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REVIEW

Oral antimicrobial peptides: Types and role in the oral cavity

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Abstract Antimicrobial peptides (AMPs) are a wide-ranging class of host-defense molecules that act early to contest against microbial invasion and challenge. These are small cationic peptides that play an important in the development of innate immunity. In the oral cavity, the AMPs are produced by the salivary glands and the oral epithelium and serve defensive purposes. 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.

Contents

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1. Introduction

All living organisms have defense systems for combating microorganisms and potential pathogens (Zasloff, 2002; Dale et al., 2006; Martin et al., 2015). In the higher vertebrates, prior to the evolution of adaptive immunity, a more simpler and nonspecific system of innate immunity evolved and still continues to play a role as the principal defense system for almost all living organisms (Adonogianaki et al., 1993, 1996; Aguilera et al., 1998). The innate immunity modulates its antimicrobial functionality by small cationic peptides with activity against gram-positive and negative bacteria, parasites, fungi and some viruses (Akalin et al., 1993; Allaker et al., 1999; Allgrove et al., 2008). The mechanism of action against microbes and pathogens is principally attributed to the disruption of the microbial cell membrane (van't Hof et al., 2001; Shai, 2002). However, complete understanding of the exact process or processes is deficient and it is plausible that other mechanisms are at play which are yet to be identified (Quinones-Mateu et al., 2003; Sinha et al., 2003; Wang et al., 2004; Yasin et al., 2004; Gordon et al., 2005a,b).

The innate immune system augments the physical and chemical barriers e.g. skin and mucous membranes by producing antimicrobial peptides (AMPs) (Hancock and Sahl, 2006). AMPs have a widespread distribution in human body and have antimicrobial activity against microorganisms (Zasloff, 2002; Gordon et al., 2005a,b). All AMPs are extracted from larger precursors and comprise of a signal sequence with post-translational modification that includes glycosylation (Sewald and Jakubke, 2002), proteolysis (Vos et al., 1995), amino-acids isomerization, carboxy-terminal amidation and halogenation (Bulet et al., 1993). To date around 106 Human host defense peptides have been identified (Wang, 2014). AMPs are found in oral saliva, in the epithelium and in neutrophils (Dale et al., 2006). AMPs are classified in different classes according to amino acid composition, size and conformational structures (Table 1) (Hancock and Lehrer, 1998; Brogden, 2005; Harris et al., 2009).

The oral cavity has a very unique environment and microorganisms and pathogens have easy access to it and the rest of the body through epithelium and the gastrointestinal tract (Dale and Fredericks, 2005). Despite the high microbial load of the oral cavity that can potentially be disease forming, abrasions, cuts and minor surgical procedures rarely lead to infection. This indicates the highly effective host-defense mechanisms that exist and are active (Zasloff, 2002). Oral epithelial cells, salivary glands and neutrophils secrete at least forty-five identifiable antimicrobial gene products that are found in saliva. Saliva acts as a potent line of defense owing to its antibacterial, antioxidant and antifungal properties along with the oral mucosa, which plays a role as an important barrier (Amerongen and Veerman, 2002; Yoshio et al., 2004). The most common AMPs that express in the oral cavity are listed in Table 2. Subsets of these AMPs are also expressed in the crevicular fluid and are more concentrated than in saliva (Alves and Olivia Pereira, 2014; Ashby et al., 2014). In addition to their role played as antimicrobials, AMPs also serve as effective biological molecules in immune activation, inflammation and wound healing (Yang et al., 2002; Koczulla and Bals, 2003; Yang et al., 2004) and are being extensively researched upon for clinical applications (Koczulla and Bals, 2003; Dale et al., 2006; Meyer and Harder, 2007; Kang et al., 2014; Vale et al., 2014).

Table 1 Representation of antimicrobial peptides classification on different basis.

