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Profound Study for Functions of Antimicrobial Peptides in Prevention of Oral Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Author MYK designed the study, wrote the protocol and analyses of the study performed. Author MSA wrote the first draft of the manuscript. Author GA managed the literature search. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Antimicrobial peptides (AMPs) have a widespread distribution in human body and have antimicrobial activity against microorganisms with wide-range class of host-defense molecules. These are small cationic peptides that play an important role in the development of innate immunity with activity against gram-positive and negative bacteria, parasites, fungi and some viruses.

In the oral cavity, the AMPs are produced by the salivary glands and the oral epithelium and serve as defensive purposes. At least forty-five identifiable antimicrobial gene products found in saliva are secreted from oral epithelial cells, salivary glands and neutrophils. AMPs also serve as effective biological molecules in immune response activation, inflammation and wound healing

The aim of this review was to discuss the types and functions of oral AMPs and their role in combating microorganisms and infections in the oral cavity.

AMPs have a promising potential to be used against oral microbes in order to control their growth and biofilm formation. There are many challenges that need to be overcome in order to design and synthesize AMPs that have the ability to with stand the unique and harsh oral environment. AMPs are expected in the future to be used as models for developing effective oral microbial antibiotics.

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1. INTRODUCTION

The oral cavity, the gateway for both the gastrointestinal and respiratory tracts, is composed of a unique anatomical structure, represented by the soft and hard tissues. The open entry allows for constant exposure to the microbes, many of which are commensal, that could colonize and lead to oral disease.

In order to provide an efficient defense, the oral cavity is supplied with various defense mechanisms against invading microbial pathogens: nonspecific barriers, innate immunity and adaptive immunity.

The nonspecific barriers in oral cavity are represented by saliva as chemical and mechanical barriers and by oral epithelium as a physical barrier. Saliva acts as a potent line of defense because of its antimicrobial effect. The flow of saliva has a mechanical effect, flushing microorganisms from mucosal and tooth surfaces, while a neutral pH and antimicrobial peptides in saliva contribute to the chemical shield on the surface of the oral mucosa, the intact stratified squamous epithelium presents a physical barrier [1,2].

The innate immunity is the mainstay of oral cavity protection, which is provided by innate immune cells in oral cavity such as epithelial barriers, phagocytes and by secreting of several classes of molecules known as antimicrobial peptides (AMP), or as host defense peptides (HDPs).

Antimicrobial activity of saliva is a key component of the innate host defence against infection in the mouth. The saliva contains many molecular elements which restrict microbial growth: for example lysozyme cleaves bacterial cell walls, lactoferrin complexes iron ions which are an essential microbial nutrient, salivary amylase, cystatins, prolin-rich proteins, mucins, peroxidases, AMPs such as defensins, cathelicidins, and histatins (and others), are primarily responsible for innate immunity which forms oral antimicrobial barrier [3].

In other hand, secretary IgA (sIgA) antibodies and lymphocytes are the fundamental adaptive immune defense in oral cavity. Salivary antibodies act in the mucus layer on the epithelial surfaces by performing immune exclusion of antigens in the saliva [4] and in the acquired pellicle on the tooth surfaces. They are constitutively excreted into the saliva. There are two major antibody classes in human saliva, namely secretory IgA (sIgA) and IgG [3].

2. EXPRESSION OF ANTIMICROBIAL PEPTIDES (AMPS) IN ORAL CAVITY

In the oral cavity, it has been recognized more than forty-five AMPs, which are secreted by oral epithelial cells, salivary glands and phagocytes [1]. Most AMPs exist in saliva and in gingival crevicular fluid. Thirteen from these AMPs are up-regulated in periodontal disease while 11 are down-regulated [5,6]. Subsets of these AMPs are more concentrated in the crevicular fluid than in saliva [7,8].

Existing of AMPs in saliva [9,10] and in crevicular fluid [11,12] suggesting that they play a role in the maintenance of microbial homeostasis.

AMPs are synthesized as precursors that are proteolytically activated and released during inflammation [13-15]. They are localized in different sites in oral cavity (Table 1). These AMPs have synergistic effects, and their presence in saliva may provide natural antimicrobial barrier [16].

