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Antimicrobial peptides in human skin disease

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Abstract

The skin continuously encounters microbial pathogens. To defend against this, cells of the epidermis and dermis have evolved several innate strategies to prevent infection. Antimicrobial peptides are one of the primary mechanisms used by the skin in the early stages of immune defense. In general, antimicrobial peptides have broad antibacterial activity against gram-positive and negative bacteria and also show antifungal and antiviral activity. The antimicrobial activity of most peptides occurs as a result of unique structural characteristics that enable them to disrupt the microbial membrane while leaving human cell membranes intact. However, antimicrobial peptides also act on host cells to stimulate cytokine production, cell migration, proliferation, maturation, and extracellular matrix synthesis. The production by human skin of antimicrobial peptides such as defensins and cathelicidins occurs constitutively but also greatly increases after infection, inflammation or injury. Some skin diseases show altered expression of antimicrobial peptides, partially explaining the pathophysiology of these diseases. Thus, current research suggests that understanding how antimicrobial peptides modify susceptibility to microbes, influence skin inflammation, and modify wound healing, provides greater insight into the pathophysiology of skin disorders and offers new therapeutic opportunities.

Keywords

antimicrobial peptides; defensin; cathelicidin; dermcidin; innate immunity; skin diseases

The human epidermis forms a protective shield consisting of a dense mechanical barrier composed of the cornified envelope, keratin, and lipid layers to prevent invasion of microbes. However, resident cells of the epidermis not only form a passive mechanical barrier but also secret molecules to fight against exogenous pathogens. This initial defense response is defined as the “innate immune” response of the skin and has three major functions; 1) recognition of pathogens, 2) induction of molecules to activate host cells whose purpose is to eliminate pathogens, and 3) secretion of molecules to directly kill pathogens. This review will focus on one group of molecules that have important actions in both of the latter two functions of innate immunity, the “antimicrobial peptides”.

Antimicrobial peptides (AMPs)[1] have been found in vertebrates and in vertebrates, and act in organisms with complex adaptive immune systems as well as those that lack an acquired immune system. Although the sequences of AMPs are variable, many peptides have broad-

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[1]**The abbreviations used are:** AMP, antimicrobial peptide; HNP, human neutrophils peptide; HD, human defensin; hBD, human beta defensin; CAMP, cathelicidin antimicrobial peptide; mCRAMP, mouse cathelin-related antimicrobial peptide; hCAP18, human cationic antimicrobial protein 18 kDa; SCTE, stratum corneum tryptic enzyme (kallikrein 5/KLK5, hK5); SCCE, stratum corneum chymotryptic protease (kallikrein 7/KLK7, hK7); SLPI, secretory leukocyte protease inhibitor; ALP, antiluekoprotease; ESI, elastase-specific inhibitor, SKALP, skin-derived antileukoprotease; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LPS, lypopolysaccharide; FPRL1, formyl peptide receptor-like 1; EGF, epidermal growth factor; AD, atopic dermatitis; SCN, severe congenital neutropenia;

spectrum antimicrobial activity against bacteria, fungi, and viruses. These peptides are usually cationic and 20 to 60 amino acids in length. The cationic nature of these peptides allow them to bind to negatively charged bacterial membrane molecules such as lypopolysaccharude and lipoteichoic acid [1-4].

AMPs are usually organized structurally such that they have hydrophobic and hydrophilic sides. This enables them to interact in both the aqueous environment and the lipid-rich membrane. These peptides can act together with other proteins with antimicrobial activity, like lactoferrin, lysozyme, bactericidal/permeability-increasing protein, phospholipase A2 and antileukoproteas in neutrophils to increase the potency of the combinded mixture [5-7]. Extensive studies of these evolutionally conserved molecules have shown that they not only kill microbes but also have multiple functions against the host cells themselves. Therefore, the term AMP is in fact a bit of a misnomer, and many of the peptides in this group might be better called “alarmins” to recognize their capacity to alert host cells to the potential for infection or the presence of injury [8]. Continued progress in understanding new aspects of the behavior of these unique and ubiquitous small peptides is rapidly increasing our knowledge of the innate immune systems of many species, including humans. Human skin is a major source of AMPs. The AMPs produced in human skin include defensins, cathelicidins, dermcidin, and other short proteins first discovered for other biological activities such as neuropeptides and chemokines. Many other larger proteins with direct antimicrobial action also can be found in the skin such as lysozyme, elastase, complement, S100 proteins, and others. This paper summarizes AMPs identified in resident cells of the skin, and their functions in skin homeostasis and dynamics.

Defensins

The defensins are a group of small cationic peptides and are categorized in three subfamilies, α, β-, and circular θ-defensins. The consensus sequences of defensin mature peptides contain six conserved cysteines, which form three disulfides bridges and β-hairpin structures (figure 1) [9]. α- and β-defensins are distinguished by the position of three disulfides bridges; α—defensins have disulfides bridges between cysteines 1-6, 2—4, and 3-5, and β-defensins between cysteines 1-5, 2-4, and 3-6 [10,11]. Six α- defensin peptides have been identified from 5 genes in human, HNP (human neutrophil peptide)-1 to -4, HD-5, and HD-6 [12]. HNP-1, -2, and 3 were first identified in neutrophils and are stored in azurophilic granules [13]. HNP-2 is a truncated form of HNP-1 or HNP-3 peptides and derived from HNP-1 or -3 genes [14]. α-defensins HNP-1, -2, and -3 are mainly produced by neutrophils and, to date, not isolated from human keratinocytes or cells derived from skin appendages. HD-5 and HD-6 are predominantly expressed in Paneth cells in small intestine [15]. Recent computational genomic approach revealed 5 additional α-defensin pseudogenes, DEFA7P ~ DEFA11P and these genes products have not been identified so far [16]. Expression and function of four β-defensins (hBD-1 to 4) are well characterized, and keratinocytes express hBD-1 to 4. Computational genomic research predicts 28 new human β-defensins [17], and the expression of these genes in human skin cells is unknown. θ-defensins were primarily found in primates [18]. Although a θ-defensin pseudogene has been found in human bone marrow, the peptide has not been identified in humans to date [19].

