Review Article

Role of Antimicrobial Peptides in Atopic Dermatitis

Supaporn Suwanchote[1], Palapun Waitayangkoon[1], Bussabong Chancheewa[2], Thananya Inthanachai[1], Nattarika Niwetbowornchai[1], Steven W Edwards[4], Sita Virakul[1], Arsa Thammahong[1], Chanisa Kiatsurayanon[3], Pawinee Rerknimitr[2] and Direkrit Chiewchengchol[1]

[1]Center of Excellence in Immunology and Immune-mediated diseases, Department of Microbiology, [2]Division of Dermatology, Skin and Allergy Research Unit, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3]Institute of Dermatology, Department of Medical Services, Ministry of Public Health, Bangkok, Thailand and [4]Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, United Kingdom

Corresponding author:

Direkrit Chiewchengchol, MD, PhD, Center of Excellence in Immunology and Immune-mediated diseases, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Rama 4 Road, Pathumwan, Bangkok, Thailand, 10330

E-mail: *cdirekrit@live.com*

Office phone: +662-256-4470 ext 626 Fax: +662-252-5952

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Abstract

Host defense peptides (HDPs) or antimicrobial peptides (AMPs) are short cationic amphipathic peptides of divergent sequences, which are part of the innate immune system and produced by various types of cells and tissues. The predominant role of HDPs is to respond to and protect humans against infection and inflammation. Common human HDPs include defensins, cathelicidin, psoriasin, dermcidin and ribonucleases but these peptides may be dysregulated in the skin of patients with atopic dermatitis (AD). Current evidence suggests that the antimicrobial properties and immunomodulatory effects of HDPs are involved in AD pathogenesis, making HDPs research a promising area for predicting disease severity and developing novel treatments for AD. In this review, we describe a potential role for human HDPs in the development, exacerbation and progression of AD, and propose their potential therapeutic benefits.

Keywords : host defense peptides, antimicrobial peptides, atopic dermatitis

Abbreviations : Host defense peptides (HDPs), antimicrobial peptides (AMPs), atopic dermatitis (AD), *Filaggrin* (*FLG*), T helper (Th), Interleukin (IL), thymic stromal lymphopoietin (TSLP), IFN (Interferon), regulatory T cell (Treg), prostaglandin D2 (PGD2), human neutrophil peptide (HNP), human α-defensin (HD), immunoglobulin E (IgE), human β-defensins (hBDs), Staphylococcus aureus (*S. Aureus)* , methicillin-resistant Staphylococcus aureus (MRSA), messenger ribonucleic acid (mRNA), herpes simplex virus (HSV), Cathelicidins (LL-37), psoriasin (S100A7), Escherichia coli (*E. coli*.), tumor necrosis factor (TNF), Dermcidin (DCD), Ribonuclease7 (RNase7)

1. Introduction

Host defense peptides or antimicrobial peptides are small molecules expressed by many human cells, including the epithelial cells lining many tissues. They are one of the most important factors in the innate immune mechanism functioning as a chemical barrier with antimicrobial

activities against a broad range of microbes.(1, 2) Human epithelial cells (e.g. epidermal cells or keratinocytes, intestinal mucosal cells and lung epithelial cells) constitutively release HDPs to primarily protect the organs from microbial invasion on their surfaces. However, the production of HDPs is also regulated by various types of microorganisms including microbiota and inflammatory molecules such as cytokines.(3) Many families of HDPs have been recently described but the most well-known families are the defensins, cathelicidin, psoriasin, dermcidin and ribonucleases (Table 1). These are expressed by a variety of cells, including immune cells, epithelial cells and keratinocytes. Figure 1 schematizes HDPs in normal skin barrier.

Keratinocytes are major sources of HDPs and produce the peptides from deeper epidermal layers, store them in lamellar bodies in the upper layers, and eventually release them onto the uppermost layer of epidermis or stratum corneum.(4) HDPs are also produced by other cells inside the skin, such as sebocytes, epithelial cells of sweat glands, neutrophils and mast cells.(5, 6) HDPs possess numerous broad-spectrum killing activities against bacteria, fungi, and viruses and their highly-positive charges (Table 2) bind to negatively-charged membranes of the target organism forming multiple pores and causing microbial cell lysis(7). Although HDPs can preserve the balance of commensal/pathogenic organisms and promote normal immune regulation(8), the immunomodulatory effects of HDPs influences cell proliferation, migration and differentiation(1). For example, it has been shown that HDPs induce cytokine production to promote barrier function and facilitate wound healing by inducing angiogenesis(9, 10).