Chung et al. [17] suggested that there may be complex regulatory mechanisms involved in gingival innate immunity to produce AMPs, and further suggest that AMPs play a crucial role in the maintenance of gingival health and prevention of periodontal disease.

3. THE MAIN MAJOR FAMILLY OF AMPS ARE DEFENSINS, CATHELICIDINS, AND HISTATINS

3.1 Defensins

Human defensins are classified as α, β and θ on the basis of their length, location, position of cysteine and folding of peptide chains [10,18].

Defensins are extensively studied due to their wide expression in human body and the capability to kill all kind of gram-positive and negative bacteria, fungi as well as viruses such as herpes simplex [19-21].

Table 1. Antimicrobial peptides expressed in the oral cavity-Saliva

Antimicrobial peptide	Site of expression	Role	Salivary concentration (mg L^{-1})	References
Defensin HNP1-4	Neutrophils Gingival sulcus Inflammation site Salivary duct cells	Antibacterial Antifungal Antiviral	HNP 1 : 20.0 HNP 2 : 0.6	Goebel et al. (2000) Tao et al. (2005) Raj et al. (2000) Zhang et al. (2002)
Defensin HβD 1-3	Epithelia Salivary duct cells	Antibacterial Antifungal Antiviral Active part protective barrier	HβD 1 : 0.5 HβD 2 : 0.5 HβD 3 : 0.3	Tanida et al. (2003) Tao et al. (2005) Joly et al. (2004) Maisetta et al.(2003)
Histatin Histatin 5 Histatin 8	Neutrophils Gingival sulcus Salivary duct cells	Antifungal	 His 5 : 15.3 His 8 : 20.0	Castagnola et al.(2001) Oppenheim et al.(1988)
Cathelicidin LL 37	Neutrophils Gingival sulcus Salivary duct cells	Primarily antibacterial	LL 37 : 3.1	Tao et al. 2005) Tanaka et al.(2000) Ouhara et al.(2005)

3.1.1 Alpha-defensins

In humans, they are expressed in neutrophils as part of their non-oxidative antimicrobial mechanisms [22]. Six different human alpha defensins have been identified [23].

During gingivitis, neutrophils dominate the lesion area, but the relative proportion compared to plasma cells and lymphocytes in neutrophils decreases during the transition to periodontitis [24,25]. Disorders in neutrophil production have been associated with destruction of periodontal tissue and eventual periodontal disease [26].

It has been observed an increase in human neutrophil peptides (HNP) levels in the saliva in oral diseases [27]. However, variability in levels of HNP in gingival crevicular fluid in both healthy persons and those with periodontitis [28] suggests that they may be regulated by pathogens that affect neutrophil migration and function, such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans.

3.1.2 Beta-defensins

The human beta-defensins (hBDs) are small cationic antimicrobial peptides made primarily by epithelial cells and expressed in all human epithelia [29]. Four different human β-defensins (hBD1-4) have been identified and they are all expressed in epithelial cells as well as certain cell types of the myeloid lineage (Phagocytes) [30].

Beta-defensins 1 and 2 (hBD-1 and hBD-2) are found in normal, uninflamed gingival tissues as part of the innate host defense mechanism [31,32]. Furthermore, hBD-1 and hBD-2 are localized at the gingival margin where there is the most exposure to oral bacteria of the plaque on the tooth surface, but not in the junctional epithelium. Thus, the junctional epithelium is protected by alpha-defensins and LL-37 released from neutrophils, while the differentiated, stratified epithelia are protected by beta-defensins (Fig. 1) [32].

In addition, a recent study revealed that the expression of hBD-3 in response to another periodontal pathogen *T. denticola* is regulated via (Toll like receptor 2) TLR2. All these studies strongly suggest gingival epithelia are able to sense microbes, distinguish between commensal and periopathogenic bacteria, and regulate the appropriate responses for inflammation via regulation of AMPs [33].

3.2 Cathelicidins

The sole human cathelicidin, LL-37, the only member in human cathelicidin family, found at the C-terminus of the human cationic antimicrobial protein 18 (hCAP-18) encoded by the cathelicidin antimicrobial peptide gene (CAMP) [34,35].

