterial infections, and stroke.

Sickle-cell disease occurs when a person inherits two abnormal copies of the hemoglobin gene, one from each parent. Several subtypes exist, depending on the exact mutation in each hemoglobin gene. An attack can be set off by temperature changes, stress, dehydration, and high altitude. A person with a single abnormal copy does not usually have symptoms and is said to have sickle-cell trait. Such people are also referred to as carriers.

The care of people with sickle-cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication. Other measures may include blood transfusion, and the medication hydroxycarbamide (hydroxyurea). A small proportion of people can be cured by a transplant of bone marrow cells.

As of 2013 about 3.2 million people have sickle-cell disease while an additional 43 million have sickle-cell trait. About 80% of sickle-cell disease cases are believed to occur in sub-Saharan Africa. It also occurs relatively frequently in parts of India, the Arabian peninsula, and among people of African origin living in other parts of the world. In 2013, it resulted in 176,000 deaths, up from 113,000 deaths in 1990.

https://en.wikipedia.org/wiki/Sickle-cell_disease

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https://en.wikipedia.org/wiki/Sickle-cell_disease

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Chapter 2 - Structure & Function: Amino Acids

Sigma Factor

A sigma factor (σ factor) is a protein needed only for initiation of RNA synthesis. It is a bacterial transcription initiation factor that enables specific binding of RNA polymerase to gene promoters. The specific sigma factor used to initiate transcription of a given gene will vary, depending on the gene and on the environmental signals needed to initiate transcription of that gene.

Every molecule of RNA polymerase holoenzyme contains exactly one σ factor subunit, which in the model bacterium *Escherichia coli* is one of those listed below. The number of σ factors varies between bacterial species. *E. coli* has seven σ factors. σ factors are distinguished by their characteristic molecular weights. For example, σ70 refers to the sigma factor with a molecular weight of 70 kDa.

RNA polymerase holoenzyme complex consisting of core RNA polymerase and a sigma factor executes transcription of a DNA template strand. Once initiation of RNA transcription is complete, the σ factor can leave the complex.

Different sigma factors are utilized under different environmental conditions. These specialized sigma factors bind the promoters of genes appropriate to the environmental conditions, increasing the transcription of those genes.
σ factors in *E. coli*:

• σ70(RpoD) - σA - the "housekeeping" σ factor or also called as primary σ factor, transcribes most genes in growing cells. Every cell has a “housekeeping” σ factor that keeps essential genes and pathways operating. In the case of *E. coli* and other gram-negative rod-shaped bacteria, the "housekeeping" σ factor is σ70. Genes recognized by σ70 all contain similar promoter consensus sequences consisting of two parts. Relative to the DNA base corresponding to the start of the RNA transcript, the consensus promoter sequences are characteristically centered at 10 and 35 nucleotides before the start of transcription (–10 and –35).
• σ19 (FecI) - the ferric citrate σ factor, regulates the fec gene for iron transport
• σ24 (RpoE) - the extracytoplasmic/extreme heat stress σ factor
• σ28 (RpoF) - the flagellar σ factor
• σ32 (RpoH) - the heat shock σ factor, it is turned on when the bacteria are exposed to heat. Due to the higher expression, the factor will bind with a high probability to the polymerase-core-enzyme. Doing so, other heatshock proteins are expressed, which enable the cell to survive higher temperatures. Some of the enzymes that are expressed upon activation of σ32 are chaperones, proteases and DNA-repair enzymes.
• σ38 (RpoS) - the starvation/stationary phase σ factor
• σ54 (RpoN) - the nitrogen-limitation σ factor
There are also anti-σ factors that inhibit the function of σ factors and anti-anti-σ factors that restore σ factor function.

https://en.wikipedia.org/wiki/Sigma_factor

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Sigmoidal

Sigmoidal is a term used to describe the S-like shape of graphical plots. Sig
shapes are seen in the binding curve of oxygen in hemoglobin (plotted as %
bound versus oxygen concentration) and in reaction velocities of allosteric
(plotted as V_0 versus [substrate].

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Signal Peptidase I

Signal peptidase I is an enzyme that catalyses the cleavage of hydrophobic, signal or leader sequences off of a precursor protein. This enzyme is presen rial membranes and in chloroplast thylakoid membranes.

https://en.wikipedia.org/wiki/Signal_peptidase_I

Related Glossary Terms

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Signal Peptidase II

Signal peptidase II is an enzyme that catalyses the release of signal peptides
rial membrane prolipoproteins, including murein prolipoprotein. It also hy
-Xaa-Yaa-Zaa-(S,diacylglyceryl)Cys-, in which Xaa is hydrophobic (preferal
and Yaa (Ala or Ser) and Zaa (Gly or Ala) have small, neutral sidechains. Th
is present in bacterial inner membranes.

https://en.wikipedia.org/wiki/Signal_peptidase_II

Related Glossary Terms

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Signal Peptide Sequences

A signal peptide (sometimes referred to as signal sequence, targeting signal, localization signal, localization sequence, transit peptide, leader sequence or leader peptide) is a short (5-30 amino acids long) peptide present at the N-terminus of the majority of newly synthesized proteins that are destined towards the secretory pathway. These proteins include those that reside either inside certain organelles (the endoplasmic reticulum, golgi or endosomes), secreted from the cell, or inserted into most cellular membranes. Although most type I membrane-bound proteins have signal peptides, the majority of type II and multi-spanning membrane-bound proteins are targeted to the secretory pathway by their first transmembrane domain, which biochemically resembles a signal sequence except that it is not cleaved.

The core of the signal peptide contains a long stretch of hydrophobic amino acids (about 5-16 residues long) that has a tendency to form a single alpha-helix and is also referred to as the "h-region". In addition, many signal peptides begin with a short positively charged stretch of amino acids, which may help to enforce proper topology of the polypeptide during translocation by what is known as the positive-inside rule. Because of its close location to the N-terminus it is called the "n-region". At the end of the signal peptide there is typically a stretch of amino acids that is recognized and cleaved by signal peptidase and therefore named cleavage site. However this cleavage site is absent from transmembrane-domains that serve as signal peptides, which are sometimes referred to as signal anchor sequences. Signal peptidase may cleave either during or after completion of translocation to generate a free signal peptide and a mature protein. The free signal peptides are then digested by specific proteases.

In both prokaryotes and eukaryotes signal sequences may act co-translationally or post-translationally.

https://en.wikipedia.org/wiki/Signal_peptide

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Signal Recognition Particle

The signal recognition particle (SRP) is an abundant, cytosolic, universally conserved ribonucleoprotein (protein-RNA complex) that recognizes and targets specific proteins to the endoplasmic reticulum in eukaryotes and the plasma membrane in prokaryotes.

In eukaryotes, SRP binds to the signal sequence of a newly synthesized peptide as it emerges from the ribosome. This binding leads to the slowing of protein synthesis known as "elongation arrest," a conserved function of SRP that facilitates the coupling of the protein translation and the protein translocation processes. SRP then targets this entire complex (the ribosome-nascent chain complex) to the protein-conducting channel, also known as the translocon, in the ER (endoplasmic reticulum) membrane. This occurs via the interaction and docking of SRP with its cognate SRP receptor that is located in close proximity to the translocon.

In eukaryotes there are three domains between SRP and its receptor that function in guanosine triphosphate (GTP) binding and hydrolysis. These are located in two related subunits in the SRP receptor (SRα and SRβ) and the SRP protein SRP54 (known as Ffh in bacteria). The coordinated binding of GTP by SRP and the SRP receptor has been shown to be a prerequisite for the successful targeting of SRP to the SRP receptor.

Upon docking, the nascent peptide chain is inserted into the translocon channel where it enters into the ER. Protein synthesis resumes as SRP is released from the ribosome. The SRP-SRP receptor complex dissociates via GTP hydrolysis and the cycle of SRP-mediated protein translocation continues.

Once inside the ER, the signal sequence is cleaved from the core protein by signal peptidase. Signal sequences are therefore not a part of mature proteins.

https://en.wikipedia.org/wiki/Signal_recognition_particle

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Signal Transduction

Signal transduction refers to the process of communicating information across a cellular membrane into a cell. It occurs when an extracellular signaling molecule activates a specific receptor located on the cell surface or inside the cell. In turn, this receptor triggers a biochemical chain of events inside the cell, eventually eliciting a response. Depending on the cell, the response may alter the cell's metabolism, shape, gene expression, or ability to divide. The signal can be amplified at any step. Thus, one signaling molecule can generate a response involving hundreds to millions of molecules.

Signal transduction involves the binding of extracellular signaling molecules, also called ligands, to receptors that trigger events inside the cell. The combination of a signaling molecule with a receptor causes a change in the conformation of the receptor, known as receptor activation. This activation is always the initial step (the cause) leading to the cell's ultimate responses (effect) to the messenger. Despite the myriad of these ultimate responses, they are all directly due to changes in particular cell proteins. Intracellular signaling cascades can be started through cell-substratum interactions. Examples are the integrin that binds ligands in the extracellular matrix and steroids. Most steroid hormones have receptors within the cytoplasm and act by stimulating the binding of their receptors to the promoter region of steroid-responsive genes. Examples of signaling molecules include the hormone melatonin, the neurotransmitter acetylcholine and the cytokine interferon γ.

The classifications of signaling molecules do not take into account the molecular nature of each class member. Neurotransmitters range in size from small molecules such as dopamine to neuropeptides such as endorphins. Some molecules may fit into more than one class. For example, epinephrine is a neurotransmitter when secreted by the central nervous system and a hormone when secreted by the adrenal medulla.

https://en.wikipedia.org/wiki/Signal_transduction

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Signaling

Cell signaling is part of a complex system of communication that governs basic activities of cells and coordinates cell actions. The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis. Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes.

Cell signaling can be classified to be mechanical and biochemical based on the type of the signal. Mechanical signals are the forces exerted on the cell and the forces produced by the cell. These forces can both be sensed and responded by the cells. Biochemical signals are the biochemical molecules such as proteins, lipids, ions and gases. These signals can be categorized based on the distance between signaling and responder cells.

Signaling within, between, and among cells is subdivided into the following classifications:
• Intracrine signals are produced by the target cell that stay within the target cell.
• Autocrine signals are produced by the target cell, are secreted, and affect the target cell itself via receptors. Sometimes autocrine cells can target cells close by if they are the same type of cell as the emitting cell. An example of this are immune cells.
• Juxtacrine signals target adjacent (touching) cells. These signals are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.
• Paracrine signals target cells in the vicinity of the emitting cell. Neurotransmitters represent an example.
• Endocrine signals target distant cells. Endocrine cells produce hormones that travel through the blood to reach all parts of the body.

Cells communicate with each other via direct contact (juxtacrine signaling), over short distances (paracrine signaling), or over large distances and/or scales (endocrine signaling). Some cell–cell communication requires direct cell–cell contact. Some cells can form gap junctions that connect their cytoplasm to the cytoplasm of adjacent cells. In cardiac muscle, gap junctions between adjacent cells allows for action potential propagation from the cardiac pacemaker region of the heart to spread and coordinately cause contraction of the heart.

The notch signaling mechanism is an example of juxtacrine signaling (also known as contact-dependent signaling) in which two adjacent cells must make physical contact in order to communicate. This requirement for direct contact allows for very precise control of cell differentiation during embryonic development. In the worm Caenorhabditis elegans, two cells of the developing gonad each have an equal chance of terminally differentiating or becoming a uterine precursor cell that continues to divide. The choice of which cell continues to divide is controlled by competition of cell surface signals. One cell will happen to produce more of a cell surface protein that activates the Notch receptor on the adjacent cell. This activates a feedback loop or system that reduces Notch expression in the cell that will differentiate and that increases Notch on the surface of the cell that continues as a stem cell.

Many cell signals are carried by molecules that are released by one cell and move to make contact with another cell. Endocrine signals are called hormones. Hormones are produced by endocrine cells and they travel through the blood to reach all parts of the body. Specificity of signaling can be controlled if only some cells can respond to a particular hormone. Paracrine signals such as retinoic acid target only cells in the vicinity of the emitting cell. Neurotransmitters represent another example of a paracrine signal. Some signaling molecules can function as both a hormone and a neurotransmitter. For example, epinephrine and norepinephrine can function as hormones when released from the adrenal gland and are transported to the heart by way of the blood stream. Norepinephrine can also be produced by neurons to function as a neurotransmitter within the brain. Estrogen can be released by the ovary and function as a hormone or act locally via paracrine or autocrine signaling. Active species of oxygen and nitric oxide can also act as cellular messengers. This process is dubbed redox signaling.

https://en.wikipedia.org/wiki/Cell_signaling

Related Glossary Terms

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Signaling Cascade

A signaling cascade is the biochemical chain of events/reactions within a ce
triggered by signal transduction, wherein an extracellular signaling molecu
a receptor located on the cell surface resulting in a quick and notable increa
nal. The cascade ultimately elicits a cellular response, which may alter the r
shape, gene expression, or cell life cycle.

https://en.wikipedia.org/wiki/Signal_transduction

Related Glossary Terms

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Chapter 2 - Structure & Function: Lipids

Signaling Pathways

A signaling pathway is the biochemical chain of events/reactions within a c
triggered by signal transduction, wherein an extracellular signaling molecu
a receptor located on the cell surface. The cascade ultimately elicits a cellula
which may alter the metabolism, shape, gene expression, or cell life cycle.

https://en.wikipedia.org/wiki/Signal_transduction

Related Glossary Terms

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Silencers

A silencer is a DNA sequence capable of binding transcription regulation fa
repressors.

A silencer is a sequence-specific element that induces a negative effect on t
tion of its particular gene. There are many positions in which a silencer ele
located in DNA. The most common position is found upstream of the targe
where it can help repress the transcription of the gene. This distance can va
between approximately -20 bp to -2000 bp upstream of a gene. Certain sile
be found downstream of a promoter located within the intron or exon of th
Silencers have also been found within the 3 prime untranslated region (3' U
mRNA.

https://en.wikipedia.org/wiki/Silencer_(DNA)

Related Glossary Terms

Drag related terms here

Silk

Silk is a natural protein fiber, some forms of which can be woven into textil
tein fiber of silk is composed mainly of fibroin and is produced by certain in
to form cocoons. Silk emitted by silkworm larvae consists of two main prote
and fibroin, fibroin being the structural center of the silk, and serecin being
material surrounding it. Fibroin is made up of the amino acids Gly-Ser-Gly
Ala and forms β pleated sheets. Hydrogen bonds form between chains, and
form above and below the plane of the hydrogen bond network.

https://en.wikipedia.org/wiki/Silk#Chemical_properties

Related Glossary Terms

Drag related terms here

SINEs

Short Interspersed Nuclear Elements (SINEs) are short DNA sequences (<5
that represent reverse-transcribed RNA molecules originally transcribed by
lymerase III into transfer RNA, 5S ribosomal RNA, and other small nuclear
mechanism of retrotransposition of these elements is more complicated tha
and less dependent solely on the actual elements that they encode. SINEs d
code a functional reverse transcriptase protein and rely on other mobile ele
transposition. In some cases they may have their own endonuclease that wi
them to cleave their way into the genome, but the majority of SINEs integra
mosomal breaks by using random DNA breaks to prime reverse transcripta
about 1,500,000 copies, SINEs make up about 11% of the human genome.

https://en.wikipedia.org/wiki/Retrotransposon#SINEs

Related Glossary Terms

Drag related terms here

Single-strand DNA Binding Protein

Single-strand DNA-binding protein (SSB) is a 178-amino-acid-long protein fou
coli that binds to single-stranded regions of DNA. Single-stranded DNA is prod
during all aspects of DNA metabolism: replication, recombination, and repair. A
as stabilizing this single-stranded DNA, SSB proteins bind to and modulate the
tion of numerous proteins involved in all of these processes.

Active *E. coli* SSB is composed of four identical 19 kDa subunits. Binding of sin
stranded DNA to the tetramer can occur in different "modes", with SSB occupy
ferent numbers of DNA bases depending on a number of factors, including salt
tration. For example, the (SSB)65 binding mode, in which approximately 65 nu
tides of DNA wrap around the SSB tetramer and contact all four of its subunits,
vored at high salt concentrations *in vitro*. At lower salt concentrations, the (SSB
binding mode, in which about 35 nucleotides bind to only two of the SSB subun
tends to form.

https://en.wikipedia.org/wiki/Single-strand_DNA-binding_protein

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Related Glossary Terms

Drag related terms here

Single-stranded DNA

Deoxyribonucleic acid (DNA) is a molecule that carries most of the genetic
used in the growth, development, functioning and reproduction of all know
ganisms and many viruses. Most DNA molecules consist of two biopolymer
coiled around each other to form a double helix. When that double helix is
into separate strands, each of these is a single-stranded DNA polynucleotid

https://en.wikipedia.org/wiki/DNA#Alternative_DNA_structures

Related Glossary Terms

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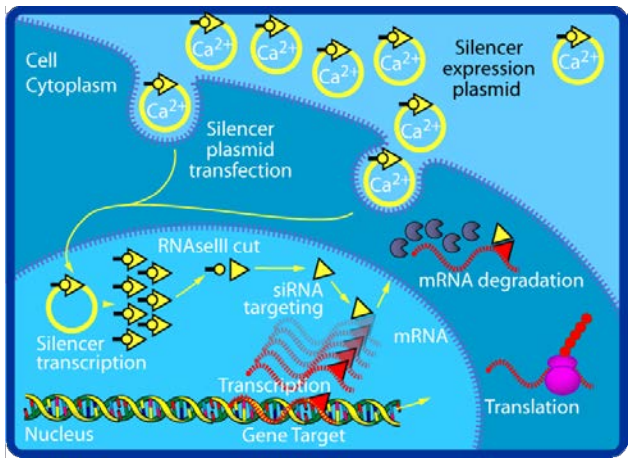
siRNAs

Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA molecules, 20-25 base pairs in length. siRNA is similar to miRNA, and operates within the RNA interference (RNAi) pathway, where it interferes with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, resulting in no translation.

The mechanism by which this occurs is as follows. Once siRNA enters the cell, it binds to a protein complex called Dicer, which dices up siRNA into smaller fragments. One strand of these fragments, in most cases the antisense strand, is loaded into another protein complex called the RNA-induced Silencing Complex (RISC). The strand RISC picks is random, which contributes to the problem of incorrect targeting in siRNA therapy, although in most cases the antisense strand is bound. The strand bound by RISC then links the complex to the messenger RNA (mRNA) by base pairing. The mRNA is cleaved and destroyed so no protein can be synthesized. This leads to a silenced gene, and the disruption of translation.

siRNA can also act in RNAi-related pathways as an antiviral mechanism or play a role in the shaping of the chromatin structure of a genome. siRNAs and their role in post-transcriptional gene silencing (PTGS) was first discovered in plants by David Baulcombe's group at the Sainsbury Laboratory in Norwich, England and reported in Science in 1999. Thomas Tuschl and colleagues soon reported in Nature that synthetic siRNAs could induce RNAi in mammalian cells. This discovery led to a surge in interest in harnessing RNAi for biomedical research and drug development. Significant developments in siRNA therapies have been made, with both organic (carbon based) and inorganic (non-carbon based) nanoparticles, such as these which have been successful in drug delivery to the brain, offering promising methods of delivery into human subjects. However, significant barriers to successful siRNA therapies remain, the most significant of which is off-targeting.



https://en.wikipedia.org/wiki/Small_interfering_RNA

Related Glossary Terms

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Sirtuin

Sirtuin or Sir2 proteins are a class of proteins that possess either mono-ADP-ribosyltransferase, or deacylase activity, including deacetylase, desuccinylase, demalonylase, demyristoylase and depalmitoylase activity. Sirtuins regulate important biological pathways in bacteria, archaea and eukaryotes, relevant to processes like aging, transcription, apoptosis, inflammation and stress resistance, as well as energy efficiency and alertness during low-calorie situations. Sirtuins can also control circadian clocks and mitochondrial biogenesis.

Yeast Sir2 and some, but not all, sirtuins are protein deacetylases. Unlike other known protein deacetylases, which simply hydrolyze acetyl-lysine residues, the sirtuin-mediated deacetylation reaction couples lysine deacetylation to NAD hydrolysis. This hydrolysis yields O-acetyl-ADP-ribose, the deacetylated substrate and nicotinamide, itself an inhibitor of sirtuin activity. The dependence of sirtuins on NAD links their enzymatic activity directly to the energy status of the cell via the cellular NAD:NADH ratio, the absolute levels of NAD, NADH or nicotinamide or a combination of these variables.

Preliminary studies with resveratrol, a possible SIRT1 activator, have led some scientists to speculate that resveratrol may extend lifespan. Further experiments conducted by Rafael de Cabo et al. showed that resveratrol-mimicking drugs such as SRT1720 could extend the lifespan of obese mice by 44%. Comparable molecules are now undergoing clinical trials in humans.

Cell culture research into the behavior of the human sirtuin SIRT1 shows that it behaves like the yeast sirtuin Sir2: SIRT2 assists in the repair of DNA and regulates genes that undergo altered expression with age. Adding resveratrol to the diet of mice inhibit gene expression profiles associated with muscle aging and age-related cardiac dysfunction.

A study performed on transgenic mice overexpressing SIRT6, showed an increased lifespan of about 15% in males. The transgenic males displayed lower serum levels of insulin-like growth factor 1 (IGF1) and changes in its metabolism, which may have contributed to the increased lifespan.

https://en.wikipedia.org/wiki/Sirtuin

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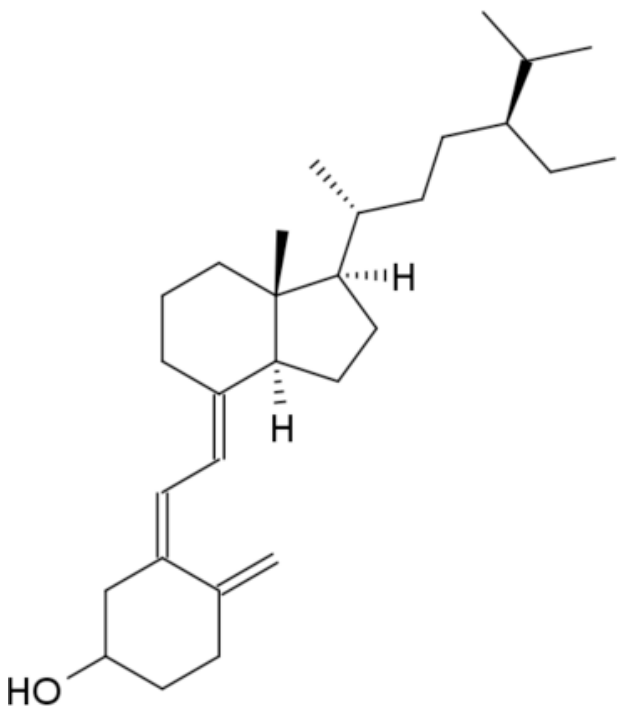
Sitocalciferol

Sitocalciferol, or Vitamin D_5 is a form of vitamin D: a group of fat-soluble secoste
responsible for increasing intestinal absorption of calcium, iron, magnesium, pho
phate, and zinc.



https://en.wikipedia.org/wiki/Vitamin_D
https://en.wikipedia.org/wiki/Vitamin_D5

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Chapter 2 - Structure & Function: Lipids

Size Exclusion Chromatography

Size-exclusion chromatography (SEC), also known as molecular sieve (or gel exclusio chromatography, is a chromatographic method in which molecules in solution are se rated by their size, and in some cases molecular weight. It is usually applied to large molecules or macromolecular complexes such as proteins and industrial polymers. Typically, when an aqueous solution is used to transport the sample through the col- umn, the technique is known as gel-filtration chromatography, versus the name gel p meation chromatography, which is used when an organic solvent is used as a mobile phase. SEC is a widely used polymer characterization method because of its ability to provide good molar mass distribution (Mw) results for polymers.

The main application of gel-filtration chromatography is the fractionation of protein and other water-soluble polymers, while gel permeation chromatography is used to analyze the molecular weight distribution of organic-soluble polymers. Either tech- nique should not be confused with gel electrophoresis, where an electric field is used "pull" or "push" molecules through the gel depending on their electrical charges.

https://en.wikipedia.org/wiki/Size-exclusion_chromatography

Related Glossary Terms

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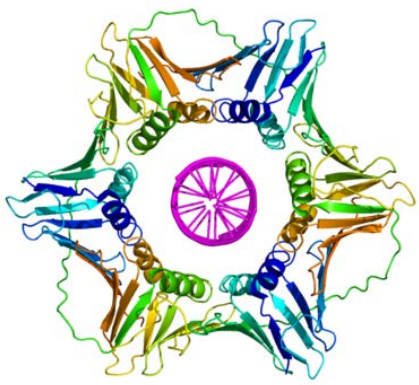
Sliding Clamp

A DNA clamp, also known as a sliding clamp, is a protein fold that serves as a processivity-promoting factor in DNA replication. As a critical component of the DNA polymerase III holoenzyme, the clamp protein binds DNA polymerase and prevents this enzyme from dissociating from the template DNA strand. The clamp-polymerase protein–protein interactions are stronger and more specific than the direct interactions between the polymerase and the template DNA strand. Because one of the rate-limiting steps in the DNA synthesis reaction is the association of the polymerase with the DNA template, the presence of the sliding clamp dramatically increases the number of nucleotides that the polymerase can add to the growing strand per association event. The presence of the DNA clamp can increase the rate of DNA synthesis up to 1,000-fold compared with a nonprocessive polymerase.

Sliding clamps are loaded onto their associated DNA template strands by specialized proteins known as "sliding clamp loaders", which also disassemble the clamps after replication has completed. The binding sites for these initiator proteins overlap with the binding sites for the DNA polymerase, so the clamp cannot simultaneously associate with a clamp loader and with a polymerase. Thus the clamp will not be actively disassembled while the polymerase remains bound. DNA clamps also associate with other factors involved in DNA and genome homeostasis, such as nucleosome assembly factors, Okazaki fragment ligases, and DNA repair proteins. All of these proteins also share a binding site on the DNA clamp that overlaps with the clamp loader site, ensuring that the clamp will not be removed while any enzyme is still working on the DNA. The activity of the clamp loader requires ATP hydrolysis to "close" the clamp around the DNA.

Pictured below - human sliding clamp with DNA in center



https://en.wikipedia.org/wiki/DNA_clamp

Related Glossary Terms

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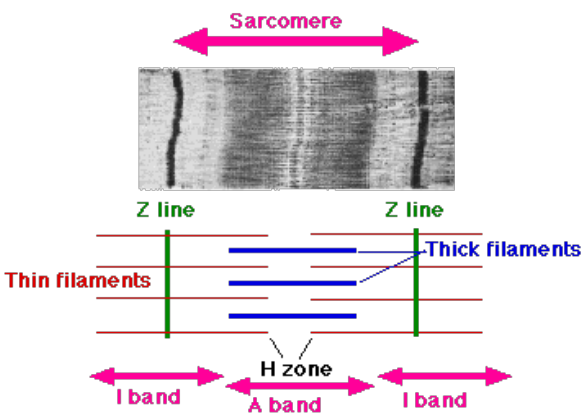
Sliding Filament Theory

The sliding filament theory explains the mechanism of muscle contraction based on muscle proteins that slide past each other to generate movement. It was independently introduced in 1954 by two research teams, one consisting of Andrew F. Huxley and Rolf Niedergerke from the University of Cambridge, and the other consisting of Hugh Huxley and Jean Hanson from the Massachusetts Institute of Technology. It was originally conceived by Hugh Huxley in 1953. Andrew Huxley and Niedergerke introduced it as a "very attractive" hypothesis.

According to the sliding filament theory, the actin (thin) filaments of muscle fibers slide past the myosin (thick) filaments during muscle contraction, while the two groups of filaments remain at relatively constant length. Before the 1950s there were several competing theories on muscle contraction, including electrical attraction, protein folding, and protein modification. The novel theory directly introduced a new concept called cross-bridge theory (classically swinging cross-bridge, now mostly referred to as cross-bridge cycle) which explains the molecular mechanism of sliding filament. Cross-bridge theory states that actin and myosin form a protein complex (classically called actomyosin) by attachment of myosin head on the actin filament, thereby forming a sort of cross-bridge between the two filaments. The two complementary hypotheses turned out to be the correct description, and became a universally accepted explanation of the mechanism of muscle movement.



The theory states that:
1 The backbone of a muscle fiber is actin filaments which extend from Z line up to one end of H zone, where they are attached to an elastic component which they named S filament;
2 Myosin filaments extend from one end of the A band through the H zone up to the other end of the A band;
3 Myosin filaments remain in relatively constant length during muscle stretch or contraction;
4 If myosin filaments contract beyond the length of A band, their ends fold up to form contraction bands;
5 Myosin and actin filamens lie side-by-side in the A band and in the absence of ATP they do not form cross-linkages;
6 During stretching, only the I bands and H zone increase in length, while A bands remain the same;
7 During contraction, actin filaments move into the A bands and the H zone is filled up, the I bands shorten, the Z line comes in contact with the A bands; and
8 The possible driving force of contraction is the actin-myosin linkages which depend on ATP hydrolysis by the myosin.

https://en.wikipedia.org/wiki/Sliding_filament_theory

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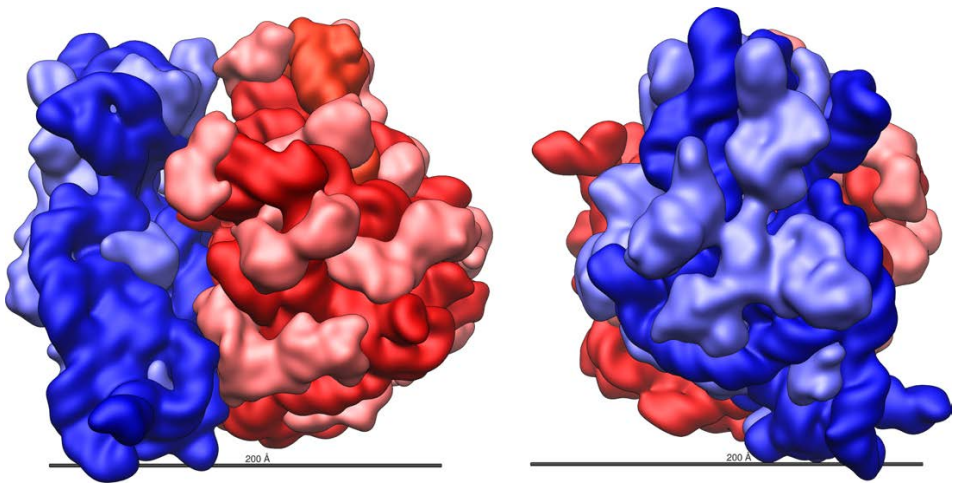
Small Subunit

Ribosomes contain two subunits, a large subunit and a small subunit. In bacteria, the large subunit has a size of 50S and the small subunit has a size of 30S. It is the 30S subunit that holds the 16S rRNA and also the one that is the first one to bind mRNA in the initiation phase of translation. The small subunit below is shown in blue.

The 30S subunit is the site of inhibition for antibiotics such as tetracycline and amino-glycosides.



https://commons.wikimedia.org/wiki/File:Ribosome_shape.png

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Smooth Muscle

Smooth muscle is an involuntary non-striated muscle. It is divided into two the single-unit (unitary) and multiunit smooth muscle. Within single-unit m whole bundle or sheet contracts as a syncytium (i.e. a multinucleate mass o that is not separated into cells). Multiunit smooth muscle tissues innervate cells; as such, they allow for fine control and gradual responses, much like r recruitment in skeletal muscle. The structure and function is basically the s smooth muscle cells in different organs, but the inducing stimuli differ subs order to perform individual effects in the body at individual times.

https://en.wikipedia.org/wiki/Smooth_muscle_tissue

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Chapter 1 - Chemistry, Buffers, and Energy

SNAREs

SNARE proteins (an acronym derived from "SNAP (Soluble NSF Attachment Protein) REceptor") are a large protein superfamily consisting of more than 60 members in yeast and mammalian cells. The primary role of SNARE proteins is to mediate vesicle fusion, that is, the fusion of vesicles with their target membrane bound compartments (such as a lysosome). The best studied SNAREs are those that mediate docking of synaptic vesicles with the presynaptic membrane in neurons. These SNAREs are the targets of the bacterial neurotoxins responsible for botulism and tetanus.

During membrane fusion, v-SNARE and t-SNARE proteins on separate membranes combine to form a trans-SNARE complex, also known as a "SNAREpin". Depending on the stage of fusion of the membranes, these complexes may be referred to differently. During fusion of trans-SNARE complexes, the membranes merge and SNARE proteins involved in complex formation after fusion are then referred to as a "cis"-SNARE complex, because they now reside in a single (or cis) resultant membrane. After fusion, the cis-SNARE complex is bound and disassembled by an adaptor protein, alphaSNAP. Then, the hexameric AAA-ATPase NSF catalyzes the ATP-dependent unfolding of the SNARE proteins and releases them into the cytosol for recycling.

SNAREs are thought to be the core required components of the fusion machinery and can function independently of additional cytosolic accessory proteins. This was demonstrated by engineering "flipped" SNAREs, where the SNARE domains face the extracellular space rather than the cytosol. When cells containing v-SNAREs contact cells containing t-SNAREs, trans-SNARE complexes form and cell-cell fusion ensues.

https://en.wikipedia.org/wiki/SNARE_(protein)

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snoRNAs

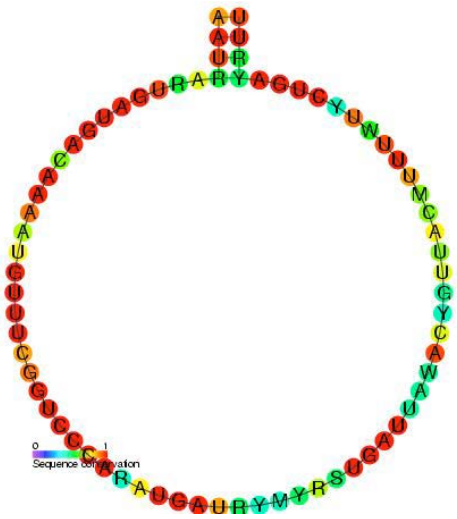
Small nucleolar RNAs (snoRNAs) are a class of small RNA molecules that primarily guide chemical modifications of other RNAs, mainly ribosomal RNAs, transfer RNAs and small nuclear RNAs. There are two main classes of snoRNA, the C/D box snoRNAs, which are associated with methylation, and the H/ACA box snoRNAs, which are associated with pseudouridylation. SnoRNAs are commonly referred to as guide RNAs but should not be confused with the guide RNAs that direct RNA editing in trypanosomes.

After transcription, nascent rRNA molecules (termed pre-rRNA) undergo a series of processing steps to generate the mature rRNA molecule. Prior to cleavage by exo- and endonucleases, the pre-rRNA undergoes a complex pattern of nucleoside modifications. These include methylations and pseudouridylations, guided by snoRNAs.

• Methylation is the attachment or substitution of a methyl group onto various substrates. The rRNA of humans contain approximately 115 methyl group modifications. The majority of these are 2'O-ribose-methylations (where the methyl group is attached to the ribose group).
• Pseudouridylation is the conversion (isomerization) of the nucleoside uridine to a different isomeric form pseudouridine (Ψ). Mature human rRNAs contain approximately 95 Ψ modifications.

Each snoRNA molecule acts as a guide for only one (or two) individual modifications in a target RNA. In order to carry out modification, each snoRNA associates with at least four protein molecules in an RNA/protein complex referred to as a small nucleolar ribonucleoprotein (snoRNP). The proteins associated with each RNA depend on the type of snoRNA molecule (see snoRNA guide families below). The snoRNA molecule contains an antisense element (a stretch of 10-20 nucleotides), which are base complementary to the sequence surrounding the base (nucleotide) targeted for modification in the pre-RNA molecule. This enables the snoRNP to recognize and bind to the target RNA. Once the snoRNP has bound to the target site, the associated proteins are in the correct physical location to catalyze the chemical modification of the target base.

Pictured below - one snoRNA secondary structure.



https://en.wikipedia.org/wiki/Small_nucleolar_RNA

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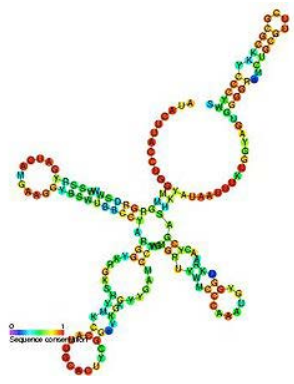
snRNAs

Small nuclear ribonucleic acid (snRNA), also commonly referred to as U-RNA, is a class of small RNA molecules that are found within the splicing speckles and Cajal bodies of the cell nucleus in eukaryotic cells. The length of an average snRNA is approximately 150 nucleotides. They are transcribed by either RNA polymerase II or RNA polymerase III, and studies have shown that their primary function is in the processing of pre-messenger RNA (hnRNA) in the nucleus. They have also been shown to aid in the regulation of transcription factors or RNA polymerase II, and maintaining the telomeres.

snRNA are always associated with a set of specific proteins, and the complexes are referred to as small nuclear ribonucleoproteins (snRNP, often pronounced "snurps"). Each snRNP particle is composed of several Sm proteins, the snRNA component, and snRNP-specific proteins. The most common snRNA components of these complexes are known, respectively, as: U1 spliceosomal RNA, U2 spliceosomal RNA, U4 spliceosomal RNA, U5 spliceosomal RNA, and U6 spliceosomal RNA. Their nomenclature derives from their high uridine content.

A large group of snRNAs is known as small nucleolar RNAs (snoRNAs). These are small RNA molecules that play an essential role in RNA biogenesis and guide chemical modifications of ribosomal RNAs (rRNAs) and other RNA genes (tRNA and snRNAs). They are located in the nucleolus and the Cajal bodies of eukaryotic cells (the major sites of RNA synthesis), where they are called scaRNAs (small Cajal body-specific RNAs).

Shown below - U1 snRNA



https://en.wikipedia.org/wiki/Small_nuclear_RNA

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snRNPs

snRNPs (pronounced "snurps"), or small nuclear ribonucleo proteins, are RNA-protein complexes that combine with unmodified pre-mRNA and various other proteins to form a spliceosome, a large RNA-protein molecular complex upon which splicing of pre-mRNA occurs. The action of snRNPs is essential to the removal of introns from pre-mRNA, a critical aspect of post-transcriptional modification of RNA, occurring only in the nucleus of eukaryotic cells. Additionally, U7 snRNP is not involved in splicing at all, as U7 snRNP is responsible for processing the 3′ stem-loop of histone pre-mRNA.

The two essential components of snRNPs are protein molecules and RNA. The RNA found within each snRNP particle is known as small nuclear RNA, or snRNA, and is usually about 150 nucleotides in length. The snRNA component of the snRNP gives specificity to individual introns by "recognizing" the sequences of critical splicing signals at the 5' and 3' ends and branch site of introns. The snRNA in snRNPs is similar to ribosomal RNA in that it directly incorporates both an enzymatic and a structural role.

At least five different kinds of snRNPs join the spliceosome to participate in splicing. They can be visualized by gel electrophoresis and are known individually as: U1, U2, U4, U5, and U6. Their snRNA components are known, respectively, as: U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, and U6 snRNA.

https://en.wikipedia.org/wiki/SnRNP

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Sodium Channels

Sodium channels are integral membrane proteins that form ion channels, conducting sodium ions (Na^+) through a cell's plasma membrane. They are classified according to the trigger that opens the channel for such ions, i.e. either a voltage-change ("Voltage-gated", "voltage-sensitive", or "voltage-dependent" sodium channel also called "VGSCs" or "Nav channel") or a binding of a substance (a ligand) to the channel (ligand-gated sodium channels).

In excitable cells such as neurons, myocytes, and certain types of glia, sodium channels are responsible for the rising phase of action potentials.

Voltage-gated sodium channels play an important role in action potentials. If enough channels open when there is a change in the cell's membrane potential, a small but significant number of Na^+ ions will move into the cell down their electrochemical gradient, further depolarizing the cell. Thus, the more Na^+ channels localized in a region of a cell's membrane the faster the action potential will propagate and the more excitable that area of the cell will be. This is an example of a positive feedback loop. The ability of these channels to assume a closed-inactivated state causes the refractory period and is critical for the propagation of action potentials down an axon.

Na^+ channels both open and close more quickly than K^+ channels, producing an influx of positive charge (Na^+) toward the beginning of the action potential and an efflux (K^+) toward the end. Ligand-gated sodium channels, on the other hand, create the change in the membrane potential in the first place, in response to the binding of a ligand to it.

https://en.wikipedia.org/wiki/Sodium_channel

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Sodium Chloride

Sodium chloride, also known as salt or halite, is an ionic compound with th
formula NaCl, representing a 1:1 ratio of sodium and chloride ions. Sodium
the salt most responsible for the salinity of seawater and of the extracellula
many multicellular organisms.

The long held belief that a high-salt diet raises the risk of cardio-vascular d
coming under scrutiny. More recently, dietary salt was demonstrated to att
tric oxide production. Nitric oxide (NO) contributes to vessel homeostasis b
vascular smooth muscle contraction and growth, platelet aggregation, and l
adhesion to the endothelium.

https://en.wikipedia.org/wiki/Sodium_chloride

Related Glossary Terms

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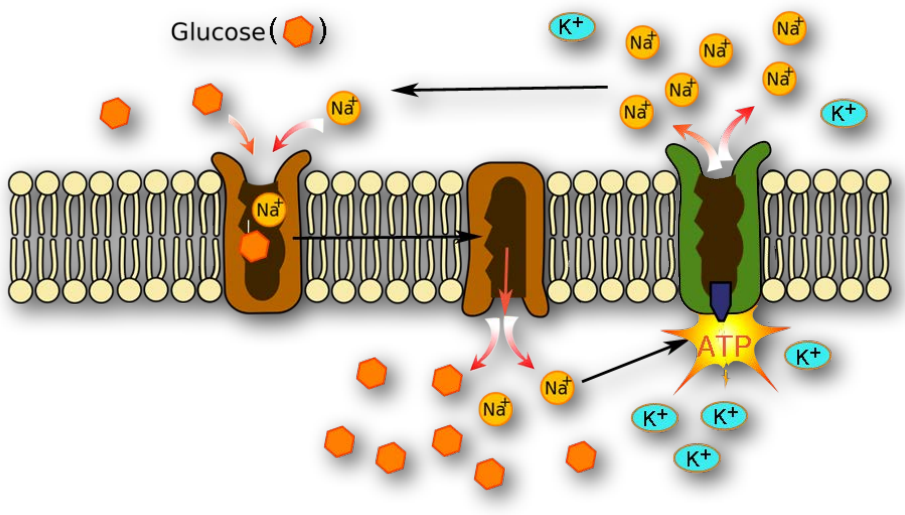
Chapter 1 - Introduction: Water and Buffers

Sodium-glucose Transporter

Sodium-dependent glucose cotransporters (or sodium-glucose linked transporter, SGLT) are a family of glucose transporter found in the intestinal mucosa (enterocytes) of the small intestine (SGLT1) and the proximal tubule of the nephron (SGLT2 in PCT and SGLT1 in PST). They contribute to renal glucose reabsorption.
The SGLT proteins use the energy from the downhill sodium ion gradient created by the ATPase pump to transport glucose across the apical membrane, against an uphill glucose gradient. These co-transporters are an example of secondary active transport.

The Na+/K+ ATPase pump on the basolateral membrane of a cell uses ATP to move 3 sodium ions outward into the blood, while bringing in 2 potassium ions. This action creates a downhill sodium ion gradient from the outside to the inside of the proximal tubule cell (that is, in comparison to both the blood and the tubule itself).

The SGLT proteins use the energy from this downhill sodium ion gradient created by the ATPase pump to transport glucose across the apical membrane, against an uphill glucose gradient. These co-transporters are an example of secondary active transport. Members of the GLUT family of glucose uniporters then transport the glucose across the basolateral membrane, and into the peritubular capillaries. Because sodium and glucose are in the same direction across the membrane, SGLT1 and SGLT2 are known as symporters.



https://en.wikipedia.org/wiki/Sodium-glucose_transport_proteins

Solvent

A solvent is a substance that dissolves a solute (a chemically different liquid
gas), resulting in a solution. A solvent is usually a liquid but can also be a so
The quantity of solute that can dissolve in a specific volume of solvent varie
perature.

https://en.wikipedia.org/wiki/Solvent

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Sonication

Sonication is the act of applying sound energy to agitate particles in a samp
ous purposes. Ultrasonic frequencies (>20 kHz) are usually used, leading to
ess also being known as ultrasonication or ultra-sonication. Sonication can
the production of nanoparticles, such as nanoemulsions, nanocrystals, lipos
wax emulsions, as well as for wastewater purification, degassing, extraction
oil, extraction of anthocyanins and antioxidants, production of biofuels, cru
phurization, cell disruption, polymer and epoxy processing, adhesive thinn
many other processes.

https://en.wikipedia.org/wiki/Sonication

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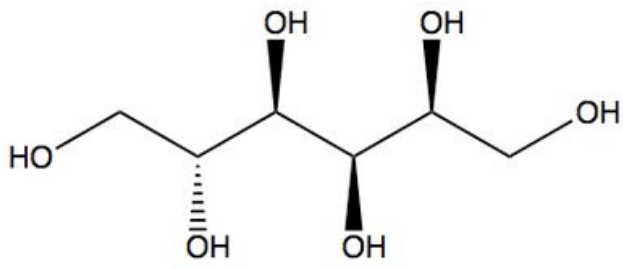
Sorbitol

Sorbitol, also known as glucitol, is a sugar alcohol with a sweet taste which the human body metabolizes slowly. It can be obtained by reduction of glucose, changing the aldehyde group to a hydroxyl group. Most sorbitol is made from corn syrup, but it is also found in apples, pears, peaches, and prunes. It is converted to fructose by sorbitol-6-phosphate 2-dehydrogenase. Sorbitol is an isomer of mannitol, another sugar alcohol. The two differ only in the orientation of the hydroxyl group on carbon 2. While similar, the two sugar alcohols have very different sources in nature, melting points, and uses.

Sorbitol is a sugar substitute. It may be listed under the inactive ingredients listed for some foods and products. Its INS number and E number is 420. Sorbitol has approximately 60% the sweetness of sucrose (table sugar). Sorbitol is referred to as a nutritive sweetener because it provides dietary energy: 2.6 kilocalories (11 kilojoules) per gram versus the average 4 kilocalories (17 kilojoules) for carbohydrates. It is often used in diet foods (including diet drinks and ice cream), mints, cough syrups, and sugar-free chewing gum.



https://en.wikipedia.org/wiki/Sorbitol

Related Glossary Terms

SOS Box

SOS box is the region in the promoter of various genes to which the LexA re
binds to repress the transcription of SOS-induced proteins. This occurs in t
of DNA damage. In the presence of DNA damage the binding of LexA is ina
the RecA activator. SOS boxes differ in DNA sequences and binding affinity
LexA from organism to organism. Furthermore, SOS boxes may be present
fashion, which indicates that more than one SOS box can be within the sam

https://en.wikipedia.org/wiki/SOS_box

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SOS Repair

The SOS response is a global response to DNA damage in which the cell cycle is arrested and DNA repair and mutagenesis are induced. The system involves the RecA protein (Rad51 in eukaryotes). The RecA protein, stimulated by single-stranded DNA, is involved in the inactivation of the LexA repressor thereby inducing the response. It is an error-prone repair system that is attributed to mutagenesis.

During normal growth, the SOS genes are negatively regulated by LexA repressor protein dimers. Under normal conditions, LexA binds to a 20-bp consensus sequence (the SOS box) in the operator region for those genes. Some of these SOS genes are expressed at certain levels even in the repressed state, according to the affinity of LexA for their SOS box. Activation of the SOS genes occurs after DNA damage by the accumulation of single stranded (ssDNA) regions generated at replication forks, where DNA polymerase is blocked. RecA forms a filament around these ssDNA regions in an ATP-dependent fashion, and becomes activated. The activated form of RecA interacts with the LexA repressor to facilitate the LexA repressor's self-cleavage from the operator.

Once the pool of LexA decreases, repression of the SOS genes goes down according to the level of LexA affinity for the SOS boxes. Operators that bind LexA weakly are the first to be fully expressed. In this way LexA can sequentially activate different mechanisms of repair. Genes having a weak SOS box (such as lexA, recA, uvrA, uvrB, and uvrD) are fully induced in response to even weak SOS-inducing treatments. Thus the first SOS repair mechanism to be induced is nucleotide excision repair (NER), whose aim is to fix DNA damage without commitment to a full-fledged SOS response.

If, however, NER does not suffice to fix the damage, the LexA concentration is further reduced, so the expression of genes with stronger LexA boxes (such as sulA, umuD, umuC - these are expressed late) is induced. SulA stops cell division by binding to FtsZ, the initiating protein in this process. This causes filamentation, and the induction of UmuDC-dependent mutagenic repair. As a result of these properties, some genes may be partially induced in response to even endogenous levels of DNA damage, while other genes appear to be induced only when high or persistent DNA damage is present in the cell.

https://en.wikipedia.org/wiki/SOS_response

Southern Blot

A Southern blot is a method used in molecular biology for detection of a specific DNA sequence in DNA samples. Southern blotting combines transfer of electrophoresis-separated DNA fragments to a filter membrane and subsequent fragment detection by probe hybridization. Hybridization of the probe to a specific DNA fragment on the filter membrane indicates that this fragment contains DNA sequence that is complementary to the probe. The transfer step of the DNA from the electrophoresis gel to a membrane permits easy binding of the labeled hybridization probe to the size-fractionated DNA. It also allows for the fixation of the target-probe hybrids, required for analysis by autoradiography or other detection methods.

Southern blots performed with restriction enzyme-digested genomic DNA may be used to determine the number of sequences (e.g., gene copies) in a genome. A probe that hybridizes only to a single DNA segment that has not been cut by the restriction enzyme will produce a single band on a Southern blot, whereas multiple bands will likely be observed when the probe hybridizes to several highly similar sequences (e.g., those that may be the result of sequence duplication). Modification of the hybridization conditions (for example, increasing the hybridization temperature or decreasing salt concentration) may be used to increase specificity and decrease hybridization of the probe to sequences that are less than 100% similar.

The technique is performed as follows:

1 Restriction endonucleases are used to cut high-molecular-weight DNA strands into smaller fragments.
2 The DNA fragments are then electrophoresed on an agarose gel to separate them by size.
3 If some of the DNA fragments are larger than 15 kb, then prior to blotting, the gel may be treated with an acid, such as dilute HCl. This depurinates the DNA fragments, breaking the DNA into smaller pieces, thereby allowing more efficient transfer from the gel to membrane.
4 If alkaline transfer methods are used, the DNA gel is placed into an alkaline solution (typically containing sodium hydroxide) to denature the double-stranded DNA. The denaturation in an alkaline environment may improve binding of the negatively charged thymine residues of DNA to a positively charged amino groups of membrane, separating it into single DNA strands for later hybridization to the probe (see below), and destroys any residual RNA that may still be present in the DNA. The choice of alkaline over neutral transfer methods, however, is often empirical and may result in equivalent results.
5 A sheet of nitrocellulose (or, alternatively, nylon) membrane is placed on top of (or below, depending on the direction of the transfer) the gel. Pressure is applied evenly to the gel (either using suction, or by placing a stack of paper towels and a weight on top of the membrane and gel), to ensure good and even contact between gel and membrane. If transferring by suction, 20X SSC buffer is used to ensure a seal and prevent drying of the gel. Buffer transfer by capillary action from a region of high water potential to a region of low water potential (usually filter paper and paper tissues) is then used to move the DNA from the gel onto the membrane. Ion exchange interactions bind the DNA to the membrane due to the negative charge of the DNA and positive charge of the membrane.
6 The membrane is then baked in a vacuum or regular oven at 80 °C for 2 hours (standard conditions, nitrocellulose or nylon membrane) or exposed to ultraviolet radiation (nylon membrane) to permanently attach the transferred DNA to the membrane.
7 The membrane is then exposed to a hybridization probe—a single DNA fragment with a specific sequence whose presence in the target DNA is to be determined. The probe DNA is labelled so that it can be detected, usually by incorporating radioactivity or tagging the molecule with a fluorescent or chromogenic dye. In some cases, the hybridization probe may be made from RNA, rather than DNA. To ensure the specificity of the binding of the probe to the sample DNA, most common hybridization methods use salmon or herring sperm DNA for blocking of the membrane surface and target DNA, deionized formamide, and detergents such as SDS to reduce non-specific binding of the probe.
8 After hybridization, excess probe is washed from the membrane (typically using SSC buffer), and the pattern of hybridization is visualized on X-ray film by autoradiography in the case of a radioactive or fluorescent probe, or by development of color on the membrane if a chromogenic detection method is used.

https://en.wikipedia.org/wiki/Southern_blot

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Chapter 9 - Point by Point: Techniques

Spectrin

Spectrin is a cytoskeletal protein that lines the intracellular side of the plasma membrane in eukaryotic cells. Spectrin forms pentagonal or hexagonal arrangements, forming a scaffolding and playing an important role in maintenance of plasma membrane integrity and cytoskeletal structure. The hexagonal arrangements are formed by tetramers of spectrin subunits associating with short actin filaments at either end of the tetramer. These short actin filaments act as junctional complexes allowing the formation of the hexagonal mesh.

The protein is named spectrin since it was first isolated as a major protein component of human red blood cells which had been treated with mild detergents. The detergents lysed the cells and the hemoglobin and other cytoplasmic components were washed out. In the light microscope the basic shape of the red blood cell could still be seen as the spectrin containing submembranous cytoskeleton preserved the shape of the cell in outline. This became known as a red blood cell "ghost" (spectre), and so the major protein of the ghost was named spectrin.

In certain types of brain injury such as diffuse axonal injury, spectrin is irreversibly cleaved by the proteolytic enzyme calpain, destroying the cytoskeleton. Spectrin cleavage causes the membrane to form blebs and ultimately to be degraded, usually leading to the death of the cell. Spectrin subunits may also be cleaved by caspase family enzymes, and calpain and caspase produce different spectrin breakdown products which can be detected by western blotting with appropriate antibodies. Calpain cleavage may indicate activation of necrosis, while caspase cleavage may indicate apoptosis.

https://en.wikipedia.org/wiki/Spectrin

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Spectroscopy

Spectroscopy is the study of the interaction between matter and electromagnetic radiation. Spectroscopy and spectrography are terms used to refer to the measurement of radiation intensity as a function of wavelength and are often used to describe experimental spectroscopic methods. Spectral measurement devices are referred to as spectrometers, spectrophotometers, spectrographs or spectral analyzers.

Types of spectroscopy are distinguished by the type of radiative energy involved in the interaction. In many applications, the spectrum is determined by measuring changes in the intensity or frequency of this energy. The types of radiative energy studied include:

• Electromagnetic radiation was the first source of energy used for spectroscopic studies. Techniques that employ electromagnetic radiation are typically classified by the wavelength region of the spectrum and include microwave, terahertz, infrared, near infrared, visible and ultraviolet, x-ray and gamma spectroscopy.
• Particles, due to their de Broglie wavelength, can also be a source of radiative energy and both electrons and neutrons are commonly used. For a particle, its kinetic energy determines its wavelength.
• Acoustic spectroscopy involves radiated pressure waves.
• Mechanical methods can be employed to impart radiating energy, similar to acoustic waves, to solid materials.

Types of spectroscopy can also be distinguished by the nature of the interaction between the energy and the material. These interactions include:

• Absorption occurs when energy from the radiative source is absorbed by the material. Absorption is often determined by measuring the fraction of energy transmitted through the material; absorption will decrease the transmitted portion.
• Emission indicates that radiative energy is released by the material. A material's blackbody spectrum is a spontaneous emission spectrum determined by its temperature; this feature can be measured in the infrared by instruments such as the Atmospheric Emitted Radiance Interferometer (AERI). Emission can also be induced by other sources of energy such as flames or sparks or electromagnetic radiation in the case of fluorescence.
• Elastic scattering and reflection spectroscopy determine how incident radiation is reflected or scattered by a material. Crystallography employs the scattering of high energy radiation, such as x-rays and electrons, to examine the arrangement of atoms in proteins and solid crystals.
• Impedance spectroscopy studies the ability of a medium to impede or slow the transmittance of energy. For optical applications, this is characterized by the index of refraction.
• Inelastic scattering phenomena involve an exchange of energy between the radiation and the matter that shifts the wavelength of the scattered radiation. These include Raman and Compton scattering.
• Coherent or resonance spectroscopy are techniques where the radiative energy couples two quantum states of the material in a coherent interaction that is sustained by the radiating field. The coherence can be disrupted by other interactions, such as particle collisions and energy transfer, and so often require high intensity radiation to be sustained. Nuclear magnetic resonance (NMR) spectroscopy is a widely used resonance method and ultrafast laser methods are also now possible in the infrared and visible spectral regions.

https://en.wikipedia.org/wiki/Spectroscopy

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Chapter 2 - Structure & Function: Proteins I

Sphingolipid

Sphingolipids, or glycosylceramides, are a class of lipids containing a backbone of sphingoid bases, a set of aliphatic amino alcohols that includes sphingosine. These compounds play important roles in signal transmission and cell recognition. Sphingolipidoses, or disorders of sphingolipid metabolism, have particular impact on neural tissue. A sphingolipid with an R group consisting of a hydrogen atom only is a ceramide. Other common R groups include phosphocholine, yielding a sphingomyelin, and various sugar monomers or dimers, yielding cerebrosides and globosides, respectively. Cerebrosides and globosides are collectively known as glycosphingolipids.

Simple sphingolipids, which include the sphingoid bases and ceramides, make up the early products of the sphingolipid synthetic pathways.
• Sphingoid bases are the fundamental building blocks of all sphingolipids. The main mammalian sphingoid bases are dihydrosphingosine and sphingosine, while dihydrosphingosine and phytosphingosine are the principle sphingoid bases in yeast. Sphingosine, dihydrosphingosine, and phytosphingosine may be phosphorylated.
• Ceramides, as a general class, are N-acylated sphingoid bases lacking additional head groups.
• Dihydroceramide is produced by N-acylation of dihydrosphingosine. Dihydroceramide is found in both yeast and mammalian systems.
• Ceramide is produced in mammalian systems by desaturation of dihydroceramide by dihydroceramide desaturase 1 (DES1). This highly bioactive molecule may also be phosphorylated to form ceramide-1-phosphate.
• Phytoceramide is produced in yeast by hydroxylation of dihydroceramide at C-4.

Complex sphingolipids may be formed by addition of head groups to ceramide or phytoceramide:
• Sphingomyelins have a phosphocholine or phosphoethanolamine molecule with an ester linkage to the 1-hydroxy group of a ceramide.
• Glycosphingolipids are ceramides with one or more sugar residues joined in a β-glycosidic linkage at the 1-hydroxyl position (see image).
• Cerebrosides have a single glucose or galactose at the 1-hydroxy position.
• Sulfatides are sulfated cerebrosides.
• Gangliosides have at least three sugars, one of which must be sialic acid.
• Inositol-containing ceramides, which are derived from phytoceramide, are produced in yeast. These include inositol phosphorylceramide, mannose inositol phosphorylceramide, and mannose diinositol phosphorylceramide.

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Sphingolipids

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https://en.wikipedia.org/wiki/Sphingolipid

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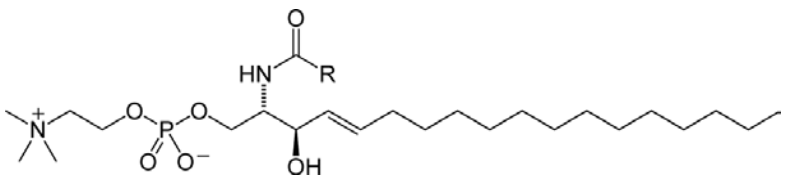
Sphingomyelin

Sphingomyelin is a type of sphingolipid found in animal cell membranes, especially in the membranous myelin sheath that surrounds some nerve cell axons. It usually consists of phosphocholine and ceramide, or a phosphoethanolamine head group. Therefore, sphingomyelins can also be classified as sphingophospholipids. In humans, SPH represents ~85% of all sphingolipids, and typically make up 10-20 mol % of plasma membrane lipids.

Sphingomyelins contain phosphocholine or phosphoethanolamine as their polar head group and are therefore classified along with glycerophospholipids as phospholipids. Indeed, sphingomyelins resemble phosphatidylcholines in their general properties and three-dimensional structure, and in having no net charge on their head groups . Sphingomyelins are present in the plasma membranes of animal cells and are especially prominent in myelin, a membranous sheath that surrounds and insulates the axons of some neurons—thus the name “sphingomyelins.

Ideally, sphingomyelin molecules are shaped like a cylinder, however many molecules of sphingomyelin have a significant chain mismatch (the lengths of the two hydrophobic chains are significantly different). The hydrophobic chains of sphingomyelin tend to be much more saturated than other phospholipids. The main transition phase temperature of sphingomyelins is also higher compared to the phase transition temperature of similar phospholipids, near 37 C. This can introduce lateral heterogeneity in the membrane, generating domains in the membrane bilayer (including abundance in lipid rafts).

Sphingomyelin undergoes significant interactions with cholesterol. Cholesterol has the ability to eliminate the liquid to solid phase transition in phospholipids. Due to sphingomyelin transition temperature being within physiological temperature ranges, cholesterol can play a significant role in the phase of sphingomyelin. Sphingomyelin are also more prone to intermolecular hydrogen bonding than other phospholipids.



https://en.wikipedia.org/wiki/Sphingomyelin

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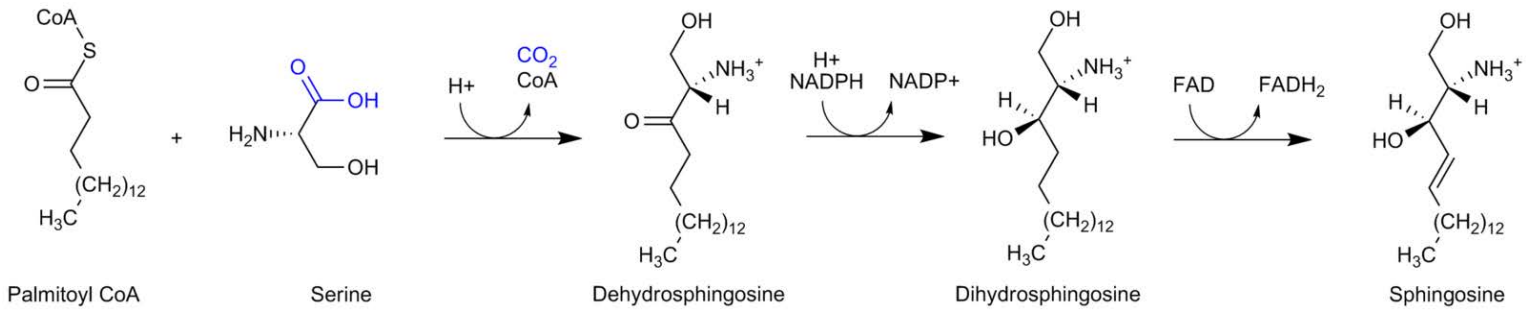
Sphingosine

Sphingosine (2-amino-4-octadecene-1,3-diol) is an 18-carbon amino alcohol with an unsaturated hydrocarbon chain, which forms a primary part of sphingolipids, a class of cell membrane lipids that include sphingomyelin, an important phospholipid.

Sphingosine can be phosphorylated in vivo via two kinases, sphingosine kinase type 1 and sphingosine kinase type 2. This leads to the formation of sphingosine-1-phosphate, a potent signaling lipid. Sphingolipid metabolites, such as ceramides, sphingosine and sphingosine-1-phosphate, are lipid signaling molecules involved in diverse cellular processes.

Sphingosine is synthesized from palmitoyl CoA and serine in a condensation required to yield dehydrosphingosine. Dehydrosphingosine is then reduced by NADPH to dihydrosphingosine (sphinganine), and finally oxidized by FAD to sphingosine.

There is no direct route of synthesis from sphinganine to sphingosine. It has to be acylated first to dihydroceramide, which is then dehydrogenated to ceramide. Sphingosine is formed via degradation of sphingolipid in the lysosome.



https://en.wikipedia.org/wiki/Sphingosine

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Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

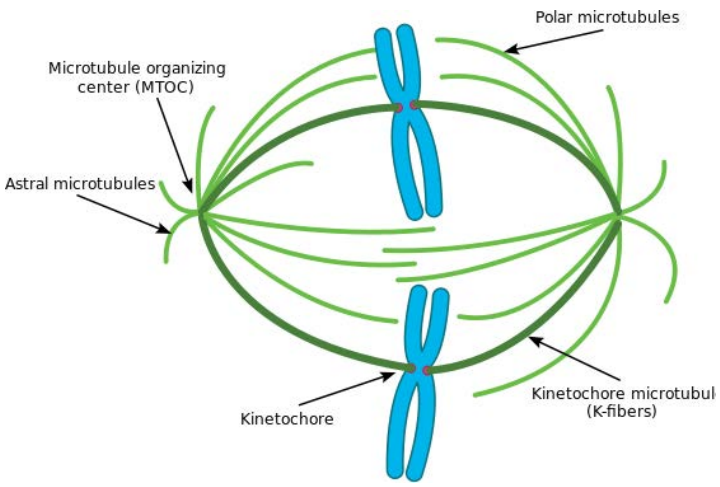
Chapter 9 - Point by Point: Membranes

Spindle

In cell biology, the spindle apparatus refers to the cytoskeletal structure of eukaryotic cells that forms during cell division to separate sister chromatids between daughter cells. It is referred to as the mitotic spindle during mitosis, a process that produces genetically identical daughter cells, or the meiotic spindle during meiosis, a process that produces gametes with half the number of chromosomes of the parent cell.

Besides chromosomes, the spindle apparatus is composed of hundreds of proteins. Microtubules comprise the most abundant components of the machinery. Attachment of microtubules to chromosomes is mediated by kinetochores, which actively monitor spindle formation and prevent premature anaphase onset. Microtubule polymerization and depolymerization dynamics drive chromosome congression. Depolymerization of microtubules generates tension at kinetochores. Bipolar attachment of sister kinetochores to microtubules emanating from opposite cell poles couples opposing tension forces, aligning chromosomes at the cell equator and poising them for segregation to daughter cells. Once every chromosome is bi-oriented, anaphase commences and cohesin, which couples sister chromatids, is severed, permitting the transit of the sister chromatids to opposite poles.

The cellular spindle apparatus includes the spindle microtubules, associated proteins, which include kinesin and dynein molecular motors, condensed chromosomes, and any centrosomes or asters that may be present at the spindle poles depending on the cell type. The spindle apparatus is vaguely ellipsoid in cross section and tapers at the ends. In the wide middle portion, known as the spindle midzone, antiparallel microtubules are bundled by kinesins. At the pointed ends, known as spindle poles, microtubules are nucleated by the centrosomes in most animal cells. Acentrosomal or anastral spindles lack centrosomes or asters at the spindle poles, respectively, and occur for example during female meiosis in most animals. In this instance, a Ran GTP gradient is the main regulator of spindle microtubule organization and assembly. In fungi, spindles form between spindle pole bodies embedded in the nuclear envelope, which does not break down during mitosis.



https://en.wikipedia.org/wiki/Spindle_apparatus

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Spindle Formation

Spindle assembly is largely regulated by phosphorylation events catalyzed by mitotic kinases. Cyclin dependent kinase complexes (CDKs) are activated by mitotic cyclins, whose translation increases during mitosis. CDK1 (also called CDC2) is considered the main mitotic kinase in mammalian cells and is activated by Cyclin B1. Aurora kinases are required for proper spindle assembly and separation.