In the skin, HDPs play a major role in cutaneous innate immunity by binding directly to immune cell receptors for example modulating toll-like receptor signaling and triggering chemotaxis, cell maturation, and cytokine production.(11) Recent studies have shown that dysregulation of HDP expression is involved in the pathogenesis of certain inflammatory skin diseases including atopic dermatitis.(12, 13) Therefore, understanding the mechanisms of how HDPs regulate and influence AD pathogenesis is essential to evaluate possible contributions of HDPs as predictive markers of disease or for therapeutic intervention for AD patients.

2. Atopic Dermatitis and immune pathogenesis

Atopic dermatitis is one of the most common chronic inflammatory skin diseases. Although the etiology of AD has yet to be fully-elucidated, several genetic and environmental factors have been shown to be associated in the pathogenesis of the disease. Foods, house dust mites, pets, pollens, climate factors, air pollutants and tobacco exposure are among the common environmental factors associated with AD.(14, 15) In terms of endogenous factors, *Filaggrin* (*FLG*) gene mutation is one of the most common genes that plays a significant role in epidermal barrier defects and skin sensitization in AD.(16) Another important factor is immunomodulatory dysregulation, which contributes to skin barrier impairment and explains an increased susceptibility to various types of infections in AD patients. For example, bacterial- (impetigo, folliculitis, abscess), viral- (eczema herpeticum, molluscum contagiosum), and fungal- (candidiasis, dermatophytosis) infections are commonly found in AD patients.(17, 18)

The most important immunological factor implicated in the pathogenesis of AD development is dysregulation of T helper 2 (Th2) cells.(19) Interleukin-5 (IL-5), IL-13, and IL-31 secreted by Th2 cells are increased in the biopsied skin tissues of AD patients.(20) When traumatized (e.g. scratching), the keratinocytes release thymic stromal lymphopoietin (TSLP) and IL-33, inducing the development of Th2-associated inflammation in AD by enhancing IL-31 expression in Th2 cells and IFN-γ expression in $CD4^+$ T cells, which increases the expression of IL-31 receptors on the surface of keratinocytes.(21) Moreover, keratinocytes releasing thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 can activate innate effector cells, such as dendritic cells, mast cells, basophils and type-2 innate lymphoid cells (ILC2s) to enhance skin inflammation in AD.(22) These innate effector cells, together with Th2 cytokines, also inhibit HDPs expression (e.g. cathelicidin, hBDs, S100A7, RNase7) from keratinocytes.(23) Additional stimuli that increase IL-31 receptor expression in monocytes and

104 macrophages are IL-4, IL-13, and staphylococcus toxins. IFN-γ, then in turn, enhances IL-33
105 production from keratinocytes.(24, 25)

106 Other cytokines involved in the immune dysregulation of AD are IL-9 and IL-10 and
107 their receptors. It has been shown that these cytokines are significantly increased in the lesional
108 skin of AD compared to normal skin (24). IL-9 is produced by Th9, Th17, and Th22 cells
109 whereas IL-10 is produced by regulatory T cells (Treg). IL-9 promotes tissue accumulation,
110 survival and activation of mast cells, eosinophils and innate lymphoid cells, which are key
111 components in AD pathogenesis. However, the role of IL-10 in AD is equivocal as some studies
112 have shown that IL-10 was involved in HDP production, especially for human β-defensins-2 and
113 cathelicidins in AD patients(26), whilst other evidence demonstrated an inverse correlation
114 between IL-10 levels and disease severity.(27, 28)

115 The precise role of HDPs in the pathogenesis of AD has yet to be elucidated. Ong *et al*.
116 demonstrated a decrease in human β-defensins-2 and cathelicidins in AD compared to psoriatic
117 skin.(29, 30) These relative deficiencies may result in increased susceptibility to *S. aureus*
118 infection (31). In contrast, other HDPs (e.g. RNase7 and psoriasin) were increased in the lesional
119 skin of untreated AD(32), suggesting that increased HDPs were also associated with, and might
120 be responsible for, AD exacerbation. Moreover, a previous study showed that hBD could attract
121 and activate mast cells and dendritic cells allowing the release of histamine, prostaglandin D2
122 (PGD2) and IL-31 causing skin inflammation and itchiness in AD patients.(33) Figure 2
123 summarizes the immune pathogenesis of AD.