Cathelicidin is detected and expressed in higher amounts within neutrophils that migrate through the junctional epithelium to the gingival sulcus [32]. The expression of LL-37 is detected in wide range of epithelia and other body sites, including junctional epithelium, inflamed epidermal keratinocytes, tongue, buccal mucosa and saliva following inflammatory stimulation [36-38]. LL-37

has broad-spectrum activity similar to that of defensins, against both Gram-positive and Gram-negative bacteria, as well as Candida albicans [34].

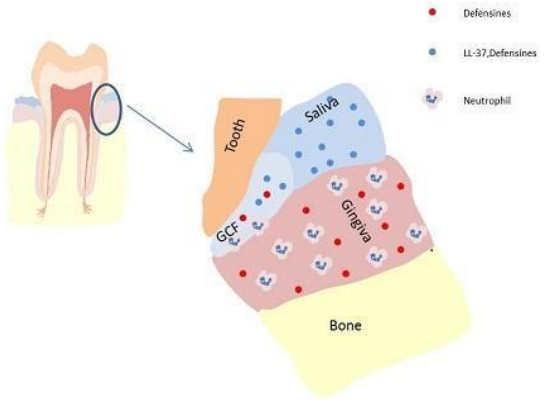

Fig. 1. AMPs in gingival crevicular fluid

3.3 Histatins

Histatins are a salivary proteins,they are a family of histidine-rich, α-helical antimicrobial peptides with low molecular weight cationic peptides mainly found in human parotid salivary secretions (the parotid and submandibular salivary ducts cells) [39,40].

Histatins are predominantly antifungal and comprise of three main members (His- 1, His-3 and His-5) [41,42].Along with the capability of inhibiting the growth of Candida species, they have other functions such as regulating oral hemostasis [43,44].

4. FUNCTIONS OF AMPS IN ORAL CAVITY

4.1 Antibacterial Activity

The major oral antimicrobial peptides families cathelicidin, defensins and Histatins are principally involved in prevention overgrowth of microbes and maintain harmless and stable ecosystem in oral cavity [45].

AMPs have showed a variable antibacterial activity in the oral cavity. That is illustrated by several studies, for example, human β-defensins has greater activity against aerobic species compared with anaerobic species [46]. Furthermore, periodontopathogenic bacteria are more resistant to both LL-37 and hBD3 than were non-pathogenic bacteria [47]. hBD-3 in oral cavity showed, that a wide range of oral bacteria is susceptible to its antibacterial activity, including periodontal pathogens *A. actinomycetemcomitans* and *P. gingivalis*, and cariogenic bacteria *Streptococcus mutans* [48].

LL-37 has shown antimicrobial activities against periodontal pathogen *A. actinomycetemcomitans* [49], while is ineffective against some cariogenic bacteria, including *Streptococcus. mutans, Streptococcus sobrinus* and *Actinomyces viscosus*, as well as periodontal pathogen *P. gingivalis* [50].

4.2 Antiviral Activity

Antiviral activity of defensins was reviewed by Klotman and Chang, they showed the role of defensins as antiviral [51].

Chong KT, et al. [52] study showed that a high level of gene expression of hBD-1, -2, and -3 was detected in papilloma virus-induced epithelial lesions compared with normal oral epithelial cells.

Viruses could be neutralized by defensins in different ways: Direct and indirect. Direct antiviral activity of defensins against human immunodeficiency virus (HIV) in vitro is demonstrated by several studies [53-55].

Indirect antiviral activity of human α-defensins HNP 1-3 has been shown through their activity against human papilloma virus by blocking viral escape from endocytotic vesicles, but not by viral binding and internalization [56]. Also indirect antiviral activity of hBD-2 and hBD-3 is found through their ability to modulate HIV entry into T-lymphocytes [57].

The antimicrobial LL-37 has also been demonstrated to inhibit HIV replication, although the mechanism is not known [58].

4.3 Antifungal Activity

It has been mentioned by Lehrer and Ganz that hBD 1-4 show antifungal activity [59]. Histatins have a potent activity primarily against fungi, including both forms of *Candida albicans* [9].

4.4 A Potent Wound Healing Peptide

In addition to their role played as antimicrobials, AMPs also serve as effective biological

molecules in immune activation, inflammation and wound healing [60,61]. Histatins stimulate of wound healing in the mouth [62].