Regulation of defensin expression and activity

The genomic structure of defensins consists of two exons and one intron, and this translates to a proprotein consisting of an N-terminal signal peptide and C-terminal mature peptide [16, 20,21]. HNP-1 and -3 genes (DEFA1 and DEFA3) and hBD-1 ~ 4 genes are clustered in chromosome 8p23.1, which is known to be a frequent site of chromosomal rearrangements, and copy numbers of defensin genes vary with individuals [22,23]. Genomic copy number of defensins correlate with levels of those messenger RNA transcript [22,23]. hBD-1 constitutively expresses at low levels in human epidermis and sweat gland ducts [24-26],

whereas hBD-2 to -3 are inducible in keratinocytes by bacterial infection, cytokines (IL-1α, IL-1β and TNF-α), and differentiation [27,28]. hBD-2 ~ 4 can also be induced by calcium and PMA (phorbol 12-myristate 13-acetate, and can be inhibited or suppressed by retinoic acid pretreatment, indicating retinoic acid is an important regulator of the innate immune system in epidermis [29]. Propionibacterium acnes and lipopolysaccharide induce hBD-2 in sebocytes [30]. Defensins are secreted as proproteins and post-translational processing cleaves out the C-terminal mature peptide from α–defensin proprotein [31]. Local proteases affect processing of defensins, and multiple forms of N-terminal truncated α- defensins have been identified in various tissue or cells [32-35]. Although defensin processing enzymes in human skin are unknown, the requirement for processing of the proprotein to activate AMP activity predicts that proteases in skin will affect the activity of defensins.

The consensus sequences of defensin mature peptides contain six conserved cysteines, which form three disulfides bridges and β-hairpin structures. Formation of disulfides bridges in hBD-3 is affected by the oxidative conditions and can affect its function as a chemoattractive molecule [36]. Crystallographic studies showed HNP-3 forms a symmetric dimer [37], and hBD-2 can further form an octamer [38], whereas hBD-1 forms asymmetric dimers and does not form higher oligomers though the monomer structure is similar with hBD-2 [39]. Further studies are required to elucidate precise relations between structural changes and functions of defensins. Genome wide search has predicted more than 30 β-defensins [17]. These peptides have a conserved cysteine motif, but the amino acid contents are variable. Potentially, these polymorphisms of hBD peptides might have served to adapt activity to various microbes.

Functions of defensins

α- and β-defensins show a broad antibacterial activity against gram-positive and negative bacteria [12,13], and have antifungal activity [40,41]. Binding of the positively charged defensin with the negatively charged bacterial membrane precedes membrane permeabilization and is thought to be the mechanism of bacterial killing by defensins. Defensins also have antiviral properties against adenovirus [42], papilloma virus [43], human immunodeficiency virus (HIV) [44,45], and herpes simplex virus (HSV) [46]. Variable mechanisms have been proposed for the action of defensins against viral infection. hBD-2 and hBD-3 modulate cell surface CXCR4 coreceptor expression on immunocompetent cells and suppressed HIV infection *in vitro* [47,48]. HSV infects cells using HSV glycoprotein B as a ligand to host surface heparan sulfate [49]. HNPs 1, 2, 3, and HD 5 bind HSV glycoprotein B, and HNP-4 and HD 6 bind heparan sulfate to inhibit HSV infection *in vivo* and *in vitro* [46]. hBD-3 binds both of HSV glycoprotein B and heparan sulfate [46]. HNPs 1, 2, 3, and HD 5 block virion escape of papilloma pseudoviruses from endocytic vesicles that lead microbes to lysosomes *in vitro* [43]. Thus, defensins inhibit multi steps of microbe infectivity with variable mechanisms.

Although directly antimicrobial *in vitro*, the effect of defensins on mammalian cells is an important component of how these peptides affect immunity. α- and β–defensins modify cell migration and maturation. β-defensins are chemoattractive for immature-dendritic cells and memory T-cells through chemokine receptor CCR6 activation [50]. Mouse β-defensin-29 induces angiogenesis by recruiting bone marrow-derived dendritic cells and inducing endothelial-like differentiation thorough CCR6 activation in tumor vasculization [51]. In contrast, α-defensin HNPs inhibit endothelial cell migration by inhibition of binding of the endothelial cell α5β1 integrin to fibronectin [52]. Murine β-defensin 2 acts on TLR-4 and induces dendritic cell maturation [53].

Defensins also induce cytokines and other molecules secreted from host cells. α -defensin [HNPs] up-regulate the expression of TNF-α and IL-1β in monocytes activated with *Staphylococcus aureus* [54]. Defensins induce IL-8 and proinflammatory cytokines in lung

epithelial cells [55,56]. hBD-1 ~ 4 induce IL-18 in human primary keratinocytes [57]. HNP-1 and -4 induce histamine release from mast cells [58], and hBD-2 ~ -4 induces histamine and prostaglandin D2 release from mast cells [59,60]. Coadministration of α-defensin (HNP-1, -2) and β-defensin (hBD-1, -2) augments antigenspecific serum IgG production in mice immunized intra-nasally with the antigen ovalbumin [61,62]. In sum, current evidence of the multiple functions of defensins in addition to their antimicrobial properties suggest that defensins work in both innate and adaptive immunity.

