REVIEW

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Reddish, scaly, and itchy: how proteases and their inhibitors contribute to inflammatory skin diseases

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Abstract

The skin protects us from water loss and mechanical damage. The surface-exposed epidermis, a self-renewing stratified squamous epithelium composed of several layers of keratinocytes, is most important in the barrier defense against these challenges. Endogenous and exogenous proteases such as kallikreins, matriptase, caspases, cathepsins, and proteases derived from microorganisms are important in the desquamation process of the stratum corneum and are able to activate and inactivate defense molecules in human epidermis. Protease inhibitors such as like LEKTI, elafin, SLPI, SERPINs, and cystatins regulate their proteolytic activity and contribute to the integrity and protective barrier function of the skin. Changes in the proteolytic balance of the skin can result in inflammation, which leads to the typical clinical signs of redness, scaling, and itching. This review summarizes the current knowledge of how proteases, their inhibitors, and their target proteins, including filaggrin, protease-activated receptors, and corneodesmosin, contribute to the pathophysiology of inflammation of the skin and highlight their role in common inflammatory skin diseases such as atopic dermatitis, rosacea, and psoriasis.

Key words: atopic dermatitis, proteases, epidermal barrier, innate immunity, protease inhibitors, psoriasis.

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INTRODUCTION

The skin protects us from water loss and mechanical damage. Its physical barrier is complemented by a chemical barrier consisting of antimicrobial peptides and proteins to defend the host from the surrounding microflora. The surface-exposed epidermis, a self-renewing stratified squamous epithelium composed of several layers of keratinocytes, is most important for the barrier defense against these challenges. Keratinocytes in the outermost stratum corneum of the epidermis are shed and replaced by newly differentiated cells originating from epidermal stem cells located in the basal layer. These undergo a specific differentiation process and form the cornified envelope, which is a rigid and insoluble protein and lipid structure with the essential properties of barrier function (Candi et al. 2005; Kalinin et al. 2001). Under normal circumstances we do not notice this steady turnover and consider it as healthy skin. This healthy state can turn to an inflammatory state for different reasons, such as mechanical barrier disruption, toxic or allergic reactions, microorganisms, as well as genetic predisposition and disease. Over the last two centuries, dermatologists have given many names, often descriptive, to these inflammatory skin diseases. In the eye of a dermatologically unskilled beholder, many of these diseases look the same because certain features frequently occur: the skin turns red, shedding is more prominent, and the skin may become thicker if the inflammation becomes chronic and, most annoyingly, the site of the reaction becomes itchy. In recent years we have learned many of the causes of diseases, though some common skin diseases, such as atopic dermatitis (AD) and psoriasis, are still not fully understood. The discovery of the genetic defects in some rare inherited diseases has led to new approaches in understanding inflammatory skin diseases. Animal models are useful tools for studying specific gene functions *in vivo* and add to this understanding. However, if a skin phenotype occurs in a knockout mouse, its signs are often only described as reddish, scaling, and itching. It seems that many gene knockouts are redundant in this respect, but this might also result from the lack of dermatological knowledge of murine skin diseases.

Recent discoveries have highlighted the importance of various proteases, protease-inhibitors, and protease targets as key players in epidermal barrier function (Fig. 1 and 2). This review aims to compile these findings, which will finally lead to the question if general proteolytic reactions underlie the general features of inflammatory skin diseases, i.e. redness, scaling, and itch.

