



Expression of antimicrobial peptides in atopic dermatitis and possible immunoregulatory functions

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Purpose of review

To summarize the findings on the expression of antimicrobial peptides in the skin in inflammatory skin diseases and particularly in atopic dermatitis. Moreover, the literature addressing the functions of antimicrobial peptides (AMPs) beyond antimicrobial activities with impact on allergic skin inflammation is summarized as well.

Recent findings

Although lower expressed than in psoriasis, most AMPs have been shown to be either constitutively expressed or upregulated in atopic dermatitis as well. A number of immunoregulatory functions which might impact on allergic skin inflammation have been described for several antimicrobial peptides, mainly for human β -defensins and the cathelicidin LL-37.

Summary

From the recent literature, there is considerable evidence that AMPs are induced in the skin in atopic dermatitis. However, some studies suggest that the induction, release or mobilization of some AMPs in atopic dermatitis may not reach sufficient levels to provide adequate control of cutaneous microbial colonization. Th2 cytokines appear to negatively influence the expression and induction of some AMPs. A number of immunoregulatory functions have been described for several AMPs. Most of them point to a proinflammatory function of AMPs in addition to their antimicrobial activities. Further studies are needed to clarify the role of AMPs in atopic dermatitis.

Keywords

allergic skin inflammation, antimicrobial peptide, atopic dermatitis

INTRODUCTION

The skin is the primary interface between the body and the environment, and provides the first line of defence against the environmental influences [1[■]]. During the last decade, antimicrobial peptides (AMPs) emerged to be an essential part of the innate immune response in human skin [2]. AMPs are a heterogeneous group of usually highly cationic small peptides and proteins which represent a chemical defence system against various bacteria, fungi and viruses. On the basis of their structure, mammalian AMPs have been divided into several different families. In the skin, members of two major groups, the cathelicidins and human β -defensins (hBDs), are most well characterized. However, members from other AMP families such as the S100 protein psoriasin and RNase 7, a member of the RNase A family, came into the focus of interest during the last years [3,4]. In light of their important role in the skin defence system, the expression of different AMPs in chronic inflammatory skin

diseases, in particular, in atopic dermatitis, has been studied during recent years – with partly conflicting results. Of note, in addition to their antimicrobial activity, immunoregulatory functions have been discovered for several AMPs, raising the idea that regulation of AMP expression also may influence the adaptive immune responses in inflammatory skin diseases.

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KEY POINTS

- There is clear evidence that AMPs are induced in the lesional skin of atopic dermatitis patients.
- Recent studies contradict the hypothesis that the high *S. aureus* colonization rates seen in atopic dermatitis are caused by a general AMP deficiency.
- Immunoregulatory functions have been described for several AMPs, which may influence the adaptive immune responses in allergic inflammatory skin diseases.

IS THERE A GENERAL DEFICIENCY IN THE EXPRESSION AND FUNCTION OF ANTIMICROBIAL PEPTIDES IN ATOPIC SKIN?

The major source of AMPs in the skin are keratinocytes. Other cellular sources of AMP are mast cells in the dermis, which store large amounts of cathelicidin in preformed granules. A disturbed function of AMP in atopic dermatitis has been first suggested by Ong *et al.* [5], who reported on a diminished expression of LL-37 and hBD-2 in atopic dermatitis compared with psoriasis. A possible molecular explanation for this observation was provided by experiments showing that the induction of hBD-2 in HaCaT keratinocytes was inhibited by the Th2 cytokines IL-4 and IL-13. These findings suggest the presence of an AMP deficiency in atopic dermatitis, which may trigger increased bacterial colonization and infection seen in atopic skin. This hypothesis was supported by another study of this group reporting microarray data, revealing that the expression of innate immune response genes encoding for hBD-2, IL-8 and inducible NO synthetase (iNOS) is decreased in atopic dermatitis compared with psoriasis. In line with this, immunohistochemistry and real-time PCR revealed a decreased expression of hBD-3 in atopic skin compared with psoriatic skin. Increased IL-13 levels were correlated with decreased hBD-3 levels, and cell culture experiments showed an inhibition of TNF- α -induced and IFN- γ -induced hBD-2 and hBD-3 gene expression by the Th2 cytokines IL-4 and IL-13 [6]. Another study of the same group provided further evidence that a Th2 cytokine milieu in atopic dermatitis skin negatively influences hBD-3 expression. Antibody-mediated neutralization of Th2 cytokines IL-4, IL-10 and IL-13 resulted in an increased expression of hBD-3 in atopic dermatitis skin explants [7]. In addition, treatment of atopic dermatitis skin explants with anti-IL-10 increased the expression of both hBD-2 and LL-37

[8]. Taken together, these findings support the hypothesis that a Th2 cytokine milieu may hamper the induction of AMPs in atopic dermatitis.

A deficiency of AMP expression related to atopic dermatitis was also reported for the sweat-gland-derived AMP dermcidin [9]. The sweat of atopic dermatitis patients contained lower amounts of dermcidin than that of healthy controls. In addition, atopic dermatitis patients with a history of bacterial and viral skin infections were found to have significantly less dermcidin in their sweat. Finally, in comparison to healthy individuals, atopic dermatitis patients exhibited a reduced antibacterial activity on the skin surface after sweating. Thus, reduced production of dermcidin by the sweat glands of atopic dermatitis patients may trigger increased bacterial colonization.

Another role of AMPs in atopic dermatitis has been introduced by Kisich *et al.* [10]. They reported that constitutive levels of hBD-3 in keratinocytes were similar between normal individuals and those with atopic dermatitis, whereas the mobilization of hBD-3 onto *Staphylococcus aureus* was impaired in individuals with atopic dermatitis. Mobilization of hBD-3 and the subsequent bactericidal activity were reduced by Th2 cytokines. Treatment of skin samples from patients with atopic dermatitis with antibodies to the Th2 cytokines IL-4, IL-10 and IL-13 did not influence keratinocytes' hBD-3 expression, but enhanced the deposition of hBD-3 to the surface of *S. aureus*. The authors conclude that patients with atopic dermatitis bear abnormally high burdens of *S. aureus* on the skin because high levels of Th2 cytokines interfere with constitutive killing by epidermal keratinocytes [10].

There are also a few reports indicating the role of AMPs for virus infection in atopic dermatitis. For example, a subset of patients with atopic dermatitis suffer from spreading herpes simplex virus (HSV) infections (AD patients with eczema herpeticum, ADEH). It has been reported that LL-37 exhibits activity against HSV, and mice deficient in the LL-37 orthologue showed higher levels of HSV-2 replication in their skin. In addition, the skin from atopic dermatitis patients with ADEH exhibited significantly lower levels of LL-37 than that from patients with atopic dermatitis. Thus, reduced levels of LL-37 may render atopic dermatitis patients susceptible to ADEH [11].

Another study [12] comparing ADEH with atopic dermatitis and psoriasis suggested an inability to adequately induce LL-37, hBD-2 and hBD-3 in the skin of ADEH patients. This was shown by a real-time PCR-based analysis calculating the AMP expression in lesional skin biopsies minus expression in non-lesional skin biopsies. However, as the expression

levels of hBD-2 and hBD-3 in nonlesional ADEH skin were surprisingly higher than in nonlesional skin of atopic dermatitis and psoriasis patients, it remains to be shown whether significantly less hBD-2 and hBD-3 is expressed in the lesional skin of ADEH patients compared with the lesional skin of patients with atopic dermatitis and psoriasis [12]. Individuals with atopic dermatitis show a predisposition to develop eczema vaccinatum following vaccination with vaccinia virus. It has been documented that atopic dermatitis skin exhibited increased vaccinia virus replication and decreased LL-37 expression compared with normal or psoriasis skin. IL-4 and IL-13 enhanced vaccinia virus replication and inhibited LL-37 expression in vaccinia virus-treated keratinocytes. Neutralizing IL-4 and IL-13 in atopic dermatitis skin increased LL-37 expression and inhibited vaccinia virus replication. The application of exogenous LL-37 controlled viral replication in vaccinia virus-infected keratinocytes. In addition, the skin of mice deficient in the LL-37 orthologue showed a reduced capacity to control vaccinia virus infection. Taken together, this study [13] identified LL-37 as an important defence molecule controlling vaccinia virus, an activity which was abrogated in the skin of atopic dermatitis patients, likely because of an inability to adequately induce LL-37 production.

GROWING EVIDENCE: ANTIMICROBIAL PEPTIDES ARE INDUCED IN THE SKIN OF ATOPIC DERMATITIS

In concordance with the idea of an AMP deficiency in atopic dermatitis compared to psoriasis, microarray and real-time PCR analysis performed by De Jongh and colleagues revealed that several AMPs such as hBD-2, psoriasin, elafin and calprotectin were higher expressed in psoriasis than in atopic dermatitis [14]. Surprisingly, a significant overexpression of LL-37 in psoriasis compared with atopic dermatitis was not observed in this study. The authors hypothesized that the use of purified epidermis rather than full-thickness skin biopsies may explain these differences, especially because LL-37 is known to be expressed at high levels in infiltrating cells. In addition, no lower gene expression of hBD-3 in atopic dermatitis epidermis compared with psoriasis was detected. Compared with healthy skin, however, a higher expression of hBD-3 as well as several other AMPs such as hBD-2, psoriasin, elafin and calprotectin was found in the skin in atopic dermatitis [14]. These data provided first evidence that there is no general defect in the induction of AMPs in atopic dermatitis.