Cathelicidin

Cathelicidin is named for the conserved prosequence domain of the precursor protein that resembles the cathelin protein, originally isolated as a cathepsin L inhibitor [63]. The structure of the cathelicidin proprotein consists of a N-terminal signal domain, a highly conserved prosequence domain (cathelin domain), and the C-terminal peptide domain (figure 2A) [64]. Cathelicidin is secreted as a proprotein that consists of the cathelin domain and C-terminal cationic domain, and this proprotein is inactive as an antimicrobial molecule [65]. Post-transcriptional processing cleaves out the C-terminal peptide from the prosequence and makes the active AMPs [66,67]. C-terminal peptides of cathelicidins in different species include β-sheets and linear peptides rich in proline or tryptophan but most, including the human cathelicidin LL-37, is an amphipathic cationic peptide deduced to be α-helical in some buffer conditions [68]. Most cathelicidin peptides form an α-helical structure, which has both a hydrophobic and a hydrophilic side (figure 2D). This amphipathic structure and cationic charge enables cathelicidin peptides to interact in the aqueous environment, the lipid-rich membrane, and bind negatively charged bacterial membranes.

Regulation of cathelicidin activity

Cathelicidin expression and function is regulated by two major steps; transcription to mRNA and post-translational processing to active peptides. In the human genome, the cathelicidin exons 1-4 are found on chromosome 3p21. These are transcribed as a single gene, *CAMP* (cathelicidin antimicrobial peptide), which translates to a 18 kDa proprotein referred to as "hCAP18" (human cationic antimicrobial protein 18 kDa). The other nomenclature commonly used to describe the protein is "hCAP18/LL-37" because LL-37 was the first isolated mature peptide dominantly expressed in neutrophils [67,69]. In human keratinocytes, cathelicidin is inducible with skin inflammation from basal expression levels that are low and barely detectible [70]. 1,25-dehydroxy vitamin D3 is a potent inducer of cathelicidin mRNA transcription and the presence of vitamin D3 seems to be essential to cathelicidin induction in skin infection and wounding [71-73]. hCAP18 is stored in lamellar bodies in keratinocytes and secreted in the granular to spinous layer of the epidermis [74]. After secretion, local proteases cleave the c-terminal peptides to form active AMPs. As the proteolytic activity of various cells and tissues differs, hCAP18 can be processed to multiple mature peptides in addition to the form LL-37 found in neutrophils. Nomenclature for these alternatively processed cathelicidin peptides follows the format set for LL-37 which defines the first two N-terminal amino acids and the length of peptide. For example, LL-37 consists of 37 amino acids starting with two leucines, cleaved in neutrophils from hCAP18 by proteinase 3 [67]. On the skin surface, SCTE (stratum corneum tryptic enzyme, kallikrein 5/hK5) first processes hCAP18 to LL-37 and a combination of SCTE and SCCE (stratum corneum chymotryptic protease, kallikrein 7/hK7) further process to smaller peptides known as RK-31 and KS-30 (figure 2C) [66,75]. These peptides (RK-31 and KS-30) in human skin have increased antimicrobial activity and show different ability to induce cytokines than LL-37, suggesting postsecretory enzymatic processing is a key step to dictate the activity and function of cathelicidin peptides [75,76].

Functions of cathelicidin

Human cathelicidin peptides have broad antimicrobial activity against gram positive and negative bacteria [77-79], vaccinia virus [80], and fungi [81,82]. Cathelicidin peptides are cationic and, like defensins, thought to directly bind to the anionic cell wall and membrane of the microbe, increasing permeability of the microbes' cell wall [83,84]. Human and Rabbit cathelicidin CAP18 has also been identified as a lipopolysaccharide (LPS)-binding protein, and pretreatment with cathelicidin peptides suppress LPS-dependent TNF-α expression from CD14(+) cells and protected mice from LPS lethality [4,85,86]. Furthermore, LL-37 can directly inhibit the function of TLR4 on dendritic cells, preventing their maturation as well as their response to LPS or other TLR4 ligands such as low molecular weight Hyaluronan [87, 88]. These observations, which unlike any other AMP have also been validated *in vivo* by mouse genetic models, suggests cathelicidin can both kill microbes and modulate the endotoxin response of the host [77,87].

In addition to actions against microorganisms, LL-37 induces cellular signaling and activates keratinocytes and leukocytes. LL-37 is chemoattractive to neutrophils, monocytes, and T cells by activating the G-protein-coupled receptor FPRL1 (formyl peptide receptor-like 1) [89]. LL-37 also signals throught FPRL1 to induce angiogenesis [90]. Transactivation of the epidermal growth factor receptor (EGFR) by LL-37 was observed in human epidermal keratinocytes, and this induces keratinocyte migration [91]. Cathelicidin also induces proinflammatory cytokine secretion. LL-37 stimulates IL-8 secretion from human epidermal keratinocytes and airway epithelial cells via direct or indirect activation of epidermal growth factor receptor [76,92]. LL-37 induces IL-18 via p38 and ERK1/2 MAP kinase pathway in keratinocytes [57]. Another G-protein-coupled receptor P2X7 can also be activated by LL-37, inducing IL-1β processing and release from LPS-primed monocytes [93]. These reports show the many functions of cathelicidin peptides to activate the innate immune system of host cells in response to microbes. An explanation for these diverse effects, acting through multiple specific cell surface receptors such as TLR4, EGFR, FPRL1 and P2X7, is that association of the LL- 37 peptide with the membrane surrounding the receptor, rather than specific binding to the receptor itself, which leads the structures changes on cell membrane and the observed cell activation events [87].

Dermcidin

Dermcidin (DCD) was identified in the eccrine gland [94]. Dermcidin gene and the mature peptide (principally DCD-1L, 47 aa) have been identified in humans, but not isolated from other species to date. In contrast to the defensins and cathelicidins, Dermcidin is constitutively secreted in human sweat and not inducible by skin injury or inflammation [95]. Dermcidin is also secreted as proprotein. Postsecretory processing by cathepsin D cleaves the peptide from the C-terminus of the proprotein, and dermcidin peptides are distributed to the skin surface with sweat [96]. YP-30 peptide, which consist of 30 aa and is derived from N-terminal side of dermcidin proprotein, works as a survival factor in developing neural cells and peripheral blood mononuclear cells in thymus [97], indicating dermcidin proprotein generates at least two functionally different peptides (figure 3A).