Aurora A associates with centrosomes and is believed to regulate mitotic entry. Aurora B is a member of the chromosomal passenger complex and mediates chromosome-microtubule attachment and sister chromatid cohesion. Polo-like kinase, also known as PLK, especially PLK1 has important roles in the spindle maintenance by regulating microtubule dynamics.

By the end of DNA replication, sister chromatids are bound together in an amorphous mass of tangled DNA and protein that would be virtually impossible to partition into each daughter cell. To avoid this problem, mitotic entry triggers a dramatic reorganization of the duplicated genome. Sister chromatids are disentangled and resolved from one another. Chromosomes also shorten in length, up to 10,000 fold in animal cells, in a process called condensation. Condensation begins in prophase and chromosomes are maximally compacted into rod-shaped structures by the time they are aligned in the middle of the spindle at metaphase. This gives mitotic chromosomes the classic “X” shape seen in karyotypes, with each condensed sister chromatid linked along their lengths by cohesin proteins and joined, often near the center, at the centromere.

While these dynamic rearrangements are vitally important to ensure accurate and high-fidelity segregation of the genome, our understanding of mitotic chromosome structure remains largely incomplete. A few specific molecular players have been identified, however: Topoisomerase II uses ATP hydrolysis to catalyze decatenation of DNA entanglements, promoting sister chromatid resolution. Condensins are 5-subunit complexes that also use ATP-hydrolysis to promote chromosome condensation. Experiments in *Xenopus* egg extracts have also implicated linker Histone H1 as an important regulator of mitotic chromosome compaction.

https://en.wikipedia.org/wiki/Spindle_apparatus#Regulation_of_spindle_assembly

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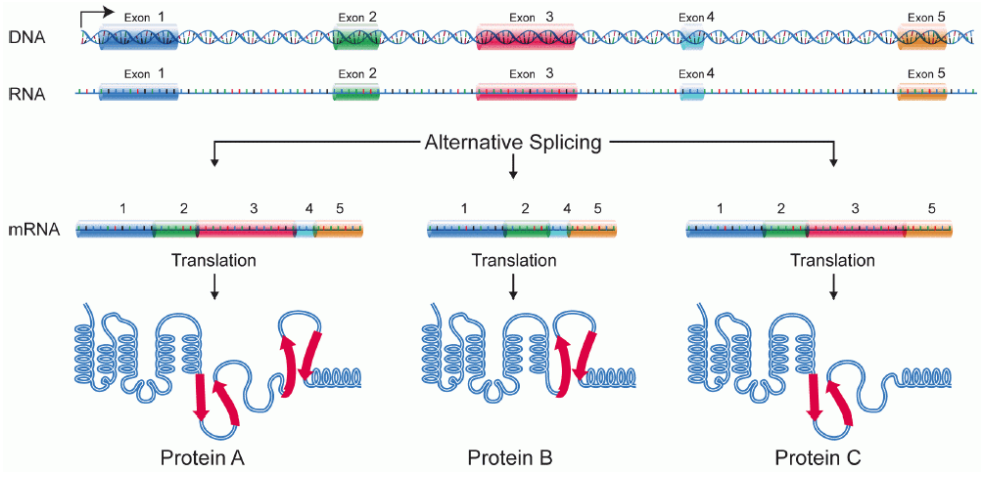
Splice Variant

Alternative splicing is a regulated process during gene expression that results in a single gene coding for multiple proteins. These multiple proteins from the same gene are known as splice variants. In this process, particular exons of a gene may be included within or excluded from the final, processed messenger RNA (mRNA) produced from that gene. Consequently, the proteins translated from alternatively spliced mRNAs will contain differences in their amino acid sequence and, often, in their biological functions. Notably, alternative splicing allows the human genome to direct the synthesis of many more proteins than would be expected from its 20,000 protein-coding genes. Alternative splicing is sometimes termed differential splicing.

Alternative splicing occurs as a normal phenomenon in eukaryotes, where it greatly increases the biodiversity of proteins that can be encoded by the genome. In humans, ~95% of multi-exonic genes are alternatively spliced. There are numerous modes of alternative splicing observed, of which the most common is exon skipping. In this mode, a particular exon may be included in mRNAs under some conditions or in particular tissues, and omitted from the mRNA in others.

The production of alternatively spliced mRNAs is regulated by a system of *trans*-acting proteins that bind to *cis*-acting sites on the primary transcript itself. Such proteins include splicing activators that promote the usage of a particular splice site, and splicing repressors that reduce the usage of a particular site. Mechanisms of alternative splicing are highly variable, and new examples are constantly being found, particularly through the use of high-throughput techniques. Researchers hope to fully elucidate the regulatory systems involved in splicing, so that alternative splicing products from a given gene under particular conditions could be predicted by a "splicing code".

Abnormal variations in splicing are also implicated in disease. A large proportion of human genetic disorders result from splicing variants. Abnormal splicing variants are also thought to contribute to the development of cancer, and splicing factor genes are frequently mutated in different types of cancer.



https://en.wikipedia.org/wiki/Alternative_splicing

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Chapter 6 - Metabolism: Fats and Fatty Acids

Spliceosome

A spliceosome is a large and complex molecular machine found primarily within the splicing speckles of the cell nucleus of eukaryotic cells. The spliceosome is assembled from snRNAs and protein complexes. The spliceosome removes introns from a transcribed pre-mRNA, a kind of primary transcript. This process is generally referred to as splicing. Only eukaryotes have spliceosomes and metazoans have a second spliceosome, the minor spliceosome.

Each spliceosome is composed of five small nuclear RNAs (snRNA), and a range of associated protein factors. When these small RNA are combined with the protein factors, they make an RNA-protein complex called snRNP.

The snRNAs that make up the major spliceosome are named U1, U2, U4, U5, and U6, and participate in several RNA-RNA and RNA-protein interactions. The RNA component of the small nuclear ribonucleic protein or snRNP (pronounced "snurp") is rich in uridine (the nucleoside analog of the uracil nucleotide).

The canonical assembly of the spliceosome occurs anew on each hnRNA (pre-mRNA). The hnRNA contains specific sequence elements that are recognized and utilized during spliceosome assembly. These include the 5' end splice, the branch point sequence, the polypyrimidine tract, and the 3' end splice site. The spliceosome catalyzes the removal of introns, and the ligation of the flanking exons.

Introns typically have a GU nucleotide sequence at the 5' end splice site, and an AG at the 3' end splice site. The 3' splice site can be further defined by a variable length of polypyrimidines, called the polypyrimidine tract (PPT), which serves the dual function of recruiting factors to the 3' splice site and possibly recruiting factors to the branch point sequence (BPS). The BPS contains the conserved adenosine required for the first step of splicing.

https://en.wikipedia.org/wiki/Spliceosome

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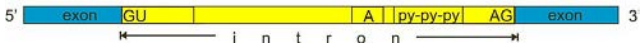
Splicing

In molecular biology, splicing is the editing of the nascent pre-messenger RNA (pre-mRNA) transcript. After splicing, introns are removed and exons are joined together (ligated). For nuclear-encoded genes, splicing takes place within the nucleus either co-transcriptionally or immediately after transcription. For those eukaryotic genes that contain introns, splicing is usually required in order to create an mRNA molecule that can be translated into protein. For many eukaryotic introns, splicing is carried out in a series of reactions which are catalyzed by the spliceosome, a complex of small nuclear ribonucleoproteins (snRNPs). Self-splicing introns, or ribozymes capable of catalyzing their own excision from their parent RNA molecule, also exist.

Spliceosomal introns often reside within the sequence of eukaryotic protein-coding genes. Within the intron, a donor site (5' end of the intron), a branch site (near the 3' end of the intron) and an acceptor site (3' end of the intron) are required for splicing. The splice donor site includes an almost invariant sequence GU at the 5' end of the intron, within a larger, less highly conserved region. The splice acceptor site at the 3' end of the intron terminates the intron with an almost invariant AG sequence. Upstream (5'-ward) from the AG there is a region high in pyrimidines (C and U), or polypyrimidine tract. Further upstream from the polypyrimidine tract is the branchpoint, which includes an adenine nucleotide involved in lariat formation. The consensus sequence for an intron (in IUPAC nucleic acid notation) is: G-G-[cut]-G-U-R-A-G-U (donor site) ... intron sequence ... Y-U-R-A-C (pyrimidine-rich branch sequence 20-50 nucleotides upstream of acceptor site) ... Y-rich-N-C-A-G-[cut]-G (acceptor site).



The spliceosome is a large RNA-protein complex composed of five small nuclear ribonucleoproteins (snRNPs, pronounced 'snurps'). Assembly and activity of the spliceosome occurs during transcription of the pre-mRNA. The RNA components of snRNPs interact with the intron and are involved in catalysis. Two types of spliceosomes have been identified (major and minor) which contain different snRNPs.

- The major spliceosome splices introns containing GU at the 5' splice site and AG at the 3' splice site. It is composed of the U1, U2, U4, U5, and U6 snRNPs and is active in the nucleus. In addition, a number of proteins including U2 small nuclear RNA auxiliary factor 1 (U2AF35), U2AF2 (U2AF65) and SF1 are required for the assembly of the spliceosome. The spliceosome forms different complexes during the splicing process:

Complex E
- The U1 snRNP binds to the GU sequence at the 5' splice site of an intron;
- Splicing factor 1 binds to the intron branch point sequence;
- U2AF1 binds at the 3' splice site of the intron;
- U2AF2 binds to the polypyrimidine tract;

Complex A (pre-spliceosome)
- The U2 snRNP displaces SF1 and binds to the branch point sequence and ATP is hydrolyzed;

Complex B (pre-catalytic spliceosome)
- The U5/U4/U6 snRNP trimer binds, and the U5 snRNP binds exons at the 5' site, with U6 binding to U2;

Complex B*
- The U1 snRNP is released, U5 shifts from exon to intron, and the U6 binds at the 5' splice site;

Complex C (catalytic spliceosome)
- U4 is released, U6/U2 catalyzes transesterification, making the 5'-end of the intron ligate to the A on intron and form a lariat, U5 binds exon at 3' splice site, and the 5' site is cleaved, resulting in the formation of the lariat;

Complex C* (post-spliceosomal complex)
- U2/U5/U6 remain bound to the lariat, and the 3' site is cleaved and exons are ligated using ATP hydrolysis. The spliced RNA is released, the lariat is released and degraded, and the snRNPs are recycled.

This type of splicing is termed canonical splicing or termed the lariat pathway, which accounts for more than 99% of splicing. By contrast, when the intronic flanking sequences do not follow the GU-AG rule, noncanonical splicing is said to occur.

https://en.wikipedia.org/wiki/RNA_splicing

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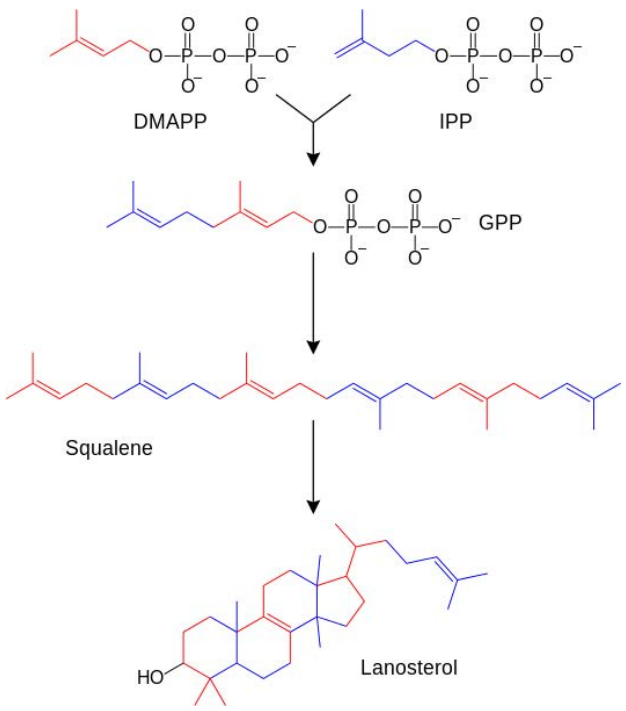
Squalene

Squalene is a natural 30-carbon organic compound originally obtained for commercial purposes primarily from shark liver oil (hence its name), although plant sources (primarily vegetable oils) are now used as well, including amaranth seed, rice bran, wheat germ, and olives. It is also found in high concentrations in the stomach oil of birds in the order *Procellariiformes*. All plants and animals produce squalene as a biochemical intermediate, including humans.

Squalene is a hydrocarbon and a triterpene, and is a natural and vital part of the synthesis of all plant and animal sterols, including cholesterol, steroid hormones, and vitamin D in the human body.

Squalene is used in cosmetics, and more recently as an immunologic adjuvant in vaccines. Squalene has been proposed to be an important part of the Mediterranean diet as it may be a chemopreventive substance that protects people from cancer.

In animals, squalene is the biochemical precursor to the whole family of steroids. Oxidation (via squalene monooxygenase) of one of the terminal double bonds of squalene yields 2,3-squalene oxide, which undergoes enzyme-catalyzed cyclization to afford lanosterol, which is then elaborated into cholesterol and other steroids.



https://commons.wikimedia.org/wiki/File:Sterol_synthesis.svg

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Src

Src (pronounced "sarc" as it is short for sarcoma) is a proto-oncogene encoding a tyrosine kinase. Proto-oncogene tyrosine-protein kinase Src, also known as proto-oncogene c-Src or simply c-Src , is a non-receptor tyrosine kinase protein that phosphorylates specific tyrosine residues in other proteins. An elevated level of activity of c-Src tyrosine kinase is suggested to be linked to cancer progression by promoting other signals.

c-Src includes an SH2 domain, an SH3 domain, and a tyrosine kinase domain. c-Src stands for "cellular Src kinase" and should not be confused with "C-terminal Src kinase" (CSK) which is an enzyme which phosphorylates c-Src at its C-terminus and provides negative regulation of Src's enzymatic activity. c-Src is a widely studied member of non-receptor tyrosine kinases which are not associated with a cell-surface receptor.

There are 9 members part of the Src family kinases: c-Src , Yes, Fyn, Fgr, Yrk, Lyn, Blk, Hck, and Lck. c-Src is made up of 6 functional regions: Src homology (SH) 4 domain (SH4 domain), unique region, SH3 domain, SH2 domain, catalytic domain and short regulatory tail. When Src is inactive, the phosphorylated tyrosine group at the 527 position interacts with the SH2 domain which helps the SH3 domain interact with the flexible linker domain and thereby keeps the inactive unit tightly bound. The activation of c-Src causes the dephosphorylation of the tyrosine 527. This induces long-range allostery via protein domain dynamics, causing the structure to be destabilized, resulting in the opening up of the SH3, SH2 and kinase domains and the autophosphorylation of the residue tyrosine 416.

c-Src can be activated by many transmembrane proteins that include: adhesion receptors, receptor tyrosine kinases, G-protein coupled receptors and cytokine receptors. Most studies have looked at the receptor tyrosine kinases and examples of these are platelet derived growth factor receptor (PDGFR) pathway and epidermal growth factor receptor (EGFR). When src is activated, it promotes survival, angiogenesis, proliferation and invasion pathways. It also regulates angiogenic factors and vascular permeability after focal cerebral ischemia-reperfusion.

Src contains at least three flexible protein domains, which, in conjunction with myristoylation, can mediate attachment to membranes and determine subcellular localization. The activation of the c-Src pathway has been observed in about 50% of tumors from colon, liver, lung, breast and the pancreas. Since the activation of c-Src leads to the promotion of survival, angiogenesis, proliferation and invasion pathways, the aberrant growth of tumors in cancers is observed. A common mechanism is that there are genetic mutations that result in the increased activity or the overexpression of the c-Src leading to the constant activation of the c-Src.

https://en.wikipedia.org/wiki/Proto-oncogene_tyrosine-protein_kinase_Src

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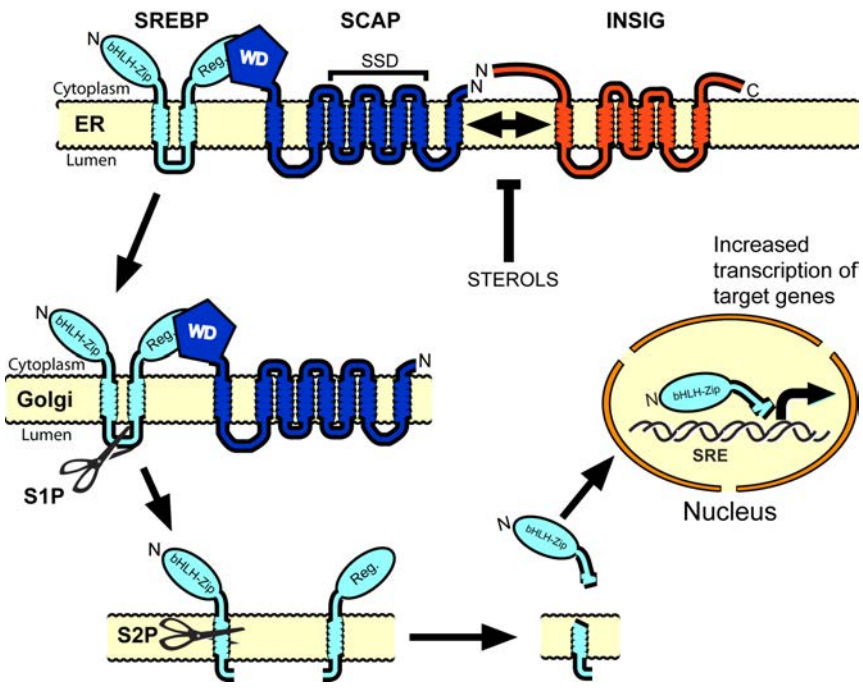
SREBP

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Mammalian SREBPs are encoded by the genes SREBF1 and SREBF2. SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors. Unactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes. In cells with low levels of sterols, SREBPs are cleaved to a water-soluble N-terminal domain that is translocated to the nucleus. These activated SREBPs then bind to specific sterol regulatory element DNA sequences, thus upregulating the synthesis of enzymes involved in sterol biosynthesis. Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feed back loop.

SREB proteins are indirectly required for cholesterol biosynthesis and for uptake and fatty acid biosynthesis. These proteins work with asymmetric sterol regulatory element (StRE). SREBPs have a structure similar to E-box-binding helix-loop-helix (HLH) proteins. However, in contrast to E-box-binding HLH proteins, an arginine residue is replaced with tyrosine making them capable of recognizing StREs and thereby regulating membrane biosynthesis.

A feature of the SREBP pathway is the proteolytic release of a membrane-bound transcription factor, SREBP. Proteolytic cleavage frees it to move through the cytoplasm to the nucleus. Once in the nucleus, SREBP can bind to specific DNA sequences (the sterol regulatory elements or SREs) that are found in the control regions of the genes that encode enzymes needed to make lipids. This binding to DNA leads to the increased transcription of the target genes.



https://en.wikipedia.org/wiki/Sterol_regulatory_element-binding_protein

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Ssp I

Ssp I is a restriction enzyme that recognizes and cuts the following se

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Standard Gibbs Free Energy Change

The change in the standard Gibbs free energy of formation of a compound (
change of Gibbs free energy that accompanies the formation of 1 mole of a s
its standard state from its constituent elements in their standard states (the
ble form of the element at 1 bar of pressure and the specified temperature, u
298.15 K or 25 °C). In biological systems, a slightly modified ΔG° is employ
known as ΔG°’ since it substitutes a solution of pH of 7 instead of having pr
1M, a concentration living systems do not function at.

https://en.wikipedia.org/wiki/Standard_Gibbs_free_energy_of_formatio

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Standard Hydrogen Electrode

The Standard hydrogen electrode (abbreviated SHE), is a redox electrode which forms the basis of the thermodynamic scale of oxidation-reduction potentials. Its absolute electrode potential is estimated to be 4.44 ± 0.02 V at 25 °C, but to form a basis for comparison with all other electrode reactions, hydrogen's standard electrode potential (E_0) is declared to be zero volts at all temperatures. Potentials of any other electrodes are compared with that of the standard hydrogen electrode at the same temperature.

Hydrogen electrode is based on the redox half cell:

$2\ H^+(aq) + 2\ e^- \rightarrow H_2(g)$

This redox reaction occurs at a platinized platinum electrode. The electrode is dipped in an acidic solution and pure hydrogen gas is bubbled through it. The concentration of both the reduced form and oxidized form is maintained at unity. That implies that the pressure of hydrogen gas is 1 bar (100 kPa) and the activity of hydrogen ions in the solution is unity. The activity of hydrogen ions is their effective concentration, which is equal to the formal concentration times the activity coefficient. These unit-less activity coefficients are close to 1.00 for very dilute water solutions, but usually lower for more concentrated solutions.

https://en.wikipedia.org/wiki/Standard_hydrogen_electrode

Related Glossary Terms

Standard Reduction Potential

The standard reduction potential is measured under standard conditions: 2
tivity for each ion participating in the reaction, a partial pressure of 1 bar fo
that is part of the reaction, and metals in their pure state. The standard red
tential is defined relative to a standard hydrogen electrode (SHE) reference
which is arbitrarily given a potential of 0.00 volts.

https://en.wikipedia.org/wiki/Reduction_potential#Standard_reduction_

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Stanley Prusiner

Stanley Benjamin Prusiner M.D (born May 28, 1942) is an American neurologist and biochemist. He is currently the director of the Institute for Neurodegenerative Diseas at University of California, San Francisco (UCSF). Prusiner discovered prions, a class of infectious self-reproducing pathogens primarily or solely composed of protein. He received the Albert Lasker Award for Basic Medical Research in 1994 and the Nobel Prize in Physiology or Medicine in 1997 for his prion research.

https://en.wikipedia.org/wiki/Stanley_B._Prusiner

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Starch

Starch or amylum is a carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. This polysaccharide is produced by most green plants as an energy store. It is the most common carbohydrate in human diets and is contained in large amounts in staple foods such as potatoes, wheat, maize (corn), rice, and cassava.

Pure starch is a white, tasteless and odorless powder that is insoluble in cold water or alcohol. It consists of two types of molecules: the linear and helical amylose and the branched amylopectin. Depending on the plant, starch generally contains 20 to 25% amylose and 75 to 80% amylopectin by weight. Glycogen, the glucose store of animals, is a more branched version of amylopectin.

Starch is processed to produce many of the sugars in processed foods. Dissolving starch in warm water gives wheatpaste, which can be used as a thickening, stiffening or gluing agent. The biggest industrial non-food use of starch is as adhesive in the paper-making process. Starch can be applied to parts of some garments before ironing, to stiffen them.

https://en.wikipedia.org/wiki/Starch

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Start Codon

The start codon is the first codon of a messenger RNA (mRNA) transcript translated by a ribosome. The start codon always codes for methionine in eukaryotes and a modified Met (fMet) in prokaryotes. The most common start codon is AUG.

The start codon is often preceded by a 5' untranslated region (5' UTR). In prokaryotes this includes the ribosome binding site.

Alternative start codons are different from the standard AUG codon and are found in both prokaryotes (bacteria) and eukaryotes. Alternate start codons are still translated as Met when they are at the start of a protein (even if the codon encodes a different amino acid otherwise). This is because a separate transfer RNA (tRNA) is used for initiation.

https://en.wikipedia.org/wiki/Start_codon

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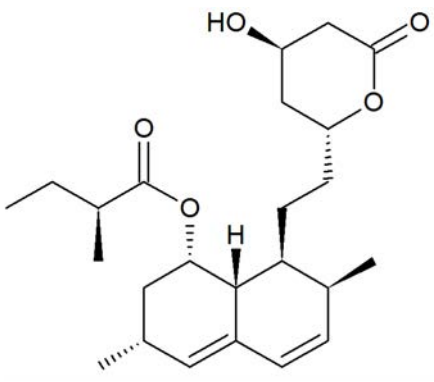
Statin

Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications that inhibit the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol. High cholesterol levels have been associated with cardiovascular disease (CVD). Statins have been found to reduce cardiovascular disease and mortality in those who are at high risk. The evidence is strong that statins are effective for treating CVD in the early stages of a disease (secondary prevention) and in those at elevated risk but without CVD (primary prevention). Side effects of statins include muscle pain, increased risk of diabetes mellitus, and abnormalities in liver enzyme tests. Additionally, they have rare but severe adverse effects, particularly muscle damage.

As of 2010, a number of statins are on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Several combination preparations of a statin and another agent, such as ezetimibe/simvastatin, are also available.

Most evidence suggests that statins are effective in preventing heart disease in those with high cholesterol, but no history of heart disease. A 2013 Cochrane review found a decrease in risk of death and other poor outcomes without any evidence of harm. For every 138 people treated for 5 years one fewer dies and for every 49 treated one fewer has an episode of heart disease. A 2011 review reached similar conclusions and a 2012 review found benefits in both women and men. A 2010 review concluded that treating people with no history of cardiovascular disease reduces cardiovascular events in men but not women, and provides no mortality benefit in either sex. Two other meta analyses published that year, one of which used data obtained exclusively from women, found no mortality benefit in primary prevention.



https://en.wikipedia.org/wiki/Statin

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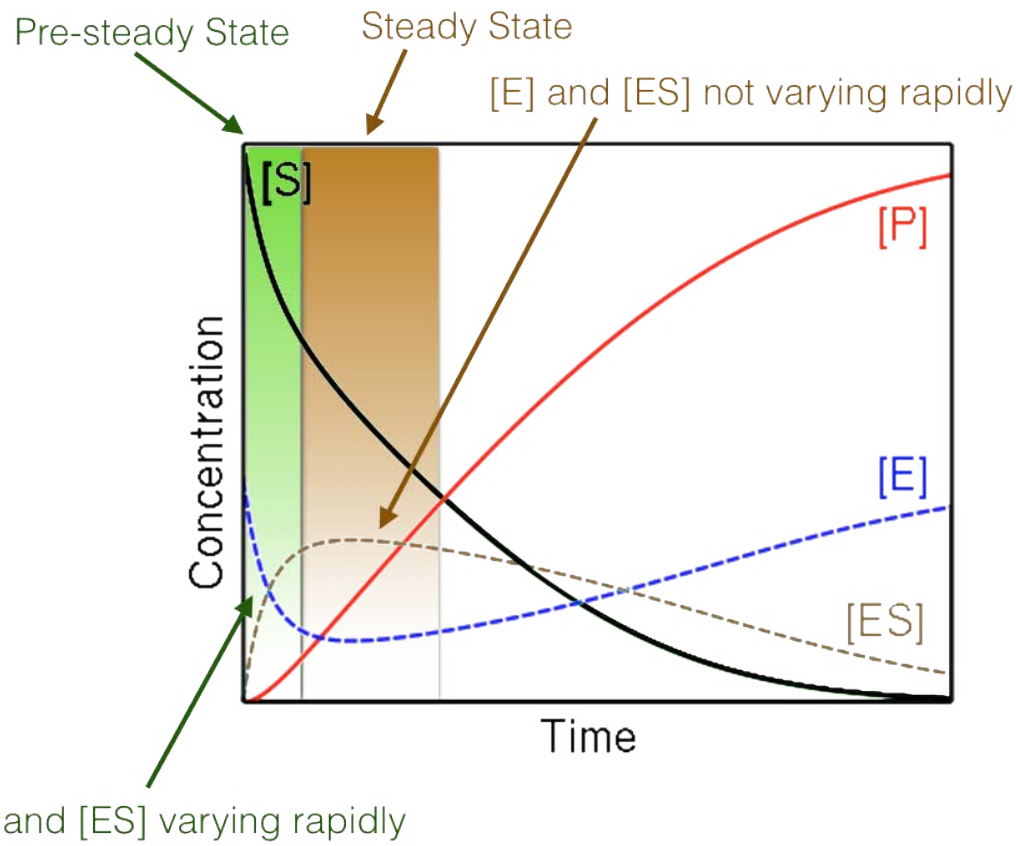
Steady State

In Michaelis-Menten enzyme kinetics, reactions are assumed to be occurring under steady state condition. In this state, the concentration of the ES complex (see below) is relatively constant. This is in contrast to pre-steady state conditions in which the amount of ES complex is rapidly varying.



https://en.wikipedia.org/wiki/Michaelis–Menten_kinetics#Quasi-steady-state_approximation

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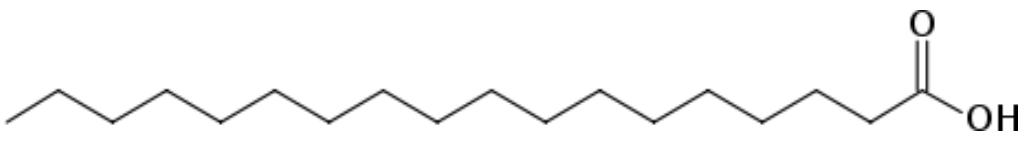
Stearate

Stearic acid (stair-ik or steer-ik) is a saturated fatty acid with an 18-carbon chain and has the IUPAC name octadecanoic acid. It is a waxy solid and its chemical formula is $C_{17}H_{35}CO_2H$. Its name comes from the Greek word στέαρ "stéar", which means tallow. The salts and esters of stearic acid are called stearates. As its ester, stearic acid is one of the most common saturated fatty acids found in nature following palmitic acid. The triglyceride derived from three molecules of stearic acid is called stearin.

Stearic acid is mainly used in the production of detergents, soaps, and cosmetics such as shampoos and shaving cream products. Soaps are not made directly from stearic acid, but indirectly by saponification of triglycerides consisting of stearic acid esters. Esters of stearic acid with ethylene glycol, glycol stearate, and glycol distearate are used to produce a pearly effect in shampoos, soaps, and other cosmetic products. They are added to the product in molten form and allowed to crystallize under controlled conditions. Detergents are obtained from amides and quaternary alkylammonium derivatives of stearic acid.



https://en.wikipedia.org/wiki/Stearic_acid

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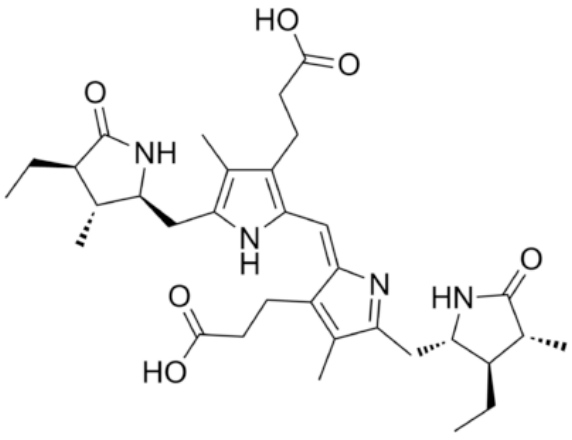
Stercobilin

Stercobilin is a tetrapyrrolic bile pigment and is one end-product of heme catabolism. It is the chemical responsible for the brown color of human feces and was originally isolated from feces in 1932. Stercobilin (and related urobilin) can be used as a marker for biochemical identification of fecal pollution levels in rivers.

Stercobilin results from breakdown of the heme moiety of hemoglobin found in erythrocytes. Macrophages break down senescent erythrocytes and break the heme down into biliverdin, which rapidly reduces to free bilirubin. Bilirubin binds tightly to plasma proteins (especially albumin) in the blood stream and is transported to the liver, where it is conjugated with one or two glucuronic acid residues into bilirubin diglucuronide, and secreted into the small intestine as bile. In the small intestine, some bilirubin glucuronide is converted back to bilirubin via bacterial enzymes in the terminal ileum. This bilirubin is further converted to colorless urobilinogen. Urobilinogen that remains in the colon can either be reduced to stercobilinogen and finally oxidized to stercobilin, or it can be directly reduced to stercobilin. Stercobilin is responsible for the brown color of human feces. Stercobilin is then excreted in the feces.



https://en.wikipedia.org/wiki/Stercobilin

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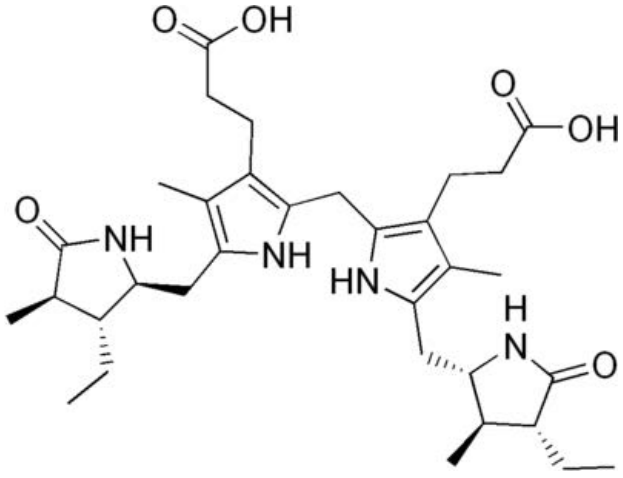
Stercobilinogen

Stercobilinogen (fecal urobilinogen) is a chemical created by bacteria in the gut. It is made of broken-down hemoglobin. It is further processed to become the chemical that gives feces its brown color.

Bilirubin is a pigment that results from the breakdown of the heme portion of hemoglobin. The liver conjugates bilirubin, making it water-soluble and the conjugated form is then excreted in urine as urobilinogen, giving urine its color. In the intestine, bilirubin is converted by bacteria to stercobilinogen. Stercobilinogen is absorbed and excreted by either the liver or the kidney. Stercobilinogen is oxidized to stercobilin, which is responsible for the pigmentation of feces.

In early liver disease, impaired biliary excretion causes sterocobilinogen to be absorbed mostly by the kidney, and, therefore, stercobilinogen will appear in the urine in excess as urobilinogen. This happens because "Stercobilinogen" is simply the name given to Urobilinogen in the GI tract. In fact, its use as a separate term has fallen out of favor due to the confusion.



https://en.wikipedia.org/wiki/Stercobilinogen

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Stereochemistry

Stereochemistry, a subdiscipline of chemistry, involves the study of the relat
arrangement of atoms that form the structure of molecules and their manipu
important branch of stereochemistry is the study of chiral molecules. Stereo
is also known as 3D chemistry because the prefix "stereo-" means "three-
dimensionality".

The study of stereochemistry focuses on stereoisomers and spans the entire s
of organic, inorganic, biological, physical and especially supramolecular che
Stereochemistry includes methods for determining and describing these rela
the effect on the physical or biological properties these relationships impart
molecules in question, and the manner in which these relationships influenc
tivity of the molecules in question (dynamic stereochemistry).

https://en.wikipedia.org/wiki/Stereochemistry

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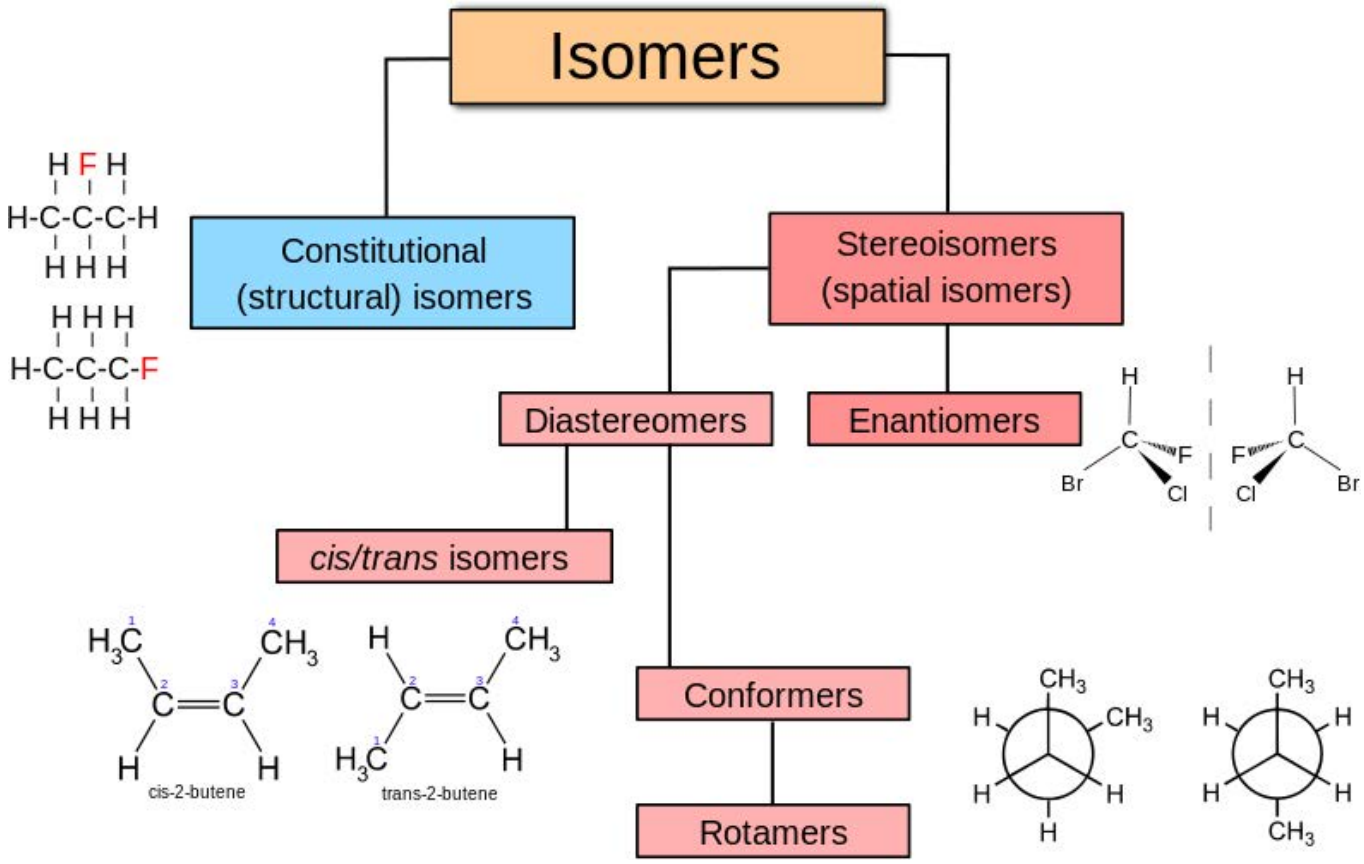
Stereoisomers

Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms (constitution), but differ in the three-dimensional orientations of their atoms in space. This contrasts with structural isomers, which share the same molecular formula, but the bond connections or their order differs. By definition, molecules that are stereoisomers of each other represent the same structural isomer.



https://en.wikipedia.org/wiki/Stereoisomerism

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Steric Hindrance

Steric hindrance occurs when the large size of groups within a molecule pre
chemical reactions that are observed in related molecules with smaller grou

https://en.wikipedia.org/wiki/Steric_effects#Steric_hindrance

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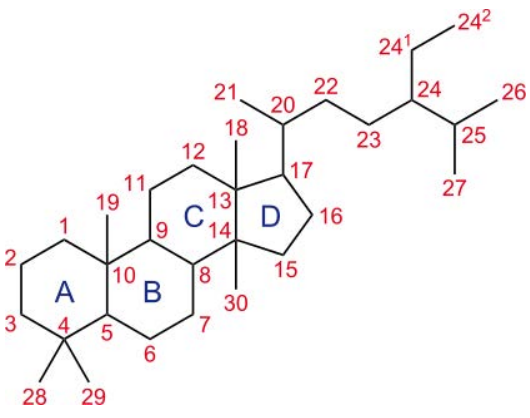
Steroid

A steroid is an organic compound with four rings arranged in a specific configuration. Examples include the dietary lipid cholesterol, the sex hormones estradiol and testosterone and the anti-inflammatory drug dexamethasone. Steroids have two principal biological functions: certain steroids (such as cholesterol) are important components of cell membranes which alter membrane fluidity, and many steroids are signaling molecules which activate steroid hormone receptors.

The steroid core structure is composed of seventeen carbon atoms, bonded in four "fused" rings: three six-member cyclohexane rings (rings A, B and C in the first illustration) and one five-member cyclopentane ring (the D ring). Steroids vary by the functional groups attached to this four-ring core and by the oxidation state of the rings. Sterols are forms of steroids with a hydroxyl group at position three and a skeleton derived from cholestane. They can also vary more markedly by changes to the ring structure (for example, ring scissions which produce secosteroids such as vitamin D3).

Hundreds of steroids are found in plants, animals and fungi. All steroids are manufactured in cells from the sterols lanosterol (animals and fungi) or cycloartenol (plants). Lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene.



https://en.wikipedia.org/wiki/Steroid

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Steroid Hormone Receptors

Steroid hormone receptors are found in the nucleus, cytosol, and also on the plasma membrane of target cells. They are generally intracellular receptors (typically cytoplasmic or nuclear) and initiate signal transduction for steroid hormones which lead to changes in gene expression over a time period of hours to days. The best studied steroid hormone receptors are members of the nuclear receptor subfamily 3 (NR3) that include receptors for estrogen (group NR3A) and 3-ketosteroids (group NR3C). In addition to nuclear receptors, several G protein-coupled receptors and ion channels act as cell surface receptors for certain steroid hormones.

Steroid receptors of the nuclear receptor family are all transcription factors. Depending upon the type of receptor, they are either located in the cytosol and move to the cell nucleus upon activation, or remain in the nucleus waiting for the steroid hormone to enter and activate them. This uptake into the nucleus is facilitated by nuclear localization signal (NLS) found in the hinge region of the receptor. This region of the receptor is covered up by heat shock proteins (HSPs) which bind the receptor until the hormone is present. Upon binding by the hormone the receptor undergoes a conformational change releasing the HSP, and the receptor together with the bound hormone enter the nucleus to act upon transcription.

https://en.wikipedia.org/wiki/Steroid_hormone_receptor

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Steroid Hormones

A steroid hormone is a steroid that acts as a hormone. Steroid hormones can be grouped into 2 classes, corticosteroids (typically made in the adrenal cortex, hence cortico-) and sex steroids (typically made in the gonads or placenta). Within those 2 classes are 5 types according to the receptors to which they bind: glucocorticoids and mineralocorticoids (corticosteroids) and androgens, estrogens, and progestogens (sex steroids). Within those 2 classes are 5 types according to the receptors to which they bind: glucocorticoids and mineralocorticoids (corticosteroids) and androgens, estrogens, and progestogens (sex steroids). Vitamin D derivatives are a sixth closely related hormone system with homologous receptors. They have some of the characteristics of true steroids as receptor ligands.

Steroid hormones help control metabolism, inflammation, immune functions, salt and water balance, development of sexual characteristics, and the ability to withstand illness and injury. The term steroid describes both hormones produced by the body and artificially produced medications that duplicate the action for the naturally occurring steroids.

The natural steroid hormones are generally synthesized from cholesterol in the gonads and adrenal glands. These forms of hormones are lipids. They can pass through the cell membrane as they are fat-soluble, and then bind to steroid hormone receptors (which may be nuclear or cytosolic depending on the steroid hormone) to bring about changes within the cell. Steroid hormones are generally carried in the blood, bound to specific carrier proteins such as sex hormone-binding globulin or corticosteroid-binding globulin. Further conversions and catabolism occurs in the liver, in other "peripheral" tissues, and in the target tissues.

Steroids exert a wide variety of effects, mediated by slow genomic as well as by rapid nongenomic mechanisms. They bind to nuclear receptors in the cell nucleus for genomic actions. Membrane-associated steroid receptors activate intracellular signaling cascades involved in nongenomic actions.

Because steroids and sterols are lipid-soluble, they can diffuse fairly freely from the blood through the cell membrane and into the cytoplasm of target cells. This is in contrast to the actions of non-steroid hormones, which are water-soluble typically peptide hormones, acting through membrane bound receptors and intracellular second messenger systems to exert their effects. In the cytoplasm, the steroid may or may not undergo an enzyme-mediated alteration such as reduction, hydroxylation, or aromatization. In the cytoplasm, the steroid binds to the specific receptor, a large metalloprotein. Upon steroid binding, many kinds of steroid receptor dimerize: Two receptor subunits join together to form one functional DNA-binding unit that can enter the cell nucleus. In some of the hormone systems known, the receptor is associated with a heat shock protein, which is released on the binding of the ligand, the hormone. Once in the nucleus, the steroid-receptor ligand complex binds to specific DNA sequences and induces transcription of its target genes.

https://en.wikipedia.org/wiki/Steroid_hormone

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Sterol

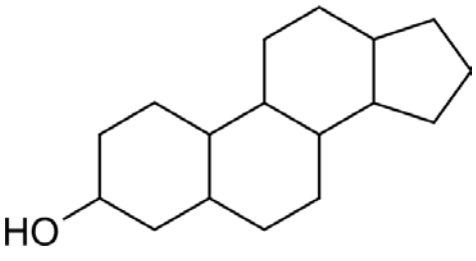
Sterols, also known as steroid alcohols, are a subgroup of the steroids and an important class of organic molecules. They occur naturally in plants, animals, and fungi, with the most familiar type of animal sterol being cholesterol. Cholesterol is vital to animal cell membrane structure and function as a precursor to fat-soluble vitamins and steroid hormones.

Sterols of plants are called phytosterols and sterols of animals are called zoosterols. The most important zoosterol is cholesterol. Notable phytosterols include campesterol, sitosterol, and stigmasterol. Ergosterol is a sterol present in the cell membrane of fungi, where it serves a role similar to cholesterol in animal cells.

Phytosterols, more commonly known as plant sterols, have been shown in clinical trials to block cholesterol absorption sites in the human intestine, thus helping to reduce cholesterol in humans. They are currently approved by the U.S. Food and Drug Administration for use as a food additive. However, there is some concern that they may block absorption not only of cholesterol but of other important nutrients as well. At present the American Heart Association has recommended that supplemental plant sterols be taken only by those diagnosed with elevated cholesterol, and has particularly recommended that they not be taken by pregnant women or nursing mothers.

Sterols and related compounds play essential roles in the physiology of eukaryotic organisms. For example, cholesterol forms part of the cellular membrane in animals, where it affects the cell membrane's fluidity and serves as secondary messenger in developmental signaling. In humans and other animals, corticosteroids, such as cortisol act as signaling compounds in cellular communication and general metabolism. Sterols are common components of human skin oils.

Shown below - general sterol structure



https://en.wikipedia.org/wiki/Sterol

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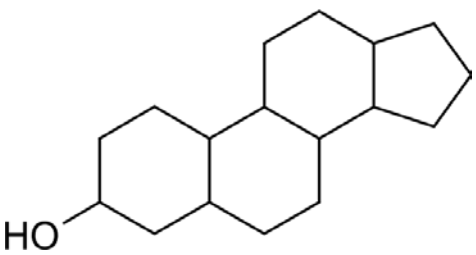

https://en.wikipedia.org/wiki/Sterol

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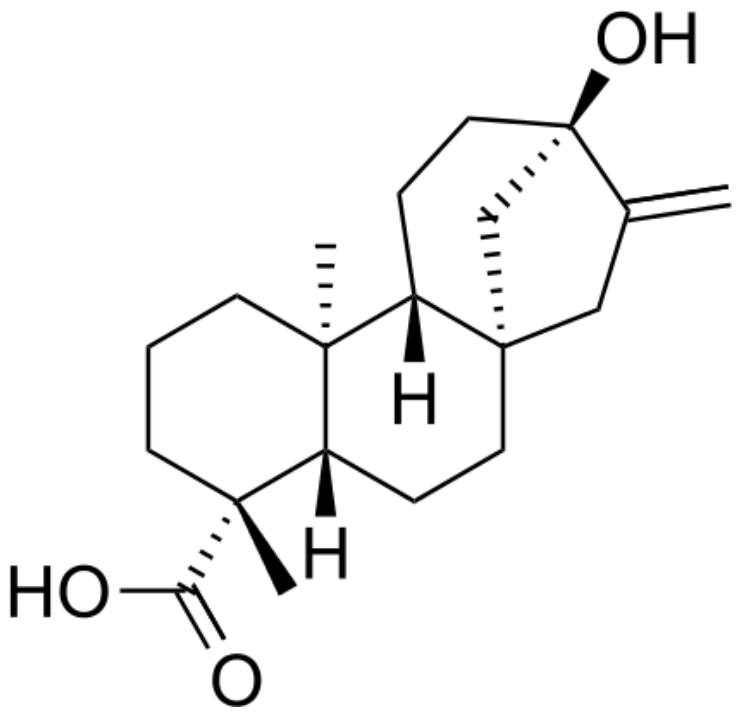
Chapter 3 - Membranes: Transport

Stevia

Stevia is a sweetener and sugar substitute extracted from the leaves of the p
Stevia rebaudiana.



https://en.wikipedia.org/wiki/Stevia

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Chapter 2 - Structure & Function: Carbohydrates

Sticky End

Sticky ends are most often created by restriction endonucleases when they
Very often they cut the two DNA strands four to six base pairs from each ot
ing a 5' overhang in one molecule and a complementary 5' overhang in the
ends are called cohesive since they are easily joined back together by a ligas

https://en.wikipedia.org/wiki/Sticky_and_blunt_ends#Overhangs_and_s

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Related Glossary Terms

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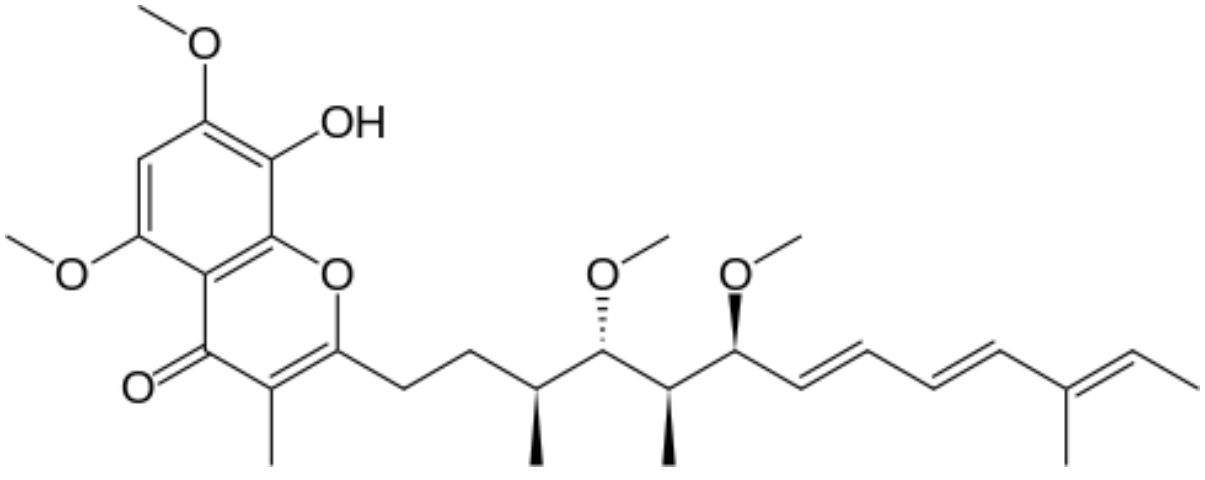
Stigmatellin

Stigmatellin is a potent inhibitor of the quinol oxidation (Q_o) site of the cyt
complex in mitochondria and the cytochrome b6f complex of thylakoid me



https://en.wikipedia.org/wiki/Stigmatellin

Related Glossary Terms

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Stop Codon

In the genetic code, a stop codon (or termination codon) is a nucleotide triplet within messenger RNA that signals a termination of translation. Proteins are based on polypeptides, which are unique sequences of amino acids. Most codons in messenger RNA (from DNA) correspond to the addition of an amino acid to a growing polypeptide chain, which may ultimately become a protein. Stop codons signal the termination of this process by binding release factors, which cause the ribosomal subunits to disassociate, releasing the amino acid chain. While start codons need nearby sequences or initiation factors to start translation, a stop codon alone is sufficient to initiate termination.

In the standard genetic code, there are three different stop codons:

- in RNA:
- UAG ("amber")
- UAA ("ochre")
- UGA ("opal")

The UGA codon has recently been identified as the codon coding for selenocysteine (Sec). This amino acid is found in 25 selenoproteins where it is located in the active site of the protein. Transcription of this codon is enabled by the proximity of the SECIS element (SElenoCysteine Incorporation Sequence). The UAG codon can translate into pyrrolysine in a similar manner.

Distribution of stop codons within the genome of an organism is non-random and can correlate with GC-content. For example, the *E. coli* K-12 genome contains 2705 TAA (63%), 1257 TGA (29%), and 326 TAG (8%) stop codons (GC content 50.8%). Also the substrates for the stop codons release factor 1 or release factor 2 are strongly correlated to the abundance of stop codons. Large scale study of bacteria with a broad range of GC-contents shows that while the frequency of occurrence of TAA is negatively correlated to the GC-content and the frequency of occurrence of TGA is positively correlated to the GC-content, the frequency of occurrence of the TAG stop codon, which is often the minimally used stop codon in a genome, is not influenced by the GC-content.

Nonsense mutations are changes in DNA sequence that introduce a premature stop codon, causing any resulting protein to be abnormally shortened. This often causes a loss of function in the protein, as critical parts of the amino acid chain are no longer created. Because of this terminology, stop codons have also been referred to as nonsense codons.

https://en.wikipedia.org/wiki/Stop_codon

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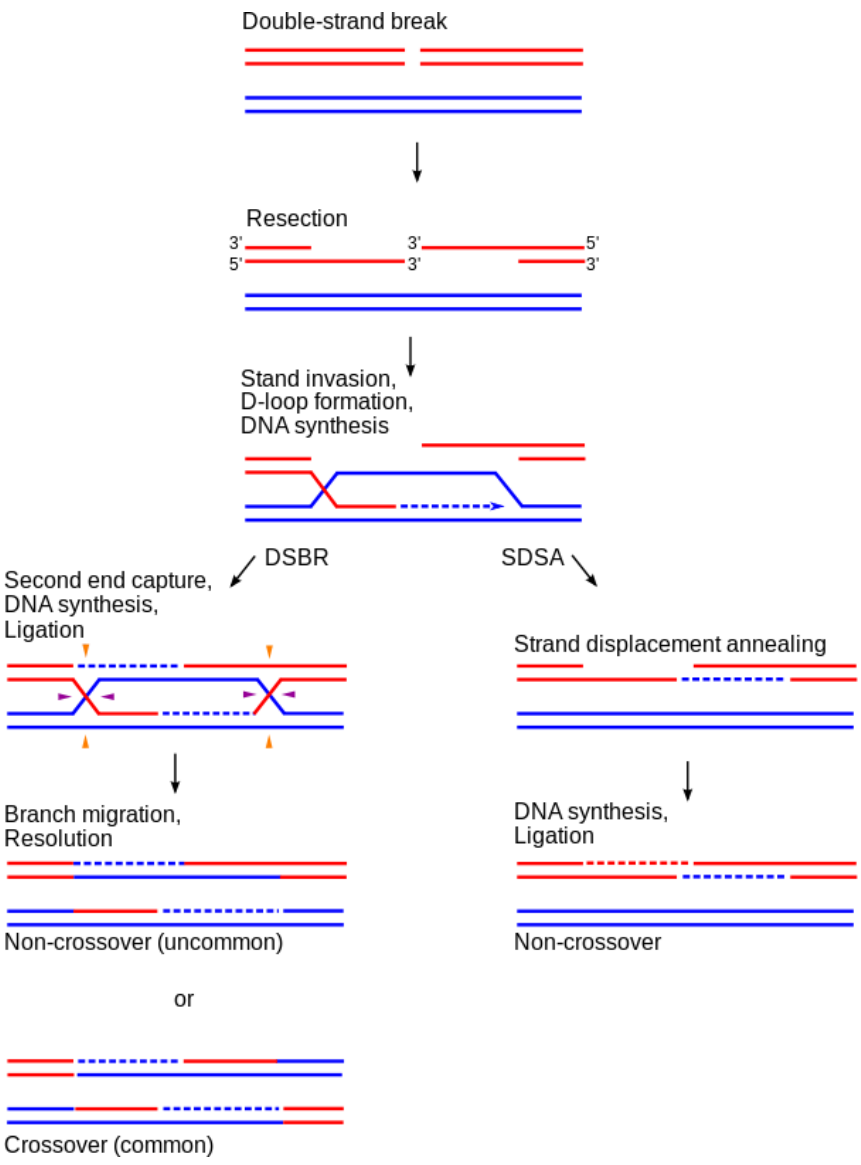
Strand Invasion

Homologous recombination varies widely among different organisms and cell types, but most forms involve the same basic steps. After a double-strand break occurs, sections of DNA around the 5' ends of the break are cut away in a process called resection. In the strand invasion step that follows, an overhanging 3' end of the broken DNA molecule then "invades" a similar or identical DNA molecule that is not broken. After strand invasion, the further sequence of events may follow either of two main pathways discussed below - the DSBR (double-strand break repair) pathway or the SDSA (synthesis-dependent strand annealing) pathway. Homologous recombination that occurs during DNA repair tends to result in non-crossover products, in effect restoring the damaged DNA molecule as it existed before the double-strand break.



https://en.wikipedia.org/wiki/Homologous_recombination

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Chapter 7 - DNA Repair

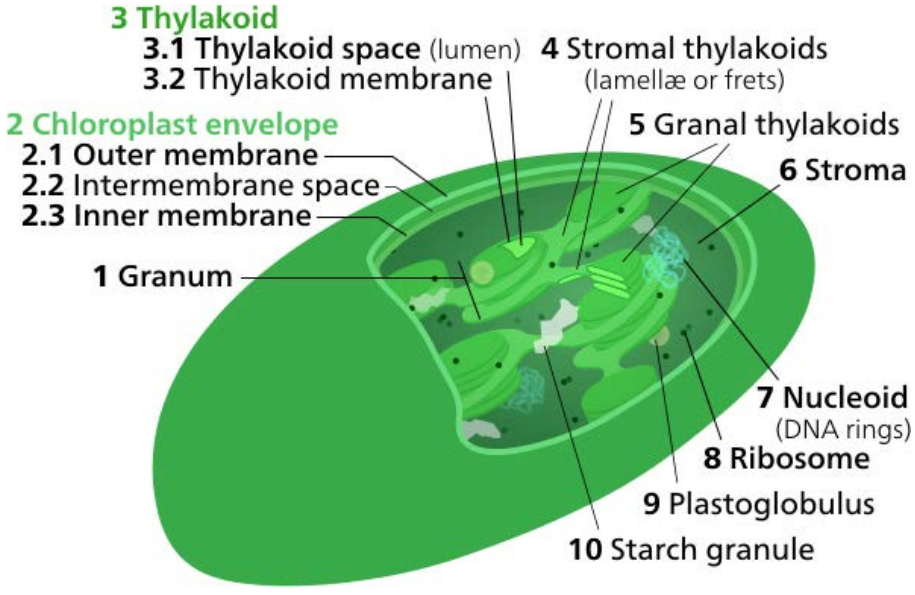
Stroma

Stroma, in botany, refers to the colorless fluid surrounding the grana within the chloroplast. Within the stroma are grana, stacks of thylakoids, the sub-organelles, the daughter cells, where photosynthesis is commenced before the chemical changes are completed in the stroma.

Photosynthesis occurs in two stages. In the first stage, light-dependent reactions capture the energy of light and use it to make the energy-storage molecules ATP and NADPH. During the second stage, the light-independent reactions use these products to capture and reduce carbon dioxide.

The series of biochemical redox reactions which take place in the stroma are collectively called the Calvin cycle or light-independent reactions. There are three phases: carbon fixation, reduction reactions, and ribulose 1,5-bisphosphate (RuBP) regeneration.

The stroma is also the location of chloroplast DNA and chloroplast ribosomes, and thus also the location of molecular processes including chloroplast DNA replication, and transcription/translation of some chloroplast proteins.



https://en.wikipedia.org/wiki/Stroma_(fluid)

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Structural Domains

A protein domain is a conserved part of a given protein sequence and (tertiary) struc
ture that can evolve, function, and exist independently of the rest of the protein chai
Each domain forms a compact three-dimensional structure and often can be indepen
ently stable and folded. Many proteins consist of several structural domains. One do-
main may appear in a variety of different proteins. Molecular evolution uses domain
as building blocks and these may be recombined in different arrangements to create
proteins with different functions. Domains vary in length from between about 25
amino acids up to 500 amino acids in length. The shortest domains such as zinc finge
are stabilized by metal ions or disulfide bridges. Domains often form functional units
such as the calcium-binding EF hand domain of calmodulin. Because they are inde-
pendently stable, domains can be "swapped" by genetic engineering between one pro
tein and another to make chimeric proteins.

https://en.wikipedia.org/wiki/Protein_domain

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Structural Motif

In a chain-like biological molecule, such as a protein or nucleic acid, a struc
is a supersecondary structure, which also appears in a variety of other mole
proteins, a structural motif describes the connectivity between secondary st
ments. An individual motif usually consists of only a few elements, e.g., the
helix' motif which has just three. Note that, while the spatial sequence of el
be identical in all instances of a motif, they may be encoded in any order wi
derlying gene. In addition to secondary structural elements, protein structu
often include loops of variable length and unspecified structure.

https://en.wikipedia.org/wiki/Structural_motif

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https://en.wikipedia.org/wiki/Structural_motif

Related Glossary Terms

Drag related terms here

Substrate

A substrate is typically a chemical species participating in a reaction, which reacts to generate a product. In synthetic and organic chemistry, the substrate is the chemical of interest that is being modified. In biochemistry, the substrate is a molecule that binds to an enzyme and is converted to product.

https://en.wikipedia.org/wiki/Substrate_(chemistry)

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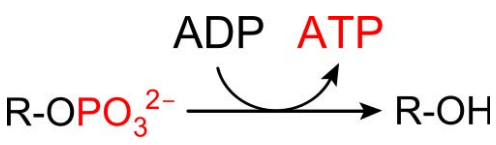
Substrate Level Phosphorylation

Substrate-level phosphorylation is a type of metabolic reaction that results in the formation of adenosine triphosphate (ATP) or guanosine triphosphate (GTP) by the direct transfer and donation of a phosphoryl (PO_3) group to adenosine diphosphate (ADP) or guanosine diphosphate (GDP) from a phosphorylated reactive intermediate. Note that the phosphate group does not have to come directly from the substrate.

An alternative way to create ATP is through oxidative phosphorylation, which takes place during the process of cellular respiration, in addition to the substrate-level phosphorylation that occurs during glycolysis and the Krebs cycle. During oxidative phosphorylation, NADH is oxidized to NAD^+, yielding 2.5 ATPs, and $FADH_2$ (flavin adenine dinucleotide) yields 1.5 ATPs when it is oxidized. Oxidative phosphorylation uses an electrochemical or chemiosmotic gradient of protons (H^+) across the inner mitochondrial membrane to generate ATP from ADP and a molecule of inorganic phosphate, which is a key difference from substrate-level phosphorylation.

Unlike oxidative phosphorylation, oxidation and phosphorylation are not coupled in the process of substrate-level phosphorylation, although both types of phosphorylation result in the formation of ATP, and reactive intermediates are most often gained in course of oxidation processes in catabolism. However, usually most of the ATP is generated by oxidative phosphorylation in aerobic or anaerobic respiration. Substrate-level phosphorylation serves as fast source of ATP independent of external electron acceptors and respiration. This is the case for example in human erythrocytes, which have no mitochondria, and in the muscle during oxygen depression.



https://en.wikipedia.org/wiki/Substrate-level_phosphorylation

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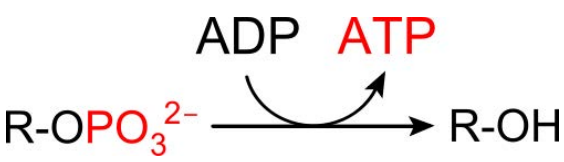

https://en.wikipedia.org/wiki/Substrate-level_phosphorylation

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Subtilisin

Subtilisins belong to subtilases, a group of serine proteases that - like all serine proteases - initiate the nucleophilic attack on the peptide (amide) bond through a serine residue at the active site. Subtilisins typically have molecular weights of about 20,000 to 45,000 Daltons.

The active site features a charge-relay network involving Asp-32, His-64, and active site Ser-221 arranged in a catalytic triad. The charge-relay network functions as follows: The carboxylate side-chain of Asp-32 hydrogen-bonds to a nitrogen-bonded proton on His-64's imidazole ring. This is possible because Asp is negatively charged at physiological pH. The other nitrogen on His-64 hydrogen-bonds to the O-H proton of Ser-221. This last interaction results in charge-separation of O-H, with the oxygen atom being more nucleophilic. This allows the oxygen atom of Ser-221 to attack incoming substrates (i.e., peptide bonds), assisted by a neighboring carboxyamide side-chain of Asn-155.

Even though Asp-32, His-64, and Ser-221 are sequentially far apart, they converge in the 3D structure to form the active site.

To summarize the interactions described above, Ser-221 acts as a nucleophile and cleaves peptide bonds with its partially negative oxygen atom. This is possible due to the nature of the charge-relay site of subtilisin.

https://en.wikipedia.org/wiki/Subtilisin

Related Glossary Terms

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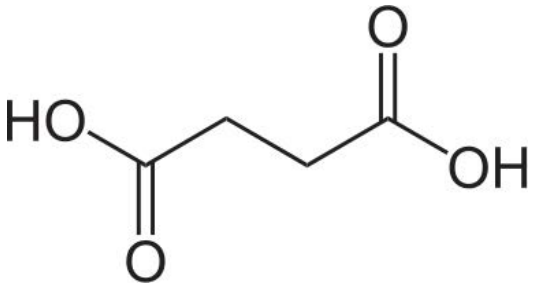
Succinate

Succinate is an intermediate in the citric acid cycle. It serves as an electron donor to the electron transport chain.

It reacts in the citric acid cycle as follows:

Succinate + FAD → Fumarate + $FADH_2$

This conversion is catalyzed by the enzyme succinate dehydrogenase (or complex II of the mitochondrial ETC). The complex is a 4 subunit membrane-bound lipoprotein which couples the oxidation of succinate to the reduction of ubiquinone. Intermediate electron carriers are FAD and three 2Fe-2S clusters part of subunit B.



https://en.wikipedia.org/wiki/Succinic_acid#Biochemistry

Related Glossary Terms

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Succinate Dehydrogenase

Succinate dehydrogenase or succinate-coenzyme Q reductase (SQR) or respiratory Complex II is an enzyme complex, bound to the inner mitochondrial membrane of mammalian mitochondria and many bacterial cells. It is the only enzyme that partic pates in both the citric acid cycle and the electron transport chain.

The reaction it catalyzes is as follows:

Succinate + FAD → Fumarate + $FADH_2$

https://en.wikipedia.org/wiki/Succinate_dehydrogenase

Related Glossary Terms

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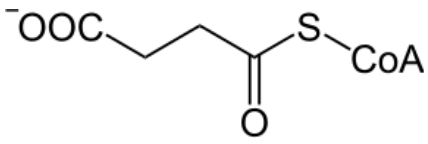
Succinyl-CoA

Succinyl-Coenzyme A, abbreviated as Succinyl-CoA is a combination of succinic acid and coenzyme A. It is an important intermediate in the citric acid cycle, where it is synthesized from α-Ketoglutarate by α-ketoglutarate dehydrogenase through decarboxylation. During the process, coenzyme A is added.