124
125 **3. Atopic dermatitis and dysregulation of host defense peptides**

126 **3.1 Defensins**

127 Human defensins are categorized into two major subfamilies, α- and β-defensins, and the
128 number and position of cysteine disulfide bonds(9) plus the affinity of the intramolecular
129 disulfide bonds in the peptides differentiates α- defensins from β-defensins (8).

Human α-defensins 1-4 largely reside in neutrophilic granules and therefore they are also known as human neutrophil peptides (HNP-1-4), whereas α-defensins 5-6 (HD-5 and-6) are mostly present in the intestinal Paneth cells.(34) In addition to antimicrobial activities, α-defensins induce chemotactic activity and are involved in pro-inflammatory cytokine induction (35). Interestingly, a previous study demonstrated that during exacerbation of AD, plasma levels of α-defensins 1-3 were increased and had a positive correlation with AD severity, itch intensity, and serum IL-8 and IgE levels (Table 3) (36).

The expression of human β-defensins (hBDs) 1–4 is predominant in the skin epithelia. While human β-defensin-1 (hBD-1) is only inducible by bacterial components, hBD 2-4 can be released following stimulation of wound healing and injury, as well as microorganisms.(37) HBD-2 showed preferential antimicrobial activity towards gram-negative bacteria but the activity was substantially decreased in a high salt environment, such as physiologic sweating (38). HBD-3 is uniquely bactericidal against many multi-drug resistant pathogens including MRSA even in the presence of physiological salt concentrations (39). Unlike the other hBDs, the expression of hBD-4 is limited only to the mRNA level.(40)

Previous studies have shown lower concentrations of hBD-2 and hBD-3 in the skin biopsies of AD when compared with psoriasis.(29, 30) It is proposed that these hBD deficiencies were caused by overproduction of Th2-derived cytokines that inhibited hBD production(41, 42), and lack of hBD inducers such as IFN-γ, IL-17 and IL-22.(30) Decreased hBD was also thought to be one of the contributing factors for an increase in susceptibility to infections in AD patients (Table 3)(43), particularly hBD-2 and hBD-3 which exhibited antimicrobial activities against *S. aureus*, herpes simplex virus (HSV) and vaccinia virus, the most frequent organisms that colonize AD skin.(44) However, when compared to healthy control skin, hBD-2 and hBD-3 were increased in the lesional AD skin.(45)

Although it is controversial whether high or low hBD expression is related to AD pathogenesis, a previous study demonstrated that hBD-1 and hBD-3 enhanced the tight junctions

and reconditioned the permeability of disrupted epidermis in AD skin(46-48) and subsequently improved skin barrier function. This finding established the possibility of hBD-3 as a promising future treatment for AD.

3.2 Cathelicidins

Cathelicidins are found in a variety of species, but in humans the sole cathelicidin, also known as LL-37, is expressed by neutrophils, mast cells, and monocytes, and predominantly stored intracellularly in an inactive form in the superficial epidermis with a small amount present in the extracellular space of the stratum corneum.(49) The peptides are activated and released when the cells have been stimulated by traumatization, infection or inflammation.(50) Cathelicidins bind directly to the cell membrane of gram-negative and gram-positive bacteria, fungi, viruses and parasites(9), causing cell death (51).

The effects of cathelicidins include both pro-inflammatory and anti-inflammatory activities as well as immunomodulatory functions.(52) It was shown that cathelicidins were able to downregulate IL-10 in keratinocytes and induce mast cell degranulation (53), which might be associated with an itchy sensation in AD. Cathelicidins were also involved in promotion of cutaneous immunity by upregulating the expression and membrane distribution of tight junction components thereby improving the skin barrier.(54, 55)

In AD patients, it has been demonstrated that cathelicidins are significantly decreased in the lesional AD skin and the level of cathelicidin is associated with exacerbations of AD infection and correlated with the resistance to cutaneous *S. aureus* infections (Table 3).(29) One of the reasons behind this finding was suggested in the experiment of Zasloff and Otte *et al*., which revealed that cathelicidins were able to suppress epithelial cell apoptosis during skin infection.(56, 57)

3.3 Psoriasin

Psoriasin is also known as S100A7 and is a low molecular weight calcium-binding protein of the S100 protein family.(58) Although it was initially identified as an antimicrobial

peptide overproduced by keratinocytes in psoriatic lesions(59), psoriasin was later recognized as a keratinocyte-derived host defense peptide against bacteria such as *E. coli*.(60) S100A7 acts as a chemotactic factor promoting cell proliferation and differentiation, angiogenesis, and strengthens the skin barrier.(61) The production of psoriasin is induced by numerous endogenous and exogenous factors including tumor necrosis factor-α (TNF-α), IL-1β, vitamin D3, as well as microbial products (62).