4.5 Other Immune Functions

In addition to their direct antimicrobial activity, AMPs has numerous other biological activities [60].

4.5.1 Chemotactic activity

AMPs have a selective chemotactic activity for a variety of immune cells. Specifically, HNP1-3 and hBD1-3 are chemotactic for immature dendritic cells [63]. LL-37 demonstrates chemotactic activity for neutrophils, monocytes, and some T-cells [63] and induces IL-8 secretion from epithelial cell lines [64].

4.5.2 AMPs stimulate the acquired immune system and initiate link between innate and adaptive immunity

AMPs stimulate the acquired immune system and could function to enhance IgA production as well as IgG production. Furthermore, LL-37 affects dendritic cell (DC) maturation, and can act synergistically with the DC-maturation cytokine GM-CSF to activate signal transduction pathways in monocytes [65]. These multiple activities of LL-37 suggest that it plays an important, multifunctional role in host defense.

5. ROLE OF AMPS IN ORAL DISEASES

Oral disorders caused by microbes are very common, in particular dental caries, periodontitis and halitosis.

5.1 Dental Caries

It cannot be determined if the level of salivary alpha-defensin is predictive of future caries, but it has been shown that children with caries have significantly lower levels of alpha-defensins based on their concentration in saliva. This is important because of the need for new approaches for caries risk assessment in young children, when preventive measures are likely to have the greatest impact. Tao et al. [16] observed an association between lower levels of salivary α-defensins HNP1-3 and the presence of dental caries. The role of LL-37 in oral immune competency has been investigated, and high LL-37 levels in saliva have been correlated with resistance to caries. LL-37 is present in gingival crevicular fluid, where it may contribute as a marker for oral health status.

5.2 Morbus Kostmann Syndrome (MK)

Morbus Kostmann syndrome is an inherited disorder that causes lower than normal levels of neutrophils, have been found to be more susceptible to periodontal disease [66]. MK is associated with a complete absence of LL-37 and lower concentrations of HNP1-3 in saliva, and is characterized by chronic periodontitis and overgrowth with *A. actinomycetemcomitans* [66]. However, when these patients receive a bone marrow transplant, normal concentration of LL-37 is found in their saliva [66].

5.3 Papillon-Lefèvre Syndrome

Papillon-Lefèvre Syndrome demonstrate a deficiency in LL-37 and exhibit severe periodontitis. This may be due to a deficiency in the serine proteinases that process hCAP-18 to the mature, active LL-37 peptide [67]. Together, these studies suggest a role for LL-37 in the natural defense against colonization by periodontal pathogens.

5.4 Periodontal Disease

The antimicrobial peptide LL-37, a component of innate immunity, has an important role in maintaining oral health. This study aimed to investigate the concentration of free LL-37 in whole saliva of periodontally healthy, edentulous and chronic periodontitis subjects.

The present findings show that edentulism correlates with a substantial decrease in salivary levels of free LL-37, thus indicating the considerable contribution of the gingival tissues in the secretion of the peptide in the oral environment [68].

Gingival tissue samples from chronic periodontitis patients showed elevated mRNA expression of LL-37 and higher immunostaining on neutrophils, while the LL-37 levels were also elevated in the GCF of periodontitis patients [69].

5.5 Oral Candidiasis

Histatins clearly demonstrate potential as novel agents against oral candidiasis [70].

5.6 Oral Lichen Planus

Limited knowledge exists on its role in oral diseases and oral lichen planus (OLP) in particular. Salivary concentration of LL-37 correlates to the manifestation of mucosa lesions in OLP patients, the highest levels being observed in the most severe cases. This increase in peptide levels may protect against lesion infection and promote a quick wound healing [71].

It is tempting to suggest that the changes in the LL-37 concentration, found presently in OLP patients and in previous studies on ulcerating oral diseases, arise from the targeted action of the innate defense mechanisms in the local soft tissues to prevent the establishment of infection in the ulcers and to enable healing of the lesions [72].

6. POTENTIAL OF AMPS (USE OF PEPTIDES AND PEPTIDE GENES)

Since AMPs reveal broad-spectrum antimicrobial activity, and demonstrate a decreased ability to develop resistance [73], they represent an ideal potential therapeutic agent in any tissue or system that is a site for microbial infection, including the lung and oral cavity. After their initial discovery, numerous AMPs were examined for such therapeutic use. Unfortunately, several issues stood in the way of their development [74]. These include: difficulty and expense of manufacturing; short half-lives due to proteolytic degradation; and inhibition by host molecules [74,75].