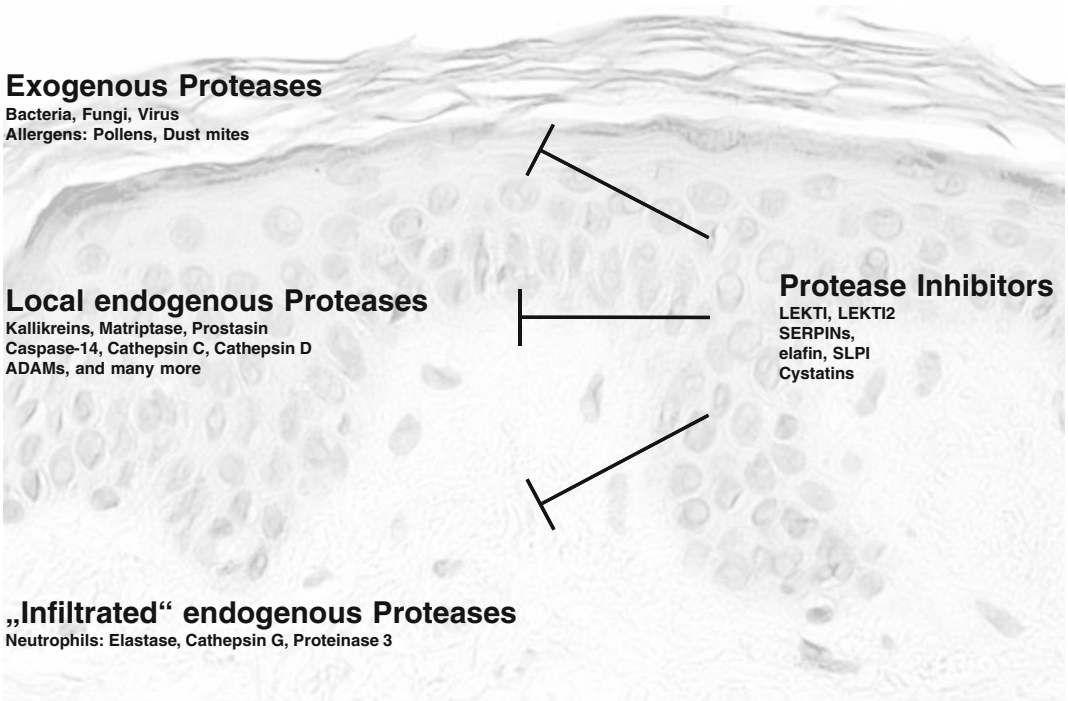

Fig. 1. Various proteases contribute to the protease/protease inhibitor balance in the skin. Proteases can be expressed endogenously in the skin, they can come from infiltrating cells such as neutrophils, or they might be of exogenous origin, as from microorganisms, allergens and others. Various cutaneous protease inhibitors protect the skin from these proteases.

