Review Article

Host defense peptides: An insight into the antimicrobial world

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Abstract

A serious challenge to antimicrobial therapies has emerged due to rapid increase in drug-resistant infections creating an urge for the development of alternative therapeutics. Antimicrobial peptides (AMPs) have gained importance because of their broad-spectrum antimicrobial activities and mediator-like functions linking innate and adaptive immune responses. The multidimensional properties of these peptides hold promising potentials as prophylactic and antimicrobial agents. This review discusses various AMPs and their role in combating microorganisms and infections along with its clinical implication.

Keywords: Antimicrobial, inflammation and innate immunity, periodontitis

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Received: 08.07.2016, **Accepted:** 27.04.2018

To make the reader understand the concept of how antimicrobial peptides (AMPs) play a role in the host defense and thereby provide an outlook for the implications of these proteins in therapeutics.

INTRODUCTION

The oral cavity comprises approximately of 700 microorganisms, of which nearly 150–200 species are present in all the individuals.[1] Four hundred bacterial species can be found in periodontal pocket; however, only eight bacterial species have consistently been associated with the development of periodontitis including *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia), Treponema denticola, Fusobacterium nucleatum, Eubacterium nodatum, Prevotella intermedia* and *Prevotella nigrescens*.[2] The innate immune system rich in antimicrobial proteins and peptides initially controls this bacterial microflora.

AMPs are oligopeptides that are biologically active molecules produced by different sources including plants, animals, microorganisms and mammals. In humans, AMPs are widely distributed in saliva, epithelium and neutrophils having a broad range of antimicrobial activity and are effective in immune activation, wound healing and inflammation.[3] AMPs are less toxic and have antimicrobial specificity due to which they kill specific target cells without affecting the host cells; therefore, decreased resistance is developed by target cells against them.[4] They also serve as antitumor agents, contraceptive agents, drug delivery vectors, mitogenic agents and signaling molecules in signal transduction pathways. Approximately 106 human AMPs have been identified to date, of which at least 45 different AMPs are present in human saliva and gingival crevicular fluid (GCF).[5]

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.JOMFP_113_16

How to cite this article: Gupta S, Bhatia G, Sharma A, Saxena S. Host defense peptides: An insight into the antimicrobial world. J Oral Maxillofac Pathol 2018;22:239-44.

MECHANISM OF ACTION

Interactions of AMPs with microbial cell membranes have led to dynamic interchange in their structure and topologies.[6] The primary mechanism for antimicrobial activity of AMPs is the electrostatic interaction of peptides with negatively charged molecules on the membrane. In target cells, AMPs can also exert antimicrobial activity by cell membrane translocation and inhibition of essential cellular processes including nucleic acid synthesis, cell wall synthesis, protein synthesis and enzymatic activities.[7] Based on the mechanism of action, they are broadly categorized into membrane acting peptides, for example, defensin, LL-37, melittin and nonmembrane acting peptides, for example, human neutrophil peptide (hNP)-1, buforin II, pleurocidin and dermaseptin.[8,9] In target cells, the damage of membrane is promoted by AMPs either by the formation of pores, by thinning of membrane or by disruption of lipid bilayer as explained by various models summarized in Table 1.[9-14]

CLASSIFICATION OF ANTIMICROBIAL PEPTIDES

Antimicrobial peptide database (APD) has proposed a three-dimensional structure classification approach.[15] According to the classification, AMP structures are classified into four families: α, β, αβ and non-αβ based on the types of secondary structures. AMPs in the α family consist of α-helical structure. Peptides in the β family are characterized by at least a pair of two β-strands in the structure. The αβ family contains both α and β structures; in contrast, the non-αβ family has neither α nor β structure.

More recently, the APD3 proposed a classification according to the covalent bonding pattern of polypeptide chains.[15] In this, AMPs were divided into four classes. All linear peptides where chemical modifications occur within the same amino acid belonged to the first class (UCLL). In the second class (UCSS), peptides in which one chemical bond is present between the side chains of different amino acids of the polypeptide were included in the study. The peptides in which a chemical bond occurred between the side chain of one residue and backbone of other residue were grouped in Class 3 (UCSB). The fourth class (UCBB) comprised of all peptides with a circular backbone wherein a covalent bond is formed between the N- and C-termini of the polypeptide.[15]

