
7 Desquamation

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7.1 INTRODUCTION

The stratum corneum is a cellular tissue. Its building blocks, the corneocytes, are highly resistant to physical and chemical trauma. The mechanical strength of an individual corneocyte, emanating from its tightly packed keratin bundles and the cross-linked proteins of the cornified envelope, is outstanding. The mechanical resistance of individual corneocytes is mirrored by the pronounced mechanical strength of the entire stratum corneum, implying a strong cell cohesion within the tissue. The corneocytes and their intercellular cohesive structures are prerequisites for the function of the stratum corneum as the physical–chemical barrier between body interior and exterior, serving as an important part of the barrier as well as a backbone for the intercellular barrier lipids.

The stratum corneum is continuously being formed in the process of terminal keratinocyte differentiation. The rate of stratum corneum renewal is determined by the rate of cell proliferation in the basal layer of the epidermis. The fact that the thickness of the stratum corneum is fairly constant at a given body site implies that a fraction of the most superficial parts of the stratum corneum must be continuously shed at a rate that balances *de novo* production of corneocytes. This process, desquamation, normally occurs invisibly with shedding of individual cells or small aggregates of cells, resulting in the smooth appearance of the skin surface associated with a “normal” skin condition. Disturbances in this process, due to either increased production of corneocytes or a decreased rate of cell shedding, results in the accumulation on the skin surface of only partially detached cells with or without a concomitant thickening of the stratum corneum. The severity of the disturbance may vary from modest to very pronounced, from a barely visible scaling combined with a feeling of roughness and dryness of the skin surface to the accumulation of thick brittle scales such as in psoriasis or in the various forms of ichthyosis.

Thus, it can be concluded that there must be mechanisms within the stratum corneum, which are responsible for a well-regulated desquamation. A closer look at the criteria that must be fulfilled by these mechanisms suggests that they are likely to be of significant complexity. As stated previously, the barrier function of the stratum corneum depends on a strong cohesion between individual

corneocytes. The elimination of cell cohesion, a prerequisite for desquamation, would be deleterious if it took place in the barrier-forming parts of the stratum corneum. Under normal conditions the turnover time of the stratum corneum is two to four weeks. Moreover, corneocytes are “dead” in the sense that they have no protein synthesis, they have no active turnover of cell surface structures, and they are unresponsive to cellular signaling. Thus, chemical reactions leading to structural and functional changes within the stratum corneum may be considered as the final steps of a series of events initiated in viable parts of the epidermis. The process, which occur spontaneously without further input of regulatory signals, but yet in a well-regulated manner, depends on enzymes and other components produced by still living keratinocytes. In other words, at the time when a viable keratinocyte of the stratum granulosum is transformed to a corneocyte of the stratum corneum, the cell and the tissue it becomes part of must be “programed” in a way that allows the cell to be strongly linked to contiguous cells for a certain period of time, after which its cohesion to its neighbors should decrease to an extent, which will eventually allow it to be shed from the skin surface.

It seems reasonable to believe that a better understanding of desquamation and the mechanisms involved would give us possibilities to design better treatments for skin disorders associated with disturbances in stratum corneum turnover, be they common “dry skin problems” or results of more or less handicapping skin diseases. One strategy to understand desquamation would be to first identify mechanisms of cell cohesion in the stratum corneum, the structures involved, and the changes these structures undergo as cell cohesion decreases. The next step would be the identification of chemical reactions taking place, which would immediately give clues as to the nature of enzymes likely to be involved. Another fruitful strategy would be to elucidate the molecular basis and pathophysiology of diseases such as ichthyoses (see [Chapter 8](#)). The elucidation of ichthyosis-like conditions induced by certain drugs may also be expected to be productive in this context.^{1,2}

The most likely site at that the events that eventually lead to desquamation take place is the stratum corneum intercellular space. As described in other chapters of this book, the chemical composition, organization, and interactions of this part of the stratum corneum are extremely complex. The stratum corneum intercellular space may be considered as a multiphase system consisting of a complex mixture of lipids in which structural proteins, enzymes, and other nonstructural proteins; a range of low molecular weight substances with different degrees of hydrophilicity; and water in low but significant concentrations are dispersed and interact with each other. A full understanding of stratum corneum cell cohesion and desquamation will rely on our understanding of the complex interactions of the many constituents of the intercorneocyte space. Although important steps forward have been taken in recent years, much has still to be learned. It should therefore be stated that our present knowledge about desquamation is quite rudimentary. Some clues have emerged, however, and will be summarized below.