Although dermal sebocytes produce psoriasin and secrete this peptide together with sebum lipids in order to prevent infection (60), the exact mechanism of antimicrobial activity of psoriasin is not well clarified. In addition, no studies have demonstrated the antimicrobial mechanism against *S. aureus* or dermatophytes, the most common causes of infection in AD.

It is well recognized that the production of psoriasin can be augmented following disruption of the skin barrier(32), and a higher level of psoriasin was associated with increased susceptibility to infections in patients with AD (Table 3).(63) However, the correlation between psoriasin levels in AD skin and disease activity is currently questionable. A previous study showed an increase in psoriasin level in the lesional AD skin compared to the healthy skin(32, 63), whereas another study showed only a minimum level of this peptide in stratum granulosum of the epidermis.(64, 65)

3.4 Dermcidin

Dermcidin (DCD) is the only HDP identified in humans that is exclusively secreted by sweat glands before being transported to the epidermal surface.(66) Once proteolyzed to its active form, dermcidin-1L (DCD-1L), it inhibits bacterial RNA and protein synthesis (67) and forms ion channels within the bacterial membrane resulting in cell death.(68) The antimicrobial properties of dermcidin are effective against various pathogenic microorganisms including *S. aureus* (69).

What makes dermcidin unique is that the antimicrobial activity of DCD-1L is well-maintained over a broad pH range and in high salt environments including human sweat. Unlike

other HDPs, the secretion of dermcidin cannot be induced by skin injury or inflammation (70). In terms of immunomodulation, DCD-1L stimulates the production of IL-4, IL-13, IL-31, and TNF- α from keratinocytes.(71)

A decrease in dermcidin levels was detected in the sweat of patients with AD(70), suggesting that the high susceptibility to certain skin infections and altered colonization in these patients may be associated with diminished antimicrobial peptides in the sweat (Table 3). However, one immunohistochemistry study showed a stronger intensity of dermcidin antigen detected in the sweat glands of AD patients in comparison to those with lichen planus and psoriasis (67). These inconsistent results indicated that the dysfunction of sweat glands and delivery system might play a role in AD (72). The studies on filaggrin mutant mice demonstrate that decreased filaggrin levels lead to acrosyringium obstruction and eventually gives rise to sweating impairment(73) which could indirectly affect dermcidin activity.

3.5 Ribonuclease7

Ribonuclease7 (RNase7) is primarily produced by keratinocytes and is constitutively expressed in the epidermis of healthy human skin with a high concentration in the stratum corneum.(74) The upregulation of RNase7 can be induced by pro-inflammatory cytokines, skin injury and certain infections.(32, 74, 75) The antimicrobial properties of RNase7 against bacteria and fungus, including *S. aureus*, are well established.(75)

Besides its antimicrobial functions, RNase7 also has immunomodulatory effects on Th2 cells in the skin.(76, 77) An immunohistochemistry study on skin biopsies of AD revealed the upregulation of RNase7 expression when compared with psoriatic or normal skin.(32) Kopfnagel et al. demonstrated that, when stimulated with RNase7, CD4+T cells from AD patients produced less IL-4, IL-5 and IL-13 compared to controls, accentuating the importance of RNase7 in AD pathogenesis (77) as these Th2 cytokines play an important role in the development of AD (Table 3).

4. HDPs in skin barrier repair: an option for AD treatment

As HDPs show antimicrobial and immunomodulatory activities, they could potentially be used as an adjunct treatment in AD patients. Among published data on all HDPs, hBD-3 seems to be the most promising candidate for AD barrier repair. Evidence shows that hBD-3 treatment improves the disrupted tight junctions and promotes skin barrier function in AD skin in vitro.(46,47) In view of this observation, hBD-3 treatment could be additionally incorporated into management of AD patients and clinical trials of the effectiveness of hBD-3-containing therapy should be conducted to evaluate its usefulness. However, other HDPs seem to be good candidates for skin barrier repair but it remains unclear whether treatment with these HDPs enhances skin barrier in AD patients and therefore, further investigations are required.