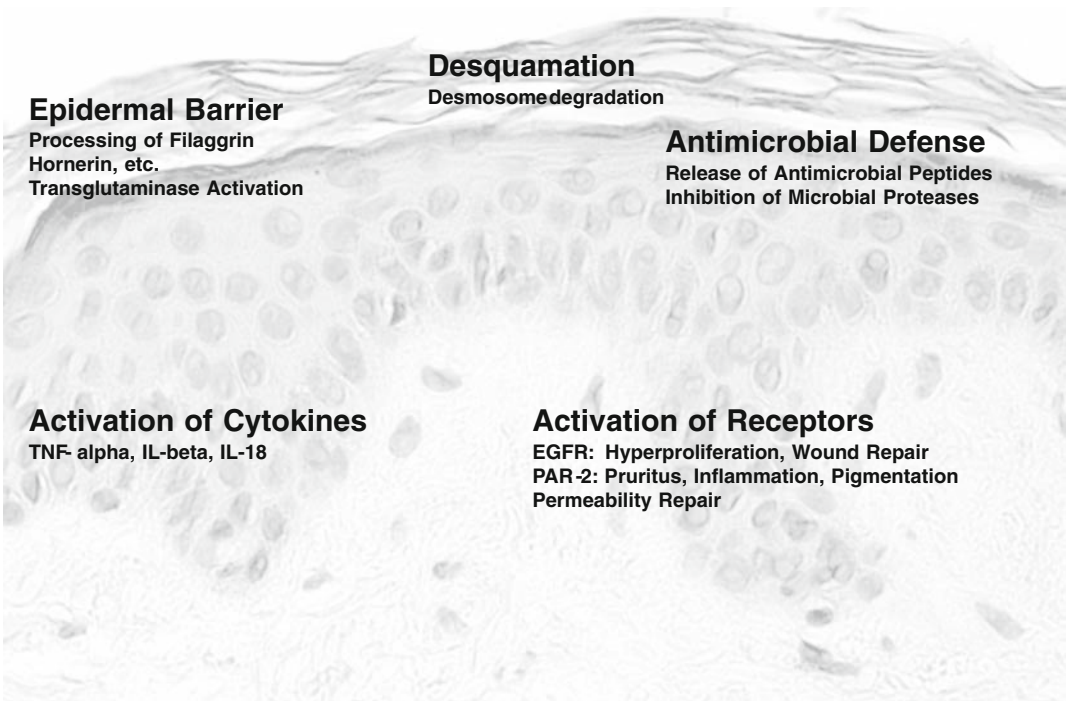

Fig. 2. Protease targets in the skin include structural proteins such as filaggrin, cytokines, and receptors. Proteolytic processing of these proteins contributes to the inflammatory response, which is often visible as redness and scaling of the skin.

Proteases in the skin

The specific differentiation program in stratified skin requires a specialized proteolytic system to detach the corneocytes from each other without causing a barrier defect. A number of different proteases have been reported to be involved in the desquamation process and to contribute to the barrier function of the skin. Based on their proteolytic domain, proteases are classified into serine, threonine, cysteine, aspertate, metallo, and glutamate proteases. Especially serine proteases (SPs) seem to be involved in epidermal permeability barrier homeostasis as it was reported that SP activity was increased after acute barrier disruption and that blockade by topical SP inhibitors accelerated barrier recovery after acute abrogation (Hachem et al. 2006a).

KALLIKREIN-RELATED PEPTIDASES

Human tissue kallikreins, or kallikrein-related peptidases (KLKs), are the largest family of trypsin- or chymotrypsin-like secreted SPs encoded by 15 genes on chromosome 19q13.4 (Yousef and Diamandis 2001). They are secreted to the extracellular space, where they have been partly identified due to their proteolytic activities. At least eight KLKs are expressed in normal skin, of which KLK5, KLK7, KLK8, and KLK14 have been reported to be the most important (Komatsu et al. 2005; Komatsu et al. 2006; Komatsu et al. 2003). Their putative function in skin biology has been excellently reviewed by Drs. Lundwall and Brattsand (Lundwall and Brattsand 2008). KLKs are capable of cleaving corneodesmosomes (Egelrud 2000). Furthermore, kallikrein-mediated proteolysis regulates the antimicrobial effects of cathelicidins in skin (Yamasaki et al. 2006) and contributes to the pathogenesis of rosacea (Yamasaki et al. 2007). Moreover, KLK5 and KLK14 have been reported to activate protease-activated receptor (PAR)-2 (Stefansson et al. 2008), which is a signaling receptor in epidermal inflammation (Steinhoff et al. 2005) and a regulator of epidermal barrier function (Hachem et al. 2006a). Epidermal overexpression of KLK7 resulted in pathological skin changes with increased epidermal thickness, hyperkeratosis, dermal inflammation, and severe pruritus (Hansson et al. 2002). These findings stress the importance of KLKs in inflammatory skin diseases. Besides KLKs, other proteases have been reported in epidermal function.

MATRIPTASE AND PROSTASIN

Reduced expression of the epithelial type II transmembrane serine protease matriptase was shown to be associated with incomplete terminal differentiation of epidermis, epidermal appendages, and oral epithelium (Bugge et al. 2007). Mutations of the matriptase gene *ST14* lead to ichthyosis (MIM 602400), as demonstrated by several recent reports (Alef et al. 2009; Basel-Vanagaite et al. 2007; List et al. 2007). Marked skin hyperkeratosis due to impaired degradation of the stratum corneum corneodesmosomes was observed in the affected individuals, which suggests that matriptase plays a significant role in epidermal desquamation. The loss of matriptase in differentiated patient keratinocytes reduced the proteolytic activation of prostasin, a glycosylphosphatidylinositol-anchored membrane SP, and disturbed the processing of profilaggrin. As filaggrin monomers play a pivotal role in epidermal barrier formation, these findings reveal the link between congenital disorders of keratinization and filaggrin processing in the human skin. The two membrane-bound serine proteases matriptase and prostasin are therefore involved in the processing of profilaggrin, stratum corneum formation, and the acquisition of epidermal barrier function (Netzel-Arnett et al. 2006). It remains unclear whether the two proteases are mainly involved in skin homeostasis or if they play an active role in inflammation. This question is under current investigation.