TYPES OF ORAL ANTIMICROBIAL PEPTIDES AND THEIR ROLE IN DISEASE

Defensins

These are innate defense molecules due to their capability of killing all kinds of Gram-positive and negative bacteria, fungi as well as viruses such as herpes simplex.[5] These peptides are short, cationic with low molecular weight and unique, characteristic beta-sheet fold structure which consists of three disulfide bonds among six cysteines. On the basis of their length, location, position of cysteine and folding of peptide chains, human defensins are classified as α-defensins (hNP) and β-defensins.[16]

Alpha-defensins

They are further subclassified into six types, such as hNP-1, hNP-2, hNP-3, hNP-4 and hNP-5 and hNP-6 (paneth cells of intestinal mucosa). In amino acid sequences, the neutrophils secreting them are almost identical except at the N-terminus resulting a change in antimicrobial spectrum of defensins. The hNP-1 or hNP-2 actively destroy *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* as compared to hNP-3 and hNP-4[17] which are active against *Candida albicans*, *E. coli* and *Streptococcus faecalis*.[18] hNP-5 and hNP-6 are not expressed in the oral cavity as they are present in the enteric system.[19]

Polymorphonuclear neutrophils present in the junctional epithelium consist of hNP in the periodontium, hence can be detected in GCF. The most abundant peptide

Table 1: Mechanism of action of antimicrobial peptides

Energy independent uptake mechanisms[9-15]			Energy dependent uptake mechanism[9-15]
Barrel stave model	**Toroidal pore model**	**Carpet model**	**Macropinocytosis**
Peptides insert perpendicularly into the lipid core of target membrane-forming barrels ↓ Transmembrane pores ↓ Leakage of cytoplasmic content ↓ Cell lysis	Peptides insert into the lipid membrane Forces the lipid membrane to bend constantly into the pores ↓ Transmembrane pores get lined by inserted peptides as well as lipid head groups ↓ Depolarization of membrane ↓ Cell death	AMPs cover the membrane like a carpet ↓ When these peptides reach a threshold concentration ↓ Membrane disintegration ↓ Cell lysis	Peptides bind with the membrane ↓ Inward folding of plasma membrane ↓ Vesicle formation (called macropinosomes) ↓ Antimicrobial action

AMP: Antimicrobial peptides

present in saliva is hNP-1-3 (99%).[19] In patients with lichen planus, leukoplakia and squamous cell carcinoma, a higher concentration of salivary hNP-1 is seen.[20,21] Patients having dental caries have low salivary levels of α-defensins (hNP-1, -2 and-3) and are used as caries risk assessment.[22]

Beta-defensins

They are small, cationic peptides having antimicrobial activity that are principally expressed in epithelial cells of various tissues and organs such as gingiva, skin, gastrointestinal tract, respiratory tract and kidney.[1] In the oral cavity, only human beta-defensins (hBD-1, hBD-2 and hBD-3) are expressed.[23] Out of 28 hBD genes, only 4 (hBD 1-4) have been detected in the gingival epithelium.[24] Within the suprabasal layer of normal gingiva, hBD-1 and-2 are localized, and within the basal layer in undifferentiated epithelial cells, hBD-3 peptide is expressed.[25]

During gingivitis, chronic periodontitis and aggressive periodontitis, different patterns of expression for hBD have been suggested. hBD-1 obstructs normal flora from becoming opportunistic and is expressed continuously; on the other hand, hBD-2 and-3 are more effective against almost all pathogens and are induced in response to bacterial lipopolysaccharides (LPS), tumor necrosis factors (TNF-α), pro-inflammatory mediators (interleukins [IL-1 β] and interferons).[26-28] hBD-1 and-2 were detected less frequently in tissue samples from patients with gingivitis as compared to healthy subjects; however, expression of hBD-3 was at similar levels in both. The expression of hBD-2 gene was higher in gingival tissue samples when compared with expression of hBD-1 and-3 and detected more strongly in aggressive periodontitis patients as compared to gingivitis and chronic periodontitis subjects.[29,30] Furthermore, in samples from patients with peri-implantitis, hBD-1 was expressed more strongly than hBD-2.[31]

Histatins

These are cationic peptides with low molecular weight, synthesized by the parotid and submandibular salivary ducts cells in healthy adults at a concentration of 50–425 μg/ml.[32] They are named as histidine-rich proteins, comprising 7–38 amino acid residues in length and have at least 12 histidine residues. These are predominantly antifungal and the three main members are His-1, His-3 and His-5. However, by means of proteolytic cleavage of these members, the other members are generated.[33] Certain functions of histatins are inhibition of growth of *Candida* species, bonding of metal ions in saliva, regulation of oral hemostasis[34] and formation of acquired enamel pellicle due to high affinity for enamel surfaces.[35]

Histatins at physiological concentration (15–30 lM), especially Hst-5, inhibit *Candida* species. The *Candida*cidal activity of Hst M (middle portion of Hst-3) is similar to the full-length molecule indicating the potential future use of short length antifungal peptides for oral ointments.[36] In patients with human immunodeficiency virus (HIV), histatin 5 12-mer P113 (Demegen) appears to be a promising AMP and works as a mouth rinse for oral candidiasis.[1]

Cathelicidins (LL-37)

These belong to the α-helical peptides family, do not have cysteine and are located at the carboxyl terminus of a 15–18 kDa highly conserved cathepsin-L-inhibitor (cathelin)-like domain.[37] Human cationic antimicrobial peptide (hCAP18) is the only cathelicidin that has been found in humans in the oral cavity and respiratory tract.[38] It was demonstrated that saliva, sweat, neutrophils, monocytes and epithelial cells of tongue, buccal and lingual gingival epithelium express LL-37/CAP18.[39]

Functions[40-44]

- It acts as a chemotactic factor for monocytes, neutrophils, mast cells and T-cells
- Potent antimicrobial and antiviral activity against many Gram-negative and positive bacteria, fungi, viruses and parasites
- Neutralizes the activity of LPS by binding with it
- Suppresses the reverse transcriptase activity of HIV-1.

In patients with aggressive and chronic periodontitis, high levels of LL-37 were found.[45] An inherited bone marrow disorder with a severe congenital neutropenia is seen in patients with Kostmann syndrome, as there is a lack of LL-37 in saliva and plasma along with severe periodontal destruction.[46] Treating patients with recombinant granulocyte colony-stimulating factor restores the neutrophil levels, but this result is not similar in higher concentrations of LL-37 and is also associated with recurrence of periodontal infection. On the contrary, restored neutrophil levels with normal plasma concentration of LL-37 are seen in patients who have received bone marrow transplants.[47]

Adrenomedullin

Adrenomedullin is produced from cells of adrenal medulla, kidney, lung as well as epithelial lining of skin, gut and oral cavity[48] when microbes come in contact with epithelial cells. The expression of adrenomedullin gene is upregulated by pro-inflammatory cytokines such as IL-1 and TNF-α.[49]

AMP is present mostly in the GCF and saliva with larger concentrations in whole saliva approximately

55–65 pg/mL. It is effective against both Gram-positive and Gram-negative bacteria of the oral cavity.[50,51] Adrenomedullin is increased in periodontally affected sites as compared to healthy sites.[52]

Statherin

It is a 5.4 kDa basic histadine-rich peptide present in saliva and GCF with antimicrobial properties. In C-terminal peptide, growth of statherin inhibits anaerobic bacteria and prevents plaque formation as crystallization of calcium phosphate is restrained by them.[53] It is used as a biomarker in the proteomic analysis of saliva.[54]

Azurocidin

It is a 37 kDa cationic antimicrobial protein identified by salivary proteomics and is expressed in azurophil granules of neutrophils. Azurocidin is a 251-amino acid protein and consists of two cysteine residues in positions 52 and 68. They have a strong affinity for LPS and therefore exhibit strong antibacterial properties towards Gram-negative bacteria.[55]

C–C motif chemokine 28

It is present mostly in saliva and exhibits both broad-spectral antimicrobial activity and chemotactic activity. This is a 128-amino acid peptide secreted by epithelial cells and salivary glands.[54] C–C motif chemokine 28 is a salt-sensitive peptide and causes an increase in permeability of cell membrane.[56]

Neuropeptides

The neuropeptides, calcitonin gene-related peptide and substance *P* are expressed in GCF,[57] salivary fluids contains neuropeptide Y and vasoactive intestinal peptide.[58] Since the minimum inhibitory concentrations (MIC) required to be effective against *C. Albicans* and bacteria are higher than their concentrations which varies from 2 to 45 pg/ml; therefore, their antimicrobial role is extremely limited.[59]

The site of expression of the explained AMPs along with their MIC for targeted microorganisms is summarized in Table 2.[26-28,59-64]

Table 2: Antimicrobial peptide genes and their dosage for targeted microorganisms