5. Future directions

Many recent studies have demonstrated that the pattern of skin microbiota in AD patients is significantly different from healthy individuals.(78, 79) As it has been demonstrated that the relationship between HDPs and skin microbiota is an important feature of developing cutaneous innate immunity(80), studies focusing on the skin microbiome and HDPs in AD patients should be further investigated in order to better understand the inter-relationship between dysregulation of our first line defense and skin microbiota in AD. Additionally, the identification and characterization of gene and protein expression is another approach to determine the precise role of HDPs in AD. Identification and characterization of genes encoding HDPs could be one of the techniques that help define how these peptides regulate and participate in AD pathogenesis. Such molecular genetic analysis should provide a clearer picture of AD and possibly yield information for developing biomarkers and targeted therapies.

6. Summary

HDPs are important components in cutaneous innate immunity exhibiting antimicrobial and immunomodulatory activities, which play an important role in AD pathogenesis.(40) Recent studies have shown that dysregulation of HDPs could be one of the contributing factors in AD development, increased susceptibility to skin infection and disease exacerbation. We propose that some HDPs could potentially be used as a predictive marker in AD while other HDPs could be used as an adjunct agent in treatment of AD patients. However, other while some HDPs appear to be good candidates for skin barrier repair, others may exacerbate symptoms. Therefore, further investigations and systematic studies on the beneficial effects of different HDPs in AD are required in order to evaluate this promising strategy for AD treatment.

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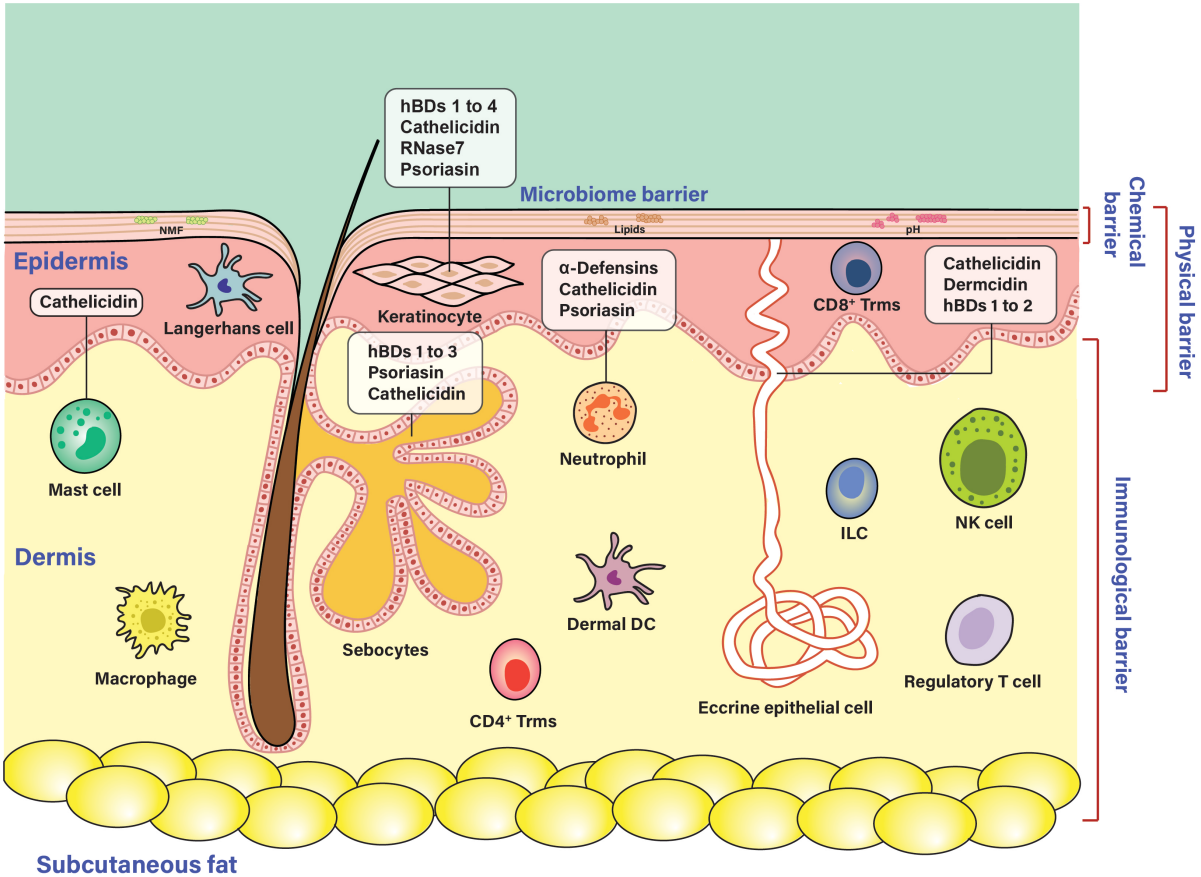