CASPASE-14

Cysteine peptidases are phylogenetically ubiquitous enzymes that can be classified into clans of evolutionarily independent proteins based on the structural organization of the active site. In mammals, two of the major clans represented in the genome are the CA clan, whose members share a structure and evolutionary history with papain, and the CD clan, which includes the legumains and caspases. Caspase-14 is an epidermal cysteinyl aspartate-specific proteinase. Caspase-14-deficient mice underscored its importance in the correct degradation of filaggrin and in the formation of the epidermal barrier that protects against dehydration and UVB radiation (Demerjian et al. 2008; Denecker et al. 2007). The recent review by Dr. Denecker and colleagues excellently summarizes current knowledge of caspase-14 (Denecker et al. 2008).

CATHEPSIN C

Cathepsin C is a lysosomal cysteine peptidase of the papain family C1A that has a role in the intracellular degradation of proteins and appears to be important for the activation of serine proteases in immune cells (Rao et al. 1997). It was found that mutations in the cathepsin C gene are responsible for Papillon-Lefevre syndrome (PLS, MIM 24500) (Hart et al. 1999; Toomes et al. 1999). PLS is a palmoplantar keratoderma with the characteristic clinical features of palmoplantar hyperkeratosis and periodontal destruction. The phenotype of this rare autosomal recessive disorder shows severe early onset periodontitis, premature tooth loss, and thickening

and scaling of the skin of palms and soles. Furthermore, cathepsin C mutations were found to be responsible for Haim-Munk syndrome (HMS, MIM 245010), an allelic variant of PLS with some other clinical features (e.g. nail deformities, acroosteolysis) that is only found among members of a small community of Jews from Cochin, India (Hart et al. 2000). Thus cathepsin C might be essential for establishing and maintaining the structural organization of the epidermis of the extremities and the integrity of the tissues surrounding the teeth and may indirectly contribute to the processing of proteins such as keratins. Reduced expression of the cornified envelope proteins was observed in cathepsin D knockout mice. Cathepsin C knockout mice have revealed that cathepsin C plays an essential role in the processing and activation of granzymes A and B, which are required for T cell--mediated cell killing (Pham and Ley 1999). Therefore it was suggested that loss-of-function mutations in the cathepsin C gene could result in an altered immune response to infection in PLS and HMS. However, these cathepsin C-deficient mice do not resemble the human disorders mentioned above; they developed normally, appeared healthy, and were fertile. This shows impressively that mouse studies cannot be transferred to the human homologue one by one. Cathepsin C deficiency in humans is associated with a severe reduction in the levels and activities of the neutrophil-derived serine proteases elastase, cathepsin G, and proteinase 3 (Pham et al. 2004), which are described later.

CATHEPSIN D

Cathepsin D is the main aspartatic protease of endolysosomes, and in skin this protease is thought to be associated with the final stage of desquamation (Horikoshi et al. 1999). It was demonstrated that cathepsin D is crucially involved in the activation of transglutaminase 1 and reduced protein levels of the cornified envelope proteins involucrin and loricrin during epidermal differentiation, which results in dry skin and hyperkeratosis (Egberts et al. 2004). Thus cathepsin contributes indirectly to the barrier function of human skin by the diminished ability of corneocytes to bind intercellular lipids, caused by the reduced expression of involucrin and loricrin in the stratum corneum.

Protease inhibitors in the skin

To control the activity of proteolytically active enzymes, a number of more or less specialized protease inhibitors come into play. They modulate proteolytic activity where it is needed. A deregulation of protease and protease inhibitor is often found in inflammatory disorders. This part of the review wants to introduce some of the most important epithelial protease inhibitors.

