Novel Insight Into the Role of Antimicrobial (Host Defense) Peptides/Proteins in Human Skin Diseases

FRANÇOIS NIYONSABA*1 2)

*1)Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan, *2)Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan

In addition to functioning as a physical barrier, the skin has evolved several innate defense mechanisms for the rapid recognition of and protection against harmful microorganisms. As a part of this process, the skin releases a vast and powerful arsenal of antimicrobial peptides/proteins (AMPs), also called host defense peptides/proteins (HDPs), which are key players in the cutaneous immune system. Although originally named antimicrobial peptides, recent evidence has demonstrated that AMPs/HDPs play additional roles in orchestrating the adaptive immune response, such as the regulation of inflammation, induction of cell proliferation and differentiation, regulation of cytokine/chemokine production, facilitation of cell migration, promotion of wound healing and regulation of tight junction barriers. Additionally, numerous skin diseases show altered expression of AMPs/HDPs in the lesional skin, suggesting the crucial roles of these molecules in the pathophysiology of skin diseases. The purpose of this review is to describe the current knowledge regarding some of the most common and well-known AMPs/HDPs derived from the skin, to discuss the regulation of their expression and their antimicrobial and immunomodulatory functions, and to outline their roles in various skin diseases. We believe that understanding the basic knowledge of skin-derived AMPs/HDPs would provide new insight into the pathophysiology of skin disorders and offer novel therapeutic opportunities for skin infectious diseases.

Key words: antimicrobial (host defense) peptide/protein, keratinocyte, skin disease, skin immunity, therapeutic agent

Introduction

The human skin is continuously exposed to external threats, although the infection rate remains low. This low infection rate is in part attributed to the fact that the skin protects the body from harmful factors through the combination of physical and chemical barrier properties, including its structural integrity, slight acidic pH, and secretion of various cytokines and chemokines. Furthermore, as an antimicrobial barrier, resident and infiltrating cells in the skin such as keratinocytes, phagocytes and mast cells are able to generate a number of small powerful molecules called antimicrobial peptides (AMPs), which are generally short (10–50 amino acids in length), typically having a net positive charge as a result of excess lysine and arginine residues. AMPs are able to fold into amphiphilic structures and provide a rapid, direct but non-specific first-line chemical shield in innate immunity by killing a broad spectrum of bacteria, fungi, and viruses. In
addition to their killing properties, there is irrefutable evidence that AMPs also play major roles in immunomodulation. For example, AMPs control host patho-physiological functions such as cell migration, proliferation, differentiation, apoptosis, production of cytokines and chemokines, angiogenesis and wound healing\(^1\)\(^2\). Accordingly, the term “antimicrobial” is actually a bit of a misnomer and is misleading because it describes more about the history of discovery rather than the major functions of these peptides. Therefore, alternative names such as host defense peptide (HDP) or alarmin have been recently suggested\(^3\)\(^4\). In this review, the term AMP/HDP will be used throughout the entire text to appreciate both the history of the discovery and the functions of these peptides/proteins.

To date, more than 2,300 AMPs/HDPs from different origins including bacteria, plants, reptiles and mammals have been reported in the AMP database (http://aps.unmc.edu/AP/main.php). Human AMPs/HDPs have been detected in several cell types and tissues, including the skin, mucosa of airways, gastro-intestine and genito-urinary ducts\(^1\)\(^2\). In the human skin, several hundred AMPs/HDPs have been discovered and are expressed constitutively or inducibly in response to dangerous situations such as skin injury, infection and chronic inflammation. Recent reports have shown the close association between altered expression of AMPs/HDPs and various human diseases. For example, AMPs/HDPs have been demonstrated to play intriguing roles in many skin disorders such as psoriasis, atopic dermatitis (AD), rosacea, wound healing, burns and other conditions\(^1\)\(^2\).

In this review, we discuss some potentially important AMPs/HDPs and their contribution to human skin infectious diseases. These AMPs/HDPs include, but not limited to human β-defensins (hBDs), cathelicidin LL-37 and S100 proteins. We also summarize a number of AMPs/HDPs or their derivatives that might have clinical potential for the treatment of skin diseases.