7.2 SKIN DISEASES WITH DESQUAMATION DISTURBANCES

An accumulation of scales on the skin surface may be due to either an increased production of corneocytes, such as in psoriasis, or to a delayed desquamation. It may be predicted that conditions with delayed desquamation, once their pathophysiology on the molecular level is understood, will be highly informative with regard to the understanding of desquamation. Two such conditions are recessive X-linked ichthyosis (RXI) and lamellar ichthyosis.

The elucidation of the molecular genetics RXI has had a major impact on our understanding of stratum corneum turnover. Individuals with RXI lack an enzyme, cholesterol sulfatase,^{3,4} which catalyzes the transformation of cholesterol sulfate (CS) to cholesterol and free sulfate. As a result there is an accumulation of CS in the stratum corneum intercellular space. Possible mechanisms by which this change in intercellular lipid composition of the stratum corneum can cause disturbances in desquamation, leading to ichthyosis, will be discussed later.

A group of individuals with severe ichthyosis (recessive autosomal lamellar ichthyosis) has been found to have mutations in the gene for epidermal transglutaminase.⁵⁻⁷ By means of catalyzing cross-linking of constituent proteins, this enzyme plays a crucial role in the formation of the cornified envelope of the corneocyte. How this type of molecular defect can cause ichthyosis is unknown. It may be expected that further studies on this condition will give important contributions to our understanding of desquamation. Similarly, we can expect that the soon-to-come elucidation of the molecular genetics of inherited lamellar ichthyoses with similar phenotypes, but without transglutaminase mutations,⁸ will be informative.

7.3 STRATUM CORNEUM CELL DISSOCIATION INVOLVES PROTEOLYSIS

Experimental evidence that protein structures are involved in stratum corneum cell cohesion was presented by Bisset et al.⁹ They induced cell dissociation in pig and human nonpalmo-plantar stratum corneum by means of incubation of the tissue in the presence of the zwitterionic surfactant 6-octadecyldimethyl ammoniohexanoate. Cell dissociation could not be induced when the tissue had been pretreated with the serine protease inhibitor phenylmethylsulfonyl fluoride (PMSF). The fact that cell dissociation was found only in the presence of EDTA suggested a role also for calcium in stratum corneum cell cohesion.

Lundström and Egelrud¹⁰ found a unipolar spontaneous cell dissociation in pieces of hypertrophic human plantar stratum corneum incubated in a simple buffer. The cell dissociation occurred only at the surface that had faced outward *in vivo*. The rate of cell dissociation was increased in the presence of EDTA. It was inhibited by inhibitors of serine proteases, but not by inhibitors of other groups of proteases. Since the tissue had not been treated with exogenous proteases before the experiments, it was concluded that the observed cell dissociation was mediated by an endogenous serine protease. This experimental system has been used as an *in vitro* model of desquamation. In addition to information about the enzyme(s) involved in the cell dissociation, it has provided information about the nature of the cohesive structures in the stratum corneum.

There is evidence that protein structures are also responsible for cell cohesion in nonpalmo-plantar stratum corneum. When punch biopsies of normal human gluteal skin were incubated in a buffer containing a mixture of the zwitterionic surfactant *N,N*,-dimethyldodecylamine and the anionic surfactant sodium dodecyl sulfate,¹¹ there was dissociation of cells in the stratum corneum but not in the rest of the epidermis. The cell dissociation took place only in the presence of EDTA and was inhibited by the serine protease inhibitor aprotinin.¹² Suzuki et al.^{13,14} presented evidence that spontaneous cell dissociation in nonpalmo-plantar stratum corneum could be inhibited by a combination of inhibitors of trypsin-like and chymotrypsin-like enzymes. Thus, nonpalmo-plantar stratum corneum contains endogenous proteases that mediate cell dissociation.

7.4 DESMOSOMES AND CORNEODESMOSOMES

Desmosomes mediate mechanical contacts between viable epithelial cells such as keratinocytes.¹⁵⁻¹⁸ A desmosome is a round or oval, button-like structure with a diameter of 0.2 to 1 μm . It consists of two symmetrical halves, each one belonging to one of two contiguous cells and consisting of an intracellular, a transmembranal, and an extracellular part. Inside the cell, just below the plasma membrane, is the desmosomal plaque. To this structure are linked intracellular keratin filaments as well as glycoproteins belonging to the cadherin family named desmogleins and desmocollins (for a review of desmosomal cadherins, see Reference 19). These glycoproteins cross the plasma membrane, and their glycosylated parts occupy the extracellular space where they interact with their counterparts from the contiguous cell, thus forming a cohesive structure between the cells. In the electron microscope the desmosomal plaque is visible as an electron dense structure, approximately

15 nm in width, on the inner aspect of the plasma membrane. The extracellular parts of desmosomes between uncornified keratinocytes has a moderately electron dense, plate-like appearance, approximately 30 nm in width, and has a zigzag formed electron dense central line. Desmosomes and keratin filaments form functional units, the desmosome-intermediate filament complexes.¹⁷ These complexes link the keratin filament cytoskeleton of individual cells into a network comprising the whole epithelium.