Classes	Comments
Anionic peptides	They are small, rich in glutamic acids and aspartic acids, present in human, cattle and sheep
Linear cationic α-helical peptides	They are short of cysteine and short peptides. e.g. LL37 from human
Cationic peptides enriched for specific amino acids	They are proline rich peptides e.g. abaecin from honeybees
Anionic and cationic peptides (contain cysteine and disulfide bonds)	They contain cysteines with one or more disulfide bonds e.g. protegrin from pigs, tachyplesins from horse crabs and α–β-defensins from humans, cattle, mice and pigs
Anionic and cationic peptides fragments of larger proteins	They are similar to other AMPs but their role in innate immunity is not yet clear. e.g. lactoferricin from Lactoferrin and casocidin-I from human casein

Table 2 Complete list of human oral antimicrobial peptides from Antimicrobial Peptide Database (APD).

Antimicrobial peptides	Year	Site of expression
α-Defensins (HNP-1)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α-Defensins (HNP-2)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α-Defensins (HNP-3)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α-Defensins (HNP-4)	1989	Neutrophils
β-Defensins (hBD-1)	1995	Suprabasal layer of stratified epithelium and saliva
β-Defensins (hBD-2)	1997	Gingival epithelium and saliva
β-Defensins (hBD-3)	2001	Skin and salivary gland
Histatin-1	1988	Saliva (parotid and submandibular)
Histatin-3	1988	Saliva (parotid and submandibular)
Histatin-5	1988	Saliva (parotid and submandibular)
Adrenomedullin	1993	Epithelium
Cathelicidins (LL-37)	1995	Neutrophils, inflamed epithelia, submandibular glands and saliva

http://aps.unmc.edu/AP/.

2. Mechanisms of action

Many studies have previously researched and reported the mechanisms of action of AMPs against microorganisms (Vos et al., 1995; Gennaro et al., 2002; Ganz, 2003; Brogden, 2005; Dale et al., 2006; Gorr, 2009; Melo and Castanho, 2012; Tomasinsig et al., 2012; Haney et al., 2013; Wang, 2014). However, the mechanisms most widely accepted are the barrel-stave model, carpet model, and toroidal model for killing organisms. 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 (Fig. 1a). 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 (Fig. 1b). 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 (Fig. 1c) (Epand and Vogel, 1999; Bocchinfuso et al., 2009). Types and role of antimicrobial peptides have been discussed here.

3. Types of oral antimicrobial peptides

3.1. Defensins

Defensins are short, cationic, low molecular weight (~4–5 kDa) peptides with ~6–8 cysteine residues which form 3–4 intramolecular disulfide bonds (White et al., 1995). 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 (Ganz, 2003; Wang et al., 2004; Diamond and Ryan, 2011; Wang, 2014). Human defensins are classified as

