Antimicrobial peptides: Old Molecules with New Ideas

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Abstract
Almost 90 years have passed since Alexander Fleming discovered the antimicrobial activity of lysozyme, the first natural antibiotic isolated from our body. Since then, various types of molecules with antibiotic activity have been isolated from animals, insects, plants and bacteria, and their use has revolutionised clinical medicine. So far, more than 1200 types of peptides with antimicrobial activity have been isolated from various cells and tissues, and it appears all living organisms employ these antimicrobial peptides (AMPs) in their host defense. In the last decade, innate AMPs produced by mammals have been shown to be essential for the protection of skin and other organs. Their importance is due to their pleiotrophic functions to not only kill microbes but also control host physiological functions such as inflammation, angiogenesis and wound healing. Recent advances in our understanding of the function of AMPs have associated their altered production with various human diseases such as psoriasis, atopic dermatitis and rosacea. In this review, we summarize the history of AMP biology and provide an overview of recent research progress in this field.

AMPs: A diverse group of molecules
The antimicrobial peptides (AMPs) have redefined the way we think about immune defense and human disease. Unfortunately, this name is misleading as the term “antimicrobial” describes more about their history of discovery than the potent influence these molecules have on cell behavior. As such, alternative terms for AMPs have also appeared. These include better descriptive terms such as “host defense peptides”, “alarmins” and even “defensins” (used in a broad context instead of the gene family). However, to appreciate the history of the discovery of these molecules as well their common unifying function to kill microbes, the term AMPs will be used in this review.

Over the last two decades more than 1200 AMPs have been identified or predicted from various organisms. For a partial list of these, see the Antimicrobial Peptide Database (APD: http://aps.unmc.edu/AP/main.php). AMPs in general consist of 10–50 amino acid residues. These peptides lack any specific consensus amino acid sequences that are associated with biological activity, but most of them maintain certain common features, such as containing...
positive charge and relatively hydrophobic and amphipathic structure. Based on their amino acid composition, size and conformational structures, AMPs can be divided into several categories, such as peptides with α-helix structures, peptides with β-sheet structures stabilized by disulfide bridges or peptides with extended or loop structures, reviewed in (Lai and Gallo, 2009). Classic AMPs, such as LL-37 and human β-defensins (hBDs), are amphipathic molecules that possess clusters of positively charged and hydrophobic charged amino acid chains. This amphipathic feature is thought to allow them to interact with negatively charged phospholipid head groups and hydrophobic fatty acid chains of microbial membranes, resulting in pore formation on the microbial membrane and release of cytosol components (Glaser et al., 2005; Wimley, 2010). It is the membrane active nature of the AMPs that likely controls their function, but as we continue to study these molecules we learn that their function is much more than originally expected.

**AMPs: The hot new topic preceded by 90 years of discovery**

Many immunologists consider the study of AMPs as a relatively new topic that led the way towards recognition of our modern understanding of innate immunity. AMPs are a primary effector system that acts with the detection system generated by microbial pattern recognition genes such as the toll-like receptors (TLRs). However, the history of discovery of innate antimicrobials goes back much further in history. Alexander Fleming first recognized the presence of a soluble antimicrobial substance produced by humans about 90 years ago. Fleming observed the bactericidal and bacteriostatic activities of nasal secretions from a patient suffering from acute coryza when he treated bacterial culture plates with this material (Fleming, 1922). He named the activity lysozyme because of its capacity to “lyse” bacterial lawns on a dish. Subsequently, he found lysozyme activity in various human physiological fluids and tissues of animals, as well as egg whites. Such observations indicated to him that lysozyme performed a wide range of functions as a part of our immune system. In 1928, Fleming subsequently discovered that penicillin extracted from the culture of green mold, *Penicillium notatum*, stopped the growth of various bacteria (Fleming, 1929). In the 1940’s, Howard Florey and Ernst Chain brought penicillin’s potential for medical use to fruition. They shared the 1945 Nobel Prize for Medicine along with Fleming for the discovery of penicillin and its therapeutic effects. About forty years after Fleming’s lysozyme discovery, the primary structure of egg white lysozyme was characterized (Canfield, 1963), but by this point the interest in natural host antibiotics had decreased and the importance of this immune defense strategy was all but forgotten.