The corneodesmosomes, that is, desmosomes in the stratum corneum, have a somewhat different appearance in the electron microscope.^{20–22} Due to the densely packed and electron dense intracellular keratin filaments, it is not possible to identify the intracellular desmosomal plaque. The extracellular plate-like parts of corneodesmosomes have a homogenous and high electron density with no visible central line. Analyses of total number of desmosomes, measured as percentage of the cell periphery occupied by extracellular parts of desmosomes, showed a difference between the stratum corneum in palms and soles and stratum corneum at other body sites. In nonpalmo-plantar stratum corneum the number of desmosomes in deeper layers was comparable to the number of desmosomes in the stratum granulosum, whereas it was only around 20% of this number in the superficial layers close to the skin surface. This was true, however, only if the whole corneocyte periphery was considered. Whereas there were few desmosomes in the central parts of superficial corneocytes, the number of desmosomes per unit length of cell periphery at the overlapping edges of corneocytes was essentially the same as in deeper layers of the tissue. Thus, extracellular parts of desmosomes in the central parts of corneocytes disappear as the cells move upward in the stratum corneum, whereas desmosomes at the edges remain as long as the cells have not been shed. In palmo-plantar stratum corneum the number of desmosomes per unit length of corneocyte periphery is constant and high throughout the tissue until the cells are shed.²³

The ultrastructural appearance of corneodesmosomes suggest that they are modified during the transition between viable and cornified epidermal layers. Part of this modification may be due to the incorporation of a recently discovered protein, corneodesmosin.^{24–26} This is a 52-kDa protein, which is specifically expressed in keratinizing epithelia. In the stratum granulosum it is found intracellularly in association with lamellar bodies. In the transition zone between the stratum granulosum and the stratum corneum, coinciding with the change in the ultrastructural appearance of the desmosomes, corneodesmosin is translocated to the extracellular parts of desmosomes.²⁷ Immunoblot analyses have suggested that corneodesmosin is continuously degraded to smaller components in the stratum corneum.²⁶ It is not yet known to what extent this protein contributes to the cohesive capacity of corneodesmosomes. It has been speculated that corneodesmosin degradation may be part of the regulatory events involved in desquamation.²⁶

7.5 DESQUAMATION INVOLVES DEGRADATION OF CORNEODESMOSOMES

Evidence that degradation of corneodesmosomes is a prerequisite for desquamation comes from ultrastructural and immunochemical studies. In the so-called retention ichthyoses, in which it is believed that a delayed desquamation causes the thickening of the stratum corneum and the accumulation of squames, there is an increased number of corneodesmosomes in the superficial layers of the stratum corneum.^{28,29} In plantar stratum corneum undergoing spontaneous cell dissociation, electron microscopy of dissociating cells suggested that degradation of the intercellular parts of desmosomes preceded the widening of the intercellular space.³⁰ Chapman and Walsh³¹ showed by means of electron microscopy that desquamation in pig skin was associated with morphological signs of desmosomal degradation.

Immunoblot analyses with antibodies specific for the transmembranal desmosomal glycoprotein desmoglein I (DG I) of plantar stratum corneum undergoing spontaneous cell dissociation³⁰ showed that although the still cohesive tissue contained only intact DG I, dissociated cells contained no

intact DG I, instead they contained degradation products of this protein. Analyses of surface cells that had been shed from plantar skin *in vivo* gave similar results.³² In xerotic skin superficial stratum corneum contained more extractable intact DG I than in normal skin,³³ suggesting that delayed desmosomal degradation may contribute to the accumulation of squames. Increased amounts of intact DG I in superficial stratum corneum was found also in a mouse model with experimentally induced scaling.³⁴ Taken together, these ultrastructural and immunochemical results strongly suggest that corneodesmosomes are responsible for cell cohesion in the stratum corneum and that proteolytic degradation of their extracellular parts is a prerequisite for desquamation.