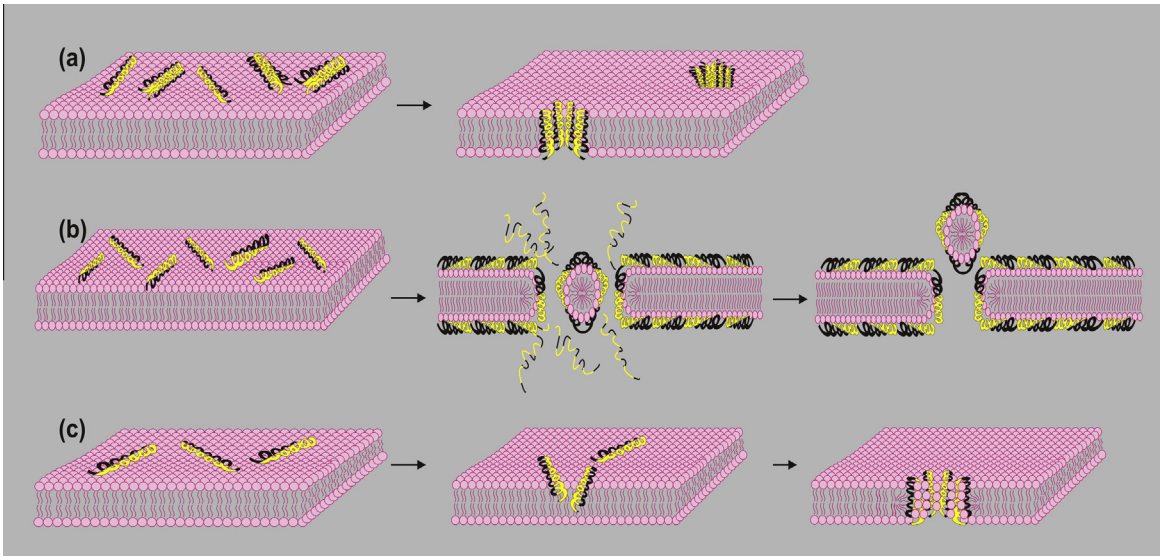

Figure 1 Illustration representing model of antimicrobial peptides for killing microorganisms. (a) Barrel-stave model, (b) carpet model and (c) toroidal model.

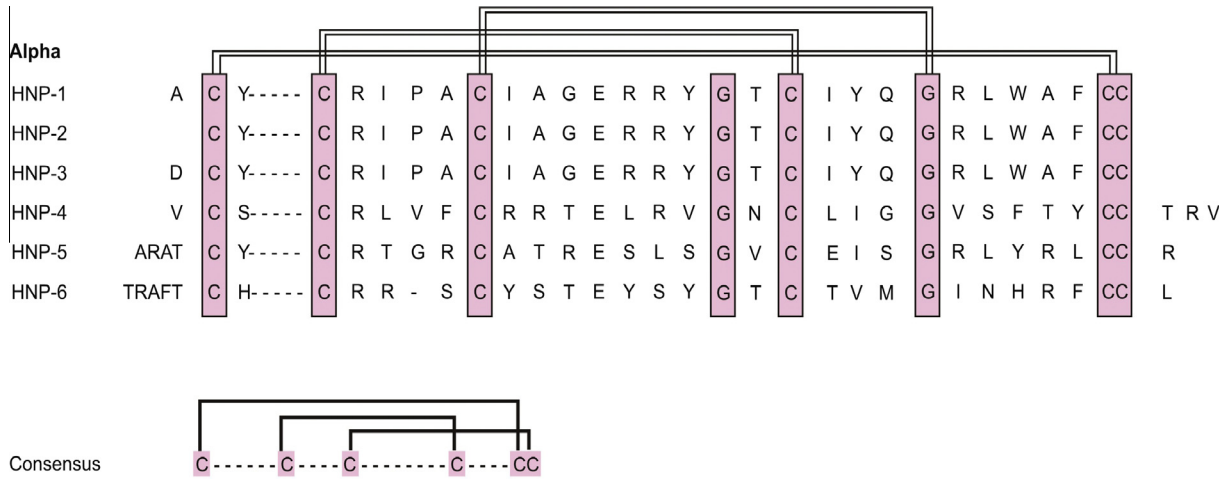

Figure 2 Molecular structure of human α-defensins with their cysteine consensus.

α-, β- and θ- on the basis of their length, location, position of cysteine and folding of peptide chains (Abiko et al., 2007; Greer et al., 2013).