LYMPHOEPITHELIAL KAZAL-TYPE-RELATED INHIBITOR

The importance of epithelial protease inhibitors has been revealed impressively in Netherton's disease (NS). NS (MIM 56500) is an autosomal recessive disorder caused by mutations in the serine protease inhibitor Kazal-type5 (*SPINK5*) gene (Chavanas et al. 2000). NS presents as an ichthyosiform dermatosis with variable erythroderma, hair-shaft defects (bamboo hair), atopic features, and growth retardation (Griffiths et al. 1998). Lymphoepithelial Kazal-type-related inhibitor (LEKTI) (Magert et al. 1999), the product of *SPINK5*, includes in its primary structure 15 different serine protease--inhibitory domains (Magert et al. 1999). The inhibitory functions of LEKTI are highly diverse, i.e. they are directed towards trypsin, plasmin, subtilisin A, cathepsin G, and human neutrophil elastase (Mitsudo et al. 2003). However, it is thought that the natural protease partners of LEKTI are members of the KLK family. KLKs and their natural inhibitor LEKTI are separated in lamellar bodies but are secreted together into the intercellular space, in the uppermost stratum granulosum (Ishida--Yamamoto et al. 2004; Ishida-Yamamoto et al. 2005; Sondell et al. 1995). Overall, trypsin-like and/or chymotrypsin-like activities are considerably elevated in the skin of *SPINK5*-deficient mice (Descargues et al. 2005) and in NS patients (Hachem et al. 2006b; Komatsu et al. 2006). The elevated activities cause increased degradation of corneodesmosomal cadherins in NS patients (Descargues et al. 2006). Altogether, these accumulating data strongly suggest that in skin, KLKs are desquamation-related serine proteases and that the balance between serine proteases and inhibitors may be essential not only for steady desquamation, but also for skin barrier function. Since NS patients show atopic features, it was speculated whether AD patients carry SPINK5 mutations. Early genome-wide linkage analysis of AD family studies suggested a potential locus on 5q31, and after identification of six common polymorphisms in *SPINK5*, the variant Lys420Ser was associated with eczema in a cohort of British children (Walley et al. 2001). This association has been replicated in two small Japanese studies (Kato et al. 2003; Nishio et al. 2003) and another recent study (Weidinger et al. 2008), though other studies have failed to reproduce this association. SPINK5 might therefore be of minor importance as a genetic factor in AD, but it points to a possible role of epidermal protease inhibitors in the pathogenesis of AD.

LEKTI-2

Recently, a novel member of the SPINK gene family, *Spink9*, and its product LEKTI-2 were discovered in human skin. LEKTI-2, which contains only one Kazal--type domain, was shown to be only expressed at the stratum granulosum of palmar and plantar skin (Brattsand et al. 2009; Meyer-Hoffert et al. 2009). Most

notably, LEKTI-2 exhibited only inhibiting activity against tryptic KLK5, but not against the chymotryptic KLK7, tryptic KLK14, or all the several serine proteases tested, including trypsin and chymotrypsin. LEKTI-2 activity differs in this respect from that of LEKTI. The K_i of LEKTI-2 against KLK5 was reported to be between 60 and 250 nM. Several LEKTI domains have been reported to inhibit KLK5 in various reports. In comparison, the determined K_i of LEKTI domains to inhibit KLK5 was in the range of 3 nM (domain 8–11) to 120 nM (domain 9–15) (Deraison et al. 2007; Egelrud et al. 2005; Schechter et al. 2005). It remains to be shown whether LEKTI-2 plays a role in cutaneous diseases as LEKTI does. Considering its specific expression at palmoplantar sites, it is intriguing to speculate that LEKTI-2 could be an important factor in hyperkeratotic hand and foot eczema.

SECRETORY LEUKOCYTE PROTEASE INHIBITOR/ELAFIN

Keratinocytes produce specific protease inhibitors of neutrophil serine proteases such as anti-leukoprotease (or secretory leukocyte protease inhibitor, SLPI) and elafin (Wiedow et al. 1991; Wiedow et al. 1990; Wiedow et al. 1993) to protect the skin when neutrophils infiltrate in the epidermis. Besides their anti-protease activity, they exhibit antimicrobial activity and contribute to the antimicrobial defense shield of the skin (Meyer-Hoffert et al. 2003; Wiedow et al. 1998). Elafin is not only expressed in healthy skin, but is highly up-regulated during inflammation (Meyer-Hoffert et al. 2003), probably to protect the skin from excessive neutrophil proteases during the inflammatory response.