Antibiotics were also recognized in prokaryotic cells at an early stage in modern medicine. In 1939, René Dubos isolated antimicrobial substances, named gramicidin, from culture supernatant of soil bacteria, *Bacillus brevis*. Gramicidin exhibited bactericidal or bacteriostatic activity against a wide-range of Gram-positive bacteria *in vitro* and *in vivo* (Dubos, 1939a, b). Gramicidin was later shown to be a heterogeneous mixture of six AMPs that was identified as N-formylated polypeptides with alternating L- and D-amino acids (Sarges and Witkop, 1965a, b, c). In addition, application of gramicidin on infected wounds on guinea-pig skin rapidly disinfected pathogenic bacteria and successfully suppressed infection, indicating the therapeutic potential of gramicidin for clinical use (Gause and Brazhnicova, 1944). To our knowledge, gramicidins were the first AMPs for which the
primary structures were characterized and the first antibiotics to be commercially
manufactured. This is available today as an over-the-counter antibiotic.

AMPs are now known to exist in all kingdoms. In contrast to the large size of lysozymes,
relatively small antimicrobial molecules were observed to be induced in the hemolymph of
wax moth larvae after challenging with *Pseudomonas aeruginosa* (Stephens and Marshall,
1962). Remarkably, normal larvae that had received hemolymph from pathogen-challenged
larvae exhibited passive protection against bacterial infection, thus proving these innate
protective molecules were soluble. In 1981, Hans Boman at the Karolinska Institute
pioneered the field of modern innate immunity by seeking to identify the structure of innate
insect antimicrobial defense molecules. Initially, Steiner et al., characterized primary
structures of two AMPs, named cecropins A and B, in hemolymph of the cecropia silk moth,
*Hyalophora cecropia* (Steiner et al., 1981). Later, an AMP was isolated from pig small
intestines which showed a high similarity with the insect cecropins, therefore it was named
cecropin P1 (Lee et al., 1989). However, the research group that discovered the peptide later
corrected their original conclusion and discovered that this peptide in fact originated from
parasite *Ascaris* nematodes (Andersson et al., 2003).

AMPs are also an integral part of the immune systems in plants. In the early 1940’s, Stuart
and Harris demonstrated that a crystalline protein isolated from wheat flour exhibited
antimicrobial effects against some human pathogenic bacteria and yeast (Stuart and Harris,
1942). It was a low molecular weight proteinaceous material with high sulfur content and
defined purothionin (Balls et al., 1942). In the 1990’s, a group of small basic proteins was
isolated from wheat endosperm and characterized as purothionin homologs, so they are
called γ-purothionins (Colilla et al., 1990). However, subsequent study has established that
purothionins and γ-purothionins are structurally unrelated (Bruix et al., 1993). Considering
that γ-purothionins show a high structural analogy with insect defensins, adapting β-sheets
and a single α-helix structures stabilized by an eight cysteine-motif, they are renamed as
plant defensins (Broekaert et al., 1995) (see below for defensins). Transgenic plants over-
expressing AMPs have been explored for decades as a mechanism for disease resistance. For
example, expression of defensins in plants confers enhanced resistance to phytopathogen
attacks (De Coninck et al., 2010; Jha et al., 2009).

