

Review

The Role of Kallikrein-Related Peptidases in Atopic Dermatitis

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Excessive protease activity is a characteristic abnormality that affects the epidermal barrier in patients with atopic dermatitis (AD). Kallikrein-related peptidases (KLKs) are excessively expressed in AD lesions, and it is suggested that the abnormal action of KLKs is involved in the skin barrier dysfunction in AD. In other words, overexpressed KLKs disrupt the normal barrier function, and due to that breakdown, external substances that can become antigens of AD easily invade the epidermis, resulting in dermatitis, coupled with the induction of Th2 cytokines. Further investigations are required to elucidate the role of KLKs in AD; this knowledge could contribute to the design of new therapeutic and prophylactic drugs for AD.

Key words: atopic dermatitis, kallikrein-related peptidases, epidermal barrier dysfunction

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease which is considered a multifactorial disease caused by both genetic and environmental factors [1]. The pathophysiology of AD is roughly divided into two elements: barrier dysfunction in the epidermal keratinocyte layer of the skin surface, and systemic inflammatory reaction by various cytokines/chemokines, mainly Th2 cytokines [1]. In relation to the barrier dysfunction, Palmer *et al.* reported that the patients from Ireland with AD showed a high rate of genetic defects in filaggrin, an epidermal barrier component [2]. However, there are quite a few AD patients who do not carry any filaggrin gene mutations, and some individuals with filaggrin gene mutations do not develop AD [3]. Therefore, other epidermal barrier factors are also likely to be associated with the pathogenesis of AD. There are many reports about the influence of interleukin (IL)-4 and IL-13, which are Th2 cytokines, on immune cells such as T cells [4]. The effects of these cytokines on the epidermal barrier mechanism have also been described [4, 5].

A protease with the ability to release bradykinin from kininogen was reported in 1930, and it was named "kallikrein", which is derived from the Greek word for pancreas, "kallikreas" [6]. The protease is now known as tissue kallikrein 1 (KLK1). Plasma kallikrein (KLKB1) was later also discovered as another kallikrein that is produced mainly in the liver and circulates in the blood [7]. Currently, 15 types of tissue kallikreins have been reported, and the 14 kallikreins other than KLK1 are called kallikrein-related peptidases (KLK2-KLK15) [8]. *KLK1* to *KLK15* form gene clusters in the long arm of chromosome 19 (*KLKB1* is located on chromosome 4q34-35) [8]. *KLK1* to *KLK15* are transcribed to mRNA with five coding exons. KLKs are produced as pre-proteins, with N-terminal signal peptides [8]. The signal peptides are removed during secretion into the extracellular space, and the propeptides are removed extracellularly by autocatalysis or by other KLKs or endopeptidases [8].

Epidermal keratinocyte-derived serine proteases affect the barrier formation of the epidermal stratum corneum. Especially, KLK5 (a trypsin-like serine pro-

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tease) and KLK7 (a chymotrypsin-like serine protease) are well known to be highly expressed in skin epidermal keratinocytes [9]. These KLKs are thought to promote the desquamation of the epidermal stratum corneum in normal skin by cleaving adhesion molecules such as desmoglein 1 (DSG1), desmocollin 1 (DSC1), and corneodesmosin (CDSN) (Fig. 1) [9]. KLKs also activate IL-1 β in the skin [10-12]. The elevation of pH enhances the serine protease activities, and the stratum corneum pH is increased in AD lesions [1, 13, 14].

On the other hand, in a mouse model of abnormal KLK activation (the mice are deficient in the KLK inhibitory factor lympho-epithelial Kazal-type-related inhibitor [LEKTI]), a decrease in stratum corneum barrier function and skin eczematous inflammation are induced, accompanied by the accelerated decomposition of filaggrin [15]. Loss-of-function mutations of *SPINK5*, which encodes LEKTI, are found in patients with human Netherton syndrome [16], and it is interesting that these patients develop AD-like symptoms and hyper-IgEemia. p.K420E, a single-nucleotide polymorphism (SNP) of *SPINK5*, was reported to be associated with the pathogenesis of AD [17-23], but not in all populations [24-29]. Fortugno *et al.* showed that this variant has altered serine protease inhibitor function that results in protease deregulation [30]. It was also reported that KLKs are excessively expressed in AD lesions [31], and it was suggested that the abnormal action of KLKs is involved in skin barrier dysfunction in AD. In other words, overexpressed KLKs disrupt the normal barrier function, and due to that breakdown, external substances that can become antigens of AD

easily invade the epidermis, resulting in dermatitis, coupled with the induction of Th2 cytokines (Fig. 2).

