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Invited Review Article

Physiological and pathological roles of kallikrein-related peptidases in the epidermis

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ABSTRACT

Identifying the function of kallikrein-related peptidases (KLKs) in the epidermis has elicited great interest over recent decades. KLKs comprise 15 serine proteases, and their activities are regulated by complex and fine-tuned mechanisms involving the proteolytic activation cascade, endogenous inhibitors, and environmental factors. When the balance is disrupted, excessive or insufficient protease activity can impair epidermal barrier homeostasis. KLKs are involved in various events, such as skin inflammation, wound healing, pruritus, anti-bacterial activity, and viral susceptibility. One of the primary roles of KLKs, mainly KLK5 and KLK7, is physiological desquamation. Both proteases are also involved in the development of inflammatory skin diseases with barrier abnormalities, e.g., Netherton syndrome and atopic dermatitis (AD). In Netherton syndrome, unrestricted activity of KLK5 due to loss of the major endogenous inhibitor, lymphoepithelial Kazal-type-related inhibitor (LEKTI), destroys the component molecules of corneodesmosome, leading to Th2 and Th17 inflammation. Meanwhile, the increased activity of KLK7 in the hyperkeratotic lesions of chronic AD is suppressed by upregulated LEKTI. The functions and implications of other KLKs including KLK6 and KLK8 in healthy and diseased skin such as psoriasis represent an exciting but relatively unexplored area. Clarifying the function of epidermal KLKs will enable development of disease-specific biomarkers and new therapeutic strategies.

1. Introduction

Human kallikrein-related peptidases (KLKs) are differently expressed in many tissues, and exist as a subgroup of 15 serine proteases encoded by a tightly clustered multigene family on chromosome 19q13. 4 [1]. According to the comprehensive nomenclature, KLK1 is tissue kallikrein, and the other 14 KLKs (KLK2- KLK15) are kallikrein-related peptidases [2]. Five coding exons of the gene encode these proteases, with the second, third, and last exons containing the histidine, aspartate and serine residues of the catalytic triad [3]. KLK7 and KLK9 exert chymotryptic-like cleavage preference, and other KLKs show trypsin-like activity. In the KLK family, KLK3/PSA is the most well-known KLK, as a biomarker of prostate cancer. In the epidermis, KLK5 and KLK7 play primary function, and some of the other KLKs have also become known by specific functions, but remain relatively unexplored.

The activity of KLKs is regulated by complex mechanisms, involving various factors such as other proteases, endogenous inhibitors, and physiological environment. Aberrant expression and activity of KLKs affect the barrier function of the stratum corneum, inducing a variety of pathological events, including inflammation. This article will address the role of epidermal KLKs in physiological barrier formation and inflammatory skin diseases.

2. Expression and function of KLKs in healthy skin

The epidermal KLKs are predominantly localized in the upper stratum granulosum and stratum corneum at different levels of expression, and are currently thought to number at least 11: KLK1, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK12, KLK13, and KLK14 [4,5]. These proteases are synthesized as pre-pro-enzymes (precursor or zymogene) transported separately by lamellar granules in the granular layer [6]. After secretion into the intercellular space, pre-KLKs are activated by removal of

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an NH_2-terminus signal peptide by themselves and other proteases [7].

The expression of KLKs in healthy skin depends on age, gender, and body site, and is influenced by glucocorticoid steroids, sex hormones, 1,25-dihydroxy vitamin D3, and retinoic acid [8,9]. Regardless of age, epidermal KLK6 is profoundly expressed in males across body regions, probably influenced by sex hormones [10]. KLK6 is increased in the epidermal atrophy induced by long-term application of topical corticosteroids, participating in the development of glucocorticoid resistance (tachyphylaxis) [11].

The most well-known function of KLKs is physiological desquamation. KLK5 and KLK7 are thought to play the main essential roles in skin desquamation by directly degrading the corneodesmosome. According to a previous *in vitro* experiment, KLK5 can cleave all three of the corneodesmosome component proteins: desmoglein 1 (DSG1), desmocollin 1 (DSC1) and corneodesmosin (CDSN) [12]. KLK7 is capable of cleaving DSC1 and CDSN [12]. Moreover, KLK6 and KLK14 have the potential to cleave DSG1 [13].

Some KLKs, mainly KLK5 and KLK7, also contribute to the processing of profilaggrin in the cytoplasm of the stratum granulosum [14] and extracellular lipid processing enzymes (ß-glucocerebrosidase, and acidic sphingomyelinase) in the stratum corneum [15]. Both KLK5 and KLK7 also control the intrinsic antimicrobial activity of the skin by processing human cathelicidin precursor into the mature LL-37 form [16]. KLK8 also has the potential to generate shorter fragments of LL-37, including active antimicrobial peptides [17].

KLKs thus play essential roles in the physical and biochemical barrier functions of the stratum corneum and are involved in some age- and sex-associated changes to the skin barrier.

3. Regulation of KLKs activity in the epidermis

3.1. KLKs activation cascade in the epidermis

The activity of a KLK is typically controlled by itself or other KLKs in the proteolytic activation cascade (Fig. 1). Briefly, KLK5 is thought to initiate the cascade reaction through auto-activation, and is activated by other proteases including the transmembrane serine protease matriptase and matrix metalloproteases. KLK5 activates other KLKs, like KLK7 and KLK14. Moreover, the activated KLK14 can then activate pro-KLK5 via positive feedback [7]. KLK5 also activates KLK8. The activated KLK8 can process pro-KLK1 and pro-KLK11 *in vitro* [17]. KLK6 is capable of activating KLK5 and KLK11. Until now, the place of some KLKs such as KLK11 and KLK13 in the activation cascade has remained unclear. The metalloprotease meprin β can trigger desquamation through the activation of pro-KLK7, whereas KLK5 and KLK8 have the potential to activate meprin β [18].

3.2. Epidermal endogenous inhibitors

Protease inhibitors are crucial in the control of protease activity. Lymphoepithelial Kazal-type-related inhibitor (LEKTI) encoded by *SPINK5* (serine protease inhibitor of Kazal-type 5) is a major intrinsic inhibitor of epidermal KLKs. LEKTI requires proteolytic processing by furin to generate mature inhibitory domains. Each bioactive LEKTI fragment inhibits KLK5, KLK6, KLK7, KLK13, and KLK14 to varying extents, depending on each inhibitory property [19]. SPINK6 expressed at various anatomical sites efficiently inhibits several KLKs, particularly KLK5 and KLK14 [20]. LEKTI-2, encoded by *SPINK9*, mainly detected in the palmoplantar epidermis, significantly inhibits KLK5 and to a lesser extent KLK8 [21]. Skin-derived antileukoproteinase (SKALP/elafin), secretory leukocyte protease inhibitor (SLPI), or serine protease inhibitors (SERPINs) can function as KLK inhibitors [22].

3.3. Other factors

Physiological circumstances such as pH and ion concentration can influence protease activity. The physiological pH is acidic (4.5–5.3) at the surface of the stratum corneum and gradually becomes more neutral (6.8–7.5) at the innermost layers. The pH of the skin surface is increased to neutral in inflammatory skin diseases such as atopic dermatitis (AD) and psoriasis. Since the optimal pH of KLKs is neutral, activity is almost reduced at pH 5.0. Although the interaction of the KLK-LEKTI complex is robust at neutral pH, contributing to the prevention of premature desquamation [23], skin alkalinization is sufficient to develop KLK5-mediated barrier disruption and Th2 inflammation leading to AD-like dermatitis [24]. Mesotrypsin can degrade LEKTI domains that are capable of recovering the KLKs activity in KLK-LEKTI complex [25]. Zinc ion inhibits the activity of KLK5, KLK7, and KLK8. Environmental conditions such as pH, moisture, and cationic ions are regarded as indispensable factors to regulate the activity of KLKs and maintain epidermal barrier homeostasis [26].

4. Pathophysiological role of KLKs in inflammatory skin diseases

KLKs are thought to be involved in various types of skin inflammation. For instance, upregulated KLK5 and KLK7 can excessively degrade LL-37 into shorter inflammatory peptides known as the primary pathogenetic factor in rosacea [16]. The following explains the pathological role of KLKs, focusing on Netherton syndrome (NS), AD, and psoriasis.

4.1. NS

NS is a congenital ichthyosis with erythroderma, hair shaft abnormalities, and atopic features, caused by loss-of-function mutations in *SPINK5* encoding LEKTI. In the LEKTI-deficient

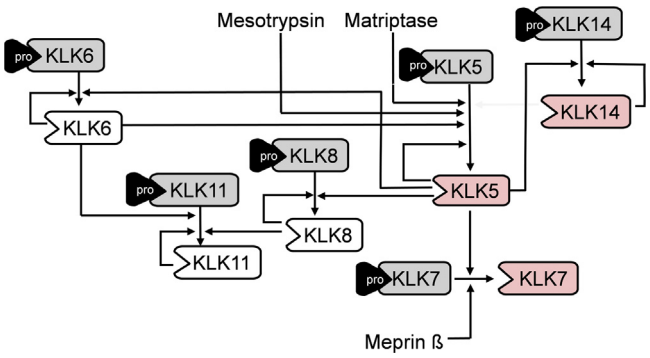

Fig. 1. Putative KLKs activation cascade in the epidermis.
KLK5 acts as an initiator, activated by other proteases such as mesotrypsin and matriptase as well as itself, and then activates other KLKs. KLK14 and KLK6 can activate pro-KLK5. KLK5 and KLK8 are capable of activating pro-KLK7 via the activation of meprin β. KLK5, KLK7, and KLK14 mainly play essential roles in degrading corneodesmosome component proteins such as desmoglein 1, desmocollin 1, and corneodesmosin.