**AMPs/HDPs in human skin**

1. **Human β-defensins (hBDs)**

Human defensins are group of AMPs/HDPs characterized by the presence of six conserved cysteine residues that form three pairs of intramolecular disulfide bridges. Defensins are classified into α-, β-, and θ-defensins based upon their typical spaces between the cysteine residues and their disulfide alignment\(^5\)\(^6\). In humans, 6 α-defensins have been identified: human neutrophil peptide (HNP) –1 to –4 that are found in the azurophilic granules of neutrophils\(^7\), and human defensin (HD) –5 and –6 that are abundantly expressed in the Paneth cells of the small intestine\(^8\)\(^9\). The θ-defensins are found in the neutrophils of “old world” non-human primates such as the gorilla and chimpanzee, but have not been identified in humans\(^10\). To date, six different hBDs have been identified and characterized in humans. hBD-1 to –4 are predominantly found in the epithelia, including the epidermis of skin, respiratory and urogenital tracts, and hBD-5 and hBD-6 are specifically detected in the epididymis\(^1\)\(^2\). hBD-1 is constitutively expressed in the skin epidermis, sweat ducts and sebaceous glands and could also be inducible by pathogen-derived molecules such as lipopolysaccharide (LPS) and peptidoglycan\(^11\). Conversely, the expression of hBD-2 to –4 is mostly inducible following wound healing, infection and inflammation\(^1\)\(^2\). Inducers of hBD-2, –3 and –4 include T-helper (Th) 1- and Th17-derived pro-inflammatory cytokines such as interleukin (IL)-1α and -1β, IL-17A, IL-22, tumor necrosis factor (TNF)-α and interferon (IFN)-γ. Other strong inducers of hBDs include growth factors such as insulin-like growth factor-1 (IGF-1) and transforming growth factor-α (TGF-α), bacteria and microbial products\(^1\)\(^2\). Higher levels of hBD-1 and hBD-2 are detected in the differentiated layers of the epidermis compared with the basal layers. hBD-2 is stored in the lamellar bodies and is secreted to the stratum corneum - stratum granulosum junctions\(^12\)\(^13\). In contrast to hBD-1 and hBD-2, hBD-3 is found in the epithelia and is also abundantly present in non-epithelial tissues, including the heart and skeletal muscles\(^14\). hBD-4 has been only detected at the mRNA level in keratinocytes, and its synthetic form has been functionally characterized; however, the demonstration of the presence of a native hBD-4 protein in the skin has failed to date\(^15\). hBDs exhibit a broad spectrum of antimicrobial activity against multiple pathogenic microorganisms, including both Gram-positive and -negative bacteria, fungi and viruses. The antimicrobial
activity of hBD-1, -2 and -4 is salt-sensitive, whereas hBD-3 demonstrates a strong antimicrobial effect against many microbes at physiologic salt concentrations. Furthermore, the antimicrobial activity of hBD-3 is more potent than that of other hBDs, probably because of its amphipathic dimer structure and the fact that hBD-3 is highly positively charged, with a net charge of +11 as opposed to +4 to +7 for the other hBDs. It is believed that the killing mechanism of AMPs/HDPs is mainly by binding and disrupting negatively charged microbial membranes resulting in the membrane permeabilization, although some AMPs/HDPs might act through different mechanisms of action.

In addition to their antimicrobial properties, hBDs perform various immune system modulating activities. For example, hBDs act as chemotactic agents for mast cells, neutrophils, T cells, dendritic cells, monocytes, macrophages and keratinocytes. Furthermore, hBD-2 to -4 induce mast cell degranulation and the production of eicosanoid metabolites such as prostaglandins (PGs) and leukotrienes and regulate skin vascular permeability via mast cell activation. hBDs also regulate the production of pro-and anti-inflammatory cytokines and chemokines, including those involved in the pathology of various skin diseases. hBDs also enhance cell proliferation and differentiation and promote angiogenesis and accelerate the wound healing process. Furthermore, hBD-2 and hBD-3 are able to bind to and neutralize LPS, and hBD-3 also inhibits neutrophil apoptosis. Moreover, our group recently demonstrated that hBD-3, but not other hBDs, is crucial for the improvement of tight junction barrier function in human keratinocyte layers. Similar to other AMPs/HDPs, hBDs exhibit their immunomodulatory roles through several molecular mechanisms. These peptides bind to specific pertussis toxin-sensitive G protein-coupled receptors (GPCRs) such as the CC chemokine receptor 2 (CCR2), CCR6, Mas-related G-protein coupled receptor X2 (MrgX2), and other GPCRs which have yet to be identified. hBDs also utilize Toll-like receptor (TLR) 1 and TLR2 to stimulate a variety of immune cells, and transactivate the membrane-bound epidermal growth factor receptor (EGFR) to promote keratinocyte migration and proliferation.