This article reviews the association between KLKs and AD. In the skin, KLK5, 6, 7, 8, 10, 11, 13, and 14 are expressed at the protein level [32]. The article, therefore, focuses on these eight KLKs associated with AD.

KLK5 and AD. KLK5 is a major trypsin-like serine protease in the epidermis, and it was first reported and cloned as “stratum corneum tryptic enzyme (SCTE)” in 1999 [33]. KLK5 is capable of cleaving DSG1, DSC1, and CDSN, leading to desquamation of the corneal layers (Fig. 1) [9]. KLK5 is indirectly involved in the processing of (pro) filaggrin by activating elastase-2, which is a serine protease expressed in the epidermal layer [34]. It was recently pointed out that KLK5 is localized not only in lamellar granules but also in keratohyalin granules, and KLK5 may be directly involved in the processing of profilaggrin [35]. KLK5 also has the potential to activate the human cathelicidin antimicrobial peptide LL-37 [36]. KLK5 self-activates, and is also activated by KLK14 (Fig. 3) [37].

Both KLK5 expression and trypsin-like serine protease activity are upregulated in AD lesions, and the latter effect is thought to decrease epidermal barrier function [31, 38]. Transcription factor specificity protein 1 (Sp1) is significantly decreased in AD lesions, and Sp1 silencing upregulates KLK5 expression in epidermal keratinocytes, suggesting that Sp1 expression deficiency leads to abnormally increased KLK5 in AD [39]. IL-4 has been reported to suppress Sp1 mRNA expression in

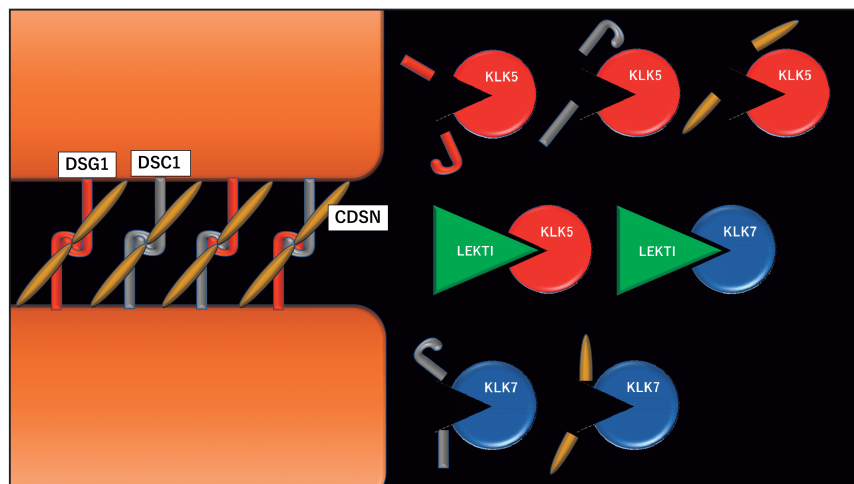


Fig. 1 The roles of KLKs in normal skin. KLK5 cleaves DSG1, DSC1, and CDSN, and KLK7 is capable of cleaving the latter two. These cleavages lead to the desquamation of the corneal layers in normal skin. LEKTI tightly regulates the activities of KLKs.

cultured keratinocytes, but it did not show any direct effect on KLK5 expression in the cells [5, 40]. Further investigation is required to clarify the exact mechanism of the increase of KLK5 in AD lesions.

In addition, KLK5 induces the expression of thymic stromal lymphopoietin (TSLP) via protease-activated receptor-2 (PAR2), which creates a Th2-rich environment [41]. The elevation of the skin pH also directly modulates KLK5 activity against PAR2 [14]. However, Zhu *et al.* reported that persistent KLK5 activation induces AD-like skin architecture independent of PAR2 activity [42].

