

MINIREVIEW

Susceptibility to Infectious Diseases Based on Antimicrobial Peptide Production[∇]

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In the last few years, the great impact of antimicrobial peptides on infectious disease susceptibility and natural resistance has been reported. In some cases, susceptibility to diseases is related to antimicrobial peptide polymorphisms and gene copy numbers, but for the vast majority of infectious diseases, these phenomena need to be elucidated. This review is focused on the current knowledge about susceptibility and resistance conferred by genetic variations in antimicrobial peptide expression in infectious diseases.

Antimicrobial peptides (AMPs) are genetically encoded and represent a very important part of the innate immune response (35, 76, 79). In mammals, AMPs are present mainly in phagocytic cells of the immune system for the killing of engulfed or invasive bacteria and in epithelial cells for the prevention of pathogen colonization of host tissue (35). In addition to a direct antimicrobial effect, AMPs possess the ability to modulate the immune response through a variety of mechanisms (48). Although antimicrobial activity is crucial, AMPs also exert immunomodulatory effects, such as chemotaxis, activation of immature dendritic cells, lipopolysaccharide blockage, angiogenesis, and cytokine induction (5, 8, 34, 35, 48, 54, 56, 75–79). Immunomodulatory capabilities could comprise the main action mode of these molecules.

Over the past 2 decades, several families of AMPs have been described as existing in many living organisms. In humans, there are three families of AMPs, including defensins, cathelicidins, and histatins (17, 20, 34). Nevertheless, there are other antimicrobial and immunomodulatory peptides that are not included within these families, such as granulysin, lactoferrin, and hepcidin (56, 61, 76).

Recently, there has been growing interest in the role of these peptides in several inflammatory and infectious diseases. A broad review and a detailed discussion of the potential mechanisms of action of AMPs are beyond the scope of this review. Instead, we will focus on recent observations regarding infectious disease susceptibility associated with genetic and transcriptional variations of AMP production.

AMPs AND INFECTIOUS DISEASES

A number of studies have suggested that a relationship exists between the activation of innate immunity and the pathogenesis of several diseases manifested at different sites throughout the body (Table 1). Several authors have suggested that a

disease's outcome will depend on appropriate AMP production, as will be discussed later. The immune response mounted during primary infection is directly related to inflammation, including recruitment of inflammatory cells by chemokines and production of proinflammatory cytokines and a variety of AMPs. A correct mounting of these responses will determine the outcome of infection, i.e., rejection of infection or establishment of the microorganism.

INFECTIOUS DISEASES OF THE SKIN

There are reports showing the importance of AMPs in infectious diseases of the skin. In atopic dermatitis, viral and bacterial infections perpetuate cutaneous inflammation and complicate successful therapy. AMP expression in patients with atopic dermatitis demonstrates that AMP induction is greatly reduced in lesional skin (47). The diminished antimicrobial barrier that results correlates with the increased susceptibility of these patients to microbial superinfections (22, 23). Patients with atopic dermatitis have a significantly lower production of dermcidin 1 than do healthy subjects (53); dermcidin 1 is a skin AMP that is constitutively produced in sweat glands (61).

Patients with atopic eczema often suffer from *Staphylococcus aureus* skin infections. These patients have a decreased expression of human β -defensin-2 (HBD-2), HBD-3, and the cathelicidin LL-37 (45, 47). Thermal injury results in the removal or destruction of tight junctions and the lack of HBD-2 production by the skin (49). Also, a lack of HBD-2 might contribute to skin infections that subsequently cause sepsis and are frequently fatal.