The discoveries of defensins and cathelicidins led the way for the emergence of our
appreciation of AMPs in mammals. Arginine-rich cationic peptides possessing potent
antimicrobial activity against both Gram-positive and Gram-negative bacteria were first
identified in the lysosomal fraction of guinea-pig polymorphonuclear leukocytes by mobility
to the cathode (Zeya and Spitznagel, 1963). Selsted et al. characterized primary structures of
the six cationic AMPs purified from rabbit neutrophils and named these defensins (now
classified as α-defensins) (Selsted et al., 1985; Selsted et al., 1984). The research group
subsequently identified three defensins from normal human neutrophils and also
demonstrated that the peptides directly inactivated herpes simplex virus (Ganz et al., 1985).
These defensins have a characteristic six-cysteine motif which forms three intramolecular
disulfide bonds (Cys1–Cys6, Cys2–Cys4 and Cys3–Cys5). Selsted et al. isolated and
characterized 13 AMPs with 38–42 amino acid residues and the six-cysteine motif of
defensin in bovine granulocytes (Selsted et al., 1993). However, these defensin-like AMPs
differed from α-defensins by relatively longer amino acid residues and different disulfide pairings (Cys1–Cys5, Cys2–Cys4 and Cys3–Cys6), therefore they were newly classified as β-defensins. Genomic-based approach have identified 28 human and 43 mouse β-defensin genes (Schutte et al., 2002). Tang et al., characterized an AMP in the leukocytes of rhesus monkey, which consisted of 18 amino acid residues with the six-cysteine motif of defensin, and in which the peptide backbone is naturally cyclized (Tang et al., 1999). This AMP was classified as θ-defensin. Interestingly, θ-defensin mRNA transcripts are present in human bone marrow, spleen, thymus, testis, and skeletal muscle, but a premature stop codon aborts their translation (Nguyen et al., 2003). In addition to the antibacterial activity, defensins also offer effective antiviral and antifungal activities through multiple modes of action. Mammalian defensins exhibit strong viral neutralizing activities by directly interacting with viral envelope proteins (Doss et al., 2009; Hazrati et al., 2006). In addition, α- and θ-defensins directly interact with specific viral receptors on the host cell, antagonizing viral attachment, entry, or intracellular shuttling (Cole et al., 2002; Furci et al., 2007). α-defensins also kill Candida albicans by lysing cells, possibly in a similar way to their antibacterial activity (Lehrer et al., 1985; Patterson-Delafield et al., 1980).

Zanetti et al. cloned a full-length cDNA of Bac5, a proline-rich AMP which had previously been isolated from bovine neutrophils (Frank et al., 1990), from myeloid bone marrow cell mRNA (Zanetti et al., 1993). The region upstream of mature Bac5 peptide was found to share high homology to cathelin (more than 70% identity), an inhibitor of the cysteine proteinase cathepsin L isolated from pig leukocytes (Kopitar et al., 1989). Bovine or porcine leukocytes both contained at least 10 structurally-diverse AMPs composed of 12–100 amino acid residues whose precursor proteins have cathelin-like domains in the N-terminal, therefore these AMPs were named cathelicidins (Zanetti et al., 1995). Interestingly, the number of different cathelicidins varies substantially among species. In contrast to the multiplicity of cathelicidins in bovine and porcine neutrophils, the human and murine neutrophils express only a single cathelicidin gene (CAMP) that encodes an inactive precursor proteins, hCAP18 in human and CRAMP in mouse (Agerberth et al., 1995; Cowland et al., 1995; Gallo et al., 1997). Post-transcriptional processing cleaves out the C-terminal cathelin domain from cathelicidin precursor protein and makes the active AMP. In human, for example, active AMP composed of 37 amino acids beginning with two leucines, named LL-37, is generated from hCAP18 (Zanetti, 2004). hCAP18 is cleaved extracellularly by protease 3 or kallikrein family serine proteases to generate the active LL-37 peptides (Sorensen et al., 2001; Yamasaki et al., 2006). After the cleavage, the N-terminal cathelin domain also exhibits antimicrobial activity (Zaiou et al., 2003). The cathelicidin AMPs generated from CAMP genes found between species show little similarity to each other and are referred to as a group solely because of the similarity of the precursor protein that is predominated by the large cathelin domain. In addition, they are remarkably variable in secondary structures. Many of them adopt an α-helical structure followed or not by a hydrophobic unstructured tail (human LL-37, mouse CRAMP, rabbit CAT-18), while others are proline/arginine-rich (bovine Bac-5 and porcine PR-39), tryptophan rich (bovine indolicidin and porcine tritrpticin), and β-hairpin-like structure (porcine protegrins) (Bulet et al., 2004; Lehrer and Ganz, 2002). The cathelicidins have been cloned not only mammals,
but also fish (Chang et al., 2005; Maier et al., 2008), chicken (van Dijk et al., 2005), snakes (Wang et al., 2008; Zhao et al., 2008) and hagfish (Uzzell et al., 2003).