2. Human cathelicidin LL-37

Cathelicidins form a large family of AMPs/HDPs characterized by an N-terminal pro-sequence and a C-terminal antimicrobial peptide domain. The members of the family mostly form an α-helical structure. In humans, LL-37 is the sole member of the cathelicidin family, and its name comes from a 37-amino acid residue peptide starting with a pair of leucines. LL-37 is generated from hCAP18 (human cationic antibacterial protein of 18 kDa) following enzymatic cleavage by proteinase 3 and serine proteases of the kallikrein family. LL-37 was initially detected as a constitutive product of neutrophil granules; however, this peptide is also produced by other cell types, including keratinocytes, epithelial cells of the airways and intestine, mast cells, macrophages, T cells, natural killer cells and monocytes. The regulation of LL-37 expression is controlled by cytokines, growth factors, bacteria, viruses, injury and vitamin D. In healthy skin, the expression of LL-37 is barely detected, but it strongly increases following infection or skin injury.

Similar to hBDs, LL-37 also exhibits a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi and viruses. Furthermore, a number of studies have shown that LL-37 is able to act additively or synergistically with other AMPs/HDPs such as hBDs and lysozyme to kill pathogenic microorganisms. Experimental studies utilizing a murine ortholog of human LL-37, mCRAMP (murine cathelin-related antimicrobial peptide) have demonstrated the in vivo importance of LL-37 in various infections. For example, mice deficient in CRAMP exhibit increased bacterial colonization and invasion in the skin and intestine. Furthermore, CRAMP knock-out mice are more susceptible to meningococcal infection and Escherichia coli (E. coli) infection in the urinary tract. The antimicrobial activity of LL-37 is variable according to the species and strains of microorganisms; it is salt-sensitive against Gram-positive bacteria but salt-insensitive against Gram-negative bacteria.

In addition to its antimicrobial properties, LL-37 could also modify the host immune responses. First, LL-37 has both pro-inflammatory and anti-inflammatory activities that might be modulated by the disease background. LL-37-mediated pro-inflammatory activities include the production of pro-and anti-inflammatory cytokines and chemokines, including those involved in the pathology of various skin diseases.
responses include the downregulation of IL-10, upregulation of IL-1β, IL-12p40, IL-18, and cooperation with IL-1β to enhance the induction of inflammatory mediators.  

LL-37 also induces mast cell degranulation, the production of lipid mediators and pruritogenic factors, and increases vascular permeability.  

LL-37-mediated anti-inflammatory responses include the inhibition of IFN-γ, TNF-α, IL-4 and IL-12 production. Second, LL-37 is a chemoattractant for many cell types, including keratinocytes, mast cells, neutrophils, T cells, monocytes and eosinophils.  

Third, LL-37 regulates cell death through the inhibition of apoptosis in neutrophils, keratinocytes, airway and intestinal epithelial cells. LL-37 regulates the production of reactive oxygen species and enhances the release of α-defensins by neutrophils.  

Fourth, LL-37 enhances cell proliferation and differentiation, exhibits angiogenic and wound healing activities through promoting neovascularization and re-epithelialization, maintains skin homeostasis and strengthens the skin's barrier function. Finally, like hBDs, LL-37 mediates its immunomodulatory functions via the activation of various cell-surface receptors, such as the IMLP receptor FPLR-1, the ATP-gated purinergic receptor P2X7, EGFR, TLR4 and MrgX2, and intracellular GAPDH. Furthermore, still-uncharactized GPCRs have also been suggested to be responsible for LL-37-mediated mast cell chemotaxis.

3. S100 proteins

S100 proteins constitute an extensive family of AMPs/HDPs characterized by the presence of two calcium-binding EF-hand motifs. Twenty-one types of S100 proteins have been identified, and the majority of these proteins (13 members) are located in the epidermal differentiation complex region, which also encodes various members of epidermal differentiation markers. These proteins expressed in the epidermis have been involved in the pathology of various skin diseases. S100 proteins regulate cell metabolism, proliferation, differentiation, intercellular adhesion, invasion and metastasis. Among S100 proteins, S100A7 (psoriasin), S100A8 (calgranulin A), S100A9 (calgranulin B), S100A12 (calgranulin C), and S100A15 (koebnerisin) exhibit antimicrobial activity. S100A7 has been well studied and owes its name to the fact that it is detected in high quantity in psoriatic skin lesions compared with normal skin. S100A7 (psoriasin) is believed to be the principal AMP/HDP constitutively expressed in normal skin, although its expression is also inducible by Th1-, Th17- and Th22-cytokines, EGF, IGF-1, vitamin D, calcium, sodium butyrate, bacteria and microbial products.

Both S100A7 and S100A15 efficiently kill E. coli but only have weak antimicrobial activity toward Gram-positive bacteria and other microorganisms, whereas the S100A8/S100A9 complex and S100A12 have antimicrobial activities against viruses and fungi. The abundance of E. coli-cidal S100A7 on human skin suggests a key protective role of this protein against E. coli colonization and infection. This finding has been confirmed by experiments on skin from healthy people that demonstrated that S100A7 is a major AMP/HDP that kills E. coli. It has been hypothesized that the killing mechanism of S100A7 is mainly mediated by zinc deprivation, because zinc is an essential element for bacterial metabolism. In addition to having antimicrobial activity, S100A7 and S100A15 are chemoattractant for T cells, monocytes and neutrophils, therefore linking innate and adaptive immunity. S100A7 also enhances the production of reactive oxygen species, increases the cytokine/chemokine production from neutrophils and keratinocytes, and promotes angiogenesis by the induction of endothelial cell proliferation. Furthermore, our recent work demonstrated that S100A7 improves skin tight junction barriers in association with keratinocyte differentiation. The major sources of S100A7 and S100A15 are keratinocytes and neutrophils, whereas S100A8 and S100A9 are mainly produced by neutrophils, monocytes and macrophages, although the expression of these proteins might also be induced in keratinocytes and endothelial cells. S100A8 and S100A9 also exhibit chemotactic and angiogenic activities. S100A7, S100A8, S100A9 and S100A12 act through the multiligand receptor for advanced glycated end products (RAGE), whereas S100A15 acts through a pertussis toxin-sensitive GPCR.

4. Other AMPs/HDPs

In addition to hBDs, LL-37 and S100 proteins, the skin produces many other AMPs/HDPs such as...
RNases, dermcidin, lysozyme, elafin, secretory leukocyte protease inhibitor (SLPI), adrenomedullin, lactoferrin and catestatin. Among 8 members of RNase family, RNase 1, 4, 5 and 7 are expressed in keratinocytes, with the latter being the highest expressed. RNase 7 was originally isolated from extracts of the stratum corneum where its expression is even higher than that of hBDs, LL-37 and S100A7. In addition to their antimicrobial and ribonucleolytic activities, RNase family members have neurotoxic, angiogenic and immunomodulatory activities. Dermcidin peptides are primarily constitutively found in the eccrine sweat glands within the dermis of the human skin and secreted into the sweat. They exhibit antimicrobial activity, stimulate keratinocytes to produce cytokines and chemokines, and enhance cell growth and the survival of breast cancer cells. Lysozyme protects against bacteria and viruses, and we have shown that this effect is synergistic with other AMPs/HDPs such as hBDs and LL-37. Elafin and SLPI are members of the antileukoproteinase superfamily of proteinase inhibitors and protect tissues from protease damage during inflammation. Both elafin and SLPI possess antimicrobial, chemotactic and wound healing activities, and are involved in inflammation regulation. Elafin and SLPI are expressed in the epidermis and dermis, where they play a role in wound healing and angiogenesis in endothelial cells and keratinocytes.

The role of important AMPs in human skin diseases

1. AMPs/HDPs in psoriasis

Psoriasis is an inflammatory non-infectious skin disorder with an estimated worldwide prevalence of 3%; the disorder causes significant morbidity and affects the quality of life in many patients. The foremost clinical features of psoriasis include a typical hyper-proliferation and abnormal differentiation of keratinocytes, which is associated with the excessive production of pro-inflammatory cytokines/chemokines and activated T cells and plasmacytoid dendritic cells (pDCs). The psoriatic skin produces almost all well-known AMPs/HDPs, including hBD-1, hBD-2, hBD-3, LL-37, S100A7, S100A8, S100A9, S100A15, RNase 7, lysozyme, elafin and SLPI. hBD-2 and hBD-3 were first identified in psoriatic scales, and S100A7 was named psoriasin due to its abundance in psoriatic skin. The excessive production of AMPs/HDPs in psoriatic skin has been suggested to be a major explanation of the unexpected observation that patients with psoriasis experience fewer bacterial and viral infections compared with AD patients. The mechanism of AMP/HDP overexpression in psoriatic skin is not well understood; however, it appears that an abundance of Th1- and Th17-derived inflammatory cytokines in psoriasis is a major cause of this induction.

In addition to protecting against pathogenic microorganisms in psoriasis, AMPs/HDPs initiate anti-inflammatory functions in psoriatic keratinocytes. We recently reported that hBD-3 primes keratinocytes to express an anti-inflammatory cytokine IL-37, which is a novel target for the pathogenesis and therapy of psoriasis. Intracellular or cytosolic LL-37 has been shown to block activation of DNA-induced formation of inflammasomes in keratinocytes, resulting in the inhibition of IL-1β release. Furthermore, the overexpression of S100A8 and S100A9 leads to induction of keratinocyte differentiation and inhibition of keratinocyte proliferation and survival, key features of psoriasis. These observations suggest that AMPs/HDPs might contribute to the suppression of psoriatic skin inflammatory and innate immune responses.

The presence of AMPs/HDPs in psoriasis might also contribute to its pathogenesis. First, LL-37 inhibits keratinocyte apoptosis, and similar to hBDs and S100A8/S100A9, LL-37 induces keratinocyte proliferation and migration. Second, LL-37, hBD-2 and hBD-3 activate pDCs through the formation of aggregates with self-DNA, resulting in production of IFN-α, TNF-α and IL-6, therefore initiating auto-inflammatory responses in psoriasis. Third, hBDs, LL-37 and S100A proteins trigger recruitment of immune cells such as T cells, DCs, neutrophils, monocytes/macrophages, which play a key role in the pathogenesis of psoriasis. Fourth, AMPs/HDPs prime keratinocytes for enhanced secretion of various pro-inflammatory cytokines and chemokines that play
important roles in the development of psoriatic lesions. \textsuperscript{42} \textsuperscript{43} hBDs and LL-37 also cause mast cell degranulation and the production of lipid mediators and pruritogenic factors, which might contribute to pruritus in psoriasis. \textsuperscript{19} \textsuperscript{20} \textsuperscript{21} Fifth, hBDs, LL-37 and S100A7 induce the proliferation and migration of endothelial cells and promote angiogenesis and neovascularization in psoriatic lesions. \textsuperscript{44} \textsuperscript{45} \textsuperscript{95}.

2. AMPs/HDPs in AD

AD, also known as atopic eczema, is one of the most common chronic and relapsing inflammatory skin diseases and is frequently associated with recurrent bacterial (particularly \textit{S. aureus}) and viral infections. \textsuperscript{96} \textsuperscript{97} AD pathogenesis, which is complex and still not fully understood, involves both genetic and environmental components, together with immune dysregulation and epidermal barrier disruption. \textsuperscript{98} The defect in innate immune response in AD was proposed by Ong \textit{et al}. in 2002 when a deficiency in the expression of hBD-2 and LL-37 was observed in lesional AD skin in contrast to the increased expression in psoriatic skin. \textsuperscript{81} and this finding was further confirmed by de Jongh \textit{et al}. \textsuperscript{99} Furthermore, patients with eczema herpeticum, one of the uncommon complications of AD, have pronounced defects in the expression of hBD-2, hBD-3 and LL-37 in their lesional skin compared with patients with AD or psoriasis. \textsuperscript{100} AD skin has increased production of the Th2-derived cytokines IL-4, IL-10 and IL-13 and reduced production of IL-1\(\beta\), IL-22, IFN-\(\gamma\) and TNF-\(\alpha\), which are crucial for the induction of AMPs/HDPs. \textsuperscript{84} \textsuperscript{101} \textsuperscript{102} The down-regulation of inducible AMPs/HDPs in AD has been attributed to the inhibitory effects of overexpressed Th2 cytokines on these peptides. \textsuperscript{103} This finding is also supported by the observation that neutralization of Th2 cytokines resulted into elevated expression of hBD-2, hBD-3 and LL-37 in AD skin. \textsuperscript{100} In contrast, Kisich \textit{et al}. reported that the mobilization of hBD-3 on \textit{S. aureus} is impaired in AD patients compared with healthy subjects because of excess amounts of Th2 cytokines that interfere with antimicrobial activity. \textsuperscript{104} Therefore, it could be assumed that controlling the overproduction of Th2 cytokines in AD skin might lead to recovery of inducible AMPs/HDPs, reducing the frequent bacterial and viral infections seen in AD patients. A recent report found that pimecrolimus, a drug used in the treatment of AD, induces S100A8 and S100A9 expression, which is undetectable in AD skin. \textsuperscript{105}.

It is important to note that AD is not associated with a general deficiency in the production of AMPs/HDPs. Enhanced expression of hBD-2, hBD-3, S100A7 and RNase 7 was demonstrated in lesional skin compared with non-lesional skin. \textsuperscript{90} \textsuperscript{106} \textsuperscript{107} It is believed that increased expression of AMPs/HDPs in AD lesional skin is a result of the disturbed skin barrier, because expression of hBD-3, S100A7 and RNase 7 was upregulated by experimental barrier disruption caused by tape stripping. \textsuperscript{90} \textsuperscript{106} However, although LL-37 expression is rapidly increased in healthy skin following wounding, this expression is suppressed in wounded AD lesions, suggesting that not all AMPs/HDPs could be induced by barrier disruption in AD skin. \textsuperscript{108}

AMPs/HDPs might contribute to the development of AD pathogenesis. A recent investigation by Kanda \textit{et al}. showed that hBD-2 and hBD-3 enable keratinocytes to produce the Th2 cytokines IL-4, IL-13 and IL-31. \textsuperscript{109} Furthermore, our group has demonstrated that hBD-2, hBD-3, hBD-4 and LL-37 induce mast cell degranulation and the production of PGD\(_2\), PGE\(_2\), leukotriene C\(_4\) and IL-31. \textsuperscript{109} \textsuperscript{20} \textsuperscript{21} These observations imply that AMPs/HDPs might aggravate allergic reactions such as pruritus in AD skin. However, contrastingly, we recently showed that LL-37 induces upregulation of an epidermal nerve repulsion factor, semaphorin 3A by human keratinocytes. \textsuperscript{110} Because the levels of both LL-37 and semaphorin 3A are reduced in AD patients, recovery of this peptide in AD patients might be useful to suppress itch. Moreover, LL-37 suppresses double-stranded RNA-induced thymic stromal lymphopoietin, suggesting that LL-37 might contribute to the suppression of Th2-driven AD skin inflammation induced by viral or self-double-stranded RNA. \textsuperscript{111} Taken together, the complete picture of the roles of AMPs/HDPs in AD remains to be further elucidated.

3. AMPs/HDPs in rosacea

Rosacea is another common chronic inflammatory skin disease characterized by persistent facial erythema, telangiectasias, edema, inflammatory papules and pustules that primarily affect the nose,
cheeks, central forehead and chin\(^\text{122, 113}\). Until now, the complete pathophysiology of rosacea has been uncertain. It was proposed that rosacea is associated with abnormal skin vasculature and inflammation, but recently, it was shown that factors that trigger innate immune responses such as aberrant release of LL-37 and its derived peptides by keratinocytes could aggravate the clinical symptoms of rosacea. Abnormally high expression and processing of LL-37 has been found in rosacea patients\(^\text{114, 115}\). In lesional skin of rosacea, increased activity of a serine protease of the kallikrein family, kallikrein 5, leads to LL-37 activation and processing into smaller fragments that are not found in normal skin\(^\text{115, 116}\). These abnormal LL-37 fragments control leukocyte recruitment, angiogenesis, the expression of extracellular matrix components and production of vasoactive and pro-inflammatory cytokine IL-8\(^\text{95, 117, 118}\). An injection of these proteolytic fragments into mice results in the typical clinical presentations of rosacea, which include erythema, vascular dilatation, flushing and telangiectasias\(^\text{113, 119}\). These findings suggest that high levels of kallikrein 5 along with very high concentrations of LL-37 and abnormally processed LL-37 isoforms play a crucial role in the chronic inflammation patients with rosacea. Although the mechanism by which LL-37 expression is elevated in rosacea has not been fully elucidated, the vitamin D\(^-\) and TLR2-pathways are likely involved. Vitamin D is a stronger inducer of LL-37, and genetic polymorphisms of the vitamin D receptor have been associated with some types of rosacea\(^\text{120}\). This association suggests that the vitamin plays a role in the development of rosacea. Because exposure to UVB causes activation of vitamin D and subsequent augmentation of LL-37 expression in keratinocytes\(^\text{121, 122}\), this finding might explain the frequency of rosacea in the face. Avoiding exposure to sun light might be recommended in rosacea patients.