On a healthy skin surface, LL-37 is normally processed into smaller peptides with enhanced antimicrobial functions but with fewer inflammatory effects (43). Patients with rosacea express abnormally high levels of cathelicidins in the LL-37 peptide form (73). In addition, proteolytically processed forms of cathelicidin found in patients with rosacea are found to be dramatically different from those in healthy individuals, in whom LL-37 is rare and in whom shorter forms predominate. Cathelicidin peptides in patients with rosacea are a result of a posttranslational processing abnormality associated with an in-

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TABLE 1. Diseases associated with AMP production changes

Condition	Changes in AMP ^a	Reference(s)
Atopic dermatitis	↓ LL-37, HBD-2, and dermcidin	22, 23, 47, 53
Atopic eczema	↓ HBD-2, HBD-3, and LL-37	22, 23, 45, 47, 53
Thermal injury	Lack of HBD-2 production	49
Rosacea	↑ LL-37 peptide form	73
Psoriasis	↑ LL-37	21, 32, 47
Infectious diarrhea	↓ α-defensin	28
Crohn's disease	↓ HBD-2 mRNA	15
Diabetes type I	SNPs in HBD-1; ↓ LL-37	26
Oral bacterial infection in morbus Kostmann	↓ LL-37, ↓ human neutrophil peptides	51
Chediak-Higashi syndrome	↓ AMP in neutrophil granules	17
HIV-1 infection risk	DEFB1 polymorphism	41, 62
Tuberculosis	↓ mBD-3 and mBD-4; progressive disease ↑ mBD-3 and HBD-2; latent infection ↑ LL-37 and <i>CAMP</i> ; progressive disease	3, 54, 55, 57, 58

^a ↓, diminished production; ↑, augmented production.

crease in protease activity in the epidermis (73). The central role of cathelicidin is further supported by results in mice with a targeted deletion of the cathelicidin gene, *Cnlp*; in these mice, increased serine protease activity does not induce inflammation. Thus, in patients with rosacea, an excess of AMP and abnormal processing lead to disease.

Another example of a human inflammatory skin disease associated with abnormal AMP expression and activity is psoriasis (21, 47). Cathelicidin is increased in lesional skin in patients with psoriasis (32, 47). Psoriasis is a chronic inflammatory skin disease, and an autoimmune reaction is suspected to play a major role in the course of the disease. The autoantigens triggering inflammation in psoriasis remain unknown. A recent study showed that LL-37 isolated from lesional skin forms complexes with human self-DNA to activate plasmacytoid dendritic cells (pDCs) (32). pDCs do not normally respond to self-DNA, but binding to LL-37 converts DNA into a potent stimulus for pDC activation. Therefore, in this cathelicidin-associated case, the response of an AMP might be normal but critical to the amplification loop that results in disease.

Mature human cathelicidin (LL-37) and mouse cathelicidin (CRAMP) peptides are encoded by orthologous genes (*CAMP* and *Cnlp*, respectively) and have similar α-helical structures, antimicrobial activity spectra, and tissue distribution (75). In mice with cathelicidin gene knockout, an increase in susceptibility to necrotic skin infections caused by group A streptococcus compared with that in wild-type mice has been reported (44). As a whole, the previously mentioned studies suggest the importance of cathelicidin for infectious disease control in skin. In terms of clinical applications in skin infections associated with burn wounds, transient cutaneous adenoviral delivery of the host defense peptide hCAP-18/LL-37 exhibits significant bacterial inhibition that might be a potential adjunct for wound treatment in the near future (9, 25). Skin infection susceptibility based on genetic polymorphisms or copy number of AMP genes is not yet fully studied.

GASTROINTESTINAL INFECTIOUS DISEASES

AMP expression in the gastrointestinal tract is either constitutive or inducible. For example, HBD-1 is expressed constitutively at multiple epithelial sites, including the esophagus,

stomach, and colon, whereas α-defensins are expressed only in the small intestine, mainly in Paneth cells (72). Defensins synthesized in the colon comprise HBD-1, HBD-2, HBD-3, and, in smaller amounts, HBD-4 (14, 46, 71). Cathelicidin is expressed in the stomach and lower small bowel and throughout the colon (71, 72). Nonetheless, no microbial or inflammatory stimulus is identified as being a cathelicidin inducer in the colon.

The healthy intestinal tract is characterized by a sensitive balance of host AMPs and intestinal microbes. This balance is disturbed in Crohn's disease. Owing to insufficient expression of HBD-2, HBD-3, and HBD-4, microbes are able to invade the mucosa, which leads to inflammatory responses (30, 69, 71). A recent study shows that an HBD-2 gene copy number of <4 is associated with diminished mucosal HBD-2 mRNA production, which predisposes an individual to colonic Crohn's disease (15). Because HBD-3 and HBD-4 are encoded on the same gene locus, it is likely that the expression pattern of these other defensins is due to the same mechanism (69). The same group demonstrates that genetic variants of *Wnt* transcription factor TCF-4, which directly controls Paneth cell defensin expression, are associated with small intestinal Crohn's disease (30).

The role of AMPs in gastrointestinal infections is well documented; for example, in some African adults, low α-defensin expression could be associated with a higher risk of infectious diarrhea (28). Interestingly, *Shigella* spp. are able to downregulate or turn off LL-37, HBD-1, HBD-3 and the gene expression of other innate immune molecules during infection (63), presumably by means of the MxiE bacterial regulator, which controls a regulon encompassing a set of virulence plasmid-encoded effectors injected into host cells and regulating innate signaling. The MxiE bacterial regulator is considered responsible for this dedicated regulatory process plasmid DNA, which can turn off several innate immunity molecules and could be an important factor contributing to colonization by second-wave invaders (24). On the other hand but within the same context, *Salmonella enterica* serovar Typhimurium downregulates basal α-defensin and lysozyme expression through the type III secretion system (59). Another research group reports that the protozoan intracellular parasite *Cryptosporidium parvum* develops in epithelial cells and is an important causative agent of

infectious diarrhea in humans and animals; this protozoan downregulates HBD-1 and HBD-2, which leads to disease progression. The mechanisms utilized by *C. parvum* to downregulate defensin expression are unknown (74). These findings suggest that other highly pathogenic microorganisms might use these mechanisms to evade innate immunity and to establish infection. However, to find ways to counterattack these strategies, some research groups are investigating AMP inducers, such as butyrate in the colon (52), vitamin D (37), and other organic molecules in the lung (B. Rivas-Santiago and R. Hernández-Pando, submitted for publication), to prevent microorganisms from turning off the synthesis of AMPs. Likewise, HD-5 overexpression in transgenic mice leads to marked resistance to oral challenge with virulent *S. enterica* serovar Typhimurium (60). The susceptibility of infectious disease viruses to protozoa based on AMP production in the gastrointestinal tract requires further study.

ORAL INFECTIOUS DISEASES

Oral AMPs provide a first line of defense against a wide spectrum of pathogens. Members of the three main AMP families are found in the oral cavity: LL-37, α - and β -defensins, and peptides with an unusually high proportion of specific amino acids, such as histatins (11). The great variation of defensin concentrations in saliva and in oral tissues could be attributed to the organization of their genes and copy number polymorphisms; this probably determines susceptibility to caries among individuals, but further studies are required (11). Single-nucleotide polymorphisms (SNPs) in genes encoding HBD-1 in patients with type 1 diabetes mellitus are correlated with high rates of *Candida albicans* carriage, in contrast to controls without type 1 diabetes mellitus (26). Similarly, in a genetically mediated state termed morbus Kostmann, patients experience frequent oral bacterial infections and severe periodontal disease, which correlate with a deficiency in the production of cathelicidin peptide LL-37 and human neutrophil peptides at the oral level (51). Another clear example of the importance of AMPs is that the concentrations of human neutrophil peptides 1 to 3 in saliva from children with caries are much lower than those in children without caries (11). This interesting finding suggests that normal AMP concentrations can control oral bacteria growth, thus preventing caries; the question of whether this phenomenon occurs during adulthood and its use in caries susceptibility screening need to be studied further. The possible therapeutic use of AMPs in oral disease is reviewed elsewhere (1, 29).