7.6 ENZYMES INVOLVED IN DESQUAMATION

The best-characterized enzyme so far with a proposed function in desquamation is stratum corneum chymotryptic enzyme (SCCE, also named human kallikrein 7; hK 7).³⁵ The discovery of SCCE was a result of the search for the enzyme responsible for the degradation of cohesive structures in the *in vitro* model of desquamation in hypertrophic plantar stratum corneum. SCCE has several properties compatible with a role in desquamation also *in vivo*.^{36,37} SCCE has been purified from plantar stratum corneum.³⁸ It has been cloned and expressed in mammalian cells.³⁹ In reduced form SCCE has a molecular mass of around 28 kDa, it is partially glycosylated, and it has a basic isoelectric point. Although having a neutral to alkaline pH-optimum, it is active also at pH 5.5, that is, it is active at the pH of the stratum corneum.⁴⁰ SCCE is produced as an inactive precursor with a propeptide seven amino acid residues long. Removal of the propeptide by means of trypsin treatment of recombinant pro-SCCE yields a proteolytically active enzyme.³⁹ The mechanisms of SCCE activation *in vivo* remain to be elucidated. The deduced amino acid sequence contains the conserved regions typical of serine proteases, but is otherwise, at most, only around 40% homologous with other known human enzymes. SCCE shows similarities, but also significant differences regarding the activity on peptide substrates and the sensitivity to various protease inhibitors when compared to other chymotryptic enzymes such as bovine chymotrypsin and human cathepsin G.³⁸ This may be explained, at least partially, by the fact that in SCCE there is an asparagine residue in the bottom of the deduced primary substrate binding pouch, whereas this site is occupied by serine and alanine residues in chymotrypsin and cathepsin G, respectively.³⁹

Analyses of mRNA from a large number of various human tissues has shown high expression of SCCE only in the skin.³⁹ Immunohistochemical studies have shown that SCCE is expressed in high suprabasal keratinocytes in the epidermis. In hair follicles and sebaceous glands it is expressed at a site where there is formation of cornified keratinocytes and hence a need for desquamation-like processes. In the oral cavity SCCE staining is found in the cornified epithelium of the hard palate, but not in the buccal mucosa or at other sites with noncornified epithelium. Thus, these findings suggest that SCCE expression is related to a differentiation process, leading to the formation of a cornified squamous epithelium.⁴¹⁻⁴⁴

Results from enzymologic studies have suggested that SCCE has an extracellular localization in the stratum corneum.⁴⁵ This has been corroborated by means of immunoelectron microscopy. With this method SCCE was found intracellularly in association with lamellar bodies in the stratum granulosum. In the transition between the stratum granulosum and the stratum corneum, SCCE is extruded to the extracellular space together with the lamellar bodies. In the stratum corneum specific labeling is found only in the extracellular space, often in association with corneodesmosomes.⁴⁶

Results from *in vitro* experiments, catalytic properties, and tissue localization are all compatible with the role of SCCE in the degradation of intercellular cohesive structures in the stratum corneum as part of the events leading to remodeling of the tissue and eventually to desquamation. Increased expression of SCCE in the epidermis of transgenic mice leads to impaired barrier function with increased transepidermal water loss. The transgenic animals have a thickened epidermis and a marked hyperkeratosis, possibly reflecting compensatory reactions.⁴⁷⁻⁴⁸ There are also other proteases

present in the stratum corneum, some of which may be involved in desquamation.^{13,14,37,38,49–51} Of these proteases, a 33 kDa serine protease named stratum corneum tryptic enzyme (SCTE; human kallikrein 5; hK 5)^{35,52} with trypsin-like primary substrate specificity may be of special interest. The tissue distribution of SCTE is similar as for SCCE and it has been postulated that SCTE has a complementary role to that of SCCE in degradation of structures involved in stratum corneum cell cohesion during desquamation.^{13,53} In addition SCTE is a candidate for being responsible for the activation of the SCCE precursor. Additional information in this respect will be crucial for the understanding of the role of SCCE and related enzymes in the formation and turnover of the stratum corneum.

7.7 REGULATION OF DESQUAMATION

We are very far from an understanding of how and by which mechanisms desquamation is regulated. If we assume, however, that proteolytic degradation of corneodesmosomes plays a major role in desquamation, a number of possible mechanisms can be postulated on the basis of the present knowledge. These are summarized in Table 7.1.

The activation of enzyme precursors is likely to be of central importance. A significant fraction of the total SCCE present in the stratum corneum is in the form of inactive proenzyme.^{53,54} A change in the ratio of precursor to active enzyme may be expected to cause marked changes in the rate of corneodesmosomal degradation. *In vitro* pro-SCCE can be activated by pancreatic trypsin.³⁹ As mentioned earlier SCTE has been suggested to act as an SCCE activator, but this remains to be elucidated. It is possible that SCCE is just one of a number of enzymes constituting a “proteolytic cascade” in the stratum corneum, in which one enzyme serves as activator of another enzyme.