**AMPs in the skin: Demonstrating Relevance**

As described above, in the early 1990s AMPs were being discovered in a wide range of organisms and cell types. Despite this, we were surprised to discover that AMPs were abundantly present in mammalian skin (Gallo et al., 1994). These observations were first made in pig wounds with the discovery of the porcine cathelicidin PR-39. Following this discovery, Harder et al. described the production of hBD-2 in human skin, lung, uterus and trachea epitheliums, and elevated hBD-2 expression in human keratinocytes exposed to pathogenic bacteria (Harder et al., 1997). Subsequent work from our group and others demonstrated that AMPs are induced in the skin by injury and are abundantly found in some inflammatory processes such as psoriasis (Dorschner et al., 2001; Frohm et al., 1997). The unique inflammatory environment of psoriasis has been subsequently exploited for discovery of multiple AMPs including α- and β-defensins, psoriasin and RNase7 (Harder and Schroder, 2005). A key advance for the field came with the capacity to not only purify and test antimicrobial activity of isolated AMPs, but also to apply modern mouse molecular genetic approaches to evaluation of their function. These studies led the way to revise perceptions of AMPs as evolutionarily ancient molecules that have relatively insignificant roles in organisms that have developed adaptive immune defense systems. The key initial finding was that targeted deletion of cathelicidin proved this AMP was essential to the normal immune response and resistance to bacterial skin infection (Nizet et al., 2001). This critical role for cathelicidin has been now shown in many tissues, mucosa and body fluids, and for a wide range of pathogenic bacteria, several viruses and funguses as well as Leishmania (Doss et al., 2010; Gallo et al., 1997; Gordon et al., 2005; Gutner et al., 2009; Kulkarni et al., 2011). Targeted deletion of other molecules involved in pattern recognition and processing of AMPs have shown similar results (Takeuchi et al., 2000). Although similar in vivo data with defensins have been more difficult to generate due to the extensive gene duplication of the α- and β-defensin gene families, several reports have successfully demonstrated an important roles for defensins in host defense against bacteria and some viruses in vivo. Metalloprotease-7-deficient mice, lacking all mature α-defensins due to the loss of the protease required for proteolytic cleavage, displayed a reduced clearance of bacteria and higher mortality rates upon pathogen challenge (Wilson et al., 1999). Mouse β-defensin-1 knockout mice showed earlier weight loss and higher mortality after influenza virus infection than wild-type mice (Ryan et al., 2011). Conversely, transgenic overexpression and knock-in of AMPs further supported these conclusions by showing that the addition of excess AMPs can increase resistance to some microbes (Lee et al., 2005; Salzman et al., 2003).

Today, cathelicidins and β-defensins are the most well characterized AMPs found in the human skin (Lai and Gallo, 2009; Wiesner and Vilcinskas, 2010). hBD-1 is constitutively expressed in keratinocytes, but exhibits only minor antibiotic killing activity in comparison with other defensins (Yadava et al., 2006; Zaalouk et al., 2004). More recently, the reduced form of hBD-1 has been shown to become a potent antimicrobial peptide, of which reduction is catalyzed by thioredoxin expressed in the epidermis (Schroeder et al., 2011).
This suggests that the redox regulation is crucial for the innate immune protection by hBD-1. The expression levels of hBD-2, hBD-3, and human cathelicidin in keratinocytes are very low at the steady state and typically upregulated during infection, inflammation and wounding (Froy, 2005; Gallo et al., 2002). This suggests that with these AMPs it is the secondary response of increasing expression that serves to limit the severity of clinical symptoms when the primary line of defense (constitutive expression of AMPs) fails. Human keratinocytes also express many molecules that were first discovered for reasons other than action as an AMP, but subsequently found to also inhibit microbial growth. Once example of these are the ribonucleotidases (RNases). Of these, RNases 5 and 7 exhibit antimicrobial activity against many pathogenic microorganisms independent of the RNase activity (Abtin et al., 2009; Huang et al., 2007; Zanger et al., 2009). The antimicrobial activity of those RNases is inhibited by RNase inhibitor protein expressed in epidermal keratinocytes, and, in turn, activated when the RNase inhibitor is cleaved by stratum corneum serine proteases (Abtin et al., 2009). An antimicrobial heterodimeric complex, S100A8/S100A9 (calprotectin), is induced in epidermal keratinocytes during Gram-negative bacteria infection and sensing of bacterial flagellin by TLR5 is critical for the regulation of calprotectin (Abtin et al., 2010). Cathelicidin, hBD-2 and -3 and antimicrobial histone H4 are detected in the cultured human sebocytes, and their expression levels are upregulated in the presence of Gram positive bacteria or sebum free fatty acids (Lee et al., 2009a; Nagy et al., 2006; Nakatsuji et al., 2010). Large amounts of psoriasin antimicrobial peptide accumulate in the epidermis of sebaceous skin as well as sebaceous glands and secreted to the external skin surface (Glaser et al., 2005). Sweat eccrine glands are also known as an important supplier of AMPs to the epidermal surface. Dermcidin is an AMP constitutively expressed as a small precursor protein in eccrine sweat glands and secreted into sweat where active AMPs are proteolytically generated (Schittek et al., 2001).