SYSTEMIC INFECTIOUS DISEASES

Chediak-Higashi syndrome is a rare autosomal recessive disorder in which an altered lysosome/granule size is found in all body cells. These patients have recurrent pyogenic infections which can be observed as early as a few weeks after birth and continue through the lifetime of the patient. The most common infections involve the skin and respiratory tract, where pathogens such as beta-hemolytic *Streptococcus*, *Staphylococcus aureus*, *Aspergillus*, and *Candida* are prevalent (70). The defects in resistance to bacterial infections can be attributed to the failure of enlarged vesicles to be moved to the appropriate

site of action (17, 27). Since several AMPs are stored within cellular granules, it is possible that the absence of motility in these granules impedes the AMPs' antimicrobial and immunomodulatory effects, contributing to infectious disease establishment. However the precise role of AMPs in this syndrome needs to be further elucidated.

It has been reported that β -defensins can also block human immunodeficiency virus type 1 (HIV-1) replication in vitro due to the direct antiviral effect or competition for the chemokine receptors that HIV-1 uses to enter the cell (18). Several works relating susceptibility to diseases and polymorphisms in β -defensin genes have been published (36, 39, 50). It appears that HBD-1 overexpression may confer protection against infectious diseases; for instance, there is a significant correlation between the high frequency of an SNP in the 5' untranslated region of the DEFB1 gene in HIV-1-infected mothers and their children and an augmented potential risk of mother-to-child HIV-1 transmission in the different studied cohorts (7, 41). Whether the presence of this SNP would affect the expression of other AMPs or whether similar SNPs are present in the 5' untranslated region of other AMP genes needs to be investigated.

Recently it was reported that the copy number of the gene *DEFB104*, which encodes HBD-4, is significantly lower in HIV-positive subjects than in HIV-exposed, uninfected children, suggesting *DEFB104* as a candidate HIV-protective gene (40).

Although β -defensins are in the spotlight as protective genes in HIV-1 infection, some reports regarding α -defensin have been published. A study of seronegative women who were exposed constantly to HIV-1 demonstrates that their CD8⁺ cells exhibit extensive α -defensin production at both peripheral and mucosal levels. The α -defensin expression level in these seronegative women was 10-fold higher than that of control subjects (66). Likewise, overexpression of α -defensins in breast milk results in a low rate of HIV-1 transmission from mother to infant (31).

Some reports suggest a role of cathelicidins in protection against HIV-1 replication, since agonistic ligation of FPRL-1 by cathelicidins can also induce downregulation of HIV-1 chemokine receptors and reduce susceptibility to HIV-1 infection in vitro (6). However, further investigation is necessary to elucidate whether cathelicidin production alteration could be related to susceptibility to HIV-1.

URINARY TRACT DISEASES

Although susceptibility to infectious diseases based on AMP production in the urinary tract is not yet detailed, there are reviews addressing normal and infection-associated AMP expression (78). The studies described below explored the susceptibility to disease based on AMP production in the urinary tract.

Both defensins and cathelicidins are produced along the human urinary tract. HBD-1 is produced constitutively by collecting ducts, distal tubules, and loops of Henle (68). Mice in which an HBD-1-analogous defensin gene is deleted do not maintain urine sterility; ca. 30% of healthy *Defb*^{-/-} mice had *Staphylococcus* species in bladder urine (42). Another study describes that inducible HBD-2 gene and protein expression

was found in tubulus epithelia with chronic infections but not in normal renal tissue (33). As discussed previously, bacterial contact with urinary tract epithelial cells results in rapid production and secretion of AMPs. Epithelium-derived cathelicidins contribute substantially to protection of the urinary tract against infection, as shown using CRAMP-deficient and neutrophil-depleted mice; these animals experience a higher rate of ascending infection than wild-type animals (10). Upregulated expression of defensins and cathelicidins in renal tubulus epithelia indicates that these AMPs act as antimicrobial host defense mechanisms to counterattack infection. Whether a higher level of expression of these AMPs would confer resistance to infection on certain human individuals or whether the lack of production of these peptides would confer susceptibility to infection on the urinary tract remains elusive.