Succinyl CoA can also be formed from methylmalonyl CoA through the utilization of deoxyadenosyl-B_{12} (deoxyadenosylcobalamin) by the enzyme methylmalonyl-CoA mutase. This reaction, which requires vitamin B_{12} as a cofactor, is important in the catabolism of some branched-chain amino acids as well as odd-chain fatty acids.



https://en.wikipedia.org/wiki/Succinyl-CoA

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Succinyl-CoA Synthetase

Succinyl-CoA synthetase is an enzyme that catalyzes the reversible reaction of s
CoA to succinate. The enzyme facilitates the coupling of this reaction to the forr
of a nucleoside triphosphate molecule (either GTP or ATP) from an inorganic p
phate molecule and a nucleoside diphosphate molecule (either GDP or ADP). It
key role as one of the catalysts involved in the citric acid cycle, a central pathwa
lular metabolism, and it is located within the mitochondrial matrix of a cell.

Succinyl CoA synthetase catalyzes the following reversible reaction:

$$\text{Succinyl CoA} + P_i + \text{NDP} \leftrightarrow \text{Succinate} + \text{CoA} + \text{NTP}$$

where P_i denotes inorganic phosphate, NDP denotes nucleoside diphosphate (e
GDP or ADP), and NTP denotes nucleoside triphosphate (either GTP or ATP).

https://en.wikipedia.org/wiki/Succinyl_coenzyme_A_synthetase

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Succinyl-diaminopimelate Desuccinylase

Duccinyl-diaminopimelate desuccinylase is an enzyme that catalyzes the ch
tion

N-succinyl-LL-2,6-diaminoheptanedioate + H_2O <=> Succinate + LL-2,6-
diaminoheptanedioate

This enzyme belongs to the family of hydrolases, those acting on carbon-nit
bonds other than peptide bonds, specifically in linear amides. The systemat
this enzyme class is N-succinyl-LL-2,6-diaminoheptanedioate amidohydro
zyme is also called N-succinyl-L-alpha,epsilon-diaminopimelic acid deacyla
ticipates in lysine biosynthesis.

https://en.wikipedia.org/wiki/Succinyl-diaminopimelate_desuccinylase

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Related Glossary Terms

Drag related terms here

Succinyl-diaminopimelate Transaminase

Succinyldiaminopimelate transaminase is an enzyme that catalyzes the chem
tion

N-succinyl-L-2,6-diaminoheptanedioate + 2-oxoglutarate <=> N-succinyl-L
6-oxoheptanedioate + L-glutamate

This enzyme belongs to the family of transferases, specifically the transamin
which transfer nitrogenous groups. The systematic name of this enzyme clas
N-succinyl-L-2,6-diaminoheptanedioate:2-oxoglutarate aminotransferase. C
names in common use include succinyldiaminopimelate aminotransferase, a
succinyl-L-diaminopimelic glutamic transaminase. This enzyme participates
biosynthesis. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Succinyldiaminopimelate_transaminase

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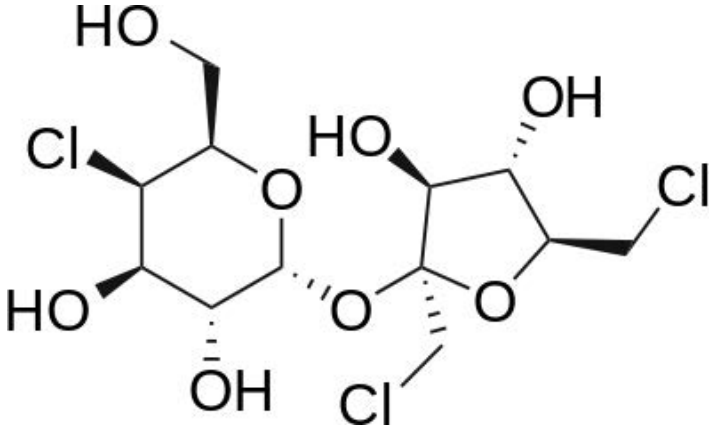
Related Glossary Terms

Drag related terms here

Sucralose

Sucralose is a non-nutritive sweetener. The majority of ingested sucralose is not broken down by the body, so it is noncaloric. Sucralose is about 320 to 1,000 times sweeter than sucrose, three times as sweet as aspartame and twice as sweet as saccharin. It is stable under heat and over a broad range of pH conditions. Therefore, it can be used in baking or in products that require a longer shelf life. The commercial success of sucralose-based products stems from its favorable comparison to other low-calorie sweeteners in terms of taste, stability, and safety. Common brand names of sucralose-based sweeteners are Splenda, Zerocal, Sukrana, SucraPlus, Candys, Cukren, and Nevella.

Sucralose is manufactured by the selective chlorination of sucrose in a multistep synthesis, which substitutes three of the hydroxyl groups of sucrose with chlorine atoms. This chlorination is achieved by selective protection of a primary alcohol group, followed by chlorination of the partially acetylated sugar with excess chlorinating agent, and then by removal of the acetyl groups to give the desired sucralose product.



https://en.wikipedia.org/wiki/Sucralose

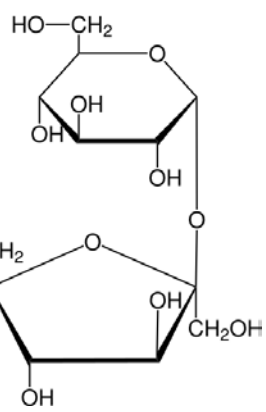
Related Glossary Terms

Sucrose

Sucrose is a common, naturally occurring carbohydrate found in many plants and plant parts. The molecule is a disaccharide combination of the monosaccharides glucose and fructose with the formula $C_{12}H_{22}O_{11}$.

In sucrose, the components glucose and fructose are linked via an acetal bond between C_1 on the glucosyl subunit and C_2 on the fructosyl unit. The bond is called a glycosidic linkage. Glucose exists predominantly as two isomeric "pyranoses" (α and β), but only one of these forms links to the fructose. Fructose itself exists as a mixture of "furanoses", each of which having α and β isomers, but only one particular isomer links to the glucosyl unit. What is notable about sucrose is that, unlike most disaccharides, the glycosidic bond is formed between the reducing ends of both glucose and fructose, and not between the reducing end of one and the nonreducing end of the other. This linkage inhibits further bonding to other saccharide units. Since it contains no anomeric hydroxyl groups, it is classified as a non-reducing sugar.

Hydrolysis breaks the glycosidic bond converting sucrose into glucose and fructose. Hydrolysis is, however, so slow that solutions of sucrose can sit for years with negligible change. If the enzyme sucrase is added, however, the reaction will proceed rapidly. Hydrolysis can also be accelerated with acids, such as cream of tartar or lemon juice, both weak acids. Likewise, gastric acidity converts sucrose to glucose and fructose during digestion the bond between them being an acetal bond which can be broken by an acid.



https://en.wikipedia.org/wiki/Sucrose

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Sucrose Synthase

Sucrose synthase (EC 2.4.1.13) is an enzyme that catalyzes the chemical reac

NDP-glucose + D-fructose <=> NDP + Sucrose

The reaction is reversible and can be used to split the two sugars of sucrose.

This enzyme belongs to the family of glycosyltransferases, specifically the he
ferases. The systematic name of this enzyme class is NDP-glucose:D-fructose
D-glucosyltransferase. Other names in common use include UDPglucose-fru
cosyltransferase, sucrose synthetase, sucrose-UDP glucosyltransferase, sucro
uridine diphosphate glucosyltransferase, and uridine diphosphoglucose-fruc
syltransferase. This enzyme participates in starch and sucrose metabolism.

https://en.wikipedia.org/wiki/Sucrose_synthase

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Chapter 6 - Metabolism: Sugars

Sugar

Sugar is the generalized name for sweet, short-chain, soluble carbohydrates, many of which are used in food. They are composed of carbon, hydrogen, and oxygen. There are various types of sugar derived from different sources. Simple sugars are called monosaccharides and include glucose (also known as dextrose), fructose, and galactose. The table or granulated sugar most customarily used as food is sucrose, a disaccharide. (In the body, sucrose hydrolyzes into fructose and glucose.) Other disaccharides include maltose and lactose. Longer chains of sugars are called oligosaccharides. Chemically-different substances may also have a sweet taste, but are not classified as sugars. Some are used as lower-calorie food substitutes for sugar described as artificial sweeteners.

Since the latter part of the twentieth century, it has been questioned whether a diet high in sugars, especially refined sugars, is good for human health. Sugar has been linked to obesity, and suspected of, or fully implicated as a cause in the occurrence of diabetes, cardiovascular disease, dementia, macular degeneration, and tooth decay. Numerous studies have been undertaken to try to clarify the position, but with varying results, mainly because of the difficulty of finding populations for use as controls that do not consume or are largely free of any sugar consumption.

https://en.wikipedia.org/wiki/Sugar

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Sugar Alcohol

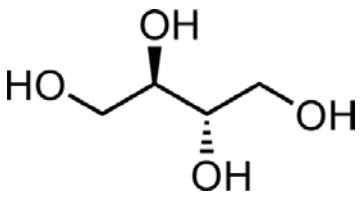
Sugar alcohols are organic compounds, typically derived from sugars, that comprise a class of polyols. Contrary to what the name may suggest, a sugar alcohol is not a sugar nor an alcoholic beverage. They are white, water-soluble solids that can occur naturally or be produced industrially from sugars. Sugar alcohols are used widely in the food industry as thickeners and sweeteners. In commercial foodstuffs, sugar alcohols are commonly used in place of table sugar (sucrose), often in combination with high intensity artificial sweeteners to counter the low sweetness. Xylitol is perhaps the most popular sugar alcohol due to its similarity to sucrose in visual appearance and sweetness.

As a group, sugar alcohols are not as sweet as sucrose, and they have less food energy than sucrose. Their flavor is like sucrose, and they can be used to mask the unpleasant aftertastes of some high intensity sweeteners. Sugar alcohols are not metabolized by oral bacteria, and so they do not contribute to tooth decay. They do not brown or caramelize when heated.

In addition to their sweetness, some sugar alcohols can produce a noticeable cooling sensation in the mouth when highly concentrated, for instance in sugar-free hard candy or chewing gum. This happens, for example, with the crystalline phase of sorbitol, erythritol, xylitol, mannitol, lactitol and maltitol. The cooling sensation is due to the dissolution of the sugar alcohol being an endothermic (heat-absorbing) reaction, one with a strong heat of solution.

Sugar alcohols are usually incompletely absorbed into the blood stream from the small intestines which generally results in a smaller change in blood glucose than "regular" sugar (sucrose). This property makes them popular sweeteners among diabetics and people on low-carbohydrate diets. However, like many other incompletely digestible substances, overconsumption of sugar alcohols can lead to bloating, diarrhea and flatulence because they are not absorbed in the small intestine. Some individuals experience such symptoms even in a single-serving quantity. With continued use, most people develop a degree of tolerance to sugar alcohols and no longer experience these symptoms. As an exception, erythritol is actually absorbed in the small intestine and excreted unchanged through urine, so it contributes no calories even though it is rather sweet.

Shown below - erythritol



https://en.wikipedia.org/wiki/Sugar_alcohol

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Sugars

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https://en.wikipedia.org/wiki/Sugar

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Suicide Inhibition

Suicide inhibition, also known as suicide inactivation or mechanism-based inhibition, is an irreversible form of enzyme inhibition that occurs when an enzyme binds a substrate analogue and forms an irreversible complex with it through a covalent bond during the "normal" catalysis reaction. The inhibitor binds to the active site where it is modified by the enzyme to produce a reactive group that reacts irreversibly to form a stable inhibitor-enzyme complex. This usually uses a prosthetic group or a coenzyme, forming electrophilic alpha and beta unsaturated carbonyl compounds and imines.

Some clinical examples of suicide inhibitors include:
• Aspirin, which inhibits cyclooxygenase 1 and 2 enzymes.
• Penicillin, which inhibits DD-transpeptidase from building bacterial cell walls.
• Sulbactam, which prohibits penicillin-resistant strains of bacteria from metabolizing penicillin.
• Allopurinol, which inhibits uric acid production by xanthine oxidase in the treatment of gout.
• AZT (zidovudine) and other chain-terminating nucleoside analogues used to inhibit HIV-1 reverse transcriptase in the treatment of HIV/AIDS.

https://en.wikipedia.org/wiki/Suicide_inhibition

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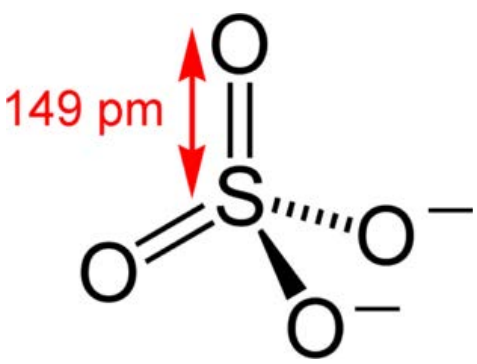
Sulfate

The sulfate or ion is a polyatomic anion $SO_4^{=}$ .Sulfates are salts of sulfuric acid and many are prepared from that acid. The anion consists of a central sulfur atom surrounded by four equivalent oxygen atoms in a tetrahedral arrangement. The symmetry is the same as that of methane. The sulfur atom is in the +6 oxidation state while the four oxygen atoms are each in the −2 state. The sulfate ion carries a negative two charge and is the conjugate base of the bisulfate (or hydrogen sulfate) ion, HSO_4^-, which is the conjugate base of H_2SO_4, sulfuric acid. Organic sulfate esters, such as dimethyl sulfate, are covalent compounds and esters of sulfuric acid.



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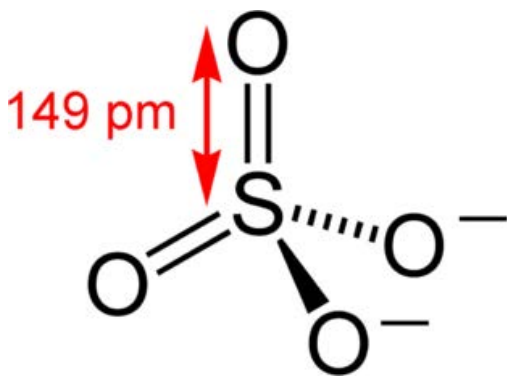

https://en.wikipedia.org/wiki/Sulfate

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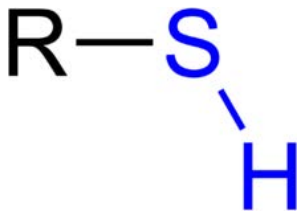
Sulfhydryl

Thiol is an organosulfur compound that contains a carbon-bonded sulfhydryl or sulphydryl (–C–SH or R–SH) group (where R represents an alkyl or other organic substituent). Thiols are the sulfur analogue of alcohols (that is, sulfur takes the place of oxygen in the hydroxyl group of an alcohol). The –SH functional group itself is referred to as either a thiol group or a sulfhydryl group.

Many thiols have strong odors resembling that of garlic or rotten eggs. Thiols are used as odorants to assist in the detection of natural gas (which in pure form is odorless), and the "smell of natural gas" is due to the smell of the thiol used as the odorant.



https://en.wikipedia.org/wiki/Thiol

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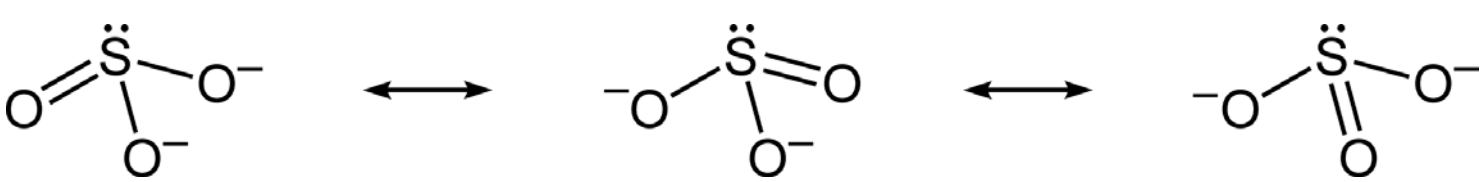
Sulfite

A compound that contains the sulfite ion (or the sulfate (IV) ion, from its correct systematic name), $SO_3^=$.

The structure of the sulfite anion can be described with three equivalent resonance structures. In each resonance structure, the sulfur atom is double-bonded to one oxygen atom with a formal charge of zero (neutral), and sulfur is singly bonded to the other two oxygen atoms, which each carry a formal charge of –1, together accounting for the –2 charge on the anion. There is also a non-bonded lone pair on the sulfur, so the structure predicted by VSEPR theory is trigonal pyramidal, as in ammonia (NH_3). In the hybrid resonance structure, the S-O bonds are equivalently of bond order one and one-third.



Sulfites occur naturally in all wines to some extent. Sulfites are commonly introduced to arrest fermentation at a desired time, and may also be added to wine as preservatives to prevent spoilage and oxidation at several stages of the winemaking. Sulfur dioxide (SO_2, sulfur with two atoms of oxygen) protects wine from not only oxidation, but also from bacteria. Without sulfites, grape juice would quickly turn to vinegar.

Organic wines are not necessarily sulfite-free, but generally have lower amounts and regulations stipulate lower maximum sulfite contents for these wines. In general, white wines contain more sulfites than red wines and sweeter wines contain more sulfites than drier ones.

https://en.wikipedia.org/wiki/Sulfite

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 9 - Point by Point: Metabolism

Sumoylation

Small Ubiquitin-like Modifier (or SUMO) proteins are a family of small proteins that are covalently attached to and detached from other proteins in cells to modify their function. SUMOylation is a post-translational modification involved in various cellular processes, such as nuclear-cytosolic transport, transcriptional regulation, apoptosis, protein stability, response to stress, and progression through the cell cycle.

SUMO proteins are similar to ubiquitin, and SUMOylation is directed by an enzymatic cascade analogous to that involved in ubiquitination. In contrast to ubiquitin, SUMO is not used to tag proteins for degradation. Mature SUMO is produced when the last four amino acids of the C-terminus have been cleaved off to allow formation of an isopeptide bond between the C-terminal glycine residue of SUMO and an acceptor lysine on the target protein.

SUMO modification of proteins has many functions. Among the most frequent and best studied are protein stability, nuclear-cytosolic transport, and transcriptional regulation. Typically, only a small fraction of a given protein is SUMOylated and this modification is rapidly reversed by the action of deSUMOylating enzymes. SUMOylation of target proteins has been shown to cause a number of different outcomes including altered localization and binding partners. The SUMO-1 modification of $RanGAP_1$ (the first identified SUMO substrate) leads to its trafficking from cytosol to nuclear pore complex. The SUMO modification of hNinein leads to its movement from the centrosome to the nucleus. In many cases, SUMO modification of transcriptional regulators correlates with inhibition of transcription.

https://en.wikipedia.org/wiki/SUMO_protein

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Super-secondary Structures

A supersecondary structure is a compact three-dimensional protein structu
eral adjacent elements of a secondary structure that is smaller than a protei
or a subunit. Supersecondary structures can act as nucleations in the proce
folding. Examples include β-hairpins, α-helix hairpins, and β-α-β motifs.

https://en.wikipedia.org/wiki/Supersecondary_structure

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Chapter 2 - Structure & Function: Proteins I

Supercoil

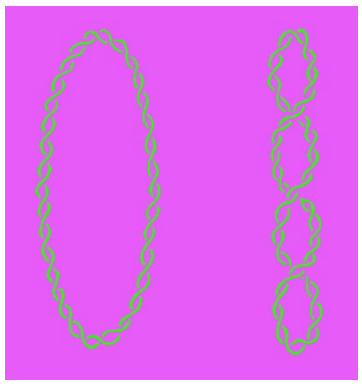
DNA supercoiling refers to the over- or under-winding of a DNA strand. Relative to the winding of relaxed B-DNA (10.5 bp per turn), over- or under-winding (making fewer or more bp/turn, respectively) creates strain on the strands in a duplex. Supercoiling (winding of the duplex with itself0 occurs, then, to relieve the strain.

Supercoiling is important in a number of biological processes, such as compacting DNA, and by regulating access to the genetic code, DNA supercoiling strongly affects DNA metabolism and possibly gene expression. Additionally, certain enzymes such as topoisomerases are able to change DNA topology to facilitate functions such as DNA replication or transcription. Mathematical expressions are used to describe supercoiling by comparing different coiled states to relaxed B-form DNA.

In a "relaxed" double-helical segment of B-DNA, the two strands twist around the helical axis once every 10.4–10.5 base pairs of sequence. Adding or subtracting twists, as some enzymes can do, imposes strain. If a DNA segment under twist strain were closed into a circle by joining its two ends and then allowed to move freely, the circular DNA would contort into a new shape, such as a simple figure-eight. Such a contortion is a supercoil. The noun form "supercoil" is often used in the context of DNA topology.

Positively supercoiled (overwound) DNA is transiently generated during DNA replication and transcription, and, if not promptly relaxed, inhibits (regulates) these processes. The simple figure eight is the simplest supercoil, and is the shape a circular DNA assumes to accommodate one too many or one too few helical twists. The two lobes of the figure eight will appear rotated either clockwise or counterclockwise with respect to one another, depending on whether the helix is over- or underwound. For each additional helical twist being accommodated, the lobes will show one more rotation about their axis. As a general rule, the DNA of most organisms is negatively supercoiled.

Shown below - relaxed (left) and supercoiled (right) DNA.



https://en.wikipedia.org/wiki/DNA_supercoil

Superoxide

A superoxide, is a compound that contains the superoxide anion with the chemical formula O_2^-. Superoxide anion is particularly important as the product of the one-electron reduction of dioxygen O_2, which occurs widely in nature. Whereas molecular oxygen (dioxygen) is a diradical containing two unpaired electrons, the addition of a second electron fills one of its two degenerate molecular orbitals, leaving a charged ionic species with single unpaired electron and a net negative charge of –1. Both dioxygen and superoxide ion are free radicals that exhibit paramagnetism.

Superoxide is biologically quite toxic and is deployed by the immune system to kill invading microorganisms. In phagocytes, superoxide is produced in large quantities by the enzyme NADPH oxidase for use in oxygen-dependent killing mechanisms of invading pathogens. Mutations in the gene coding for the NADPH oxidase cause an immunodeficiency syndrome called chronic granulomatous disease, characterized by extreme susceptibility to infection, especially catalase-positive organisms. In turn, microorganisms genetically engineered to lack superoxide dismutase (SOD) lose virulence. Superoxide is also deleterious when produced as a byproduct of mitochondrial respiration (most notably by Complex I and Complex III), as well as several other enzymes, for example xanthine oxidase.

Because superoxide is toxic, nearly all organisms living in the presence of oxygen contain isoforms of the superoxide-scavenging enzyme superoxide dismutase, or SOD. SOD is an extremely efficient enzyme. It catalyzes the neutralization of superoxide nearly as fast as the two can diffuse together spontaneously in solution. Other proteins that can be both oxidized and reduced by superoxide (e.g., hemoglobin) have weak SOD-like activity. Genetic inactivation ("knockout") of SOD produces deleterious phenotypes in organisms ranging from bacteria to mice and have provided important clues as to the mechanisms of toxicity of superoxide *in vivo*.

Yeast lacking both mitochondrial and cytosolic SOD grow very poorly in air, but quite well under anaerobic conditions. Absence of cytosolic SOD causes a dramatic increase in mutagenesis and genomic instability. Mice lacking mitochondrial SOD (MnSOD) die around 21 days after birth due to neurodegeneration, cardiomyopathy, and lactic acidosis. Mice lacking cytosolic SOD (CuZnSOD) are viable but suffer from multiple pathologies, including reduced lifespan, liver cancer, muscle atrophy, cataracts, thymic involution, haemolytic anemia and a very rapid age-dependent decline in female fertility.

Superoxide may contribute to the pathogenesis of many diseases (the evidence is particularly strong for radiation poisoning and hyperoxic injury), and perhaps also to aging via the oxidative damage that it inflicts on cells. While the action of superoxide in the pathogenesis of some conditions is strong (for instance, mice and rats overexpressing CuZnSOD or MnSOD are more resistant to strokes and heart attacks), the role of superoxide in aging must be regarded as unproven for now. In model organisms (yeast, the fruit fly *Drosophila* and mice), genetically knocking out CuZnSOD shortens lifespan and accelerates certain features of aging (cataracts, muscle atrophy, macular degeneration, thymic involution). But the converse, increasing the levels of CuZnSOD, does not seem (except perhaps in *Drosophila*), to consistently increase lifespan. The most widely accepted view is that oxidative damage (resulting from multiple causes, including superoxide) is but one of several factors limiting lifespan.

https://en.wikipedia.org/wiki/Superoxide

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Superoxide Dismutase

Superoxide dismutase (SOD, EC 1.15.1.1) is an enzyme that alternately catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into either ordinary molecular oxygen (O_2) or hydrogen peroxide (H_2O_2). Superoxide is produced as a by-product of oxygen metabolism and, if not regulated, causes many types of cell damage. Hydrogen peroxide is also damaging, but less so, and is degraded by other enzymes such as catalase. Thus, SOD is an important antioxidant defense in nearly all living cells exposed to oxygen. One exception is *Lactobacillus plantarum* and related lactobacilli, which use a different mechanism to prevent damage from reactive (O_2^-).

SOD enzymes deal with the superoxide radical by alternately adding or removing an electron from the superoxide molecules it encounters, thus changing the O_2^- into one of two less damaging species: either molecular oxygen (O2) or hydrogen peroxide (H2O2). This SOD-catalyzed dismutation of superoxide may be written, for Cu,Zn SOD, with the following half-reactions :

- Cu^{2+}-SOD + O_2^- → Cu^{+}-SOD + O_2
- Cu^{+}-SOD + O_2^- + $2H^+$ → Cu^{2+}-SOD + H_2O_2

The general form, applicable to all the different metal-coordinated forms of SOD, can be written as follows:

- $M^{(n+1)+}$-SOD + O_2^- → M^{n+}-SOD + O_2

M^{n+}-SOD + O_2^- + $2H^+$ → $M^{(n+1)+}$-SOD + H_2O_2

where M = Cu (n=1) ; Mn (n=2) ; Fe (n=2) ; Ni (n=2).

In a series of such reactions, the oxidation state and the charge of the metal cation oscillates between n and n+1: +1 and +2 for Cu, or +2 and +3 for the other metals.

https://en.wikipedia.org/wiki/Superoxide_dismutase

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https://en.wikipedia.org/wiki/Superoxide_dismutase

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Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Chapter 5 - Energy: Electron Transport & Oxidative Phosphorylation

Supersecondary Structure

A supersecondary structure is a compact three-dimensional protein structu
eral adjacent elements of a secondary structure that is smaller than a protei
or a subunit. Supersecondary structures can act as nucleations in the proce
folding. Examples include β-hairpins, α-helix hairpins, and β-α-β motifs.

https://en.wikipedia.org/wiki/Supersecondary_structure

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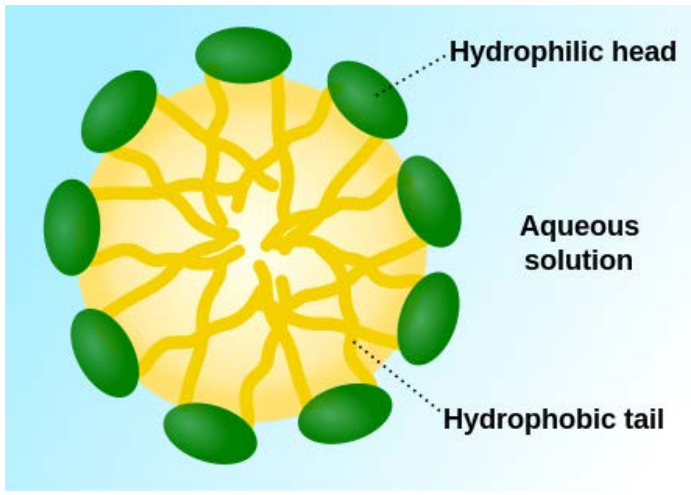
Surfactants

Surfactants are compounds that lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid. Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants.

Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads). Therefore, a surfactant contains both a water-insoluble (or oil-soluble) component and a water-soluble component. Surfactants will diffuse in water and adsorb at interfaces between air and water or at the interface between oil and water, in the case where water is mixed with oil. The water-insoluble hydrophobic group may extend out of the bulk water phase, into the air or into the oil phase, while the water-soluble head group remains in the water phase.



https://en.wikipedia.org/wiki/Surfactant

Related Glossary Terms

Svedberg Units

A svedberg unit (symbol S, sometimes Sv) is a non-SI unit for sedimentation rate. The sedimentation rate for a particle of a given size and shape measures how fast the particle 'settles', the sedimentation. It is often used to reflect the rate at which a molecule travels to the bottom of a test tube under the centrifugal force of a centrifuge. The svedberg is actually a measure of time. It is defined as exactly 10^{-13} seconds (100 fs).

The Svedberg unit (S) offers a measure of particle size based on its rate of travel in a tube subjected to high g-force. The Svedberg coefficient is a nonlinear function. A particle's mass, density, and shape will determine its S value. It depends on the frictional forces retarding its movement, which, in turn, are related to the average cross-sectional area of the particle.

The sedimentation coefficient is the ratio of the speed of a substance in a centrifuge to its acceleration in comparable units. A substance with a sedimentation coefficient of 26S (26×10^{-13} s) will travel at 26 micrometers per second (26×10^{-6} m/s) under the influence of an acceleration of a million gravities (10^7 m/s2). Centrifugal acceleration is given as $r\omega^2$, where r is the radial distance from the rotation axis and ω is the angular velocity in radians per second.

Bigger particles tend to sediment faster and so have higher svedberg values. Svedberg units are not directly additive since they represent a rate of sedimentation, not weight.

https://en.wikipedia.org/wiki/Svedberg

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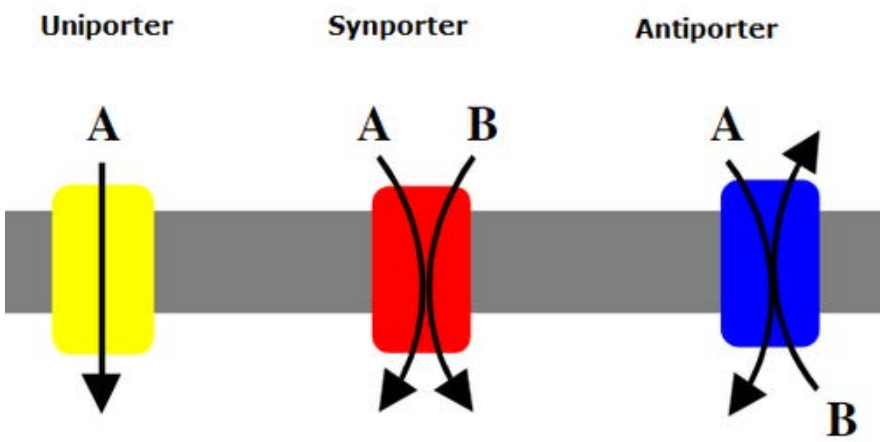
Symport(er)

A symporter is an integral membrane protein that is involved in the transport of many differing types of molecules across the cell membrane. The symporter works in the plasma membrane and molecules are transported across the cell membrane at the same time, and is, therefore, a type of co-transporter. The transporter is called a symporter, because the molecules will travel in the same direction in relation to each other. This is in contrast to the antiport transporter. Typically, the ion(s) will move down the electrochemical gradient, allowing the other molecule(s) to move against the concentration gradient. The movement of the ion(s) across the membrane is facilitated diffusion, and is coupled with the active transport of the molecule(s).



https://en.wikipedia.org/wiki/Symporter

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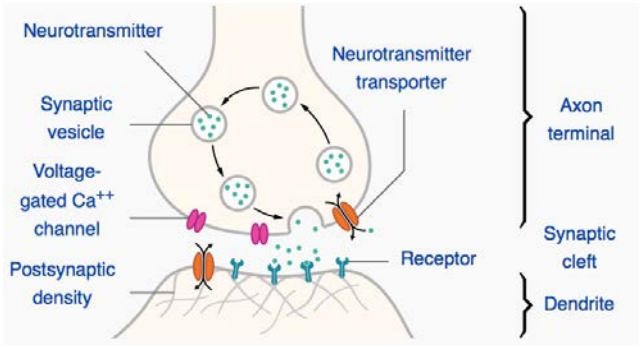
Synaptic Cleft

Synapses are functional connections between neurons, or between neurons and other types of cells. A typical neuron gives rise to several thousand synapses, although there are some types that make far fewer. Most synapses connect axons to dendrites, but there are also other types of connections, including axon-to-cell-body, axon-to-axon, and dendrite-to-dendrite. Synapses are generally too small to be recognizable using a light microscope except as points where the membranes of two cells appear to touch, but their cellular elements can be visualized clearly using an electron microscope.

Chemical synapses pass information directionally from a presynaptic cell to a post-synaptic cell and are therefore asymmetric in structure and function. The presynaptic terminal, or synaptic bouton, is a specialized area within the axon of the presynaptic cell that contains neurotransmitters enclosed in small membrane-bound spheres called synaptic vesicles (as well as a number of other supporting structures and organ-elles, such as mitochondria and endoplasmic reticulum). Synaptic vesicles are docked at the presynaptic plasma membrane at regions called active zones.

Immediately opposite is a region of the postsynaptic cell containing neurotransmitter receptors. For synapses between two neurons, the postsynaptic region may be found on the dendrites or cell body. Immediately behind the postsynaptic membrane is an elaborate complex of interlinked proteins called the postsynaptic density (PSD).

Proteins in the PSD are involved in anchoring and trafficking neurotransmitter recep-tors and modulating the activity of these receptors. The receptors and PSDs are often found in specialized protrusions from the main dendritic shaft called dendritic spines. Synapses may be described as symmetric or asymmetric. When examined under an electron microscope, asymmetric synapses are characterized by rounded vesicles in the presynaptic cell, and a prominent postsynaptic density. Asymmetric synapses are typi-cally excitatory. Symmetric synapses in contrast have flattened or elongated vesicles, and do not contain a prominent postsynaptic density. Symmetric synapses are typically inhibitory.



https://en.wikipedia.org/wiki/Chemical_synapse

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Synaptic Vesicles

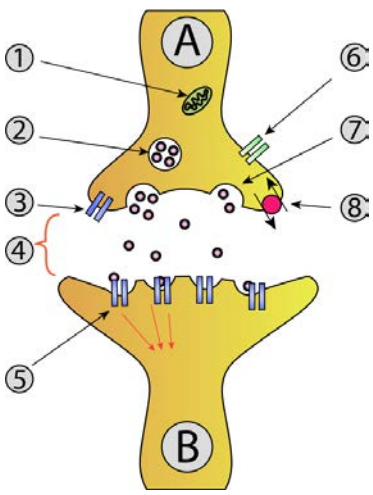
Synaptic vesicles store various neurotransmitters that are released at the synapse. The release is regulated by a voltage-dependent calcium channel. Vesicles are essential for propagating nerve impulses between neurons and are constantly recreated by the cell.

Synaptic vesicles contain two classes of obligatory components: transport proteins involved in neurotransmitter uptake, and trafficking proteins that participate in synaptic vesicle exocytosis, endocytosis, and recycling.

- Transport proteins are composed of proton pumps that generate electrochemical gradients, which allow for neurotransmitter uptake, and neurotransmitter transporters that regulate the actual uptake of neurotransmitters. The necessary proton gradient is created by V-ATPase, which breaks down ATP for energy. Vesicular transporters move neurotransmitters from the cells' cytoplasm into the synaptic vesicles. Vesicular glutamate transporters, for example, sequester glutamate into vesicles by this process.
- Trafficking proteins are more complex. They include intrinsic membrane proteins, peripherally bound proteins, and proteins such as SNAREs. These proteins do not share a characteristic that would make them identifiable as synaptic vesicle proteins, and little is known about how these proteins are specifically deposited into synaptic vesicles. Many but not all of the known synaptic vesicle proteins interact with non-vesicular proteins and are linked to specific functions.

Some neurotoxins, such as batrachotoxin, are known to destroy synaptic vesicles. The tetanus toxin damages vesicle-associated membrane proteins (VAMP), a type of v-SNARE, while botulinum toxins damage t-SNARES and v-SNARES and thus inhibit synaptic transmission. A spider toxin called α-Latrotoxin binds to neurexins, damaging vesicles and causing massive release of neurotransmitters.

In the figure below, 1 = mitochondrion; 2 = synaptic vesicle with neurotransmitters; 3 = autoreceptor; 4 = synapse with neurotransmitter released; 5 = postsynaptic receptors activated by neurotransmitter (induction of a postsynaptic potential); 6 = calcium channel; 7 = exocytosis of a vesicle; 8 = recaptured neurotransmitter.



https://en.wikipedia.org/wiki/Synaptic_vesicle

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Syndecans

Syndecans are single transmembrane domain proteins that are thought to act as coreceptors, especially for G protein-coupled receptors. These core proteins carry three to five heparan sulfate and chondroitin sulfate chains, which allow for interaction with a large variety of ligands including fibroblast growth factors, vascular endothelial growth factor, transforming growth factor-beta, fibronectin and antithrombin-1. Interactions between fibronectin and some syndecans can be modulated by the extracellular matrix protein tenascin C.

Functions of syndecan can be categorized in four ways. First is growth-factor-receptor activation. Glycosaminoglycans attached to the syndecan help binding of the various growth factors for activation of important cellular signaling mechanisms. Growth factors such as FGF2, HGF, EGF, VEGF, neuregulins and others interact with syndecans. For example, at the site of tissue injury, the soluble syndecan-1 ectodomains are cleaved by heparanases, producing heparin-like fragments that activate bFGF. Whereas most growth factors interact with syndecans via heparan sulfate chains, the prosecretory mitogen lacritin requires heparanase to both expose and create a binding site in the N-terminus of syndecan 1.

The second function is matrix adhesion. Syndecans bind to structural extracellular matrix molecules such as collagens I, III, V, fibronectin, thrombospondin, and tenascin to provide structural support for the adhesion.

A third function is cell–cell adhesion. Evidence for syndecan's role in cell–cell adhesion comes from the human myeloma cell line. These myeloma cells had a deficiency in the ability to adhere to one another in a rotation-mediated aggregation matrix. This deficiency is attributed to the lack of syndecan 1 expression. Syndecan 4 also interacts with integrin proteins for cell–cell adhesion.

A final role is in tumor suppression and progression. Syndecans act as tumor inhibitors by preventing cellular proliferation of tumor cell lines. For example, in the epithelial-derived tumor cell line, S115, the syndecan 1 ectodomain suppresses the growth of S115 cells without affecting the growth of normal epithelial cells. However, syndecan 1 expression also has a role in tumor progression in myeloma and other cancers.

https://en.wikipedia.org/wiki/Syndecan

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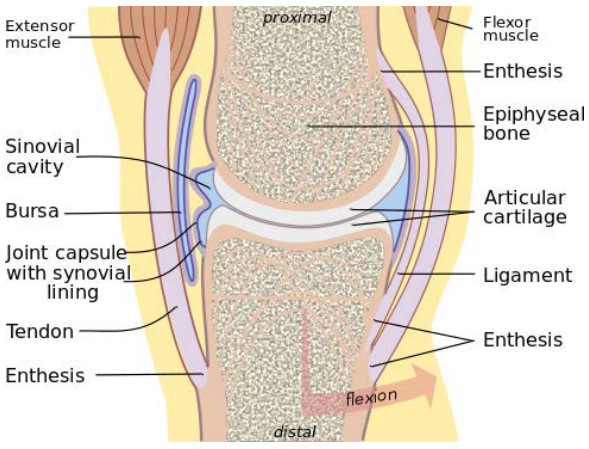
Synovial Fluid

Synovial fluid is a viscous, non-Newtonian fluid found in the cavities of synovial joints. With its egg white–like consistency, the principal role of synovial fluid is to reduce friction between the articular cartilage of synovial joints during movement.

The inner membrane of synovial joints is called the synovial membrane and secretes synovial fluid into the joint cavity. Synovial fluid is an ultrafiltrate from plasma, and contains proteins derived from the blood plasma and proteins that are produced by cells within the joint tissues. The fluid contains hyaluronan secreted by fibroblast-like cells in the synovial membrane, lubricin (proteoglycan 4; PRG4) secreted by the surface chondrocytes of the articular cartilage and interstitial fluid filtered from the blood plasma. This fluid forms a thin layer (roughly 50 μm) at the surface of cartilage and also seeps into microcavities and irregularities in the articular cartilage surface, filling all empty space. The fluid in articular cartilage effectively serves as a synovial fluid reserve. During movement, the synovial fluid held in the cartilage is squeezed out mechanically to maintain a layer of fluid on the cartilage surface (so-called weeping lubrication). The functions of the synovial fluid include:

- reduction of friction — synovial fluid lubricates the articulating joints
- shock absorption — as a dilatant fluid, that possesses rheopectic properties, becoming more viscous under applied pressure. The synovial fluid in diarthrotic joints becomes thick the moment shear is applied in order to protect the joint and subsequently, thins to normal viscosity instantaneously to resume its lubricating function between shocks.
- nutrient and waste transportation — the fluid supplies oxygen and nutrients and removes carbon dioxide and metabolic wastes from the chondrocytes within the surrounding cartilage
- molecular sieving - pressure within the joint forces hyaluronan in the fluid against the synovial membrane forming a barrier against cells migrating into, or fluid migrating out of, the joint space. This function is dependent on the molecular weight of the hyaluronan.



https://en.wikipedia.org/wiki/Synovial_fluid

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T-cell Receptor

The T cell receptor or TCR is a molecule found on the surface of T lymphocytes (or T cells) that is responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex (MHC) molecules. The binding between TCR and antigen peptides is of relatively low affinity and is degenerate: that is, many TCRs recognize the same antigen peptide and many antigen peptides are recognized by the same TCR.

The TCR is composed of two different protein chains (that is, it is a heterodimer). In humans, in 95% of T cells the TCR consists of an alpha (α) and beta (β) chain, whereas in 5% of T cells the TCR consists of gamma and delta (γ/δ) chains. This ratio changes during ontogeny and in diseased states as well as in different species.

When the TCR engages with antigenic peptide and MHC (peptide/MHC), the T lymphocyte is activated through signal transduction, that is, a series of biochemical events mediated by associated enzymes, co-receptors, specialized adaptor molecules, and activated or released transcription factors.

https://en.wikipedia.org/wiki/T_cell_receptor

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T-SNARES

SNARE proteins (an acronym derived from "SNAP (Soluble NSF Attachment REceptor") are a large protein superfamily consisting of more than 60 membe yeast and mammalian cells. The primary role of SNARE proteins is to mediate fusion, that is, the fusion of vesicles with their target membrane bound compa (such as a lysosome). The best studied SNAREs are those that mediate dockin aptic vesicles with the presynaptic membrane in neurons. These SNAREs are gets of the bacterial neurotoxins responsible for botulism and tetanus.

SNAREs can be divided into two categories: vesicle or v-SNAREs, which are in rated into the membranes of transport vesicles during budding, and target or SNAREs, which are located in the membranes of target compartments. Evider gests that t-SNAREs form stable subcomplexes which serve as guides for v-SN binding to complete the formation of the SNARE complex.

https://en.wikipedia.org/wiki/SNARE_(protein)

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T-state

The Monod-Wyman-Changeux (MWC) model for concerted allosteric transitions eplored the phenomenon of cooperativity based on thermodynamics and three-dimensional conformations. It was originally formulated for oligomeric proteins with symmetrically arranged, identical subunits, each of which has one ligand binding site. According to this framework, two (or more) interconvertible conformational states of an allosteric protein coexist in a thermal equilibrium. The states - often termed tense (T) and relaxed (R) - differ in affinity for the ligand molecule. The ratio between the two states is regulated by the binding of ligand molecules that stabilizes the higher-affinity state. Importantly, all subunits of a molecule change states at the same time, a phenomenon known as "concerted transition".

https://en.wikipedia.org/wiki/Cooperative_binding

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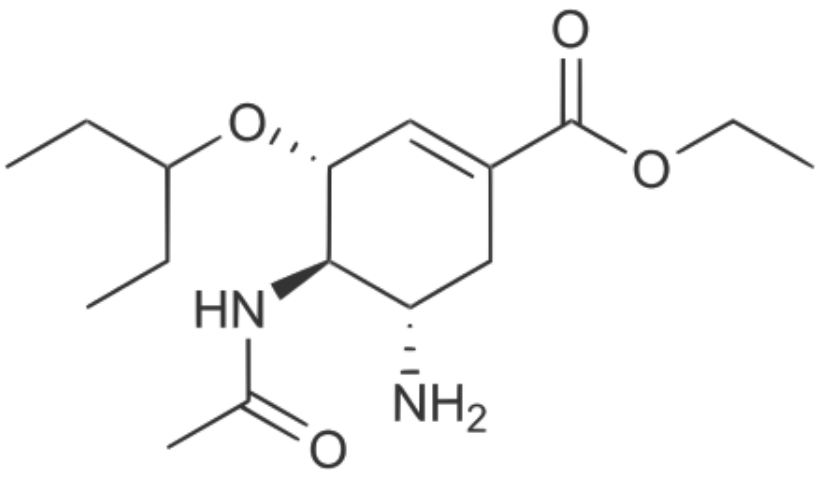
Tamiflu

Oseltamivir, marketed under the trade name Tamiflu, is an antiviral medication used to treat influenza A and influenza B (flu), and to prevent flu after exposure. It was the first orally administered neuraminidase inhibitor commercially developed.

The prodrug oseltamivir is itself not virally effective. However, once in the liver it is hydrolyzed to its active metabolite – the free oseltamivir carboxylate.

Oseltamivir is a neuraminidase inhibitor, serving as a competitive inhibitor of the activity of the viral neuraminidase (NA) enzyme upon sialic acid, found on glycoproteins on the surface of normal host cells. By blocking the activity of the enzyme, oseltamivir prevents new viral particles from being released through the cleaving of terminal sialic acid on glycosylated hemagglutinin and thus fail to facilitate virus release.

https://en.wikipedia.org/wiki/Oseltamivir



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Tardigrade

Tardigrades (also known as water bears or moss piglets) are water-dwelling, eight-legged, segmented micro-animals. They were first discovered by the German pastor J hann August Ephraim Goeze in 1773. The name Tardigrada (meaning "slow stepper" was given three years later by the Italian biologist Lazzaro Spallanzani. They have be found everywhere from mountaintops to the deep sea, from tropical rain forests to th Antarctic.

Tardigrades are notable for being perhaps the most durable of known organisms: the can survive extreme conditions that would be rapidly fatal to nearly all other known life forms. They can withstand temperature ranges from 1 K (–458 °F; –272 °C) to about 420 K (300 °F; 150 °C), pressures about six times greater than those found in the deepest ocean trenches, ionizing radiation at doses hundreds of times higher tha the lethal dose for a human, and the vacuum of outer space. They can go without foo or water for more than 30 years, drying out to the point where they are 3% or less wa ter, only to rehydrate, forage, and reproduce.

https://en.wikipedia.org/wiki/Tardigrade

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TATA Box

In molecular biology, the TATA box (also called the Goldberg-Hogness box) is a DNA sequence (cis-regulatory element) found in the promoter region of genes in archaea and eukaryotes. Approximately 24% of human genes contain a TATA box within the core promoter.

Considered to be the core promoter sequence, it is the binding site of either general transcription factors or histones (the binding of a transcription factor blocks the binding of a histone and vice versa) and is involved in the process of transcription by RNA polymerase.

The TATA box has the core DNA sequence 5'-TATAAA-3' or a variant, which is usually followed by three or more adenine bases[citation needed]. It is usually located 25-35 base pairs upstream of the transcription start site. The sequence is believed to have remained consistent throughout much of the evolutionary process, possibly originating in an ancient eukaryotic organism.

During the process of transcription, the TATA binding protein (TBP) normally binds to the TATA-box sequence, which unwinds the DNA and bends it through 80°. The AT-rich sequence of the TATA-box facilitates easy unwinding, due to weaker base-pairing interactions between A and T bases, as compared to between G and C. The TBP is an unusual protein in that it binds to the minor groove and binds with a β sheet.

The TATA box is usually found at the binding site of RNA polymerase II. TFIID, a transcription factor, binds to the TATA box, followed by TFIIA binding to the upstream part of the TFIID protein. TFIIB then binds to the downstream part of TFIID. RNA polymerase can then recognize this multi-protein complex and bind to it, along with various other transcription factors such as TFIIF, TFIIE and TFIIH. Transcription is then initiated, and the polymerase moves along the DNA strand, leaving TFIID and TFIIA bound to the TATA box. These can then facilitate the binding of additional RNA polymerase II molecules.

This cluster of RNA polymerase II and various transcription factors is known as a basal transcriptional complex or BTC. In this state, it only gives a low level of transcription. Other factors must stimulate the BTC to increase transcription levels. One such example of a BTC stimulating region of DNA is the CAAT box.

Most genes lack a TATA box and use an initiator element or downstream core promoter instead. Nevertheless, TBP is always involved and is forced to bind without sequence specificity. A genome-wide study put the fraction of TATA-dependent human promoters at ~10%. An earlier study of ~1,000 genes found 32% of the promoters had a TATA box.

https://en.wikipedia.org/wiki/TATA_box

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Tau Protein

Tau proteins (or τ proteins, after the Greek letter by that name) are protein
lize microtubules. They are abundant in neurons of the central nervous syst
less common elsewhere, but are also expressed at very low levels in CNS as
oligodendrocytes. Pathologies and dementias of the nervous system such as
heimer's disease and Parkinson's disease are associated with tau proteins t
come defective and no longer stabilize microtubules properly.

The tau proteins are the product of alternative splicing from a single gene t
mans is designated MAPT (microtubule-associated protein tau) and is locat
mosome 17.

https://en.wikipedia.org/wiki/Tau_protein

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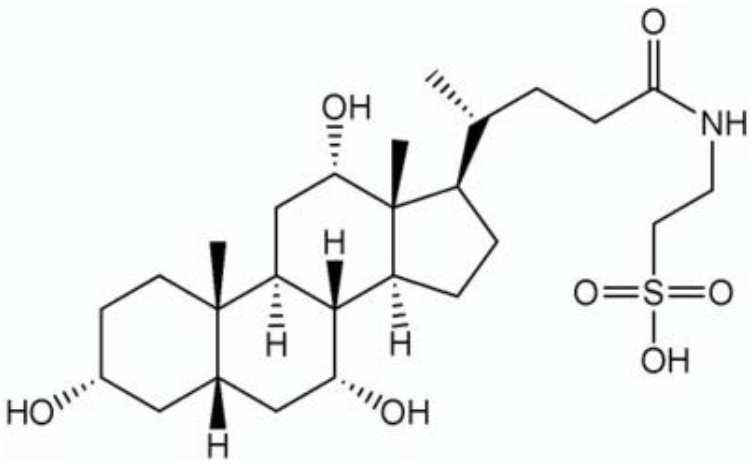
Taurocholic Acid

Taurocholic acid, known also as cholaic acid, cholyltaurine, or acidum cholatauricum is a deliquescent yellowish crystalline bile acid involved in the emulsification of fats. occurs as a sodium salt in the bile of mammals. It is a conjugate of cholic acid with taurine. In medical use, it is administered as a cholagogue and choleretic. Hydrolysis of taurocholic acid yields taurine.

For commercial use, taurocholic acid is manufactured from cattle bile, a byproduct o the meat-processing industry. This acid is also one of the many molecules in the bod that has cholesterol as its precursor.



https://en.wikipedia.org/wiki/Taurocholic_acid

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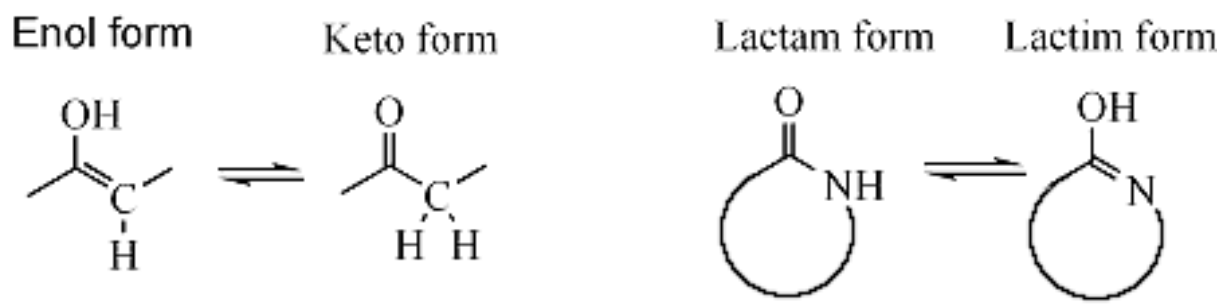
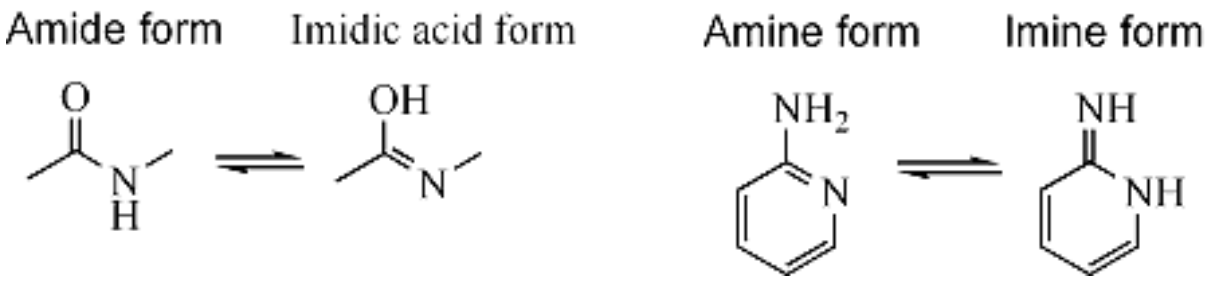
Tautomerize

Tautomers are constitutional isomers of organic compounds that readily interconvert with each other. The chemical reaction interconverting the two is called tautomerization. This reaction commonly results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. The concept of tautomerizations is called tautomerism. Because of the rapid interconversion, tautomers are generally considered to be the same chemical compound. Tautomerism should be distinguished from resonance, where two structures differing only in the position of electrons coexist in quantum superposition, rather than as a rapidly-interconverting mixture. Tautomerism is a special case of structural isomerism and can play an important role in non-canonical base pairing in DNA and especially RNA molecules.





https://en.wikipedia.org/wiki/Tautomer

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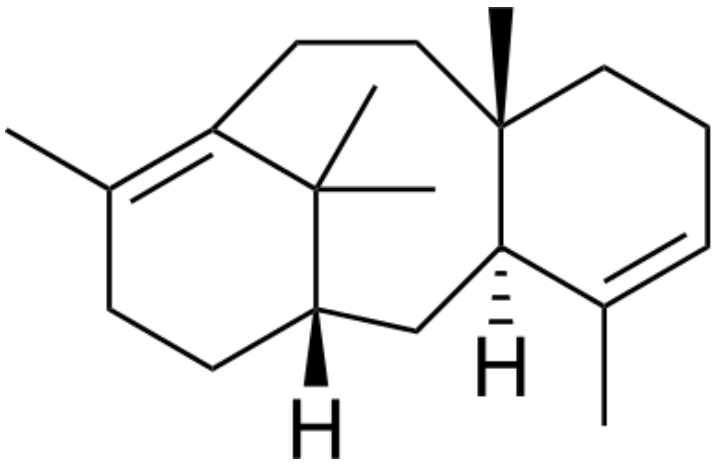
Taxadiene

Taxadiene (taxa-4,11-diene) is a diterpene. Taxadiene is the first committed intermed
ate in the synthesis of taxol. Six hydroxylation reactions, and a few others, are neede
to convert taxadiene to baccatin III.

Enzymatically, taxadiene is produced from geranylgeranyl pyrophosphate by taxadie
synthase. A biochemical gram-scale production of taxadiene has been reported in 20
using genetically engineered *Escherichia coli*.



https://en.wikipedia.org/wiki/Taxadiene

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Chapter 2 - Structure & Function: Lipids

TBP

The TATA-binding protein (TBP) is a general transcription factor that binds specifically to a DNA sequence called the TATA box. This DNA sequence is found about 30 base pairs upstream of the transcription start site in some eukaryotic gene promoters. TBP, along with a variety of TBP-associated factors, make up the TFIID, a general transcription factor that in turn makes up part of the RNA polymerase II preinitiation complex. As one of the few proteins in the preinitiation complex that binds DNA in a sequence-specific manner, it helps position RNA polymerase II over the transcription start site of the gene. However, it is estimated that only 10–20% of human promoters have TATA boxes. Therefore, TBP is probably not the only protein involved in positioning RNA polymerase II.

TBP is involved in DNA melting (double strand separation) by bending the DNA by 80° (the AT-rich sequence to which it binds facilitates easy melting). The TBP is an unusual protein in that it binds the minor groove using a β sheet.

TBP is a subunit of the eukaryotic transcription factor TFIID. TFIID is the first protein to bind to DNA during the formation of the pre-initiation transcription complex of RNA polymerase II (RNA Pol II). Binding of TFIID to the TATA box in the promoter region of the gene initiates the recruitment of other factors required for RNA Pol II to begin transcription. Some of the other recruited transcription factors include TFIIA, TFIIB, and TFIIF. Each of these transcription factors is formed from the interaction of many protein subunits, indicating that transcription is a heavily regulated process.

TBP is also a component of RNA polymerase I and RNA polymerase III and is therefore involved in transcription initiation by all three RNA polymerases. In specific cell types or on specific promoters TBP can be replaced by one of several TBP-related factors.

When TBP binds to a TATA box within the DNA, it distorts the DNA by inserting amino acid side-chains between base pairs, partially unwinding the helix, and doubly kinking it. The distortion is accomplished through a great amount of surface contact between the protein and DNA. TBP binds with the negatively charged phosphates in the DNA backbone through positively charged lysine and arginine amino acid residues. The sharp bend in the DNA is produced through projection of four bulky phenylalanine residues into the minor groove. As the DNA bends, its contact with TBP increases, thus enhancing the DNA-protein interaction.

The strain imposed on the DNA through this interaction initiates melting, or separation, of the strands.

https://en.wikipedia.org/wiki/TATA-binding_protein

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Telomerase

Telomerase, also called terminal transferase, is a ribonucleoprotein that adds a species-dependent telomere repeat sequence to the 3' end of telomeres. A telomere is a region of repetitive sequences at each end of a eukaryotic chromatid, which protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes. Telomerase, active in normal stem cells, is normally absent from, or at very low levels in, most somatic cells.

Telomerase is a reverse transcriptase enzyme that carries its own RNA molecule (e.g., with the sequence "CCCAAUCCC" in vertebrates) which is used as a template when it elongates telomeres.

The human telomerase enzyme complex consists of two molecules each of human telomerase reverse transcriptase (TERT), telomerase RNA (TR or TERC), and dyskerin (DKC1).

By using TERC, TERT can add a six-nucleotide repeating sequence, 5'-TTAGGG (in vertebrates, the sequence differs in other organisms) to the 3' strand of chromosomes. These TTAGGG repeats (with their various protein binding partners) are called telomeres. The template region of TERC is 3'-CAAUCCCAAUC-5'.

Telomerase can bind the first few nucleotides of the template to the last telomere sequence on the chromosome, add a new telomere repeat (5'-GGTTAG-3') sequence, let go, realign the new 3'-end of telomere to the template, and repeat the process. Telomerase reverses telomere shortening.

https://en.wikipedia.org/wiki/Telomerase

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Telomeres

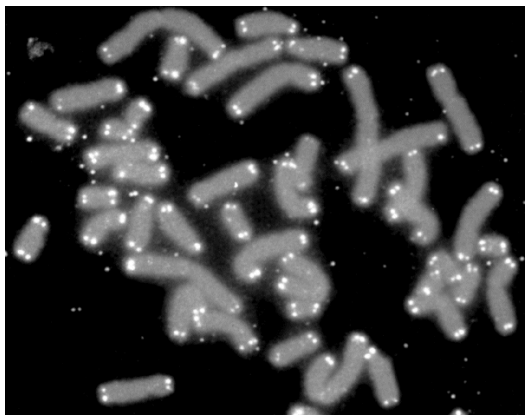
A telomere is a region of repetitive nucleotide sequences at each end of a chromosome, which protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes. For vertebrates, the sequence of nucleotides in telomeres is TTAGGG. This sequence of TTAGGG is repeated approximately 2,500 times in humans.

During chromosome replication, the enzymes that duplicate DNA cannot continue their duplication all the way to the end of a chromosome, so in each duplication the end of the chromosome is shortened (this is because the synthesis of Okazaki fragments requires RNA primers attaching ahead on the lagging strand). The telomeres are disposable buffers at the ends of chromosomes which are truncated during cell division; their presence protects the genes before them on the chromosome from being truncated instead.

For vertebrates, the sequence of nucleotides in telomeres is TTAGGG. Most prokaryotes, lacking this linear arrangement, do not have telomeres. Telomeres compensate for incomplete semi-conservative DNA replication at chromosomal ends. A protein complex known as shelterin serves as protection against double-strand break (DSB) repair by homologous recombination (HR) and non-homologous end joining (NHEJ).

In most prokaryotes, chromosomes are circular and, thus, do not have ends to suffer premature replication termination. A small fraction of bacterial chromosomes (such as those in *Streptomyces*, *Agrobacterium*, and *Borrelia*) are linear and possess telomeres, which are very different from those of the eukaryotic chromosomes in structure and functions. The known structures of bacterial telomeres take the form of proteins bound to the ends of linear chromosomes, or hairpin loops of single-stranded DNA at the ends of the linear chromosomes.

While replicating DNA, the eukaryotic DNA replication enzymes (the DNA polymerase protein complex) cannot replicate the sequences present at the ends of the chromosomes (or more precisely the chromatid fibers). Hence, these sequences and the information they carry may get lost. This is the reason telomeres are so important in context of successful cell division: They "cap" the end-sequences and themselves get lost in the process of DNA replication. But the cell has an enzyme called telomerase, which carries out the task of adding repetitive nucleotide sequences to the ends of the DNA. Telomerase, thus, "replenishes" the telomere "cap" of the DNA. In most multicellular eukaryotic organisms, telomerase is active only in germ cells, some types of stem cells such as embryonic stem cells, and certain white blood cells. Telomerase can be re activated and telomeres reset back to an embryonic state by somatic cell nuclear transfer. There are theories that claim that the steady shortening of telomeres with each replication in somatic (body) cells may have a role in senescence and in the prevention of cancer. This is because the telomeres act as a sort of time-delay "fuse", eventually running out after a certain number of cell divisions and resulting in the eventual loss of vital genetic information from the cell's chromosome with future divisions.



https://en.wikipedia.org/wiki/Telomere

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Template

In copying a DNA, the word template refers to the strand being copied by a polymerase using the rules of base-pairing. The word template is appropriate for making DNA or for making RNA and the strand being copied can be DNA or RNA, depending on the system. For transcription, where only one strand of a DNA duplex, the strand being copied is known as the template strand and the other strand is known as the coding strand.

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Termination of Transcription

In genetics, a transcription terminator is a section of nucleic acid sequence that marks the end of a gene or operon in genomic DNA during transcription. This sequence mediates transcriptional termination by providing signals in the newly synthesized mRNA that trigger processes which release the mRNA from the transcriptional complex. These processes include the direct interaction of the mRNA secondary structure with the complex and/or the indirect activities of recruited termination factors. Release of the transcriptional complex frees RNA polymerase and related transcriptional machinery to begin transcription of new mRNAs.

Termination is part of the process of transcribing RNA. In eukaryotes, a termination factor is required to release the newly made (nascent) RNA from the transcription complex. Prokaryote mRNAs often do not require a termination factor: an inverted repeat followed by a string of Us (uracils) in the mRNA template strand forms a stem-loop structure which destabilizes binding by the RNA polymerase and causes ρ-independent transcription termination.

The most extensively studied transcriptional termination factor is the ρ (rho) protein of *E. coli*. The ρ protein recognizes a cytosine-rich region of the elongating mRNA, but the exact features of the recognized sequences remain unknown. ρ forms a ring-shaped hexamer and advances along the mRNA, hydrolyzing ATP, toward RNA polymerase (5' to 3' with respect to the mRNA). When the ρ protein reaches the RNA polymerase complex, transcription is terminated by dissociation of the RNA polymerase from the DNA. The structure, as well as the activity, of the Rho protein is similar to that of the F_1 subunit of ATP synthase, supporting the theory that the two share an evolutionary link. The antibiotic bicyclomycin works by inhibiting ρ.

The process of transcriptional termination is less well understood in eukaryotes, which have extensive post-transcriptional RNA processing. Each of the three types of eukaryotic RNA polymerase has a different termination system. Eukaryotic termination factors bind to the termination signal region and disturb RNA polymerase II as it moves by, causing it to fall off the DNA strand within the next 300 base pairs. This 300 bp region is removed during processing, before poly(A)tailing.

https://en.wikipedia.org/wiki/Termination_factor

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Terminator Site

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https://en.wikipedia.org/wiki/Termination_factor

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Terpenes

Terpenes are a large and diverse class of organic compounds, produced by a variety of plants, particularly conifers, though also by some insects such as termites or swallowtail butterflies, which emit terpenes from their osmeteria. They are often strong-smelling. They may protect the plants that produce them by deterring herbivores and by attracting predators and parasites of herbivores. Many terpenes are aromatic hydrocarbons and thus may have had a protective function. The difference between terpenes and terpenoids is that terpenes are hydrocarbons, whereas terpenoids contain additional functional groups.

They are the major components of resin, and of turpentine produced from resin. The name "terpene" is derived from the word "turpentine". In addition to their roles as end-products in many organisms, terpenes are major biosynthetic building blocks within nearly every living creature. Steroids, for example, are derivatives of the triterpene squalene.

When terpenes are modified chemically, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are generally referred to as terpenoids. Some authors will use the term terpene to include all terpenoids. Terpenoids are also known as isoprenoids.

Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers. Essential oils are used widely as fragrances in perfumery, and in medicine and alternative medicines such as aromatherapy. Synthetic variations and derivatives of natural terpenes and terpenoids also greatly expand the variety of aromas used in perfumery and flavors used in food additives. Vitamin A is a terpene.

https://en.wikipedia.org/wiki/Terpene

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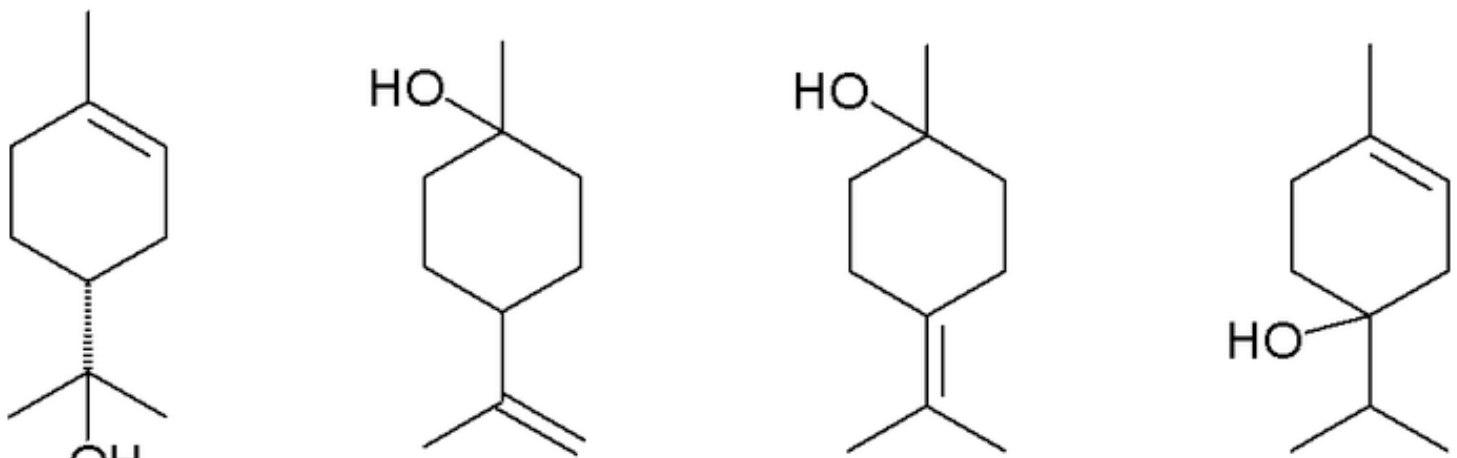
Terpineol

Terpineol is a naturally occurring monoterpene alcohol that has been isolated fr
variety of sources such as cajuput oil, pine oil, and petitgrain oil. There are four i
mers, α-, β-, γ-terpineol, and terpinen-4-ol. β- and γ-terpineol differ only by the
tion of the double bond. Terpineol is usually a mixture of these isomers with α-
terpineol as the major constituent.



https://en.wikipedia.org/wiki/Terpineol

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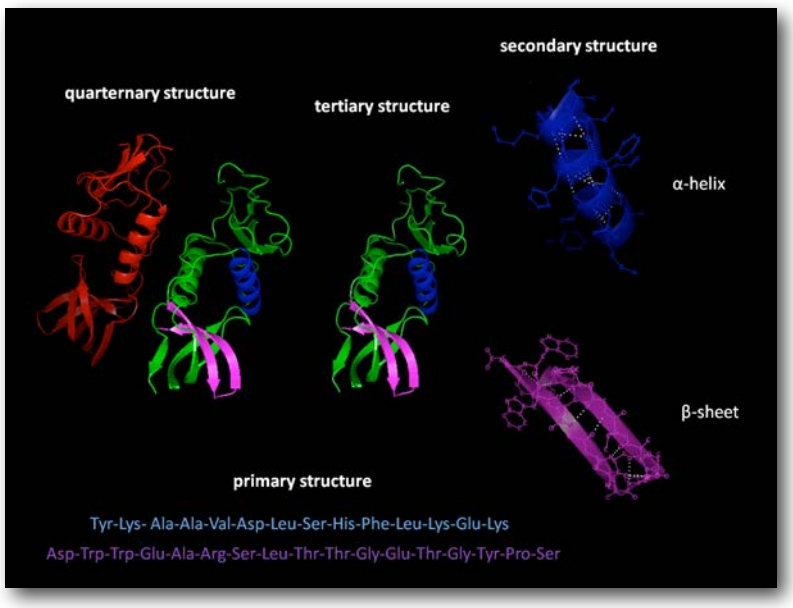
Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

Tertiary Structure

Biomolecular structure is the intricate folded, three-dimensional shape that is formed by a protein, DNA, or RNA molecule, and that is important to its function. The structure of these molecules is frequently decomposed into primary structure, secondary structure, tertiary structure, and quaternary structure. The scaffold for this structure is provided by secondary structural elements that are hydrogen bonds within the molecule. This leads to several recognizable "domains" of protein structure and nucleic acid structure, including secondary structure like hairpin loops, bulges and internal loops for nucleic acids, and alpha helices and beta sheets for proteins.

The tertiary structure of a protein or any other macromolecule is its three-dimensional structure, as defined by the atomic coordinates. Proteins and nucleic acids are capable of diverse functions ranging from molecular recognition to catalysis. Such functions require a precise three-dimensional tertiary structure. While such structures are diverse and seemingly complex, they are composed of recurring, easily recognizable tertiary structure motifs that serve as molecular building blocks. Tertiary structure is considered to be largely determined by the biomolecule's primary structure, or the sequence of amino acids or nucleotides of which it is composed. Efforts to predict tertiary structure from the primary structure are in general known as structure prediction.



https://en.wikipedia.org/wiki/Biomolecular_structure#Tertiary_structure

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Testosterone

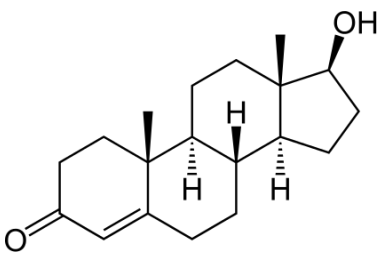
Testosterone is a steroid hormone from the androgen group and is found in humans and other vertebrates. In humans and other mammals, testosterone is secreted primarily by the testicles of males and, to a lesser extent, the ovaries of females. Small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid.

In men, testosterone plays a key role in the development of male reproductive tissues such as the testis and prostate as well as promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair. In addition, testosterone is essential for health and well-being as well as the prevention of osteoporosis.

In general, androgens promote protein synthesis and growth of those tissues with androgen receptors. Testosterone effects can be classified as virilizing and anabolic, though the distinction is somewhat artificial, as many of the effects can be considered both.

• Anabolic effects include growth of muscle mass and strength, increased bone density and strength, and stimulation of linear growth and bone maturation.

• Androgenic effects include maturation of the sex organs, particularly the penis and the formation of the scrotum in the fetus, and after birth (usually at puberty) a deepening of the voice, growth of the beard and axillary hair. Many of these fall into the category of male secondary sex characteristics.



https://en.wikipedia.org/wiki/Testosterone

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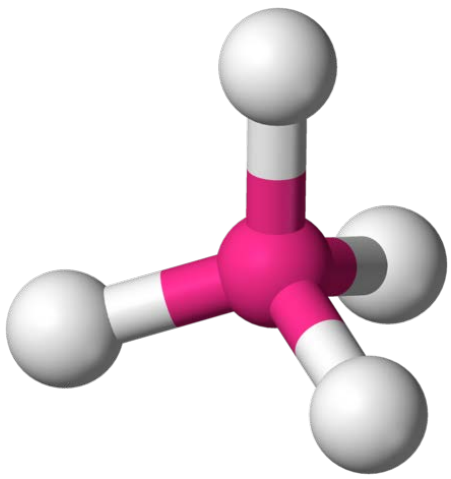
Tetrahedral

In a tetrahedral molecular geometry, a central atom is located at the center
substituents that are located at the corners of a tetrahedron. The bond angle
109.5° when all four substituents are the same, as in methane (CH_4). The pe
metrical tetrahedron belongs to point group Td, but most tetrahedral molec
have lower symmetry. Tetrahedral molecules can be chiral.



https://en.wikipedia.org/wiki/Tetrahedral_molecular_geometry

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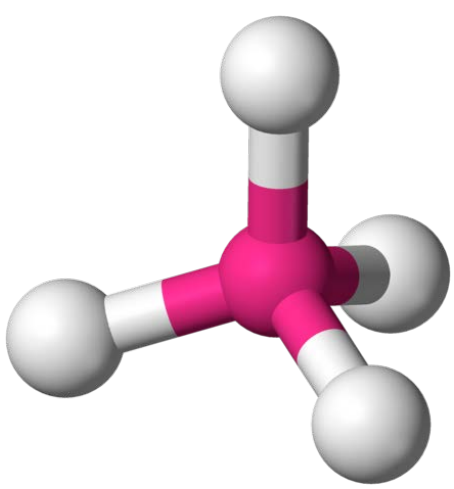

https://en.wikipedia.org/wiki/Tetrahedral_molecular_geometry

Related Glossary Terms

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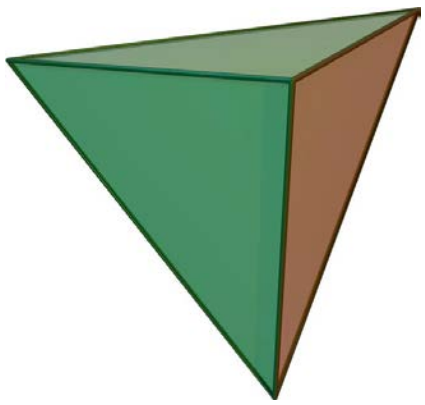
Tetrahedron

In geometry, a tetrahedron (plural: tetrahedra or tetrahedrons) is a polyhedron
posed of four triangular faces, six straight edges, and four vertex corners. The te
dron is the simplest of all the ordinary convex polyhedra and the only one that l
fewer than 5 faces.

The tetrahedron is the three-dimensional case of the more general concept of a
ean simplex.



https://en.wikipedia.org/wiki/Tetrahedron

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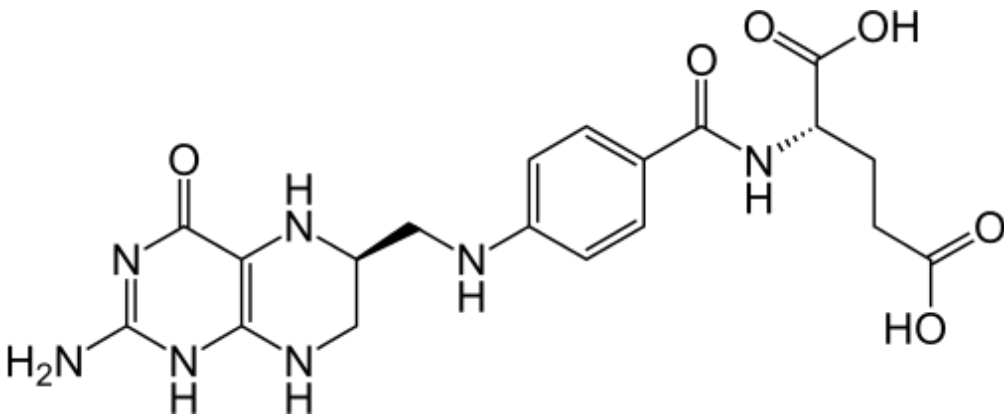
Tetrahydrofolate

Tetrahydrofolic acid, or tetrahydrofolate, is a folic acid derivative that is produced from dihydrofolic acid by dihydrofolate reductase. This reaction is inhibited by methotrexate. It is converted into 5,10-methylenetetrahydrofolate by serine hydroxy-methyltransferase.

Tetrahydrofolate is a cofactor in many reactions, especially in the metabolism of amino acids and nucleic acids. It acts as a donor of a group with one carbon atom. It gets this carbon atom by sequestering formaldehyde produced in other processes. A shortage in tetrahydrofolic acid (FH_4) can cause megaloblastic anemia.



https://en.wikipedia.org/wiki/Tetrahydrofolic_acid

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Tetraterpenes

Tetraterpenes are terpenes consisting of eight isoprene units and have the m
formula $C_{40}H_{64}$. Tetraterpenoids (carotenoids) are tetraterpenes that have be
fied by chemical transformations such as oxidation or cyclization.

Tetraterpenes include:
• Phytoene

Biologically important tetraterpenoids include:
• Carotenes and carotenoids, such as the acyclic lycopene, the monocyclic γ-c
and the bicyclic α- and β-carotenes
• Xanthophylls, pigments distributed widely in nature

https://en.wikipedia.org/wiki/Tetraterpene

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TFIIA

Transcription factor TFIIA is a nuclear protein involved in the RNA polymerase II-dependent transcription of DNA. TFIIA is one of several general (basal) transcription factors (GTFs) that are required for all transcription events that use RNA polymerase II. Other GTFs include TFIID, a complex composed of the TATA binding protein TBP and TBP-associated factors (TAFs), as well as the factors TFIIB, TFIIE, TFIIF, and TFIIH. Together, these factors are responsible for promoter recognition and the formation of a transcription pre-initiation complex (PIC) capable of initiating RNA synthesis from a DNA template.

TFIIA interacts with the TBP subunit of TFIID and aids in the binding of TBP to TATA-box containing promoter DNA. Interaction of TFIIA with TBP facilitates formation of and stabilizes the pre-initiation complex. Interaction of TFIIA with TBP also results in the exclusion of negative (repressive) factors that might otherwise bind to TBP and interfere with PIC formation. TFIIA also acts as a co-activator for some transcriptional activators, assisting with their ability to increase, or activate, transcription. The requirement for TFIIA *in vitro* transcription systems has been variable, and it can be considered either as a GTF and/or a loosely associated TAF-like co-activator. Genetic analysis in yeast has shown that TFIIA is essential for viability.

https://en.wikipedia.org/wiki/Transcription_factor_II_A

Related Glossary Terms

Drag related terms here

TFIIB

Transcription Factor II B (TFIIB) is a general transcription factor that is involved in the formation of the RNA polymerase II preinitiation complex (PIC) and aids in stimulating transcription initiation. TFIIB is localized to the nucleus and provides a platform for PIC formation by binding and stabilizing the DNA-TBP (TATA-binding protein) complex and by recruiting RNA polymerase II and other transcription factors. It is encoded by the TFIIB gene.

There are six steps in the mechanism of TFIIB action in the formation of the PIC and transcription initiation:

1 The DNA is recruited to RNA polymerase II through the B ribbon and it is then positioned by the B core.
2 DNA opening occurs aided by the B linker, the template strand is then placed into the RNA polymerase II cleft and the bubble is stabilized by the B reader (open complex formation).
3 RNA polymerase II and B reader scan the DNA for the Inr in order to position the transcription start site.
4 The first phosphodiester bond is formed.
5 Production of short abortive transcripts due to clashes with the B reader loop.
6 The growth of nascent RNA chain to 12-13 bases leads to ejection of TFIIB due to further clashes with TFIIB.

https://en.wikipedia.org/wiki/Transcription_factor_II_B

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TFIID

Transcription factor II D (TFIID) is one of several general transcription factors make up the RNA polymerase II preinitiation complex. RNA polymerase II holo zyme is a form of eukaryotic RNA polymerase II that is recruited to the promot protein-coding genes in living cells. It consists of RNA polymerase II, a subset o eral transcription factors, and regulatory proteins known as SRB proteins. Befo start of transcription, the transcription Factor II D (TFIID) complex binds to th box in the core promoter of the gene.

TFIID:

• Coordinates the activities of more than 70 polypeptides required for initiation scription by RNA polymerase II

• Binds to the core promoter to position the polymerase properly

• Serves as the scaffold for assembly of the remainder of the transcription comp

Acts as a channel for regulatory signals

https://en.wikipedia.org/wiki/Transcription_factor_II_D

Related Glossary Terms

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TFIIE

Transcription factor II E (TFIIE) is one of several general transcription fact
make up the RNA polymerase II preinitiation complex.

Transcription Factor II E is encoded by the GTF2E1 and GTF2E2 genes TF
thought to be involved in DNA melting at the promoter. It contains a zinc r
that can bind single stranded DNA.

https://en.wikipedia.org/wiki/Transcription_factor_II_E

Related Glossary Terms

Drag related terms here

TFIIF

Transcription factor IIF (TFIIF) is one of several general transcription facto
make up the RNA polymerase II pre-initiation complex. Transcription Fac
coded by the GTF2F1, GTF2F2, and GTF2F2L genes.

TFIIF binds to RNA PolII when the enzyme is already unbound to any othe
tion factor, thus avoiding it from contacting DNA outside the promoter. Fu
TFIIF stabilizes the RNA polymerase II while it's contacting TBP and TFIIE

https://en.wikipedia.org/wiki/Transcription_factor_II_F

Related Glossary Terms

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TFIIH

Transcription factor II Human (TFIIH) is one of several general transcription factors that make up the RNA polymerase II preinitiation complex. TFIIH consists of ten subunits, 7 of which (XPD, XPB, p62, p52, p44, p34 and TTDA) form the core complex. The cyclin activating kinase-subcomplex (CDK7, MAT1, and cyclin H) is linked to the core via the XPD protein. Two of the subunits, ERCC2/XPD and ERCC3/XPB, have helicase and ATPase activities and help create the transcription bubble. In a test tube these subunits are only required for transcription if the DNA template is not already denatured or if it is supercoiled.

Two other TFIIH subunits, CDK7 and cyclin H, phosphorylate serine amino acids on the RNA polymerase II C-terminal domain and possibly other proteins involved in the cell cycle. Next to a vital function in transcription initiation, TFIIH is also involved in nucleotide excision repair.

It is responsible for giving the 'go' signal which is why it is assembled last.

https://en.wikipedia.org/wiki/Transcription_factor_II_H

Related Glossary Terms

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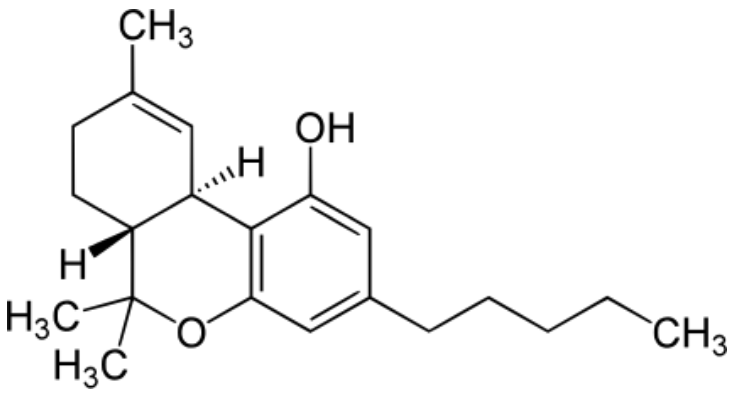
THC

Tetrahydrocannabinol (THC, dronabinol by INN), or more precisely its main isomer (–)-*trans*-Δ9-tetrahydrocannabinol, is the principal psychoactive constituent (or can nabinoid) of cannabis. It can be an amber or gold colored glassy solid when cold, whi becomes viscous and sticky if warmed.

Like most pharmacologically-active secondary metabolites of plants, THC in Cannabi is assumed to be involved in self-defense, perhaps against herbivores. THC also pos- sesses high UV-B (280–315 nm) absorption properties, which, it has been speculated could protect the plant from harmful UV radiation exposure.



https://en.wikipedia.org/wiki/Tetrahydrocannabinol

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Chapter 2 - Structure & Function: Lipids

Thermogenin

Thermogenin (called uncoupling protein by its discoverers and now known as uncoupling protein 1, or UCP1) is an uncoupling protein found in the mitochondria of brown adipose tissue (BAT). It is used to generate heat by non-shivering thermogenesis, and makes a quantitatively important contribution to countering heat loss in neonates which would otherwise occur due to the high surface area-volume ratio.

UCPs are transmembrane proteins that decrease the proton gradient generated in oxidative phosphorylation. They do this by increasing the permeability of the inner mitochondrial membrane, allowing protons that have been pumped into the intermembrane space to return to the mitochondrial matrix. UCP1-mediated heat generation in brown fat uncouples the respiratory chain, allowing for fast substrate oxidation with a low rate of ATP production.

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https://en.wikipedia.org/wiki/Thermogenin

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Thermolysin

Thermolysin is a thermostable neutral metalloproteinase enzyme produced by the Gram-positive bacteria Bacillus thermoproteolyticus. It requires one zinc ion for enzyme activity and four calcium ions for structural stability. Thermolysin specifically catalyzes the hydrolysis of peptide bonds containing hydrophobic amino acids. However thermolysin is also widely used for peptide bond formation through the reverse action of hydrolysis. Thermolysin is the most stable member of a family of metalloproteinases produced by various Bacillus species. These enzymes are also termed 'neutral proteinases or thermolysin -like proteinases (TLPs).

In contrast to many proteins that undergo conformational changes upon heating and denaturation, thermolysin does not undergo any major conformational changes until at least 70 °C. The thermal stability of members of the TLP family is measured in terms of a T50 temperature. At this temperature incubation for 30 minutes reduces the enzymes activity by half. Thermolysin has a T50 value of 86.9 °C, making it the most thermo stable member of the TLP family.

https://en.wikipedia.org/wiki/Thermolysin

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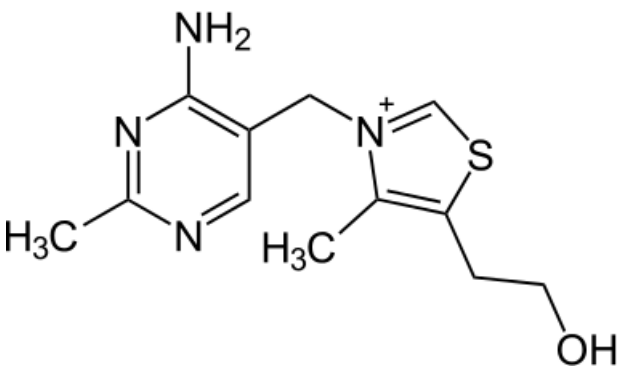
Thiamine

Thiamine was named as the "thio-vitamine" ("sulfur-containing vitamin") is a vitamin of the B complex. First named aneurin for the detrimental neurological effects if not present in the diet, it was eventually assigned the generic descriptor name vitamin B1. Its phosphate derivatives are involved in many cellular processes. The best-characterized form is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids. In yeast, TPP is also required in the first step of alcoholic fermentation.

All living organisms use thiamine, but it is synthesized only in bacteria, fungi, and plants. Animals must obtain it from their diet, and thus, for humans, it is an essential nutrient. Insufficient intake in birds produces a characteristic polyneuritis. In mammals, deficiency results in Korsakoff's syndrome, optic neuropathy, and a disease called beriberi that affects the peripheral nervous system (polyneuritis) and/or the cardiovascular system. Thiamine deficiency has a potentially fatal outcome if it remains untreated. In less severe cases, nonspecific signs include malaise, weight loss, irritability and confusion.

ThDP is a coenzyme for several enzymes that catalyze the transfer of two-carbon units and in particular the dehydrogenation (decarboxylation and subsequent conjugation with coenzyme A) of 2-oxoacids (α-keto acids).



https://en.wikipedia.org/wiki/Thiamine

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Thiamine Diphosphokinase

Thiamine diphosphokinase (EC 2.7.6.2) is an enzyme that catalyzes the che
tion

ATP + Thiamine $\rightleftharpoons$ AMP + Thiamine Pyrophosphate

This enzyme belongs to the family of transferases, specifically those transfe
phosphorus-containing groups (diphosphotransferases). The systematic na
enzyme class is ATP:thiamine diphosphotransferase. Other names in comm
clude thiamin kinase, thiamine pyrophosphokinase, ATP:thiamin pyrophos
rase, thiamin pyrophosphokinase, thiamin pyrophosphotransferase, thiami
thiamin:ATP pyrophosphotransferase, and TPTase.

This enzyme participates in thiamine metabolism.

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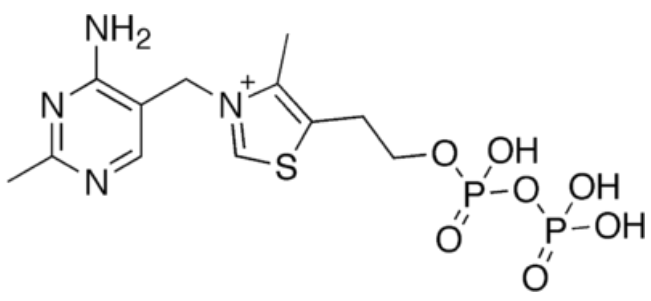
Thiamine Pyrophosphate

Thiamine pyrophosphate (TPP or ThPP), or thiamine diphosphate (ThDP), or cocarboxylase is a thiamine (vitamin B_1) derivative which is produced by the enzyme thiamine diphosphokinase. Thiamine pyrophosphate is a cofactor that is present in all living systems, in which it catalyzes several biochemical reactions. It was first discovered as an essential nutrient (vitamin) in humans through its link with the peripheral nervous system disease Beriberi, which results from a deficiency of thiamine in the diet.

TPP works as a coenzyme in many enzymatic reactions, such as:

- Pyruvate dehydrogenase complex
- Pyruvate decarboxylase in ethanol fermentation
- α-ketoglutarate dehydrogenase complex
- Branched-chain amino acid dehydrogenase complex
- 2-hydroxyphytanoyl-CoA lyase
- Transketolase



https://en.wikipedia.org/wiki/Thiamine_pyrophosphate

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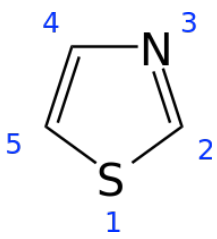
Thiazole Ring

Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen. The term 'thiazole' also refers to a large family of derivatives. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS. The thiazole ring is notable as a component of the vitamin thiamine (B_1).

Thiazole rings are planar and aromatic. Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazoles and have therefore greater aromaticity.

Thiazoles are members of the azoles, heterocycles that include imidazoles and oxazoles. Thiazole can also be considered a functional group. Oxazoles are related compounds, with sulfur replaced by oxygen. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen.

Thiazole rings are planar and aromatic. Thiazoles are characterized by larger pi-electron delocalization than the corresponding oxazoles and have therefore greater aromaticity. This aromaticity is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current. The calculated pi-electron density marks C_5 as the primary site for electrophilic substitution, and C_2 as the site for nucleophilic substitution.



https://en.wikipedia.org/wiki/Thiazole

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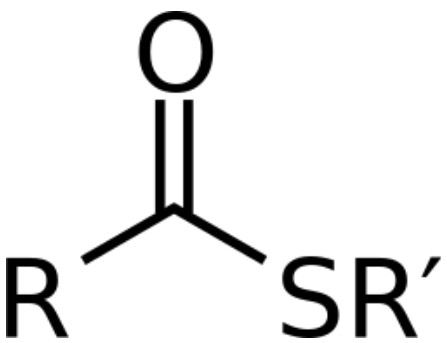
Thioester

Thioesters are compounds with the functional group C–S–CO–C. They are the pr
of esterification between a carboxylic acid and a thiol. Thioesters are widespread
chemistry, the best-known derivative being acetyl-CoA.

Thioesters are common intermediates in many biosynthetic reactions, including t
mation and degradation of fatty acids and mevalonate, precursor to steroids. Exa
include palmitoyl-CoA, malonyl-CoA, acetoacetyl-CoA, propionyl-CoA, and cinna
CoA.



https://en.wikipedia.org/wiki/Thioester

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Thioesterase

Thioesterases are enzymes which belong to the esterase family. Esterases, i
one type of the several hydrolases known.

Thioesterases exhibit esterase activity (splitting of an ester into acid and al
presence of water) specifically at a thiol group. Acetyl-CoA hydrolase, palm
hydrolase, succinyl-CoA hydrolase, formyl-CoA hydrolase, acyl-CoA hydrol
few examples of this group of enzymes. Ubiquitin thiolesterase is a well-kn
ple, whose structure has been analyzed.

https://en.wikipedia.org/wiki/Thioesterase

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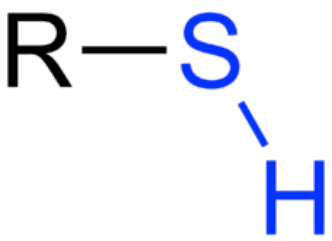
Thiol

A thiol is an organosulfur compound that contains a carbon-bonded sulfhydryl or su
phydryl (–C–SH or R–SH) group (where R represents an alkyl or other organic sub
stituent). Thiols are the sulfur analogue of alcohols (that is, sulfur takes the place of
oxygen in the hydroxyl group of an alcohol), and the word is a portmanteau of "thio
+ "alcohol," with the first word deriving from Greek θεῖον (theion) = "sulfur". The –
functional group itself is referred to as either a thiol group or a sulfhydryl group.

Many thiols have strong odors resembling that of garlic or rotten eggs. Thiols are us
as odorants to assist in the detection of natural gas (which in pure form is odorless)
and the "smell of natural gas" is due to the smell of the thiol used as the odorant.



https://en.wikipedia.org/wiki/Thiol

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Thiolase

Thiolases, also known as acetyl-coenzyme A acetyltransferases (ACAT), are enzy
which convert two units of acetyl-CoA to acetoacetyl CoA in the mevalonate path
Thiolases are ubiquitous enzymes that have key roles in many vital biochemical p
ways, including the β oxidation pathway of fatty acid degradation (where they ca
formation of acetyl-CoA and various biosynthetic pathways. Members of the thio
family can be divided into two broad categories: degradative thiolases and biosyn
thiolases.

https://en.wikipedia.org/wiki/Thiolase

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Thiolytic Cleavage

Thiolytic cleavage occurs in β-oxidation of fatty acids in the reaction catalyz
lase to form acetyl-CoA and a fatty acid shortened by two carbons.

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Thioredoxin

Thioredoxin is a class of small redox proteins known to be present in all organisms. It plays a role in many important biological processes, including redox signaling. In humans, it is encoded by the TXN gene. Loss-of-function mutation of either of the two human thioredoxin genes is lethal at the four-cell stage of the developing embryo. Although not entirely understood, thioredoxin plays a central role in humans and is increasingly linked to medicine through their response to reactive oxygen species (ROS).

In plants, thioredoxins regulate a spectrum of critical functions, ranging from photosynthesis to growth, flowering and the development and germination of seeds. It has also recently been found to play a role in cell-to-cell communication.

Thioredoxins act as antioxidants by facilitating the reduction of other proteins by cysteine thiol-disulfide exchange. Thioredoxins are found in nearly all known organisms and are essential for life in mammals.

The thioredoxins are kept in the reduced state by the flavoenzyme thioredoxin reductase, in a NADPH-dependent reaction. Thioredoxins act as electron donors to peroxidases and ribonucleotide reductase. The related glutaredoxins share many of the functions of thioredoxins, but are reduced by glutathione rather than a specific reductase.

The benefit of thioredoxins to reduce oxidative stress is shown by transgenic mice that overexpress thioredoxin, are more resistant to inflammation, and live 35% longer — supporting the free radical theory of aging. However, the controls of this study were short lived, which may have contributed to the apparent increase in longevity.

https://en.wikipedia.org/wiki/Thioredoxin

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Thioredoxin Reductase

Thioredoxin reductases (TR, TrxR) are the only known enzymes to reduce t
(Trx). Two classes of thioredoxin reductase have been identified: one class
and some eukaryotes and one in animals. Both classes are flavoproteins wh
as homodimers. Each monomer contains a FAD prosthetic group, a NADPH
domain, and an active site containing a redox-active disulfide bond.

https://en.wikipedia.org/wiki/Thioredoxin_reductase

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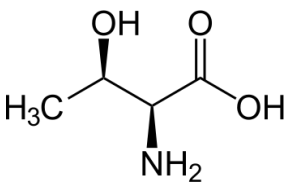
Threonine

Threonine (abbreviated as Thr or T) encoded by the codons ACU, ACC, ACA, and ACG is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and an alcohol containing side chain, classifying it as a polar, uncharged(at physiological pH) amino acid. It is essential in humans, meaning the body cannot synthesize it, and must be ingested in our diet. Threonine is synthesized from aspartate in bacteria such as *E. coli*.

As an essential amino acid, threonine is not synthesized in humans, hence we must ingest threonine in the form of threonine-containing proteins. In plants and microorganisms, threonine is synthesized from aspartic acid via α-aspartyl-semialdehyde and homoserine. Homoserine undergoes O-phosphorylation; this phosphate ester undergoes hydrolysis concomitant with relocation of the OH group.

Threonine is metabolized in two ways:
- It is converted to pyruvate via threonine dehydrogenase. An intermediate in this pathway can undergo thiolysis with CoA to produce acetyl-CoA and glycine.
- In humans, it is converted to α-ketobutyrate in a less common pathway via the enzyme serine dehydratase, and thereby enters the pathway leading to succinyl-CoA.



https://en.wikipedia.org/wiki/Threonine

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Threonine Deaminase

Threonine ammonia-lyase, also commonly referred to as threonine deaminase or threonine dehydratase, is an enzyme responsible for catalyzing the conversion of L-threonine into alpha-ketobutyrate and ammonia. α-ketobutyrate can be converted into L-isoleucine, so threonine ammonia-lyase functions as a key enzyme in BCAA synthesis. It employs a pyridoxal-5'-phosphate cofactor, similar to many enzymes involved in amino acid metabolism. It is found in bacteria, yeast, and plants, though most research to date has focused on forms of the enzyme in bacteria. This enzyme was one of the first in which negative feedback inhibition by the end product of a metabolic pathway was directly observed and studied. The enzyme serves as an excellent example of the regulatory strategies used in amino acid homeostasis.

Threonine ammonia-lyase has been shown to not follow Michaelis-Menten kinetics, rather, it is subject to complex allosteric control. The enzyme is inhibited by isoleucine, the product of the pathway it participates in, and is activated by valine, the product of a parallel pathway. Thus, an increase in isoleucine concentration shuts off its production, and an increase in valine concentration diverts starting material (Hydroxyethyl-TPP) away from valine production. The enzyme has two binding sites for isoleucine. One has a high affinity for isoleucine and the other has a low affinity. The binding of isoleucine to the high affinity site increases the binding affinity of the low affinity site, and enzyme deactivation occurs when isoleucine binds to the low affinity site. Valine promotes enzyme activity by competitively binding to the high affinity site, preventing isoleucine from having an inhibitory effect. The combination of these two feedback methods balances the concentration of BCAAs.

https://en.wikipedia.org/wiki/Threonine_ammonia-lyase

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Threonine Protease

Threnonine proteases are a family of proteolytic enzymes harboring a threonine (Thr) residue within the active site. The prototype members of this class of enzymes are the catalytic subunits of the proteasome, however the acyltransferases convergently evolved the same active site geometry and mechanism.

Threonine proteases use the secondary alcohol of their N-terminal threonine as a nucleophile to perform catalysis. The threonine must be N-terminal since the terminal amide of the same residue acts as a general base by polarizing an ordered water which deprotonates the alcohol to increase its reactivity as a nucleophile.

Catalysis takes place in two steps:
• Firstly the nucleophile attacks the substrate to form a covalent acyl-enzyme intermediate, releasing the first product.
• Secondly the immediate is hydrolized by water to regenerate the free enzyme and release the second product.
• In ornithine acyltransferase, instead of water, the substrate ornithine (the acceptor) performs the second nucleophilic attack and so leaves with the acyl group.

https://en.wikipedia.org/wiki/Threonine_protease

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Threonine Synthase

Threonine synthase is an enzyme that catalyzes the chemical reaction:

O-phospho-L-homoserine + H_2O ⇌ L-threonine + P_i

This enzyme belongs to the family of lyases, specifically those carbon-oxyge
ing on phosphates.

This enzyme participates in glycine, serine and threonine metabolism and v
metabolism. It employs one cofactor, pyridoxal phosphate.

https://en.wikipedia.org/wiki/Threonine_synthase

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Thrombin

Thrombin is a serine protease that, in humans, is encoded by the F2 gene. Prothrombin (coagulation factor II) is proteolytically cleaved to form thrombin in the coagulation cascade, the clotting process. Thrombin in turn acts as a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions.

In the blood coagulation pathway, thrombin acts to convert factor XI to XIa, VIII to VIIIa, V to Va, fibrinogen to fibrin, and XIII to XIIIa. Factor XIIIa is a transglutaminase that catalyzes the formation of covalent bonds between lysine and glutamine residues in fibrin. The covalent bonds increase the stability of the fibrin clot. Thrombin interacts with thrombomodulin. As part of its activity in the coagulation cascade, thrombin also promotes platelet activation and aggregation via activation of protease-activated receptors on the cell membrane of the platelet.

https://en.wikipedia.org/wiki/Thrombin

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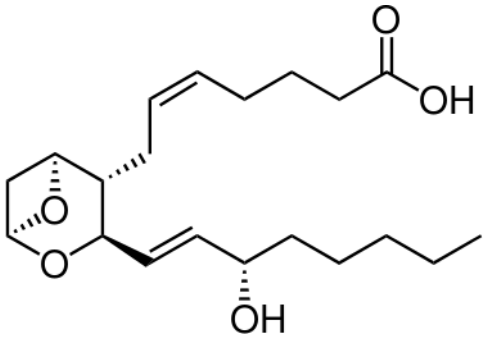
Thromboxane A_2

Thromboxane A_2 (TXA_2) is a type of thromboxane that is produced by activated platelets and has prothrombotic properties: it stimulates activation of new platelets as well as increases platelet aggregation. This is achieved by increasing expression of the glycoprotein complex GPIIb/IIIa on the cell membrane of platelets. The same effect is also achieved by ADP in platelet stimulation, which is blocked by clopidogrel. Circulating fibrinogen binds these receptors on adjacent platelets, further strengthening the clot. Thromboxane A_2 is also a known vasoconstrictor and is especially important during tissue injury and inflammation. It is also regarded as responsible for Prinzmetal's angina.

TXA_2 is generated from prostaglandin H_2 by thromboxane-A synthase in a metabolic reaction which generates approximately equal amounts of 12-hydroxyheptadecatrienoic acid (12-HHT). Aspirin irreversibly inhibits platelet cyclooxygenase 1 preventing the formation of prostaglandin H_2, and therefore thromboxane A_2.



https://en.wikipedia.org/wiki/Thromboxane_A2

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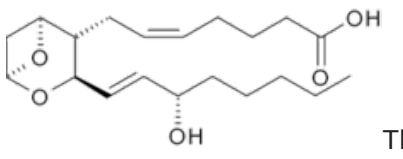
Chapter 4 - Catalysis: Blood Clotting

Thromboxanes

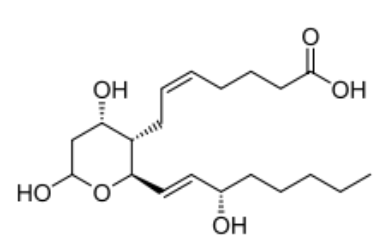
Thromboxane is a member of the family of lipids known as eicosanoids. The two major thromboxanes are thromboxane A_2 and thromboxane B_2. The distinguishing feature of thromboxanes is a 6-membered ether-containing ring. Thromboxane is named for its role in clot formation (thrombosis).

Thromboxane is a vasoconstrictor and a potent hypertensive agent, and it facilitates platelet aggregation. It is in homeostatic balance in the circulatory system with prostacyclin, a related compound. The mechanism of secretion of thromboxanes from platelets is still unclear. They act in the formation of blood clots and reduce blood flow to the site of a clot.

It is believed that the vasoconstriction caused by thromboxanes plays a role in Prinzmetal's angina. ω-3 fatty acids are metabolized to produce higher levels of TxA,3 which is relatively less potent than TxA_2 and PGI_3. Therefore, there is a balance shift toward inhibition of vasoconstriction and platelet aggregation. It is believed that this shift in balance lowers the incidence of myocardial infarction (heart attack) and stroke. Vasoconstriction and, perhaps, various proinflammatory effects exerted by TxA on tissue microvasculature, is probable reason why the TxA is pathogenic in various diseases, such as ischemia-reperfusion injury, hepatic inflammatory processes, acute hepatotoxicity etc. TxB2, a stable degradation product of TxA_2, plays a role in acute hepatoxicity induced by acetaminophen.



Thromboxane A2



Thromboxane B2

https://en.wikipedia.org/wiki/Thromboxane

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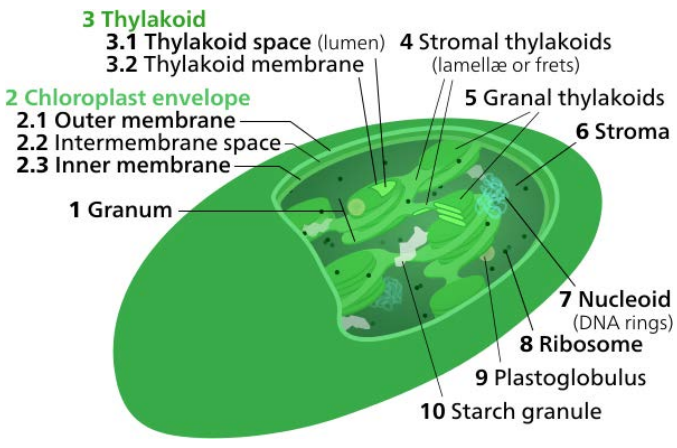
Thylakoid Membrane

The thylakoid membrane is the site of the light-dependent reactions of photosynthesis with the photosynthetic pigments embedded directly in the membrane. It is an alternating pattern of dark and light bands measuring each 1 nanometre. The thylakoid lipid bilayer shares characteristic features with prokaryotic membranes and the inner chloroplast membrane. For example, acidic lipids can be found in thylakoid membranes, cyanobacteria and other photosynthetic bacteria and are involved in the functional integrity of the photosystems.

The thylakoid membranes of higher plants are composed primarily of phospholipids and galactolipids that are asymmetrically arranged along and across the membranes. Thylakoid membranes are richer in galactolipids rather than phospholipids. Also they predominantly consist of hexagonal phase II forming monogalacotosyl diglyceride lipid. Despite this unique composition, plant thylakoid membranes have been shown to assume largely lipid-bilayer dynamic organization. Lipids forming the thylakoid membranes, richest in high-fluidity linolenic acid are synthesized in a complex pathway involving exchange of lipid precursors between the endoplasmic reticulum and inner membrane of the plastid envelope and transported from the inner membrane to the thylakoids via vesicles.

In higher plants thylakoids are organized into a granum-stroma membrane assembly. A granum (plural grana) is a stack of thylakoid discs. Chloroplasts can have from 10 to 100 grana. Grana are connected by stroma thylakoids, also called intergranal thylakoids or lamellae. Grana thylakoids and stroma thylakoids can be distinguished by their different protein composition. Grana contribute to chloroplasts' large surface area to volume ratio. Different interpretations of electron tomography imaging of thylakoid membranes has resulted in two models for grana structure. Both posit that lamellae intersect grana stacks in parallel sheets, though whether these sheets intersect in planes perpendicular to the grana stack axis, or are arranged in a right-handed helix is debated.



https://en.wikipedia.org/wiki/Thylakoid

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Chapter 5 - Energy: Photophosphorylation
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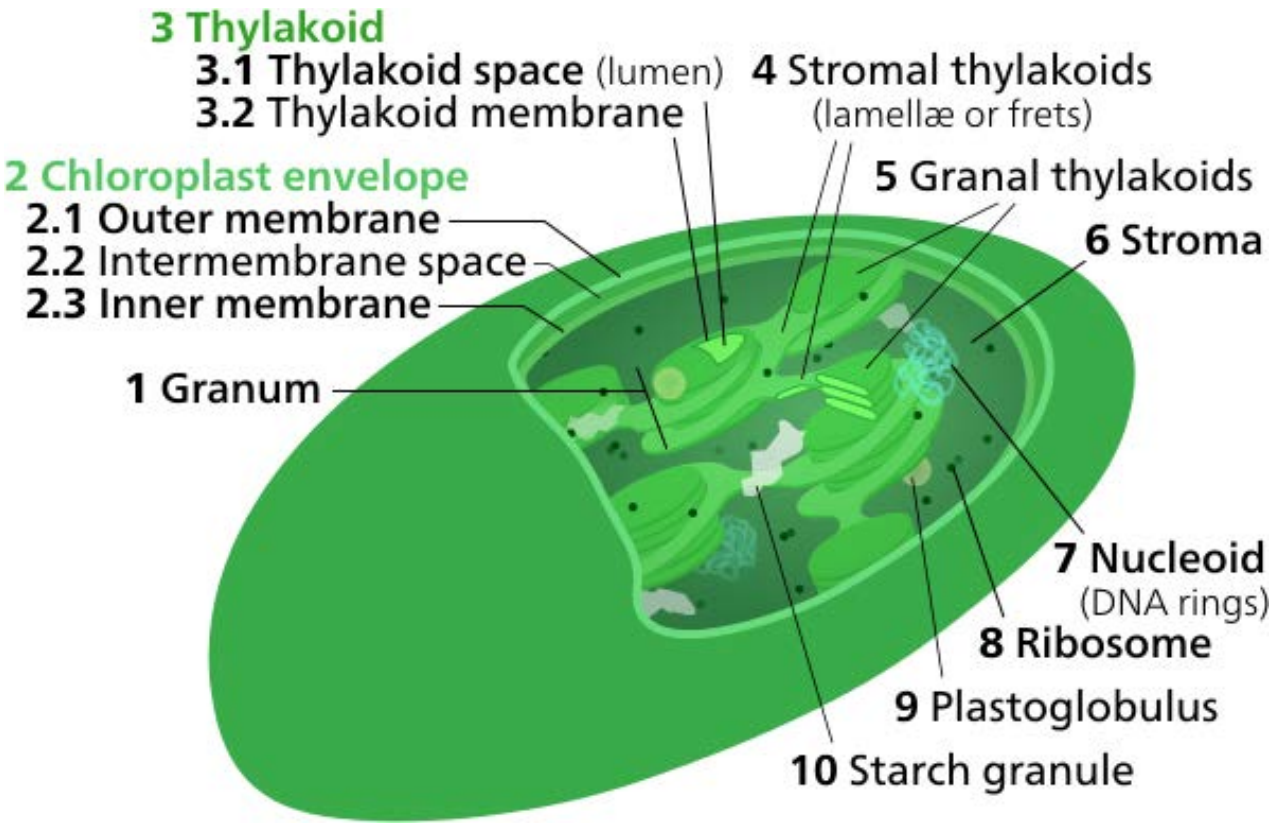
Chapter 9 - Short & Sweet: Energy
Chapter 9 - Short & Sweet: Energy
Chapter 9 - Point by Point: Metabolism

Thylakoid Space

The thylakoid lumen (space) is a continuous aqueous phase enclosed by the thylakoid membrane. It plays an important role for photophosphorylation during photosynthesis. During the light-dependent reaction, protons are pumped across the thylakoid membrane into the lumen making it acidic down to pH 4.



https://en.wikipedia.org/wiki/Thylakoid

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Chapter 9 - Short & Sweet: Energy

Thylakoids

A thylakoid is a membrane-bound compartment inside chloroplasts and cy
They are the site of the light-dependent reactions of photosynthesis. Thylak
of a thylakoid membrane surrounding a thylakoid lumen. Chloroplast thyla
quently form stacks of disks referred to as grana (singular: granum). Grana
nected by intergranal or stroma thylakoids, which join granum stacks toget
gle functional compartment.

https://en.wikipedia.org/wiki/Thylakoid

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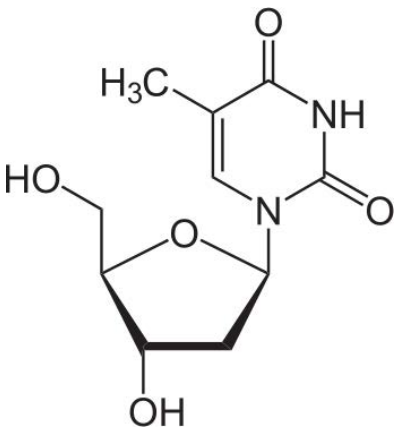
Thymidine

Thymidine is a pyrimidine deoxynucleoside. Deoxythymidine is the DNA nucleoside T, which pairs with deoxyadenosine (A) in double-stranded DNA. In cell biology it is used to synchronize the cells in G1/early S phase. Thymidine occurs almost exclusively in DNA but also occurs in the T-loop of tRNA.

In its composition, deoxythymidine is a nucleoside composed of deoxyribose (a pentose sugar) joined to the pyrimidine base thymine. Deoxythymidine can be phosphorylated with one, two or three phosphoric acid groups, creating respectively dTMP, dTDP or dTTP (deoxythymidine mono- di- or triphosphate).

Deoxythymidine is non-toxic and as part of one of the four nucleotides in DNA it is a naturally occurring compound that exists in all living organisms and DNA viruses. RNA has uridine (uracil joined to ribose) instead. Uracil is chemically very similar to thymine, the latter being 5-methyluracil. Since thymine nucleotides are precursors of DNA, not RNA, the prefix "deoxy" is often left out, i.e., deoxythymidine is often just called thymidine.



https://en.wikipedia.org/wiki/Thymidine

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Thymidylate Synthetase

Thymidylate synthetase (TS) is an enzyme that catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Thymidine is one of the nucleotides in DNA. With inhibition of TS, an imbalance of deoxynucleotides and increased levels of dUTP arise. Both cause DNA damage.

The following reaction is catalyzed by thymidylate synthetase:

5,10-methylenetetrahydrofolate + dUMP ⇌ Dihydrofolate + dTMP

This provides the sole *de novo* pathway for production of dTMP and is the only enzyme in folate metabolism in which the 5,10-methylenetetrahydrofolate is oxidized during one-carbon transfer. The enzyme is essential for regulating the balanced supply of the four DNA precursors in normal DNA replication: defects in the enzyme activity affecting the regulation process cause various biological and genetic abnormalities, such as thymineless death. The enzyme is an important target for certain chemotherapeutic drugs. Thymidylate synthase is an enzyme of about 30 to 35 Kd in most species except in protozoan and plants where it exists as a bifunctional enzyme that includes a dihydrofolate reductase domain. A cysteine residue is involved in the catalytic mechanism (it covalently binds the 5,6-dihydro-dUMP intermediate). The sequence around the active site of this enzyme is conserved from phages to vertebrates.

The use of TS inhibitors has become a main focus of using TS as a drug target. The most widely used inhibitor is 5-Fluorouracil (5-FU), which acts as an antimetabolite that irreversibly inhibits TS by competitive binding. However, due to a low level of 5-FU found in many patients, it has been discovered that in combination with leucovorin (LV), 5-FU has greater success in down regulating tumor progression mechanisms and increasing immune system activity.

https://en.wikipedia.org/wiki/Thymidylate_synthase

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Thymine

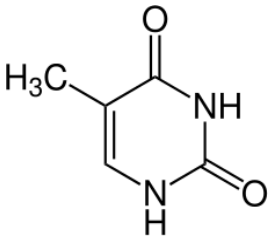
Thymine is one of the four nucleobases in the nucleic acid of DNA that are represented by the letters G–C–A–T. The others are adenine, guanine, and cytosine. Thymine is also known as 5-methyluracil, a pyrimidine nucleobase. In RNA, thymine is replaced by the nucleobase uracil.

As its alternate name (5-methyluracil) suggests, thymine may be derived by methylation of uracil at the 5th carbon. In RNA, thymine is replaced with uracil in most cases. In DNA, thymine (T) binds to adenine (A) via two hydrogen bonds, thereby stabilizing the nucleic acid structures.

Thymine combined with deoxyribose creates the nucleoside deoxythymidine, which is synonymous with the term thymidine. Thymidine can be phosphorylated with one, two, or three phosphoric acid groups, creating, respectively, TMP, TDP, or TTP (thymidine mono-, di-, or triphosphate).

One of the common mutations of DNA involves two adjacent thymines or cytosine, which, in presence of ultraviolet light, may form thymine dimers, causing "kinks" in the DNA molecule that inhibit normal function.

Thymine could also be a target for actions of 5-fluorouracil (5-FU) in cancer treatment. 5-FU can be a metabolic analog of thymine (in DNA synthesis) or uracil (in RNA synthesis). Substitution of this analog inhibits DNA synthesis in actively dividing cells. Thymine bases are frequently oxidized to hydantoins over time after the death of an organism.



https://en.wikipedia.org/wiki/Thymine

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Thymosin

Thymosins are small proteins present in many animal tissues. They are nar
ins because they were originally isolated from the thymus, but most are nov
be present in many other tissues. Thymosins have diverse biological activit
in particular, thymosins α1 and β4, have potentially important uses in med
of which have already progressed from the laboratory to the clinic. In relati
eases, thymosins have been categorized as biological response modifiers.

https://en.wikipedia.org/wiki/Thymosins

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Thyroglobulin

Thyroglobulin (Tg) is a 660 kDa, dimeric protein produced by the follicular cells of the thyroid and used entirely within the thyroid gland. Thyroglobulin protein accounts for approximately half of the protein content of the thyroid gland.

The protein is a precursor of the thyroid hormones. These are produced when thyroglobulin's tyrosine residues are combined with iodine and the protein is subsequently cleaved. Each thyroglobulin molecule contains approximately 100-120 tyrosine residues, but only a small number (20) of these are subject to iodination by thyroperoxidase in the follicular colloid. Therefore, each Tg molecule forms only approximately 10 thyroid hormone molecules.

Tg is used by the thyroid gland to produce the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). The active form of triiodothyronine, 3, 5, 3' triiodothyronine, is produced both within the thyroid gland and in the periphery by 5'-deiodinase (which has been referred to as tetraiodothyronine 5' deiodinase). It is presumed that Tg and thyroid are also an important storage of iodine for all body needs, in particular, for many iodine-concentrating organs such as breast, stomach, salivary glands, thymus, choroid plexus and cerebrospinal fluid, etc.

Tg is produced by the thyroid epithelial cells, called thyrocytes, which form spherical follicles. Tg is secreted and stored in the follicular lumen.

https://en.wikipedia.org/wiki/Thyroglobulin

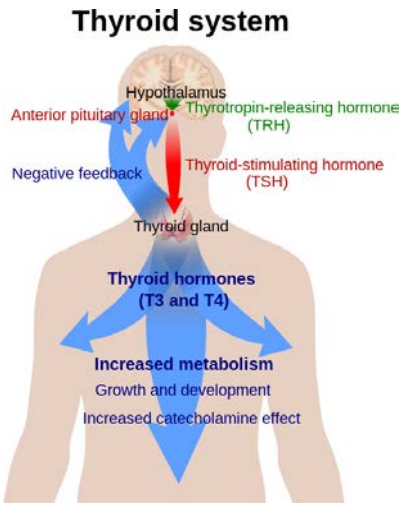
Related Glossary Terms

Thyroid Hormones

The thyroid hormones, triiodothyronine (T_3) and its prohormone, thyroxine (T_4), are tyrosine-based hormones produced by the thyroid gland that are primarily responsible for regulation of metabolism. T_3 and T_4 are partially composed of iodine. A deficiency of iodine leads to decreased production of T_3 and T_4, enlarges the thyroid tissue and will cause the disease known as simple goiter. The major form of thyroid hormone in the blood is thyroxine (T_4), which has a longer half-life than T_3. In humans, the ratio of T_4 to T_3 released into the blood is between 14 to 1 and 20 to 1. T_4 is converted to the active T_3 (three to four times more potent than T_4) within cells by deiodinases (5'-iodinase).

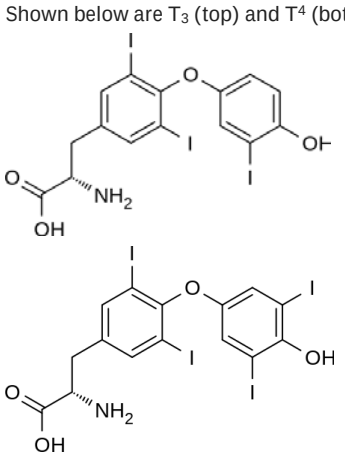
These are further processed by decarboxylation and deiodination to produce iodothyronamine (T_{1a}) and thyronamine (T_{0a}). All three isoforms of the deiodinases are selenium-containing enzymes, thus dietary selenium is essential for T_3 production.

The thyroid hormones act on nearly every cell in the body. They act to increase the basal metabolic rate, affect protein synthesis, help regulate long bone growth (synergy with growth hormone) and neural maturation, and increase the body's sensitivity to catecholamines (such as adrenaline) by permissiveness. The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. They also stimulate vitamin metabolism. Numerous physiological and pathological stimuli influence thyroid hormone synthesis.



Thyroid hormone leads to heat generation in humans. However, the thyronamines function via some unknown mechanism to inhibit neuronal activity. This plays an important role in the hibernation cycles of mammals and the molting behavior of birds. One effect of administering the thyronamines is a severe drop in body temperature.

Shown below are T_3 (top) and T^4 (bottom)



https://en.wikipedia.org/wiki/Thyroid_hormone

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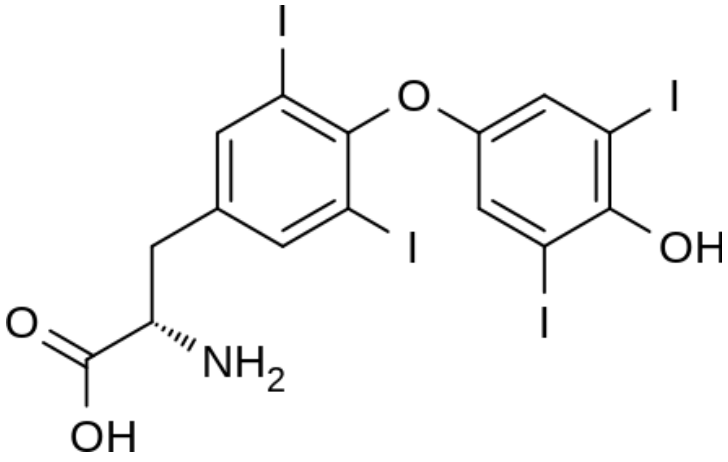
Thyroxine

The thyroid hormones, triiodothyronine (T_3) and its prohormone, thyroxine (T_4), are tyrosine-based hormones produced by the thyroid gland that are primarily responsible for regulation of metabolism. T_3 and T_4 are partially composed of iodine (see molecular model). A deficiency of iodine leads to decreased production of T_3 and T_4, enlarges the thyroid tissue and will cause the disease known as simple goiter. The major form of thyroid hormone in the blood is thyroxine (T_4), which has a longer half-life than T_3. In humans, the ratio of T_4 to T_3 released into the blood is between 14 to 1 and 20 to 1. T_4 is converted to the active T_3 (three to four times more potent than T_4) within cells by deiodinases (5'-iodinase).

These are further processed by decarboxylation and deiodination to produce iodothyronamine (T_{1a}) and thyronamine (T_{0a}). All three isoforms of the deiodinases are selenium-containing enzymes, thus dietary selenium is essential for T_3 production.



https://en.wikipedia.org/wiki/Thyroid_hormone

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Tight Coupling

Oxidative phosphorylation works by using energy-releasing chemical reacti
energy-requiring reactions: The two sets of reactions are said to be couple
means one cannot occur without the other. The flow of electrons through th
transport chain, from electron donors such as NADH to electron acceptors
gen, is an exergonic process – it releases energy, whereas the synthesis of A
dergonic process, which requires an input of energy. Both the electron tran
and the ATP synthase are embedded in a membrane, and energy is transfer
electron transport chain to the ATP synthase by movements of protons acr
membrane, in a process called chemiosmosis.

https://en.wikipedia.org/wiki/Oxidative_phosphorylation#Overview_of_e
sfer_by_chemiosmosis

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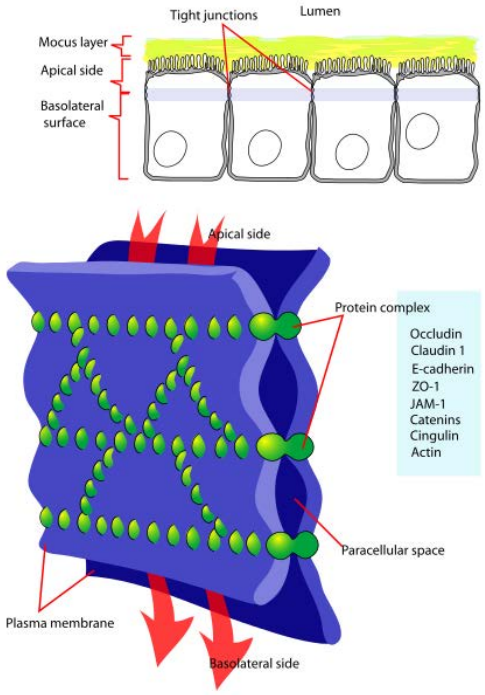
Tight Junctions

Tight junctions are the closely associated areas of two cells whose membranes join together forming a virtually impermeable barrier to fluid. It is a type of junctional complex present only in vertebrates. The corresponding junctions that occur in invertebrates are septate junctions.

Tight junctions are composed of a branching network of sealing strands, each strand acting independently from the others. Therefore, the efficiency of the junction in preventing ion passage increases exponentially with the number of strands. Each strand is formed from a row of transmembrane proteins embedded in both plasma membranes, with extracellular domains joining one another directly.

Tight junctions perform vital functions:

- They hold cells together.
- Barrier function, which can be further subdivided into protective barriers and functional barriers serving purposes such as material transport and maintenance of osmotic balance:
- Tight Junctions help to maintain the polarity of cells by preventing the lateral diffusion of integral membrane proteins between the apical and lateral/basal surfaces, allowing the specialized functions of each surface (for example receptor-mediated endocytosis at the apical surface and exocytosis at the basolateral surface) to be preserved. This aims to preserve the transcellular transport.
- Tight Junctions prevent the passage of molecules and ions through the space between plasma membranes of adjacent cells, so materials must actually enter the cells (by diffusion or active transport) in order to pass through the tissue. Investigation using freeze-fracture methods in electron microscopy is ideal for revealing the lateral extent of tight junctions in cell membranes and has been useful in showing how tight junctions are formed. The constrained intracellular pathway exacted by the tight junction barrier system allows precise control over which substances can pass through a particular tissue. (Tight junctions play this role in maintaining the blood–brain barrier.) At the present time, it is still unclear whether the control is active or passive and how these pathways are formed. In one study for paracellular transport across the tight junction in kidney proximal tubule, a dual pathway model is proposed: large slit breaks formed by infrequent discontinuities in the TJ complex and numerous small circular pores.



https://en.wikipedia.org/wiki/Tight_junction

Tightly Coupled

Oxidative phosphorylation works by using energy-releasing chemical reacti
energy-requiring reactions: The two sets of reactions are said to be couple
means one cannot occur without the other. The flow of electrons through th
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dergonic process, which requires an input of energy. Both the electron tran
and the ATP synthase are embedded in a membrane, and energy is transfer
electron transport chain to the ATP synthase by movements of protons acro
membrane, in a process called chemiosmosis.

https://en.wikipedia.org/wiki/Oxidative_phosphorylation#Overview_of_e
sfer_by_chemiosmosis

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Tissue Plasminogen Activator

Tissue plasminogen activator (abbreviated tPA or PLAT) is a protein involved in the breakdown of blood clots. It is a serine protease found on endothelial cells, the cells that line the blood vessels. As an enzyme, it catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown. Because it works on the clotting system, tPA is used in clinical medicine to treat embolic or thrombotic stroke. Use is contraindicated in hemorrhagic stroke and head trauma. The antidote for tPA in case of toxicity is aminocaproic acid.

tPA and plasmin are the key enzymes of the fibrinolytic pathway in which tPA mediated plasmin generation occurs. To be specific, tPA cleaves the zymogen plasminogen at its Arg561 - Val562 peptide bond, into the serine protease plasmin.

Increased enzymatic activity causes hyperfibrinolysis, which manifests as excessive bleeding. Decreased activity leads to hypofibrinolysis which can result in thrombosis or embolism. In ischemic stroke patients, decreased tPA activity was reported to be associated with an increase in plasma P-selectin concentration.

Tissue plasminogen activator also plays a role in cell migration and tissue remodeling.

https://en.wikipedia.org/wiki/Tissue_plasminogen_activator

Related Glossary Terms

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Titin

Titin also known as connectin, is a protein that, in humans, is encoded by the TTN gene. Titin is a giant protein, greater than 1 µm in length, that functions as a molecular spring which is responsible for the passive elasticity of muscle. It is composed of 244 individually folded protein domains connected by unstructured peptide sequences. These domains unfold when the protein is stretched and refold when the tension is removed.

Titin is important in the contraction of striated muscle tissues. It connects the Z line to the M line in the sarcomere. The protein contributes to force transmission at the Z line and resting tension in the I band region. It limits the range of motion of the sarcomere in tension, thus contributing to the passive stiffness of muscle. Variations in the sequence of titin between different types of muscle (e.g., cardiac or skeletal) have been correlated with differences in the mechanical properties of these muscles.

After myosin and actin, titin is the third most abundant protein in muscle and an adult human contains approximately 0.5 kg of titin. With its length of ~27,000 to ~33,000 amino acids (depending on the splice isoform), titin is the largest known protein. Furthermore, the gene for titin contains the largest number of exons (363) discovered in any single gene, as well as the longest single exon (17,106 bp).

https://en.wikipedia.org/wiki/Titin

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Titration

Titration, also known as titrimetry, is a common laboratory method of quan
chemical analysis that is used to determine the unknown concentration of a
analyte.

A reagent, called the titrant or titrator is prepared as a standard solution. A
centration and volume of titrant reacts with a solution of analyte or titrand
mine concentration. The volume of titrant reacted is called titration volume

https://en.wikipedia.org/wiki/Titration

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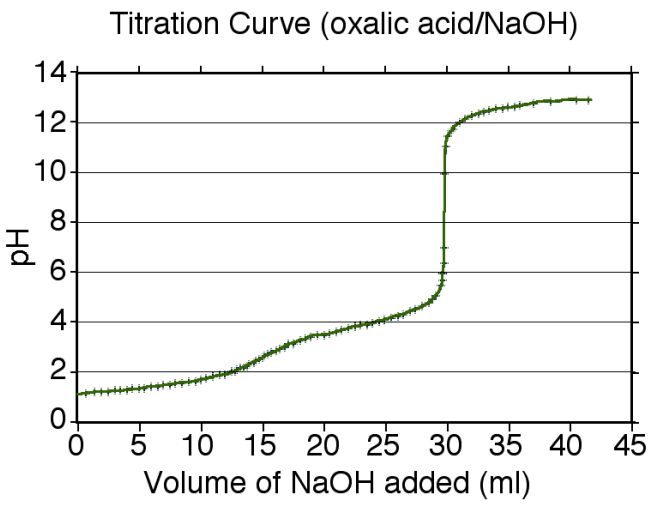
Titration Curve

A titration curve is a curve in the plane whose x-coordinate is the volume of titrant added since the beginning of the titration, and whose y-coordinate is the concentration of the analyte at the corresponding stage of the titration (in an acid-base titration, the y-coordinate is usually the pH of the solution).

In an acid-base titration, the titration curve reflects the strength of the corresponding acid and base. For a strong acid and a strong base, the curve will be relatively smooth and very steep near the equivalence point. Because of this, a small change in titrant volume near the equivalence point results in a large pH change and many indicators would be appropriate (for instance litmus, phenolphthalein or bromothymol blue).

Titrations are often recorded on graphs called titration curves, which generally contain the volume of the titrant as the independent variable and the pH of the solution as the dependent variable (because it changes depending on the composition of the two solutions).

The equivalence point on the graph is where all of the starting solution (usually an acid) has been neutralized by the titrant (usually a base). It can be calculated precisely by finding the second derivative of the titration curve and computing the points of inflection (where the graph changes concavity). However, in most cases, simple visual inspection of the curve will suffice.



https://en.wikipedia.org/wiki/Titration_curve

T_m

The melting point (or, rarely, liquefaction point) of a solid is the temperature
it changes state from solid to liquid at atmospheric pressure. At the melting po
solid and liquid phase exist in equilibrium. The melting point of a substance d
on pressure and is usually specified at standard pressure.

https://en.wikipedia.org/wiki/Melting_point

Nucleic acid thermodynamics is the study of how temperature affects the nucl
structure of double-stranded DNA (dsDNA). The melting temperature (T_m) is
as the temperature at which half of the DNA strands are in the random coil or
stranded (ssDNA) state. T_m depends on the length of the DNA molecule and it
nucleotide sequence.

https://en.wikipedia.org/wiki/Nucleic_acid_thermodynamics

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Chapter 9 - Point by Point: Membranes

Chapter 9 - Point by Point: Membranes

Tocopherols

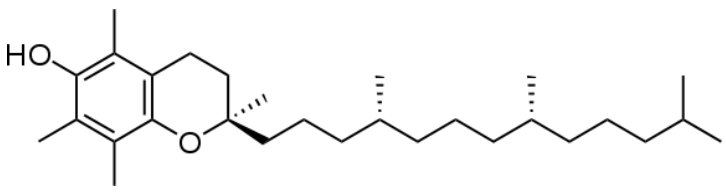
Tocopherols (TCP) are a class of organic chemical compounds (more precisely, various methylated phenols), many of which have vitamin E activity. Because the vitamin activity was first identified in 1936 from a dietary fertility factor in rats, it was given the name "tocopherol" from the Greek words "τόκος" [tókos, birth], and "φέρειν", [phérein, to bear or carry] meaning in sum "to carry a pregnancy," with the ending "-ol" signifying its status as a chemical alcohol.