### 4. AMPs/HDPs in acne vulgaris

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit (hair follicle, hair shaft and sebaceous gland), which often occurs on the face, chest and back of adolescents and young adults. The pathogenesis of acne involves several factors including inflammation, abnormal keratinization, excess sebum production and colonization with \textit{Propionibacterium acnes} (\textit{P. acnes})\(^\text{123}\). \textit{P. acnes} contributes to acne inflammation through the release of extracellular enzymes, recruitment of neutrophils, and activation of monocytes to release pro-inflammatory cytokines\(^\text{124}\). Upregulation of AMPs/HDPs such as hBD-1, hBD-2 and hBD-4, was observed in lesional skin biopsies from acne patients compared with controls\(^\text{125-127}\). This finding suggests that these peptides might play a role in acne vulgaris. Furthermore, cathelicidin LL-37 and S100A7 are expressed in keratinocytes and sebocytes and act synergistically to inhibit the colonization of \textit{P. acnes}. Taken together, given that numerous AMPs/HDPs possess killing ability against \textit{P. acnes}, neutralize pro-inflammatory bacterial factors and directly inhibit the production of inflammatory cytokines from host cells\(^\text{1, 2}\), these peptides are potential candidates for the prevention and treatment of acne vulgaris.

### 5. AMPs/HDPs in other skin disorders

In addition to the above-mentioned skin diseases, AMPs/HDPs also play roles in the pathogenesis in a myriad of skin conditions. For example, burns are generally associated with decreased levels of AMPs/HDPs, which might explain the increased susceptibility to bacterial infection and sepsis in burned patients\(^\text{128, 129}\). In contrast, the expression of hBDs, LL-37, S100A7 and RNase 7 is enhanced after skin injury. These peptides promote angiogenesis, vascularization, wound re-epithelization and wound healing\(^\text{1, 2}\), suggesting that AMPs/HDPs are promising agents for therapeutic development for wound healing. hBDs have been reported to be increased in folliculitis, scleroderma and lichen planus\(^\text{130-132}\); however, their precise functions in these diseases remain to be further clarified. LL-37 has been found to be strongly expressed in hidradenitis suppurativa, systemic lupus erythematosus and contact dermatitis to nickel, verruca vulgaris and condyloma acuminata\(^\text{1, 2}\). In addition to psoriasis and AD, S100A7 is also over-expressed in many other epidermal inflammatory diseases, including mycosis fungoides, Darier’s disease, and inflammatory lichen sclerosus et atrophicus, and squamous cell carcinoma of the skin\(^\text{1, 2}\). AMPs/HDPs are implicated in many skin diseases; however, their precise functions in these disorders have yet to be clarified.
Conclusions and outlook

In addition to the prevention of pathogen invasion, AMPs/HDPs are strong regulators of the cutaneous immune system. Despite notable findings reported on the multiple functions of these proteins/peptides in normal human skin and numerous infectious and/or inflammatory skin diseases, much more work needs to be done to understand their cellular/molecular mechanisms. Mastering the biological functions and the underlying mechanisms of AMPs/HDPs would improve our understanding in the pathophysiology of skin disorders and enable us to develop novel therapeutic targets or improve established treatments for several dermatological conditions. A summary of selected AMPs/HDPs or their derivatives in drug development for various skin diseases is shown in Table-1. Further research should focus on how to reduce the cytotoxicity of AMPs/HDPs and at the same time improve their antimicrobial and immunomodulatory activities. This improvement could lead to innovative treatments for many skin diseases through the effects of AMPs/HDPs.

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References


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**Table-1** Selected AMPs/HDPs in clinical trials for skin diseases

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<thead>
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<th>Name</th>
<th>Parent peptide/source</th>
<th>Company</th>
<th>Application</th>
<th>Clinical trial stage</th>
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<td>Pergamum</td>
<td>Venous leg ulcers</td>
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<td>Phase II</td>
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<td>Migenix/BioWest Therapeutics</td>
<td>Prevention of acne</td>
<td>Phase III</td>
</tr>
<tr>
<td>Omiganan (CL5001)</td>
<td>Indolicidin</td>
<td>Cutanea Life Sciences/Migenix</td>
<td>Severe acne and rosacea</td>
<td>Phase II/III</td>
</tr>
</tbody>
</table>

BPI: Bactericidal permeability-increasing protein
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