Fathoming the Role of Host Defence Peptides in Periodontal Health and Disease

CN Guruprasad1*, M Bhavani2 and S Ramadevi3

1Associate professor, Department of Periodontology, GDCRI, Bangalore
2Post graduate student, Department of Periodontology, GDCRI, Bangalore
3Post graduate student, Department of Orthodontics, The Oxford Dental College and Hospital, Bangalore

Introduction

The warm and moist environment of the oral cavity acts as a shielding interface between the external and internal environment and is the only area of the body in which hard tissues rupture through the epithelial surface. The tooth structure provides a unique niche suitable for microorganisms to colonize, proliferate and live in harmony as a community, so called Biofilm [1]. The oral epithelium adjacent the tooth is precise to form a seal and attachment around the tooth. This function is challenged by development of bacterial biofilm and the host response to biofilm bacteria and their toxins leading to certain vulnerabilities allied with periodontal disease. Oral epithelial cells counters the microbial challenges from dental plaque by the production of host defence peptides (HDP’s), chemokines and cytokines that boost inflammation and immune response of periodontal tissues. Host defence peptides are diverse group of biologically active molecules with multidimensional properties. Besides their direct antimicrobial function, they have multiple roles as mediators of inflammation with impact on epithelial and inflammatory cells influencing diverse processes such as cytokine release, cell proliferation, angiogenesis, wound healing, chemotaxis, immune induction, and protease-antiprotease balance. In the oral cavity, the HDPs are produced by the salivary glands and the oral epithelium and they are Defensins and Cathelicidin. This mini review summarizes the current understanding of various oral host defence peptides involved in maintaining balance between periodontal health and disease.

Keywords: Host defence peptides; Inflammation; Innate immunity

Antimicrobial action of HDPs

Many mechanisms of action of HDPs against microorganisms have been reported. However, the following mechanisms are most widely accepted. In barrel-stave model, peptides position themselves for binding on the cell membranes, this leads to peptide aggregation and conversion to a bilayer membrane. So, in this way the hydrophobic peptides align with the lipid...
core and hydrophilic peptides form an access pore in the interior part of membrane. The carpet model is described as a disruption of the membrane by the binding of peptides to the outer surface (phospholipids) of cell membrane and forming a prolonged layer or carpet. In the toroidal model, attached peptides start aggregation and force the lipid monolayer to bend incessantly through the pores. In this way the core is lined by both the inserted peptides and the lipid head groups [5].

HDPs not only lyse the bacteria but also neutralize endotoxins, including lipopolysaccharides (LPS) from gram negative bacteria. The cell lytic action of HDPs is definitely important in the phagosomes of leukocytes and in the core of inflammation, e.g., in the periodontal lesion. However, when it comes to the complex and intricate homeostasis between the microbiome and HDPs in the oral cavity, the neutralizing effects of HDPs on bacterial endotoxins may be more important, as it occurs at lower concentrations of HDPs typically associated with health. Also, the HDPs have several additional features like they are chemotactic for leukocytes or are involved in the regulation of cell proliferation, epithelialization, angiogenesis, wound healing, or adaptive immunity [6].

Table 1: Expression sites of Host defence peptides.

| Antimicrobial Peptides | Site of Expression |
|------------------------|--------------------|
| α-Defensins (HNP-1)    | Neutrophils (azurophilic granules), gingival crevicular fluid |
| α-Defensins (HNP-2)    | Neutrophils (azurophilic granules), gingival crevicular fluid |
| α-Defensins (HNP-3)    | Neutrophils (azurophilic granules), gingival crevicular fluid |
| α-Defensins (HNP-4)    | Neutrophils |
| β-Defensins (hBD-1)    | Suprabasal layer of stratified epithelium and saliva |
| β-Defensins (hBD-2)    | Gingival epithelium and saliva |
| β-Defensins (hBD-3)    | Saliva |
| Histatin-1             | Saliva (parotid and submandibular) |
| Histatin-3             | Saliva (parotid and submandibular) |
| Histatin-5             | Saliva (parotid and submandibular) |
| Adrenomedullin         | Epithelium |
| Cathelicidins (LL-37)  | Neutrophils, inflamed epithelia, submandibular glands and saliva |