7. SUMMARY

Most antimicrobial peptides in oral cavity are not only part of the immune response but are also expressed in healthy tissues where they contribute to host homeostasis. Accumulated evidences suggest that defensins, cathelicidin, histatins, and other antimicrobial peptides have a key role in maintaining the oral health.

Diverse biological functions have been documented for AMPs in a broad antimicrobial activity and augmentation of innate immune functions. Clinical studies are now identifying associations between changes in AMPs production or function and human infectious diseases, inflammatory syndromes, or immune deficiencies.

It appears that the development of oral biofilms, the host-response to biofilm bacteria and their toxins are important factors in the progression to periodontal disease. The host-response consists of a cascade of events by the innate and acquired immune systems. An early component of this cascade is the secretion of antimicrobial proteins and peptides (AMPs) by salivary glands, oral epithelial cells and neutrophils.

AMPs have a widespread distribution in human body and have antimicrobial activity against microorganisms. Oral epithelial cells, salivary glands and neutrophils secrete at least forty-five identifiable antimicrobial gene which they are found in saliva, AMPs also serve as effective biological molecules in immune response activation, inflammation and wound healing.

AMPs have a promising potential to be used against oral microbes in order to control their growth and biofilm formation. There are many challenges that need to be overcome in order to design and synthesize AMPs that have the ability to withstand the unique and harsh oral environment. AMPs are expected in the future to be used as models for developing effective oral microbial antibiotics.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Amerongen A, Veerman E. Saliva – The defender of the oral cavity. Oral Dis. 2002;8(1):12–22.
2. Yoshio H, Lagercrantz H, Gudmundsson GH, Agerberth B. First line of defense in early human life. Seminars in Perinatology. Elsevier; 2004.
3. Fábián TK, Fejérdy P, Csermely P. Saliva in health and disease (Chemical Biology of). In Wiley Encyclopedia of Chemical Biology, 1st ed.; Begley TP, Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA. 2008;4:1–9.