SERINE PROTEASE INHIBITORS

The group of serine protease inhibitors (SERPINs) encompasses approximately 40 members, of which many have been implicated in diseases (Kaiserman et al. 2006). They inhibit their target proteases by a unique mechanism, while leading to a conformational change of the protease and the inhibitor after covalent binding of the protease to the SERPIN. Some members of the SERPIN family have been reported to be expressed in human skin, such as SERPINB3 (squamous cell carcinoma antigen-1), SERPINB4 (squamous cell carcinoma antigen-2), and SERPINB13 (headpin/hurpin). They have been implicated in carcinogenesis of squamous cell carcinoma (Silverman et al. 1998; Walz et al. 2007). SERPINs also widely interact with microorganisms. For example, SERPINA1 and SERPINA2 have been demonstrated to inhibit proteinase K (Komiyama et al. 1996). SERPINB9 and SERPINB8 have been demonstrated to inhibit subtilisin A (Dahlen et al. 1997a; Dahlen et al. 1997b). SERPINA1 was reported to be inactivated by some bacterial proteases (Nelson et al. 1999). Furthermore, the C-terminal part of SERPINA1 was identified to inhibit HIV-1 entry by interacting with the gp41 fusion peptide (Munch et al. 2007). Therefore we think that epithelial-expressed SERPINs are likely candidates for protecting the host from bacterial proteases.

CYSTATINS

Cystatins are specific inhibitors of endogenous mammalian lysosomal cysteine proteases (Turk and Bode 1991) and exogenous microbial cysteine proteases (Bjorck 1990). Several studies have indicated that cystatins provide important regulatory and protective functions against uncontrolled proteolysis by cysteine proteases of host and pathogen origin (Bobek and Levine 1992). Cystatin A and cystatin C were reported to be epidermal protease inhibitors with antimicrobial function. In contrast, cystatin M/E regulates the cross-linking of structural proteins by transglutaminase 3 in the cornification process of the epidermis and hair follicle by controlling cathepsin L and legumain activities (Cheng et al. 2006; Zeeuwen et al. 2004). It was demonstrated that human cathepsin L is an elusive enzyme that is able to process and activate human transglutaminase 3, an epidermis-specific enzyme responsible for the cross-linking of loricrin and small proline-rich proteins in the cornification process of the skin (Cheng et al. 2006). Dysregulation of this pathway by unrestrained protease activity, as seen in cystatin M/E-deficient mice, leads to abnormal stratum corneum and hair follicle formation, disturbance of skin barrier function, and neonatal death (Zeeuwen et al. 2002; Zeeuwen et al. 2004).

Target proteins for proteases in the skin

To understand the protease network in the skin, a deeper look at their target proteins is needed. It is of general importance to realize that the target proteins are not simply digested by proteolytic cleavage. Proteolytic processing is often needed to alter the function of a protein, whether it be activation, inactivation, or modulation. During recent years, one protein was attracted special notice: filaggrin.

FILAGGRIN

AD is a common chronic inflammatory skin disease with a complex multifactorial cause and a strong genetic component (Morar et al. 2006). The identification of two common (R501X and 2282del4) and several rare mutations within the filaggrin gene (*FLG*) causing a deficiency of this key protein involved in skin barrier function delineated a major genetic risk for AD (Palmer et al. 2006; Sandilands et al. 2006; Smith et al. 2006). These observations suggest that the breakdown of the epidermal barrier represents one of the primary events

in the development of AD. This breach might then allow increased penetration of antigens, allergens, and irritants from the environment and thereby predispose to allergic sensitization and aberrant responses to microbial infection, especially by *Staphylococcus aureus*. Filaggrin is initially synthesized as biologically inactive profilaggrin, which is expressed as a highly phosphorylated insoluble protein in the granular layer of the epidermis. During the transition from granular cells to flattened squamous cells, profilaggrin is processed to biologically active filaggrin monomers through several dephosphorylation and proteolytic steps (Resing et al. 1984; Resing et al. 1989). Two of the proteases that are implicated in profilaggrin processing are KLK5 and 7 (Descargues et al. 2005; Resing et al. 1995). Finally, filaggrin monomers are thought to be digested to the amino-acid level by unknown proteolytic events and form moisturizing factor, which is important for skin hydration (Rawlings and Harding 2004).