Induction of AMPs in atopic dermatitis was further supported by a study by Ballardini *et al.*

[15], who reported on higher levels of LL-37 in lesional skin than in nonlesional skin in atopic dermatitis. Furthermore, Gambichler *et al.* [16] who investigated a relatively large number of full-thickness skin samples derived from psoriasis and atopic dermatitis patients showed that most AMPs investigated in this study were significantly overexpressed both in lesions in atopic dermatitis and in psoriasis vulgaris. In line with the previous studies, a lower induction of hBD-2 in atopic dermatitis compared with psoriasis was observed. In contrast, LL-37 was not found to be significantly overexpressed in the skin of patients with atopic dermatitis or psoriasis. In concordance with the above-mentioned data of De Jongh *et al.* [14], gene expression of hBD-3 in atopic dermatitis and psoriasis was not different. Moreover, RNase 7 even showed a higher expression in atopic dermatitis than in psoriasis [16]. There is evidence that hBD-3 and RNase 7 are major skin-derived AMPs with high anti-*S. aureus* activity. Thus, this study did not support the hypothesis that the high *S. aureus* colonization rates seen in atopic dermatitis are based on an AMP deficiency.

Why did the different studies on this topic reveal contrasting results? In addition to the general differences in methodology, Gambichler *et al.* [16] speculate that it may be of particular relevance whether patients with intrinsic or extrinsic atopic dermatitis are recruited and whether biopsies are harvested from acute or chronic lesions. The different cytokine milieu of acute and chronic atopic dermatitis may directly influence AMP expression. Furthermore, the actual cutaneous microbial colonization and the use of pure epidermis or full-thickness skin samples may be of importance.

Recent studies confirm the induced expression of several AMPs such as hBD-2, psoriasin and RNase 7 in the skin of atopic dermatitis patients. Recovery of AMPs on the skin surface revealed increased amounts in atopic dermatitis lesions compared with the healthy control group. This was also verified by immunohistochemistry [17,18]. Superficial barrier disruption in the atopic lesions may trigger the release of AMPs because expression of psoriasin, hBD-3 and RNase 7 was increased upon tape stripping-induced barrier disruption. Moreover, enhanced psoriasin and RNase 7 secretion was detected already 1 h after experimental epidermal barrier disruption [17,18]. However, in the case of LL-37, a recent study [19] indicates that the normal injury-mediated induction of LL-37 in wounded atopic dermatitis lesions is suppressed. This suggests that the skin of atopic dermatitis patients fails to adequately upregulate LL-37 upon

cutaneous injury. Whether other AMPs behave in a similar way remains to be shown.

Induced production of hBD-2 in atopic dermatitis has also been reported by two studies investigating the presence of hBD-2 in the stratum corneum. Asano *et al.* [20] detected increased amounts of hBD-2 in the stratum corneum of atopic dermatitis patients. Comparison of *S. aureus* colony numbers and beta-defensin-2 levels demonstrated a positive correlation, indicating that decreased hBD-2 level are not associated with vulnerability to *S. aureus* colonization. Clausen *et al.* [21] also detected increased concentrations of hBD-2 in the stratum corneum of atopic dermatitis patients, with highest amounts found in lesional skin.

IMMUNOMODULATORY FUNCTIONS

Human β -defensins (hBDs-1–4) have been shown to attract and activate a broad range of leukocytes by acting on different receptors. It is known that hBD-2 is chemotactic for immature dendritic cells, memory T-cells and TH17 cells by binding to CCR6 [22]. More recently, hBD-2 and hBD-3 have been found to bind to CCR2 which is expressed on myeloid cells, such as monocytes, macrophages and neutrophils [23]. Therefore, hBDs can influence the innate and adaptive immune response in the skin by acting as chemoattractants. Interestingly, hBD-2 not only acts as a chemokine, but also has been shown to influence cytokine production by T-cells.

Recent work by Kanda *et al.* [24] showed that hBD-2 may enhance skin inflammation and favour a TH1 cytokine milieu by stimulating the production of IFN γ by activated T-cells. However, they found that hBD-2 also might downregulate the T-cell responses by suppressing IL-17 and promoting IL-10 production. Further evidence that hBD-2 might influence T-cell cytokine responses in the skin came from the same group: the authors provided evidence that hBD-2 and, especially, hBD-3 might also support Th2 responses in the skin under certain conditions. Their data indicate that the stimulation of activated human T-cells with hBD-2 may enhance IL-22 and oncostatin M production under certain experimental conditions which may have impact on the development and course of atopic dermatitis. In turn, these cytokines induce the production of hBD-2 by keratinocytes, which may result in a positive feedback loop. Furthermore, they found that hBD-2 and, even more potently, hBD-3 induced the production of the Th2 cytokines IL-4, IL-13 and IL-31, whereas the production of IL-25 by T-cells and of TSLP (thymic stromal lymphopoietin) by keratinocytes was downregulated [25].