4. Brandtzaeg P. Do salivary antibodies reliably reflect both mucosal and systemic immunity? Ann. NY Acad. Sci. 2007;1098: 288–311.
5. Gorr S-U. Antimicrobial peptides of the oral cavity. Periodontology. 2009;51:152–180.
6. Gorr S-U, Abdolhosseini M. Antimicrobial peptides and periodontal disease. J Clin Periodontol. 2011;38(Suppl 1):126–41.
7. Alves D, Olivia Pereira M. Mini-review: Antimicrobial peptides and enzymes as promising candidates to functionalize biomaterial surfaces. Biofouling. 2014; 30(4):483–499.
8. Ashby M, Petkova A, Hilpert K. Cationic antimicrobial peptides as potential new therapeutic agents in neonates and children: A review. Curr. Opin. Infect Dis. 2014;27(3):258–267.
9. Edgerton M, Koshlukova SE. Salivary histatin 5 and its similarities to the other antimicrobial proteins in human saliva. Adv Dent Res. 2000;14:16–21.
10. Abiko Y, Saitoh M. Salivary defensins and their importance in oral health and disease. Curr Pharm Des. 2007;13:3065–3072.
11. Diamond DL, Kimball JR, Krisanaprakornkit S, Ganz T, Dale BA. Detection of beta-defensins secreted by human oral epithelial cells. J Immunol Methods. 2001;256:65–76.
12. Dale BA, Tao R, Kimball JR, Jurevic RJ. Oral antimicrobial peptides and biological control of caries. BMC Oral Health. 2006;6(Suppl 1):13.
13. Rock FL, Hardiman G, Timans JC, Kastelein RA, Bazan JF. A family of human receptors structurally related to Drosophila Toll. Proc Natl Acad Sci USA. 1998;95: 588-593.
14. Wilson CL, Ouellette AJ, et al. Regulation of intestinal alpha-defensin activation by the metalloproteinase matrilysin in innate host defense. Science. 1999;286(5437): 113-7.
15. Sahasrabudhe KS, Kimball JR, Morton T, Weinberg W, Dale BA. Expression of the antimicrobial peptide, human b-defensin 1, in duct cells of minor salivary glands and detection in saliva. Journal of Dental Research. 2000;79:1669-1674.
16. Tao R, Jurevic RJ, et al. Salivary anti-microbial peptide expression and dental caries experience in children. Antimicrob Agents Chemother. 2005;49(9):3883-8.
17. Chung WO, Dommisch H, et al. Expression of defensins in gingiva and their role in periodontal health and disease. Curr Pharm Des. 2007;13(30):3073-83.
18. Greer A, Zenobia C, Darveau RP. Defensins and LL-37: A review of function in the gingival epithelium. Periodontology. 2013;63(1):67–79.
19. Ganz T. Defensins: Antimicrobial peptides of innate immunity. Nat. Rev. Immunol. 2003;3(9):710–720.
20. Wang W, Owen SM, Rudolph DL, Cole AM, Hong T, Waring AJ, Lal RB, Lehrer RI. Activity of alpha and theta-defensins against primary isolates of HIV-1. J. Immunol. 2004;173(1):515–520.
21. Diamond G, Ryan L. Beta-defensins: What are they really doing in the oral cavity? Oral Dis. 2011;17(7):628–635.
22. Lehrer RI, Lichtenstein AK, et al. Defensins: Antimicrobial and cytotoxic peptides of mammalian cells. Annu Rev Immunol. 1993;11:105-28.
23. Cunliffe RN. Alpha-defensins in the gastrointestinal tract. Mol Immunol. 2003; 40(7):463-7.
24. Kinane D, Bouchard P. Periodontal diseases and health: Consensus report of the sixth European Workshop on Periodontology. J Clin Periodontol. 2008; 35(8 Suppl):333-7.
25. Nussbaum G, Shapira L. How has neutrophil research improved our under-standing of periodontal pathogenesis? J Clin Periodontol. 2011;38(Suppl 11):49-59.
26. Crawford JM, Wilton JM, et al. Neutrophils die in the gingival crevice, periodontal pocket, and oral cavity by necrosis and not apoptosis. J Periodontol. 2000;71(7):1121-9.
27. Mizukawa N, Sugiyama K, Ueno T, Mishima K, Takagi S, Sugahara T. Levels of human defensin-1, an antimicrobial peptide, in saliva of patients with oral inflammation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87:539–543.
28. Lundy FT, Orr DF, Gallagher JR, Maxwell P, Shaw C, Napier SS, et al. Identification and overexpression of human neutrophil alpha-defensins (human neutrophil peptides 1, 2 and 3) in squamous cell carcinomas of the human tongue. Oral Oncol. 2004;40:139–144.