Filaggrin belongs to the family of S100-fused-type proteins (SFTP). In humans, the SFTPs include profilaggrin, trichohyalin, repetin, cornulin, hornerin, and filaggrin-2. They are generally thought to be cross-linked by transglutaminases to maintain an intact physical barrier with characteristic resistance and insolubility. SFTP genes consist of three exons, a tiny untranslated exon 1, a small exon 2 containing the translation start site and encoding a 46-residue S100 domain, and a large exon 3 encoding an EF-hand domain and internal tandem repeats, which are characteristic of cornified envelope precursor proteins. Recently a repeat domain of hornerin was identified in human stratum corneum (Wu et al. 2009b), pointing to a proteolytic processing of this 245-kDa protein, which contains 95% tandem quasi-repeating glycine- and serine-rich domains. It was reported that the proteolytic products of hornerin form high-molecular aggregates which might have special characteristics such as water-binding and elastic properties. Whether hornerin plays a similar role to filaggrin in skin diseases is not yet clear and needs further investigation. The same is true for the recently identified filaggrin-2, which is expressed similarly to filaggrin (Wu et al. 2009a). Thus FLG2 and filaggrin may have overlapping and perhaps synergistic roles in the formation of the epidermal barrier, protecting the skin from environmental insults and the escape of moisture by offering precursors of natural moisturizing factors.

CORNEODESMOSIN

Corneodesmosomes mediate the strong intercellular cohesion in the cornified layers that is crucial for the physical and chemical barrier function of the epidermis. They are ultimately degraded at the time of desquamation. Human corneodesmosin (Cdsn), a 52- to 56-kDa basic glycoprotein specific to the cornified epithelia and the inner root sheath of hair follicles, is first detected in the secretory vesicles of the keratinocytes of the uppermost spinous and granular layers. It is also present in the extracellular part of the granular keratinocyte desmosomes and remains in these structures after their transformation into corneodesmosomes. In the cornified layers, Cdsn is covalently linked to the cornified envelope. Detachment of corneocytes during desquamation is done by proteolytic cleavage of Cdsn. KLKs are thought to be the major enzymes to cleave Cdsn (Egelrud 2000). Interestingly, mutations of cell-cell contact proteins of tight junctions, gap junctions, adherens junctions, and desmosomes often result in genetic disorders with cutaneous inflammation and its characteristic redness, scaling, and hyperkeratosis, reviewed in (Lai-Cheong et al. 2007). Uncontrolled proteolytic degradation during inflammation might result in inactivation of these contact proteins.

ANTIMICROBIAL PEPTIDES

Proteolytic processing of higher molecules can lead to the release of antimicrobially active peptide fragments, as demonstrated for kininogen (Frick et al. 2006). Activation of the complement system also leads to the release of antimicrobial fragments (Nordahl et al. 2004). The human cathelicidin hCAP-18 is cleaved to its antimicrobially active fragments by, for example, KLKs (Yamasaki et al. 2006). The release of antimicrobial peptides by proteolytic cleavage of the precursor proteins provides a fast protection against microorganisms immediately after bacterial challenge and provides the first line of defense against microorganisms.

PROTEASE-ACTIVATED RECEPTORS

The discovery of a group of seven-transmembrane receptors which are activated directly by proteolytic cleavage and are therefore named PARs has dramatically changed the traditional view of protease-mediated signaling. Following proteolysis, a new N-terminus of the extracellular part of PARs occurs which now acts as a tethered ligand (Ossovskaya and Bunnett 2004). Four members of PARs are known. PAR-1, PAR-3, and PAR-4 are activated by thrombin and PAR-2 by trypsin and chymotrypsin. PARs are expressed in various cells and organs and the functions described so far reflect this variety. PAR-2 is highly expressed in human skin and contributes to the inflammatory response and, most notably, to the genesis of itch (Steinhoff et al. 2005).