Cathelicidin and defensins are cationic peptides, which bind to and permeabilize bacterial membranes. In contrast, DCD-1L is an anionic peptide, and the molecular mechanism to kill bacteria appears different from cationic AMPs. Steffen *et al.* tested several truncated dermcidin peptides and showed that net charge of peptides did not affect bactericidal activity [98]. Dermcidin peptides also form an α-helical structure like the cathelicidin peptide and binds to bacterial membranes, but do not permeabilize bacterial membranes (figure 3B) [98]. Lai *et al.* demonstrated recombinant dermcidin peptides could have flexible structure with α-helical and β-sheet structures depending on buffer condition [99]. The structure flexibility of

dermcidin peptides might determine the antimicrobial activity, and dermcidin likely kills microbes by a completely different mechanism from cathelicidin and defensins. Lai et al. tested antimicrobial activity of recombinant DCD–1L with the condition of 10 mM sodium phosphate buffer (pH 6.5) with 100 mM sodium chloride and successfully showed the potent antimicrobial activity against *S. aureus, E. coli*, and *C. albicans* [99], however, synthetic dermcidin peptides have little antimicrobial activity when tested in systems alongside cathelicidins with the condition of 10% tryptic soy broth in 10 mM phosphate buffer (pH 7.2) [75]. Thus, Dermcidin peptides appear to be expressed specifically and exclusively in human skin eccrine glands, but the precise functions and molecular mechanisms of dermcidin to kill bacteria remain to be elucidated.

Other antimicrobial proteins/peptides

Defensins, cathelicidins and dermcidin are all true peptides that were first discovered for their action to kill microbes, thus they have been grouped into the functionally defined family called AMPs. However, exploration of the microbial defense mechanisms have revealed antimicrobial activity for many other proteins and peptides that were known first for other functions. These include proteinase inhibitors, chemokines, and neural protein/peptides. Human skin expresses many of these molecules (table 1)

RNase 7 was identified in fractions of human skin extracts, which had antimicrobial activity, and inducible by IL-1 β and IFN-γ in cultured keratinocytes [100]. RNase 7 exhibits broad-spectrum antimicrobial activity against Gram-positive bacteria (*S. aureus*, *Propionibacterium acnes*), Gram-negative bacteria (*Pseudomonas aeruginosa*, *E. coli*) and the yeast *Candida albicans*. RNase 7 has homology to RNase A superfamily and has RNase activity. Other members of RNase A family, such as RNase 2/EDN (eosinophil-derived neurotoxin), RNase 3/ECP (eosinophil-cationic protein), RNase 5/angiogenin (mouse Angiogenin-4), also have antimicrobial activity and would be secreted from infiltrated cells in skin [101-104].

Several groups independently discovered S100A7/psoriasin. It was identified as a low molecular weight protein that is highly expressed in psoriatic skin [105]. S100A7/psoriasin is inducible in keratinocytes by differentiation [106,107]. Psoriasin was also identified as a retinoic acid-inducible skin-specific gene (RIS-1) in human skin [108], and reported as calcium- and zinc- binding protein [106]. Recently, Glaser *et al.* reported S100A7/psoriasin has antimicrobial activity and treatment of human skin by antibodies against S100A7/psoriasin inhibited skin antibacterial activity against *E. coli* [109], suggesting S100A7/psoriasin is one of the innate skin barrier on human skin surface.

Lactoferrin is a member of the transferrin family and involved in iron metabolisim [110,111]. Lactoferrin and lactoferricin, peptides derived from the amino terminus of Lactoferrin, have been shown to have antimicrobial activity against bacteria and viruses [112,113], and appear to be two of the molecules in the innate immune system of neonates. Lactoferrin is detectible in human skin epidermis and can induce Langerhans cell migration [114], suggesting lactoferrin and derivative peptides may play a part in both the innate and adaptive immune system of human skin.

Human epidermis and epidermal keratinocytes express serine protease inhibitors, and these protease inhibitors influence epidermal differentiation. Some of these serine proteases inhibitors also have antimicrobial activity. The secretory leukocyte protease inhibitor (SLPI)/ antiluekoprotease (ALP) is a cationic protein consisting of 107 amino acids [115,116]. SLPI/ ALP inhibits leukocyte-derived proteinases, also has anti- HIV-1 activity [117], antibacterial function against *E. coli and S. aureus* [118], and antifungal properties against *Aspergillus fumigatus* and *Candida albicans* [119]. SLPI/ALP is constitutively expressed in the human epidermis and increased expression was observed in injured and psoriatic epidermis [120]. The

neutrophil elastase inhibitor, elafin/elastase-specific inhibitor (ESI)/skin-derived antileukoprotease (SKALP), was identified in bronchial mucus, and inhibits human neutrophil elastase and proteinase-3 [121]. Elafin/SKALP was independently identified as a human skin elastase inhibitor [122] and secreted from cultured human keratinocytes [123]. Mature elafin/SKALP protein is 57 aa, and is generated by posttranscriptional processing from the carboxyl-terminus of a 95 aa proprotein [123]. Elafin/SKALP has antimicrobial properties against *P. auerginosa* and *S. aureus* [124], and is increased in injured human skin and lesional epidermis of psoriasis patients [125,126]. *In vitro* studies show proinflamatory cytokines TNF-α and IL-1β increased elafin/SKALP secretion from human keratinocytes [127,128]. Inducible and constitutively expressed SLPI/ALP and elafin/SKALP might work as antimicrobial molecules and proteinase inhibitors, which suppress microbial infectivity and modulate inflammatory reactions by proteinases secreted from infiltrating cells.