An essential nutrient for the body, vitamin E is made up of four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ). The slight difference between tocotrienols and tocopherols lies in the unsaturated side chain of tocotrienols, having three double bonds in its farnesyl isoprenoid tail.

α-Tocopherol is the main source found in supplements and in the European diet, where the main dietary sources are olive and sunflower oils, while γ-tocopherol is the most common form in the American diet due to a higher intake of soybean and corn oil.

Tocotrienols, which are related compounds, also have vitamin E activity. All of these various derivatives with vitamin activity may correctly be referred to as "vitamin E". Tocopherols and tocotrienols are fat-soluble antioxidants but also seem to have many other functions in the body.

Shown below is a-tocopherol



https://en.wikipedia.org/wiki/Tocotrienol

Tocotrienols

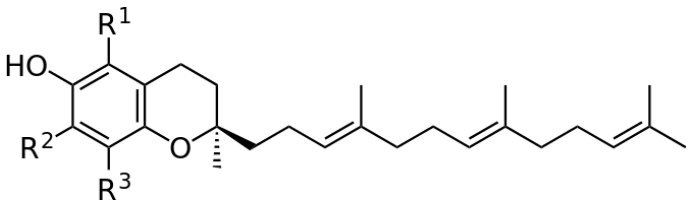
Tocotrienols are members of the vitamin E family. An essential nutrient for the body, vitamin E is made up of four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ). The slight difference between tocotrienols and tocopherols lies in the unsaturated side chain of tocotrienols, having three double bonds in its farnesyl isoprenoid tail.

Tocotrienols are natural compounds found in select vegetable oils, including rice bran oil and palm oil, wheat germ, barley, saw palmetto, anatto, and certain other types of seeds, nuts, grains, and the oils derived from them. This variant of vitamin E typically only occurs at very low levels in nature.

Chemically, vitamin E in all of its forms functions as an antioxidant. All of the tocotrienol and tocopherol isomers have this antioxidant activity due to the ability to donate a hydrogen atom (a proton plus electron) from the hydroxyl group on the chromanol ring, to a free radical in the body. This process inactivates ("quenches") the free radical by effectively donating a single unpaired electron (which comes with the hydrogen atom) to the radical. Thus, one model for the function of vitamin E in the body is that it protects cell membranes, active enzyme sites, and DNA from free radical damage. Although the many vitamers of vitamin E have different distributions and metabolic fates, there is as yet no accepted evidence that any of the active forms of vitamin E are able to do any essential function in the body that each of the others is not also able to do. Specifically, symptoms caused by α-tocopherol deficiency can be alleviated by tocotrienols. Thus, tocotrienols may be viewed as being members of the natural vitamin E family not only structurally but also functionally.

While the majority of research on vitamin E has focused on α-tocopherol, studies into tocotrienols account for less than 1% of all research into vitamin E. More recently, tocotrienols have been the subject of increased scientific attention, with research on tocotrienols accounting for nearly 30% of all peer-reviewed articles published on vitamin E between 2009 and 2010.

The human body makes cholesterol in the liver. Tocotrienols can decrease the liver's capacity to manufacture cholesterol. They do so by inhibiting HMG-CoA reductase, the enzyme responsible for cholesterol synthesis.



https://en.wikipedia.org/wiki/Tocotrienol

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Topoisomerases

Topoisomerases are enzymes that regulate the overwinding or underwinding of DNA. The winding problem of DNA arises due to the intertwined nature of its double-helical structure. During DNA replication and transcription, DNA becomes overwound ahead of a replication fork. If left unabated, this torsion would eventually stop the ability of RNA & DNA polymerase involved in these processes to continue down the DNA strand.

In order to prevent and correct these types of topological problems caused by the double helix, topoisomerases bind to either single-stranded or double-stranded DNA and cut the phosphate backbone of the DNA. This intermediate break allows the DNA to be untangled or unwound, and, at the end of these processes, the DNA backbone is re-sealed again. Since the overall chemical composition and connectivity of the DNA do not change, the tangled and untangled DNAs are chemical isomers, differing only in their global topology, thus their name. Topoisomerases are isomerase enzymes that act on the topology of DNA.

The double-helical configuration that DNA strands naturally reside, makes them difficult to separate and yet they must be separated by helicase enzymes, if other enzymes are to transcribe the sequences that encode proteins, or if chromosomes are to be replicated. In so-called circular DNA, in which double-helical DNA is bent around and joined in a circle, the two strands are topologically linked, or knotted. Otherwise identical loops of DNA, having different numbers of twists, are topoisomers, and cannot be interconverted by any process that does not involve the breaking of DNA strands. Topoisomerases catalyze and guide the unknotting or unkinking of DNA by creating transient breaks in the DNA using a conserved Tyrosine as the catalytic residue.

https://en.wikipedia.org/wiki/Topoisomerase

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Trans fats

Trans fats, or *trans*-unsaturated fatty acids, *trans* fatty acids, are a type of unsaturated fat that is uncommon in nature but became commonly produced industrially from vegetable fats for use in margarine, snack food, packaged baked goods and frying fast food starting in the 1950s. *Trans* fat has been shown to consistently be associated, in an intake-dependent way, with increased risk of coronary heart disease, a leading cause of death in Western nations.

Fats contain long hydrocarbon chains, which can either be unsaturated, i.e. have double bonds, or saturated, i.e. have no double bonds. In nature, unsaturated fatty acids generally have *cis* as opposed to *trans* configurations. In food production, liquid *cis*-unsaturated fats such as vegetable oils are hydrogenated to produce saturated fats, which have more desirable physical properties, e.g. they melt at a desirable temperature (30–40 °C). Partial hydrogenation of the unsaturated fat converts some of the *cis* double bonds into *trans* double bonds by an isomerization reaction with the catalyst used for the hydrogenation, which yields a *trans* fat. Although *trans* fats are edible, consumption of *trans* fats has shown to increase the risk of coronary heart disease in part by raising levels of the lipoprotein LDL (so-called "bad cholesterol"), lowering levels of the lipoprotein HDL ("good cholesterol"), increasing triglycerides in the bloodstream and promoting systemic inflammation.

https://en.wikipedia.org/wiki/Trans_fat

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Transaldolase

Transaldolase is an enzyme of the non-oxidative phase of the pentose phosp
way. In humans, transaldolase is encoded by the TALDO1 gene. The follow
cal reaction is catalyzed by transaldolase:

Sedoheptulose 7-phosphate + Glyceraldehyde 3-phosphate <---> Erythrose
phosphate + Fructose 6-phosphate

https://en.wikipedia.org/wiki/Transaldolase

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Transaminases

In biochemistry, a transaminase or an aminotransferase is an enzyme that catalyzes a type of reaction between an amino acid and an α-keto acid. They are important in the synthesis of amino acids, which form proteins. In medicine, they are an important indicator of liver damage.

An amino acid contains an amine (NH_2) group. A keto acid contains a keto (=O) group. In transamination, the NH_2 group on one molecule is exchanged with the =O group on the other molecule. The amino acid becomes a keto acid, and the keto acid becomes an amino acid.

https://en.wikipedia.org/wiki/Transaminase

Related Glossary Terms

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Transamination

Most amino acids are deaminated by transamination, a chemical reaction that transfers an amino group to a ketoacid to form new amino acids. Transamination in biochemistry is accomplished by enzymes called transaminases or aminotransferases. α-ketoglutarate acts as the predominant amino group acceptor and produces glutamate as the new amino acid.

Amino acid + α-ketoglutarate ↔ α-keto acid + Glutamate

Glutamate's amino group, in turn, is transferred to oxaloacetate in a second transamination reaction yielding aspartate.

Glutamate + Oxaloacetate ↔ α-ketoglutarate + Aspartate

The product of transamination reactions depend on the availability of α-keto acids. The products usually are either alanine, aspartate or glutamate, since their corresponding α-keto acids are produced through metabolism of fuels. Lysine proline and threonine are the only three amino acids that do not always undergo transamination.

https://en.wikipedia.org/wiki/Transamination

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Transcription

Transcription is the first step of gene expression, in which a particular segment of DNA is copied into RNA (mRNA) by the enzyme RNA polymerase. Both RNA and DNA are nucleic acids, which use base pairs of nucleotides as a complementary language. The two can be converted back and forth from DNA to RNA by the action of the correct enzymes. During transcription, a DNA sequence is read by an RNA polymerase, which produces a complementary, antiparallel RNA strand called a primary transcript.

Transcription proceeds in the following general steps:
1 One or more sigma factor protein binds to the RNA polymerase holoenzyme, allowing it to bind to promoter DNA.
2 RNA polymerase creates a transcription bubble, which separates the two strands of the DNA helix. This is done by breaking the hydrogen bonds between complementary DNA nucleotides.
3 RNA polymerase adds matching RNA nucleotides to the complementary nucleotides of one DNA strand.
4 RNA sugar-phosphate backbone forms with assistance from RNA polymerase to form an RNA strand.
5 Hydrogen bonds of the untwisted RNA–DNA helix break, freeing the newly synthesized RNA strand.
6 If the cell has a nucleus, the RNA may be further processed. This may include polyadenylation, capping, and splicing.
7 The RNA may remain in the nucleus or exit to the cytoplasm through the nuclear pore complex.

The stretch of DNA transcribed into an RNA molecule is called a transcript. If the gene transcribed encodes a protein, messenger RNA (mRNA) will be transcribed, and the mRNA will in turn serve as a template for the protein's synthesis through translation. Alternatively, the transcribed gene may encode for either non-coding RNA (such as microRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), or other enzymatic RNA molecules called ribozymes. Overall, RNA helps synthesize, regulate, and process proteins; it therefore plays a fundamental role in performing functions within a cell.

https://en.wikipedia.org/wiki/Transcription_(genetics)

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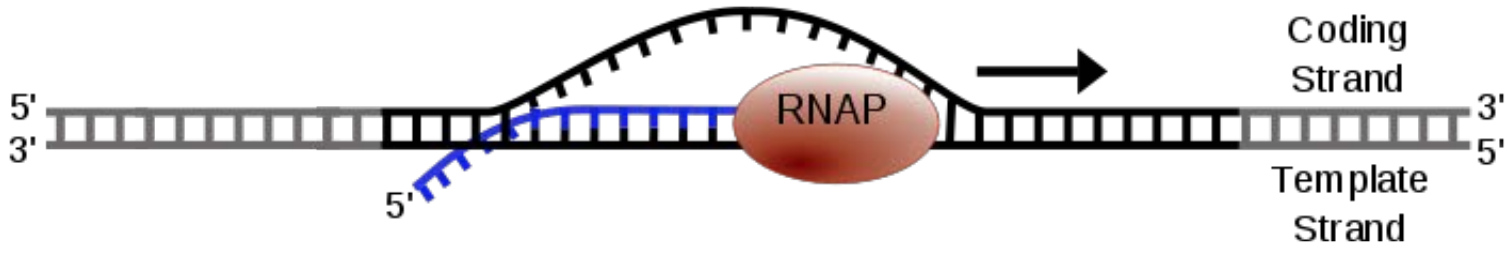
Transcription Bubble

A transcription bubble is a molecular structure that occurs during the transcription of DNA when a limited portion of the DNA double strand is unwound. RNA polymerase may then bind to the exposed DNA and begin synthesizing a new strand of RNA. As RNA polymerase progresses down the DNA strand in the 5' to 3' direction, more of the DNA double strand is unwound downstream of the polymerase while DNA upstream of the polymerase re-anneals, moving a transcription bubble in the process that may be seen with specialized staining techniques, spectroscopy or microscopy.



https://en.wikipedia.org/wiki/Transcription_bubble

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Transcription Factor

In molecular biology and genetics, a transcription factor (sometimes called a sequence-specific DNA-binding factor) is a protein that binds to specific DNA sequences, thereby controlling the rate of transcription of genetic information from DNA to messenger RNA. Transcription factors perform this function alone or with other proteins in a complex, by promoting (as an activator), or blocking (as a repressor) the recruitment of RNA polymerase (the enzyme that performs the transcription of genetic information from DNA to RNA) to specific genes.

A defining feature of transcription factors is that they contain one or more DNA-binding domains (DBDs), which attach to specific sequences of DNA adjacent to the genes that they regulate. Additional proteins such as coactivators, chromatin remodelers, histone acetylases, deacetylases, kinases, and methylases, while also playing crucial roles in gene regulation, lack DNA-binding domains, and, therefore, are not classified as transcription factors.

Transcription factors are essential for the regulation of gene expression and are, as a consequence, found in all living organisms. The number of transcription factors found within an organism increases with genome size, and larger genomes tend to have more transcription factors per gene.

There are approximately 2600 proteins in the human genome that contain DNA-binding domains, and most of these are presumed to function as transcription factors, though other studies indicate it to be a smaller number. Therefore, approximately 10% of genes in the genome code for transcription factors, which makes this family the single largest family of human proteins. Furthermore, genes are often flanked by several binding sites for distinct transcription factors, and efficient expression of each of these genes requires the cooperative action of several different transcription factors (see, for example, hepatocyte nuclear factors). Hence, the combinatorial use of a subset of the approximately 2000 human transcription factors easily accounts for the unique regulation of each gene in the human genome during development.

https://en.wikipedia.org/wiki/Transcription_factor

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Transcription Initiation Complex

In eukaryotes, a core promoter sequence in the DNA must be present for RNA polymerase to initiate transcription. Promoters are regions of DNA that promote transcription - in eukaryotes, they are found at -30, -75, and -90 base pairs upstream from the transcription start site (abbreviated to TSS). Transcription factors are proteins that bind to these promoter sequences and facilitate the binding of RNA Polymerase.

The most characterized type of core promoter in eukaryotes is a short DNA sequence known as a TATA box, found 25-30 base pairs upstream from the TSS. The TATA box, as a core promoter, is the binding site for a transcription factor known as TATA-binding protein (TBP) (which is itself a subunit of another transcription factor, called Transcription Factor II D (TFIID)). After TFIID binds to the TATA box via the TBP, five more transcription factors and RNA polymerase combine around the TATA box in a series of stages to form a preinitiation complex. One transcription factor, Transcription factor II H, has two components with helicase activity and so is involved in the separating of opposing strands of double-stranded DNA to form the initial transcription bubble. However, the preinitiation complex produces only a low transcription rate on its own. Other proteins known as activators and repressors, along with any associated coactivators or corepressors, are responsible for modulating transcription rate.

Thus, preinitiation complex contains:

1. Core Promoter Sequence
2. Transcription Factors
3. RNA Polymerase
4. Activators and Repressors

https://en.wikipedia.org/wiki/Transcription_(genetics)

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Transcription-coupled Repair

There are two general categories of nucleotide excision repair (NER) - Transcription-coupled repair (TC-NER) and global genomic repair (GG-NER). At any given time, most of the genome in an organism is not undergoing transcription. There is a difference in nucleotide excision repair (NER) efficiency between transcriptionally silent and transcriptionally active regions of the genome. For many types of lesions, NER repairs the transcribed strands of transcriptionally active genes faster than it repairs non-transcribed strands and transcriptionally silent DNA.

TC-NER and GG-NER differ only in the initial steps of DNA damage recognition. The principal difference between TC-NER and GG-NER is that TC-NER does not require XPC or DDB proteins for distortion recognition in mammalian cells. Instead TC-NER initiates when RNA polymerase stalls at a lesion in DNA: the blocked RNA polymerase serves as a damage recognition signal, which replaces the need for the distortion recognition properties of the XPC-RAD23B and DDB complexes. CS proteins (CSA and CSB) bind some types of DNA damage instead of XPC-Rad23B.

TC-NER initiates when RNA polymerase stalls at a lesion in DNA, whereupon protein complexes help move the polymerase backwards. Mutations in TC-NER machinery are responsible for multiple genetic disorders including:

• Trichothiodystrophy (TTD): some individuals are photosensitive, ichthyosis, mental/physical retardation
• Cockayne syndrome (CS): photosensitivity, mental retardation, progeria-like features, microcephaly

https://en.wikipedia.org/wiki/Nucleotide_excision_repair#Transcription_coupled_repair_.28TC-NER.29

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Transcriptomics

The transcriptome is the set of all messenger RNA molecules in one cell or a po
tion of cells. It differs from the exome in that it includes only those RNA molecu
found in a specified cell population, and usually includes the amount or concen
of each RNA molecule in addition to the molecular identities.

The transcriptomes of stem cells and cancer cells are of particular interest to re
ers who seek to understand the processes of cellular differentiation and carcino
Analysis of the transcriptomes of human oocytes and embryos is used to unders
the molecular mechanisms and signaling pathways controlling early embryonic
opment, and could theoretically be a powerful tool in making proper embryo se
in *in vitro* fertilization. Transcriptomics is an emerging and continually growin
in biomarker discovery for use in assessing the safety of drugs or chemical risk
ment.

https://en.wikipedia.org/wiki/Transcriptome

Related Glossary Terms

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Chapter 9 - Point by Point: Techniques

Transferase

In biochemistry, transferase is the general name for the class of enzymes th
transfer of specific functional groups (e.g. a methyl or glycosyl group) from
cule (called the donor) to another (called the acceptor). They are involved i
of different biochemical pathways throughout biology, and are integral to s
most important processes.

https://en.wikipedia.org/wiki/Transferase

Related Glossary Terms

Drag related terms here

Transferrin

Transferrins are iron-binding blood plasma glycoproteins that control the level of free iron in biological fluids. Human transferrin is encoded by the TF gene.

Transferrin glycoproteins bind iron tightly, but reversibly. Transferrin has a molecular weight of around 80 KDa and contains two specific high-affinity Fe(III) binding sites. The affinity of transferrin for Fe(III) is extremely high (association constant is 1020 M^{-1} at pH 7.4) but decreases progressively with decreasing pH below neutrality.

When a transferrin protein loaded with iron encounters a transferrin receptor on the surface of a cell (e.g., to erythroid precursors in the bone marrow), it binds to it and, as a consequence, is transported into the cell in a vesicle by receptor-mediated endocytosis. The pH of the vesicle is reduced by hydrogen ion pumps (H^+ ATPases) to about 5.5, causing transferrin to release its iron ions. The receptor (with its ligand, transferrin, bound) is then transported through the endocytic cycle back to the cell surface, ready for another round of iron uptake. Each transferrin molecule has the ability to carry two iron ions in the ferric form (Fe^{3+}).

https://en.wikipedia.org/wiki/Transferrin

Related Glossary Terms

Drag related terms here

Transferrin Receptor

Transferrin receptor (TfR) is a carrier protein for transferrin. It is needed for the import of iron into the cell and is regulated in response to intracellular iron concentration. It imports iron by internalizing the transferrin-iron complex through receptor-mediated endocytosis.

Low iron concentrations promote increased levels of transferrin receptor, to increase iron intake into the cell. Thus, transferrin receptor maintains cellular iron homeostasis.

TfR production in the cell is regulated according to iron levels by iron-responsive element-binding proteins, IRP1 and IRP2. In the absence of iron, one of these proteins (generally IRP2) binds to the hairpin like structure (IRE) that is in the 3' UTR of the TfR mRNA. Once binding occurs, the mRNA is stabilized and degradation is inhibited.

https://en.wikipedia.org/wiki/Transferrin_receptor

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Transformation

In molecular biology, transformation is the genetic alteration of a cell resul
the direct uptake and incorporation of exogenous genetic material (exogen
from its surroundings through the cell membrane(s). Transformation occu
in some species of bacteria, but it can also be effected by artificial means in
For transformation to happen, bacteria must be in a state of competence, w
occur as a time-limited response to environmental conditions such as starv
cell density.

https://en.wikipedia.org/wiki/Transformation_(genetics)

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Transglutaminase

A transglutaminase is an enzyme that catalyzes the formation of an isopeptide bond between a free amine group (e.g., protein- or peptide-bound lysine) and the acyl group at the end of the side chain of protein- or peptide-bound glutamine. The reaction also produces a molecule of ammonia. Bonds formed by transglutaminase exhibit high resistance to proteolytic degradation (proteolysis).

Transglutaminases form extensively cross-linked, generally insoluble protein polymers. These biological polymers are indispensable for an organism to create barriers and stable structures. Examples are blood clots (coagulation factor XIII), as well as skin and hair.
The catalytic reaction is generally viewed as being irreversible, and must be closely monitored through extensive control mechanisms.

Deficiency of blood factor XIII (a rare genetic condition) predisposes to hemorrhage. Concentrated enzyme can be used to correct the abnormality and reduce bleeding risk.

Anti-transglutaminase antibodies are found in celiac disease and may play a role in the small bowel damage in response to dietary gliadin that characterises this condition. In the related condition dermatitis herpetiformis, in which small bowel changes are often found and which responds to dietary exclusion of gliadin-containing wheat products, epidermal transglutaminase is the predominant autoantigen.

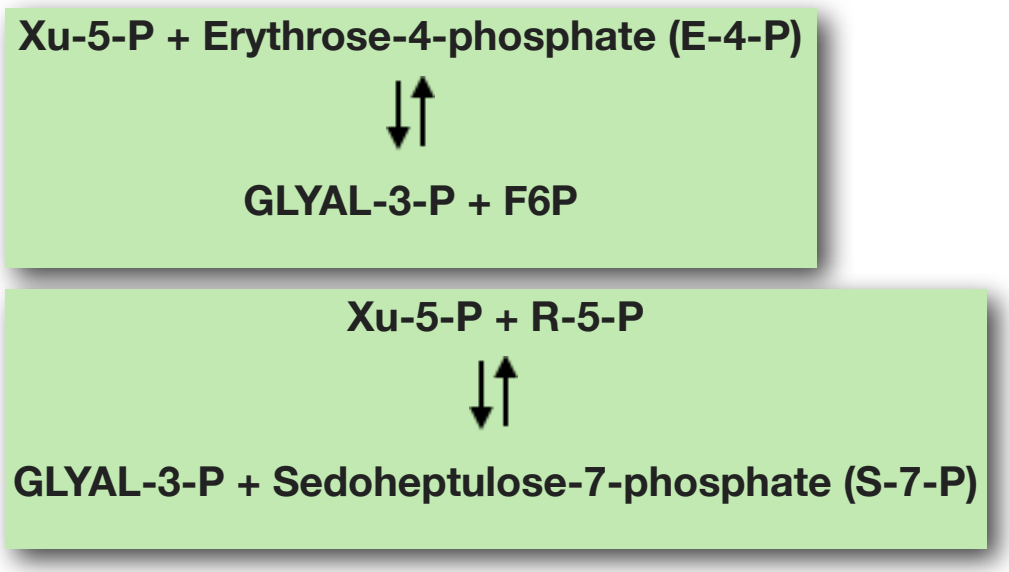
Recent research indicates that sufferers from neurological diseases like Huntington's and Parkinson's may have unusually high levels of one type of transglutaminase, tissue transglutaminase. It is hypothesized that tissue transglutaminase may be involved in the formation of the protein aggregates that causes Huntington's disease, although it is most likely not required.

Mutations in keratinocyte transglutaminase are implicated in lamellar ichthyosis.

https://en.wikipedia.org/wiki/Transglutaminase

Transketolase

Transketolase is an enzyme of both the pentose phosphate pathway in all organisms and the Calvin cycle of photosynthesis. It catalyzes two important reactions, which operate in opposite directions in these two pathways.



In mammals, transketolase connects the pentose phosphate pathway to glycolysis, feeding excess sugar phosphates into the main carbohydrate metabolic pathways. Its presence is necessary for the production of NADPH, especially in tissues actively engaged in biosyntheses, such as fatty acid synthesis by the liver and mammary glands, and for steroid synthesis by the liver and adrenal glands.

https://en.wikipedia.org/wiki/Transketolase

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Translation

In molecular biology and genetics, translation is the process in which cellular ribosomes create proteins. In translation, messenger RNA (mRNA)—produced by transcription from DNA—is decoded by a ribosome to produce a specific amino acid chain, or polypeptide. The polypeptide later folds into an active protein and performs its functions in the cell. The ribosome facilitates decoding by inducing the binding of complementary tRNA anticodon sequences to mRNA codons. The tRNAs carry specific amino acids that are chained together into a polypeptide as the mRNA passes through and is "read" by the ribosome. The entire process is a part of gene expression.

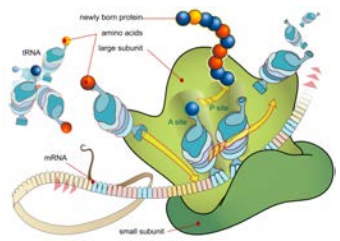
In brief, translation proceeds in three phases:
1 - Initiation: The ribosome assembles around the target mRNA. The first tRNA is attached at the start codon.
2 - Elongation: The tRNA transfers an amino acid to the tRNA corresponding to the next codon. The ribosome then moves (translocates) to the next mRNA codon to continue the process, creating an amino acid chain.
3 - Termination: When a stop codon is reached, the ribosome releases the polypeptide.

In bacteria, translation occurs in the cell's cytoplasm, where the large and small subunits of the ribosome bind to the mRNA. In eukaryotes, translation occurs in the cytosol or across the membrane of the endoplasmic reticulum in a process called vectorial synthesis. In many instances, the entire ribosome/mRNA complex binds to the outer membrane of the rough endoplasmic reticulum (ER); the newly created polypeptide is stored inside the ER for later vesicle transport and secretion outside of the cell.

The basic process of protein production is addition of one amino acid at a time to the end of a protein. This operation is performed by a ribosome. The choice of amino acid type to add is determined by an mRNA molecule. Each amino acid added is matched to a three nucleotide subsequence of the mRNA. For each such triplet possible, the corresponding amino acid is accepted. The successive amino acids added to the chain are matched to successive nucleotide triplets in the mRNA. In this way the sequence of nucleotides in the template mRNA chain determines the sequence of amino acids in the generated amino acid chain. Addition of an amino acid occurs at the C-terminus of the peptide and thus translation is said to be amino-to-carboxyl directed.

The mRNA carries genetic information encoded as a ribonucleotide sequence from the chromosomes to the ribosomes. The ribonucleotides are "read" by translational machinery in a sequence of nucleotide triplets called codons. Each of those triplets codes for a specific amino acid.

The ribosome molecules translate this code to a specific sequence of amino acids. The ribosome is a multisubunit structure containing rRNA and proteins. It is the "factory" where amino acids are assembled into proteins. tRNAs are small noncoding RNA chains (74-93 nucleotides) that transport amino acids to the ribosome. tRNAs have a site for amino acid attachment, and a site called an anticodon. The anticodon is an RNA triplet complementary to the mRNA triplet that codes for their cargo amino acid.



https://en.wikipedia.org/wiki/Translation_(biology)

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Translesion DNA Synthesis

Translesion synthesis (TLS) is a DNA damage tolerance process that allows the DNA replication machinery to replicate past DNA lesions such as thymine dimers or AP sites. It involves switching out regular DNA polymerases for specialized translesion polymerases (i.e. DNA polymerase IV or V, from the Y Polymerase family), often with larger active sites that can facilitate the insertion of bases opposite damaged nucleotides. The polymerase switching is thought to be mediated by, among other factors, the post-translational modification of the replication processivity factor PCNA.

Translesion synthesis polymerases often have low fidelity (high propensity to insert wrong bases) on undamaged templates relative to regular polymerases. However, many are extremely efficient at inserting correct bases opposite specific types of damage. For example, Pol η mediates error-free bypass of lesions induced by UV irradiation, whereas Pol ι introduces mutations at these sites. Pol η is known to add the first adenine across the T^T photodimer using Watson-Crick base pairing and the second adenine will be added in its syn conformation using Hoogsteen base pairing. From a cellular perspective, risking the introduction of point mutations during translesion synthesis may be preferable to resorting to more drastic mechanisms of DNA repair, which may cause gross chromosomal aberrations or cell death. In short, the process involves specialized polymerases either bypassing or repairing lesions at locations of stalled DNA replication.

https://en.wikipedia.org/wiki/DNA_repair#Translesion_synthesis

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Transmembrane Proteins

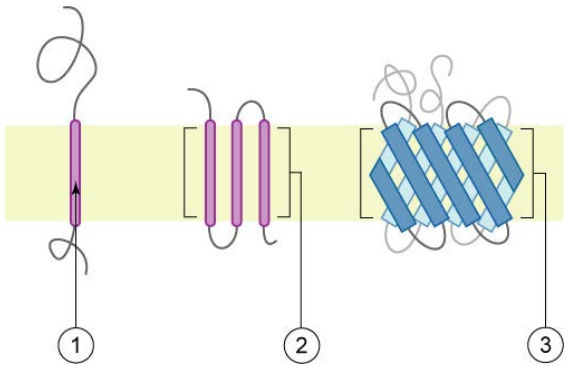
A transmembrane protein (TP) is a type of integral membrane protein that spans the entirety of the biological membrane to which it is permanently attached. Many transmembrane proteins function as gateways to permit the transport of specific substances across the biological membrane. They frequently undergo significant conformational changes to move a substance through the membrane.

Transmembrane proteins are polytopic proteins that aggregate and precipitate in water. They require detergents or nonpolar solvents for extraction, although some of them (β-barrels) can be also extracted using denaturing agents.
The other type of integral membrane protein is the integral monotopic protein that is also permanently attached to the cell membrane but does not pass through it.

There are two basic types of transmembrane proteins: α-helical and β-barrels. α-helical proteins are present in the inner membranes of bacterial cells or the plasma membrane of eukaryotes, and sometimes in the outer membranes. This is the major category of transmembrane proteins. In humans, 27% of all proteins have been estimated to be α-helical membrane proteins. β-barrel proteins are so far found only in outer membranes of gram-negative bacteria, cell wall of gram-positive bacteria, and outer membranes of mitochondria and chloroplasts. All β-barrel transmembrane proteins have simplest up-and-down topology, which may reflect their common evolutionary origin and similar folding mechanism.

Transmembrane proteins are classified by topology. Types I, II, and III are single-pass molecules, while type IV are multiple-pass molecules. Type I transmembrane proteins are anchored to the lipid membrane with a stop-transfer anchor sequence and have their N-terminal domains targeted to the ER lumen during synthesis (and the extracellular space, if mature forms are located on plasmalemma). Type II and III are anchored with a signal-anchor sequence, with type II being targeted to the ER lumen with its C-terminal domain, while type III have their N-terminal domains targeted to the ER lumen. Type IV is subdivided into IV-A, with their N-terminal domains targeted to the cytosol and IV-B, with an N-terminal domain targeted to the lumen. The implications for the division in the four types are especially manifest at the time of translocation and ER-bound translation, when the protein has to be passed through the ER membrane in a direction dependent on the type.

Pictured below are bitopic α-helix (1), polytopic α-helix (2), and polytopic β-barrel (3) transmembrane proteins.



https://en.wikipedia.org/wiki/Transmembrane_protein

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Transmethylase

Methyltransferases (transmethylases) are a large group of enzymes that all methylate their substrates but can be split into several subclasses based on their structural features. The most common class of methyltransferases is class I, all of which contain a Rossman fold for binding S-Adenosyl methionine (SAM).

The general mechanism for methyl transfer is a SN_2-like nucleophilic attack where the methionine sulfur serves as the nucleophile that transfers the methyl group to the enzyme substrate. SAM is converted to S-Adenosyl homocysteine (SAH) during this process. The breaking of the SAM-methyl bond and the formation of the substrate-methyl bond happen nearly simultaneously. These enzymatic reactions are found in many pathways and are implicated in genetic diseases, cancer, and metabolic diseases.

Methylation, as well as other epigenetic modifications, affects transcription, gene stability, and parental imprinting. It directly impacts chromatin structure and can modulate gene transcription, or even completely silence or activate genes, without mutation to the gene itself. Though the mechanisms of this genetic control are complex, hypo- and hypermethylation of DNA is implicated in many diseases.

https://en.wikipedia.org/wiki/Methyltransferase

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Transmissible Spongiform Encephalopathies

Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, a
a group of progressive conditions that affect the brain (encephalopathies) and nervo
system of many animals, including humans. According to the most widespread hy-
pothesis, they are transmitted by prions, though some other data suggest an involve-
ment of a *Spiroplasma* infection. Mental and physical abilities deteriorate and myria
tiny holes appear in the cortex causing it to appear like a sponge (hence spongiform)
when brain tissue obtained at autopsy is examined under a microscope. The disorder
cause impairment of brain function, including memory changes, personality changes
and problems with movement that worsen over time.

Prion diseases of humans include classic Creutzfeldt–Jakob disease, new variant
Creutzfeldt–Jakob disease (nvCJD, a human disorder related to bovine spongiform e
cephalopathy), Gerstmann–Sträussler–Scheinker syndrome, fatal familial insomnia
kuru, and the recently discovered variably protease-sensitive prionopathy. These cor
tions form a spectrum of diseases with overlapping signs and symptoms.

https://en.wikipedia.org/wiki/Transmissible_spongiform_encephalopathy

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Chapter 2 - Structure & Function: Proteins I

Transporter Proteins

A membrane transport protein (or simply transporter) is a membrane prote
in the movement of ions, small molecules, or macromolecules, such as anot
across a biological membrane. Transport proteins are integral transmembr
teins. That is, they exist permanently within and span the membrane acros
they transport substances. The proteins may assist in the movement of subs
facilitated diffusion or active transport. These mechanisms of action are kn
carrier-mediated transport.

https://en.wikipedia.org/wiki/Membrane_transport_protein

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carrier-mediated transport.

https://en.wikipedia.org/wiki/Membrane_transport_protein

Related Glossary Terms

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Transposable Elements

A transposable element (TE or transposon) is a DNA sequence that can change its position within a genome, sometimes creating or reversing mutations and altering the cell's genome size. Transposition often results in duplication of the TE. Barbara McClintock's discovery of these jumping genes earned her a Nobel Prize in 1983.

Transposable elements make up a large fraction of the C-value of eukaryotic cells. There are at least two classes of TEs: Class I TEs generally function via reverse transcription, while Class II TEs encode the protein transposase, which they require for insertion and excision, and some of these TEs also encode other proteins. It has been shown that TEs are important in genome function and evolution. In *Oxytricha*, which has a unique genetic system, these elements play a critical role in development. Transposons are also very useful to researchers as a means to alter DNA inside a living organism.

Transposable elements represent one of several types of mobile genetic elements. TEs are assigned to one of two classes according to their mechanism of transposition, which can be described as either copy and paste (Class I TEs) or cut and paste (Class II TEs).

https://en.wikipedia.org/wiki/Transposable_element

Related Glossary Terms

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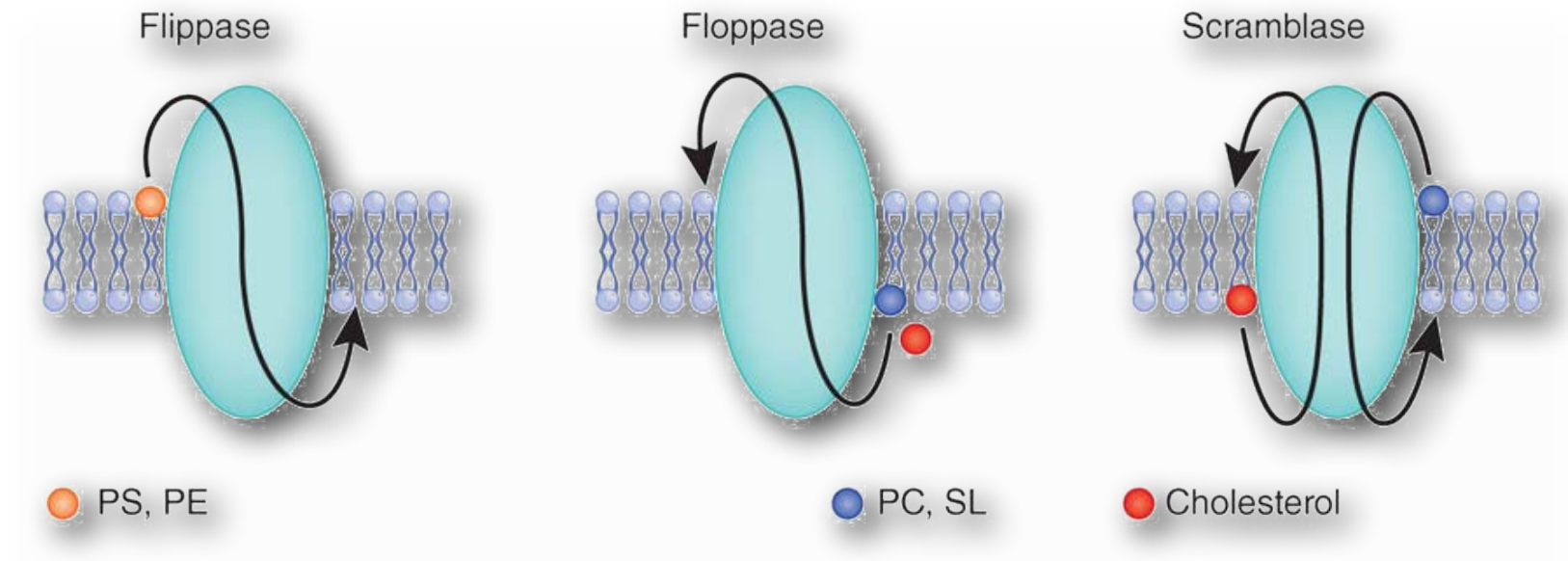
Transverse Diffusion

Lipids in lipid bilayers can move in two ways. Movements within a leaflet of the
layer are called lateral diffusion and occur readily. Movements from one leaflet
other are called transverse diffusion. They are rare and must be catalyzed by en
called flippases, floppases, or scramblases.



https://en.wikipedia.org/wiki/Flippase

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Chapter 3 - Membranes: Basic Concepts

Chapter 9 - Point by Point: Membranes

Triacylglycerides

Fat is one of the three main macronutrients: fat, carbohydrate, and protein. Fats, also known as triglycerides, triacylglycerides or triacylglycerols, are esters of three fatty acid chains and the alcohol glycerol.

The terms "oil", "fat", and "lipid" are often confused. "Oil" normally refers to a fat with short or unsaturated fatty acid chains that is liquid at room temperature, while "fat" may specifically refer to fats that are solids at room temperature. "Lipid" is the general term, as a lipid is not necessarily a triglyceride. Fats, like other lipids, are generally hydrophobic, and are soluble in organic solvents and insoluble in water.

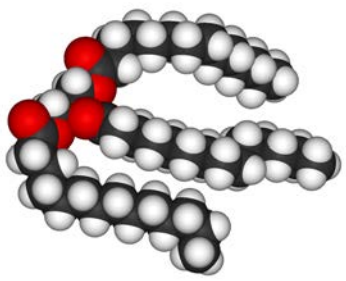
Fat is an important foodstuff for many forms of life, and fats serve both structural and metabolic functions. They are necessary part of the diet of most heterotrophs (including humans). Some fatty acids that are set free by the digestion of fats are called essential because they cannot be synthesized in the body from simpler constituents. There are two essential fatty acids (EFAs) in human nutrition: α-linolenic acid (an ω-3 fatty acid) and linoleic acid (an ω-6 fatty acid). Other lipids needed by the body can be synthesized from these and other fats. Fats and other lipids are broken down in the body by enzymes called lipases produced in the pancreas.

Fats and oils are categorized according to the number and bonding of the carbon atoms in the aliphatic chain. Fats that are saturated fats have no double bonds between the carbons in the chain. Unsaturated fats have one or more double bonded carbons in the chain. The nomenclature is based on the non-acid (non-carbonyl) end of the chain. This end is called the omega end or the n-end. Thus α-linolenic acid is called an ω-3 fatty acid because the 3rd carbon from that end is the first double bonded carbon in the chain counting from that end.

Some oils and fats have multiple double bonds and are therefore called polyunsaturated fats. Unsaturated fats can be further divided into cis fats, which are the most common in nature, and trans fats, which are rare in nature. Unsaturated fats can be altered by reaction with hydrogen effected by a catalyst. This action, called hydrogenation, tends to break all the double bonds and makes a fully saturated fat. To make vegetable shortening, then, liquid *cis*-unsaturated fats such as vegetable oils are hydrogenated to produce saturated fats, which have more desirable physical properties e.g., they melt at a desirable temperature (30–40 °C), and store well, whereas polyunsaturated oils go rancid when they react with oxygen in the air. However, *trans* fats are generated during hydrogenation as contaminants created by an unwanted side reaction on the catalyst during partial hydrogenation. Consumption of such trans fats has shown to increase the risk of coronary heart disease.

Saturated fats can stack themselves in a closely packed arrangement, so they can solidify easily and are typically solid at room temperature. For example, animal fats tallow and lard are high in saturated fatty acid content and are solids. Olive and linseed oils on the other hand are unsaturated and liquid.

Fats serve both as energy sources for the body, and as stores for energy in excess of what the body needs immediately. Each gram of fat when burned or metabolized releases about 9 food calories (37 kJ = 8.8 kcal). Fats are broken down in the healthy body to release their constituents, glycerol and fatty acids. Glycerol itself can be converted to glucose by the liver and so become a source of energy.



https://en.wikipedia.org/wiki/Fat

Triacylglycerol Lipase

Triacylglycerol lipase (EC 3.1.1.3) is the only regulated enzyme of fat breako
also known as hormone sensitive triacylglycerol lipase. It removes t
acid from the fat. Diacylglyceride lipase removes the second one and monoa
eride lipase removes the third. As noted, only the first one is regulated and
to be the rate limiting reaction when active.

This enzyme catalyses the following reaction

Triacylglycerol + H_2O <=> Diacylglycerol + Fatty acid

The pancreatic enzyme acts only on an ester-water interface.

https://en.wikipedia.org/wiki/Triacylglycerol_lipase

Related Glossary Terms

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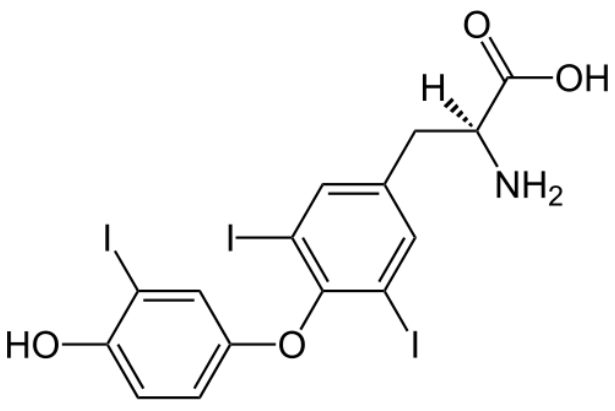
Triiodothyronine

Triiodothyronine, also known as T_3, is a thyroid hormone. It affects almost every physiological process in the body, including growth and development, metabolism, body temperature, and heart rate. Production of T_3 and its prohormone thyroxine (T_4) is activated by thyroid-stimulating hormone (TSH), which is released from the pituitary gland.

As concentrations of these hormones decrease, the pituitary gland increases production of TSH, and by these processes, a feedback control system stabilizes the amount of thyroid hormones that are in the bloodstream.

T_3 is the true hormone. Its effects on target tissues are roughly four times more potent than those of T_4. Of the thyroid hormone that is produced, just about 20% is T_3, whereas 80% is produced as T_4. Roughly 85% of the circulating T_3 is later formed in the liver and pituitary by removal of the iodine atom from the carbon atom number five of the outer ring of T_4. In any case, the concentration of T_3 in the human blood plasma is about one-fortieth that of T_4. This is observed in fact because of the short half-life of T_3, which is only 2.5 days. This compares with the half-life of T_4, which is about 6.5 days.

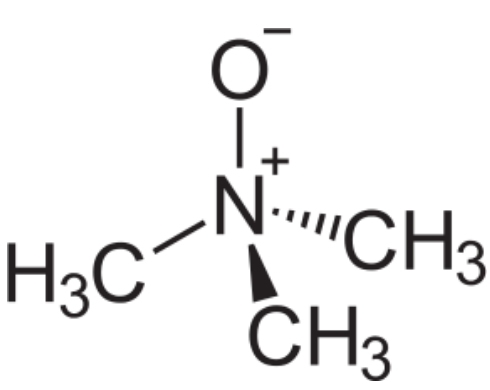


https://en.wikipedia.org/wiki/Triiodothyronine

Trimethylamine-N-oxide

Trimethylamine N-oxide (TMAO) is the organic compound in the class of amine oxides with the formula $(CH_3)_3NO$. This colorless solid is usually encountered as the dihydrate. It is a product of the oxidation of trimethylamine and a common metabolite in animals. It is a protein stabilizer that may serve to counteract urea, the major osmolyte of sharks, skates and rays. It is also higher in deep-sea fishes and crustaceans, where it may counteract the protein-destabilizing effects of pressure. TMAO decomposes to trimethylamine (TMA), which is the main odorant that is characteristic of degrading seafood.

Trimethylamine oxide is used in protein folding experiments to counteract the unfolding effects of urea.



https://en.wikipedia.org/wiki/Trimethylamine_N-oxide

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Trinucleotide Repeat

Trinucleotide repeat disorders are a set of genetic disorders caused by trinucleotide repeat expansion, a kind of mutation where trinucleotide repeats in certain genes exceed the normal, stable threshold, which differs per gene. The mutation is a subset of unstable microsatellite repeats that occur throughout all genomic sequences. If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene.

Currently, nine neurologic disorders are known to be caused by an increased number of CAG repeats, typically in coding regions of otherwise unrelated proteins. During protein synthesis, the expanded CAG repeats are translated into a series of uninterrupted glutamine residues forming what is known as a polyglutamine tract ("polyQ"). Such polyglutamine tracts may be subject to increased aggregation.

Trinucleotide repeat disorders generally show genetic anticipation, where their severity increases with each successive generation that inherits them. This is likely explained by the addition of further CAG repeats in the gene in the progeny of affected individuals. For example, Huntington's disease occurs when there are more than 35 CAG repeats on the gene coding for the protein HTT. A parent with 35 repeats would be considered "normal" and never exhibit any symptoms of the disease. That parent's offspring, however, would be at an increased risk compared to the general population of developing Huntington's, as it would take only the addition of one more CAG codon to cause the production of mHTT (mutant HTT), the protein responsible for disease. Huntington's very rarely occurs spontaneously. It is almost always the result of inheriting the defective gene from an affected parent.

https://en.wikipedia.org/wiki/Trinucleotide_repeat_disorder

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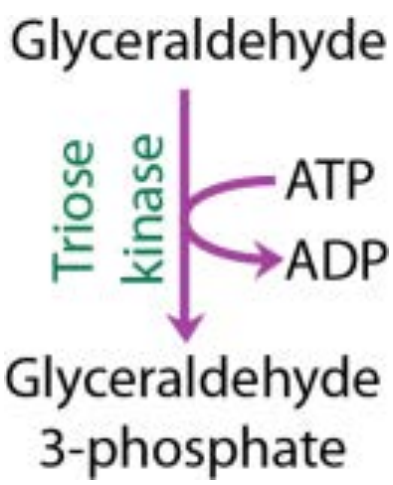
Triose Kinase

In enzymology, a triokinase is an enzyme that catalyzes the chemical reaction:

ATP + D-glyceraldehyde <---> ADP + D-glyceraldehyde 3-phosphate



This enzyme belongs to the family of transferases, specifically those transferring phosphorus-containing groups (phosphotransferases) with an alcohol group as acceptor. The systematic name of this enzyme class is ATP:D-glyceraldehyde 3-phosphotransferase. This enzyme is also called triose kinase.

This enzyme participates in fructose metabolism.

https://en.wikipedia.org/wiki/Triokinase

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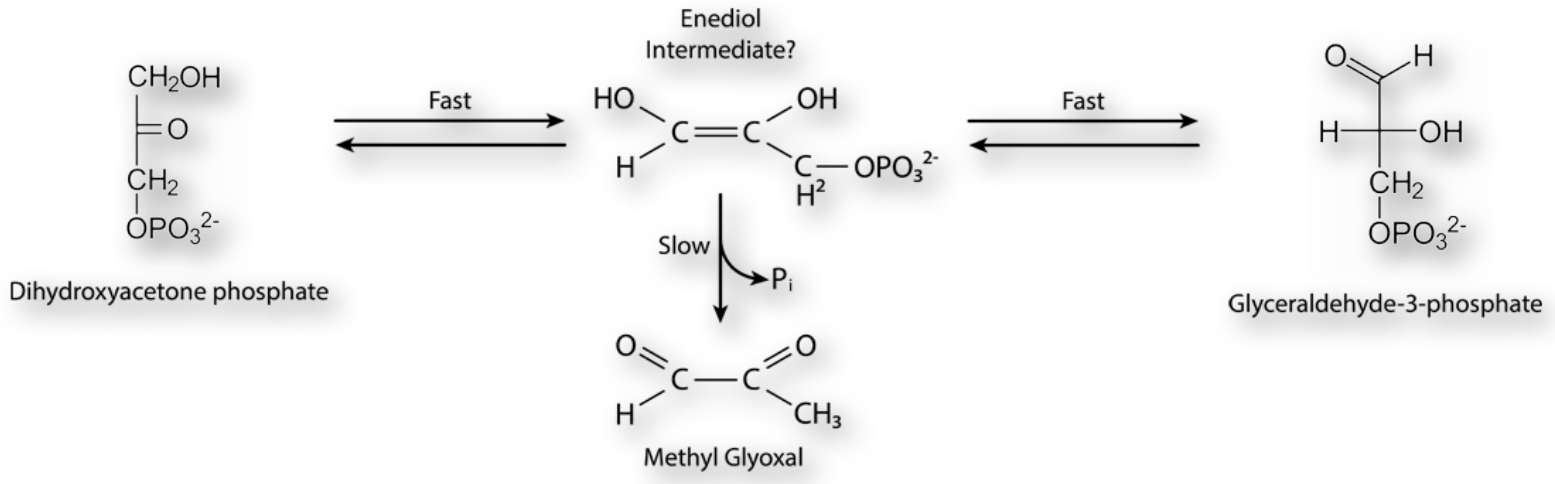
Triose Phosphate Isomerase

Triose-phosphate isomerase (TPI or TIM) is an enzyme that catalyzes the reversible interconversion of the triose phosphate isomers dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate. TPI plays an important role in glycolysis and is essential for efficient energy production.



TPI has been found in nearly every organism searched for the enzyme, including animals such as mammals and insects as well as in fungi, plants, and bacteria. However, some bacteria that do not perform glycolysis, like ureaplasmas, lack TPI.

Triose phosphate isomerase is a highly efficient enzyme, performing the reaction billions of times faster than it would occur naturally in solution. The reaction is so efficient that it is said to be catalytically perfect: It is limited only by the rate the substrate can diffuse into and out of the enzyme's active site.

https://en.wikipedia.org/wiki/Triosephosphate_isomerase

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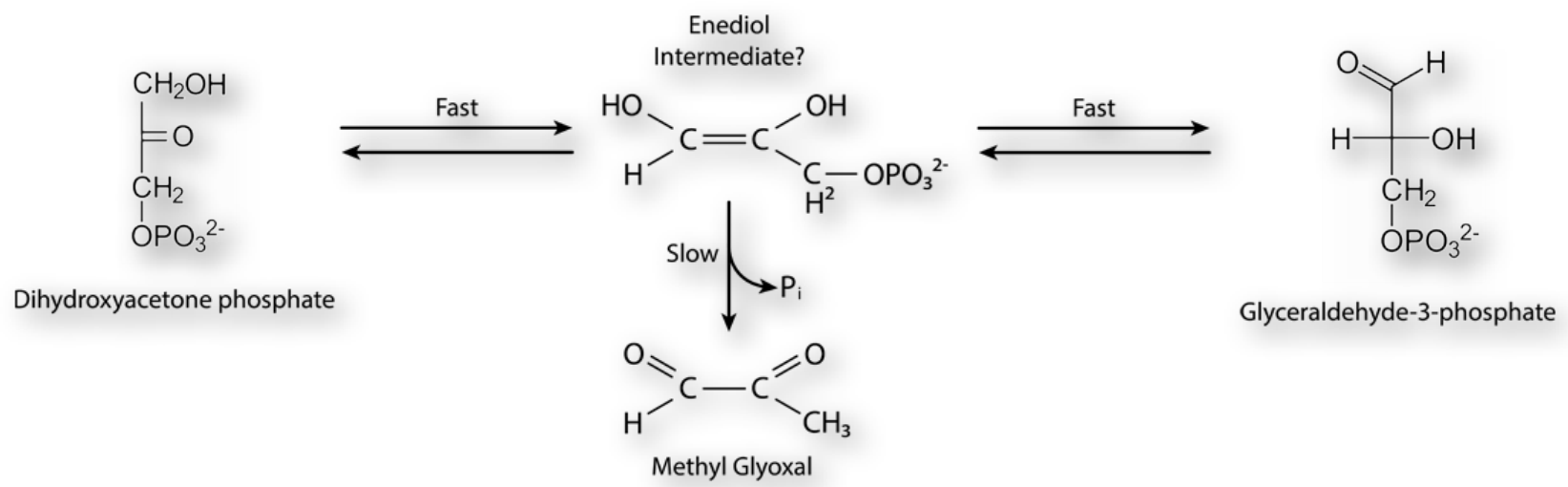

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https://en.wikipedia.org/wiki/Triosephosphate_isomerase

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Chapter 6 - Metabolism: Sugars

Chapter 9 - Point by Point: Metabolism

Triterpenes

Terpenes are a large and diverse class of organic compounds, produced by a
plants. Many terpenes are aromatic hydrocarbons and thus may have had a
function.

Triterpenes consist of six isoprene units and have the molecular formula C_3
linear triterpene squalene, the major constituent of shark liver oil, is derive
reductive coupling of two molecules of farnesyl pyrophosphate. Squalene is
essed biosynthetically to generate either lanosterol or cycloartenol, the stru
cursors to all the steroids.

https://en.wikipedia.org/wiki/Terpene

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Chapter 2 - Structure & Function: Lipids

Chapter 9 - Point by Point: Structure and Function

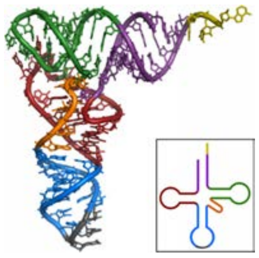
tRNA

A transfer RNA (abbreviated tRNA and archaically referred to as sRNA, for soluble RNA) is an adaptor molecule composed of RNA, typically 76 to 90 nucleotides in length, that serves as the physical link between the mRNA and the amino acid sequence of proteins. It does this by carrying an amino acid to the protein synthetic machinery of a cell (ribosome) as directed by a three-nucleotide sequence (codon) in a messenger RNA (mRNA). As such, tRNAs are a necessary component of translation, the biological synthesis of new proteins according to the genetic code.

One end of the tRNA matches the genetic code in a three-nucleotide sequence called the anticodon. The anticodon forms three base pairs with a codon in mRNA during protein biosynthesis. The mRNA encodes a protein as a series of contiguous codons, each of which is recognized by a particular tRNA. On the other end of the tRNA is a covalent attachment to the amino acid that corresponds to the anticodon sequence. Each type of tRNA molecule can be attached to only one type of amino acid, so each organism has many types of tRNA (in fact, because the genetic code contains multiple codons that specify the same amino acid, there are several tRNA molecules bearing different anticodons which also carry the same amino acid).

The covalent attachment to the tRNA 3' end is catalyzed by enzymes called aminoacyl tRNA synthetases. During protein synthesis, tRNAs with attached amino acids are delivered to the ribosome by proteins called elongation factors (EF-Tu in bacteria, eEF-1 in eukaryotes), which aid in decoding the mRNA codon sequence. If the tRNA's anticodon matches the mRNA, another tRNA already bound to the ribosome transfers the growing polypeptide chain from its 3' end to the amino acid attached to the 3' end of the newly delivered tRNA, a reaction catalyzed by the ribosome.

A large number of the individual nucleotides in a tRNA molecule may be chemically modified, often by methylation or deamidation. These unusual bases sometimes affect the tRNA's interaction with ribosomes and sometimes occur in the anticodon to alter base-pairing properties.



https://en.wikipedia.org/wiki/Transfer_RNA

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tRNA Nucleotidyl Transferase

This enzyme catalyses the following chemical reaction
a tRNA precursor + 2 CTP + ATP ⇌ a tRNA with a 3' CCA end + 3 diphosphate (ov

all reaction)

Individual reactions below:

(1a) a tRNA precursor + CTP ⇌ a tRNA with a 3' cytidine end + diphosphate

(1b) a tRNA with a 3' cytidine + CTP ⇌ a tRNA with a 3' CC end + diphosphate

(1c) a tRNA with a 3' CC end + ATP ⇌ a tRNA with a 3' CCA end + diphosphate

The acylation of all tRNAs with an amino acid occurs at the terminal ribose of a 3' C
sequence.

https://en.wikipedia.org/wiki/CCA_tRNA_nucleotidyltransferase

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Tropocollagen

Topocollagen is a type of collegen formed by processing of a collagen fiber outside of a cell. Steps in the process (that starts inside the cell) are as follows:

1 Inside the cell

1 Two types of alpha chains are formed during translation on ribosomes along the rough endoplasmic reticulum (RER): α-1 and α-2 chains. These peptide chains (known as preprocollagen) have registration peptides on each end and a signal peptide.

2 Polypeptide chains are released into the lumen of the RER.

3 Signal peptides are cleaved inside the RER and the chains are now known as pro-α chains.

4 Hydroxylation of lysine and proline amino acids occurs inside the lumen. This process is dependent on ascorbic acid (vitamin C) as a cofactor.

5 Glycosylation of specific hydroxylysine residues occurs.

6 Triple alpha helical structure is formed inside the endoplasmic reticulum from two α-1 chains and one α-2 chain.

7 Procollagen is shipped to the Golgi apparatus, where it is packaged and secreted by exocytosis.

2 Outside the cell

1 Registration peptides are cleaved and tropocollagen is formed by procollagen peptidase.

2 Multiple tropocollagen molecules form collagen fibrils, via covalent cross-linking (aldol reaction) by lysyl oxidase which links hydroxylysine and lysine residues. Multiple collagen fibrils form into collagen fibers.

3 Collagen may be attached to cell membranes via several types of protein, including fibronectin and integrin.

Related Glossary Terms

Drag related terms here

Tropoelastin

Tropoelastin is a water-soluble molecule with a molecular weight of approximately 72,000 daltons. Multiple tropoelastin molecules covalently bind together with crosslinks to form the protein elastin that is very prevalent in the body. There is only one gene for this molecule. However, alternative splicing does produce tissue specific elastin variants.

There are 36 small domains in tropoelastin and each weighs about 2 kilodaltons. Within the exons, there are alternating hydrophobic and lysine-rich domains that are important in forming elastin. Tropoelastin does not undergo cleavage and formation of the microfibril is achieved by a self-association process termed coacervation.

Tropoelastin aggregates at physiological temperature due to interactions between hydrophobic domains. This process is reversible and thermodynamically controlled. The coacervate is stabilized by cross-linking via lysyl oxidase. The coacervate then becomes insoluble and the process is irreversible. It then condenses to form a cross-linked structure of 4 residues, either Desmosine or Isodesmosine.

https://en.wikipedia.org/wiki/Tropoelastin

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Tropomyosin

Tropomyosin is a two-stranded α-helical coiled coil protein found in cell cytoskeletons.

Tropomyosins are a large family of integral components of actin filaments that play a critical role in regulating the function of actin filaments in both muscle and nonmuscle cells. These proteins consist of rod-shaped coiled-coil hetero- or homo-dimers that lie along the α-helical groove of most actin filaments. Interaction occurs along the length of the actin filament, with dimers aligning in a head-to-tail fashion.

The binding of the myosin heads to the muscle actin is a highly regulated process. The thin filament is made of actin, tropomyosin, and troponin. The contraction of skeletal muscle is triggered by nerve impulses that in turn stimulate the release of Ca^{++}. The release of Ca^{++} from the sarcoplasmic reticulum causes an increase in the concentration of Ca^{++} in the cytosol. Calcium ions then bind to troponin, which is associated with tropomyosin. Binding causes changes in the shape of troponin and subsequently causes the tropomyosin isoform to shift its position on the actin filament. This shifting in position exposes the myosin-binding sites on the actin filament, allowing the myosin heads of the thick filament to bind to the thin filament.

Structural and biochemical studies suggest that the position of tropomyosin and troponin on the thin filament regulates the interactions between the myosin heads of the thick filament and the binding sites on the actin of the thin filament. X-ray diffraction and cryoelectron microscopy suggest that tropomyosin sterically blocks the access of myosin to the actin filament.

Although this model is well-established, it is unclear as to whether the movement of tropomyosin directly causes the myosin head to engage the actin filament. As such, an alternative model has emerged, whereby the movement of the tropomyosin in the filament functions as an allosteric switch that is modulated by activating myosin binding but does not function solely by regulating myosin binding.

https://en.wikipedia.org/wiki/Tropomyosin

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Troponin

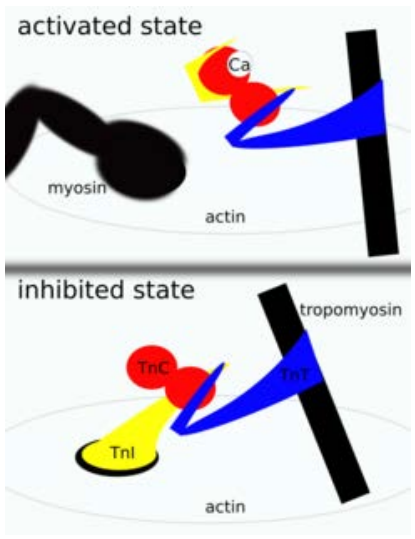
Troponin is a complex of three regulatory proteins (troponin C, troponin I, and troponin T) that is integral to muscle contraction in skeletal muscle and cardiac muscle, but not smooth muscle.

An increased level of the cardiac protein isoform of troponin circulating in the blood has been shown to be a biomarker of heart disorders, the most important of which is myocardial infarction. Raised troponin levels indicate cardiac muscle cell death as the molecule is released into the blood upon injury to the heart.

Troponin is attached to the protein tropomyosin and lies within the groove between actin filaments in muscle tissue. In a relaxed muscle, tropomyosin blocks the attachment site for the myosin crossbridge, thus preventing contraction. When the muscle cell is stimulated to contract by an action potential, calcium channels open in the sarcoplasmic membrane and release calcium into the sarcoplasm. Some of this calcium attaches to troponin, which causes it to change shape, exposing binding sites for myosin (active sites) on the actin filaments. Myosin's binding to actin causes crossbridge formation, and contraction of the muscle begins.

Troponin activation (see figure below). Troponin C (red) binds Ca^{++}, which stabilizes the activated state, where troponin I (yellow) is no longer bound to actin. Troponin T (blue) anchors the complex on tropomyosin.

Troponin is found in both skeletal muscle and cardiac muscle, but the specific versions of troponin differ between types of muscle. The main difference is that the TnC subunit of troponin in skeletal muscle has four calcium ion-binding sites, whereas in cardiac muscle there are only three. Views on the actual amount of calcium that binds to troponin vary from expert to expert and source to source.



https://en.wikipedia.org/wiki/Troponin

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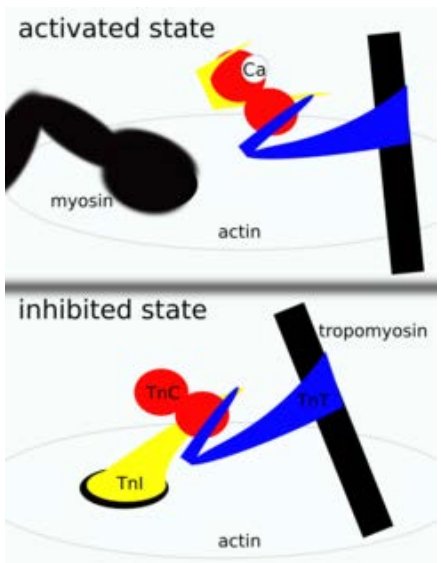

https://en.wikipedia.org/wiki/Troponin

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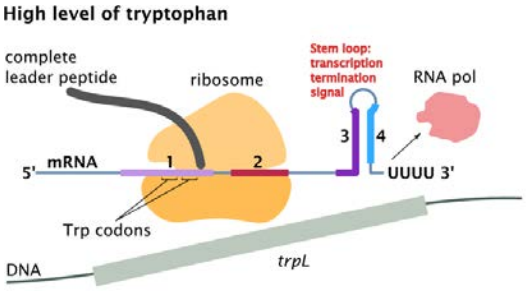
Trp Operon

The trp operon is an operon — a group of genes that are used, or transcribed, together — that codes for the components for production of tryptophan. The trp operon is present in many bacteria, but was first characterized in *Escherichia coli*. The operon is regulated so that when tryptophan is present in the environment, the genes for tryptophan synthesis are not expressed. It was an important experimental system for learning about gene regulation, and is commonly used to teach gene regulation.

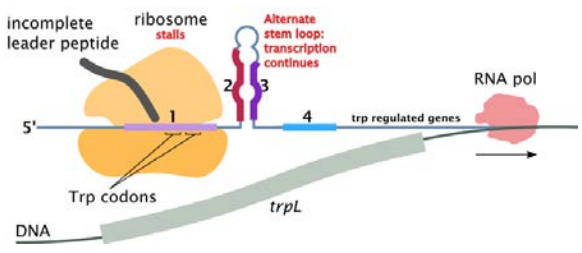
The operon operates by a negative repressible feedback mechanism. The repressor for the trp operon is produced upstream by the trpR gene, which is constitutively expressed at a low level. Synthesized TrpR monomers associate into tetramers. These tetramers are inactive and are dissolved in the nucleoplasm. When tryptophan is present, these tryptophan repressor tetramers bind to tryptophan, causing a change in the repressor conformation, allowing the repressor to bind to the operator. This prevents RNA polymerase from binding to and transcribing the operon, so tryptophan is not produced from its precursor. When tryptophan is not present, the repressor is in its inactive conformation and cannot bind the operator region, so transcription is not inhibited by the repressor.

Attenuation is a second mechanism of negative feedback in the trp operon. The repression system targets the intracellular trp concentration whereas the attenuation responds to the concentration of charged tRNAtrp. Thus, the trpR repressor decreases gene expression by altering the initiation of transcription, while attenuation does so by altering the process of transcription that's already in progress. While the TrpR repressor decreases transcription by a factor of 70, attenuation can further decrease it by a factor of 10, thus allowing accumulated repression of about 700-fold. Attenuation is made possible by the fact that in prokaryotes (which have no nucleus), the ribosomes begin translating the mRNA while RNA polymerase is still transcribing the DNA sequence. This allows the process of translation to affect transcription of the operon directly.

High level of tryptophan



Low level of tryptophan



https://en.wikipedia.org/wiki/Trp_operon

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Trypsin

Trypsin is a serine protease from the PA clan superfamily, found in the digestive system of many vertebrates, where it hydrolyzes proteins. Trypsin is formed in the small intestine when its proenzyme form, the trypsinogen produced by the pancreas, is activated. Trypsin cleaves peptide chains mainly at the carboxyl side of the amino acids lysine or arginine, except when either is followed by proline. It is used for numerous biotechnological processes. The process is commonly referred to as trypsin proteolysis or trypsinization, and proteins that have been digested/treated with trypsin are said to have been trypsinized.