Defensins

Defensins are short, cationic, low molecular weight (4-5kDa) peptides with 6-8 cysteine residues which form 3-4 intramolecular disulfide bonds. Human defensins are classified as α, β and θ on the basis of their length, location, position of cysteine and folding of peptide chains. These innate defence molecules can kill all kinds of Grampositive and negative bacteria, fungi as well as viruses such as herpes simplex [8].

Alphadefensins are further subclassified into six types, four of the six α-defensins, human neutrophil peptide -1, -2, -3, and -4, are synthesized and stored in neutrophil granules. These neutrophils are nearly identical in amino acid sequences, but the N-terminus of hNP-1 ends with alanine (Ala) and aspartate (Asp) for hNP-3. These changes affect defensin antimicrobial spectrum. In a healthy human, hNP-1 to 3 is most abundantly present in saliva (around 99%). The levels of hNP-4 are roughly 100 folds lower. The hNP1 or hNP2 actively destroy Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli as compared to hNP3 and hNP4 which are active against Candida albicans, E. coli and Streptococcus faecalis [5,9].

In the β-defensin subfamily only hBD -1, -2 and -3 are substantially expressed in the oral cavity. HBD-1 and hBD-2 peptides are localized in differentiated epithelial cells inside the suprabasal layers of standard gingival epithelium, whereas hBD-3 peptide is expressed in undifferentiated epithelial cells within the basal layer, signifying a potential role for hBD-3 as

HDPs in periodontium

Natural innate environment of the host, the oral epithelium, polymorph nuclear leukocytes (neutrophils) and saliva, all concurrently and solitarily bestow to the biofilm bacteria by production of HDPs. This involves several salivary antimicrobial peptides, the β-defensins manifested in the epithelium, the α-defensins expressed in neutrophils, and the Cathelicidin, LL-37, in both epithelium and neutrophils [7]. The oral epithelium is highly specific, and the AMP expression of anti-microbial proteins is differentially regulated by different periodontal pathogens suggesting that a specific antimicrobial “cocktail” constitutes the physiological response to individual pathogens. The gingival sulcus has a challenging mission-to maintain the epithelial barrier around the tooth, which penetrates the mucosa. To hinder the down-growth of bacteria and to sustain the junctional epithelial barrier there is a high presence of AMPs in the sulcus, due to the high inflammatory activity, even at clinically healthy sites. The high bacterial load in sulcus in itself also induces AMP-expression through toll-like receptor (TLR) and nucleotide oligomerization domain (NOD) signalling, causing a feedback loop [5] (Table 1).
a mediator to signal the underlying connective tissue cells [2].
hBD1 obstructs normal flora from becoming opportunistic and is
expressed continuously; on the other hand, hBD2 and hBD3 are more
effective against almost all pathogens and are induced in response
to bacterial lipopolysaccharides (LPS), tumor necrosis factors
(TNFα), proinflammatory mediators (interleukins 1-β [IL1 β] and
interferons [8]).

Cathelicidins (LL37)

These belong to the defensin peptides family, do not have
cysteine and are located at the carboxyl terminus of a 15-18kDa
highly conserved cathepsinLinhbitor (cathelein)like domain [7]. It
is a multifunctional peptide, comprising of 37 amino acids. Active
against gram positive and gram negative bacteria's, it directly
binds to the LPS of bacterial cells. By activating antigen-presenting
cells, it presents as a hemoattractant for immune cells, including
monocytes, T cells, etc. There is a specific correlation amongst
multiplication in LL37 levels and periodontal inflammation. Their
mode of action involves intracellular killing of the phagosomes
after phagocytosis of the bacteria, where the AMP in the neutrophil
is severed into a fully developed peptide.