Antimicrobial protein/peptides in skin diseases

Altered expression of antimicrobial peptide/proteins has been recognized in some skin diseases and appears to play a role in determining susceptibility of patients with skin disorders to pathogens.

Psoriasis

Lesional skin of psoriasis patients increases expression of several antimicrobial molecules. Cathelicidin and hBD-2 mRNA and protein expression were observed to be increased in lesional skin of psoriasis patients [129,130]. In fact, hBD-3, like hBD-2, was first identified in psoriatic scales [28]. HNP-1, -2, and 3 are detectible in psoriasis scale [131], though HNP-1-3 are exclusively produced by neutrophils and expression in human keratinocytes is not clear to date. S100A7 expression is elevated in psoriasis as named “psoriasin” [105]. SKALP/elafin and SLPI/ALP are upregulated in psoriatic epidermis [120,125]. Increased antimicrobial molecule expression might explain the decrease susceptibility of psoriatic patients to infection [132].

Atopic dermatitis

In contrast to psoriatic patients, lesional skin of atopic dermatitis (AD) patients shows less expression of AMPs than would be predicted based on the inflammation and skin damage at this site [130]. Decreased hBD-2 and hBD-3 expression in atopic dermatitis was also observed, and Th-2 cytokines IL-4 and IL-13 suppress hBD-2 and hBD-3 mRNA induction by TNF-α in keratinocytes [130,133]. Howell *et al.* reported elevated IL-10 gene expression in AD skin lesions, and treatment of AD skin explants with anti-IL-10 augmented the expression of both hBD-2 and LL-37 [134]. Reduced amounts of dermcidin expression in sweat from AD patients were also reported [135], as were multiple other AMPs as detected by gene microarray [136]. Decreased expression of these AMPs can explain the increased susceptibility of AD patients to skin infection. Association of single nucleotide polymorphisms (SNPs) in hBD-1 with atopic dermatitis have also been identified, though the biological role of these SNPs are not determined [137,138].

Rosacea

Lesional skin of the rosacea has abnormally high cathelicidin expression [139]. Mass spectrometry analysis of these cathelicidin peptides revealed that rosacea patients process cathelicidin abnormally into forms of peptide that are not found in normal skin. The post-translational processing abnormality of these cathelicidin peptides was due to an increase in stratum corneum tryptic enzyme (SCTE/ kallikrein 5) [66,139]. The significance of these observations was linked to the pathophysiology of this disorder since the peptides found in rosacea, but not those in normal skin, induced cytokine secretion from human keratinocytes

and caused skin inflammation and telangiectacia in mice [139]. Therefore, this convergence of elevated antimicrobial peptide production and excessive enzymatic processing provides an explanation for the constellation of signs and symptoms in patients with this common skin disease. These observations are the first report to show that an abnormality of antimicrobial peptides can exacerbate inflammatory skin diseases.

Severe congenital neutropenia/Kostmann syndrome

Severe congenital neutropenia (SCN; or Kostmann syndrome, morbus Kostman) shows another example of AMP disfunction leading to human disease associated with increased infections. SCN is an autosomal recessive disorder characterized by a maturation arrest of myelopoiesis at the level of promyelocytes [140]. Although the treatment of SCN patients with recombinant human granulocyte colony stimulating factor (G-CSF) leads to a significant increase in circulating neutrophils followed by a clinical improvement, patients still have recurrent infections and periodontal disease. Examination of neutrophils from Kostmann patients revealed a lack of cathelicidin/LL-37 expression and reduced concentrations of α-defensins HNP1-3, although the oxidative burst function of these neutrophils was normal [141]. This indicates proper expression of AMPs is necessary for the antibiotic function of neutrophils.

Skin injury

AMPs were first discovered in skin by the analysis of skin wounds [1]. Cathelicidin is inducible in human epidermal keratinocytes at the wound site [142]. Growth factors that are induced during injury such as TGF-β and INF-γ induce the 1-hydroxylation of 25OH-Vitamin D, thus activating it, and enabling the greatly enhanced expression of several genes involved in the innate immune response including cathelicidin and TLR2 [143]. In addition, other genes such as insulin-like growth factor-1 and transforming growth factor-α can also induce a small increase in cathelicidin, hBD-3, and SLPI/ALP in cultured keratinocytes [144]. Infiltrated neutrophils, which constitutively express cathelicidin and α-defensins, are also a major source of AMPs in skin injury. Cole *et al.* reported an inhibition of neutrophil elastase prevents cathelicidin activation to mature AMPs and increases growth of bacteria in a porcine skin wound chamber assay [145]. The expression of hBD-2 is greatly decreased in the full-thickness burn wounds and burn fluid [146,147]. Subcutaneous injection of Adenovirus vectors expressing human cathelicidin (hCAP18) reduced pseudomonas applied on rat burn wounds [148], and topical application of pig cathelicidin Protegrin-1 in rat burn wounds significantly improved bacterial clearance [149]. These reports suggest that AMP expression in wounds affects skin susceptibility to infection. AMPs not only kill bacteria but also promote wound healing itself. β-defensins hBD-2, -3, and -4 increase human keratinocyte migration and proliferation along with intracellular calcium mobilization and EGFR phosphorylation [150]. In contrast to increased cathelicidin expression in the acute wounds, Heilborn *et al.* demonstrated the absence of cathelicidin expression at the chronic wound stage. They further have shown that neutralizing antibody against LL-37 inhibited re-epithelization of wounded organcultured human skin [151]. α-defensin HNP-1 increased the expression of pro-alpha1 collagen and decreased the expression of matrix metalloproteinase-1 in cultured human fibroblasts, suggesting that HNP-1 promotes extracellular matrix deposition and controls its degradation [152]. Pig cathelicidin peptide PR-39 induces syndecan-1 and -4 in wounds, and these extracellular matrix molecules promote wound healing [1]. Application of LL-37 also promotes angiogenesis through activating FPRL1 (formyl peptide receptor-like 1) on endothelial cells, and mice lacking cathelicidin have decreased vascularization during wound repair [90]. These observations suggest that the induction and activation of AMPs after injury has a dual function, both preventing infection and assisting wound healing.