In the duodenum, trypsin catalyzes the hydrolysis of peptide bonds, breaking down proteins into smaller peptides. The peptide products are then further hydrolyzed into amino acids via other proteases, rendering them available for absorption into the blood stream. Tryptic digestion is a necessary step in protein absorption as proteins are generally too large to be absorbed through the lining of the small intestine.

Trypsin is produced as the inactive zymogen trypsinogen in the pancreas. When the pancreas is stimulated by cholecystokinin, it is then secreted into the first part of the small intestine (the duodenum) via the pancreatic duct. Once in the small intestine, the enzyme enteropeptidase activates trypsinogen into trypsin by proteolytic cleavage. Auto catalysis can happen with trypsin using trypsinogen as the substrate. This activation mechanism is common for most serine proteases, and serves to prevent autodegradation of the pancreas.

https://en.wikipedia.org/wiki/Trypsin

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Trypsinogen

Trypsinogen is the precursor form or zymogen of trypsin, a digestive enzym
duced by the pancreas, it is found in pancreatic juice, along with amylase, li
chymotrypsinogen. It is activated by enteropeptidase, which is found in the
mucosa, to form trypsin. Once activated, the trypsin can activate more tryp
into trypsin. Trypsin cleaves the peptide bond on the carboxyl side of basic
such as arginine and lysine.

https://en.wikipedia.org/wiki/Trypsinogen

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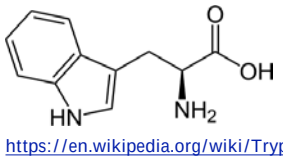
Tryptophan

Tryptophan (abbreviated as Trp or W; encoded by the codon UGG) is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain indole, classifying it as a non-polar, aromatic amino acid. It is essential in humans, meaning the body cannot synthesize it and thus it must be obtained from the diet.

For many organisms (including humans), tryptophan is needed to prevent illness or death, but cannot be synthesized by the organism and must be ingested; in short, it is an essential amino acid. Amino acids, including tryptophan, act as building blocks in protein biosynthesis, and proteins are required to sustain life. In addition, tryptophan functions as a biochemical precursor for the following compounds):
• Serotonin (a neurotransmitter), synthesized via tryptophan hydroxylase. Serotonin, in turn, can be converted to melatonin (a neurohormone), via N-acetyltransferase and 5-hydroxyindole-O-methyltransferase activities.
• Niacin, also known as vitamin B_3, is synthesized from tryptophan via kynurenine and quinolinic acids as key biosynthetic intermediates.
• Auxin (a phytohormone), is mainly synthesized from tryptophan via indole-3-pyruvic acid.

The disorder fructose malabsorption causes improper absorption of tryptophan in the intestine, reduced levels of tryptophan in the blood, and depression. Some studies did not find reduced tryptophan in cases of lactose maldigestion.

In bacteria that synthesize tryptophan, high cellular levels of this amino acid activate a repressor protein, which binds to the trp operon. Binding of this repressor to the tryptophan operon prevents transcription of downstream DNA that codes for the enzymes involved in the biosynthesis of tryptophan. So high levels of tryptophan prevent tryptophan synthesis through a negative feedback loop and, when the cell's tryptophan levels are reduced, transcription from the trp operon resumes. The genetic organization of the trp operon thus permits tightly regulated and rapid responses to changes in the cell's internal and external tryptophan levels.



https://en.wikipedia.org/wiki/Tryptophan

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Tubulin

Tubulin can refer either to the tubulin protein superfamily of globular proteins, or one of the member proteins of that superfamily. α- and β-tubulins polymerize into microtubules, a major component of the eukaryotic cytoskeleton. Microtubules function in many essential cellular processes, including mitosis. Tubulin-binding drugs kill cancerous cells by inhibiting microtubule dynamics, which are required for DNA segregation and therefore cell division.

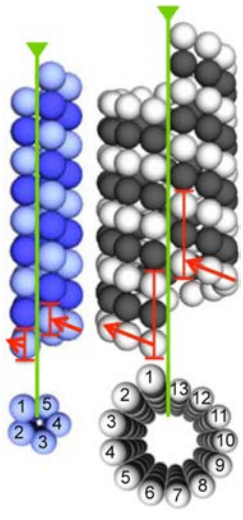
α- and β-tubulin polymerize into dynamic microtubules. In eukaryotes, microtubules are one of the major components of the cytoskeleton, and function in many processes, including structural support, intracellular transport, and DNA segregation.

α- and β-tubulin polymerize into dynamic microtubules. In eukaryotes, microtubules are one of the major components of the cytoskeleton, and function in many processes, including structural support, intracellular transport, and DNA segregation.

Microtubules are assembled from dimers of α- and β-tubulin. These subunits are slightly acidic with an isoelectric point between 5.2 and 5.8. Each has a molecular weight of approximately 50,000 Daltons.

To form microtubules, the dimers of α- and β-tubulin bind to GTP and assemble onto the (+) ends of microtubules while in the GTP-bound state. The β-tubulin subunit is exposed on the plus end of the microtubule while the α-tubulin subunit is exposed on the minus end. After the dimer is incorporated into the microtubule, the molecule of GTP bound to the β-tubulin subunit eventually hydrolyzes into GDP through inter-dimer contacts along the microtubule protofilament.

Whether the β-tubulin member of the tubulin dimer is bound to GTP or GDP influences the stability of the dimer in the microtubule. Dimers bound to GTP tend to assemble into microtubules, while dimers bound to GDP tend to fall apart; thus, this GTP cycle is essential for the dynamic instability of the microtubule.



https://en.wikipedia.org/wiki/Tubulin

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Turnips

The turnip or white turnip is a root vegetable commonly grown in temperate climates worldwide for its white, bulbous taproot. Small, tender varieties are grown for human consumption, while larger varieties are grown as feed for livestock.

Pliny the Elder considered the turnip one of the most important vegetables of his day, rating it "directly after cereals or at all events after the bean, since its utility surpasses that of any other plant".

The turnip is an old vegetable charge in heraldry. It was used by Leonhard von Keutschach, prince-archbishop of Salzburg. The turnip is still the heart shield in the arms of Keutschach am See.

https://en.wikipedia.org/wiki/Turnip

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Turnover Number

Turnover number (also termed K_{cat}) is defined as the maximum number of conversions of substrate molecules per second that a single catalytic site wi can be calculated from the maximum reaction rate $V_{\mathbf{max}}$ and catalyst site co tion $[E]_T$ as follows:

$$k_{\mathbf{cat}} = \frac{V_{\mathbf{max}}}{[E]_T}$$

For example, carbonic anhydrase has a turnover number of 400,000 to 60 which means that each carbonic anhydrase enzyme molecule can produce u 600,000 molecules of product (bicarbonate ions) per second.

https://en.wikipedia.org/wiki/Turnover_number

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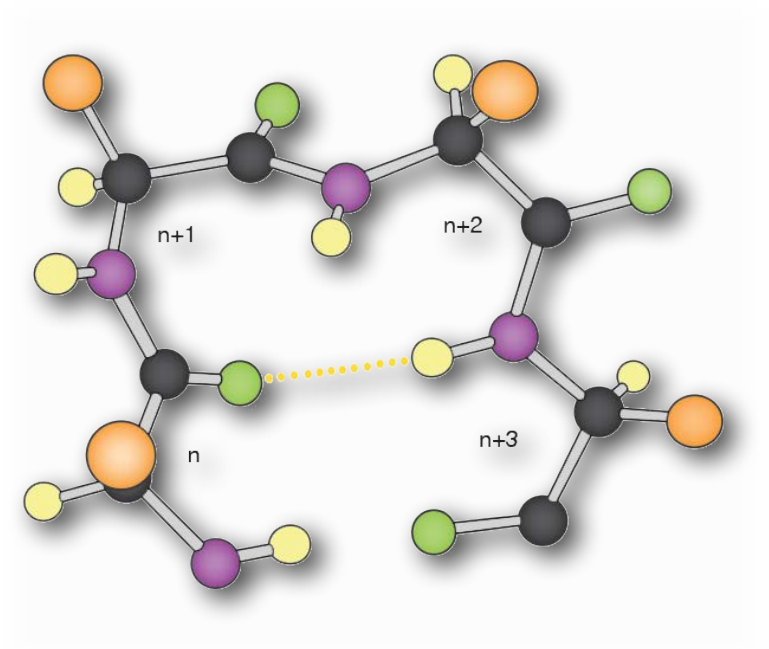
Turns

A turn is an element of secondary structure in proteins where the polypeptide chain reverses its overall direction.

According to one definition, a turn is a structural motif where the Cα atoms of two residues separated by few (usually 1 to 5) peptide bonds are close (< 7 Å), while the residues do not form a secondary structure element such as an α helix or β sheet with regularly repeating backbone dihedral angles. Although the proximity of the terminal Cα atoms usually correlates with formation of a hydrogen bond between the corresponding residues, a hydrogen bond is not a requirement in this turn definition. That said, in many cases the H-bonding and Cα-distance definitions are equivalent.



https://en.wikipedia.org/wiki/Turn_(biochemistry)

Related Glossary Terms

Drag related terms here

Turpentine

Turpentine is a fluid obtained by the distillation of resin obtained from live
mainly pines. It is mainly used as a solvent and as a source of materials for
thesis. Turpentine is composed of terpenes, mainly the monoterpenes α-pi
pinene with lesser amounts of carene, camphene, dipentene, and terpinole

Turpentine is also used as a source of raw materials in the synthesis of frag
cal compounds. Commercially used camphor, linalool, α-terpineol, and ger
usually produced from α-pinene and β-pinene, which are two of the chief cl
components of turpentine. These pinenes are separated and purified by dis
The mixture of diterpenes and triterpenes that is left as residue after turper
tion is sold as rosin.

https://en.wikipedia.org/wiki/Turpentine

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Chapter 2 - Structure & Function: Lipids

Twists

In a "relaxed" double-helical segment of B-DNA, the two strands twist arou
cal axis once every 10.4–10.5 base pairs of sequence. Adding or subtracting
some enzymes can do, imposes strain. If a DNA segment under twist strain
into a circle by joining its two ends and then allowed to move freely, the cir
would contort into a new shape, such as a simple figure-eight. Such a conto
percoil. The noun form "supercoil" is often used in the context of DNA topo

https://en.wikipedia.org/wiki/DNA_supercoil

Related Glossary Terms

Drag related terms here

Type I Transmembrane Proteins

A transmembrane protein (TP) is a type of integral membrane protein that
entirety of the biological membrane to which it is permanently attached. Ty
and III are single-pass molecules, while type IV are multiple-pass molecule
and III are anchored with a signal-anchor sequence, with type II being targ
ER lumen with its C-terminal domain, while type III have their N-terminal
targeted to the ER lumen.

https://en.wikipedia.org/wiki/Transmembrane_protein

Related Glossary Terms

Drag related terms here

Type II Transmembrane Proteins

A transmembrane protein (TP) is a type of integral membrane protein that
entirety of the biological membrane to which it is permanently attached. Ty
and III are single-pass molecules, while type IV are multiple-pass molecule
and III are anchored with a signal-anchor sequence, with type II being targ
ER lumen with its C-terminal domain, while type III have their N-terminal
targeted to the ER lumen.

https://en.wikipedia.org/wiki/Transmembrane_protein

Related Glossary Terms

Drag related terms here

Type III Transmembrane Proteins

A transmembrane protein (TP) is a type of integral membrane protein that
entirety of the biological membrane to which it is permanently attached. Ty
and III are single-pass molecules, while type IV are multiple-pass molecule
and III are anchored with a signal-anchor sequence, with type II being targ
ER lumen with its C-terminal domain, while type III have their N-terminal
targeted to the ER lumen.

https://en.wikipedia.org/wiki/Transmembrane_protein

Related Glossary Terms

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Type IV Transmembrane Proteins

A transmembrane protein (TP) is a type of integral membrane protein that
entirety of the biological membrane to which it is permanently attached. Ty
and III are single-pass molecules, while type IV are multiple-pass molecule
subdivided into IV-A, with their N-terminal domains targeted to the cytoso
with an N-terminal domain targeted to the lumen. The implications for the
the four types are especially manifest at the time of translocation and ER-b
lation, when the protein has to be passed through the ER membrane in a di
pendent on the type.

https://en.wikipedia.org/wiki/Transmembrane_protein

Related Glossary Terms

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Type V Transmembrane Proteins

A transmembrane protein (TP) is a type of integral membrane protein that
entirety of the biological membrane to which it is permanently attached. Ty
and III are single-pass molecules, while type IV are multiple-pass molecule
subdivided into IV-A, with their N-terminal domains targeted to the cytoso
with an N-terminal domain targeted to the lumen. The implications for the
the four types are especially manifest at the time of translocation and ER-b
lation, when the protein has to be passed through the ER membrane in a di
pendent on the type. Type V transmembrane proteins are not embedded in
bilayer at all, but rather attached to a lipid molecule that is itself anchored i
layer.

https://en.wikipedia.org/wiki/Transmembrane_protein

Related Glossary Terms

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Type VI Transmembrane Proteins

A transmembrane protein (TP) is a type of integral membrane protein that
entirety of the biological membrane to which it is permanently attached. Ty
and III are single-pass molecules, while type IV are multiple-pass molecule
subdivided into IV-A, with their N-terminal domains targeted to the cytoso
with an N-terminal domain targeted to the lumen. The implications for the
the four types are especially manifest at the time of translocation and ER-b
lation, when the protein has to be passed through the ER membrane in a di
pendent on the type. Type V proteins are not embedded in the lipid bilayer
rather attached to a lipid molecule that is itself anchored in the bilayer. Typ
membrane proteins have sequences crossing the lipid bilayer and are also c
linked to a lipid molecule that is anchored in the bilayer.

https://en.wikipedia.org/wiki/Transmembrane_protein

Related Glossary Terms

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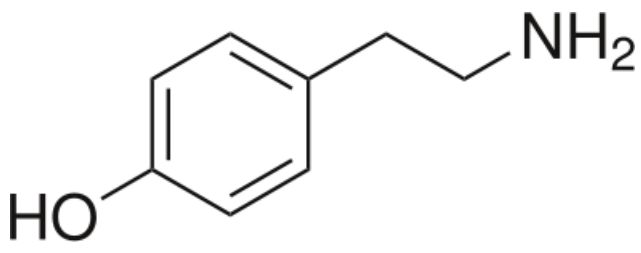
Tyramine

Tyramine (4-hydroxyphenethylamine; para-tyramine, mydrial or uteramin) rally occurring monoamine compound and trace amine derived from the am tyrosine. Tyramine acts as a catecholamine releasing agent. Notably, it is una cross the blood-brain barrier, resulting in only non-psychoactive peripheral pathomimetic effects. A hypertensive crisis can result, however, from ingesti tyramine-rich foods in conjunction with monoamine oxidase inhibitors (MA



https://en.wikipedia.org/wiki/Tyramine

Related Glossary Terms

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Tyrosine

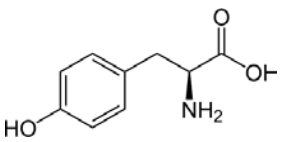
Tyrosine (Tyr or Y) or 4-hydroxyphenylalanine is one of the 22 amino acids that are used by cells to synthesize proteins. It is a non-essential amino acid with a polar side group. Its codons are UAC and UAU. The word "tyrosine" is from the Greek tyros, meaning cheese, as it was first discovered in 1846 by German chemist Justus von Liebig in the protein casein from cheese. It is called tyrosyl when referred to as a functional group or side chain. Tyrosine is a hydrophobic amino acid.

Aside from being a proteinogenic amino acid, tyrosine has a special role by virtue of the phenol functionality. It occurs in proteins that are part of signal transduction processes. It functions as a receiver of phosphate groups that are transferred by way of protein kinases (so-called receptor tyrosine kinases). Phosphorylation of the hydroxyl group changes the activity of the target protein.

A tyrosine residue also plays an important role in photosynthesis. In chloroplasts (photosystem II), it acts as an electron donor in the reduction of oxidized chlorophyll. In this process, it loses the hydrogen atom of its phenolic OH-group. This radical is subsequently reduced in the photosystem II by the four core manganese clusters.

In dopaminergic cells in the brain, tyrosine is converted to L-DOPA by the enzyme tyrosine hydroxylase (TH). TH is the rate-limiting enzyme involved in the synthesis of the neurotransmitter dopamine. Dopamine can then be converted into catecholamines, such as norepinephrine (noradrenaline) and epinephrine (adrenaline).

The thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) in the colloid of the thyroid also are derived from tyrosine.



https://en.wikipedia.org/wiki/Tyrosine

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Tyrosine Hydroxylase

Tyrosine hydroxylase or tyrosine 3-monooxygenase is the enzyme responsi
lyzing the conversion of the amino acid L-tyrosine to L-3,4-dihydroxypheny
(L-DOPA). It does so using molecular oxygen (O_2), as well as iron (Fe^{++}) an
drobiopterin as cofactors. L-DOPA is a precursor for dopamine, which, in t
cursor for the important neurotransmitters norepinephrine (noradrenaline
nephrine (adrenaline). Tyrosine hydroxylase catalyzes the rate limiting step
thesis of catecholamines. In humans, tyrosine hydroxylase is encoded by th
and the enzyme is present in the central nervous system (CNS), peripheral
neurons and the adrenal medulla. Tyrosine hydroxylase, phenylalanine hyd
and tryptophan hydroxylase together make up the family of aromatic amino
droxylases (AAAHs).

https://en.wikipedia.org/wiki/Tyrosine_hydroxylase

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Chapter 2 - Structure & Function: Amino Acids

Tyrosine Kinase

A tyrosine (protein) kinase is an enzyme that can transfer a phosphate group from ATP to a protein in a cell. It functions as an "on" or "off" switch in many cellular functions. Tyrosine kinases are a subclass of protein kinase.

The phosphate group is attached to the amino acid tyrosine on the protein. Tyrosine kinases are a subgroup of the larger class of protein kinases that attach phosphate groups to other amino acids (serine and threonine). Phosphorylation of proteins by kinases is an important mechanism in communicating signals within a cell (signal transduction) and regulating cellular activity, such as cell division.

Protein kinases can become mutated, stuck in the "on" position, and cause unregulated growth of the cell, which is a necessary step for the development of cancer. Therefore, kinase inhibitors, such as imatinib, are often effective cancer treatments.

Most tyrosine kinases have an associated protein tyrosine phosphatase, which removes the phosphate group.

Phosphorylation at tyrosine residues controls a wide range of properties in proteins such as enzyme activity, subcellular localization, and interaction between molecules. Furthermore, tyrosine kinases function in many signal transduction cascades wherein extracellular signals are transmitted through the cell membrane to the cytoplasm and often to the nucleus, where gene expression may be modified. Finally mutations can cause some tyrosine kinases to become constitutively active, a nonstop functional state that may contribute to initiation or progression of cancer.

Tyrosine kinases function in a variety of processes, pathways, and actions, and are responsible for key events in the body. The receptor tyrosine kinases function in transmembrane signaling, whereas tyrosine kinases within the cell function in signal transduction to the nucleus. Tyrosine kinase activity in the nucleus involves cell-cycle control and properties of transcription factors. In this way, in fact, tyrosine kinase activity is involved in mitogenesis, or the induction of mitosis in a cell. Proteins in the cytosol and proteins in the nucleus are phosphorylated at tyrosine residues during this process.

Cellular growth and reproduction may rely to some degree on tyrosine kinase. Tyrosine kinase function has been observed in the nuclear matrix, which comprises not the chromatin but rather the nuclear envelope and a “fibrous web” that serves to physically stabilize DNA. To be specific, Lyn, a type of kinase in the Src family that was identified in the nuclear matrix, appears to control the cell cycle. Src family tyrosine kinases are closely related but demonstrate a wide variety of functionality. Roles or expressions of Src family tyrosine kinases vary significantly according to cell type, as well as during cell growth and differentiation.

https://en.wikipedia.org/wiki/Tyrosine_kinase

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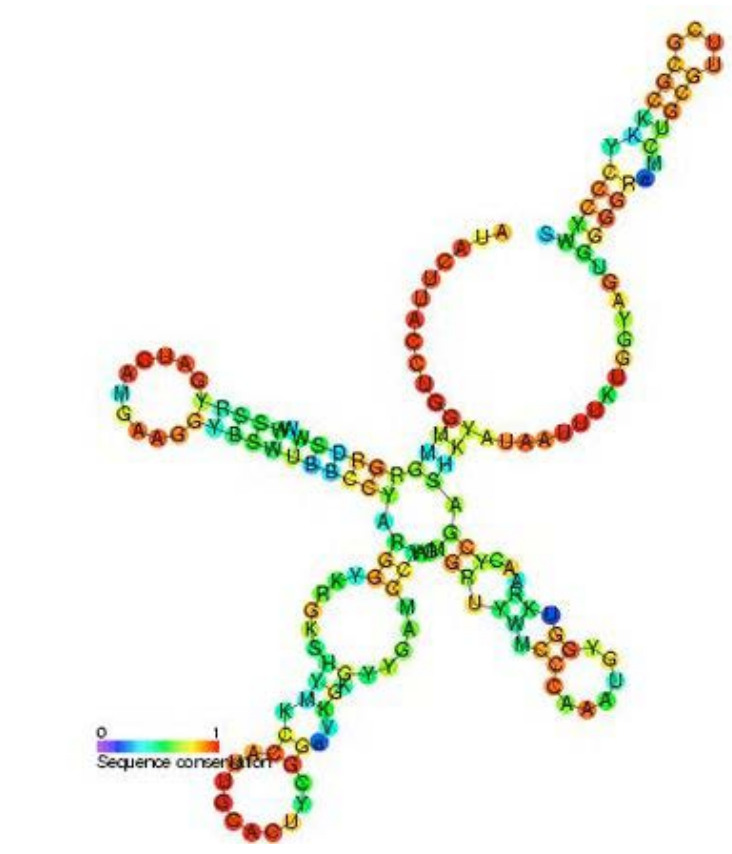
U1

U1 spliceosomal RNA is the small nuclear RNA (snRNA) component of U1 snRNP (small nuclear ribonucleoprotein), an RNA-protein complex that combines with other snRNPs, unmodified pre-mRNA, and various other proteins to assemble a spliceosome, a large RNA-protein molecular complex upon which splicing of pre-mRNA occurs. Splicing, or the removal of introns, is a major aspect of post-transcriptional modification, and takes place only in the nucleus of eukaryotes.

In humans, the U1 spliceosomal RNA is 164 bases long, forms four stem-loops, and possesses a 5'-trimethylguanosine five-prime cap. Bases 3 to 10 are a conserved sequence that base-pairs with the 5' splice site of introns during RNA splicing, and bases 126 to 133 form the Sm site, around which the Sm ring is assembled. Stem-loop I binds to the U1-70K protein, stem-loop II binds to the U1 A protein, stem-loops III and IV bind to the core RNP domain, a heteroheptameric Sm ring consisting of SmB/B', SmD1/2/3, SmE, SmF, and SmG. U1 C interacts primarily through protein-protein interactions.

Experimentation has demonstrated that the binding of U1 snRNA to the 5'-splice site is required, but not sufficient, to begin spliceosome assembly.



https://en.wikipedia.org/wiki/U1_spliceosomal_RNA

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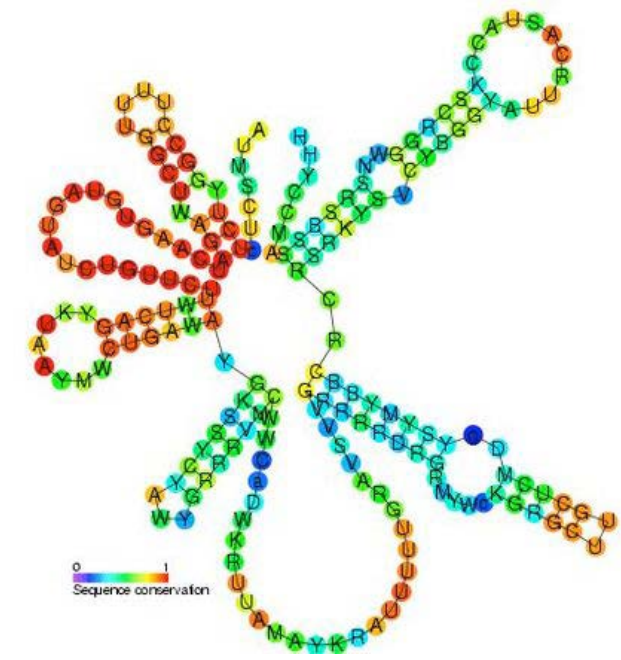
U2

U2 spliceosomal RNA is a small nuclear RNA (snRNA) component of the spliceosome (involved in pre-mRNA splicing). Complementary binding between U2 snRNA (in an area lying towards the 5' end but 3' to hairpin I) and the branchpoint sequence (BPS) of the intron results in the bulging out of an unpaired adenosine, on the BPS, which initiates a nucleophilic attack at the intronic 5' splice site, thus starting the first of two transesterification reactions that mediate splicing.

After recognition of the pre-mRNA 5’ splice site by U1 snRNA, U1 snRNA binds to this point. As soon as this bond forms, U2 snRNA binds to the branch point site, which forms a bulge at the branch point binding sequence. In addition, U6 snRNA associates with U2 snRNA and the 5’ splice site through base pairing interaction. The association of U2 snRNP with the pre-mRNA branch site plays a fundamental role during splicing assembly since it directly participates in chemical catalysis. Moreover, U2 snRNP undergoes several rearrangements along with the recognition of the branch point adenosine and formation of the base pair interaction between U2 snRNA and consensus sequence within the intron.

In humans, the U2 spliceosomal RNA is 187 base pairs long, forms five stem-loops, and possesses a 5'-trimethylguanosine five-prime cap. It is able to base-pair extensively with U6 spliceosomal RNA during the splicing process.



https://en.wikipedia.org/wiki/U2_spliceosomal_RNA

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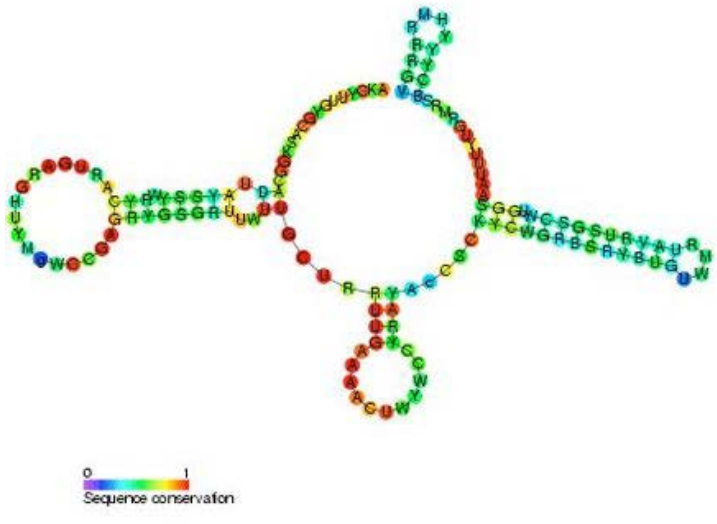
U4

The U4 small nuclear Ribo-Nucleic Acid (U4 snRNA) is a non-coding RNA component of the major or U2-dependent spliceosome – a eukaryotic molecular machine involved in the splicing of pre-messenger RNA (pre-mRNA). It forms a duplex with U6, and with each splicing round, it is displaced from the U6 snRNA (and the spliceosome) in an ATP-dependent manner, allowing U6 to re-fold and create the active site for splicing catalysis.

The U4 snRNA has been shown to exist in a number of different formats including: bound to proteins as a small nuclear Ribo-Nuclear Protein snRNP, involved with the U6 snRNA in the di-snRNP, as well as involved with both the U6 snRNA and the U5 snRNA in the tri-snRNP. The different formats have been proposed to coincide with different temporal events in the activity of the penta-snRNP, or as intermediates in the step-wise model of spliceosome assembly and activity.

The U4 snRNA (and its likely analog snR14 in yeast) has been shown not to participate directly in the specific catalytic activities of the splicing reaction, and is proposed instead to act as a regulator of the U6 snRNA. The U4 snRNA inhibits spliceosome activity during assembly by complementary base pairing between the U6 snRNA in two highly conserved stem regions. It is suggested that this base-pairing interaction prevents the U6 snRNA from assembling with the U2 snRNA into the conformation required for catalytic activity. If the U4 snRNA is degraded and thereby removed from the spliceosome, splicing is effectively halted. The U4 and U6 snRNAs are demonstratively required for splicing *in vitro*.



https://en.wikipedia.org/wiki/U4_spliceosomal_RNA

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Chapter 7 - Information Processing: RNA Processing
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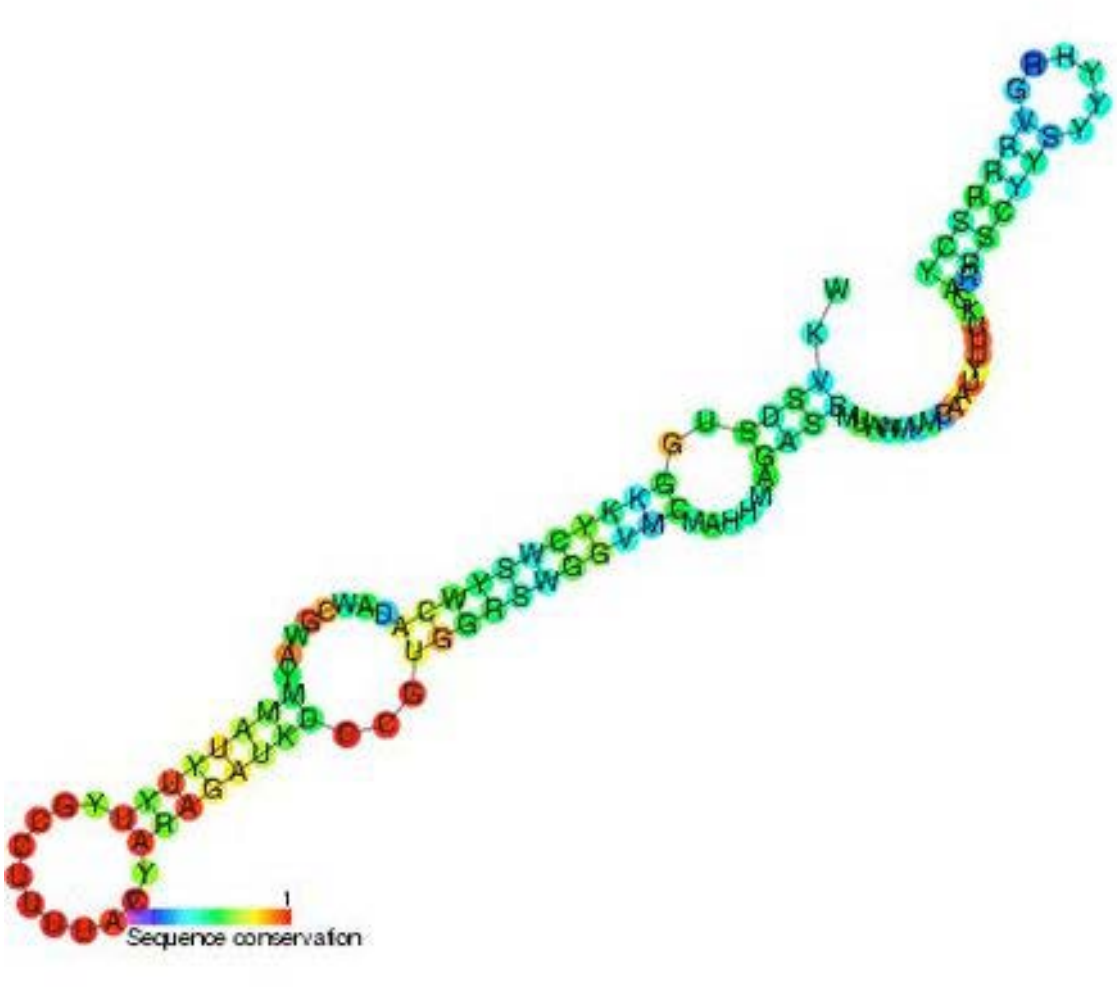
Chapter 9 - Point by Point: Information Processing
Chapter 9 - Point by Point: Information Processing

U5

U5 RNA is a non-coding RNA that is a component of both types of known spliceosome. The precise function of this molecule is unknown, though it is known that the 5' loop is required for splice site selection and p220 binding, and that both the 3' stem-loop and the Sm site are important for Sm protein binding and cap methylation.



https://en.wikipedia.org/wiki/U5_spliceosomal_RNA

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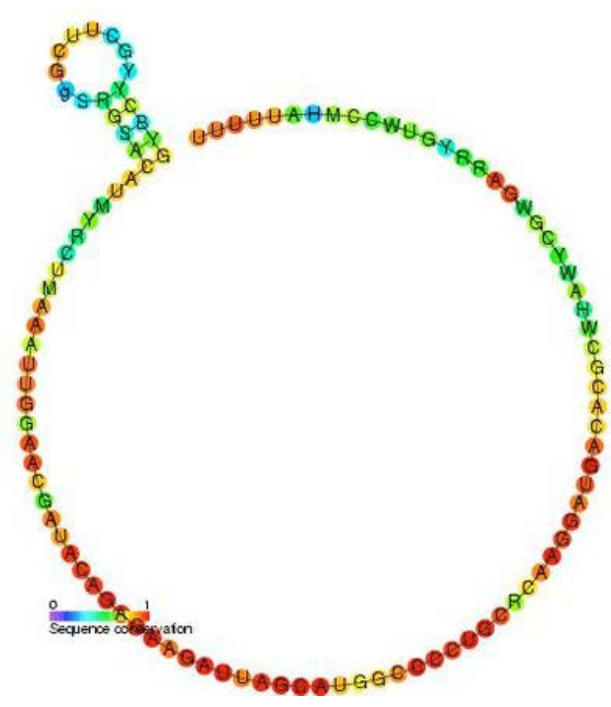
U6

U6 snRNA is the non-coding small nuclear RNA (snRNA) component of U6 snRNP (small nuclear ribonucleoprotein), an RNA-protein complex that combines with other snRNPs, unmodified pre-mRNA, and various other proteins to assemble a spliceosome, a large RNA-protein molecular complex upon which splicing of pre-mRNA occurs. Splicing, or the removal of introns, is a major aspect of post-transcriptional modification, and takes place only in the nucleus of eukaryotes.

The RNA sequence of U6 is the most highly conserved across species of all five of the snRNAs involved in the spliceosome, suggesting that the function of the U6 snRNA has remained both crucial and unchanged through evolution.

Base-pair specificity of the U6 snRNA allows the U6 snRNP to bind tightly to the U4 snRNA and loosely to the U5 snRNA of a triple-snRNP during the initial phase of the splicing reaction. As the reaction progresses, the U6 snRNA is unzipped from U4 and binds to the U2 snRNA. At each stage of this reaction, the U6 snRNA secondary structure undergoes extensive conformational changes.

The association of U6 snRNA with the 5' end of the intron via base-pairing during the splicing reaction occurs prior to the formation of the lariat (or lasso-shaped) intermediate, and is required for the splicing process to proceed. The association of U6 snRNP with U2 snRNP via base-pairing forms the U6-U2 complex, a structure that comprises the active site of the spliceosome.



https://en.wikipedia.org/wiki/U6_spliceosomal_RNA

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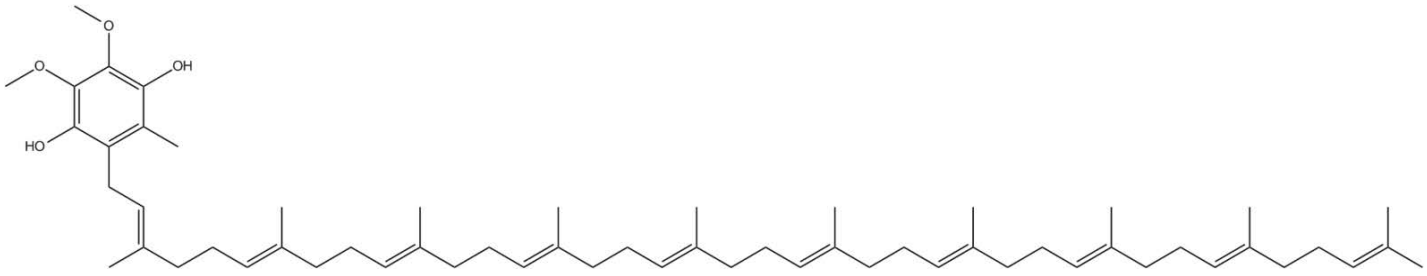
Ubiquinol

Ubiquinol is an electron-rich (reduced) form of coenzyme Q_{10}. The natural ubiquinol form of coenzyme Q_{10} is 2,3-dimethoxy-5-methyl-6-poly prenyl-1,4-benzoquinol, where the polyprenylated side-chain is 9-10 units long in mammals. Coenzyme Q_{10} (CoQ_{10}) exists in three redox states, fully oxidized (ubiquinone), partially reduced (semiquinone or ubisemiquinone), and fully reduced (ubiquinol). The redox functions of ubiquinol in cellular energy production and antioxidant protection are based on the ability to exchange two electrons in a redox cycle between ubiquinol (reduced) and the ubiquinone (oxidized) form.



https://en.wikipedia.org/wiki/Ubiquinol

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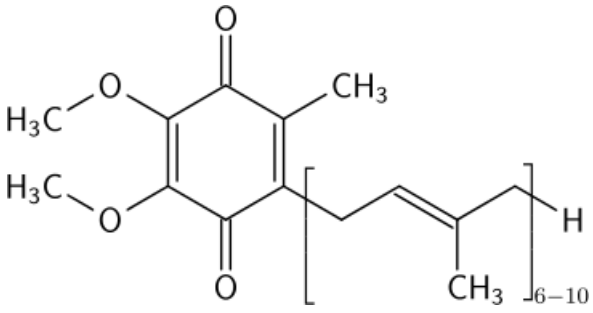
Ubiquinone

Coenzyme Q_{10}, also known as ubiquinone, ubidecarenone, coenzyme Q, and abbreviated at times to CoQ10 /ˌCoQ, or Q_{10} is a coenzyme that is ubiquitous in the bodies of most animals. It is a 1,4-benzoquinone, where Q refers to the quinone chemical group and 10 refers to the number of isoprenyl chemical subunits in its tail.

This fat-soluble substance, which resembles a vitamin, is present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, which generates energy in the form of ATP. Ninety-five percent of the human body's energy is generated this way. Therefore, those organs with the highest energy requirements—such as the heart, liver, and kidney—have the highest CoQ_{10} concentrations.

There are three redox states of CoQ_{10}: fully oxidized (ubiquinone), semiquinone (ubisemiquinone), and fully reduced (ubiquinol). The capacity of this molecule to act as a 2 electron carrier (moving between the quinone and quinol form) and 1 electron carrier (moving between the semiquinone and one of these other forms) is central to its role in the electron transport chain, and as radical-scavenging antioxidant.

https://en.wikipedia.org/wiki/Coenzyme_Q10



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Ubiquitin

Ubiquitin is a small (8.5 kDa) regulatory protein that has been found in almost all tissues (ubiquitously) of eukaryotic organisms. Ubiquitination can affect proteins in many ways: it can signal for their degradation via the proteasome, alter their cellular location, affect their activity, and promote or prevent protein interactions.

The addition of ubiquitin to a substrate protein is called ubiquitination or ubiquitylation. Ubiquitination can affect proteins in many ways: it can signal for their degradation via the proteasome, alter their cellular location, affect their activity, and promote or prevent protein interactions. Ubiquitination is carried out in three main steps: activation, conjugation, and ligation, performed by ubiquitin-activating enzymes (E_1s), ubiquitin-conjugating enzymes (E_2s), and ubiquitin ligases (E_3s), respectively. The result of this sequential cascade binds ubiquitin to lysine residues on the protein substrate via an isopeptide bond, cysteine residues through a thioester bond, serine and threonine residues through an ester bond, or the amino group of the protein's N-terminus via a peptide bond.

The protein modifications can be either a single ubiquitin protein (monoubiquitination) or a chain of ubiquitin (polyubiquitination). The ubiquitination bonds are always formed with one of the seven lysine residues as well as the very N-terminal methionine from the ubiquitin molecule. These 'linking' residues are represented by a "K" or "M" (which is the one-letter amino acid notation of lysine and methionine, respectively) and a number, referring to its position in the ubiquitin molecule. First, a ubiquitin molecule is bonded by its C-terminus to a specific lysine residue on the target protein. Poly-ubiquitination occurs when the C-terminus of another ubiquitin, will be linked to one of the seven lysine residues or the first methionine on the previously added ubiquitin molecule itself (for example on K48, K29 or M1), forming a chain. This process repeats several times, leading to the addition of several ubiquitins. Only poly-ubiquitination on defined lysines, mostly on K48 and K29, is related to degradation by the proteasome (referred to as the "molecular kiss of death"), while other polyubiquitinations (e.g. on K63, K11, K6 and M1) and monoubiquitinations may regulate processes such as endocytic trafficking, inflammation, translation and DNA repair.

https://en.wikipedia.org/wiki/Ubiquitin

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Ubiquitin Ligase

Ubiquitin ligase is a protein that recruits an E_2 ubiquitin-conjugating enzyme that
been loaded with ubiquitin, recognizes a protein substrate, and assists or directly c
lyzes the transfer of ubiquitin from the E_2 to the protein substrate. The ubiquitin is
tached to a lysine on the target protein by an isopeptide bond. E_3 ligases interact w
both the target protein and the E_2 enzyme, and so impart substrate specificity to th
E_2. Commonly, E_3 s polyubiquitinate their substrate with Lys48-linked chains of ub
uitin, targeting the substrate for destruction by the proteasome. However, many ot
types of linkages are possible and alter a protein's activity, interactions, or localizat
Ubiquitination by E_3 ligases regulates diverse areas such as cell trafficking, DNA re
pair, and signaling and is of profound importance in cell biology. E_3 ligases are also
players in cell cycle control, mediating the degradation of cyclins, as well as cyclin
pendent kinase inhibitor proteins. The human genome encodes over 600 putative
ligases, allowing for tremendous diversity in substrates.

https://en.wikipedia.org/wiki/Ubiquitin_ligase

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Ubiquitinate

The term ubiquitinate refers to modifying a protein with the addition of at le
molecule of ubiquitin.

The addition of ubiquitin to a substrate protein is called ubiquitination or ub
tion. Ubiquitination can affect proteins in many ways: it can signal for their d
tion via the proteasome, alter their cellular location, affect their activity, and
or prevent protein interactions. Ubiquitination is carried out in three main s
vation, conjugation, and ligation, performed by ubiquitin-activating enzymes
ubiquitin-conjugating enzymes (E_2s), and ubiquitin ligases (E_3s), respectivel
sult of this sequential cascade binds ubiquitin to lysine residues on the prote
strate via an isopeptide bond, cysteine residues through a thioester bond, ser
threonine residues through an ester bond, or the amino group of the protein
terminus via a peptide bond.

https://en.wikipedia.org/wiki/Ubiquitin

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Ubiquitinated

The term ubiquitinated refers to a protein that has been modified with the addi
at least one molecule of ubiquitin.

The addition of ubiquitin to a substrate protein is called ubiquitination or ubiqu
tion. Ubiquitination can affect proteins in many ways: it can signal for their deg
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terminus via a peptide bond.

https://en.wikipedia.org/wiki/Ubiquitin

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Ubiquitination

The addition of ubiquitin to a substrate protein is called ubiquitination or u
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strate via an isopeptide bond, cysteine residues through a thioester bond, s
threonine residues through an ester bond, or the amino group of the protei
terminus via a peptide bond.

https://en.wikipedia.org/wiki/Ubiquitin

Related Glossary Terms

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Ubisemiquinone

Semiquinone (or ubisemiquinone) is a free radical resulting from the remov
hydrogen atom with its electron during the process of dehydrogenation of a
none to quinone or alternatively the addition of a single H atom to a quinon
highly unstable.

It is the first of two stages in reducing the supplementary form of CoQ_{10} ubi
the active form ubiquinol.

https://en.wikipedia.org/wiki/Semiquinone

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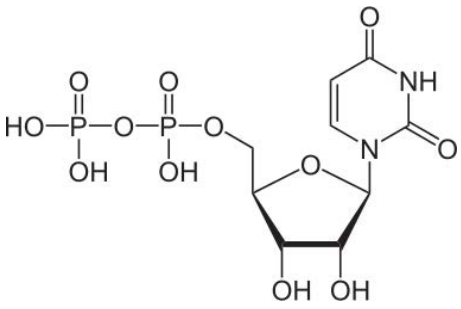
UDP

Uridine diphosphate, abbreviated UDP, is a nucleoside diphosphate. It is an ester of pyrophosphoric acid with the nucleoside uridine. UDP consists of the pyrophosphate group, the pentose sugar ribose, and the nucleobase uracil.

UDP is an important factor in glycogenesis. Before glucose can be stored as glycogen in the liver and muscles, the enzyme UDP-glucose pyrophosphorylase forms a UDP-glucose unit by combining glucose 1-phosphate with uridine triphosphate, cleaving a pyrophosphate ion in the process. Then, the enzyme glycogen synthase combines UDP-glucose units to form a glycogen chain. The UDP molecule is cleaved from the glucose ring during this process and can be reused by UDP-glucose pyrophosphorylase.



https://en.wikipedia.org/wiki/Uridine_diphosphate

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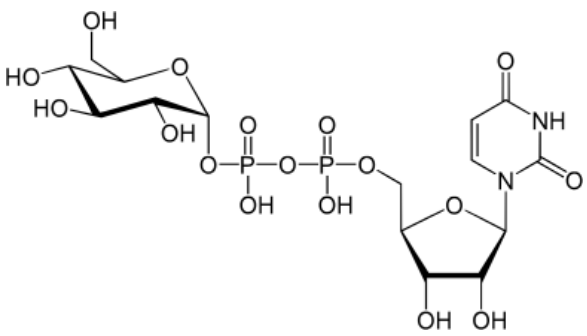
UDP-glucose

Uridine diphosphate glucose is a nucleotide sugar. It is involved in glycosyltransferase reactions in metabolism.

It is used in nucleotide sugars metabolism as an activated form of glucose as a substrate for enzymes called glucosyltransferases.

It is a precursor of glycogen and can be converted into UDP-galactose and UDP-glucuronic acid, which can then be used as substrates by the enzymes that make polysaccharides containing galactose and glucuronic acid.

UDP-glucose can also be used as a precursor of sucrose lipopolysaccharides, and glycosphingolipids.



https://en.wikipedia.org/wiki/Uridine_diphosphate_glucose

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UDP-glucose Pyrophosphorylase

UTP—glucose-1-phosphate uridylyltransferase (UDP-glucose pyrophosphorylase) is an enzyme found in yeast, plants, and mammals as it is a key player in carbohydrate metabolism. It has been studied significantly in plants as sugar metabolism and production is seen as important for understanding growth from an agricultural standpoint. Recently, human UDP-glucose pyrophosphorylase has been studied and crystallized, revealing a different type of regulation than other organisms previously studied. Its significance is derived from the many uses of UDP-Glucose including galactose usage, glycogen synthesis, glycoprotein synthesis, and glycolipid synthesis. In many species, UDP-glucose pyrophosphorylase occupies a central role in carbohydrate metabolism. Its product, UDP-glucose, is involved in multiple pathways and is a precursor for other sugar nucleotides.

In humans, galactosemia is a disorder that affects the development of newborns and children as they cannot metabolize the sugar galactose properly. It is speculated that overexpression of UDP-Glucose pyrophosphorylase may relieve symptoms in humans with galactosemia. The enzyme has also been found to be required for the biosynthesis of capsular polysaccharide, an important virulence factor of streptococcus pneumoniae, a bacterial cause of pneumonia, bronchitis, and other breathing issues.

https://en.wikipedia.org/wiki/UTP%E2%80%94glucose-1-phosphate_uridylyltransferase

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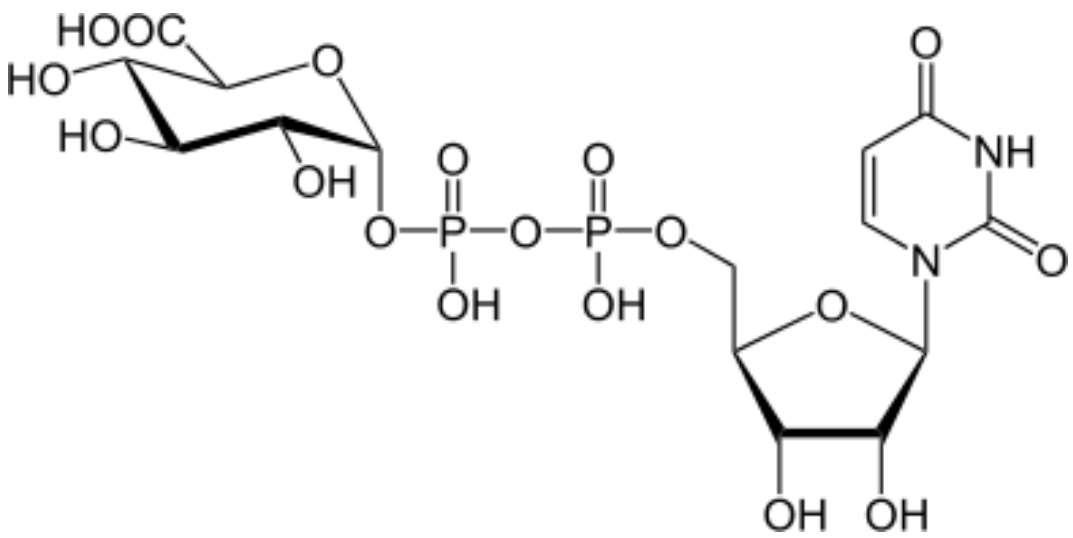
UDP-glucuronic Acid

UDP glucuronic acid is a sugar used in the creation of polysaccharides and is an
mediate in the biosynthesis of ascorbic acid (except in primates and guinea pigs).

It is made from UDP-glucose by UDP-glucose 6-dehydrogenase using NAD^+ as a
tor. It is the source of the glucuronosyl group in glucuronosyltransferase reaction



https://en.wikipedia.org/wiki/Uridine_diphosphate_glucuronic_acid

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UDP-glucuronyltransferase

Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronyltransferase, UGT) is a cytosolic glycosyltransferase that catalyzes the transfer of the glucuronic acid component of UDP-glucuronic acid to a small hydrophobic molecule.

Glucuronosyltransferases are responsible for the process of glucuronidation, a major part of phase II metabolism. Arguably the most important of the Phase II (conjugative) enzymes, UGTs have been the subject of increasing scientific inquiry since the mid-to-late 1990s.

The reaction catalyzed by the UGT enzyme involves the addition of a glucuronic acid moiety to xenobiotics and is the most important pathway for the human body's elimination of the most frequently prescribed drugs. It is also the major pathway for foreign chemical (dietary, environmental, pharmaceutical) removal for most drugs, dietary substances, toxins and endogenous substances. UGT is present in humans, other animals, plants, and bacteria. Famously, UGT enzymes are not present in the genus Felis, and this accounts for a number of unusual toxicities in the cat family.

The glucuronidation reaction consists of the transfer of the glucuronosyl group from uridine 5'-diphospho-glucuronic acid (UDPGA) to substrate molecules that contain oxygen, nitrogen, sulfur or carboxyl functional groups. The resulting glucuronide is more polar (e.g. hydrophilic) and more easily excreted than the substrate molecule. The product solubility in blood is increased allowing it to be eliminated from the body by the kidneys.

https://en.wikipedia.org/wiki/Glucuronosyltransferase

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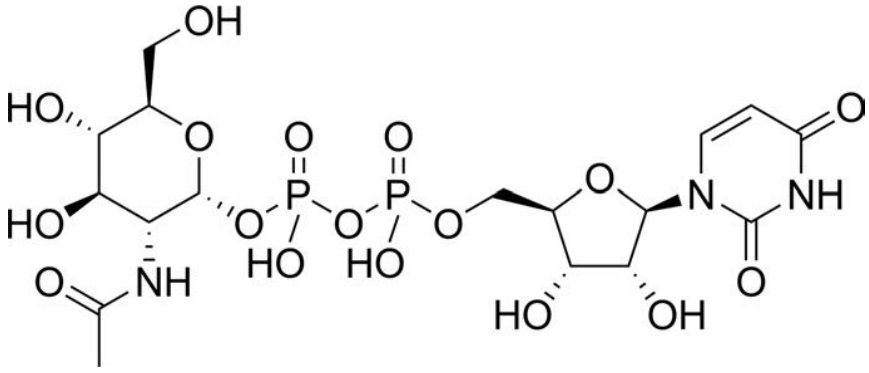
UDP-N-acetyl-glucosamine

Uridine Diphosphate N-acetylglucosamine or UDP-GlcNAc is a nucleotide sugar and a coenzyme in metabolism. It is used by glycosyltransferases to transfer N-acetylglucosamine residues to substrates. D-Glucosamine is made naturally in the form of glucosamine-6-phosphate, and is the biochemical precursor of all nitrogen-containing sugars. To be specific, glucosamine-6-phosphate is synthesized from fructose 6-phosphate and glutamine as the first step of the hexosamine biosynthesis pathway. UDP-GlcNAc is the end-product of this pathway. It is then used for making glycosaminoglycans, proteoglycans, and glycolipids.

UDP-GlcNAc is extensively involved in intracellular signaling as a substrate for O-linked N-acetylglucosamine transferases (OGTs) in a wide range of species. It is also involved in nuclear pore formation and nuclear signaling. OGTs and OG-ases play an important role in the structure of the cytoskeleton. In mammals, there is enrichment of OGT transcripts in the pancreas β-cells, and UDP-GlcNAc is thought to be part of the glucose sensing mechanism. There is also evidence that it plays a part in insulin sensitivity in other cells. In plants, it is involved in the control of gibberellin production.



https://en.wikipedia.org/wiki/Uridine_diphosphate_N-acetylglucosamine

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UDP-N-acetyl-glucosamine-1-phosphate

UDP-N-acetyl-glucosamine-1-phosphate is an intermediate in the synthesis
tidoglycan cell wall of prokaryotic cells.

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UDP-N-acetylglucosamine

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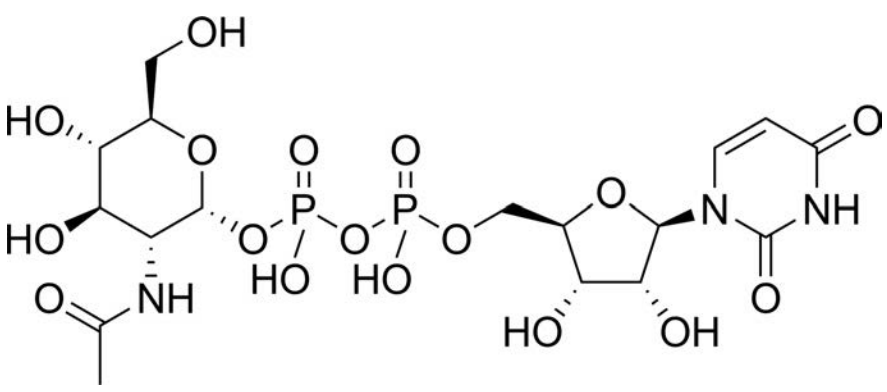

https://en.wikipedia.org/wiki/Uridine_diphosphate_N-acetylglucosamine

UDP-N-acetylmuramic acid

The peptidoglycan layer in the bacterial cell wall is a crystal lattice structure formed from linear chains of two alternating amino sugars, namely N-acetylglucosamine (GlcNAc or NAG) and N-acetylmuramic acid (MurNAc or NAM). The alternating sugars are connected by a β-(1,4)-glycosidic bond. Each MurNAc is attached to a short (4- to 5-residue) amino acid chain, containing L-alanine, D-glutamic acid, meso-diaminopimelic acid, and D-alanine in the case of *Escherichia coli* (a Gram-negative bacterium) or L-alanine, D-glutamine, L-lysine, and D-alanine with a 5-glycine interbridge between tetrapeptides in the case of Staphylococcus aureus (a Gram-positive bacterium).
Cross-linking between amino acids in different linear amino sugar chains occurs with the help of the enzyme DD-transpeptidase and results in a 3-dimensional structure that is strong and rigid. The specific amino acid sequence and molecular structure vary with the bacterial species.

Uridine-Diphosphate-N-acetylmuramic acid (UDP-MurNAc) is produced in the fifth step of the peptidoglycan synthesis pathway from UDP-GlcNAc by the addition of a lactyl group to the glucosamine. The reaction produces an enol derivative which can be reduced to a lactyl moiety by NADPH in subsequent steps.

https://en.wikipedia.org/wiki/Peptidoglycan

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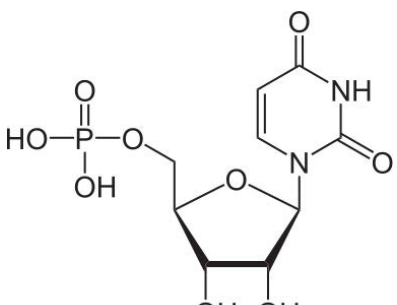
UMP

Uridine monophosphate, also known as 5'-uridylic acid and abbreviated UMP, is a nucleotide that is used as a monomer in RNA. It is an ester of phosphoric acid with the nucleoside uridine. UMP consists of the phosphate group, the pentose sugar ribose, and the nucleobase uracil. Hence, it is a ribonucleoside monophosphate. Another common shorthand for the molecule is uridylate - the deprotonated form of the molecule, which is predominant in aqueous solution.

Uridine monophosphate is formed from Orotidine 5'-monophosphate (orotidylic acid) in a decarboxylation reaction catalyzed by the enzyme orotidylate decarboxylase. Uncatalyzed, the decarboxylation reaction is extremely slow (estimated to occur on average one time per 78 million years). Adequately catalyzed, the reaction takes place once per second, an increase of 1017-fold.

In humans, the orotidylate decarboxylase function is carried out by the protein UMP synthase. Defective UMP synthase can result in orotic aciduria, a metabolic disorder.



https://en.wikipedia.org/wiki/Uridine_monophosphate

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UMP Kinase

UMP kinase is an enzyme that catalyzes the chemical reaction

ATP + UMP ↔ ADP + UDP

This enzyme belongs to the family of transferases, specifically those transfe phosphorus-containing groups (phosphotransferases) with a phosphate gro tor. The systematic name of this enzyme class is ATP:UMP phosphotransfe names in common use include uridylate kinase, UMPK, uridine monophosp nase, PyrH, UMP-kinase, and SmbA. This enzyme participates in pyrimidin lism.

https://en.wikipedia.org/wiki/UMP_kinase

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Uncompetitive Inhibition

Uncompetitive inhibition, also known as anti-competitive inhibition, takes
an enzyme inhibitor binds only to the complex formed between the enzyme
substrate (the ES complex). This reduction in the effective concentration of
plex increases the enzyme's apparent affinity for the substrate through Le C
principle (K_m is lowered) and decreases the maximum enzyme activity (V_{ma}
takes longer for the substrate or product to leave the active site. Uncompeti
tion works best when substrate concentration is high. An uncompetitive inh
not resemble the substrate of the reaction it is inhibiting.

https://en.wikipedia.org/wiki/Uncompetitive_inhibitor

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Uncoupling

Uncoupling refers to the segregation of the electron transport chain from the oxidati
phosphorylation pathways by which ATP is synthesized. Innately, the electron trans-
port chain and oxidative phosphorylation are coupled by a proton gradient across the
inner mitochondrial membrane. The efflux of protons from the mitochondrial matrix
creates an electrochemical gradient (proton gradient). This gradient is used to make
ATP via oxidative phosphorylation.

The uncoupling protein, thermogenin—present in the inner mitochondrial membran
of brown adipose tissue—provides for an alternative flow of protons back to the inner
mitochondrial matrix. So too does the chemical 2,4 dinitrophenol (2,4 DNP). Such a
ternative flow results in thermogenesis rather than ATP production.

https://en.wikipedia.org/wiki/Electron_transport_chain#Coupling_with_oxidative
phosphorylation

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Unimolecular

Molecularity is the number of molecules that come together to react in an e
reaction, and is equal to the sum of stoicheometric coefficients of reactants
molecular reaction, a single molecule forms different molecule(s). The term
lar describes one type of molecularity of an elementary reaction.

https://en.wikipedia.org/wiki/Molecularity

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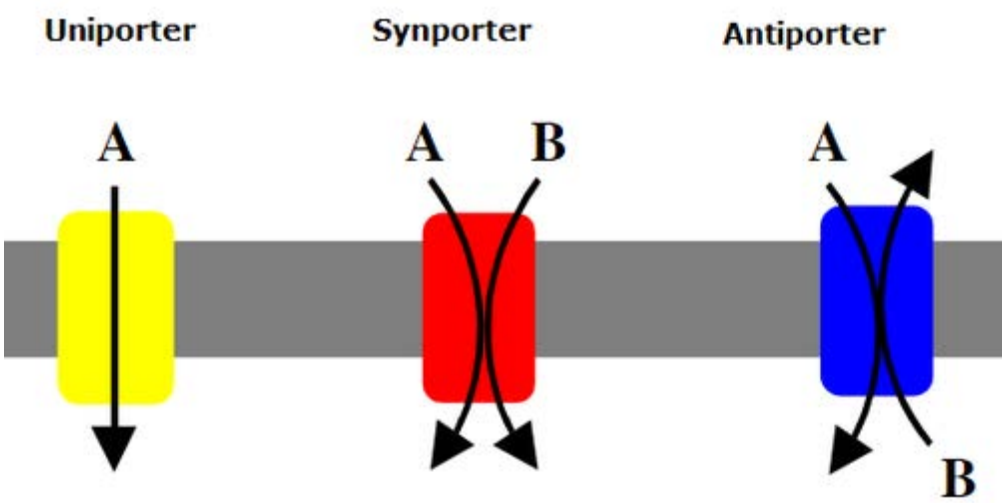
Uniport

A uniporter (uniport) is an integral membrane protein that is involved in facilitated diffusion. They can be either ion channels or carrier proteins.

Uniporter carrier proteins work by binding to one molecule of substrate at a time and transporting it with its concentration gradient. Uniporter channels open in response to a stimulus and allow the free flow of specific molecules. Both kinds of uniporters rely on passive transport, as they do not directly require cellular energy to function.



https://en.wikipedia.org/wiki/Uniporter

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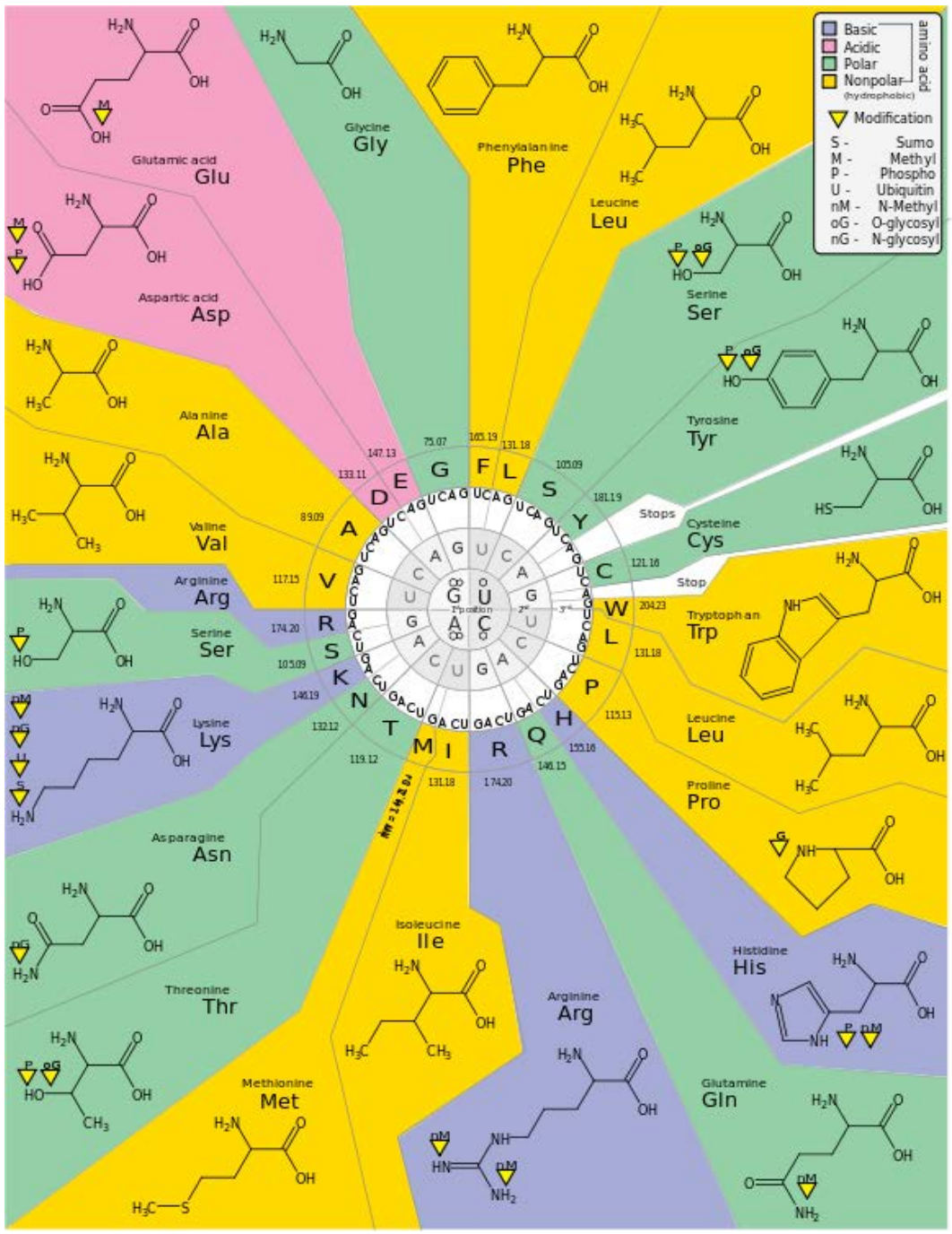
Universal Genetic Code

The universal genetic code is the set of rules by which information encoded within genetic material (DNA or mRNA sequences) can be both translated into proteins by living cells or transcribed into non-coding RNAs that serve as regulatory tools in gene regulation. Biological decoding is accomplished by the ribosome, which links amino acids in an order specified by mRNA, using transfer RNA (tRNA) molecules to carry amino acids and to read the mRNA three nucleotides (one codon) at a time. The genetic code is highly similar among all organisms and can be expressed in a simple table with 64 entries.



https://en.wikipedia.org/wiki/Genetic_code

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Unsaturated

An unsaturated compound is a chemical compound that contains carbon-carbon double bonds or triple bonds, such as those found in alkenes or alkynes, respectively. Unsaturated compounds need not consist only of a carbon atom chain. They can form straight chain, branched chain, or ring arrangements. They can have functional groups, as well.

In a chain of carbons, such as a fatty acid, a double or triple bond will cause a kink in the chain. These kinks have macro-structural implications. Unsaturated fats tend to be liquid at room temperature, rather than solid, as the kinks in the chain prevent the molecules from packing closely together to form a solid. These fats are called oils and are present in fish and plants.