29. Dale BA. Periodontal epithelium: A newly recognized role in health and disease. Periodontol 2000. 2002;30:70-8.
30. Diamond G, Laube D, Klein-Patel ME. Mammalian β-defensins in mucosal defences. In: Hancock REW, Devine DA, editors. Mammalian host defence peptides. Cambridge, UK: Cambridge University Press. 2004;111-138.
31. Krisanaprakornkit S, Weinberg A, et al. Expression of the peptide antibiotic human beta-defensin 1 in cultured gingival epithelial cells and gingival tissue. Infect Immun. 1998;66(9):4222-8.
32. Dale BA, Kimball JR, et al. Localized antimicrobial peptide expression in human gingiva. J Periodontal Res. 2001;36(5): 285-94.
33. Shin JE, Kim YS, et al. *Treponema denticola* suppresses expression of human (Venkatesh et al. C558-C565)-defensin-3 in gingival epithelial cells through inhibition of the toll-like receptor 2 axis. Infect Immun. 2010;78(2):672-9.
34. Larrick JW, Hirata M, Balint RF, Lee J, Zhong J, Wright SC. Human CAP18: A novel antimicrobial lipopolysaccharide-binding protein. Infect Immun. 1995;63: 1291–1297.
35. Gudmundsson GH, Agerberth B, Odeberg J, Bergman T, Olsson B, Salcedo R. The human gene FALL 39 and processing of the cathelin precursor to the antibacterial peptide LL-37 in granulocytes. Eur J Biochem. 1996;238:325–332.
36. Frohm M, Agerberth B, et al. The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. J Biol Chem. 1997;272(24): 15258-63.
37. Frohm Nilsson M, Sandstedt B, et al. The human cationic antimicrobial protein (hCAP18), a peptide antibiotic, is widely expressed in human squamous epithelia and colocalizes with interleukin-6. Infect Immun. 1999;67(5):2561-6.
38. Howell MD. The role of human beta defensins and cathelicidins in atopic dermatitis. Curr Opin Allergy Clin Immunol. 2007;7(5):413-7.
39. Oppenheim FG, Xu T, McMillian FM, Levitz SM, Diamond RD, Offner GD, Troxler RF. Histatins, a novel family of histidine-rich proteins in human parotid secretion. Isolation, characterization, primary structure, and fungistatic effects on *Candida albicans*. J Biol Chem. 1988;263:7472–7477.
40. de Sousa-Pereira P, Amado F, Abrantes J, Ferreira R, Esteves PJ, Vitorino R. An evolutionary perspective of mammal salivary peptide families: Cystatins, histatins, statherin and PRPs. Arch. Oral Biol. 2013;58(5):451–458.
41. MacKay B, Pollock J, Iacono V, Baum B. Isolation of milligram quantities of a group of histidine-rich polypeptides from human parotid saliva. Infect. Immun. 1984;44(3): 688–694.
42. Troxler R, Offner G, Xu T, Vanderspek J, Oppenheim F. Structural relationship between human salivary histatins. J. Dent. Res. 1990;69(1):2–6.
43. Bercier JG, Al-Hashimi I, Haghighat N, Rees TD, Oppenheim FG. Salivary histatins in patients with recurrent oral candidiasis. J. Oral Pathol. Med. 1999; 28(1):26–29.
44. Oudhoff MJ, van den Keijbus PA, Kroeze KL, Nazmi K, Gibbs S, Bolscher JG, Veerman EC. Histatins enhance wound closure with oral and non-oral cells. J. Dent. Res. 2009;88(9):846–850.
45. Van NA, Bolscher JGM, Veerman ECI. Salivary proteins: Protective and diagnostic value in cariology? Caries Res. 2004;38:247–253.
46. Joly S, Maze C, McCray PB Jr, Guthmiller JM. Human beta-defensins 2 and 3 demonstrate strain selective activity against oral microorganisms. J Clin Microbiol. 2004;42:1024–1029.
47. Ji S, Hyun J, Park E, Lee BL, Kim KK, Choi Y. Susceptibility of various oral bacteria to antimicrobial peptides and to phagocytosis by neutrophils. J Periodontal Res; 2007;42: 410–419. Erratum in J Periodontal Res. 2008;43:126.
48. Maisetta G, Batoni G, et al. Activity of human beta-defensin 3 alone or combined with other antimicrobial agents against oral bacteria. Antimicrob Agents Chemother. 2003;47(10):3349-51.
49. Gomez-Garces JL, Alos JI, et al. Bacteremia by multidrug-resistant *Capnocytophaga sputigena*. J Clin Microbiol. 1994;32(4):1067-9.
50. Altman H, Steinberg D, et al. In vitro assessment of antimicrobial peptides as potential agents against several oral

bacteria. J Antimicrob Chemother. 2006; 58(1):198-201.