Viral infection

The cathelicidin antimicrobial peptide LL-37 is induced within the epidermis during the development of condyloma acuminatum and verruca vulgaris [153]. Although the significance of the increased AMP expression in skin viral infection is unclear, some reports suggest a correlation between decreased antimicrobial molecules and viral infections in the skin and keratinocytes. Human and mouse cathelicidin reduces vaccinia virus plaque formation *in vitro* and mice lacking cathelicidin showed more vaccinia pox formation than in control mice [80,154]. Skin from AD patients with eczema herpeticum showed reduced expression of cathelicidin, and cathelicidin deficient mice showed higher levels of HSV-2 replication [154]. Decreased expression of defensins in the skin of AD patients also may explain their susceptibility to HSV infections [46]. These reports suggest patients with AD, which have increased viral infections as manifested by the characteristic clinical symptoms of eczema herpeticum and eczema vaccinatum, may be susceptible due to a deficiency of AMPs in the skin.

Other skin diseases with altered AMP expression

The expression of AMPs are typically increased in association with an inflammatory response, therefore it is not particularly surprising that an increase in AMPs have been reported in several inflammatory skin diseases. Higher amounts of cathelicidin is seen in systemic lupus erythematosus and nickel allergy [70]. LL-37 is increased in the neutrophils, eosinophils, and dendritic cells in the skin of erythema toxicum neonatorum patients [155]. Lesions of acne vulgaris have a marked increase of hBD-2 expression [156], potentially triggered by *Propionibacterium acnes* infection [157]. hBD-2 is also upregulated in superficial folliculitis [158]. hBD-1 ~ -3 mRNA levels were higher in lesional skin of localized scleroderma than unaffected skin and skin from healthy volunteers, and decreased hBD-1 and hBD-2 expression followed ultraviolet A1 phototherapy that resulted in clinical improvement of localized scleroderma [159]. High expression of HNP-3 has been seen in cutaneous T-cell lymphoma patients [160]. Basal cell carcinoma (BCC) tumor showed increased hBD-2 and decreased hBD-1 mRNA expression compared to normal skin [161]. The precise functions of AMPs in these skin diseases remain to be elucidated.

Conclusion

Current accumulated knowledge has revealed that these small peptides, so-called AMPs, have various functions against microbes and host cells. Our primary understanding of these molecules as antimicrobials define them as a part of innate immunity, however, this might be an oversimplification of the function of the AMPs. AMPs affect the host by an incompletely understood mechanism that results in a change in cytokines, cell migration, cell proliferation, cell maturation, and extracellular matrix synthesis. It is reasonable to assume that AMPs act in part as an “alarmin” to participate in danger signals, and in part as a simple antibiotic shield. As AMPs are inducible, not only by microbial infection, but also by tissue injury, they represent a primary defense system of the skin. Also, as some of AMPs function to alter dendritic cell function, the AMPs act as a bridge between innate and acquired immunity, serving at the interface between evolutionarily ancient and modern immune programs. Clinically, the physiological significance of altered expression of many of the AMPs remains to be elucidated. Human skin constitutively expresses low amounts of β-defensins and cathelicidins, and many AMPs increase following infection, inflammation, injury, and epidermal differentiation. As cathelicidin expression in mouse skin modifies susceptibility to microbes, exploring of the function and dynamics of other AMPs in human skin will likely explain other important aspects of the pathology infectious and other skin diseases. The successful therapeutic application of AMPs will be the next challenge, as lack of or decreased AMP expression in atopic dermatitis,

chronic wounds, and skin burns appears at least partially responsible for the susceptibility of these disorders to infection.

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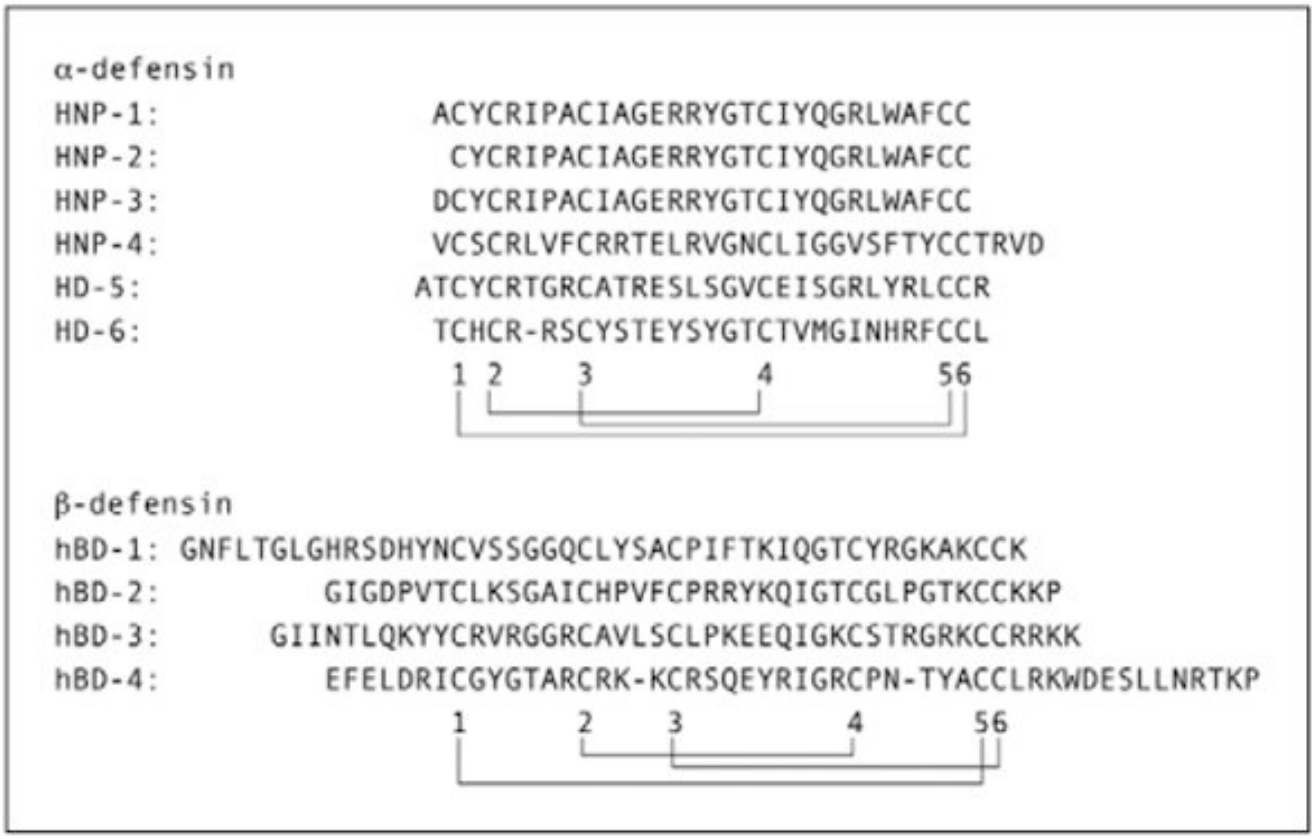