Transgenic mice overexpressing human KLK5 display cutaneous and systemic hallmarks of severe inflammation and allergy with pruritus [43]. Furthermore, KLK5 is an endogenous pruritogen in a

murine model of AD [44].

KLK6 and AD. KLK6 is a trypsin-like serine protease and its expression is detectable in the epidermis at the mRNA and protein levels [32, 45]. KLK6 is activated by KLK5 (Fig. 3) [46]. Similar to KLK5, KLK6 is capable of activating PAR2 [47]. The expression of KLK6 is increased in AD lesions [31]. Sp1 silencing also upregulates KLK6 expression in epidermal keratinocytes [39]. *Staphylococcus aureus* induces KLK6 expression and enhances the KLK6-dependent degradation of DSG1 and filaggrin, which might be involved in the pathogenesis of AD [48].

KLK7 and AD. In the KLK family, KLK7 is the sole chymotrypsin-like serine protease expressed in the epidermis, and it was first reported as “stratum corneum chymotryptic enzyme (SCCE)” in 1991 and

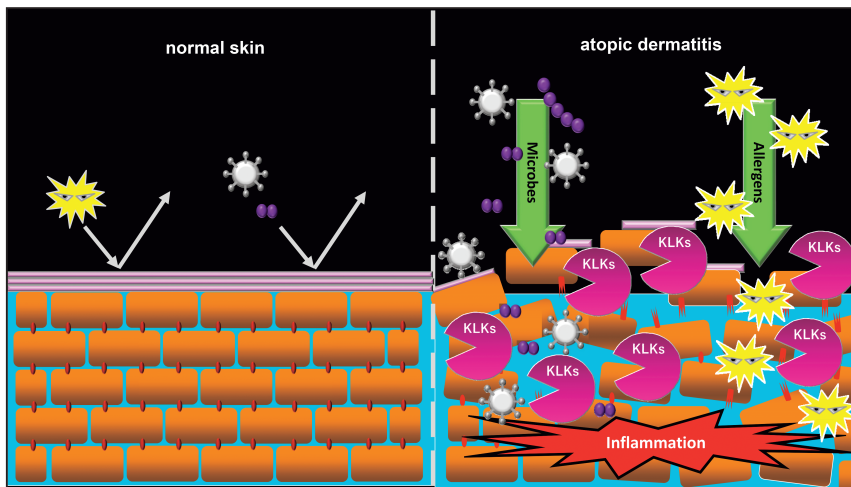


Fig. 2 Epidermal barrier dysfunction in AD. Overexpressed KLKs disrupt the normal barrier function, and due to this breakdown, external substances that can become antigens of AD easily invade the epidermis, resulting in dermatitis.

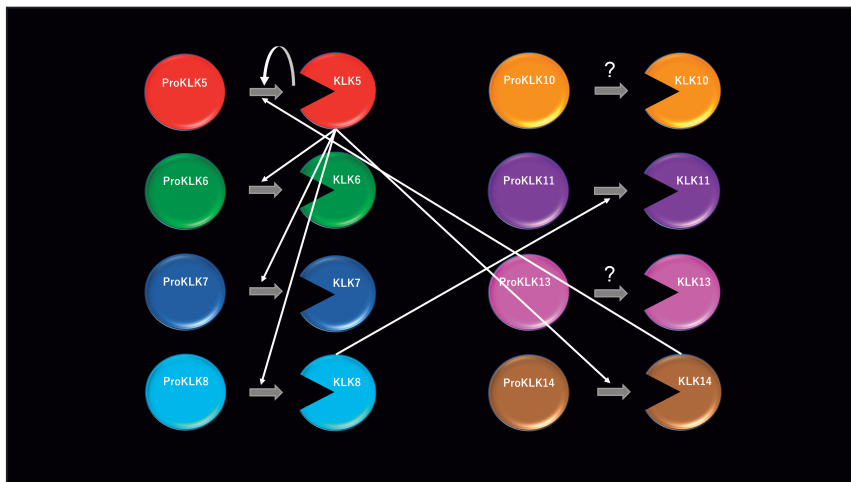


Fig. 3 KLK activation cascade. The activation cascade of eight KLKs expressed in the skin is shown.

cloned in 1994 [49,50]. KLK7 is capable of cleaving DSC1 and CDSN, leading to desquamation of the corneal layers (Fig. 1) [9]. The elevation of the pH in stratum corneum that is observed in AD lesions enhances KLK7 activity [1,13]. KLK7 is activated by KLK5 (Fig. 3) [37].