Mast cells are known to play a key role in allergic skin reactions and are described to be attracted and activated by hBDs [26,27]. A current study [28] identified MrgX2, a novel G-protein-coupled receptor (GPCR), as potential receptor for hBD-2 and hBD-3 which mediates human mast cell degranulation induced by these AMPs. Upon activation with hBD-2 and hBD-3, mast cells released several mediators such as the pruritogens histamine and prostaglandin D2 [29]. Interestingly, histamine and prostaglandin D2 have been described to induce the production of hBDs by keratinocytes [30,31]. Therefore, whereas rapid mast cell degranulation provides an important mechanism for host defence during bacterial infection, activation of mast cells by hBDs in allergic skin diseases might implement a positive feedback loop which can aggravate the allergic skin reaction.

In addition to hBDs, cathelicidin LL-37 has been described to chemoattract and degranulate mast cells as well [32]. MrgX2 was identified as a receptor for LL-37 on mast cells [33]. As MrgX2 has been found to serve as a receptor for a variety of cationic peptides, activation of mast cells via MrgX2 by other cationic AMPs might be possible [34]. Furthermore, the study [33] demonstrated that unlike most GPCRs, MrgX2 is resistant to agonist-induced receptor phosphorylation. However, mast cell protease has been shown to degrade and inactivate LL-37, which might provide a negative feedback loop to control further mast cell activation by LL-37 [35].

Of note, hBDs and LL-37 have been shown to induce the production of IL-31 in mast cells, which is supposed to play a pivotal role in the induction of pruritus in skin disorders [36]. Further evidence that LL-37 might support an inflammatory cytokine milieu in T-cell-driven skin diseases was provided by a recent study [37], which shows that activated T-cells upregulated the Th2-related cytokines IL-31, IFN γ , IL-22 and oncostatin M in the presence of LL-37.

A further important feature of LL-37 is the modulation of signalling by various Toll-like receptors (TLRs). For example, LL-37 binds to single-stranded (ss) DNA to enhance signalling by TLR9 and to ssRNA enhancing signalling by TLR7, TLR3 and TLR8 [38,39]. However, LL-37 also seems to exert anti-inflammatory features in the skin as it has been shown that binding of LL-37 to DNA inhibited the activation of the DNA-sensing inflammasome AIM2 in keratinocytes [40]. In a recent publication, Chen *et al.* [41] examined the effect of LL-37 on proinflammatory responses induced by double-stranded RNA (dsRNA) on primary human keratinocytes. They found that LL-37 inhibited

dsRNA-induced expression of CXCL8, CXCL10, CCL5 and TSLP by keratinocytes. Furthermore, LL-37 synergistically enhanced the expression of CXCL8 induced by TNF α , IFN γ or the TH17 cytokines IL-17 and IL-22, but inhibited the expression of IP-10 induced by IFN γ . These data suggest a possible involvement of LL-37 in the suppression of Th2 skin inflammation induced by viral or self dsRNA released from damaged cells.

A strong overexpression of the AMP psoriasin in the skin has been reported for TH1/TH17-mediated inflammatory skin diseases such as psoriasis. It is known that psoriasin acts as a chemoattractant for CD4⁺ T-cells and neutrophils [42]. Furthermore, psoriasin activated the neutrophils to produce a range of cytokines and chemokines [43]. A striking finding is the absence of innate immune cells such as neutrophils in lesional skin from atopic dermatitis patients, even in the setting of strong *S. aureus* colonization. As mentioned above, psoriasin was found to be enhanced in the lesional skin of patients with atopic dermatitis, which means that the absence of neutrophils cannot be explained by a defective psoriasin production. Several studies have pointed to a chemotactic defect in the neutrophils of atopic dermatitis patients [44]. A previous publication identified receptor of advanced glycosylated end-products (RAGE) as a receptor for psoriasin-mediated chemotaxis [45]. Therefore, a decreased migration of neutrophils to psoriasin in correlation with alterations in RAGE expression might be possible and needs to be investigated.

CONCLUSION

Taken together, the role of AMPs in atopic dermatitis is still emerging and remains controversial. There is clear evidence that AMPs are induced in atopic dermatitis. Some studies suggest that the induction, release or mobilization of some AMPs in atopic dermatitis may not reach sufficient levels to provide adequate control of cutaneous microbial colonization. Especially, the increasing number of immunoregulatory functions described for several AMPs and their impact on the clinical course of the skin disease is still unclear. Clearly, further studies are needed to clarify the role of AMPs in atopic dermatitis.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 582–583).

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