Figure 1. Human defensin peptide sequences

Alignment of the six human α-defensin peptides and four β-defensin peptides. The location of the six cysteins and the disulfide bond connectivity are indicated with digits and lines, respectively.

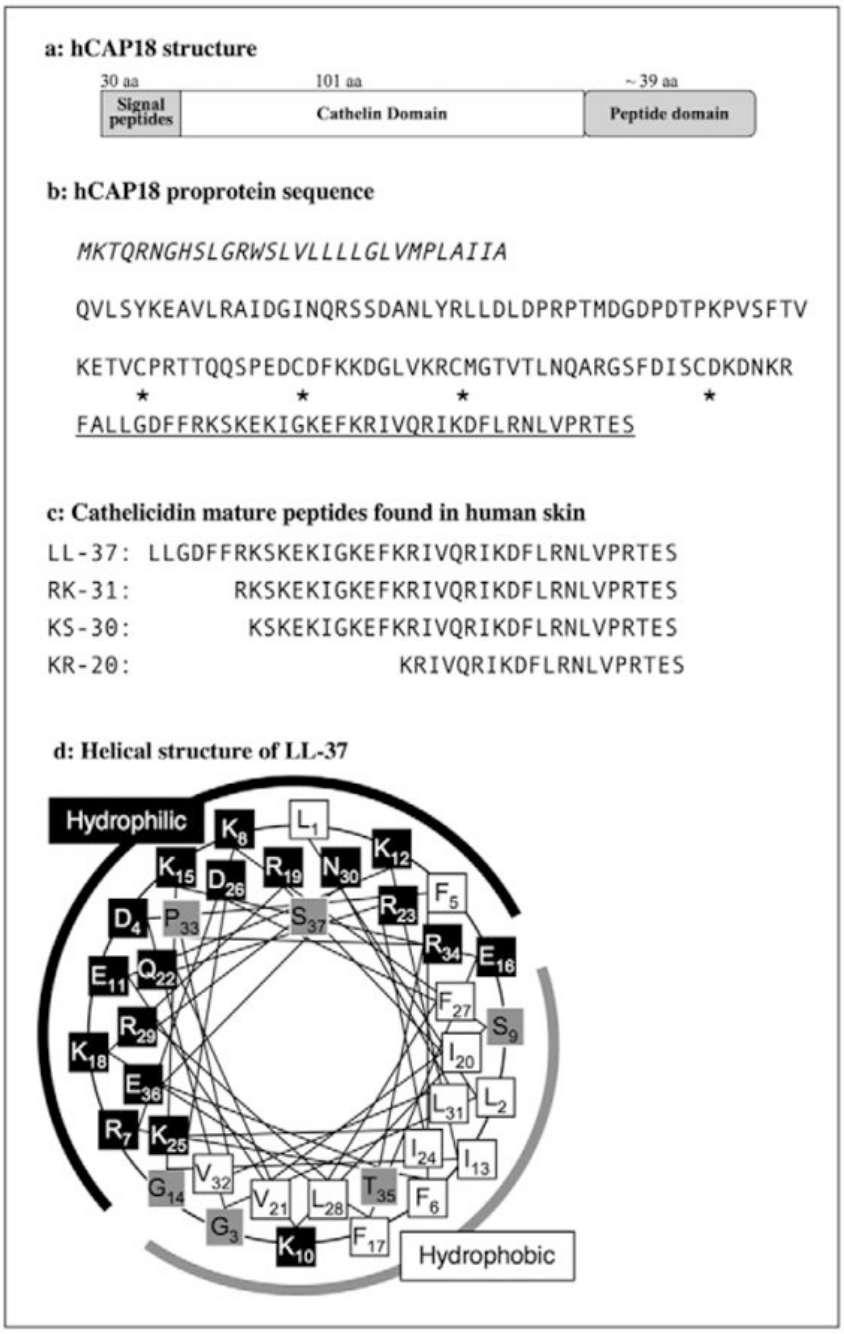

Figure 2. Human cathelicidin hCAP18 proprotein structure and sequence

A) Schematic representation of the hCAP18 proprotein structure. B) Italic characters indicate signal peptide, and mature peptide domain of LL-37 is underlined. Asterisks indicate four cysteins, which are conserved in the cathelicidin proprotein between species and form disulfide bonds in the cathelin domain. Postsecretory processing generates cathelicidin mature peptides although the sizes and sequences of mature peptides are varied and depend on tissues or cell-specific proteases. C) Four representative human skin cathelicidin peptides LL-37, RK-31, KS-30, and KR-20 are listed. *d*: α-helical wheel of LL-37. Black boxes indicate hydrophilic amino acids, white boxes indicate hydrophobic amino acids, and gray boxes are amphiphilic

amino acids [165]. Numeric numbers indicate the order in the peptide. A black line indicates the hydrophilic side and a gray line indicates the hydrophobic side of the peptides.