51. Klotman ME, Chang TL. Defensins in innate antiviral immunity. Nat Rev Immunol. 2006;6:447–456.
52. Chong KT, Xiang L, Wang X, Jun EL, Xi LF, Schweinfurth JM. High level expression of human epithelial beta-defensins (hBD-1, 2 and 3) in papillomavirus induced lesions. Virol J. 2006;3:75.
53. Zhang L, Lopez P, He T, Yu W, Ho DD. Retraction of an interpretation. Science. 2004;303:467.
54. Tanabe H, Ouellette AJ, Cocco MJ, Robinson WE Jr. Differential effects on human immunodeficiency virus type 1 replication by alpha-defensins with comparable bactericidal activities. J Virol. 2004;78:11622–11631.
55. Cole AM, Hong T, Boo LM, Nguyen T, Zhao C, Bristol G, et al. Retrocyclin: A primate peptide that protects cells from infection by T- and M-tropic strains of HIV-1. Proc Natl Acad Sci USA. 2002;99:1813–1818.
56. Buck CB, Day PM, Thompson CD, Lubkowski J, Lu W, Lowy DR, et al. Human alpha-defensins block papillomavirus infection. Proc Natl Acad Sci USA. 2006;103:1516–1521.
57. Quinones-Mateu ME, Lederman MM, Feng Z, Chakraborty B, Weber J, Rangel HR, et al. Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication. AIDS. 2003;17: 39–48.
58. Bergman P, Walter-Jallow L, Broliden K, Agerberth B, Soderlund J. The anti-microbial peptide LL-37 inhibits HIV-1 replication. Curr HIV Res. 2007;5:410–415.
59. Lehrer RI, Ganz T. Defensins of vertebrate animals. Curr Opin Immunol. 2002;14:96–102.
60. Yang D, Biragyn A, Hoover DM, Lubkowski J, Oppenheim JJ. Multiple roles of antimicrobial defensins, cathelicidins, and eosinophil-derived neurotoxin in host defense. Annu. Rev. Immunol. 2004;22: 181–215.
61. Koczulla AR, Bals R. Antimicrobial peptides: Current status and therapeutic potential. Drugs. 2003;63(4):389–406.
62. Oudhoff MJ, Blaauboer ME, Nazmi K, Scheres N, Bolscher JGM, Veerman ECI. The role of salivary histatin and the human cathelicidin LL-37 in wound healing and innate immunity. Biol Chem. 2010;391: 541–548
63. Yang D, Chen Q, Chertov O, Oppenheim JJ. Human neutrophil defensins selectively chemoattract naïve T and immature dendritic cells. J Leukoc Biol. 2000;68:9–14.
64. Tjabringa GS, Aarbiou J, Ninaber DK, Drijfhout JW, Sorensen OE, Borregaard N, et al; The antimicrobial peptide LL-37 activates innate immunity at the airway epithelial surface by transactivation of the epidermal growth factor receptor. J Immunol. 2003;171:6690–6696.
65. Scott MG, Davidson DJ, Gold MR, Bowdish D, Hancock RE. The human antimicrobial peptide LL-37 is a multifunctional modulator of innate immune responses. J Immunol. 2002;169:3883–3891.
66. Putsep K, Carlsson G, Boman HG, Andersson M. Deficiency of antibacterial peptides in patients with morbus Kostmann: An observation study. Lancet. 2002;360(9340):1144–1149.
67. de Haar SF, Hiemstra PS, van Steenbergen MT, Everts V, Beertsen W. Role of polymorphonuclear leukocyte-derived serine proteinases in defense against *Actinobacillus actinomycetemcomitans*. Infect Immun. 2006;74:5284–5291.
68. Davidopoulou S, Diza E, Sakellari D, Menexes G, Kalfas S. Salivary concentration of free LL-37 in edentulism, chronic periodontitis and healthy periodontium. Arch. Oral Biol. 2013;58(8): 930-934.
69. Turkoglu O, Kandiloglu G, et al. Antimicrobial peptide hCAP-18/LL-37 protein and mRNA expressions in different periodontal diseases." Oral Dis. 2011; 17(1):60-7.
70. Dowd KK. Histatins: Antimicrobial peptides with therapeutic potential. J Pharm Pharmacol. 2004;56:285–289.
71. Davidopoulou S, Theodoridis H, Nazer K, Kessopoulou E, Menexes G, Kalfas S. Salivary concentration of the antimicrobial peptide LL-37 in patients with oral lichen planus. J. Oral Microbiol. 2014;6:26156.
72. Bucki R, Leszczynska K, Namiot A, Sokolowski W. Cathelicidin LL-37: A multitask antimicrobial peptide. Arch Immunol Ther Exp. 2010;58:15–25.

73. Zasloff M. Antimicrobial peptides of multicellular organisms. Nature; 2002;415: 389–395.
74. Marr AK, Gooderham WJ, Hancock RE. Antibacterial peptides for therapeutic use: Obstacles and realistic outlook. Curr Opin Pharmacol. 2006;6:468–472.
75. Khurshid Z, et al. Oral antimicrobial peptides: Types and role in the oral cavity. Saudi Pharmaceutical Journal; 2015.

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