Figure 1. Host defense peptides in the normal cutaneous barrier. The cutaneous barrier against environmental factors and microbial agents is classified into four main levels according to its function: microbiome, chemical, physical, and immunological barriers. The microbiome is the outermost barrier and comprises a complex microbial community. The chemical barrier is primarily composed of host defense peptides (hBDs, cathelicidin, RNase7 and psoriasin), natural moisturizing factors, lipids and factors contributing to skin barrier pH. The crucial parts of the physical barrier are the stratum corneum and tight junction proteins of the epidermis. Diverse resident cell populations in epidermis and dermis form an immunological barrier which is interconnected with other levels of the skin barrier because of the broad distribution of skin-residing immune cells within cutaneous layers. NMF, natural moisturizing factor; hBD, human β-defensin; RNase7, ribonuclease7; DC, dendritic cell; $CD4^+$ Trm, $CD4^+$ tissue-resident memory T cell, $CD8^+$ Trm, $CD8^+$ tissue-resident memory T cell; ILC, innate lymphoid cell; NK cell, natural killer cell

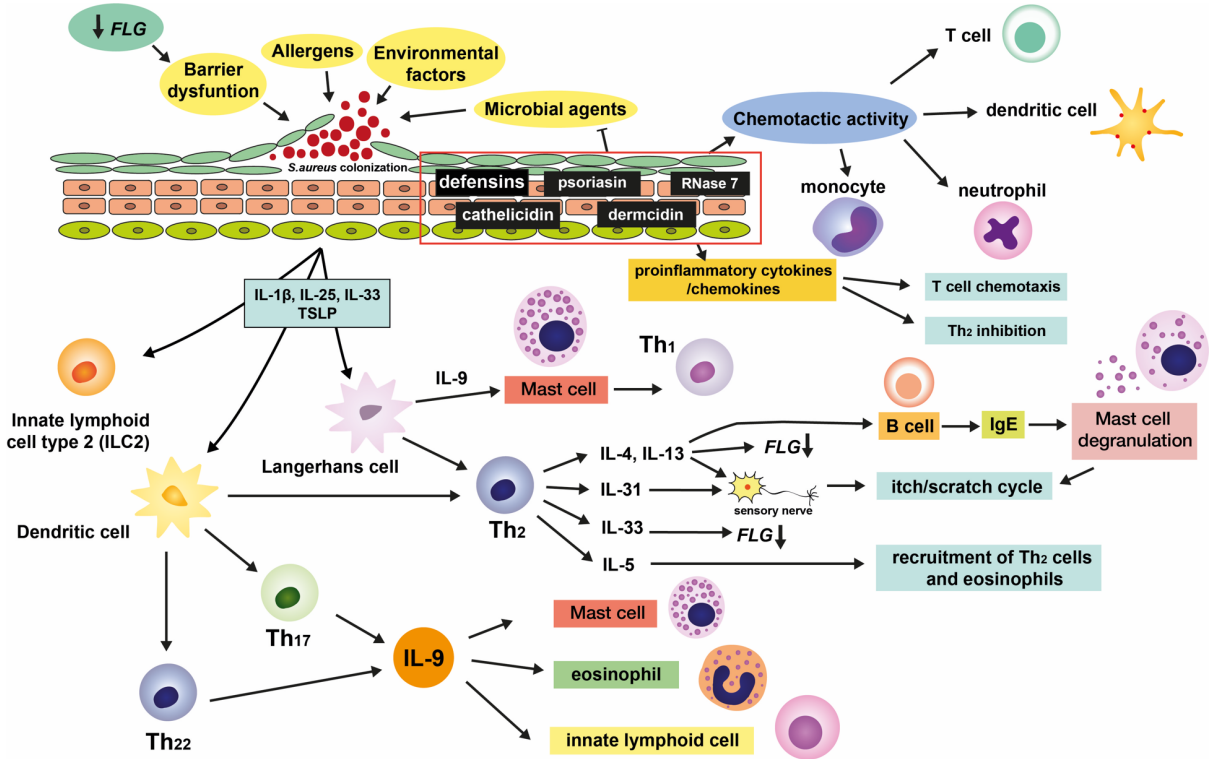

Figure 2. Immune pathogenesis of atopic dermatitis (AD) and role of host defense peptides. Barrier dysfunction, exposure of allergens and other environmental factors as well as *Staphylococcus aureus* colonization are predisposing factors of AD. Imbalance production of host defense peptides promotes skin barrier dysfunction and microbial growth leading to increased susceptibility to infections. Proinflammatory cytokine/chemokine production and chemotactic activity are also impaired. Immunoregulatory cytokines (e.g., IL-1β, IL-25, IL-33 and TSLP) produced by keratinocytes after disruption of the barrier stimulate Langerhans cells and dendritic cells causing Th2, Th17 and Th22 activation. Langerhans cells also stimulate Th1 immune response via mast cell activation. IL-4, IL-5, IL-13, IL-31 and IL-33 released by Th2 cells disturb barrier function by downregulating *FLG* gene expression. Mast cell degranulation and sensory nerve amplification induce itch-scratch cycle and aggravate barrier dysfunction. Th17 and Th22 cells increase IL-9 production that stimulates mast cells, eosinophils and innate lymphoid cells. FLG; *filaggrin* gene, Th1; T helper 1, Th2; T helper 2, TSLP; thymic stromal lymphopoietin

Table 1. Host defense peptides with their antimicrobial and immunomodulatory properties