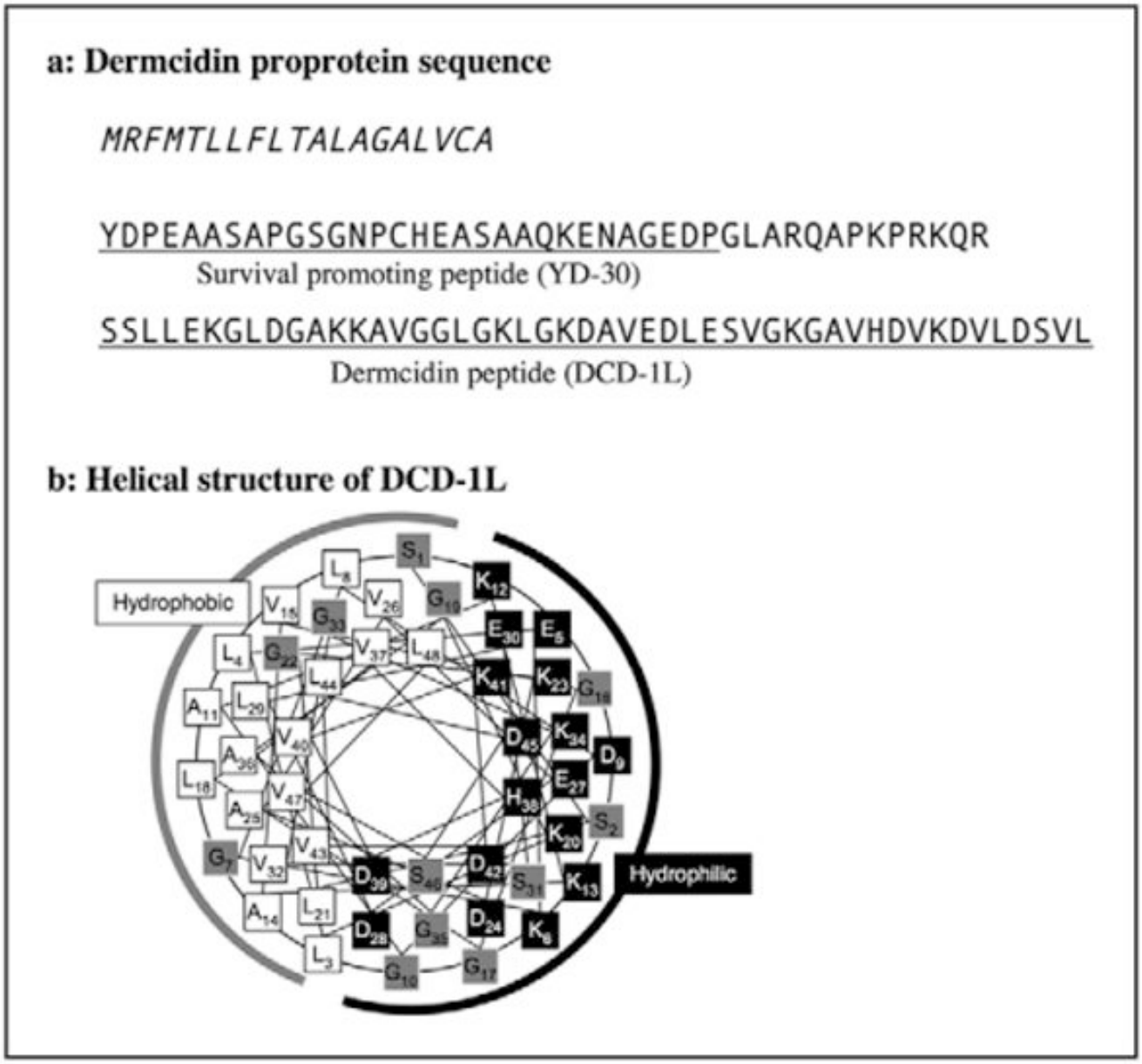

Figure 3. Human Dermcidin amino acid sequence

A) Italic characters indicate the signal peptide, and functional peptide domains are underlined. Dermcidin proprotein generates at least two different peptides; surviving promoting peptide (YD-30) and dermcidin antimicrobial peptide (DCD-1L). B) -helical wheel of DCD-1L. Black boxes indicate hydrophilic amino acids, white boxes indicate hydrophobic amino acids, and gray boxes are amphiphilic amino acids [165]. Numeric numbers indicate the order in the peptide. A black line indicates the hydrophilic side and a gray line indicates the hydrophobic side of the peptides.

Table 1

Antimicrobial molecuels identified in human skin

Skin components/cells	Antimicrobial molecules
Epidermis, hair follicle/keratinocyte	hBD-1 to -4 cathelicidin (LL-37, RK-31, KS-30, KR-20) RNase 7 S100A7/psoriasin lactoferrin/lactoferricin SLPI/ALP elafin/ESI/SKALP α-MSH (meranocyte stimulating hormone) [162,163]
Sweat gland/eccrine cells	cathelicidin (RK-31, KS-30, KR-20) dermcidin hBD-1, 2 [25,164]
Sebaceous gland/sebocyte	hBD-1, 2 [156]
Neutrophils (infiltrated)	α-defensins (HNP 1-4) cathelicidin (LL-37) lactoferrin/lactoferricin elastase
Mast cell	cathelicidin elastase