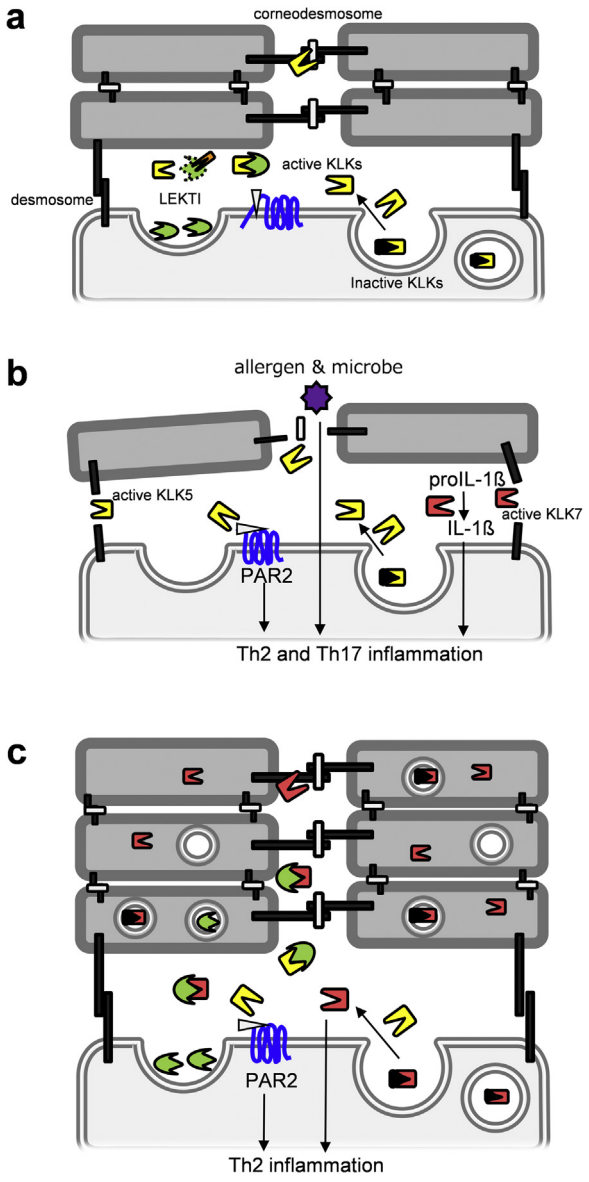

Fig. 2. Different roles of KLKs in healthy skin, Netherton syndrome, and atopic dermatitis.
Lamellar granules separately transport KLKs and are then secreted into the intercellular space, where the proteases are activated by themselves and other proteases. (a) In healthy skin, activated KLK5 bind to LEKTI in intracellular areas of the stratum granulosum and stratum corneum, preventing premature desquamation. Mesotrypsin is capable of degrading LEKTI domains in the KLK-LEKTI complex to activate KLKs. (b) In Netherton syndrome (NS), uncontrolled KLK5 and KLK7 due to loss of LEKTI excessively degrade corneodesmosomes and lead to severe barrier disruption along with the production of proinflammatory cytokines. The excessive disruption of the physical barrier induces pro-IL-1β, which can be activated by KLK7. Overactivated KLKs induce Th2 and Th17 inflammation with or without PAR2. (c) In chronic atopic dermatitis (AD) lesions, upregulated KLK7 remains trapped inside the corneocytes due to impaired lamellar granule secretion. Extracellular KLK7 is suppressed by upregulated LEKTI, leading to delayed proteolysis of the corneodesmosome and compact hyperkeratosis. Some other AD cases supposedly exhibit barrier dysfunction due to uncontrolled KLKs activity, similar to NS.