HDPs	Cells of origin	Antimicrobial mechanisms	Antimicrobial properties	Immunomodulatory properties
α-defensins	Neutrophils Intestinal Paneth cells	Bacterial membrane disruption by electrostatic interactions	-**Gram-positive bacteria**: *S. aureus, B. cereus* -**Gram-negative bacteria**: *E. aerogenes, E. coli* - **Virus**: Herpes simplex virus, Adenovirus, Papilloma virus	- Chemotactic activity - Pro-inflammatory cytokine induction - Cell migratory modification and maturation
β defensin-2	Neutrophils	similar to α-defensin	- **Gram-positive bacteria**: *S. epidermidis, C. acnes* - **Gram-negative bacteria**: *E. coli, E. faecalis, P. aeruginosa* - **Fungi**: *C. albicans* - **Virus**: Herpes simplex virus, Vaccinia virus	- Chemotactic activity on T cells and dendritic cells - Maintenance of skin barrier function and promotion of wound healing - Cell migratory modification and maturation - Cytokine/chemokine production
β defensin-3	Neutrophils	similar to α-defensin	- **Gram-positive bacteria**: MRSA, *S. pyogenes* - **Gram-negative bacteria**: vancomycin-resistant E. faecium - **Virus**: Herpes simplex virus, Vaccinia virus	- Chemotactic activity on dendritic cells, T cells and monocytes - Maintenance of skin barrier function and promotion of wound healing - Keratinocyte migration and proliferation - Cytokine/chemokine production

				- Mast cell degranulation
Cathelicidin	Neutrophils Mast cells Macrophages Monocytes	similar to α-defensin	- **Gram-positive bacteria**: *S. aureus, C. acnes* - **Gram-negative bacteria**: *E. coli, P. aeruginosa, E. faecalis, K. pneumoniae* - **Fungi**: *C. albicans* - **Viruses**: HIV-1	- Chemotactic activity - Promotion of wound healing and angiogenesis - Anti-apoptosis - Keratinocyte migration and proliferation - Cytokine/chemokine production - Mast cell activation and degranulation
Psoriasin	Keratinocytes Neutrophils	Zinc sequestration	- **Gram-positive bacteria**: *C. acnes* - **Gram-negative bacteria**: *E. Coli*	- Chemotactic activity - Cytokine/chemokine production - Induction of cell proliferation and differentiation - Promotion of angiogenesis - Increased skin barrier function
Dermcidin	Epithelial cells in sweat glands	Inhibition of bacterial RNA and protein synthesis	- **Gram-positive bacteria**: *S. aureus* - **Gram-negative bacteria**: *E. coli, E. faecalis* - **Fungi**: *C. albicans*	- Promotion of skin defense - Regulation of local and systemic inflammation - Cytokine/chemokine production
RNase 7	Keratinocytes	Not fully understood	- **Gram-positive bacteria**: *C. acnes, S. aureus,*	- Promotion of skin defense

