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ROLE OF ANTIMICROBIAL PEPTIDE IN PERIODONTAL DISEASE

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ABSTRACT

The development of oral biofilms and the host response to biofilm bacteria and their toxins are important factors in the development of periodontal disease. An early component of the host response is the secretion of antimicrobial proteins and peptides (AMPs) by salivary glands, oral epithelial cells and neutrophils. Antimicrobial peptide resistance has been increasingly recognized as a discriminating feature of some of periodontopathic pathogens. When Antimicrobial peptides are rendered ineffective as a component of barrier defense or phagocytic killing, remaining host microbial function may be insufficient to prevent the risk of invasion of periodontopathic bacteria produced by the Antimicrobial peptide resistance organism. Therefore, aim of this review was to present current understanding of various oral Antimicrobial peptides involving in maintaining balance between periodontal health and disease, participation of various residential periodontal cells in production of these oral Antimicrobial peptides, its role during periodontal disease as well as mechanism of development of resistance against oral Antimicrobial peptides by particular periodontal bacteria.

KEYWORDS: Antimicrobial Peptide, Periodontal Disease, Endogenous, Cathelicidine, Defensins.

Introduction:

Endogenous antimicrobial peptides (AMPs) are small amino acid–based molecules that have the capacity to kill microbes and are produced by the host tissues. The existence of such molecules has been known for decades, but, recently, interest in the AMPs has increased from the perspective of both the basic scientist attempting to understand immunity, and the clinician attempting to better diagnose and treat the disease. Antimicrobial peptides function within the conceptual framework of the innate immune system. Antimicrobial peptide resistance has been increasingly recognized as a discriminating feature of some of periodontopathic pathogens. When Antimicrobial peptides are rendered ineffective as a component of barrier defense or phagocytic killing, remaining host microbial function may be insufficient to prevent the risk of invasion of periodontopathic bacteria produced by the antimicrobial peptide resistance organism. Therefore, aim of this review was to present current understanding of various oral Antimicrobial peptides involving in maintaining balance between periodontal health and disease, participation of various residential periodontal cells in production of these oral Antimicrobial peptides, its role during periodontal disease as well as mechanism of development of resistance against oral Antimicrobial peptides by particular periodontal bacteria

ANTIMICROBIAL PEPTIDES

Gingival epithelium is seen as providing not only a physical barrier to infection but playing an active role in innate host defense by production of various Antimicrobial peptides. Oral antimicrobial peptides include several salivary antimicrobial peptides, the β–defensins expressed in the epithelium, the α–defensins expressed in neutrophils, and the cathelicidin, LL-37, expressed in both epithelium and neutrophils. Antimicrobial peptides are polypeptides of fewer than 100 amino acids that are found in host defense settings, and that have antimicrobial activity at physiological concentrations under conditions prevailing in the tissues of origin. In humans and other mammals, the two main antimicrobial peptide families are defensins and cathelicidins. Individual members of these two families of antimicrobial peptides have been implicated in antimicrobial activity of phagocytes, inflammatory body fluids and epithelial secretions. Defensins (Ganz et al 1985, Selsted et al 1985)[1,2] are widely distributed in mammalian epithelial cells and phagocytes, and are often present at high (up to millimolar) concentrations. Cathelicidins (Zenetti et al 1995, Lehrer and Ganz 2002)[3,4] are structurally and evolutionarily distinct antimicrobial peptides that are similar to defensins in abundance and distribution. Among these peptides, defensins was the first antimicrobial peptide identified in oral epithelium, described in bovine tongue.[5] β-defensins are found as four different types in human (hBD 1-4) and it is believed, based on genomic targeting, that 28 other human β-defensins may exist. Within the gingival epithelium, keratinocytes are able to secrete these peptides. Human α-defensins 1, 2, 3, and 4 were isolated from neutrophils initially (Ganz et al 1985),[1] so they are termed human neutrophils peptides (HNP)1, 2, 3, and 4 conventionally.[6] HNP1, 2, 3, and 4 are stored in the granules of neutrophils and monocytes/ macrophages and can be released extracellularly.[7,8] Human α-defensins 5 and 6 (HD5 and 6) are products of intestinal Paneth cells primarily (Ouellette

and Selsted 1996)[9], although defensin 5 is also detected in reproductive tissues. In most epithelia, including healthy gingival epithelium, hβD-1 is constitutively expressed, whereas hβD-2 and hβD-3 appear to be highly inducible by cytokines or after exposure to microorganisms.

Cathelicidin/ LL-37 is not only stored in neutrophil granules (Agerberth et al 2000)[10] but is also expressed by epithelial cells constitutively (Frohm Nilsson et al 1999)[11] and keratinocytes in response to inflammatory stimuli (Bals et al 1998).[12]

EXPRESSION OF ANTIMICROBIAL PEPTIDES IN ORAL AND GINGIVAL HEALTH

In vitro β-defensin has been reported to exhibit broad spectrum antimicrobial activity against gram positive and gram negative bacteria and fungi (Ganz and Lehrer 1995)[13] and provide linkage between the innate and acquired immune response.

Neutrophils express α-defensins as part of their non-oxidative antimicrobial mechanisms. Alpha defensins are expressed in oral epithelial tissues including salivary glands.[14]In addition to their antimicrobial function, the α-defensins act as chemoattractants for T cells and dendritic cells of the acquired immune systetm (Yang et al 1999)[15] atid monocytes (Territo et al 1989).[16]

LL-37 is released at the inflamed sites mainly by neutrophils that migrate through the junctional epithelium.[17,18] This pattern of expression implies a possible protective role of the peptide on both hard and soft oral tissues.[19] LL-37 has a broad antimicrobial activity against periopathogenic bacteria.[20] LL-37 also promotes angiogenesis (Koczulla et al 2003)[21] and wound healing (Heilborn et al 2003)[22], induces degranulation of mast cells (Niyonsaba et al 2001)[23], and influences dendritic cell differentiation and the polarization of T cells (Davidson et al 2004).[24] Overall, LL-37 plays a critical role in selectively balancing responses to inflammatory stimuli, such as bacterial endotoxin, in human immune cells. This peptide also possesses neutralizing activity against bacterial lipopolysaccharide (LPS).[25]

ROLE OF ANTIMICROBIAL PEPTIDES DURING PERIODONTAL DISEASE

1) β-DEFENSINS:

β-defensins have a broad spectrum of activity against both Gram-negative and Gram-positive bacteria as well as some fungi and viruses.[26,27] In addition to their direct antimicrobial activity, human β-defensins (hBDs) also directly stimulate antigen-presenting dendritic cells (DCs) and memory T cells, and thus can link innate and adaptive immune responses.[28]They also provoke efficient epithelial barrier repair to limit entry of invading bacteria.[29]

The amount of hBD-1 expression does not correlate with the degree of tissue inflammation, but varies among different individuals (Krisanaprakornkit et al 1998).[30] Similar to the inducible expression of hBD-2 by microorganisms and pro-inflammatory cytokines in other cell types, hBD-2 mRNA was up-regulated in cultured gingival epithelial cells in response to stimulation with IL-α, TNF-β, phorbol ester, a potent epithelial activator, and gram-negative periodontal bacteria, including Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, and Porphyromonas gingivalis. With respect to up-regulation of hBD-3 by oral microorganisms, hBD-3 mRNA expression was induced by live nonperiodontopathic bacteria, including Streptococcus sanguinis and Streptococcus gordonii, (Ji et al 2007)[31] and some periodontopathic bacteria, including Aggregatibacter actinomycetemcomitans, Prevotella intermedia, and Fusobacterium nucleatum (Ji et al 2007).[31]

Yin et al (2010)[32] investigated the innate immune responses between gingival epithelial cells (GECs) and immune cells (DC) in the oral cavity. Authors concluded that cytokines, chemokines and β-defensins are involved in the interaction of DCs and GECs, and the responses were bacteria-specific. Differential and coordinated regulation between these two cell types may be important in the regulation of innate immune homeostasis and responses to pathogens in the oral cavity.

Gupta et al (2010)[33] evaluated the isolation and characterization of a *F. nucleatum* (ATCC 25586)-associated defensin inducer (FAD-I) in human oral epithelial cells. Authors concluded that FAD-I or its derivates may offer a new approach in immunoregulatory therapeutics by increasing expression of innate response elements of vulnerable mucosa with both antimicrobial and adjuvant capabilities.

2) α- DEFENSINS:

α-defensins are directly involved in antimicrobial killing and appear to play a role in assisting other parts of the innate response and alerting the adaptive immune response. α- defensins are capable of activating the classical compliment pathway (Panyutich et al 1994)[34] and appear to upregulate IL-8 production (via increased gene transcription) by epithelial cells, which may intern enhance neutrophil recruitment to the site of infection (Van Wetering et al 1997)[35] α-defensins released from neutrophil are capable of being chemotactic for both CD8 and CD4/CD45RA (naive) T cells and immature dendritic cells (Zasloff 2002).[5]

Dale et al (2001)[17] studied localization of α-defensins antimicrobial peptides in gingiva from periodontitis patient. Authors concluded that defensins were localized in specific sites in the gingiva and were synthesized by different cell types, likely to play different roles in various regions of the periodontium.

Grigat et al (2007)[36] indicate that chemoattraction of macrophages, T lymphocytes, and mast cells represent an immunomodulatory function which was evolutionarily conserved within the human α-defensin family and tightly regulated by β-defensins.

3) CATHELICIDIN:

LL-37 has broad spectrum activity against gram positive

and gram negative bacteria as well as fungi and viruses (Bals et al 1998).[12] It has been reported to play a role as chemoattractive factor for T cells or dendritic cells (Yang et al 2001)[37] and neutralizes lipopolysaccharide and lipoteichoic acid, which are considered mediators of inflammation (Scott et al 1999)[38]. The concentrations of LL-37 in the gingival tissue, whether derived from neutrophils or from gingival epithelium, correlate positively with the depth of the gingival crevice, suggesting that LL-37 levels may be used as diagnostic tool in inflammatory periodontal disorders (Hosokawa et al 2006).[18]

Davidopoulou et al (2012)[39] concluded that LL-37 was an important molecule of immunity in the oral environment and it seems to play a protective role against oral diseases. LL-37 concentration in saliva may serve as a prognostic tool for the disease or that the peptide can be used as a therapeutic agent.

Ouhara et al (2005)[40] concluded that LL-37 had antimicrobial activity against periodontopathogenic bacteria, however the activity of LL-37 was different among species and strains.

ANTIMICROBIAL PEPTIDE RESISTANCE DISPLAYED BY ORAL PATHOGENS

Recent discoveries have confirmed that AMPs play a crucial role in restricting microbial proliferation to oral mucosal surfaces, and preventing spread to the deep tissues where oral infection may develop. These epithelial barrier functions are further supplemented by AMPs produced by leukocytes resident in the tissues (macrophages, dendritic cells, mast cells) or recruited in the acute inflammatory response (neutrophils). It appears that bacteria exposed to human AMPs have evolved under selective pressure to develop mechanisms of resistance. However, even though these selective pressures have existed for countless centuries, human AMPs still possess a broad-spectrum of potent activity against a diverse array of Gram-positive and Gram-negative bacteria species, fungi, as well as certain protozoan parasites and enveloped viruses. Though the ability to resist AMP killing appears to be a formidable challenge for microbial evolution, AMP resistance is increasingly recognized as a discriminating feature of some important human pathogens. When AMPs are rendered ineffective as a component of barrier defense or phagocytic killing, remaining host microbicidal functions maybe insufficient to prevent the risk of invasive infections produced by the AMP-resistant organism. Current understanding of mechanisms is that human pathogens have evolved to resist AMP killing. These include decreased affinity through cell surface alterations, external trapping mechanisms, membrane efflux pumps, peptidases, and downregulation of host AMP production.

Conclusion:

Defensins are abundant and widely distributed peptides in human and animal tissues that are involved in host defence. The oral cavity is a unique environment in which antimicrobial peptides play a key role in maintaining health. The importance of antimicrobial peptides in innate immunity and oral health is now widely recognized. For instance, deficiencies of LL37 and α-defensins are related to the occurrence of early-onset periodontal disease in the Morbus Kostmann syndrome. Markedly reduced production of LL-37 in patients with systemic diseases, including Kostmann syndrome, Papillon-Lefe`vre syndrome, and neutropenia, apparently increases susceptibility to periodontitis, leading to a higher prevalence (Putsep et al 2002, de Haar et al 2004, Karlsson et al 2007). LL-37 interferes with biofilm formation by interfering with bacterial attachment, twitching motility, and quorum sensing, as demonstrated in vitro with Pseudomonas aeruginosa (Overhage et al 2008).

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