LUNG INFECTIOUS DISEASES

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by a defect in the CF transmembrane conductance regulator (67). Although lung epithelial cells secrete cationic AMPs and proteins, the majority of endogenous peptides, such as β -defensins and LL-37, are found in low concentrations in the lung and are salt sensitive *in vitro*; therefore, these are presumably ineffective in the high-salt environment created on the apical side of CF epithelial cells (4, 19), thereby leading to bacterial multiplication and subsequent infection. More than 90% of lung infections in patients with CF are caused by *Pseudomonas aeruginosa*, and the majority of these patients subsequently die from lung damage (12). Some researchers propose the use of AMPs to control CF-associated infections (80).

One serious disease that is frequently related to HIV-1 infection is lung tuberculosis. Indeed, this disease causes many deaths worldwide, alone or in coinfection with HIV. To date, no polymorphisms in AMPs related to *Mycobacterium tuberculosis* infection have been reported, nor have genetic markers for susceptibility. The role of AMPs during primary tuberculosis has been explored, showing that these peptides may play a very important role in infection and in resistance to this disease (37, 58, 65). Experimental tuberculosis in mice demonstrates the importance of β -defensins in its control; while tuberculosis-susceptible mice express low levels of β -defensins, resistant mice express high levels of them (57). In the same landmark study (57), human LL-37 exhibited high levels of production during control of *M. tuberculosis* growth in epithelial cells, neutrophils, and alveolar macrophages, suggesting its importance in controlling infection (55). Liu and coworkers reported that Toll-like receptor activation of human macrophages upregulates expression of the vitamin D receptor and vitamin D-1-hydroxylase genes, leading to the induction of the AMP cathelicidin and the killing of intracellular *M. tuberculosis*. The authors also reported that sera from African-American individuals, known to have increased susceptibility to tuberculosis, possess low 25-hydroxy vitamin D and are inefficient in producing cathelicidin mRNA (37). Blocking of cathelicidin mRNA through the use of small interfering RNA in the human *M. tuberculosis*-infected monocytic cell line THP1 leads to exponential growth of mycobacteria (38). Correlating with these data, infection-susceptible mice produce a smaller quantity of

CRAMP than tuberculosis-resistant mice; when susceptible mice are induced to produce large quantities of CRAMP and β -defensins, infection is controlled (Rivas-Santiago and Hernández-Pando, submitted). Granulysin is a cationic, amphipatic, low-molecular-weight peptide which is produced by proteolytic cleavage and located in the granules of natural killer cells and T lymphocytes; in addition, it is considered an AMP, although it is also considered to be more a part of cellular than innate immunity. Granulysin creates cell wall lesions, promotes osmotic lysis of mycobacteria, and reduces growth in a perforin-dependent manner (13, 16, 64). Andersson and colleagues demonstrated that symptomatic chronic tuberculosis is associated with insufficient upregulation of granulysin coexpression in CD8⁺ T cells at the local infection site (2). Overall, these data suggest a certain susceptibility to tuberculosis that is related to AMP production, which might be used in the future as a disease progression marker, as well as an immunomodulator for tuberculosis therapy.

CONCLUDING REMARKS

Susceptibility to infectious diseases has been widely studied to date; however, the relationship between AMPs and infection is not as yet completely explored. In this review, we describe some AMP production deficiency-related diseases, with many of them probably involving genetic polymorphisms or variations in the AMP-codifying gene copy number. These findings suggest the possible use of AMPs to determine an individual's natural susceptibility to certain infectious diseases. Additionally, therapeutic induction of AMP expression might offer an alternative treatment option in the management of infectious diseases.

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