The double bond between two carbons prevents rotation of the atoms about the bond, locking them into specific structural formations. When attached atoms occupy similar positions on each carbon, they are referred to as "*cis*", and when they are on opposite sides, they are called "*trans*".

https://en.wikipedia.org/wiki/Saturated_and_unsaturated_compounds

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Unsaturated Fat

An unsaturated fat is a fat in which there is at least one double bond within
chain within it. A fatty acid chain is monounsaturated if it contains one dou
and polyunsaturated if it contains more than one double bond.
Where double bonds are formed, hydrogen atoms are subtracted from the c
chain. In cellular metabolism, unsaturated fat molecules contain somewhat
than an equivalent amount of saturated fat. The greater the degree of unsat
fatty acid (i.e., the more double bonds in the fatty acid) the more vulnerable
lipid peroxidation. Antioxidants can protect unsaturated fat from lipid perc

https://en.wikipedia.org/wiki/Unsaturated_fat

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Unsaturated Fatty Acid

An unsaturated fatty acid is a fatty acid in which there is at least one double bo within it. A fatty acid chain is monounsaturated if it contains one double bond, polyunsaturated if it contains more than one double bond.

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https://en.wikipedia.org/wiki/Unsaturated_fat

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Upstream Elements

Upstream elements refer to sequence elements of a eukaryotic promoter that are within a few hundred base pairs of the start sequence (also called proximal elements). Elements of a eukaryotic promoter are as follows:

- Core promoter – the minimal portion of the promoter required to properly initiate transcription
  - Includes the transcription start site (TSS) and elements directly upstream
  - A binding site for RNA polymerase
    - RNA polymerase I: transcribes genes encoding ribosomal RNA
    - RNA polymerase II: transcribes genes encoding messenger RNA and certain small nuclear RNAs and microRNA
    - RNA polymerase III: transcribes genes encoding transfer RNAs and other small RNAs
  - General transcription factor binding sites, e.g. TATA box
- Proximal promoter – the proximal sequence upstream of the gene that tends to contain primary regulatory elements
  - Approximately 250 base pairs upstream of the start site
  - Specific transcription factor binding sites
- Distal promoter – the distal sequence upstream of the gene that may contain additional regulatory elements, often with a weaker influence than the proximal promoter
  - Anything further upstream (but not an enhancer or other regulatory region whose influence is positional/orientation independent)
  - Specific transcription factor binding sites

https://en.wikipedia.org/wiki/Promoter_(genetics)

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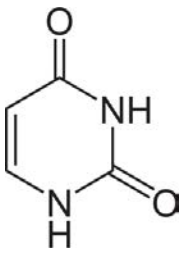
Uracil

Uracil is one of the four nucleobases in the nucleic acid of RNA. In RNA, uracil binds to adenine via two hydrogen bonds. In DNA, the uracil nucleobase is replaced by thymine. Uracil is a demethylated form of thymine. Uracil is a common and naturally occurring pyrimidine derivative. It is a planar, unsaturated compound that has the ability to absorb light.

In RNA, uracil base-pairs with adenine and replaces thymine during DNA transcription. Methylation of uracil produces thymine. In DNA, the evolutionary substitution of thymine for uracil may have increased DNA stability and improved the efficiency of DNA replication. Uracil pairs with adenine through hydrogen bonding. When base pairing with adenine, uracil acts as both a hydrogen bond acceptor and a hydrogen bond donor. In RNA, uracil binds with a ribose sugar to form the ribonucleoside uridine. When a phosphate attaches to uridine, uridine 5'-monophosphate is produced.

Uracil undergoes amide-imidic acid tautomeric shifts because any nuclear instability the molecule may have from the lack of formal aromaticity is compensated by the cyclic-amidic stability. The amide tautomer is referred to as the lactam structure, while the imidic acid tautomer is referred to as the lactim structure. These tautomeric forms are predominant at pH 7. The lactam structure is the most common form of uracil.



https://en.wikipedia.org/wiki/Uracil

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Uracil Phosphoribosyltransferase

Uracil phosphoribosyltransferase is an enzyme which creates UMP from ur
phosphoribosylpyrophosphate. This protein may use the morpheein model
regulation.

https://en.wikipedia.org/wiki/Uracil_phosphoribosyltransferase

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Uracil-DNA Glycosylase

The human gene encodes one of several uracil-DNA glycosylases. Alternative promoter usage and splicing of this gene leads to two different isoforms: the mitochondrial UNG1 and the nuclear UNG2. One important function of uracil-DNA glycosylases is to prevent mutagenesis by eliminating uracil from DNA molecules by cleaving the N-glycosylic bond and initiating the base-excision repair (BER) pathway. Uracil bases occur from cytosine deamination or misincorporation of dUMP residues. After a mutation occurs, the mutagenic threat of uracil propagates through any subsequent DNA replication steps. Once unzipped, mismatched guanine and uracil pairs are separated, and DNA polymerase inserts complementary bases to form a guanine-cytosine (GC) pair in one daughter strand and an adenine-uracil (AU) pair in the other. Half of all progeny DNA derived from the mutated template inherit a shift from GC to AU at the mutation site. UDG excises uracil in both AU and GU pairs to prevent propagation of the base mismatch to downstream transcription and translation processes. With high efficiency and specificity, this glycosylase repairs more than 10,000 bases damaged daily in the human cell. Human cells express five to six types of DNA glycosylases, all of which share a common mechanism of base eversion and excision as a means of DNA repair.

https://en.wikipedia.org/wiki/Uracil-DNA_glycosylase

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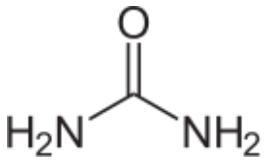
Urea

Urea, or carbamide, is an organic compound with the chemical formula $CO(NH_2)_2$. The molecule has two —NH_2 groups joined by a carbonyl (C=O) functional group.

Urea serves an important role in the metabolism of nitrogen-containing compounds by animals, and is the main nitrogen-containing substance in the urine of mammals. It is a colorless, odorless solid, is highly soluble in water, and is practically non-toxic. Dissolved in water, it is neither acidic nor alkaline. The body uses it in many processes, most notably nitrogen excretion. The liver forms it by combining two ammonia molecules (NH_3) with a carbon dioxide (CO_2) molecule in the urea cycle.

More than 90% of world industrial production of urea is destined for use as a nitrogen-release fertilizer. Urea has the highest nitrogen content of all solid nitrogenous fertilizers in common use. Therefore, it has the lowest transportation costs per unit of nitrogen nutrient. The standard crop-nutrient rating (NPK rating) of urea is 46-0-0

https://en.wikipedia.org/wiki/Urea



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Urea Cycle

The urea cycle (also known as the ornithine cycle) is a cycle of biochemical reactions occurring in many animals that produces urea ($(NH_2)_2CO$) from ammonia (NH_3).

The urea cycle consists of five reactions: two mitochondrial and three cytosolic. The cycle converts two amino groups, one from NH_4^+ and one from Asp, and a carbon atom from HCO_3^-, to the relatively nontoxic excretion product urea at the cost of four "high-energy" phosphate bonds (3 ATP hydrolyzed to 2 ADP and one AMP). Ornithine is the carrier of these carbon and nitrogen atoms.

The overall equation of the urea cycle is:

$NH_3 + CO_2 + \text{Aspartate} + 3\ ATP + 2\ H_2O \rightarrow \text{Urea} + \text{Fumarate} + 2\ ADP + 2\ P_i + AMP + PP_i$

Since fumarate is obtained by removing NH3 from aspartate (by means of reactions 3 and 4), and $PP_i + H_2O \rightarrow 2\ Pi$, the equation can be simplified as follows:

$2\ NH_3 + CO_2 + 3\ ATP + H_2O \rightarrow \text{urea} + 2\ ADP + 4\ P_i + AMP$

Note that reactions related to the urea cycle also cause the production of 2 NADH, so the urea cycle releases slightly more energy than it consumes. These NADH are produced in two ways:

One NADH molecule is reduced by the enzyme glutamate dehydrogenase in the conversion of glutamate to ammonium and α-ketoglutarate. Glutamate is the non-toxic carrier of amine groups. This provides the ammonium ion used in the initial synthesis of carbamoyl phosphate.

The fumarate released in the cytosol is converted to malate by cytosolic fumarase. This malate is then converted to oxaloacetate by cytosolic malate dehydrogenase, generating a reduced NADH in the cytosol. Oxaloacetate is one of the keto acids preferred by transaminases, and so will be recycled to aspartate, maintaining the flow of nitrogen into the urea cycle.

The two NADH produced can provide energy for the formation of 4 ATP (cytosolic NADH provides only 1.5 ATP due to the glycerol-3-phosphate shuttle who transfers the electrons from cytosolic NADH to $FADH_2$ and that gives 1.5 ATP), a net production of one high-energy phosphate bond for the urea cycle. However, if gluconeogenesis is underway in the cytosol, the latter reducing equivalent is used to drive the reversal of the GAPDH step instead of generating ATP.

The fate of oxaloacetate is either to produce aspartate via transamination or to be converted to phosphoenolpyruvate, which is a substrate for gluconeogenesis.

https://en.wikipedia.org/wiki/Urea_cycle

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Ureotelic

A ureotelic organism excretes excess nitrogen as urea. It is one of the three forms of excretion of nitrogenous waste in organisms, the others being amm and uricotelism.

https://en.wikipedia.org/wiki/Ureotelic

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Chapter 6 - Metabolism: Amino Acids and the Urea Cycle

Chapter 9 - Point by Point: Metabolism

Uric Acid

Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula $C_5H_4N_4O_3$. It forms ions and salts known as urates and acid urates, such as ammonium acid urate. Uric acid is a product of the metabolic breakdown of purine nucleotides. High blood concentrations of uric acid can lead to gout and are associated with other medical conditions including diabetes and the formation of ammonium acid urate kidney stones.

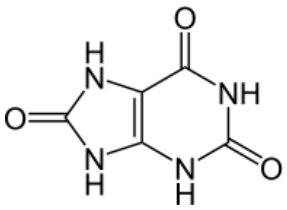
The enzyme xanthine oxidase catalyzes formation of uric acid from xanthine and hypoxanthine, which in turn are produced from other purines. Xanthine oxidase is a large enzyme whose active site consists of the metal molybdenum bound to sulfur and oxygen. Within cells, xanthine oxidase can exist as xanthine dehydrogenase and xanthine oxireductase, which has also been purified from bovine milk and spleen extracts. Uric acid is released in hypoxic conditions.

In humans and higher primates, uric acid is the final oxidation (breakdown) product of purine metabolism and is excreted in urine. In most other mammals, the enzyme uricase further oxidizes uric acid to allantoin. The loss of uricase in higher primates parallels the similar loss of the ability to synthesize ascorbic acid, leading to the suggestion that urate may partially substitute for ascorbate in such species. Both uric acid and ascorbic acid are strong reducing agents (electron donors) and potent antioxidants. In humans, over half the antioxidant capacity of blood plasma comes from uric acid.

In humans, about 70% of daily uric acid disposal occurs via the kidneys, and in 5-25% of humans, impaired renal (kidney) excretion leads to hyperuricemia. The Dalmatian dog has a genetic defect in uric acid uptake by the liver and kidneys, resulting in decreased conversion to allantoin, so this breed excretes uric acid, and not allantoin, in the urine.

In birds and reptiles, and in some desert dwelling mammals (e.g., the kangaroo rat), uric acid also is the end-product of purine metabolism, but it is excreted in feces as a dry mass. This involves a complex metabolic pathway that is energetically costly in comparison to processing of other nitrogenous wastes such as urea (from urea cycle) or ammonia, but has the advantages of reducing water loss and, hence, reducing the need for water.

Platynereis dumerilii, a marine Polychaete worm, uses uric acid as a sexual pheromone released into the water by females during mating to induce males to release sperm.



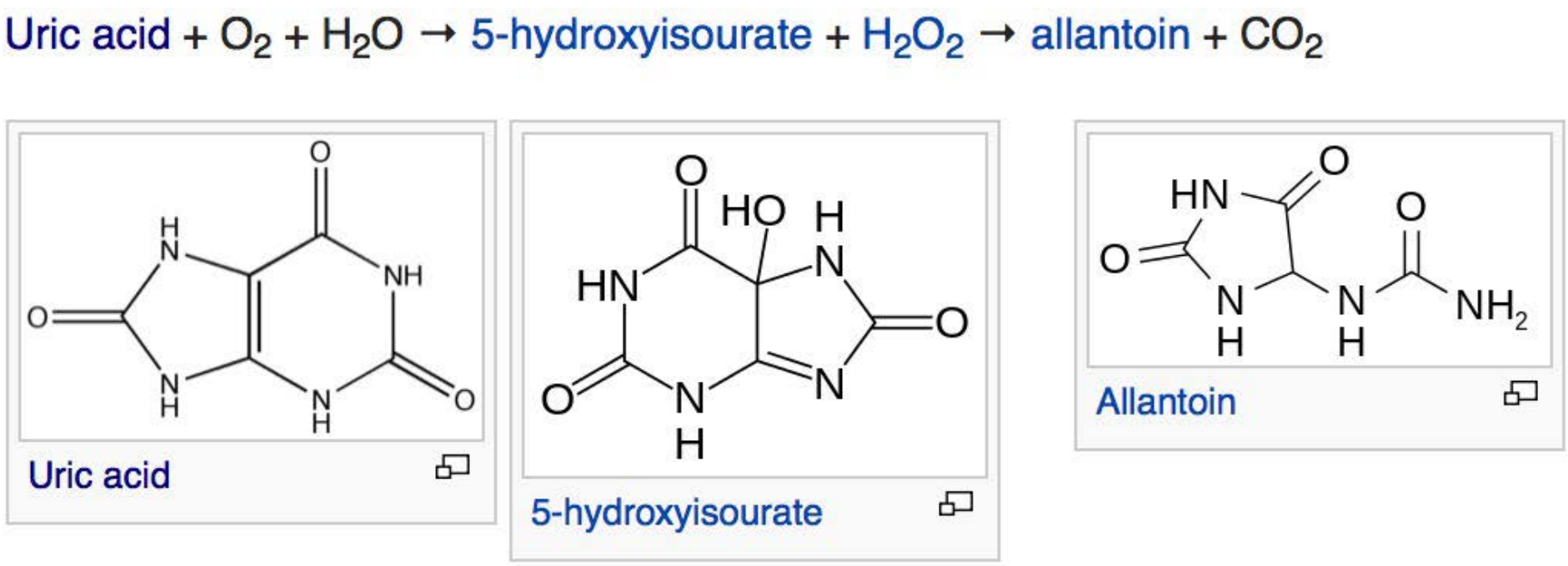
https://en.wikipedia.org/wiki/Uric_acid

Related Glossary Terms

Drag related terms here

Uricase

Uricase is an enzyme which catalyzes the oxidation of uric acid to 5-hydroxyisourate. is mainly localized in the liver, where it forms a large electron-dense paracrystalline core in many peroxisomes. The enzyme exists as a tetramer of identical subunits, each containing a possible type 2 copper-binding site. It contains four identical active sites situated at the interfaces between its four subunits.



https://en.wikipedia.org/wiki/Urate_oxidase

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Uricotelic

A uricotelic organism excretes uric acid or its salts as a result of deaminatic
the three major forms of excretion of nitrogenous waste in organisms (the c
ammonotelism and ureotelism), uric acid is the least toxic and the least sol
ter. It can be stored in cells and body tissues without toxic effects and requi
tiny amount of water. A single molecule of uric acid can also remove four at
trogen, making it more efficient than ammonotelism and ureotelism.

https://en.wikipedia.org/wiki/Uricotelic

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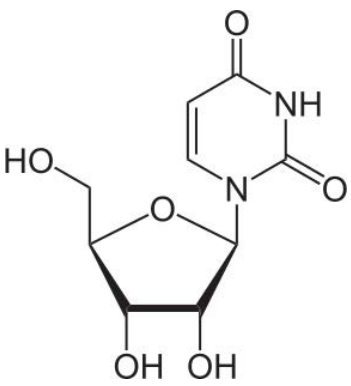
Uridine

Uridine is a glycosylated pyrimidine-analog containing uracil attached to a ribose ring (or more specifically, a ribofuranose) via a β-N1-glycosidic bond. It is one of the five standard nucleosides which make up nucleic acids. Uridine is found in RNA and not DNA.

Additionally, uridine plays a role in the glycolysis pathway of galactose. There is no catabolic process to metabolize galactose. Therefore, galactose is converted to glucose using UDP, and is subsequently metabolized in the common glucose pathway.

Uridine plays a role in the glycolysis pathway of galactose. There is no catabolic process to metabolize galactose. Therefore, galactose is converted to glucose and metabolized in the common glucose pathway. Once the incoming galactose has been converted into galactose 1-phosphate (Gal-1-P), it is involved in a reaction with UDP-glucose, a glucose molecule bonded to uridine diphosphate (UDP). This process is catalyzed by the enzyme galactose-1-phosphate uridyl transferase and transfers the UDP to the galactose molecule. The end result is UDP-galactose and glucose-1-phosphate. This process is continued to allow the proper glycolysis of galactose.



https://en.wikipedia.org/wiki/Uridine

Related Glossary Terms

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Uridine / Cytidine Kinase

Uridine/Cytidine Kinase is an enzyme that catalyzes the chemical reaction

ATP + Uridine ↔ ADP + UMP

Cytidine can also be substituted for uridine, producing CMP instead of UMP.

This enzyme is important in salvage reactions of pyrimidines. It belongs to t
of transferases, specifically those transferring phosphorus-containing groups
transferases) with an alcohol group as acceptor. The systematic name of this
class is ATP:uridine 5'-phosphotransferase. Other names in common use inc
rimidine ribonucleoside kinase, uridine kinase (phosphorylating), and uridir
phokinase. This enzyme participates in pyrimidine metabolism.

https://en.wikipedia.org/wiki/Uridine_kinase

Related Glossary Terms

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Chapter 6 - Metabolism: Nucleotides

Uridine Nucleosidase

Uridine nucleosidase is an enzyme that catalyzes the chemical reaction

Uridine + H_2O ↔ D-ribose + Uracil

The enzyme is important in salvage and catabolism of pyrimidine nucleotic

This enzyme belongs to the family of hydrolases, specifically those glycosyla
drolyze N-glycosyl compounds. The systematic name of this enzyme class is
bohydrolase. This enzyme is also called uridine hydrolase. This enzyme par
pyrimidine metabolism.

https://en.wikipedia.org/wiki/Uridine_nucleosidase

Related Glossary Terms

Drag related terms here

Uridine Phosphorylase

Uridine phosphorylase is an enzyme that catalyzes the chemical reaction

Uridine + Phosphate ⇔ Uracil + α-D-ribose-1-phosphate
The reaction is important in pyrimidine catabolism and salvage.

This enzyme belongs to the family of glycosyltransferases, specifically the p
transferases. The systematic name of this enzyme class is uridine:phosphat
ribosyltransferase. Other names in common use include pyrimidine phosph
UrdPase, UPH, and UPase. This enzyme participates in pyrimidine metabo

https://en.wikipedia.org/wiki/Uridine_phosphorylase

Related Glossary Terms

Drag related terms here

Uridine-cytidine Kinase

Uridine/Cytidine Kinase is an enzyme that catalyzes the chemical reaction

ATP + Uridine ↔ ADP + UMP

Cytidine can also be substituted for uridine, producing CMP instead of UM

This enzyme is important in salvage reactions of pyrimidines. It belongs to of transferases, specifically those transferring phosphorus-containing grou transferases) with an alcohol group as acceptor. The systematic name of thi class is ATP:uridine 5'-phosphotransferase. Other names in common use in rimidine ribonucleoside kinase, uridine kinase (phosphorylating), and urid phokinase. This enzyme participates in pyrimidine metabolism.

https://en.wikipedia.org/wiki/Uridine_kinase

Related Glossary Terms

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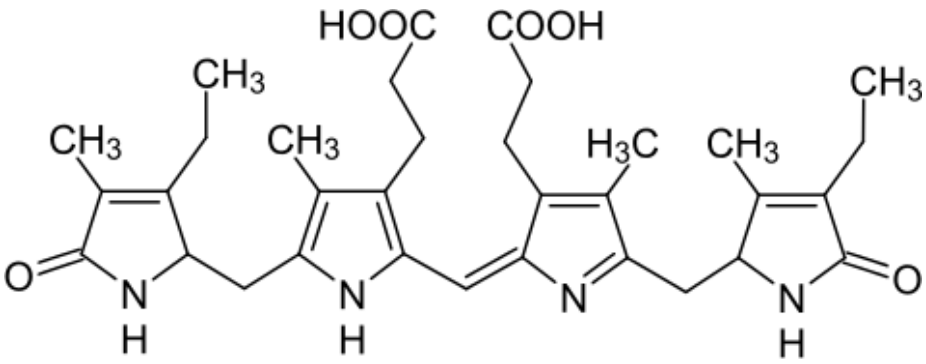
Urobilin

Urobilin or urochrome is the chemical primarily responsible for the yellow color of urine. It is a linear tetrapyrrole compound that, along with the related compound urobilinogen, are degradation products of the cyclic tetrapyrrole heme.

The heme is first degraded through biliverdin to bilirubin. Bilirubin is then excreted as bile, which is further degraded by microbes present in the large intestine to urobilinogen. Some of this remains in the large intestine, and its conversion to stercobilin gives feces its brown color. Some is reabsorbed into the bloodstream, where it is oxidized to urobilin and eventually excreted by the kidneys, giving urine its yellow color.



https://en.wikipedia.org/wiki/Urobilin

Related Glossary Terms

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Urobilinogen

Urobilinogen is a colorless by-product of bilirubin reduction. It is formed in the intestines by bacterial action on bilirubin. About half of the urobilinogen formed is reabsorbed and taken up via the portal vein to the liver, enters circulation and is excreted by the kidney.

Increased amounts of bilirubin are formed in hemolysis, which generates increased urobilinogen in the gut. In liver disease (such as hepatitis), the intrahepatic urobilinogen cycle is inhibited also increasing urobilinogen levels. Urobilinogen is converted to the yellow pigmented urobilin apparent in urine.

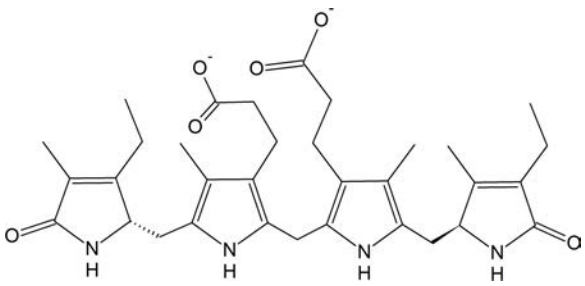
The urobilinogen in the intestine is directly reduced to brown stercobilin, which gives the feces their characteristic color. It can also be reduced to stercobilinogen, which can then be further oxidized to stercobilin. This constitutes the normal "enterohepatic urobilinogen cycle".

In biliary obstruction, below-normal amounts of conjugated bilirubin reach the intestine for conversion to urobilinogen. With limited urobilinogen available for reabsorption and excretion, the amount of urobilin found in the urine is low. High amounts of the soluble conjugated bilirubin enter the circulation where they are excreted via the kidneys. These mechanisms are responsible for the dark urine and pale stools observed in biliary obstruction.

Low urine urobilinogen may result from complete obstructive jaundice or treatment with broad-spectrum antibiotics, which destroy the intestinal bacterial flora. (Obstruction of bilirubin passage into the gut or failure of urobilinogen production in the gut.)

Low urine urobilinogen levels may result from congenital enzymatic jaundice (hyperbilirubinemia syndromes) or from treatment with drugs that acidify urine, such as ammonium chloride or ascorbic acid.

Elevated levels may indicate hemolytic anaemia (excessive breakdown of red blood cells RBC), overburdening of the liver, increased urobilinogen production, reabsorption - a large hematoma, restricted liver function, hepatic infection, poisoning or liver cirrhosis.



https://en.wikipedia.org/wiki/Urobilinogen

Related Glossary Terms

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Urokinase

Urokinase, also called urokinase-type plasminogen activator (uPA), is a serine protease. It was originally isolated from human urine, but is present in several physiological locations, such as blood stream and the extracellular matrix. The primary physiological substrate is plasminogen, which is an inactive form (zymogen) of the serine protease plasmin. Activation of plasmin triggers a proteolysis cascade that, depending on the physiological environment, participates in thrombolysis or extracellular matrix degradation. This links urokinase to vascular diseases and cancer.

Elevated expression levels of urokinase and several other components of the plasminogen activation system are found to be correlated with tumor malignancy. It is believed that the tissue degradation following plasminogen activation facilitates tissue invasion and, thus, contributes to metastasis. This makes urokinase an attractive drug target, and, so, inhibitors have been sought to be used as anticancer agents. However, incompatibilities between the human and murine systems hamper clinical evaluation of these agents. Through its interaction with the urokinase receptor, urokinase affects several other aspects of cancer biology such as cell adhesion, migration, and cellular mitotic pathways.

https://en.wikipedia.org/wiki/Urokinase

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Chapter 4 - Catalysis: Blood Clotting

Urokinase Plasminogen Activator

A variety of enzymes capable of activating plasminogen when it is bound to
cell surfaces) in its open conformation. Urokinase plasminogen activators r
brin, or urokinase plasminogen activator receptors as cofactors in the activa
urokinase plasminogen activator than converts plasminogen to plasmin via
age of the peptide bond between Arg-561 and Val-562.

https://en.wikipedia.org/wiki/Plasmin

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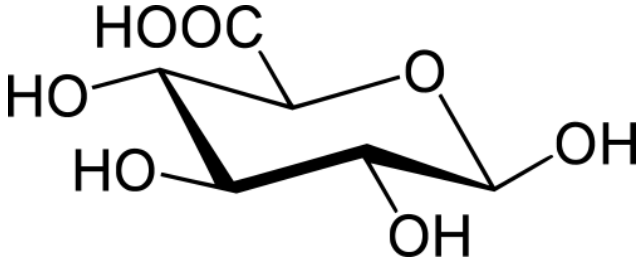
Uronic Sugar

Uronic sugars are a class of sugar-acids with both carbonyl and carboxylic acid functional groups. They are sugars in which the terminal carbon's hydroxyl group has been oxidized to a carboxylic acid. Oxidation of the terminal aldehyde instead yields an aldonic acid, while oxidation of both the terminal hydroxyl group and the aldehyde yields an aldaric acid. The names of uronic acids are generally based on their parent sugars, however some of the most common do not have direct parents, and are formed by epimerization.

Some of these compounds have important biochemical functions. For example, many wastes in the human body are excreted in the urine as their glucuronate salts, and iduronic acid is a component of some structural complexes such as proteoglycans.

Glucuronic acid is shown below.



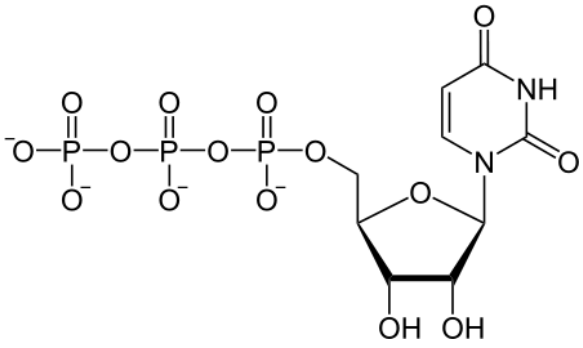
https://en.wikipedia.org/wiki/Uronic_acid

Related Glossary Terms

UTP

Uridine-5'-triphosphate (UTP) is a pyrimidine nucleotide triphosphate, consisting of the organic base uracil linked to the 1' carbon of the ribose sugar, and esterified with tri-phosphoric acid at the 5' position. Its main role is as substrate for the synthesis of RNA during transcription.

UTP also has the role of a source of energy or an activator of substrates in metabolic reactions, like that of ATP, but more specific. When UTP activates a substrate, UDP-substrate is usually formed and inorganic phosphate is released. UDP-glucose enters the synthesis of glycogen. UTP is used in the metabolism of galactose, where the activated form UDP-galactose is converted to UDP-glucose. UDP-glucuronate is used to conjugate bilirubin to a more water-soluble bilirubin diglucuronide. UTP also has roles in mediating responses by extracellular binding to the P2Y receptors of cells.



https://en.wikipedia.org/wiki/Uridine_triphosphate

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UVB

UVB radiation ranges from 290-320nm and is sourced from the sun. It can
the atmosphere, and plays an important role in multiple health conditions s
mature aging of the dermal tissues, skin cancers (melanomas) and it can da
UVB radiation is also essential for the dermal synthesis of vitamin D from c

https://en.wikipedia.org/wiki/Ultraviolet#Subtypes

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Chapter 2 - Structure & Function: Carbohydrates

uvrABC

UvrABC endonuclease is a multienzyme complex in *Escherichia coli* involv
repair by nucleotide excision repair, and it is, therefore, sometimes called a
ase. This UvrABC repair process, sometimes called the short-patch process
the removal of twelve nucleotides where a genetic mutation has occurred fo
DNA polymerase, replacing these aberrant nucleotides with the correct nuc
and completing the DNA repair. The subunits for this enzyme are encoded
uvrB, and uvrC genes. This enzyme complex is able to repair many differen
damage, including cyclobutyl dimer formation.

https://en.wikipedia.org/wiki/UvrABC_endonuclease

Related Glossary Terms

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V-SNAREs

Vesicle or v-SNAREs, which are incorporated into the membranes of transport vesicles during budding, are one of two types of SNARE proteins. The primary role of SNARE proteins is to mediate vesicle fusion, that is, the fusion of vesicles with their target membrane bound compartments (such as a lysosome). All SNAREs are small, abundant, tail-anchored proteins which are often post-translationally inserted into membranes via a C-terminal transmembrane domain. Tail-anchored proteins can be inserted into the plasma membrane, endoplasmic reticulum, mitochondria, and peroxisomes among other membranes, though any particular SNARE is targeted to a unique membrane. The targeting of SNAREs is accomplished by altering either the composition of the C-terminal flanking amino acid residues or the length of the transmembrane domain. The best studied SNAREs are those that mediate docking of synaptic vesicles with the presynaptic membrane in neurons. These SNAREs are the targets of the bacterial neurotoxins responsible for botulism and tetanus.

During membrane fusion, v-SNARE and t-SNARE proteins on separate membranes combine to form a *trans*-SNARE complex, also known as a "SNAREpin". Depending on the stage of fusion of the membranes, these complexes may be referred to differently.

During fusion of *trans*-SNARE complexes, the membranes merge and SNARE proteins involved in complex formation after fusion are then referred to as a "cis"-SNARE complex, because they now reside in a single (or *cis*) resultant membrane. After fusion, the *cis*-SNARE complex is bound and disassembled by an adaptor protein, αSNAP. Then, the hexameric AAA-ATPase NSF catalyzes the ATP-dependent unfolding of the SNARE proteins and releases them into the cytosol for recycling.

SNAREs are thought to be the core required components of the fusion machinery and can function independently of additional cytosolic accessory proteins. This was demonstrated by engineering "flipped" SNAREs, where the SNARE domains face the extracellular space rather than the cytosol. When cells containing v-SNAREs contact cells containing t-SNAREs, *trans*-SNARE complexes form and cell-cell fusion ensues.

https://en.wikipedia.org/wiki/SNARE_(protein)

V_0

V_0 is an abbreviation for the initial velocity in the Michaelis-Menten equatio single-substrate enzyme kinetics. It is dependent upon the substrate bindin rium and the rate constant, and it is related to the maximal reaction velocity susbtrate affinity (K_m) as follows:

$$v_0 = \frac{V_{max}[S]}{K_M + [S]}$$

https://en.wikipedia.org/wiki/Enzyme_kinetics

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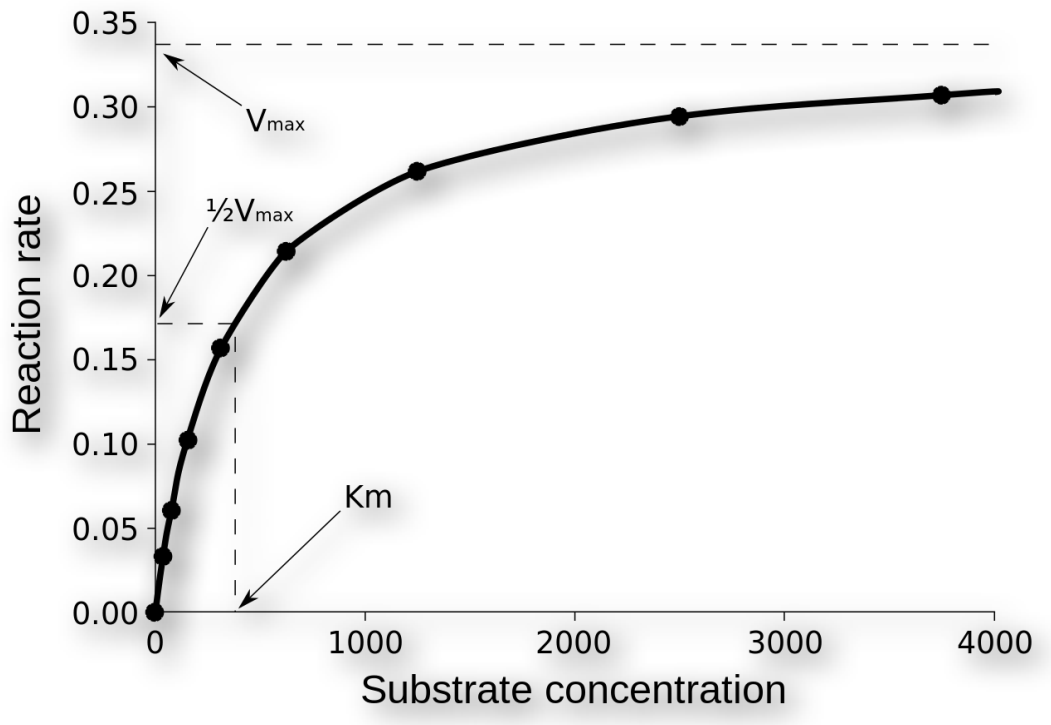
V_0 vs. [S]

Substrate concentration ([S]) comprises the x-axis and Initial velocity (V_0) comprises the y-axis of this plot of data for an enzymatic reaction. The curve can be used to derive Michaelis-Menten kinetics data (such as substrate affinity or maximum reaction rate) for an enzymatic reaction.

A V_0 vs [S] plot is shown below.



https://en.wikipedia.org/wiki/Enzyme_kinetics

Related Glossary Terms

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Vacuoles

A vacuole is a membrane-bound organelle which is present in all plant and fungal cells and some protist, animal and bacterial cells. Vacuoles are essentially enclosed compartments which are filled with water containing inorganic and organic molecules including enzymes in solution, though in certain cases they may contain solids which have been engulfed. Vacuoles are formed by the fusion of multiple membrane vesicles and are effectively just larger forms of these. The organelle has no basic shape or size; its structure varies according to the needs of the cell.

The function and significance of vacuoles varies greatly according to the type of cell in which they are present, having much greater prominence in the cells of plants, fungi and certain protists than those of animals and bacteria. In general, the functions of the vacuole include:

- Isolating materials that might be harmful or a threat to the cell
- Containing waste products
- Containing water in plant cells
- Maintaining internal hydrostatic pressure or turgor within the cell
- Maintaining an acidic internal pH
- Containing small molecules
- Exporting unwanted substances from the cell
- Allows plants to support structures such as leaves and flowers due to the pressure of the central vacuole
- In seeds, stored proteins needed for germination are kept in 'protein bodies', which are modified vacuoles.

https://en.wikipedia.org/wiki/Vacuole

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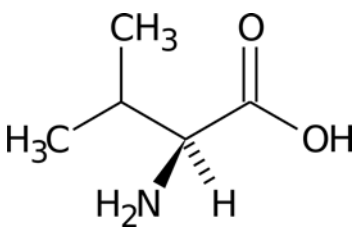
Valine

Valine (abbreviated as Val or V) is encoded by the codons GUU, GUC, GUA, and GUG. It is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group (which is in the protonated $-NH_3^+$ form under biological conditions), an α-carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain isopropyl variable group, classifying it as a non-polar amino acid. It is essential in humans, meaning the body cannot synthesize it and thus it must be obtained from the diet.



https://en.wikipedia.org/wiki/Valine

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Van der Waals Forces

Van der Waals forces (or van der Waals' interactions) are the residual attractive or repulsive forces between molecules or atomic groups that do not arise from a covalent bond, or an electrostatic interaction of ions or of ionic groups with one another or with neutral molecules. Van der Waals forces can be attractive or repulsive, and include: forces between permanent dipoles, forces between a permanent dipole and a corresponding induced dipole, or forces between instantaneously induced dipoles.

The term includes:
force between permanent dipoles
force between a permanent dipole and a corresponding induced dipole
force between instantaneously induced dipoles

It is also sometimes used loosely as a synonym for the totality of intermolecular forces. Van der Waals forces are relatively weak compared to covalent bonds, but play a fundamental role in fields as diverse as supramolecular chemistry, structural biology, polymer science, nanotechnology, surface science, and condensed matter physics. Van der Waals forces define many properties of organic compounds, including their solubility in polar and non-polar media.

In low molecular weight alcohols, the hydrogen-bonding properties of the polar hydroxyl group dominate other weaker van der Waals interactions. In higher molecular weight alcohols, the properties of the nonpolar hydrocarbon chain(s) dominate and define the solubility. Van der Waals forces quickly vanish at longer distances between interacting molecules.

https://en.wikipedia.org/wiki/Van_der_Waals_force

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Vasoconstriction

Vasoconstriction is the narrowing of the blood vessels resulting from contraction of the muscular wall of the vessels, in particular the large arteries and small arterioles. The process is the opposite of vasodilation, the widening of blood vessels. The process is particularly important in staunching hemorrhage and acute blood loss. When blood vessels constrict, the flow of blood is restricted or decreased, thus retaining body heat or increasing vascular resistance. This makes the skin turn paler because less blood reaches the surface, reducing the radiation of heat. On a larger level, vasoconstriction is one mechanism by which the body regulates and maintains mean arterial pressure.

Medications causing vasoconstriction, also known as vasoconstrictors, are one type of medicine used to raise blood pressure. Generalized vasoconstriction usually results in an increase in systemic blood pressure, but it may also occur in specific tissues, causing a localized reduction in blood flow. The extent of vasoconstriction may be slight or severe depending on the substance or circumstance. Many vasoconstrictors also cause pupil dilation. Medications that cause vasoconstriction include: antihistamines, decongestants, and stimulants. Severe vasoconstriction may result in symptoms of intermittent claudication.

https://en.wikipedia.org/wiki/Vasoconstriction

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Vasodilator

Vasodilation (or vasodilatation) refers to the widening of blood vessels. It results from relaxation of smooth muscle cells within the vessel walls, in particular in the large veins, large arteries, and smaller arterioles. The process is the opposite of vasoconstriction, which is the narrowing of blood vessels.

When blood vessels dilate, the flow of blood is increased due to a decrease in vascular resistance. Therefore, dilation of arterial blood vessels (mainly the arterioles) decreases blood pressure. The response may be intrinsic (due to local processes in the surrounding tissue) or extrinsic (due to hormones or the nervous system). In addition, the response may be localized to a specific organ (depending on the metabolic needs of a particular tissue, as during strenuous exercise), or it may be systemic (seen throughout the entire systemic circulation).

The primary function of vasodilation is to increase blood flow in the body to tissues that need it most. This is often in response to a localized need of oxygen but can occur when the tissue in question is not receiving enough glucose or lipids or other nutrients. Localized tissues utilize multiple ways to increase blood flow including releasing vasodilators, primarily adenosine, into the local interstitial fluid, which diffuses to capillary beds, provoking local vasodilation. Some physiologists have suggested that it is the lack of oxygen itself that causes capillary beds to vasodilate by the smooth muscle hypoxia of the vessels in the region. This latter hypothesis is posited due to the presence of precapillary sphincters in capillary beds. Neither of these approaches to the mechanism of vasodilation is mutually exclusive of the other.

Drugs that cause vasodilation are termed vasodilators.

https://en.wikipedia.org/wiki/Vasodilation

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Velocity

In studying the kinetics of enzymatic reactions, Michaelis-Menten condition are usually employed. In these studies, initial velocity (V_0) is used.

V_0 = [Product]/time

In Michaelis-Menten conditions, [Product] is measured only in short time windows at the beginning of a reaction before the reverse reaction becomes a factor.

V_0 is dependent upon the substrate binding equilibrium and the rate constant, and it is related to the maximal reaction velocity and the substrate affinity (K_m) as follows:

$$v_0 = \frac{V_{max}[S]}{K_M + [S]}$$

https://en.wikipedia.org/wiki/Enzyme_kinetics

Related Glossary Terms

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Velocity of a Reaction

In studying the kinetics of enzymatic reactions, Michaelis-Menten condition are usually employed. In these studies, initial velocity (V_0) is used.

V_0 = [Product]/time

In Michaelis-Menten conditions, [Product] is measured only in short time windows the beginning of a reaction before the reverse reaction becomes a factor.

V_0 is dependent upon the substrate binding equilibrium and the rate constant, and related to the maximal reaction velocity and the substrate affinity (K_m) as follows:

$$v_0 = \frac{V_{max}[S]}{K_M + [S]}$$

https://en.wikipedia.org/wiki/Enzyme_kinetics

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Versican

Versican is a large, chondroitin sulfate proteoglycan found in the extracellular matrix with an apparent molecular mass of more than 1000kDa. It possesses a versatile modular structure.

The role of versican in cell adhesion, migration, and proliferation has been extensively studied. Versican is often considered an anti-adhesion molecule. Considering the large size (>1000 kDa) and hydration capability of versican, it is possible that the interaction of integrins (large family of cell adhesion molecules) with their cell surface receptors is sterically hindered.

Expression of versican is observed in various adult tissues such as blood vessels, skin, and developing heart. Smooth muscle cells of blood vessels, epithelial cells of skin, and the cells of central and peripheral nervous system are a few examples of cell types that express versican physiologically. Versican is involved in development, guiding embryonic cell migration important in the formation of the heart and outlining the path for neural crest cell migration.

https://en.wikipedia.org/wiki/Versican

Related Glossary Terms

Drag related terms here

Vesicle

Vesicles are small structures within a cell, consisting of fluid enclosed by a lipid bilayer. Vesicles form naturally during the processes of secretion (exocytosis), uptake (phagocytosis and endocytosis) and transport of materials within the cytoplasm. Alternatively, they may be prepared artificially, in which case they are called liposomes. Vesicles perform a variety of functions. Because it is separated from the cytosol, the inside of the vesicle can be made to be different from the cytosolic environment. For this reason, vesicles are a basic tool used by the cell for organizing cellular substances. Vesicles are involved in metabolism, transport, buoyancy control, and enzyme storage. They can also act as chemical reaction chambers.

Types of Vesicles

1. Vacuoles are vesicles which contain mostly water.

• Plant cells have a large central vacuole in the center of the cell that is used for osmotic control and nutrient storage.

• Contractile vacuoles are found in certain protists, especially those in Phylum *Ciliophora*. These vacuoles take water from the cytoplasm and excrete it from the cell to avoid bursting due to osmotic pressure.

2. Lysosomes

• Lysosomes are involved in cellular digestion. Food can be taken from outside the cell into food vacuoles by a process called endocytosis. These food vacuoles fuse with lysosomes which break down the components so that they can be used in the cell. This form of cellular eating is called phagocytosis.

• Lysosomes are also used to destroy defective or damaged organelles in a process called autophagy. They fuse with the membrane of the damaged organelle, digesting it.

3. Transport vesicles

• Transport vesicles can move molecules between locations inside the cell, e.g., proteins from the rough endoplasmic reticulum to the Golgi apparatus.

• Membrane-bound and secreted proteins are made on ribosomes found in the rough endoplasmic reticulum. Most of these proteins mature in the Golgi apparatus before going to their final destination which may be to lysosomes, peroxisomes, or outside of the cell. These proteins travel within the cell inside of transport vesicles.

4. Secretory vesicles

Secretory vesicles contain materials that are to be excreted from the cell. Cells have many reasons to excrete materials. One reason is to dispose of wastes. Another reason is tied to the function of the cell. Within a larger organism, some cells are specialized to produce certain chemicals. These chemicals are stored in secretory vesicles and released when needed.

5. Extracellular vesicles

Extracellular vesicles (EVs) are produced by all domains of life including complex eukaryotes, both Gram-negative and Gram-positive bacteria, mycobacteria, and fungi. Nomenclature exists for a variety of extracellular vesicle types including :

Exosomes: membraneous vesicles of endocytic origin (50-100 nm diameter)

• Microvesicle (also referred to as shedding microvesicles, SMVs, that are shed directly from the plasma membrane, (20-1000 nm)

•Membrane particles, (50-80 nm), or large membranous vesicles (~600 nm) CD133+, CD63

•Apoptotic blebs or vesicles (1000-5000 nm diameter): released by dying cells.

These are often separated by density:Table 1 by differential centrifugation.

Ectosomes were named in 2008, but in 2012 are not considered a separate type.

https://en.wikipedia.org/wiki/Vesicle_(biology_and_chemistry)

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Vesicle Fusion

Vesicle fusion is the merging of a vesicle with other vesicles or a part of a cell membrane. In the latter case, it is the end stage of secretion from secretory vesicles, where their contents are expelled from the cell through exocytosis. Vesicles can also fuse with other target cell compartments, such as a lysosome.
Vesicle fusion may depend on SNARE proteins in the presence of increased intracellular calcium (Ca^{++}) concentration.

In synaptic vesicle fusion, the vesicle must be within a few nanometers of the target membrane for the fusion process to begin. This closeness allows the cell wall and the vesicle to exchange lipids which is mediated by certain proteins which remove water that comes between the forming junction. Once the vesicle is in position it must wait until Ca^{++} enters the cell by the propagation of an action potential to the presynaptic membrane. Ca^{++} binds to specific proteins, one of which is synaptotagmin, in neurons which triggers the complete fusion of the vesicle with the target membrane.

SNARE proteins are also thought to help mediate which membrane is the target of which vesicle.

https://en.wikipedia.org/wiki/Vesicle_fusion

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Chapter 3 - Membranes: Other Considerations

Vimentin

Vimentin is a type III intermediate filament protein that is expressed in mesenchymal cells. Intermediate filament proteins are found in all metazoan cells as well as bacteria. Intermediate filaments, along with tubulin-based microtubules and actin-based microfilaments, comprise the cytoskeleton. All intermediate filament proteins are expressed in a highly developmentally-regulated fashion. Vimentin is the major cytoskeletal component of mesenchymal cells. Because of this, vimentin is often used as a marker of mesenchymally-derived cells or cells undergoing an epithelial-to-mesenchymal transition (EMT) during both normal development and metastatic progression.

Vimentin plays a significant role in supporting and anchoring the position of the organelles in the cytosol. Vimentin is attached to the nucleus, endoplasmic reticulum, and mitochondria, either laterally or terminally.

The dynamic nature of vimentin is important when offering flexibility to the cell. Scientists found that vimentin provided cells with a resilience absent from the microtubule or actin filament networks, when under mechanical stress *in vivo*. Therefore, in general, it is accepted that vimentin is the cytoskeletal component responsible for maintaining cell integrity. (It was found that cells without vimentin are extremely delicate when disturbed with a micropuncture). Transgenic mice that lack vimentin appeared normal and did not show functional differences. It is possible that the microtubule network may have compensated for the absence of the intermediate network. This result supports an intimate interactions between microtubules and vimentin. Moreover, when microtubule depolymerizers were present, vimentin reorganization occurred, once again implying a relationship between the two systems. On the other hand, wounded mice that lack the vimentin gene heal slower than their wild type counterparts.

In essence, vimentin is responsible for maintaining cell shape, integrity of the cytoplasm, and stabilizing cytoskeletal interactions. Vimentin has been shown to eliminate toxic proteins in JUNQ and IPOD inclusion bodies in asymmetric division of mammalian cell lines.

Also, vimentin is found to control the transport of low-density lipoprotein, LDL, -derived cholesterol from a lysosome to the site of esterification. With the blocking of transport of LDL-derived cholesterol inside the cell, cells were found to store a much lower percentage of the lipoprotein than normal cells with vimentin. This dependence seems to be the first process of a biochemical function in any cell that depends on a cellular intermediate filament network. This type of dependence has ramifications on the adrenal cells, which rely on cholesteryl esters derived from LDL.

https://en.wikipedia.org/wiki/Vimentin

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Vinculin

In mammalian cells, vinculin is a membrane-cytoskeletal protein in focal adhesion plaques that is involved in linkage of integrin adhesion molecules to the actin cytoskeleton. Vinculin is a cytoskeletal protein associated with cell-cell and cell-matrix junctions, where it is thought to function as one of several interacting proteins involved in anchoring F-actin to the membrane.

Cell spreading and movement occur through the process of binding of cell surface integrin receptors to extracellular matrix adhesion molecules. Vinculin is associated with focal adhesion and adherens junctions, which are complexes that nucleate actin filaments and crosslinkers between the external medium, plasma membrane, and actin cytoskeleton. The complex at the focal adhesions consists of several proteins such as vinculin, α-actin, paxillin, and talin, at the intracellular face of the plasma membrane.

In more specific terms, the amino-terminus of vinculin binds to talin, which, in turn, binds to β-integrins, and the carboxy-terminus binds to actin, phospholipids, and paxillin-forming homodimers. The binding of vinculin to talin and actin is regulated by polyphosphoinositides and inhibited by acidic phospholipids. The complex then serves to anchor actin filaments to the membrane.

https://en.wikipedia.org/wiki/Vinculin

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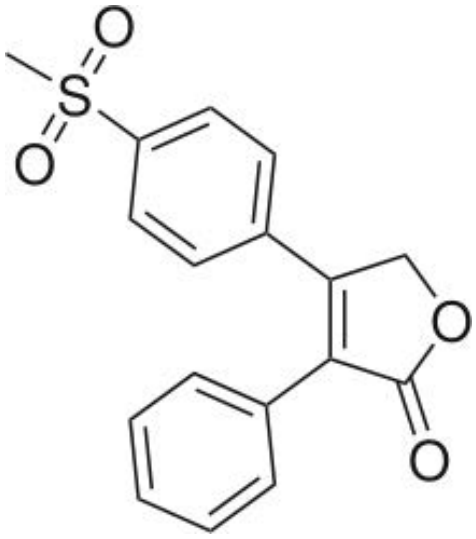
Vioxx

Vioxx was one brand name for Rofecoxib, a nonsteroidal anti-inflammatory drug (NSAID) that has now been withdrawn over safety concerns. It was marketed by Merck & Co. to treat osteoarthritis, acute pain conditions, and dysmenorrhea. It worked as a selective inhibitor for the COX-2 isoform of cyclooxygenase, which mediates the synthesis of prostaglandins responsible for pain and inflammation responses. It was cleared by the FDA in 1999, and withdrawn from the market in 2004 as between 88,000-140,000 cases of serious heart disease arose as a result of Vioxx consumption.



https://en.wikipedia.org/wiki/Rofecoxib

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Viruses

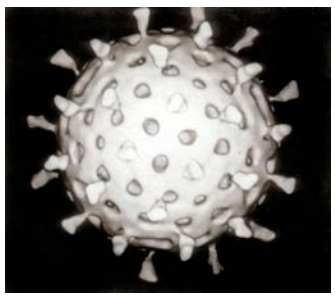
A virus is a small infectious agent that replicates only inside the living cells of other organisms. Viruses can infect all types of life forms, from animals and plants to microorganisms, including bacteria and *archaea*.

While not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent particles. These viral particles, also known as virions, consist of two or three parts: (i) the genetic material made from either DNA or RNA, long molecules that carry genetic information; (ii) a protein coat, called the capsid, which surrounds and protects the genetic material; and in some cases (iii) an envelope of lipids that surrounds the protein coat when they are outside a cell. The shapes of these virus particles range from simple helical and icosahedral forms for some virus species to more complex structures for others. Most virus species have virions that are too small to be seen with an optical microscope. The average virion is about one one-hundredth the size of the average bacterium.

Viruses display a wide diversity of shapes and sizes, called morphologies. In general, viruses are much smaller than bacteria. Most viruses that have been studied have a diameter between 20 and 300 nanometers. Some filoviruses have a total length of up to 1400 nm. Their diameters are only about 80 nm. Most viruses cannot be seen with an optical microscope so scanning and transmission electron microscopes are used to visualize virions. To increase the contrast between viruses and the background, electron-dense "stains" are used. These are solutions of salts of heavy metals, such as tungsten, that scatter the electrons from regions covered with the stain. When virions are coated with stain (positive staining), fine detail is obscured. Negative staining overcomes this problem by staining the background only.

A complete virus particle, known as a virion, consists of nucleic acid surrounded by a protective coat of protein called a capsid. These are formed from identical protein subunits called capsomeres. Viruses can have a lipid "envelope" derived from the host cell membrane. The capsid is made from proteins encoded by the viral genome and its shape serves as the basis for morphological distinction. Virally coded protein subunits will self-assemble to form a capsid, in general requiring the presence of the virus genome. Complex viruses code for proteins that assist in the construction of their capsid. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid. The capsid and entire virus structure can be mechanically (physically) probed through atomic force microscopy.

Pictured below - a rotavirus



https://en.wikipedia.org/wiki/Virus

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Vitamin

A vitamin is an organic compound and a vital nutrient that an organism requires in limited amounts. An organic chemical compound (or related set of compounds) is called a vitamin when the organism cannot synthesize the compound in sufficient quantities, and it must be obtained through the diet. The term "vitamin" is conditional upon the circumstances and the particular organism. For example, ascorbic acid (one form of vitamin C) is a vitamin for humans, but not for most other animal organisms.

By convention the term vitamin includes neither other essential nutrients, such as dietary minerals, essential fatty acids, or essential amino acids (which are needed in greater amounts than vitamins) nor the great number of other nutrients that promote health, and are required less often to maintain the health of the organism. Thirteen vitamins are universally recognized at present. Vitamins are classified by their biological and chemical activity, not their structure. Thus, each "vitamin" refers to a number of vitamer compounds that all show the biological activity associated with a particular vitamin. Such a set of chemicals is grouped under an alphabetized vitamin "generic descriptor" title, such as "vitamin A", which includes the compounds retinal, retinol, and four known carotenoids. Vitamers by definition are convertible to the active form of the vitamin in the body, and are sometimes inter-convertible to one another, as well.

Vitamins have diverse biochemical functions. Some, such as vitamin D, have hormone-like functions as regulators of mineral metabolism, or regulators of cell and tissue growth and differentiation (such as some forms of vitamin A). Others function as antioxidants (e.g., vitamin E and sometimes vitamin C). The largest number of vitamins, the B complex vitamins, function as enzyme cofactors (coenzymes) or the precursors for them. Coenzymes help enzymes in their work as catalysts in metabolism. In this role, vitamins may be tightly bound to enzymes as part of prosthetic groups: For example, biotin is part of enzymes involved in making fatty acids. They may also be less tightly bound to enzyme catalysts as coenzymes, detachable molecules that function to carry chemical groups or electrons between molecules. For example, folic acid may carry methyl, formyl, and methylene groups in the cell. Although these roles in assisting enzyme-substrate reactions are vitamins' best-known function, the other vitamin functions are equally important.

https://en.wikipedia.org/wiki/Vitamin

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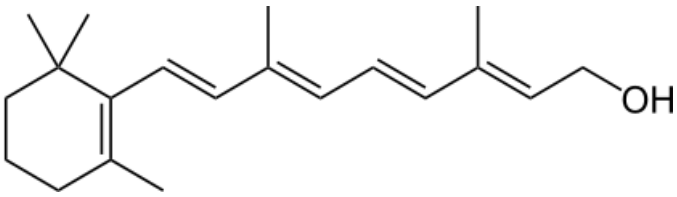
Vitamin A

Vitamin A is a group of unsaturated nutritional organic compounds that includes retinol, retinal, retinoic acid, and several provitamin A carotenoids (most notably β-carotene). Vitamin A has multiple functions. It is important for growth and development, for the maintenance of the immune system and good vision. Vitamin A is needed by the retina of the eye in the form of retinal, which combines with protein opsin to form rhodopsin, the light-absorbing molecule necessary for both low-light (scotopic vision) and color vision. Vitamin A also functions in a very different role as retinoic acid (an irreversibly oxidized form of retinol), which is an important hormone-like growth factor for epithelial and other cells.

Vitamin A plays a role in a variety of functions throughout the body, such as:

- Vision
- Gene transcription
- Immune function
- Embryonic development and reproduction
- Bone metabolism
- Hematopoiesis
- Skin and cellular health
- Antioxidant activity



https://en.wikipedia.org/wiki/Vitamin_A

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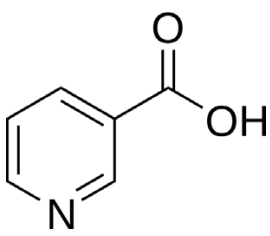
Vitamin B_3

Vitamin B_3, also called niacin, is an organic compound with the formula $C_6H_5NO_2$. Insufficient niacin in the diet can cause nausea, skin and mouth lesions, anemia, headaches, and tiredness. This colorless, water-soluble solid is a derivative of pyridine, with a carboxyl group (COOH) at the 3-position. Other forms of vitamin B_3 include the corresponding amide and nicotinamide ("niacinamide"), where the carboxyl group has been replaced by a carboxamide group ($CONH_2$), as well as more complex amides and a variety of esters.

Nicotinic acid and niacinamide are convertible to each other with steady world demand rising from 8,500 tonnes per year in the 1980s to 40,000 in recent years. Niacin cannot be directly converted to nicotinamide, but both compounds are precursors of the coenzymes nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$) *in vivo*. NAD converts to $NADP^+$ by phosphorylation in the presence of the enzyme NAD^+ kinase. $NADP^+$ and NAD^+ are coenzymes for many dehydrogenases, participating in many hydrogen transfer processes. NAD^+ is important in catabolism of fat, carbohydrate, protein, and alcohol, as well as cell signaling and DNA repair, and $NADP^+$ mostly in anabolism reactions such as fatty acid and cholesterol synthesis. High energy requirements (brain) or high turnover rate (gut, skin) organs are usually the most susceptible to their deficiency. Although the two are identical in their vitamin activity, nicotinamide does not have the same pharmacological effects (lipid modifying effects) as niacin. Nicotinamide does not reduce cholesterol or cause flushing. As the precursor for NAD^+ and $NADP^+$, niacin is also involved in DNA repair.



https://en.wikipedia.org/wiki/Niacin

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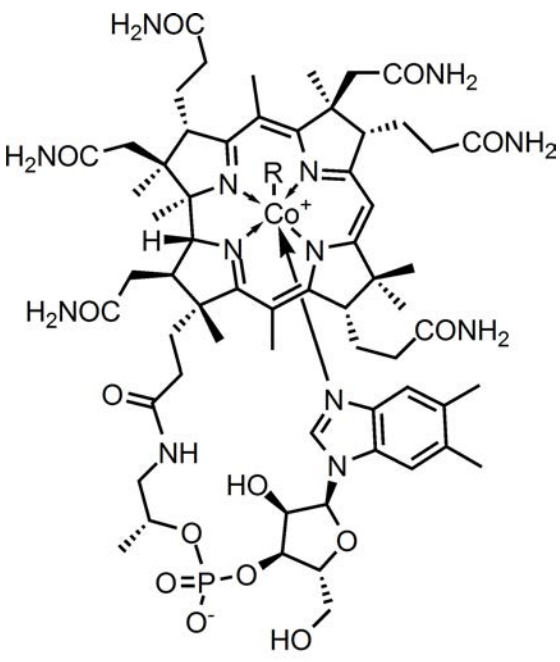
Vitamin B_{12}

Vitamin B_{12}, also called cobalamin, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system, and the formation of red blood cells. It is one of eight B vitamins. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid and amino acid metabolism. No fungi, plants, nor animals (including humans) are capable of producing vitamin B_{12}. Only bacteria and archaea have the enzymes needed for its synthesis. Some plant foods are a natural source of B_{12} because of bacterial symbiosis. B_{12} is the largest and most structurally complicated vitamin and can be produced industrially only through a bacterial fermentation-synthesis. This synthetic B_{12} is used to fortify foods and sold as a dietary supplement.

Vitamin B_{12} consists of a class of chemically related compounds (vitamers), all of which show pharmacological activity. It contains the biochemically rare element cobalt (chemical symbol Co) positioned in the center of a planar tetra-pyrrole ring called a corrin ring.



R = 5'-deoxyadenosyl, Me, OH, CN

https://en.wikipedia.org/wiki/Vitamin_B12

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Chapter 6 - Metabolism: Nucleotides
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Chapter 9 - Point by Point: Metabolism

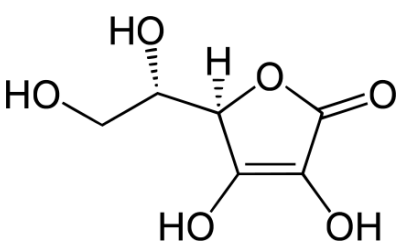
Vitamin C

Vitamin C or L-ascorbic acid, or simply ascorbate (the anion of ascorbic acid), is an essential nutrient for humans and certain other animal species. Vitamin C describes several vitamers that have vitamin C activity in animals, including ascorbic acid and its salts, and some oxidized forms of the molecule like dehydroascorbic acid. Ascorbate and ascorbic acid are both naturally present in the body when either of these is introduced into cells, since the forms interconvert according to pH.

Vitamin C is a cofactor in at least eight enzymatic reactions, including several collagen synthesis reactions that, when dysfunctional, cause the most severe symptoms of scurvy. In animals, these reactions are especially important in wound-healing and in preventing bleeding from capillaries. Ascorbate may also act as an antioxidant, protecting against oxidative stress.

Ascorbate (the anion of ascorbic acid) is required for a range of essential metabolic reactions in all animals and plants. It is made internally by almost all organisms. The main exceptions are most bats, all guinea pigs, capybaras, and the Haplorrhini (one of the two major primate suborders, consisting of tarsiers, monkeys, and humans and other apes). Ascorbate is also not synthesized by some species of birds and fish. All species that do not synthesize ascorbate require it in the diet. Deficiency in this vitamin causes the disease scurvy in humans.

The biological role of ascorbate is to act as a reducing agent, donating electrons to various enzymatic and a few non-enzymatic reactions. The one- and two-electron oxidized forms of vitamin C, semidehydroascorbic acid and dehydroascorbic acid, respectively, can be reduced in the body by glutathione and NADPH-dependent enzymatic mechanisms. The presence of glutathione in cells and extracellular fluids helps maintain ascorbate in a reduced state.



https://en.wikipedia.org/wiki/Vitamin_C

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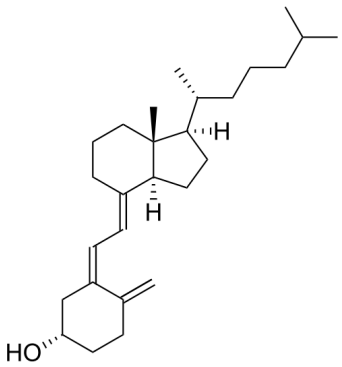
Vitamin D

Vitamin D refers to a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol - shown below) and vitamin D_2 (ergocalciferol). Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements. Very few foods contain vitamin D. Synthesis of vitamin D (specifically cholecalciferol) in the skin is the major natural source of the vitamin. Dermal synthesis of vitamin D from cholesterol is dependent on sun exposure (specifically UVB radiation).

The three steps in the synthesis of vitamin D_3 are regulated as follows:

- Cholecalciferol is synthesized in the skin from 7-dehydrocholesterol under the action of ultraviolet B (UVB) light. It reaches an equilibrium after several minutes depending on the intensity of the UVB in the sunlight - determined by latitude, season, cloud cover, and altitude - and the age and degree of pigmentation of the skin.
- Hydroxylation in the endoplasmic reticulum of liver hepatocytes of cholecalciferol to calcifediol (25-hydroxycholecalciferol) by 25-hydroxylase is loosely regulated, if at all, and blood levels of this molecule largely reflect the amount of cholecalciferol produced in the skin combined with any vitamin D_2 or D_3 ingested.
- Hydroxylation in the kidneys of calcifediol to calcitriol by 1-α-hydroxylase is tightly regulated: it is stimulated by either parathyroid hormone or hypophosphatemia and serves as the major control point in the production of the active circulating hormone calcitriol (1,25-dihydroxyvitamin D_3).



https://en.wikipedia.org/wiki/Vitamin_D

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Vitamin D Binding Protein

Vitamin D-binding protein belongs to the albumin gene family, together wi
serum albumin and α-fetoprotein. It is a multifunctional protein found in p
citic fluid, cerebrospinal fluid and on the surface of many cell types. Humar
cosylated α-globulin, ~58 kDa in size. The primary structure contains 28 cy
dues forming multiple disulfide bonds. It binds to vitamin D and its plasma
lites and transports them to target tissues.

https://en.wikipedia.org/wiki/Vitamin_D-binding_protein

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Vitamin D Receptor

The Vitamin D Receptor, also called the calcitriol receptor, is a member of the nuclear receptor family of transcription factors, and is the biological target of vitamin D. Upon activation by vitamin D, the VDR forms a heterodimer with the retinoid-X receptor and binds to hormone response elements on DNA resulting in expression or transrepression of specific geneproducts. The VDR not only regulates transcriptional responses but also involved in microRNA-directed post transcriptional mechanisms.

This gene encodes the nuclear hormone receptor for vitamin D3. This receptor also functions as a receptor for the secondary bile acid lithocholic acid. The receptor belongs to the family of trans-acting transcriptional regulatory factors and shows similarity of sequence to the steroid and thyroid hormone receptors.

Downstream targets of this nuclear hormone receptor are involved principally in mineral metabolism though the receptor regulates a variety of other metabolic pathways, such as those involved in the immune response and cancer.

Mutations in this gene are associated with type II vitamin D-resistant rickets. A single nucleotide polymorphism in the initiation codon results in an alternate translation start site three codons downstream. Alternative splicing results in multiple transcript variants encoding the same protein.