The skin provides a rapid first-line of immune defense against invading pathogens from outside environments by constitutively and actively producing various AMPs. In human skin, the main cellular sources of AMPs are keratinocytes, mast cells, neutrophils, sebocytes and eccrine epithelial cells (Figure 1). This layered system of deployment functions well because of the dual action of AMPs. First, as we have thus far described, the secretion or release of these peptides provides innate antibiotic-like action against infectious pathogens. However, a key component of the overall defense strategy of skin and other epithelial organs is that alternate defense systems are activated to provide protection in the event that microbes evade the first system. Clearly, microbes are well adapted to develop antimicrobial resistance, and many microbes are human pathogens because they have succeeded in doing this. AMPs such as Cathelicidins and Defensins therefore appear to have maintained their relevance because they also contribute to host defense by triggering inflammatory cell recruitment and cytokine release. This system often involves signaling mediated by pattern recognition receptors such as TLRs or responses to pro-inflammatory cytokines. The AMPs amplify defense by calling for help.

**AMPs and the pathophysiology of human disease**

As a result of the inherent association of AMPs with inflammation, recent evidence indicates that abnormal production of AMPs affects the pathogenesis of diseases such as psoriasis,
rosacea, and atopic dermatitis (Yamasaki and Gallo, 2008). These observations have two important consequences. First, they have further demonstrated the relevance of these evolutionarily ancient genes to human health. Secondly, the role of some AMPs in human disease appears to depend more on the actions of these peptides beyond those as an antibiotic. It is in this context that the alternative terms such as “host defense peptide” or “alarmin” are most appropriate.

Cathelicidins and hBDs were well known to be strongly induced in psoriatic lesions in comparison with normal skin, and this degree of induction mimicked expression expected when normal skin was injured. However, the induction of some AMPs such as cathelicidin and hBD-2 and 3 was found to be lower in atopic dermatitis lesions than expected, despite the presence of skin inflammation (Hata et al., 2010; Lande et al., 2007; Mallbris et al., 2010; Ong et al., 2002). In contrast, RNase7 and psoriasin are induced in atopic dermatitis lesional skin and in this case AMP induction is appropriately upregulated by barrier disruption (Harder et al., 2010). The defective expression of some AMPs in atopic dermatitis has been linked to a higher propensity to Staphylococcus aureus colonization, which is known to play important roles in the exacerbation of the infection and is correlated with its extent and severity of atopic lesions (Miller et al., 2005). Thus, in this situation, a lack of the antimicrobial function of the AMP may lead to disease. An informative contrast to the observations in atopic dermatitis can be made in analysis of the diseases rosacea and psoriasis. Our group showed that an excess of cathelicidin in the form of LL-37 exists in rosacea, and this drives inflammation and abnormal blood vessel growth by mechanisms of cell activation not related to antimicrobial action (Yamasaki et al., 2007). High amounts of LL-37 appear to result from the abnormal function of innate immune pattern recognition by TLRs, and proteases that process hCAP18 (Bensch et al., 1995; Jugeau et al., 2005; Yamasaki et al., 2007; Yamasaki et al., 2010). In psoriasis and systemic lupus erythematosus, the excess presence of LL-37 enables recognition of self-nucleic acids by both plasmacytoid dendritic cells (Lande et al., 2011; Lande et al., 2007) and keratinocytes (Morizane et al., 2011). Thus, under these conditions AMPs may be exacerbating inflammation and contributing to disease by permitting auto-inflammatory signaling. Expression of AMPs is also associated with viral infectious diseases such as mollusca contagiosum (Meyer-Hoffert et al., 2010), condyloma acuminatum, and verruca vulgaris (Conner et al., 2002), as well as autoimmune diseases, such as cutaneous lupus erythematosus (Kreuter et al., 2011).