			MRSA - **Gram-negative bacteria**: *E. coli, P. aeruginosa* - **Fungi**: *C. albicans*	- Ribonucleolytic activity - Th2 cytokines downregulation

Table 2. Amino acid sequences of host defense peptides showing net positive charges

HDPs	Amino acid sequence	Net Charge
HNP-1	ACYCRIPACIAGERRYGTCIYQGRLWAFCC	+3
HNP-2	CYCRIPACIAGERRYGTCIYQGRLWAFCC	+3
HNP-3	DCYCRIPACIAGERRYGTCIYQGRLWAFCC	+2
HNP-4	VCSCRLVFCRRTELRVGNCLIGGVSFTYCCTRV	+4
HD-5	ATCYCRTGRCATRESLSGVCEISGRLYRLCCR	+4
HD-6	AFTCHCRRSCYSTEYSYGTCTVMGINHRFCCL	+3
HBD-1	DHYNCVSSGGQCLYSACPIFTKIQGTCYRGKAKCCK	+4
HBD-2	GIGDPVTCLKSGAICHPVFCPRRYKQIGTCGLPGTKCCKKP	+7
HBD-3	GIINTLQKYYCRVRGGRCAVLSCLPKEEQIGKCSTRGRKCCRRKK	+11
HBD-4	EFELDRICGYGTARCRKKCRSQEYRIGRCPNTYACCLRKWDESLINRTKP	+6
Cathelicidin (LL37)	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	+6
Psoriasin (S100A7)	MSNTQAERSIIGMIDMFHKYTRRDDKIDKPSLLTMMKENFPNFLSACDKKGTNYLADVFEKKDKNEDKKIDFS EFLSLLGDIATDYHKQSHGAAPCSGGSQ	-1
Dermcidin	MRFMTLLFLTALAGALVCAYDPEAASAPGSNPCHEASAAQKENAGEDPGLARQAPKPRKQRSSLLEKGLDGA KKAVGGLGKLGKDAVEDLESVGKGAVHDVKDVLDSVL	-2
Ribonuclease 7	MAPARAGFCPLLLLLLLGLWVAEIPVSAKPKGMTSSQWFKIQHMQPSPQACNSAMKNINKHTKRCKDLNTFL HEPFSSVAATCQTPKIACKNGDKNCHQSHGAVSLTMCKLTSGKHPNCRYKEKRQNKSYVVACKPPQKKDSQQ FHLVPVHLDRVL	+16

Table 3. The association of host defense peptides and immune pathogenesis of atopic dermatitis

HDPs	Levels in epidermis	Causes	Outcomes
α-defensins	↑	- Triggered by LTB_4 from neutrophils	- Positive correlation with clinical severity, itch intensity and serum IgE levels. - T-cell chemoattractant
β-defensin-2	↓	- Overproduction of Th2-derived cytokines	- Increased susceptibility to infections
β-defensin-3	↓	- Overproduction of Th2-derived cytokines	- Increased susceptibility to infections - Impaired tight junction and skin barrier function
Cathelicidin	↓	- Association with downregulation of tight junction components causing skin barrier impairment	- Cutaneous *S. aureus* infection and epithelial cell apoptosis
Psoriasin	↑	- Disturbed skin barrier (autoprotective mechanism) - Stimulated by Th17 cytokines (e.g. IL-17, IL-22)	- Not vulnerable to *E. coli* skin infection
Dermcidin	↓	- Sweat duct obstruction and dysfunction due to *filaggrin* gene mutation	- Alteration of microbiota and increased susceptibility to skin infections
RNase 7	↑	- Induced by disturbed skin barrier (autoprotective mechanism) - Upregulated expression by a Th2 cytokines	- Suppression of Th2 cytokines production from skin-infiltrating T cells