Both the expression of KLK7 and the activity of chymotrypsin-like serine protease are upregulated in AD lesions, and the latter increase is thought to decrease epidermal barrier function, as with increased KLK5 activity [31,38]. However, there has been a report describing that KLK7 expression was upregulated in tape-stripped corneocytes from AD lesions, but the activity of chymotrypsin-like activity serine protease was not elevated [51]. Sp1 silencing also upregulates KLK7 expression in epidermal keratinocytes [39]. The Th2 cytokines IL-4 and IL-13 increase KLK7 expression and the protease activity in AD lesions [5]. The KLK7 protein level in the sera of patients with AD significantly correlates with the patient's IL-4 levels [5]. KLK7 also has the potential to degrade the human cathelicidin antimicrobial peptide LL-37 [36], and a decrease in LL-37 levels has been documented in AD skin [52], which might account for the susceptibility of AD patients to skin infection. Transgenic mice overexpressing human KLK7 develop chronic itchy dermatitis resembling AD [53].

A 3'-UTR (untranslated region) AACC insertion in the *KLK7* gene has been reported to be significantly and frequently observed in AD patients, and to cause increased mRNA expression without altering the gene's stability [54,55]. However, this variant was not significantly associated with AD in a French cohort study [18].

KLK8 and AD. KLK8, also known as neuropsin, has trypsin-like serine protease activity. KLK8 expression is detectable in the epidermis at the mRNA and protein levels [32,45]. KLK8 is involved in the abnormal proliferation or differentiation of epidermal keratinocytes [56,57]. This protease also has the potential to cleave LL-37 into shorter peptides [57]. KLK8 is activated by KLK5 (Fig. 3) [57]. KLK8 is the most abundant trypsin-like serine protease of the KLK family in AD lesions [31]. Sp1 silencing also upregulates KLK8 expression in epidermal keratinocytes [39].

KLK10 and AD. KLK10 is a trypsin-like serine protease and its expression is detectable in the epidermis at the mRNA and protein levels [32,45]. Although KLK10 activation in epidermal keratinocytes has not

been well studied, KLK10 expression was shown to be increased in AD lesions [31]. Sp1 silencing also upregulates KLK10 expression in epidermal keratinocytes [39]. The physiological role of KLK10 in the skin and the pathogenetic role of KLK10 in AD are not sufficiently understood.

KLK11 and AD. KLK11 is a trypsin-like serine protease and its expression is detectable in the epidermis at the mRNA and protein levels [32,45]. KLK11 is activated by KLK8 (Fig. 3) [57], and KLK11 expression is increased in AD lesions [31]. The physiological role of KLK11 in the skin and the pathogenetic role of KLK11 in AD are not sufficiently understood.

KLK13 and AD. KLK13 is a trypsin-like serine protease and its expression is detectable in the epidermis at the mRNA and protein levels [32,45]. KLK13 activation in epidermal keratinocytes has not been well studied. The expression of KLK13 is increased in AD lesions [31]. *Staphylococcus aureus* induces KLK13 expression and enhances the KLK13-dependent degradation of DSG1 and filaggrin, which might be involved in the pathogenesis of AD [48].

KLK14 and AD. KLK14 is a trypsin-like serine protease and its expression is detectable in the epidermis at the mRNA and protein levels [32,45]. Similar to KLK5, KLK14 is capable of activating PAR2 [47]. This protease also has the potential to cleave LL-37 into shorter peptides [57]. KLK14 is activated by KLK5 (Fig. 3) [37]. The expression of KLK14 is increased in AD lesions [31]. *Staphylococcus aureus* induces KLK14 expression and enhances the KLK14-dependent degradation of DSG1 and filaggrin, which might be involved in the pathogenesis of AD [48].

Conclusion

This article has reviewed the roles of KLKs in AD. Many KLKs are upregulated in AD lesions and might play a role in the disease pathogenesis by decreasing epidermal barrier functions. Further research is necessary to elucidate the role of KLKs in AD. The knowledge of the role could contribute to the design of new therapeutic and prophylactic drugs for AD.

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