**Multifunctional roles of AMPs**

As introduced by the proceeding discussion of AMPs in human diseases, these molecules have several important physiological and immunomodulatory functions. Some α- and β-defensins are chemotactic for T lymphocytes, monocytes and immature DCs, and can induce cytokine production by monocytes and epithelial cells (Yang et al., 2004). hBD-2 activates immature dendritic cells through TLR4-dependent mechanisms, inducing a robust Th1 response (Biragyn et al., 2002). Cathelicidin triggers inflammatory cell recruitment and cytokine release through various mechanisms. LL-37 is a potent chemoattractant for mast cells, monocytes, T lymphocytes and neutrophils through activating formyl peptide receptor–like 1 (FPRL1) (De et al., 2000; Niyonsaba et al., 2002). The complex of LL-37
with self-DNA or self-RNA released from dead cells activates dendritic cells by triggering TLR9 or TLR7/8, respectively, leasing productions of proinflammatory cytokines and type-I interferons (Ganguly et al., 2009; Lande et al., 2011; Lande et al., 2007). These immunomodulatory properties of AMPs can contribute to host defense against infections by attracting and activating various immune cells as well as by their direct antimicrobial activity.

LL-37 contributes to cutaneous wound healing by stimulating re-epithelialization (Heilborn et al., 2003). LL-37 also induces neovascularization which is mediated by FPRL1 signaling in endothelial cells, and the cathelicidin-mediated angiogenesis is important for cutaneous wound neovascularization (Koczulla et al., 2003). Furthermore, LL-37 induces proliferation and migration by human endothelial cells (Ramos et al., 2011). In fact, accumulation of cathelicidin has been observed in epidermal wound and blister fluid (Dorschner et al., 2001; Frohm et al., 1996; Gallo et al., 1994).

**The AMPs of our Microbiome**

A surprising recent revelation is that the AMPs that directly contribute to our skin innate immune defense are made not only by our own cells, but also in prokaryotic organisms that inhabit our epidermis. Our group has proposed that the unique peptides phenol-soluble modulin (PSM)γ and PSMδ produced by *Staphylococcus epidermidis* (*S. epidermidis*) could be beneficial to the host and thus serve as additional AMPs on normal skin surface (Cogen et al., 2010b). Although we know today from 16S sequencing approaches that the microbiome of human skin is diverse (Grice et al., 2009), *S. epidermidis* was of high interest because it is the predominant bacteria that can be cultured from healthy human skin, and thus known to thrive on the epidermis (Kloos and Musselwhite, 1975). PSMs caused membrane leakage and membrane perturbation in bacteria as well as classic AMPs such as LL-37 and hBDs, suggesting that these peptides function in a similar mechanistic manner as that of innate cutaneous AMPs. These peptides selectively exhibited bactericidal activity against skin pathogens, such as *Staphylococcus aureus* (*S. aureus*), Group A Streptococcus (GAS) and *Escherichia coli*, whereas they are not active against *S. epidermidis*. Moreover, inoculating PSMs on the mouse skin surface reduced the survival of GAS but not *S. epidermidis*. This selective activity is likely to be an important part of a normal microbial defense strategy against colonization. In addition, PSMs enhance the capacity of bacterial killing activity by human neutrophils by inducing their neutrophil extracellular traps (Cogen et al., 2010a). These lines of discovery are only at the very early stages, and considering the diversity of the human microbiome it is likely that many other microbial AMPs that benefit our immune defense will be discovered.