Histatins

Histatins are a family of salivary proteins with low molecular
weight cationic peptides synthesized by the parotid and
submandibular salivary ducts cells at around 50-425μg/ml in
healthy adults. Histamine 1, 3 and 5 are found to be predominant
of the total histatin proteins (85%) in the saliva. They have a major role
in fungicidal activity, having a noteworthy role in oral candidiasis
restraint, especially histatin-5, which also has bactericidal activities
against Porphyromonas gingivalis and Streptococcus mutans [8,10].

Adrenomedullin

Adrenomedullin is a cationic amphipathic peptide with one
disulfide bond. This HDP is present mostly in the GCF and saliva with
larger concentrations in whole saliva approximately 55-65pg/mL. It is effective against both Grampositive and Gramnegative bacteria
of the oral cavity. Adrenomedullin is increased in periodontally
affected sites as compared to healthy sites [10].

Statherin

Statherin is a 5.4kDa peptide belonging to the histatin/
statherin family present in GCF and saliva. This HDP hinders the
growth of anaerobic bacteria isolated from the oral cavity and also
restrains the crystallization of calcium phosphate thus preventing
plaque formation.

Azurocidin

It is a 37kDa cationic antimicrobial protein 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 Gramnegative bacteria.

C-C motif chemokine 28

This is a 128-amino acid peptide, which is principally expressed
in a variety of epithelial cells, and salivary glands. C-C motif
chemokine acts both as a broad-spectral antimicrobial agent and
as chemokine [5,11].

Conclusion

HDPs are diverse structural molecules exhibiting
immunomodulatory activities including modulating pro and anti-
flammatory responses, enhancing chemoattraction, killing of
extracellular and intracellular bacteria, promoting cellular
differentiation, activating the innate and adaptive compartments,
promoting wound-healing. AMPs amalgamate with other
immunomodulatory proteins and maintain inflammatory molecules
and pathways. These peptides are peculiar in keeping the level
of bacteria in control, having distinctive as well as dual roles in
maintaining oral health.

References

1. Krisanaprakornkit S, Khongkhunthian S (2010) The role of antimicrobial
peptides in periodontal disease (Part I): An overview of human defenses and
cathelicidins. Thai J Periodontol 1: 33-44.
2. Mishra A, Apeksha B, Koppolu P, Lingam SA (2015) Role of antimicrobial
peptides in periodontal innate defense mechanism. Journal of Oral
Research and Review 7(2): 74-76.
3. Mansour SC, Pena OM, Hancock RE (2014) Host defense peptides: front-
line immunomodulators. Trends Immunol 35(9): 443-450.
4. Gorr SIU, Abdolhosseini M (2011) Antimicrobial peptides and periodontal
disease. Journal of Clinical Periodontology 38 Suppl 11: 126-141.
5. Khurshid Z, Naseem M, Sheikh Z, Najeeb S, Shahab S, et al. (2016) Oral
antimicrobial peptides: Types and role in the oral cavity. Saudi Pharm J
24(S): 515-524.
6. Jönsson D (2018) Antimicrobial peptides: Roles in periodontal health
and disease. Pathogenesis of Periodontal Diseases, pp: 97-110.
7. Ved V, Fernandes G (2017) Anti-microbial peptides and their speculative
role in periodontitis. Biomedical Journal of Scientific & Technical
Research 6(1): 1802-1807.
8. Gupta S, Bhatia G, Sharma A, Saxena S (2018) Host defense peptides: An
insight into the antimicrobial world. J Oral Maxillofac Pathol 22(2):
239-244.
9. Bulet P, Stöcklin R, Menin L (2004) Anti-microbial peptides: from
invertebrates to vertebrates. Immunol Rev 198: 169-184.
10. Mallappagada S, Wadhwa A, Agrawal P (2017) Antimicrobial peptides:
The miraculous biological molecules. J Indian Soc Periodontol 21(6):
434-438.
11. Wiesner J, Vilcinskas A (2010) Antimicrobial peptides: the ancient arm
of the human immune system. Virulence 1(5): 440-464.

For possible submissions Click below: