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Antimicrobial peptides in periodontal innate defense

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Introduction

Periodontal disease is an inflammatory disease initiated by the formation of mixed biofilms on the teeth and gingival tissues. Biofilm bacteria and their toxins perturb gingival epithelial cells leading to a sequence of inflammatory and immune processes that may result in the destruction of gingival tissues, attachment loss and periodontal pockets. In susceptible patients, alveolar bone loss and tooth loss may follow as a result of periodontal disease. At least 50% of adults exhibit some level of periodontal disease [1, 2].

The oral cavity contains over 700 resident species of bacteria, of which 150–200 bacterial species are typically found in individuals. About 400 species of bacteria have been found in periodontal pockets, but a small subset of these is found in individual subjects [3]. In fact, only eight bacterial species have consistently been associated with periodontal disease, including *A. actinomycetemcomitans, P. gingivalis, T. forsythia, T. denticola, F. nucleatum, E. nodatum P. intermedia and P. nigrescens* [4–6]. *P. gingivalis, T. forsythia and T. denticola* belong to the red complex described by Socransky et al. [5] while *A. actinomycetemcomitans, P. gingivalis,* and *T. forsythia* are considered consensus pathogens [4]. However, these bacteria are found in both healthy and diseased sites, although in much higher numbers (up to 10^5 fold) in the latter sites [7]. Thus, it has been proposed that, rather than the bacterial infection *per se*, the magnitude of the inflammatory response is a determinant of the development of destructive periodontitis [8]. 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.

Antimicrobial peptides and oral bacteria

A complex mixture of over 45 antimicrobial proteins and peptides are found in oral fluids. In addition, recent salivary proteome data suggests that additional AMPs will be found in oral fluids [9]. Thus, over 1100 proteins have been identified in human saliva and a large number of these are proteins of unknown function. The known AMPs belong to six functional families [10]: 1. Cationic peptides, 2. Bacterial agglutination and adhesion, 3. Metal ion chelators, 4. Peroxidases, 5. Protease inhibitors, and 6. AMPs with activity against bacterial cell walls. It is thought that this variety of proteins and functions allows the oral innate immune system to defend against the wide variety of microbes that enter the mouth. Moreover, the variety of functions appears to be a successful strategy against bacterial AMP resistance. Interestingly, the absence of a single AMP may lead to increased periodontal disease. Thus, Morbus-Kostman disease is characterized by severe neutropenia and periodontal disease. In particular, the lack of LL-37 has been associated with periodontal disease since treatments to restore neutrophil levels did not clear the inflammation. However, in a single patient, a bone–marrow transplant restored neutrophils levels, LL-37

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levels and gingival health [11]. Similarly, Papillon-Lefevre syndrome is characterized by increased susceptibility to early-onset periodontitis and is caused by mutations in the cathepsin C gene. The lack of active cathepsin prevents the proteolytic processing of cathelicidin to the active AMP LL-37 [12, 13].

Despite the large number and variety of oral AMPs, it appears that the innate immune system is unable to cope with the normal oral flora, including oral pathogens associated with periodontal disease. Thus, in the absence of regular oral care, teeth and gingival tissues quickly acquire biofilms that, if left untreated, cause gingivitis [14]. Interestingly, the associated inflammation may be linked to modern diets since subjects adhering to a stone age diet, in the absence of oral care, develop supragingival plaque but this does not lead to an increase in the severity of gingival inflammation, bleeding on probing or pocket depths [15]. Thus, it is possible that (refined sugars in) modern diets contribute to vigorous growth of biofilms and hence overwhelm natural innate defenses.

In contrast to the ability of oral biofilms to develop in the presence of oral AMPs, tooth extraction, oral surgery or other acute injuries to the oral mucosa rarely lead to infection or damaging inflammation. It is possible that the neutrophils recruited to the site of injury provide the necessary local dose of AMPs to prevent bacterial colonization.

Expression of AMPs in oral cavity

The AMPs found in saliva and gingival crevicular fluid have recently been reviewed [10, 16]. Although the data are not complete, current evidence suggests that only a handful of AMPs, including adrenomedullin, elafin, HNP-1 and statherin, are present in saliva and gingival crevicular fluid in concentrations higher than the minimal inhibitory concentration (MIC) for oral bacteria [16]. Given the localized nature of periodontal disease, it is important to note that the saliva concentration of AMPs may be significantly diluted and that this may not be directly relevant to the concentration that would be found in the periodontal pocket. Thus, it cannot be excluded that locally higher concentrations are reached at the site of secretion from oral epithelial cells or neutrophils. Especially neutrophils are recruited to sites of injury and secrete a rich mixture of AMPs (Table 1). While this mixture of AMPs is effective against planctonic bacteria, it may nevertheless be inadequate against bacterial biofilms. Thus, when encountering a mature biofilm the neutrophils may be unable to engulf biofilm bacteria, leading to a “frustrated phagocytosis” causing the release of enzymes and products of the oxidative burst into the periodontal pocket where they can cause tissue destruction.

Over 45 AMPs have been identified in the oral cavity [10, 16]. All are found in saliva and several are also present in gingival crevicular fluid. Of these, 13 are up-regulated in periodontal disease while 11 are down-regulated (Table 2). As an example, defensins and LL-37, key components of the mucosal antimicrobial defense, are induced by bacterial stimulation of gingival epithelial cells while only LL-37 expression is induced in peripheral blood neutrophils [17]. In some cases where AMPs were measured in saliva or gingival crevicular fluid, down-regulation may be caused by proteolytic degradation of the AMP by bacterial proteases. It is not clear if the regulation of AMP expression is a functional response to the bacterial insult or if it is part of a more general stimulation of target cells. In fact, even the stimulated levels of several AMPs are below the minimal inhibitory concentration for oral pathogens [16]. Thus, other biological activities of the AMPs may play a functional role in gingival inflammation.

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Biological roles of antibacterial peptides and proteins

AMPs exhibit multiple biological activities that could play a role in the innate immune defense against oral bacteria and their toxins. In addition to direct antibacterial activity (e.g. bactericidal activity, bacterial agglutination), AMPs may affect the course of periodontal disease by inactivating bacterial or host proteases (SLPI) or bind bacterial toxins, including lipopolysaccharide (LPS) (LL-37). Several AMPs affect the inflammatory response and wound healing in mucosal tissues and can act as modulators of the immune system [18–20]. As examples of these activities, the biological activities of LL-37, secretory leukoprotease inhibitor and parotid secretory protein are reviewed.

Cathelicidin (LL-37)

LL-37 is a multifunctional 37 amino acid peptide derived from human cathelicidin by proteolytic processing following secretion [21]. The peptide is random coil in aqueous solution but assumes an alpha-helical conformation when exposed to lipid membranes. The peptide is expressed in epithelial cells and neutrophils and is found in saliva at 0.14–3 μg/ml [22, 23]. LL-37 has been detected in gingival crevicular fluid by immunoblotting and ELISA (0.5 μg/ml) and the levels are increased in chronic periodontitis [24, 25]. Within individual patients, LL-37 levels are higher in GCF from inflamed sites compared with healthy sites [26] and LL-37 deficiency has been directly implicated in the development of periodontitis [11].

The peptide is active against Gram negative and Gram positive bacteria, including *A. actinomycetemcomitans* and *P. gingivalis*. Activity (LD_{99}) against three strains of *A. actinomycetemcomitans* is about 10 μg/ml and is inhibited by 100 mM sodium chloride [27]. In a study of LL-37 activity under physiological conditions, it was noted that the inhibition by salt was mitigated by the presence of carbonate in physiological buffers. Thus, target bacteria exhibit modifications to their cell wall in the presence of carbonate that result in increased susceptibility to LL-37 under physiological conditions [28].

The MICs against different strains of *A. actinomycetemcomitans* and are 30–60 μg/ml and >125 μg/ml against *P. gingivalis* [29]. The latter result may be due to proteolytic degradation of LL-37 by gingipains secreted by *P. gingivalis*. Saliva components protect the peptide against degradation by gingipains released by the periodontal pathogen *P. gingivalis*. While the antibacterial activity of LL-37 is lowered by saliva, the net effect in vivo appears to be the protection of antibacterial activity in the presence of *P. gingivalis* proteases [30].

The concentration of LL-37 in saliva and GCF is lower than the MIC for oral bacteria, suggesting that local concentrations must be higher for effect or that other biological functions are important in the oral cavity. The high concentrations of LL-37 needed for antibacterial activity and the inactivation by serum proteins have led to the suggestion that the primary function of this and other AMPs is as an immune system alarmin, i.e. an endogenous mediator that recruits and activates antigen-presenting cells to enhance innate and adaptive immune responses. [19]. Indeed, LL-37 acts as a chemoattractant for monocytes, T-cells and neutrophils. The effect is inhibited by pertussis toxin suggesting that it involves a Gi-protein coupled receptor, which was shown to be Formyl Peptide Receptor–Like 1 [31] LL-37 has also been implicated in carcinogenesis in breast, ovarian and lung cancer but suppresses tumorigenesis in gastric cancer. Thus, the effects of LL-37 on tumorigenesis are tissue specific [32]. In lung cancer cells, LL-37 activates MAP kinase pathways and increases their proliferation and anchorage independent growth [33].

Mucus plays an important role in protecting mucosal surfaces from microbial attack. In colonic epithelium, LL-37 causes an increase in mucus thickness and expression of mucin

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genes [34]. The up-regulation of mucin expression is mediated by phosphorylation of MAP Kinase, which is upregulated by LL-37 in epithelial HT-29 cells [35]. An effect L-37 on mucin expression in oral epithelial cells has not been reported but mucin inhibits the antibacterial activity of LL-37 [36].

LL-37 directly binds LPS [37] and inhibits the inflammatory response in human gingival fibroblast stimulated with heat-killed *P. gingivalis*, bacterial LPS or *P. gingivalis* fimbriae. In each case the expression of IL6, IL8 and CXCL10 were inhibited [38].

Taken together, LL-37 is a multifunctional peptide that could affect the development of periodontal disease from bacterial colonization, bacterial toxicity and host response.

Defensins

The defensin family are prominent AMPs in oral epithelial cells and neutrophils [39]. Human beta-defensins (hBD) are primarily expressed in epithelial cells, while alpha-defensins (human neutrophil peptide; HNP) are predominantly expressed in neutrophils. Levels of HNP1-3 in gingival crevicular fluid are up-regulated 60-fold in chronic periodontitis and 15-fold in aggressive periodontitis [24]. The level reached in chronic periodontitis (70 μg/ml) is above the MIC for *S. mutans* [40] but the peptides are not active against *A. actinomycetemcomitans* or *P. gingivalis* [41, 42].

The biological activities of defensins overlap with those of LL-37. Defensin are stored in secretory granules at high concentration and may kill phagocytosed bacteria upon fusion of secretory granules with phagocytic vacuoles [39]. As for LL-37, the antibacterial effect of defensins is salt sensitive and it has been suggested that other biological activities constitute the primary function of secreted defensins. Indeed, defensins also act as alarmins that both chemoattract and activate antigen presenting cells [19]. As an example, hBD-2, but not hBD-1, acts as a chemoattractant for mast cells at a concentration of 3 μg/ml [43], i.e. similar to the concentration reached in periodontitis and significantly lower than the MIC for oral bacteria [16].

Defensins inhibibt LPS-stimulated inflammatory responses in host cells. As an example, human beta defensins and HNPs (except HNP-2) inhibit the expression of IL-1β, IL-8 and ICAM-1 in gingival fibroblast stimulated with *P. Intermedia* LPS [44].

Defensin expression in gingival epithelial cells from periodontal patients is differentially regulated by periodontal pathogens and commensals [45]. Differences were also seen when hBD expression was induced by different capsule types of *P. gingivalis* or different serotypes of *A. Actinomycetemcomitans* [45]. Periodontitis has an about 50% genetic component [46] and a recent study has found a significant associaton of periodontal disease with a SNP of the 3' untranslated region of the *DEFB1* gene (hBD-1) [47].

In addition to the potential role of defensins in oral infection and inflammation, an unusual role for the canine beta-defensin gene *CBD103* was recently reported in domestic dogs, where CBD 103 interacts with melanocortin 1 receptor in determining black coat color [48]. Interestingly, in mice another coat color gene locus - agouti - has been associated with *Psp* [49, 50], a proposed host defense gene (see below).

Secretory LeukoProtease Inhibitor (SLPI)

SLPI is an 11.7 kD non-glycosylated serine-protease inhibitor that was originally isolated from parotid saliva [51]. The protein is expressed in neutrophils, epithelial cells and salivary glands and inhibits serine proteases, including neutrophil elastase, cathepsin G, and trypsin, which are involved in inflammatory tissue destruction [52]. SLPI is also expressed in oral

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tumor tissues [53]. In addition to its protease inhibitor activity, salivary SLPI inhibits HIV-1 infection of human monocytes [54] and the protein is fungicidal against *A. fumigatus* and *C. albicans* [55].

Salivary concentrations of SLPI are 0.1–10 μg/ml [52, 56, 57]. The amount of SLPI in gingival crevicular fluid increased 3-fold from about 80 ng/ml to 300 ng/ml following periodontal treatment [58].

SLPI is associated with wound repair and its expression is increased following wounding. Accordingly, *Slpi*-null mice are defective in cutaneous wound healing and exhibit increased elastase activity and inflammation. The latter is associated with increased activation of TGFβ in the knock-out animals [59]. SLPI is secreted by macrophages and increased amounts are secreted when the cells are stimulated with apoptotic cells [60]. Together these findings suggest that SLPI plays a role in the resolution of inflammation. This is consistent with the increased expression of SLPI following periodontal treatment [58].

Parotid Secretory Protein

Parotid Secretory Protein (PSP) (Short Palate, Lung, Nasal epithelium Clone-2, SPLUNC2) was originally detected in mouse and rat salivary glands [61, 62]. Human PSP was identified in acinar and ductal epithelial cells of the parotid gland [63, 64] and the secreted protein has been detected in whole, parotid and submandibular/sublingual saliva [9, 63, 65]. PSP is expressed in human gingival epithelial cells and its expression is increased by heat-inactivated *P. gingivalis* [66] and up-regulated in saliva from generalized aggressive periodontitis patients compared to healthy controls [67].

PSP belongs to a family of oral and airway proteins that are related to palate, lung and nasal epithelium clone (PLUNC) [68]. Based on a predicted similarity to bactericidal/permeability-increasing protein and LPS-binding protein, PSP and the other members of the PLUNC protein family have been proposed to play a role in host defense [69]. Indeed, mouse PSP binds bacteria [70] and peptides derived from the human PSP sequence cause bacterial agglutination [71]. The related proteins human PLUNC and bovine BSP30 inhibit growth of *Mycoplasma pneumoniae* [72] and *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* [73], respectively.

Since PLUNC proteins are related to LPS binding proteins, the PLUNC family members human PLUNC and bovine BSP30 have also been tested for LPS binding, but with varying results. Ghafouri et al. [74] reported that PLUNC binds LPS whereas no significant binding was detected for BSP30 [73]. Recent experiments with human salivary PSP demonstrated that this protein binds immobilized LPS and this binding was specifically inhibited by a PSP peptide [75]. Together, these findings support the proposed host defense function of PSP.

As is the case for other AMPs, the PLUNC proteins also exhibit multiple functions. Thus, PLUNC and the horse protein latherin have surfactant properties that may aid in the wetting of mucosal and dermal surfaces [76, 77]. Based on sequence similarities, similar functions can be predicted for PSP and the other members of the PLUNC protein family. A specific role for PSP or other PLUNC proteins in the development of periodontitis has not yet been reported.

Antimicrobial peptides and proteins as biomarkers for periodontal disease

Saliva and gingival crevicular fluid hold promise as diagnostic tools for both oral and systemic diseases [78, 79]. The gingival changes associated with periodontitis, including changes in the expression of cytokines and AMPs and products of tissue and bone

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destruction are potential targets for oral fluid diagnostics and recent reviews have identified salivary biomarkers for periodontal disease from these protein categories [80, 81]. The potential markers include proteins involved in inflammation (e.g. C-reactive protein, IL-1β, TNFα), collagen breakdown (MMP-8, MMP-9), bone remodeling (alkaline phosphatase, osteocalcin, osteonectin) and host-defense proteins (e.g. lysozyme, lactoferrin, histatin).

Although the saliva levels of individual markers can be statistically distinguished between healthy samples and periodontitis, the large variation in individual sample values make a prospective assignment of any given saliva marker more difficult. A possible solution to this problem is the use of diagnostic panels that combine several markers [81]. Based on the known regulation of AMPs in periodontal disease, we propose that this class of proteins, which are typically expressed in response to oral bacteria or bacterial toxins, are an attractive target as markers for periodontal disease. We have previously identified 45 AMPs in saliva and gingival crevicular fluid [10, 16]. Further analysis of this data set identified 13 AMPs that are up-regulated in periodontal disease and 11 AMPs that are down-regulated (Table 2). Based on these data, we propose that panels of AMPs may be suitable for the diagnosis of periodontal disease in saliva samples. The use of ratios between up- and –downregulated proteins from individual patients may overcome individual variation and potentiate the observed differences to allow prospective assignment of any given sample as “healthy” or “diseased”. Since saliva diagnoses the overall oral condition, a positive test could then be followed by analysis of gingival crevicular fluid from suspected sites or diagnosis the periodontal practitioner. In support of this approach, the AMPs parotid secretory protein, prolactin-inducible protein, vasoactive intestinal peptide and myeloperoxidase are decreased after therapy, while SLPI and calgranulins are increased [58, 82–84]. Thus, treatment outcomes may be monitored by changes in AMP levels pre- and post-treatment.

Summary

A large number of AMPs have been identified in the oral cavity and several are regulated by and express antimicrobial activity to periodontal pathogens. However, the concentrations of these proteins found in oral fluids are often below the effective in vitro concentrations. Thus, it is thought that AMPs act intracellularly or at the site of secretion from neutrophils and epithelial cells or act through alternate biological functions, including acting as alarmins, anti-inflammatory proteins and as signaling molecules for resolution of inflammation and wound healing. It is proposed that the differential regulation of AMPs in periodontal disease make them attractive biomarkers for the disease in saliva and gingival crevicular fluid.

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Abbreviations

AMPs	antimicrobial proteins and peptides
GCF	gingival crevicular fluid
LPS	lipopolysaccharide
MIC	minimal inhibitory concentration

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PLUNC	palate, lung, nasal epithelium clone
PSP	parotid secretory protein
SLPI	secretory leukoprotease inhibitor

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TABLE 1

Oral AMPs stored in neutrophil granules:

Gene	Protein
AZU1	Azurocidin
B2M	Beta-2-microglobulin
BPI	Bactericidal/Permeability-increasing protein
CAMP	Cathelicidin (LL-37)
DEFA1	HNP-1 (Neutrophil defensin)
DEFA1, DEFA3	HNP-2
DEFA3	HNP-3
LTF	Lactoferrin
LYZ	Lysozyme
MPO	Myeloperoxidase
PGLYRP1	Peptidoglycan recognition protein 1
S100A7	Psoriasin, Protein S100-A7
SLPI	Secretory Leukoprotease inhibitor protein

Table 1 lists the AMPs stored in netrophils that are also found in the oral cavity (saliva or gingival crevicular fluid). Neutrophil data are from [85,86].

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Table 2

Antimicrobial proteins that are differentially regulated in periodontal disease.

PROTEIN	GENE	CHANGE IN PERIODONTITIS	SAMPLE	REFERENCE
Upregulated in periodontal disease				
Adrenomedullin	ADM	Up 2-fold	GCF	[87]
Beta-2-microglobulin	B2M	Up 3–10-fold	GCF	[88]
Beta defensin-1, hBD1	DEFB1	Up-regulated chronic	mRNA gingiva	[89]
Beta defensin-4A beta-defensin-2 hBD-2	DEFB4A	Up-regulated aggressive	mRNA gingiva	[89]
Calgranulin A Protein S100-A8	S100A8	Up 2–3-fold	GCF	[90]
Cathelicidin (LL-37)	CAMP	Up-regulated Aggressive and Chronic periodontitis	GCF	[24]
Cystatin C	CST3	Up-regulated	Whole Saliva	[91]
Hemoglobin Beta-globin Alpha globin	HBB HBA1 HBA2	Increased due to bleeding		
HNP-1-3 Neutrophil defensins 1–3	DEFA1	Up 15-fold Aggressive perio. Up 60-fold Chronic perio.	GCF	[24]
Lysozyme C	LYZ	Up Aggresive periodontitis	GCF	[92]
Short palate, lung and nasal epithelium clone 2 Parotid Secretory Protein	SPLUNC2	Up 3.3-fold	Whole Saliva	[67]
Transferrin Serotransferrin	TF	Upregulated	GCF	[93]
Vasoactive Intestinal Peptide	VIP	Upregulated	GCF	[83]
Down-regulated in periodontal disease				
Beta defensin-1, hBD1	DEFB1	Down regulated aggressive	mRNA gingiva	[89]
Beta Defensin 103 beta-defensin-3, hBD3	DEFB103A	Down-regulated		[94]
Calcitonin Gene Related Peptide 1	CALCA	Down regulated	GCF	[95]
Cystatin S	CST4	Down-regulated	Whole Saliva	[91]
Cystatin SA	CST2	Down regulated	Whole Saliva	[96]
Cystatin SN	CST1	Down regulated	Whole Saliva	[97]
Fibronectin	FN1	Down 2-fold with less intact fibronectin in periodontitis.	GCF	[98] [99]
Lactoferrin Lactotransferrin	LTF	Down 1.7-fold Aggressive (highly variable)	Whole Saliva	[67] [100]
Mucin 7. MG2	MUC7	Down 3-fold	Saliva	[100]
Neuropeptide Y	NPY	Down regulated in periodontitis	GCF	[101]
Secretory leukoprotease inhibitor protein	SLPI	Down regulated in periodontitis	GCF	[58]

Table 2 lists the AMPs that are up-regulated or down-regulated in periodontal disease when compared with healthy controls. When known, the table lists the fold-change, whether the change occurs in aggresive or chronic periodontitis and the sample site.