AMP's	Gene	Site of expression	Target	MIC
Adrenomedullin[60]	ADM	Epithelium	*P. gingivalis* *S. mutans* *E. coli*	MIC: 7.75×104 µg/ml MIC: 12.5 µg/ml
[]β defensin-1 hBD-1[26]	DEFB1	Suprabasal layer of stratified epithelium and saliva	*P. gingivalis* *A. actinomycetemcomitans* *F. nucleatum*	MIC: 50 µg/ml MIC: 20 µg/ml
β defensin-4 β-defensin-2 hBD-2[27]	DEFB4A	Gingival epithelium and saliva	*P. gingivalis* *S. mutans*	MIC: 34.6->250 µg/ml MIC: 4-8 µg/ml
β Defensin 103 β-defensin-3 hBD-3[61]	DEFB103A	Skin and salivary gland	*P. gingivalis* *A. Actinomycetemcomitans* *S. mutans* *T. Denticola* *F. nucleatum* *S. sanguinis* *P. intermedia*	MIC: 3-5 µg/ml MIC: 15.7 µg/ml
Cathelicidin (LL-37)[61]	LL-37	Neutrophils, inflamed epithelia, submandibular glands and saliva	*P. gingivalis* *A. actinomycetemcomitans* *S. gordonii* *P. intermedia* *F. nucleatum* *S. sanguinis*	MIC: >125 µg/ml MIC: 37.8 µg/ml
C-C motif chemokine 28[22]	CCL28	Salivary glands and saliva	*S. mutans*	IC50: 1.7 µM
HNP-1 Neutrophil defensin 1[62]	DEFA1	Neutrophils, bone marrow and gingival crevicular fluid	*S. mutans* *P. aeruginosa* *A. actinomycetemcomitans* *P. gingivalis*	MIC: 4.1 µg/ml MICl: 10.3 µg/ml
HNP-2 Neutrophil defensin 2 HNP-3 Neutrophil defensin 3[63]	DEFA1 DEFA3	Neutrophils, bone marrow and gingival crevicular fluid	*P. gingivalis* *A. actinomycetemcomitans*	No activity: (>200 µM) No activity: (>500 µg/ml)
Neuropeptide Y[59]	NPY	Salivary fluid	*P. aeruginosa* *S. mutans*	MIC: 134.3 µg/ml MIC: 210.9 µg/ml
Statherin[64]	STATH	Oral cavity	Oral anaerobes	MIC: <12.5 µg/ml, >100 µg/ml

AMP: Antimicrobial peptides, MIC: Minimum inhibitory concentrations, *P. gingivalis*: *Porphyromonas gingivalis, S. mutans*: *Streptococcus mutans, E. coli*: *Escherichia coli, A. actinomycetemcomitans*: *Aggregatibacter actinomycetemcomitans, F. nucleatum*: *Fusobacterium nucleatum, T. Denticola*: *Treponema denticola, S. sanguinis*: *Streptococcus sanguinis, P. intermedia*: *Prevotella intermedia, P. aeruginosa*: *Pseudomonas aeruginosa*

Advantages of antimicrobial peptides[22]

- Broad-spectrum activity (anti-inflammatory, antibacterial, antiviral and antifungal)
- Rapid onset of killing with potentially low levels of induced resistance.

Disadvantages of Antimicrobial peptides[22]

- Systemic and local toxicity with susceptibility to proteolysis
- Reduced activity based on salt, serum and pH sensitivity
- Sensitization and allergy after repeated application with natural resistance
- Confounding biological functions (e.g., angiogenesis)
- High manufacturing costs.

Future implications of antimicrobial peptides

AMPs have multiple functions including antimicrobial activity, innate immune response and play a key role in cancer biology.[65] Peptides from plants exhibiting antimicrobial activity may also be applied to prevent or treat infectious disease, as an alternative to human AMPs.[66] Potential use of hydroxychavicol, a piper betel leaf extract, as an oral health-care agent has been suggested, due to its inhibitory activity against oral microorganisms. Synthetically generated AMPs may also have a great potential for clinical application in addition to natural peptides.[67] At present, determination whether AMPs should be applied for prevention or treatment of periodontal infections is in primitive stage.[68]

CONCLUSION

AMPs have diverse structural and antimicrobial properties and are one of the most promising future drug candidates for reduction of infections and resistance of microbial drugs. They are potentially applied as drug delivery vectors, signaling molecules, immune modulators, antitumor agents and may also possess other biological activities. Therefore, for clinical development of peptide-based therapeutics, understanding the versatile biological properties of AMPs can be of extreme importance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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