epidermis, uncontrolled KLK5 and KLK7 excessively degrade corneodesmosomes, leading to severe barrier impairment, accompanied by hyperplasia and aberrant differentiation of epidermis, and the production of proinflammatory cytokines (Interleukin (IL)-1β, IL-8, and tumor necrosis factor (TNF) -α) [27,28]. KLK7 also contributes to recruiting innate immune cells by activation of inflammasome-related pro-inflammatory cytokine IL-1β [18]. Moreover, unopposed KLK5 and KLK7 impair profilaggrin and lipid processing via the activation of elastase 2 [29]. The resulting excessive disruption to the physical barrier and reduced LL-37 antimicrobial activity facilitate the entry of microbes and allergen into the living layer, enhancing allergic and inflammatory responses via the activation of the inflammasome and protease-activated receptor 2 (PAR2). PARs, as G-protein-coupled seven transmembrane domain receptors expressed by many cell types including epidermal keratinocytes, are activated by cleavage of the extracellular N-terminal domain, exposing a new N-terminus, which then activates the receptor as a tethered ligand [30]. Activation of PAR2 is associated with keratinocyte proliferation and differentiation, inflammation, pruritus, and pigmentation. According to *in vitro* experiment, KLK5, KLK6, KLK7, and KLK14 have the potential to activate PAR2 [31,32]. KLK5 hyperactivity has been shown to directly activate the PAR2-NF-κB pathway, resulting in the production of the pro-allergic chemokine thymic stromal lymphopoietin (TSLP) and pro-inflammatory cytokines (IL-8 and TNF-α) [33]. Moreover, persistent up-regulation of KLK5 in keratinocytes induces the secretion of TSLP, IL-8, and IL-10 via a PAR2-independent pathway [34]. The model mouse for NS with epidermis-specific overexpression of human KLK5 exhibits elevated expression of Th2 chemokines and cytokines (TSLP, IL-4, and IL-13) as well as Th17/Th22 molecules (IL-1β, IL-8, TNF-α, IL-23, and C-C motif chemokine ligand 20 (CCL20)) [35]. Recently, the immunopathogenesis of ichthyoses including NS has been demonstrated to involve the Th17/IL-23 axis, similar to psoriasis [36]. Sustained hyperactivation of KLK5 probably contributes to the induction of Th2 and Th17 inflammation with or without PAR2.

4.2. AD

AD is a common and heterogeneous multifactorial inflammatory skin disease characterized by genetic barrier dysfunction and Th2 allergic immunity, which is sustained by gene-environmental interactions. Since NS represents a severe AD phenotype, KLKs

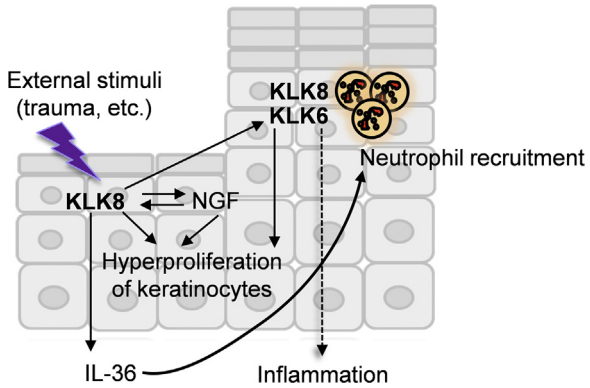

Fig. 3. Function of KLK8 in psoriasiform inflammation.
KLK8 upregulated by external stimuli such as injury induces the expression of other KLKs, including KLK6. KLK8 is involved in the induction of IL-36 cytokines associated with neutrophil recruitment to the epidermis and proliferation of keratinocytes, which are relevant to psoriasiform skin inflammation. Moreover, KLK8 and NGF seem to interact to upregulate each other, probably associated with inflammatory skin diseases including psoriasis.

have been thought to play an essential role in the pathogenesis of AD.

Among the various KLKs, KLK7 is thought to play the most crucial role in the pathogenesis of AD. Transgenic mice overexpressing KLK7 in the epidermis develop acanthosis, hyperkeratosis, and inflammation with severe pruritus, similar to the clinical features of AD [37]. KLK7 is prominently increased in the stratum corneum of AD lesions [38]. Moreover, serum KLK7 levels is correlated with the number of peripheral blood eosinophils [38]. Th2 cytokines IL-4 and -13 increase the production of KLK7 and chymotrypsin-like activity in cultured normal human epidermal keratinocytes (NHEKs) [39]. To support this, serum KLK7 and IL-4 levels in AD patients are significantly correlated [39].