The vitamin D receptor plays an important role in regulating the hair cycle. Loss of VDR is associated with hair loss in experimental animals. Experimental studies have shown that the unliganded VDR interacts with regulatory regions in cWnt (wnt signaling pathway) and sonic hedgehog target genes and is required for the induction of these pathways during the postnatal hair cycle. These studies have revealed novel actions of the unliganded VDR in regulating the post-morphogenic hair cycle.

https://en.wikipedia.org/wiki/Calcitriol_receptor

Vitamin D_1

One of the minor forms of vitamin D, vitamin D_1 is a molecular mixture of e
erol (which is a secosteroid formed by photochemical bond breaking on an
and lumisterol (a stereoisomer of ergostero produced as a photochemical b
the UVB radiation of ergosterol).

https://en.wikipedia.org/wiki/Vitamin_D#Metabolic_activation

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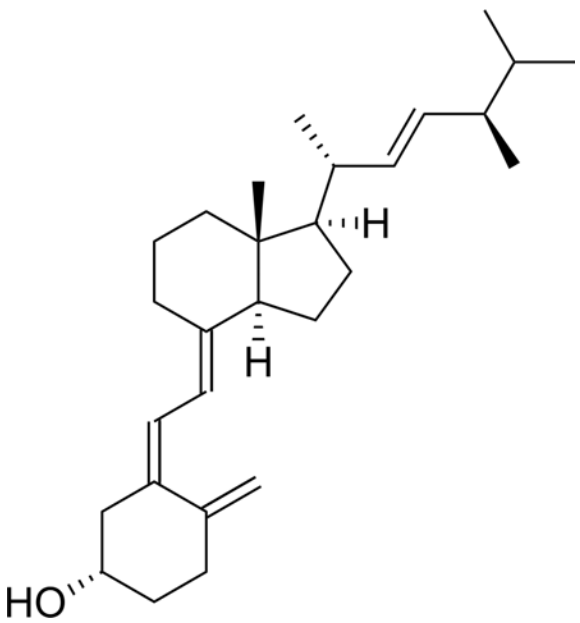
Chapter 2 - Structure & Function: Lipids

Vitamin D_2

One of two major forms of vitamin D, vitamin D_2 is chemically composed of ergocalc
erol (a secosteroid formed by a photochemical bond breaking of a steroid, specifically
by the action of ultraviolet light on ergosterol). Humans can source vitamin D_2 from
mushrooms, which contain a high concentration of the ergosterol precursor.



https://en.wikipedia.org/wiki/Vitamin_D#Metabolic_activation

Related Glossary Terms

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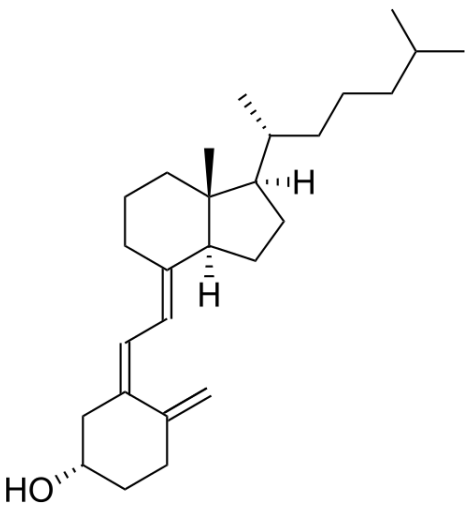
Vitamin D_3

One of two major forms of vitamin D, vitamin D_3 is chemically composed of cholecalciferol (a secosteroid made when 7-dehydrocholesterol in the skin is exposed to UVB radiation). In the human diet, vitamin D_3 is most commonly occurring in fish liver oils and fatty fish species, or in some lichens. It can also be manufactured synthetically, and provided as a dietary supplement.

The transformation that converts 7-dehydrocholesterol to vitamin D_3 occurs in two steps. First, 7-dehydrocholesterol is photolyzed by ultraviolet light in a 6-electron conrotatory ring-opening electrocyclic reaction. The product is previtamin D_3. Second, previtamin D_3 spontaneously isomerizes to vitamin D_3 (cholecalciferol) in an antarafacial sigmatropic hydride shift. At room temperature, the transformation of previtamin D_3 to vitamin D_3 in an organic solvent takes about 12 days to complete. The conversion of previtamin D_3 to vitamin D_3 in the skin is about 10 times faster than in an organic solvent.



https://en.wikipedia.org/wiki/Vitamin_D#Metabolic_activation

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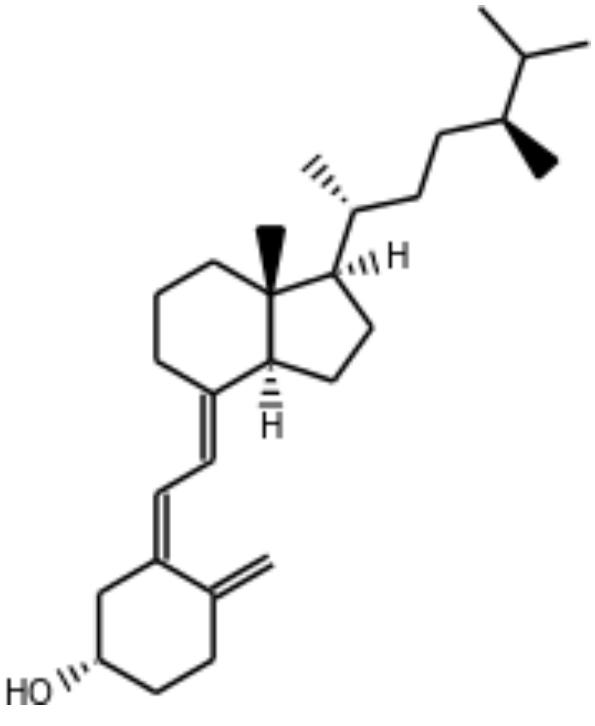
Vitamin D_4

One of the minor forms of vitamin D, vitamin D_4 is composed of 22-dihydroergocalciferol, a chemical also found in some mushrooms.



https://en.wikipedia.org/wiki/Vitamin_D#Metabolic_activation

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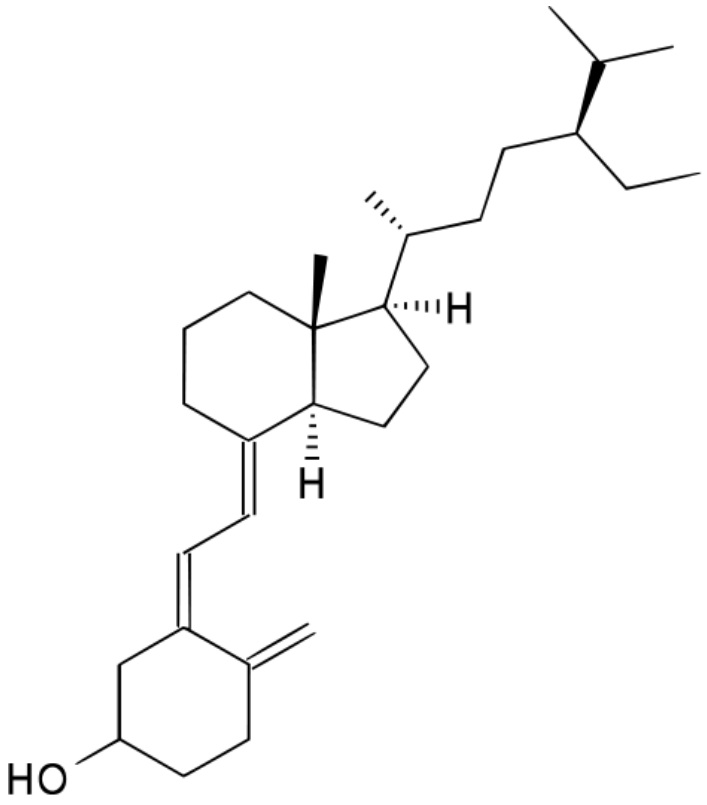
Chapter 2 - Structure & Function: Lipids

Vitamin D_5

One of the minor forms of vitamin D, vitamin D_5 is composed of sitocalciferol (a s
teroid formed from dehydrositosterol).



https://en.wikipedia.org/wiki/Vitamin_D#Metabolic_activation

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Vitamin E

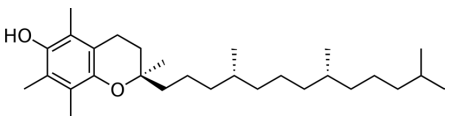
Vitamin E refers to a group of compounds that include both tocopherols and tocotrienols. Tocopherols function as antioxidants in the glutathione peroxidase pathway, and protect cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. This removes the free radical intermediates and prevents the oxidation reaction from continuing. Tocotrienols may have specialized roles in protecting neurons from damage and cholesterol reduction by inhibiting the activity of HMG-CoA reductase.

Vitamin E has many biological functions, the antioxidant function being the best known. Other functions include enzymatic activities, gene expression, and neurological function(s).

• As an antioxidant, vitamin E acts as a peroxyl radical scavenger, disabling the production of damaging free radicals in tissues, by reacting with them to form a tocopheryl radical, which will then be reduced by a hydrogen donor (such as vitamin C) and thus return to its reduced state. As it is fat-soluble, it is incorporated into cell membranes, which protects them from oxidative damage. Vitamin E has also found use as a commercial antioxidant in ultra high molecular weight polyethylene (UHMWPE) used in hip and knee implants to replace faulty joints, to help resist oxidation.
• As an enzymatic activity regulator, for instance, protein kinase C (PKC), which plays a role in smooth muscle growth, can be inhibited by α-tocopherol (shown below). α-Tocopherol has a stimulatory effect on the dephosphorylation enzyme, protein phosphatase 2A, which in turn, cleaves phosphate groups from PKC, leading to its deactivation, bringing the smooth muscle growth to a halt.
• Vitamin E also has an effect on gene expression. Macrophages rich in cholesterol are found in the atherogenetic tissue. Scavenger receptor CD36 is a class B scavenger receptor found to be up-regulated by oxidized low density lipoprotein (LDL) and binds it. Treatment with α-tocopherol was found to downregulate the expression of the CD36 scavenger receptor gene and the scavenger receptor class A (SR-A) and modulates expression of the connective tissue growth factor (CTGF). The CTGF gene, when expressed, is responsible for the repair of wounds and regeneration of the extracellular tissue lost or damaged during atherosclerosis.
• Vitamin E also plays a role in neurological functions, and inhibition of platelet coagulation.

Vitamin E also protects lipids and prevents the oxidation of polyunsaturated fatty acids.

So far, most human supplementation studies about vitamin E have used only α-tocopherol. This can affect levels of other forms of vitamin E, e.g. reducing serum γ- and δ-tocopherol concentrations. Moreover, a 2007 clinical study involving α-tocopherol concluded supplementation did not reduce the risk of major cardiovascular events in middle-aged and older men.



https://en.wikipedia.org/wiki/Vitamin_E

Related Glossary Terms

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Vitamin K

Vitamin K is a group of structurally similar, fat-soluble vitamins the human body requires for complete synthesis of certain proteins that are prerequisites for blood coagulation that the body needs for controlling binding of calcium in bones and other tissues. The vitamin K-related modification of the proteins allows them to bind calcium ions, which they cannot do otherwise. Without vitamin K, blood coagulation is seriously impaired, and uncontrolled bleeding occurs.

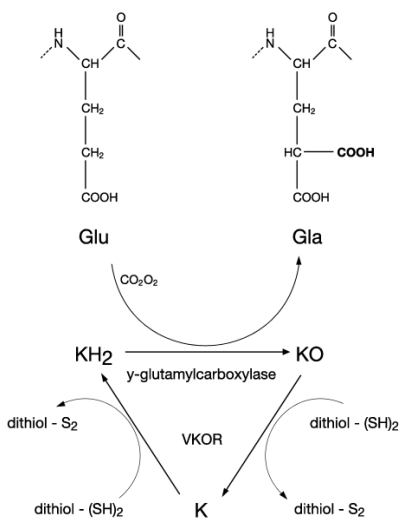
Chemically, the vitamin K family comprises 2-methyl-1,4-naphthoquinone (3-) derivatives. Vitamin K includes two natural vitamers: vitamin K_1 and vitamin K_2. Vitamin K_2, in turn, consists of a number of related chemical subtypes, with differing lengths of carbon side chains made of isoprenoid groups of atoms.

Vitamin K_1, also known as phylloquinone, phytomenadione, or phytonadione, is synthesized by plants, and is found in highest amounts in green leafy vegetables because it is directly involved in photosynthesis. It may be thought of as the "plant" form of vitamin K. It is active as a vitamin in animals and performs the classic functions of vitamin K, including its activity in the production of blood-clotting proteins. Animals may also convert it to vitamin K_2.

Bacteria in the colon (large intestine) can also convert K_1 into vitamin K_2. In addition, bacteria typically lengthen the isoprenoid side chain of vitamin K_2 to produce a range of vitamin K_2 forms, most notably the MK-7 to MK-11 homologues of vitamin K_2. All forms of K_2 other than MK-4 can only be produced by bacteria, which use these forms in anaerobic respiration. The MK-7 and other bacterially derived forms of vitamin K_2 exhibit vitamin K activity in animals, but MK-7's extra utility over MK-4, if any, is unclear and is a matter of investigation.

Three synthetic types of vitamin K are known: vitamins K_3, K_4, and K_5. Although the natural K_1 and all K_2 homologues and synthetic K_4 and K_5 have proven nontoxic, the synthetic form K_3 (menadione) has shown toxicity.

The vitamin K cycle is shown below.



https://en.wikipedia.org/wiki/Vitamin_K

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Chapter 9 - Point by Point: Structure and Function
Chapter 9 - Point by Point: Structure and Function
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Chapter 9 - Point by Point: Catalysis

Vitamin K Epoxide Reductase

Vitamin K epoxide reductase (VKOR) is an enzyme that reduces vitamin K
been oxidized in the carboxylation of glutamic acid residues in blood coagu
zymes. Its C1 subunit (VKORC1) is the target of anticoagulant warfarin. Fou
residues and one residue, which is either serine or threonine, are identified
active-site residues.

https://en.wikipedia.org/wiki/Vitamin_K_epoxide_reductase

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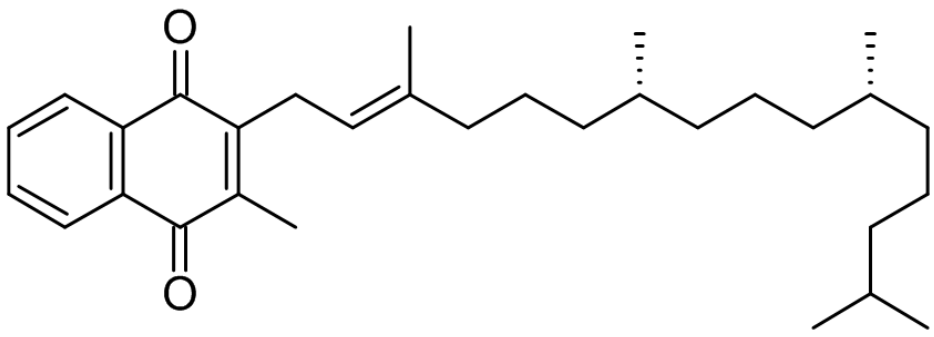
Vitamin K_1

Vitamin K_1, or phylloquinone, is a polycyclic aromatic ketone, based on 2-methyl-1,4-naphthoquinone, with a 3-phytyl substituent. It is a fat-soluble vitamin that is stable to air and moisture but decomposes in sunlight. It is found naturally in a wide variety of green plants, particularly leaves, since it functions as an electron acceptor during photosynthesis, forming part of the electron transport chain of Photosystem I.

Phylloquinone is an electron acceptor during photosynthesis, forming part of the electron transport chain of Photosystem I. Its best-known function in animals is as a cofactor in the formation of coagulation factors II (prothrombin), VII, IX, and X by the liver. It is also required for the formation of anticoagulant factors protein C and S. It is commonly used to treat warfarin toxicity, and as an antidote for coumatetralyl. Vitamin K is required for bone protein formation.



https://en.wikipedia.org/wiki/Phylloquinone

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Vitamin K_1 (phylloquinone)

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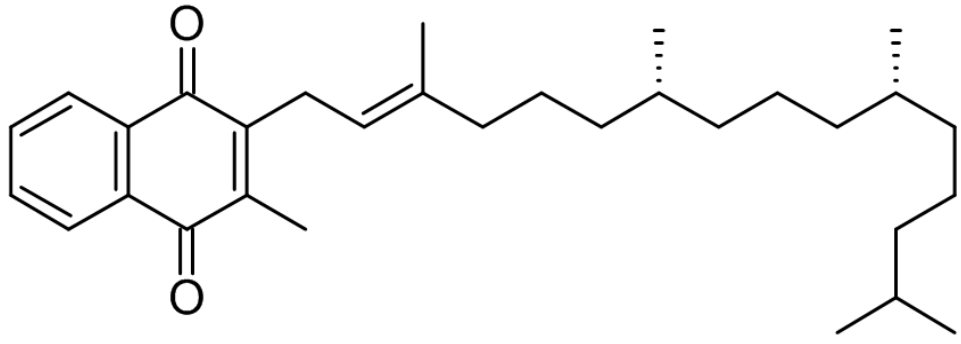

https://en.wikipedia.org/wiki/Phylloquinone

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Vitamin K_2

Vitamin K_2, the main storage form of menaquinones in animals, has several subtypes, which differ in isoprenoid chain length. These vitamin K_2 homologues are called menaquinones, and are characterized by the number of isoprenoid residues in their side chains. Their mechanism of action is similar to that of Vitamin K_1.

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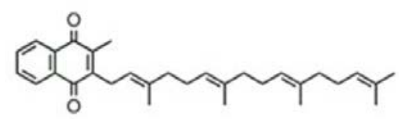
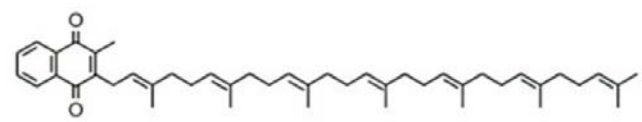
Menaquinone-7 is different from MK-4 in that it is not produced by human tissue. MK-7 may be converted from phylloquinone (K_1) in the colon by *E. coli* bacteria However, bacterially derived menaquinones (MK-7) appear to contribute minimally to overall vitamin K status. MK-4 and MK-7 are both found in the United States in dietary supplements for bone health.

The U.S. Food and Drug Administration (FDA) has not approved any form of vitamin K for the prevention or treatment of osteoporosis. However, MK-4 has been shown to decrease the incidence of fractures up to 87%. MK-4 (45 mg daily) has been approved by the Ministry of Health in Japan since 1995 for the prevention and treatment of osteoporosis.

All K vitamins are similar in structure: they share a “quinone” ring, but differ in the length and degree of saturation of the carbon tail and the number of “side chains”. The number of side chains is indicated in the name of the particular menaquinone (e.g., MK-4 means that four molecular units - called isoprene units - are attached to the carbon tail) and this influences the transport to different target tissues.

Two subtypes of vitamin K_2 are shown below.





https://en.wikipedia.org/wiki/Vitamin_K2

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Vitamin-K_2

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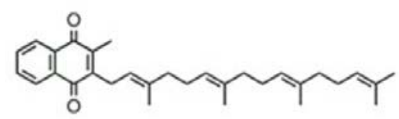

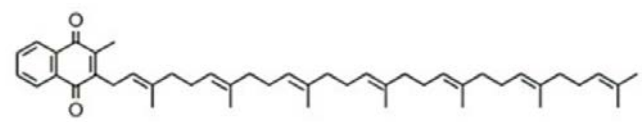

https://en.wikipedia.org/wiki/Vitamin_K2

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Vitronectin

Vitronectin (VTN or VN) is a glycoprotein of the hemopexin family which is abundantly found in serum, the extracellular matrix and bone. In humans it is encoded by the VTN gene.

Vitronectin binds to integrin α-V β-3 and thus promotes cell adhesion and spreading. It also inhibits the membrane-damaging effect of the terminal cytolytic complement pathway, and binds to several serpins (serine protease inhibitors). It is a secreted protein and exists in either a single chain form or a clipped, two chain form held together by a disulfide bond. Vitronectin has been speculated to be involved in hemostasis and tumor malignancy.

The somatomedin B domain of vitronectin binds to plasminogen activator inhibitor-1 (PAI-1), and stabilizes it. Thus vitronectin serves to regulate proteolysis initiated by plasminogen activation. In addition, vitronectin is a component of platelets and is, thus, involved in hemostasis. Vitronectin contains an RGD (45-47) sequence, which is a binding site for membrane-bound integrins, e.g., the vitronectin receptor, which serve to anchor cells to the extracellular matrix. The Somatomedin B domain interacts with the urokinase receptor, and this interaction has been implicated in cell migration and signal transduction. High plasma levels of both PAI-1 and the urokinase receptor have been shown to correlate with a negative prognosis for cancer patients. Cell adhesion and migration are directly involved in cancer metastasis, which provides a probable mechanistic explanation for this observation.

https://en.wikipedia.org/wiki/Vitronectin

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VLDLs

An abbreviation for “very-low-density-lipoprotein.” It is one of the five major groups of lipoproteins (chylomicrons, VLDL, low-density lipoprotein, intermediate-density lipoprotein, high-density lipoprotein) that enable fats and cholesterol to move within the water-based solution of the bloodstream. VLDL is assembled in the liver from triglycerides, cholesterol, and apolipoproteins. VLDL is converted in the bloodstream to low-density lipoprotein (LDL). VLDL transports endogenous products, whereas chylomicrons transport exogenous (dietary) products.

Very low-density lipoproteins transport endogenous triglycerides, phospholipids, cholesterol, and cholesteryl esters. It functions as the body's internal transport mechanism for lipids. In addition it serves for long-range transport of hydrophobic intercellular messengers, like the morphogen Indian hedgehog (protein).

Nascent VLDL released from the liver contains Apolipoprotein B-100, apolipoprotein C1 (apoC1), apolipoprotein E (apoE), cholesterol, cholestryl esters, and triglycerides. As it circulates in blood, it picks up apolipoprotein C-II (apoC-II) and additional apoE donated from high-density lipoprotein (HDL). At this point, nascent VLDL becomes a mature VLDL. Once in circulation, VLDL will come in contact with lipoprotein lipase (LPL) in the capillary beds in the body (adipose, cardiac, and skeletal muscle). LPL will remove triglycerides from VLDL for storage or energy production. VLDL now meets back up with HDL where apoC-II is transferred back to HDL (but keeps apoE). HDL also transfers cholesteryl esters to the VLDL in exchange for phospholipids and triglycerides via cholesterylester transfer protein (CETP). As more and more triglycerides are removed from the VLDL because of the action of LPL and CETP enzymes, the composition of the molecule changes, and it becomes intermediate-density lipoprotein (IDL).

Fifty percent of IDLs are recognized by receptors in the liver cells because of the apolipoprotein B-100 (apoB-100) and apoE they contain and are endocytosed. The other 50% of IDL lose apoE. When their cholesterol content becomes greater than the content of triglyceride, they become LDL, with apoB-100 as the primary apolipoprotein. The LDL is taken into a cell via the LDL receptor via endocytosis, where the contents are either stored, used for cell membrane structure, or converted into other products such as steroid hormones or bile acids.

https://en.wikipedia.org/wiki/Very_low-density_lipoprotein

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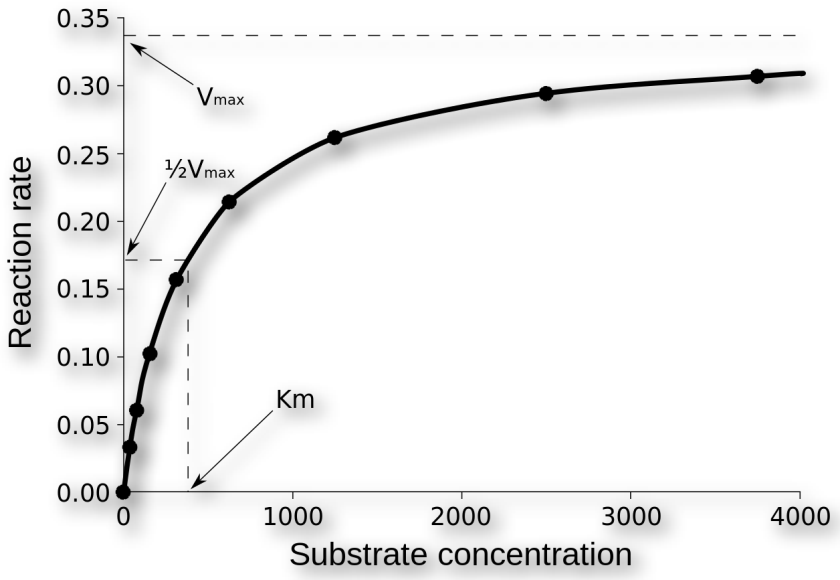
V_{max}

V_{max} refers to the maximum rate of reaction during an assay of an enzyme's kinetics. In an enzymatic reaction following Michaelis-Menten reaction parameters, V_{max} is observed as the velocity observed when enzyme becomes saturated with substrate.

The unit of V_{max} is concentration of product per time = [P]/time.

On a plot of initial velocity versus substrate concentration (V_0 vs. [S]), V_{max} is the value on the Y axis that the curve asymptotically approaches. It should be noted that the value of V_{max} depends on the amount of enzyme used in a reaction. If you double the amount of enzyme used, you will double the V_{max}. If one wanted to compare the velocities of two different enzymes, it would be necessary to use the same amounts of enzyme in the reaction each one catalyzes.



https://en.wikipedia.org/wiki/Enzyme_kinetics

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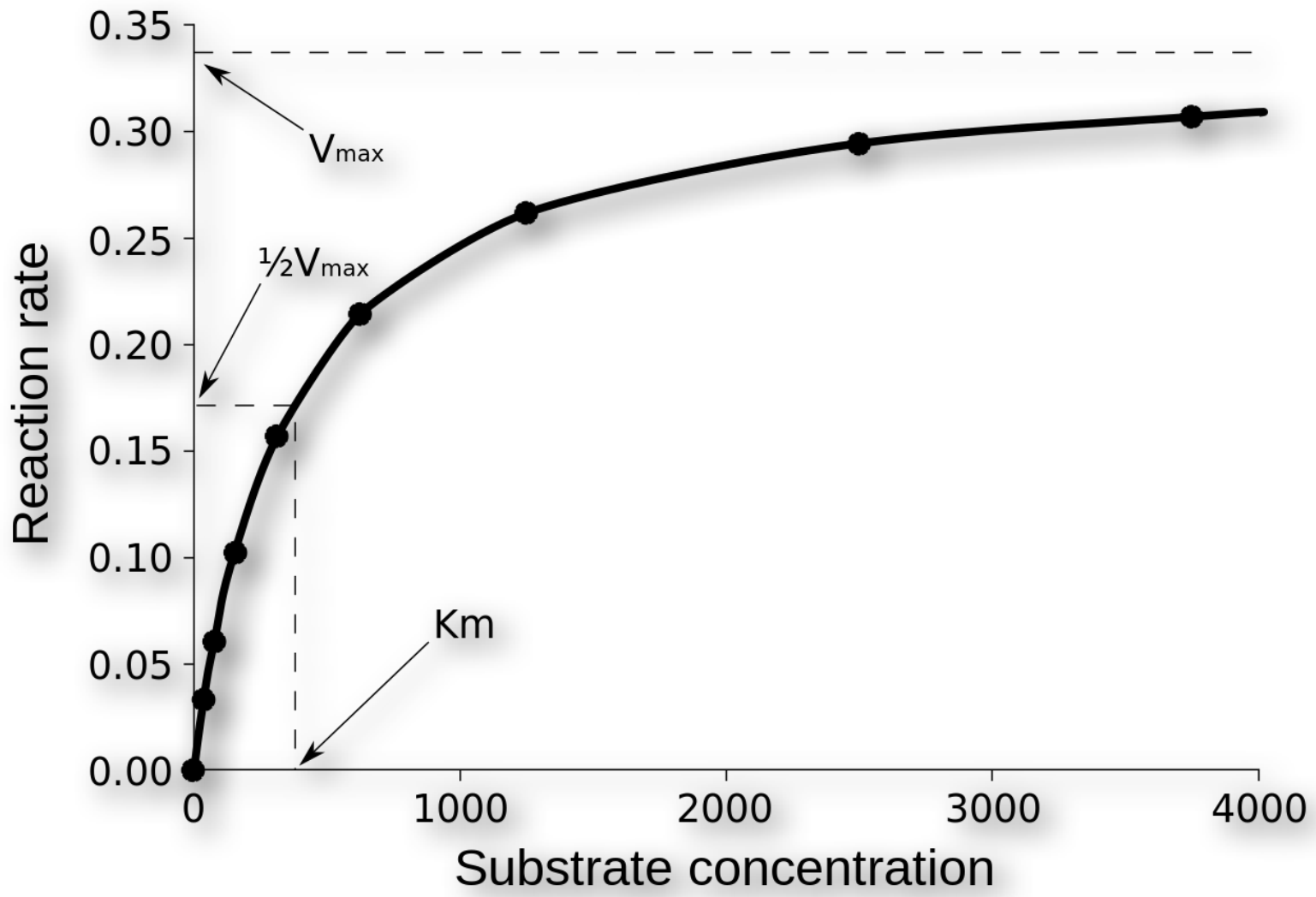
Vmax/2

In determining the K_m value of an enzyme, the substrate concentration that gives V
2 is the K_m.



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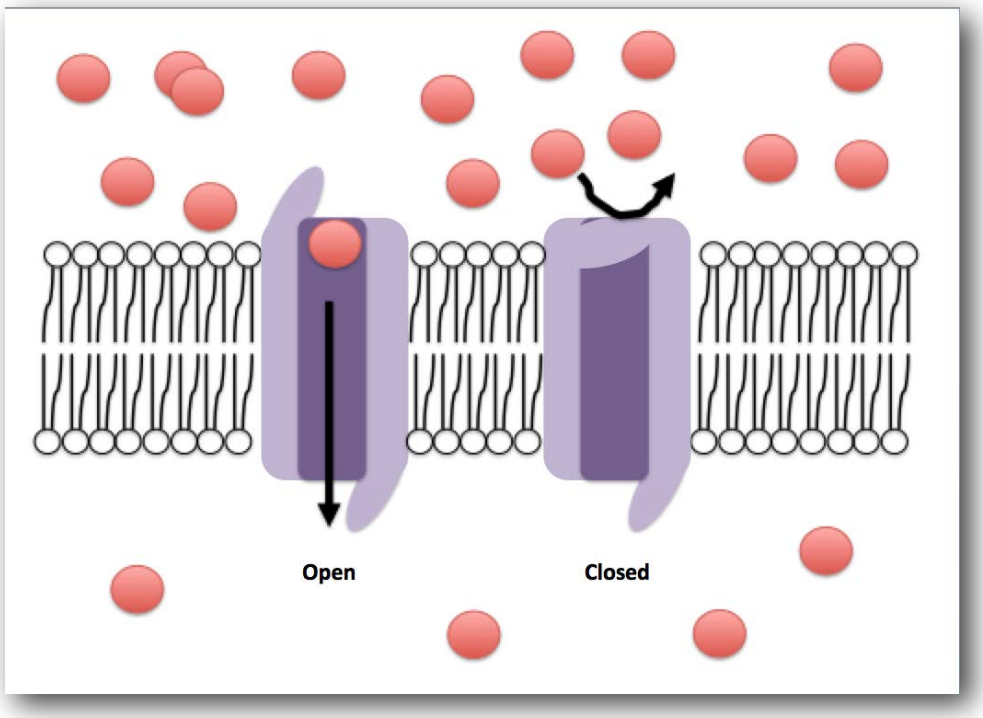
Voltage-gated Channels

Voltage-gated ion channels are a class of transmembrane proteins that form ion channels that are activated by changes in electrical membrane potential near the channel. The membrane potential alters the conformation of the channel proteins, regulating their opening and closing. Cell membranes are generally impermeable to ions, thus they must diffuse through the membrane through transmembrane protein channels. They have a crucial role in excitable cells such as neuronal and muscle tissues, allowing a rapid and coordinated depolarization in response to triggering voltage change.



https://en.wikipedia.org/wiki/Voltage-gated_ion_channel

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Von Willebrand factor

Von Willebrand factor (vWF) is a blood glycoprotein involved in hemostasis. It is deficient or defective in von Willebrand disease and is involved in a large number of other diseases, including thrombotic thrombocytopenic purpura, Heyde's syndrome, and possibly hemolytic-uremic syndrome. Increased plasma levels in a large number of cardiovascular, neoplastic, and connective tissue diseases are presumed to arise from adverse changes to the endothelium, and may contribute to an increased risk of thrombosis.

Von Willebrand factor's primary function is binding to other proteins, in particular factor VIII, and it is important in platelet adhesion to wound sites. It is not an enzyme and, thus, has no catalytic activity.
vWF binds to a number of cells and molecules. The most important ones are:
• Factor VIII is bound to vWF while inactive in circulation. Factor VIII degrades rapidly when not bound to vWF. Factor VIII is released from vWF by the action of thrombin.
• vWF binds to collagen, e.g., when it is exposed in endothelial cells due to damage occurring to the blood vessel.
• vWF binds to platelet gpIb when it forms a complex with gpIX and gpV. This binding occurs under all circumstances, but is most efficient under high shear stress (i.e., rapid blood flow in narrow blood vessels, see below).
• vWF binds to other platelet receptors when they are activated, e.g., by thrombin (i.e., when coagulation has been stimulated).

vWF plays a major role in blood coagulation. Therefore, vWF deficiency or dysfunction (von Willebrand disease) leads to a bleeding tendency, which is most apparent in tissues having high blood flow shear in narrow vessels. From studies it appears that vWF uncoils under these circumstances, decelerating passing platelets. Calcium enhances the refolding rate of vWF A_2 domain, allowing the protein to act as a shear force sensor.

https://en.wikipedia.org/wiki/Von_Willebrand_factor

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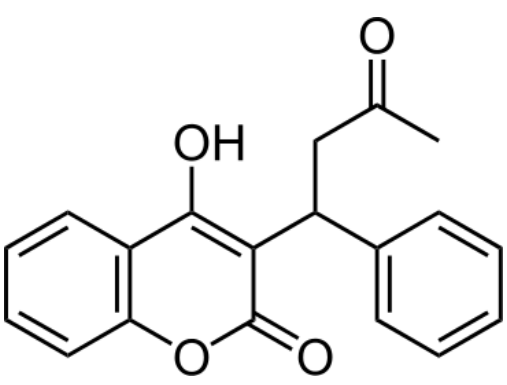
Warfarin

Warfarin, also known by the brand names Coumadin among others, is an anticoagulant normally used in the prevention of thrombosis and thromboembolism, the formation of blood clots in the blood vessels and their migration elsewhere in the body, respectively. X-ray crystallographic studies of warfarin show that it exists in tautomeric form, as the cyclic hemiketal, which is formed from the 4-hydroxycoumarin and the ketone in the 3-position substituent.

Warfarin and related 4-hydroxycoumarin-containing molecules decrease blood coagulation by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K_1 to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. Despite being labeled a vitamin K antagonist, warfarin does not antagonize the action of vitamin K_1, but rather antagonizes vitamin K_1 recycling, depleting active vitamin K_1. Thus, the pharmacologic action may always be reversed by fresh vitamin K_1. When administered, these drugs do not anticoagulate blood immediately. Instead, onset of their effect requires about two to three days before remaining active clotting factors have had time to naturally disappear in metabolism, and the duration of action of a single dose of warfarin is 2 to 5 days. Reversal of warfarin's effect by discontinuing its use, or by administering vitamin K_1, requires a similar period of time.



https://en.wikipedia.org/wiki/Warfarin

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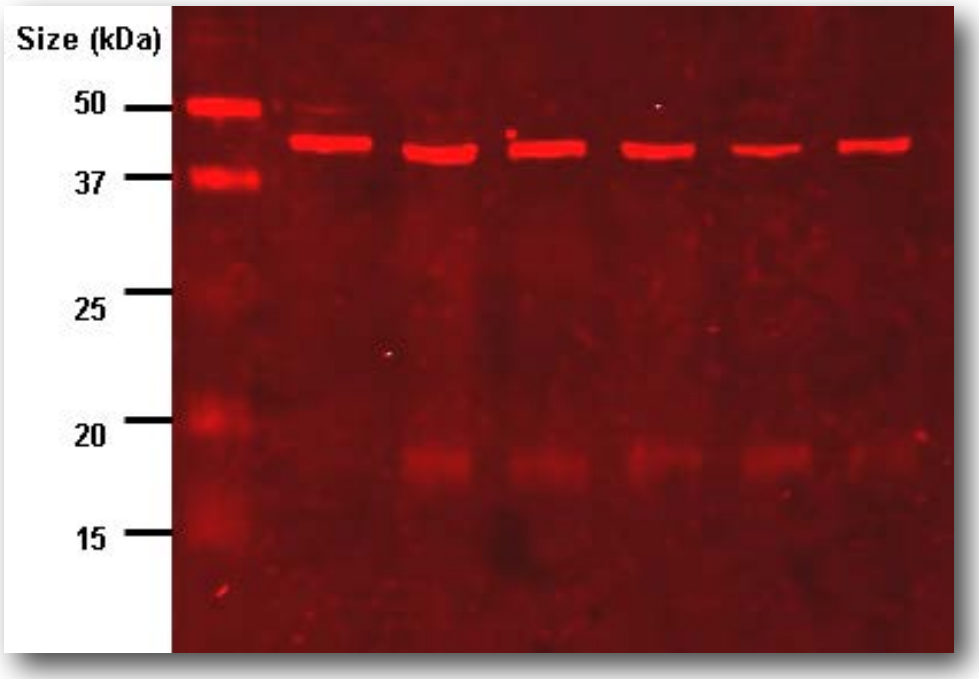
Chapter 9 - Point by Point: Catalysis

Western Blot

The western blot (sometimes called the protein immunoblot) is a widely used analytical technique used to detect specific proteins in a sample of tissue homogenate or extract. It uses gel electrophoresis to separate native proteins by 3-D structure or denatured proteins by the length of the polypeptide. The proteins are then transferred to a membrane (typically nitrocellulose or PVDF), where they are stained with antibodies specific to the target protein.



https://en.wikipedia.org/wiki/Western_blot

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Chapter 9 - Point by Point: Techniques

Wnt Signaling Pathway

The Wnt signaling pathways are a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors. Three Wnt signaling pathways have been characterized: the canonical Wnt pathway, the noncanonical planar cell polarity pathway, and the noncanonical Wnt/calcium pathway. All three pathways are activated by binding a Wnt-protein ligand to a Frizzled family receptor, which passes the biological signal to the protein dishevelled inside the cell. The canonical Wnt pathway leads to regulation of gene transcription. The noncanonical planar cell polarity pathway regulates the cytoskeleton that is responsible for the shape of the cell. The noncanonical Wnt/calcium pathway regulates calcium inside the cell. Wnt signaling pathways use either nearby cell-cell communication (paracrine) or same-cell communication (autocrine). They are highly evolutionarily conserved in animals, which means they are similar across animal species from fruit flies to humans.

Wnt signaling was first identified for its role in carcinogenesis, then for its function in embryonic development. The embryonic processes it controls include body axis patterning, cell fate specification, cell proliferation and cell migration. These processes are necessary for proper formation of important tissues including bone, heart and muscle. Its role in embryonic development was discovered when genetic mutations in Wnt pathway proteins produced abnormal fruit fly embryos. Wnt signaling also controls tissue regeneration in adult bone marrow, skin and intestine. Later research found that the genes responsible for these abnormalities also influenced breast cancer development in mice.

https://en.wikipedia.org/wiki/Wnt_signaling_pathway

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Wobble Position

In the genetic code, there are $4^3 = 64$ possible codons (tri-nucleotide sequences). For translation, each of these codons requires a tRNA molecule with a complementary anti-codon. If each tRNA molecule paired with its complementary mRNA codon using canonical Watson-Crick base pairing, then 64 types (species) of tRNA molecule would be required. In the standard genetic code, three of these 64 mRNA codons (UAA, UAG and UGA) are stop codons. These terminate translation by binding to release factors rather than tRNA molecules, so canonical pairing would require 61 species of tRNA. Since most organisms have fewer than 45 species of tRNA, some tRNA species must pair with more than one codon. In 1966, Francis Crick proposed the Wobble hypothesis to account for this.

He postulated that the 5' base on the anticodon, which binds to the 3' base on the mRNA, was not as spatially confined as the other two bases, and could, thus, have non-standard base pairing. Crick creatively named it for the small amount of play that occurs at this third codon position. Movement ("wobble") of the base in the 5' anticodon position is necessary for small conformational adjustments that affect the overall pairing geometry of anticodons of tRNA.

As an example, yeast tRNAPhe has the anticodon 5'-GmAA-3' and can recognize the codons 5'-UUC-3' and 5'-UUU-3'. It is, therefore, possible for non-Watson–Crick base pairing to occur at the third codon position, i.e., the 3' nucleotide of the mRNA codon and the 5' nucleotide of the tRNA anticodon.

https://en.wikipedia.org/wiki/Wobble_base_pair

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Chapter 7 - Information Processing: RNA Processing

Wombats

Wombats are short-legged, muscular quadrupedal marsupials that are native to Australia. They are about 1 m (40 in) in length with small, stubby tails. There are three extant species and they are all members of the family Vombatidae. They are adaptable and habitat tolerant, and are found in forested, mountainous, and heathland areas of south-eastern Australia, including Tasmania, as well as an isolated patch of about 300 ha (740 acres) in Epping Forest National Park in central Queensland.

https://en.wikipedia.org/wiki/Wombat

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Writhe

DNA supercoiling refers to the over- or under-winding of a DNA strand tha
the typical 10.5 base pairs per turn. Supercoiling is an expression of the str
strand. it is important in a number of biological processes, such as compact
and by regulating access to the genetic code, DNA supercoiling strongly affe
metabolism and possibly gene expression. Additionally, certain enzymes su
somerases are able to change DNA topology to facilitate functions such as D
tion or transcription. Mathematical expressions are used to describe superc
comparing different coiled states to relaxed B-form DNA.

To relieve the tension arising from supercoiling, DNA strands writhe. Writ
sponds to the number of times the DNA double helix crosses over itself.

https://en.wikipedia.org/wiki/Nucleic_acid_structure

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https://en.wikipedia.org/wiki/Nucleic_acid_structure

Related Glossary Terms

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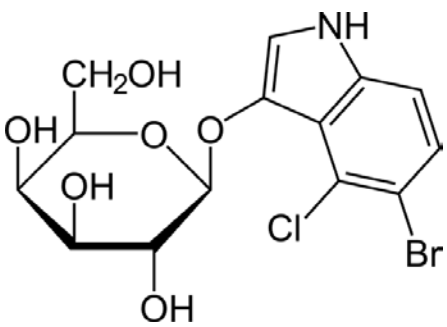
X-gal

X-gal (also abbreviated BCIG for 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside) is an organic compound consisting of galactose linked to a substituted indole. X-gal is much used in molecular biology to test for the presence of an enzyme, β-galactosidase.

X-gal is an analog of lactose, and therefore may be hydrolyzed by the β-galactosidase enzyme which cleaves the β-glycosidic bond in D-lactose. X-gal, when cleaved by β-galactosidase, yields galactose and 5-bromo-4-chloro-3-hydroxyindole. The latter then spontaneously dimerizes and is oxidized into 5,5'-dibromo-4,4'-dichloro-indigo, an intensely blue product which is insoluble. X-gal itself is colorless, so the presence of blue-colored product may therefore be used as a test for the presence of active β-galactosidase. This easy identification of an active enzyme allows the gene for β-galactosidase (the lacZ gene) to be used as a reporter gene in various applications.



https://en.wikipedia.org/wiki/X-gal

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X-ray Crystallography

X-ray crystallography is a tool used for identifying the atomic and molecular structure of a crystal, in which the crystalline atoms cause a beam of incident X-rays to diffract into many specific directions. By measuring the angles and intensities of these diffracted beams, a crystallographer can produce a three-dimensional picture of the density of electrons within the crystal. From this electron density, the mean positions of the atoms in the crystal can be determined, as well as their chemical bonds, their disorder and various other information.

In a single-crystal X-ray diffraction measurement, a crystal is mounted on a goniometer. The goniometer is used to position the crystal at selected orientations. The crystal is illuminated with a finely focused monochromatic beam of X-rays, producing a diffraction pattern of regularly spaced spots known as reflections. The two-dimensional images taken at different orientations are converted into a three-dimensional model of the density of electrons within the crystal using the mathematical method of Fourier transforms, combined with chemical data known for the sample. Poor resolution (fuzziness) or even errors may result if the crystals are too small, or not uniform enough in their internal makeup.

X-ray crystallography is related to several other methods for determining atomic structures. Similar diffraction patterns can be produced by scattering electrons or neutrons, which are likewise interpreted by Fourier transformation. If single crystals of sufficient size cannot be obtained, various other X-ray methods can be applied to obtain less detailed information. Such methods include fiber diffraction, powder diffraction and (if the sample is not crystallized) small-angle X-ray scattering (SAXS). If the material under investigation is only available in the form of nanocrystalline powders or suffers from poor crystallinity, the methods of electron crystallography can be applied for determining the atomic structure.

For all above mentioned X-ray diffraction methods, the scattering is elastic. The scattered X-rays have the same wavelength as the incoming X-ray. By contrast, inelastic X-ray scattering methods are useful in studying excitations of the sample, rather than the distribution of its atoms.

https://en.wikipedia.org/wiki/X-ray_crystallography

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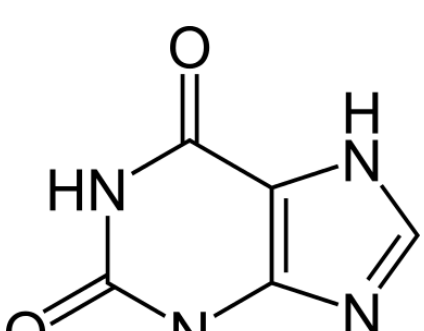
Chapter 2 - Structure & Function: Proteins I

Xanthine

Xanthine (3,7-dihydro-purine-2,6-dione), is a purine base found in most human body tissues and fluids and in other organisms. A number of stimulants are derived from xanthine, including caffeine and theobromine. Xanthine is a product on the pathway of purine degradation.

- It is created from guanine by guanine deaminase.
- It is created from hypoxanthine by xanthine oxidoreductase.
- It is also created from xanthosine by purine nucleoside phosphorylase (PNP).

Xanthine is subsequently converted to uric acid by the action of the xanthine oxidase enzyme.



https://en.wikipedia.org/wiki/Xanthine

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Xanthine Oxidase

Xanthine oxidase (XO, sometimes 'XAO') is a form of xanthine oxidoreductase, a type of enzyme that generates reactive oxygen species. These enzymes catalyze the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. These enzymes play an important role in the catabolism of purines in some species, including humans.

The following chemical reactions are catalyzed by xanthine oxidase:

- Hypoxanthine + H_2O + O_2 <=> Xanthine + H_2O_2
- Xanthine + H_2O + O_2 <=> Uric acid + H_2O_2

Xanthine oxidase can also act on certain other purines, pterins, and aldehydes. For example, it efficiently converts 1-methylxanthine (a metabolite of caffeine) to 1-methyluric acid, but has little activity on 3-methylxanthine. Under some circumstances it can produce superoxide ion

$$RH + H_2O + 2\ O_2 \ <=> ROH + 2\ O_2^- + 2\ H^+$$

https://en.wikipedia.org/wiki/Xanthine_oxidase

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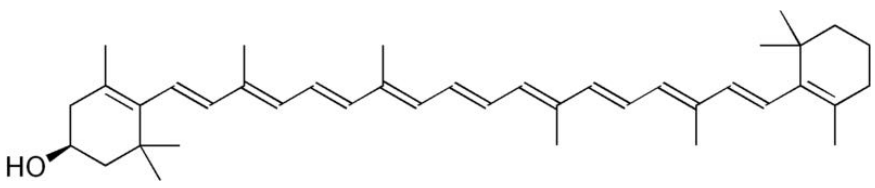
Xanthophylls

Xanthophylls (originally phylloxanthins) are yellow pigments that occur widely in nature and form one of two major divisions of the carotenoid group. The other division is formed by the carotenes. The molecular structure of xanthophylls is similar to that of carotenes, but xanthophylls contain oxygen atoms, while carotenes are purely hydrocarbons with no oxygen.

Like other carotenoids, xanthophylls are found in highest quantity in the leaves of most green plants, where they act to modulate light energy and perhaps serve as a non-photochemical quenching agent to deal with triplet chlorophyll (an excited form of chlorophyll), which is overproduced at high light levels in photosynthesis. The xanthophylls found in the bodies of animals, and in dietary animal products, are ultimately derived from plant sources in the diet. For example, the yellow color of chicken egg yolks, fat, and skin comes from ingested xanthophylls (primarily lutein, which is often added to chicken feed for this purpose).

The yellow color of the human macula lutea (literally, yellow spot) in the retina of the eye results from the lutein and zeaxanthin it contains, both xanthophylls again requiring a source in the human diet to be present in the eye. These xanthophylls protect the eye from ionizing blue and ultraviolet light, which they absorb. These two specific xanthophylls do not function in the mechanism of sight, since they cannot be converted to retinal (also called retinaldehyde or vitamin A aldehyde). Their arrangement is believed to be the cause of Haidinger's brush, an entoptic phenomenon that allows to perceive the polarization of light.

Shown below is the structure of the xanthin known as cryptoxanthin.



https://en.wikipedia.org/wiki/Xanthophyll

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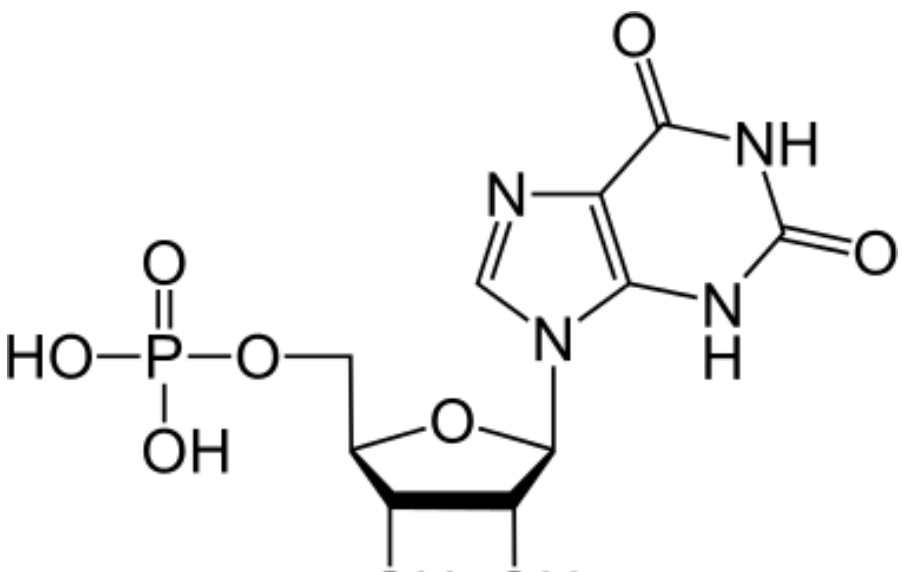
Xanthosine 5'-phosphate

Xanthosine 5’-phosphate or Xanthosine monophosphate, is an intermediate in purin
metabolism. It is a ribonucleoside monophosphate formed from IMP via the action o
IMP dehydrogenase, and it forms GMP via the action of GMP synthase. Also, XMP ca
be released from XTP by enzyme deoxyribonucleoside triphosphate pyrophosphohyd
lase containing (d)XTPase activity.



https://en.wikipedia.org/wiki/Xanthosine_monophosphate

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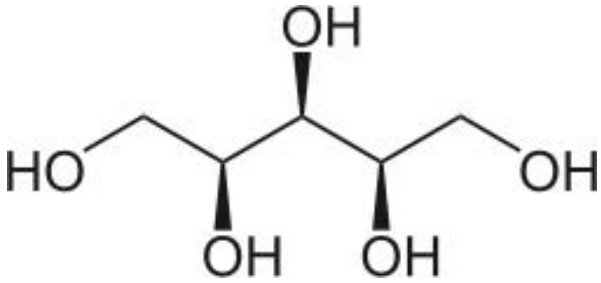
Chapter 6 - Metabolism: Nucleotides

Chapter 6 - Metabolism: Nucleotides

Xylitol

Xylitol is a sugar alcohol used as a sweetener. Xylitol is categorized as a polyalcohol or sugar alcohol (alditol). It has the formula $CH_2OH(CHOH)_3CH_2OH$ and is an achiral isomer of pentane-1,2,3,4,5-pentol. Unlike other natural or synthetic sweeteners, xylitol is actively beneficial for dental health by reducing cavities with regular use and is helpful to remineralization.

Xylitol is naturally found in low concentrations in the fibers of many fruits and vegetables, and can be extracted from various berries, oats, and mushrooms, as well as fibrous material such as corn husks and sugar cane bagasse. However, industrial production starts from xylan (a hemicellulose) extracted from hardwoods or corncobs, which is hydrolyzed into xylose and catalytically hydrogenated into xylitol. A study in laboratory rats that compared xylitol to other artificial sweeteners found that xylitol had fewer or no side effects, had fewer calories, and was less likely to cause cavities (that is, had lower cariogenicity) than sucrose (table sugar).



https://en.wikipedia.org/wiki/Xylitol

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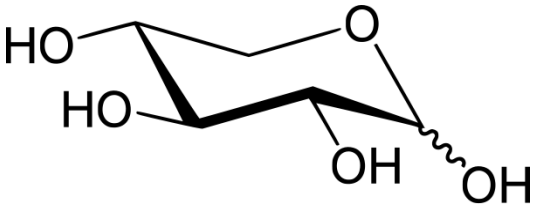
Xylose

Xylose is a sugar first isolated from wood, and named for it. Xylose is classified as a monosaccharide of the aldopentose type, which means that it contains five carbon atoms and includes a formyl functional group. It is derived from hemicellulose, one of the main constituents of biomass.

Xylose is the main building block for the hemicellulose xylan, which comprises about 30% of some plants (birch for example), far less in others (spruce and pine have about 9% xylan). Xylose is otherwise pervasive, being found in the embryos of most edible plants. It was first isolated from wood by Finnish scientist, Koch, in 1881, but first became commercially viable, with a price close to sucrose, in 1930.

Xylose is also the first saccharide added to the serine or threonine in the proteoglycan type O-glycosylation, and, so, it is the first saccharide in biosynthetic pathways of most anionic polysaccharides such as heparan sulfate and chondroitin sulfate.



https://en.wikipedia.org/wiki/Xylose

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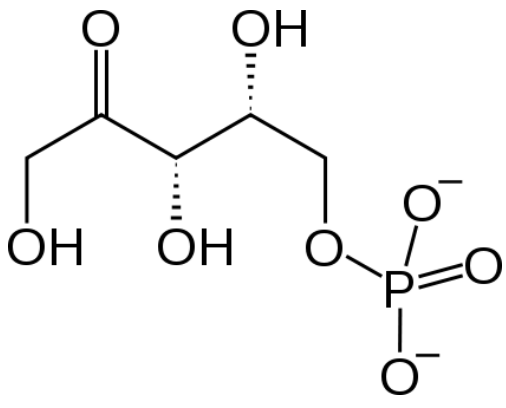
Xylulose-5-phosphate

D-Xylulose 5-phosphate (D-xylulose-5-P) is an intermediate in the pentose phosphate pathway. It is a ketose sugar formed from ribulose-5-phosphate. Although previously thought of mainly as an intermediary in the pentose phosphate pathway, recent research has shown that the sugar also has a role in gene expression, mainly by promoting the ChREBP transcription factor in the well-fed state.



https://en.wikipedia.org/wiki/Xylulose_5-phosphate

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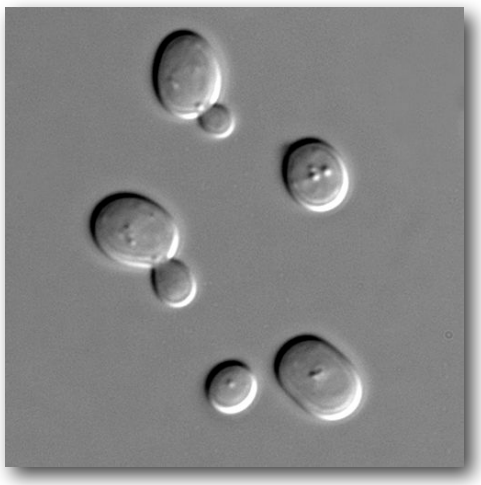
Yeast

Yeasts are eukaryotic, single-celled microorganisms classified as members of the fungus kingdom. The yeast lineage originated more than 100 million years ago, and 1,500 species are currently identified. They are estimated to constitute 1% of all described fungal species. Yeasts are unicellular organisms who evolved from multicellular ancestors, with some species having the ability to develop multicellular characteristics by forming strings of connected budding cells known as pseudohyphae or false hyphae. Yeast sizes vary greatly, depending on species and environment, typically measuring 3–4 µm in diameter, although some yeasts can grow to 40 µm in size. Most yeasts reproduce asexually by mitosis, and many do so by the asymmetric division process known as budding.

Yeasts, with their single-celled growth habit, can be contrasted with molds, which grow hyphae. Fungal species that can take both forms (depending on temperature or other conditions) are called dimorphic fungi ("dimorphic" means "having two forms").

By fermentation, the yeast species *Saccharomyces cerevisiae* converts carbohydrates to carbon dioxide and alcohols – for thousands of years the carbon dioxide has been used in baking and the alcohol in alcoholic beverages. It is also a centrally important model organism in modern cell biology research, and is one of the most thoroughly researched eukaryotic microorganisms. Researchers have used it to gather information about the biology of the eukaryotic cell and ultimately human biology. Other species of yeasts, such as *Candida albicans*, are opportunistic pathogens and can cause infections in humans. Yeasts have recently been used to generate electricity in microbial fuel cells, and produce ethanol for the biofuel industry.

Yeasts do not form a single taxonomic or phylogenetic grouping. The term "yeast" is often taken as a synonym for *Saccharomyces cerevisiae*, but the phylogenetic diversity of yeasts is shown by their placement in two separate phyla: the *Ascomycota* and the *Basidiomycota*. The budding yeasts ("true yeasts") are classified in the order *Saccharomycetales*.



https://en.wikipedia.org/wiki/Yeast

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Yeast Two-hybrid Screening

Two-hybrid screening (also known as yeast two-hybrid system or Y2H) is a molecular biology technique used to discover protein–protein interactions (PPIs) and protein–DNA interactions by testing for physical interactions (such as binding) between two proteins or a single protein and a DNA molecule, respectively.

The premise behind the test is the activation of downstream reporter gene(s) by the binding of a transcription factor onto an upstream activating sequence (UAS). For two-hybrid screening, the transcription factor is split into two separate fragments, called the binding domain (BD) and activating domain (AD). The BD is the domain responsible for binding to the UAS and the AD is the domain responsible for the activation of transcription. The Y2H is thus a protein-fragment complementation assay.

The key to the two-hybrid screen is that in most eukaryotic transcription factors, the activating and binding domains are modular and can function in proximity to each other without direct binding. This means that even though the transcription factor is split into two fragments, it can still activate transcription when the two fragments are indirectly connected.

The most common screening approach is the yeast two-hybrid assay. This system often utilizes a genetically engineered strain of yeast in which the biosynthesis of certain nutrients (usually amino acids or nucleic acids) is lacking. When grown on media that lacks these nutrients, the yeast fail to survive. This mutant yeast strain can be made to incorporate foreign DNA in the form of plasmids. In yeast two-hybrid screening, separate bait and prey plasmids are simultaneously introduced into the mutant yeast strain.

Plasmids are engineered to produce a protein product in which the DNA-binding domain (BD) fragment is fused onto a protein while another plasmid is engineered to produce a protein product in which the activation domain (AD) fragment is fused onto another protein. The protein fused to the BD may be referred to as the bait protein, and is typically a known protein the investigator is using to identify new binding partners. The protein fused to the AD may be referred to as the prey protein and can be either a single known protein or a library of known or unknown proteins. In this context, a library may consist of a collection of protein-encoding sequences that represent all the proteins expressed in a particular organism or tissue, or may be generated by synthesizing random DNA sequences. Regardless of the source, they are subsequently incorporated into the protein-encoding sequence of a plasmid, which is then transfected into the cells chosen for the screening method. This technique, when using a library, assumes that each cell is transfected with no more than a single plasmid and that, therefore, each cell ultimately expresses no more than a single member from the protein library.

If the bait and prey proteins interact (i.e., bind), then the AD and BD of the transcription factor are indirectly connected, bringing the AD in proximity to the transcription start site and transcription of reporter gene(s) can occur. If the two proteins do not interact, there is no transcription of the reporter gene. In this way, a successful interaction between the fused protein is linked to a change in the cell phenotype.

https://en.wikipedia.org/wiki/Two-hybrid_screening

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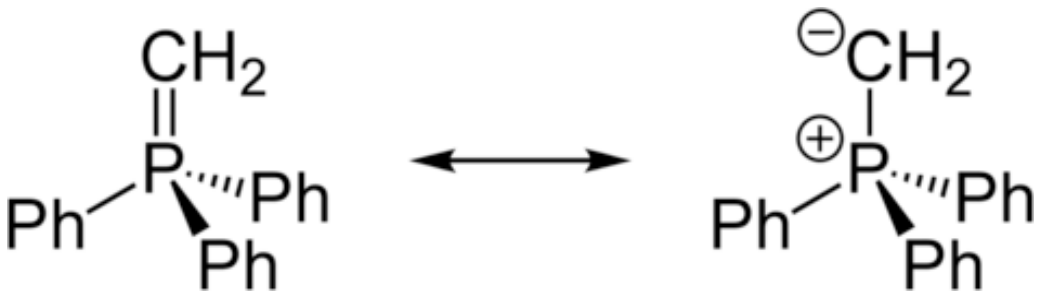
Ylide

An ylide or ylid is a neutral dipolar molecule containing a formally negatively charge atom (usually a carbanion) directly attached to a heteroatom with a formal positive charge (usually nitrogen, phosphorus or sulfur), and in which both atoms have full o tets of electrons. Ylides are thus 1,2-dipolar compounds. They appear in organic che istry as reagents or reactive intermediates.

Many ylides may be depicted by a multiple bond form in a resonance structure, know as the ylene form, shown below.



https://en.wikipedia.org/wiki/Ylide

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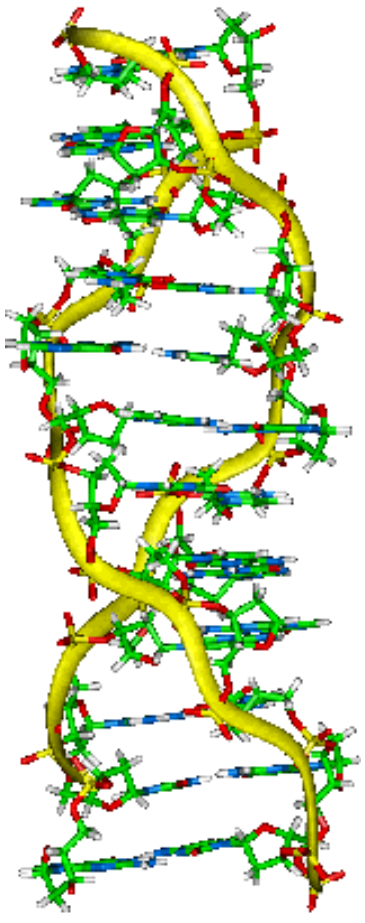
Chapter 6 - Metabolism: Citric Acid Cycle & Related Pathways

Z-DNA

Z-DNA is one of the many possible double helical structures of DNA. It is a left-handed double helical structure in which the double helix winds to the left in a zig-zag pattern (instead of to the right, like the more common B-DNA form). Z-DNA is thought to be one of three biologically active double helical structures along with A- and B-DNA.

The Z-DNA helix is left-handed and has a structure that repeats every 2 base pairs. The major and minor grooves, unlike A- and B-DNA, show little difference in width. Formation of this structure is generally unfavorable, although certain conditions can promote it; such as alternating purine-pyrimidine sequence (especially poly(dGC)2), negative DNA supercoiling or high salt and some cations (all at physiological temperature, 37 °C, and pH 7.3-7.4).



https://en.wikipedia.org/wiki/Z-DNA

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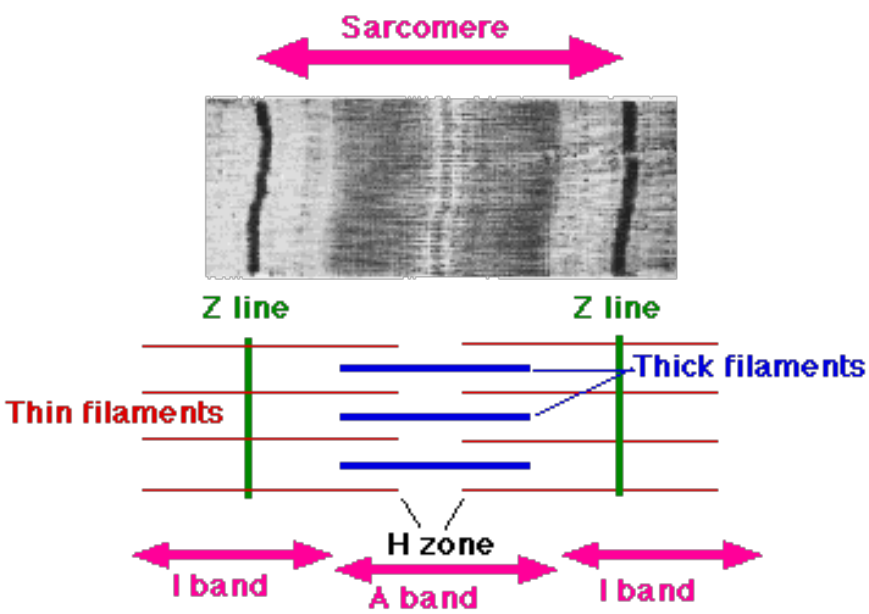
Z-lines

A myofibril (also known as a muscle fibril) is a basic rod-like unit of a muscle cell. Myofibrils are composed of long proteins including actin, myosin, and titin, and other proteins that hold them together. These proteins are organized into thick and thin filaments called myofilaments, which repeat along the length of the myofibril in sections called sarcomeres.

The names of the various sub-regions of the sarcomere are based on their relatively lighter or darker appearance when viewed through the light microscope. Each sarcomere is delimited by two very dark colored bands called Z-discs or Z-lines (from the German zwischen meaning between). These Z-discs are dense protein discs that do not easily allow the passage of light.



https://en.wikipedia.org/wiki/Myofibril

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Zinc Fingers

A zinc finger is a small protein structural motif that is characterized by the coordination of one or more zinc ions in order to stabilize the fold. Originally coined to describe the finger-like appearance of a hypothesized structure from *Xenopus laevis* transcription factor IIIA, the zinc finger name has now come to encompass a wide variety of differing protein structures.

Proteins that contain zinc fingers (zinc finger proteins) are classified into several different structural families. Unlike many other clearly defined supersecondary structures such as Greek keys or β hairpins, there are a number of types of zinc fingers, each with a unique three-dimensional architecture. A particular zinc finger protein's class is determined by this three-dimensional structure, but it can also be recognized based on the primary structure of the protein or the identity of the ligands coordinating the zinc ion. In spite of the large variety of these proteins, however, the vast majority typically function as interaction modules that bind DNA, RNA, proteins, or other small, useful molecules, and variations in structure serve primarily to alter the binding specificity of a particular protein.

https://en.wikipedia.org/wiki/Zinc_finger

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Chapter 2 - Structure and Function: Proteins

Chapter 9 - Point by Point: Structure and Function

Zymogens

A zymogen, also called a proenzyme, is an inactive precursor of an enzyme. A zymogen requires a biochemical change (such as a hydrolysis reaction revealing the active site, or changing the configuration to reveal the active site) for it to become an active enzyme. The biochemical change usually occurs in Golgi bodies, where a specific part of the precursor enzyme is cleaved in order to activate it. The inactivating piece which is cleaved off can be a peptide unit, or can be independently folding domains comprising more than 100 residues. Although they limit the enzyme's ability, these n-terminal extensions of the enzyme or a “prosegment” often aid in the stabilizing and folding of the enzyme they inhibit.

The pancreas secretes zymogens partly to prevent the enzymes from digesting proteins in the cells in which they are synthesized. Enzymes like pepsin are created in the form of pepsinogen, an inactive zymogen. Pepsinogen is activated when chief cells release it into the gastric acid, whose hydrochloric acid partially activates it. Another partially activated pepsinogen completes the activation by removing the peptide, turning the pepsinogen into pepsin.

https://en.wikipedia.org/wiki/Zymogen

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