**Targeting AMPs for therapy**

The important pleiotropic actions of AMPs, the many examples of relevance in animal models, and their associations with human disorders, all point towards this class of molecules as a new target for therapy. In cases where increasing AMP expression would be beneficial, such as when attempting to treat or prevent infectious disease, a simple therapy has shown promise. Vitamin D, long suspected of having health benefits in infectious
diseases such as influenza and tuberculosis, has been shown to be a potent stimulus of AMPs (Beard et al., 2011). Experiments with cultured cells have shown that 1–25-dihydroxyvitamin D3 enhances the expression of cathelicidin and hBD-2 by normal human keratinocytes, resulting in an enhanced antimicrobial function against S. aureus in vitro (Schauber et al., 2008; Wang et al., 2004). Pilot studies have attempted to compensate for the defective expression of AMPs in the skin of patients suffering from atopic dermatitis by administering vitamin D (Hata et al., 2008). Analysis of killing of Mycobacterium tuberculosis by monocytes has shown improvement with vitamin D (Liu et al., 2006). However, most clinical trials have not shown a conclusive association between vitamin D and infections in humans. It is possible that this lack of an ability to observe an association reflects the influence of other variables not yet understood. In psoriasis patients, decreased expression of hBD-2 and hBD-3 were observed in lesional skin following topical administration with calcipotriol, a vitamin D analog, despite increased expression of cathelicidin (Peric et al., 2009). The suppression of AMP expression was accompanied by decreased expression of interleukins-17 and -8 that play important roles to cause psoriatic inflammation. Thus, ameliorating AMP expression is also a novel therapeutic approach for the treatment of skin diseases with disturbed AMP expression such as psoriasis, rosacea or atopic dermatitis.

Conclusions

AMPs have been known for some time, but their discovery in the skin and associations with disease are a relatively recent advance that has opened a new chapter in immunology. AMPs mediate the host innate immune defense through various modes of action. A variety of factors influence AMP expression and function. For example, a recent study from our group demonstrated that a small molecule of <10 kDa secreted from S. epidermidis, the predominant commensal in healthy human skin, increased expression of hBDs in murine skin and human keratinocytes through activation of TLR2 signaling (Lai et al., 2010). Similarly, co-cultivation of differentiated human primary keratinocytes with live S. epidermidis, but not heat-inactivated bacteria, enhanced production of hBD-2, hBD-3 and RNase7. In addition, keratinocytes pre-incubated with S. epidermidis-conditioned media strongly enhanced AMP production induced by S. aureus, suggesting that S. epidermidis sensitizes human keratinocytes toward pathogenic bacteria and amplifies the innate immune response (Wanke et al., 2011). These results suggest that the recognition of Staphylococcal molecules by TLR2 may be involved in the steady-state production of AMPs in keratinocytes and enhances resistance to infection by bacterial, fungal and viral pathogens. Thus, the correlation between AMP expression and commensal microbiota may be very important to maintaining skin homeostasis. Imbalanced skin microflora would alter AMP expression in the skin, which is critical in the pathogenesis of psoriasis, rosacea, and atopic dermatitis. Indeed, many lines of evidence suggest a role for the imbalanced cutaneous microflora with pathogenicity of these disorders (Gallo and Nakatsuji, 2011). Understanding and control of AMPs is an exciting new part of the immunological revolution taking place today.
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Figure 1. The layered antimicrobial peptides of human skin

A representative partial list of AMPs produced by skin-residing cells is shown. The composition, location, timing of expression and post-translational processing of AMPs in the skin are all important variables that enable them to serve a wide range of functions in defense of the skin. These functions are not only limited to action as a natural antibiotic shield but also include the capacity to trigger cell recruitment, growth and differentiation. Numbers in parentheses indicate references. (1), (Ganz et al., 1985; Harder et al., 2001; Johnston et al., 2011); (2), (Frohm et al., 1997); (3), (Harder and Schroder, 2002); (4), (Glaser et al., 2005); (5), (Cumberbatch et al., 2000); (6), (Marchini et al., 2002); (7), (Wingens et al., 1998); (8), (Meyer-Hoffert et al., 2003); (9), (Cutuli et al., 2000; Schauer et al., 1994); (10), (Radek et al., 2008); (11), (Abtin et al., 2010); (12), (Cogen et al., 2010b); (13), (Di Nardo et al., 2003); (14), (Ganz, 2003); (15), (Agerberth et al., 1995; Cowland et al., 1995); (16), (Caccavo et al., 2002); (17), (Belaouaj et al., 2000); (18), (Murakami et al., 2004); (19), (Schittek et al., 2001); (20), (Ali et al., 2001; Oono et al., 2006); (21), (Stenger et al., 1998); (22), (Chronnell et al., 2001; Nagy et al., 2006; Nakatsuji et al., 2010); (23), (Lee et al., 2009b); (24), (Glaser et al., 2005); (25), (Lee et al., 2008).