Chronic AD lesions often develop hyperkeratosis that supposedly depends on, in part, insufficient proteolysis of corneodesmosomes. To assess protease activity more precisely, we performed *in situ* zymography of tape-stripped corneocyte. While the expression of KLK7 was upregulated in AD skin, the intensity of the main chymotryptic activity of AD corneocytes was almost the same as that of healthy subjects. Moreover, a large amount of KLK7 remains trapped inside the AD corneocytes with impaired lamellar body secretion and extracellular KLK7 is colocalized with upregulated LEKTI. In some AD lesions, KLK7 activation is insufficient, leading to delayed proteolysis of the corneodesmosomes and compact hyperkeratosis (Fig. 2b) [40]. *Klk7*$^{-/-}$*SPINK5*$^{-/-}$ mice fail to show rescue of excessive corneocyte shedding, but recover the epidermal differentiation and inflammation [41].

Skin colonization by *Staphylococcus aureus* is thought to be one of the exacerbating factors in AD. A recent report demonstrated that *S. aureus* (Newman and USA300 strains) significantly increased the trypsin-like protease activity of cultured NHEKs with the upregulation of KLK6, KLK13, and KLK14 [5]. Enhanced degradation of DSG1 and FLG by *S. aureus* is partially blocked by knockdown of KLK6 or KLK14, and KLK6 or KLK13, respectively [5].

Several KLKs, mainly KLK7, likely participate in the induction and exacerbation of barrier dysfunction as well as inflammation in AD skin to some extent with the inhibition by LEKTI. However, the roles of KLKs in AD remain controversial because the expression and activity of KLKs are variable in AD lesions, presumably depending on the severity and duration of the disease. Further analyses are required to determine the exact contributions of KLKs to the pathophysiological mechanisms underlying AD.

4.3. Psoriasis

Psoriasis is characterized by activation of the TNF/IL-23/Th17 axis. IL-23 secreted by dendritic cells and IL-17-producing T cells promoted by monocytes and macrophages synergistically exert multifunctional effects on the recruitment and activation of immune cells such as neutrophils and the hyperproliferation of keratinocytes [42]. IL-36 signaling also plays an essential role in driving psoriatic inflammation in neutrophil activation [42].

Both KLK6 and KLK8 are strongly upregulated in the psoriatic lesion. Psoriatic plaques and psoriatic arthritis synovial fluids contain high levels of KLK6 and KLK8, but not the other seven KLKs [43]. Importantly, serum levels of KLK8 correlate significantly with the clinical skin severity of psoriasis, but not with that of psoriatic arthritis [43], and might thus offer a promising marker of disease severity in psoriasis.

Our group found that mouse kallikrein (Klk) 8 is associated with acanthosis, corneocyte shedding, and skin inflammation in cooperation with other Klks (Klk6 and Klk7) in a TPA-mediated model of psoriasis-like inflammation [44]. Furthermore, in an imiquimod (IMQ)-induced murine model of psoriasis, Klk8 is involved in the microabscess formation in the upper epidermis, significantly coinciding with the induction of IL-36 cytokines, especially IL-36α [45]. Moreover, epidermal Klk8 is increased during cutaneous wound healing, which shares many features with psoriasis, accompanied by the upregulation of Klk6 and the activation of PAR2 [46]. Klk6 can directly activate PAR2, but does not require a PAR2 pathway in the development of IMQ-induced murine psoriasis [47]. As neither KLK6 nor KLK8 is dependent on PAR2 activation, these proteases might induce psoriasiform inflammation through other pathways such as PAR1 signaling.

The development of psoriasis after cutaneous trauma, i.e., Koebner phenomenon, requires various factors including nerve growth factor (NGF) to induce keratinocyte proliferation and T-cell recruitment [48]. Klk8 shows a close relationship with NGF, with each influencing the expression of the other [49]. Although details are unclear, interactions between KLK8 and NGF might contribute to the initiation of psoriasis or other inflammatory skin diseases (Fig. 3). In addition, KLK8 seem to have a distinctive function in normal skin homeostasis and skin diseases in a different way from other KLKs. KLK8 is unable to disrupt the corneodesmosome, but can potentially cleave the L1 adhesion molecule, which serves as a major capsid protein for human papillomavirus (HPV), facilitating further conformational changes during virus entry into host cells [50]. KLK8 upregulated in skin micro-injuries or inflammatory skin diseases may increase the chance of HPV infection in the epidermis.

5. Conclusion

The functions of epidermal KLKs vary widely. While KLK5 and KLK7 have significant roles in the epidermis, the function of other KLKs including KLK6 and KLK8 remain largely unresolved. Although the details are not described here, the relationships between KLKs and cutaneous malignancies have been gradually revealed. Elucidating the exact contributions of KLKs will enable the development of disease-specific biomarkers and new treatment strategies for various kinds of skin diseases.

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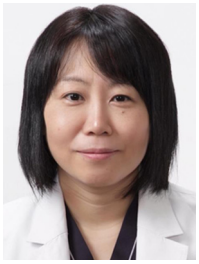

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