The stratum corneum is likely to contain a number of inhibitors of the various proteases present. CS may be of special interest. Accumulation of CS in the stratum corneum in RXI may be causative of this disease, in which there is evidence of a delayed degradation of desmosomes.²⁸ CS has been shown to inhibit pancreatic serine proteases *in vitro*, and application of CS on mouse skin *in vivo* causes a scaling condition.³⁴ In addition to direct effects on enzymes, CS could cause delayed desquamation by acting as a substrate modifier or by changing the physical–chemical conditions in the stratum corneum extracellular space.

Also, in autosomal recessive ichthyosis there are findings indicative of an impaired desmosome degradation in the stratum corneum.²⁹ The mechanisms involved have not been elucidated.

As mentioned previously for CS, substrate modifications could be of significant importance as regulating factors in proteolytic degradation of cohesive structures. Walsh and Chapman showed that pretreatment with glycosidases made preparations of stratum corneum more susceptible to cell

TABLE 7.1
Mechanisms which may be involved in regulation of desquamation

Enzyme activation
Activation of SCCE
Enzyme inhibition
Cholesterol sulfate
Antileukoprotease
Other protease inhibitors in the stratum corneum
Substrate modification
Glycosylation
pH? Water? Ions? Lipids?

Note: See text for references.

dissociation induced by exogenous proteases, suggesting that proteins involved in cell cohesion may be protected by carbohydrates against proteolytic degradation.⁵⁵

A number of protein protease inhibitors are present in the stratum corneum. Antileukoprotease has been shown to be an efficient inhibitor of SCCE at physiological concentrations.⁵⁶ Extracts of plantar stratum corneum contains covalent complexes between SCCE and α 1-antitrypsin (Egelrud, T., unpublished observation). Recent findings in the human genetic disease Netherton's syndrome (NS) have given new insights on the potential role of serine proteases and their inhibitors for epidermal homeostasis. In NS there is severe impairment of skin barrier function. The causing mutations have been found in a gene, Serine Protease Inhibitor Kazal type 5 (SPINK5),⁵⁷ encoding a complex protein, which after post-translational modifications gives rise to a number of serine protease inhibitors called LympoEpithelial Kazal-Type related Inhibitor (LEKTI).⁵⁸ It has been suggested that the lack of LEKTI, which is highly expressed in the stratum granulosum of normal epidermis,⁵⁹ may lead to increased and uncontrolled activity of epidermal serine proteases, which in turn would result in a deteriorated barrier.

There are a vast number of other factors which may be expected to influence the rate of desquamation, for instance, by affecting the rate of proteolytic reactions. pH, water, and ion concentrations, and lipid composition may all be expected to be of importance. Experimental data in this area are very scarce, but some speculations can be made. For instance, the pH dependency of SCCE activity could be of importance. SCCE has optimal activity at pH 7 to 8, but close to half its maximal activity at pH 5.5.^{36,37} This implies that rather small variations in either direction of the pH of the extracellular space should have effects on the rate of SCCE-mediated protein degradation. In support of this, the rate of spontaneous cell dissociation observed in plantar stratum corneum *in vitro* showed a marked pH dependency, being highest at neutral to weakly alkaline pH and decreasing at lower pH values.¹⁰

The effects of chelating agents in *in vitro* models for desquamation suggest that divalent ions such as calcium may play a role in the regulation of desquamation.^{12,26,60}

The composition of the stratum corneum intercellular lipids may have profound effects on desquamation. In addition to modifying effects on, for example, proteolytic enzymes and their substrates,³⁴ lipids may also be directly involved in corneocyte cohesion. The effects of cholesterol sulfate have already been mentioned. In addition to RXI, there are a number of other hereditary diseases with disorders of desquamation associated with disturbances in lipid metabolism. Furthermore, scaling as a result of treatment with lipid-lowering drugs has been observed (for review, see References 1 and 2).

7.8 CONCLUSION

A normal desquamation is of crucial importance for the maintenance of the function of the stratum corneum and for a normal skin appearance. In recent years some basic knowledge about stratum corneum cell cohesion and the role of proteolysis in desquamation has evolved. Much still has to be learned, however. In the near future we may expect to obtain information about further enzymes involved in desquamation, and the ongoing elucidation of hereditary skin diseases will give new clues with regards to regulation of mechanisms involved in desquamation. Similarly, further studies on the physical chemistry and the chemical composition, including identification of hitherto unknown proteins, of the stratum corneum intercellular space may be expected to give important contributions to this central area of skin biology.

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