Exogenous proteases

So far, this review has introduced proteases of the skin, their inhibitors, and some of their target proteins which are locally expressed in the skin, i.e. endogenous proteases. It should not be forgotten that proteases can also be of exogenous origin, either of non-host origin, such as microorganisms, allergens, and others, or

derived from cells which infiltrate the skin during inflammation (Fig. 1).

DUST MITE AND OTHER ALLERGENS

AD patients often have elevated levels of IgE against house dust mites (Stewart and Thompson 1996). Interestingly, some of these proteins are cysteine and serine proteases (Yasueda et al. 1993). Some of these proteases were shown to cleave adhesion proteins and to increase the permeability of the epithelium (Winton et al. 1998). Patch tests have demonstrated that two proteases derived from house dust mites, Der p1 and Der p, can elicit irritative or immune reactions that are not linked to increased levels of IgE against house dust mites, suggesting that these proteins cause skin irritation or immune activation through a direct proteolytic activity (Deleuran et al. 1998). Recently it was shown that Der p1 activates PAR-2 and delays epidermal permeability barrier recovery (Jeong et al. 2008). Exogenous proteases such as dust mite proteases and microbial proteases from *S. aureus* might interfere with the endogenous protease/protease-inhibitor balance and lead to exacerbation of AD.

NEUTROPHIL PROTEASES

Neutrophil infiltration is a common pathological feature in acute inflammatory disorders. The primary function of neutrophils is the phagocytosis and eradication of microorganisms. Thousands of neutrophils can accumulate in the skin and form one of the most characteristic manifestations: the pustule. After being generated in the bone marrow, neutrophils circulate in the blood stream. They adhere to the endothelium and migrate to the infected site, where they release oxygen radicals and their internal constituents, which are stored in different granules (Faurschou and Borregaard 2003). The azurophil granules, also called primary granules, contain the serine proteases human leukocyte elastase (HLE), cathepsin G, and proteinase 3 in high concentrations of around 1 pg enzyme per cell (Wiedow et al. 1996). Neutrophils are also present in inflammatory disorders without bacterial involvement. Their active enzymes are detectable at sites of inflammation even though protease inhibitors exist in plasma and in the tissue. For example, active HLE is detectable and can be quantified on the surface of psoriatic plaques in psoriasis, an inflammatory skin disorder with a typical neutrophil infiltrate into the epidermis. HLE activity corresponded to the level of inflammation and disappeared after successful treatment (Wiedow et al. 1995). In recent years, more and more attention has focused on the extracellular effects of neutrophil serine proteases. While the initial interest was aimed more at their deleterious potential, such as their matrix-degrading activity, various studies have shown evidence that neutrophil serine proteases aim specifically at a variety of regulatory functions in local inflammatory processes. For example, HLE leads to epidermal thickening by activation of the epidermal growth factor receptor (Meyer-Hoffert et al. 2004; Rogalski et al. 2002). Other inflammatory responses by neutrophil serine proteases include the release of proinflammatory cytokines, PAR activation, and specific shedding of cytokines and receptors, as reviewed in detail in (Wiedow and Meyer-Hoffert 2005). Altogether, neutrophils and their proteases are key regulators during inflammation, a circumstance which is often overlooked.

CONCLUSION

In summary, these accumulating data suggest that protease regulation, especially the proteolytic processing of filaggrin, plays an important role in epidermal barrier function and inflammatory skin diseases. A proteolytic cascade leads to the desquamation process, and any changes in its progression might result in abnormal desquamation. This abnormal desquamation can be the initiating event in cutaneous inflammation. During inflammation, exogenous proteases get into the skin either from the outside by microorganisms, allergens, and others or are released by infiltrating host cells, especially neutrophils. Moreover, many inflammatory cytokines and receptors are activated by proteolytic processes, which might perpetuate the inflammatory response. Protease inhibitors regulate the proteolytic activity specifically and might have therapeutic potential when protease activity is elevated in the skin.

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