Mature α-defensin family has been isolated from human neutrophils such as hNP-1, hNP-2, hNP-3 and hNP-4 (Selsted et al., 1985). 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 (Fig. 2). These changes affect defensin antimicrobial spectrum as already reported by Ganz et al. (1985). The hNP-3 is less active than hNP-1 or hNP-3 in destroying *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* (Ganz et al., 1985). hNP-4 has been researched and identified by Griffith et al. by chromatographic methods, as 33 amino acid sequences expressed in neutrophils with activity against *E. coli*, *Streptococcus faecalis* and *Candida albicans* (Wilde et al., 1989). The last two family members of α-human neutrophils peptides (hNP-5 and hNP-6) are present in the enteric system and do not express in the oral cavity (Gomes Pde and Fernandes, 2010). 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 (Gabay et al., 1989; Gomes Pde and Fernandes, 2010). The concentration of hNP-1 is higher in saliva of patients with oral diseases such as lichen planus, leukoplakia and squamous cell carcinoma in contrast to healthy individuals (Dunsche et al., 2001). The level of hNP-1, -2 and -3 has been shown to be reduced in edentulous patients due to the absence of gingival crevices (Fanali et al., 2007). Dale et al. have reported low salivary levels of α-defensins (hNP-1, -2 and -3) in patients having dental caries and suggested that these are biological factors that can be used for caries risk assessment in general population (Dale et al., 2006).

The β-defensins family contains six members (hBD-1-6), and principally they are all expressed in epithelial cells that cover several tissues and organs including the skin, mucosal surfaces of oral cavity, respiratory tract, gastrointestinal tract, genitourinary tract, and kidney (Gorr, 2011). The molecular structure of β-defensins is represented in Fig. 3. Research has proved that only hBD-1, hBD-2, and hBD-3 are expressed in the oral cavity (gingival epithelia, tongue, palate and buccal mucosae, salivary glands/ducts and saliva) (Dale and Krisanaprakornkit, 2001). Human Beta defensins-1 and -2 localized within the suprabasal layer of normal gingiva and

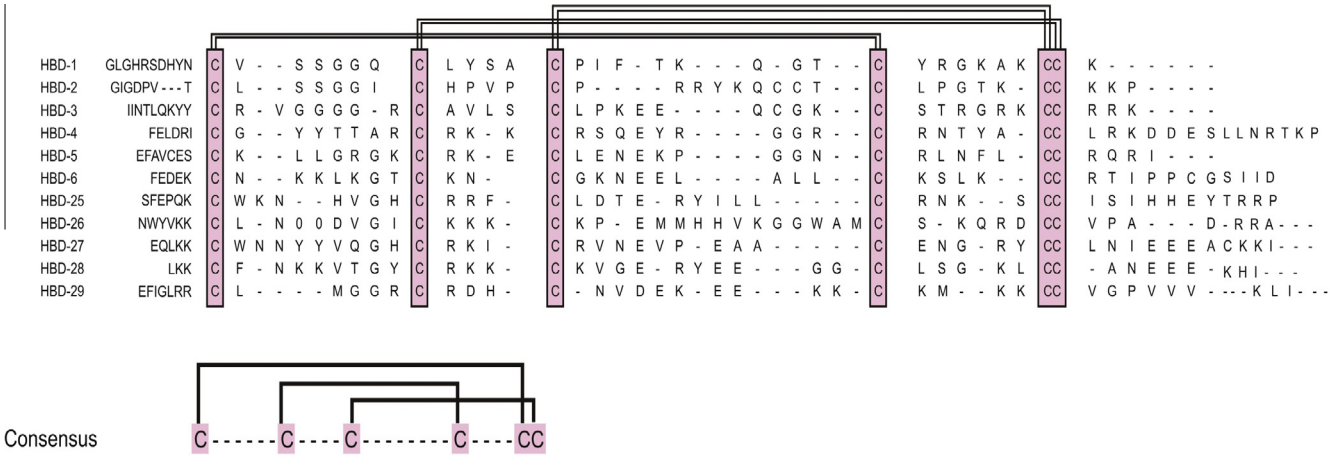

Figure 3 Molecular structures of β-defensins.

hBD-3 peptide are expressed in undifferentiated epithelial cells within the basal layer (Pisano et al., 2005). It has been suggested that hBD-1 is continuously expressed and plays a role in the impediment of normal flora from becoming opportunistic, whereas the hBD-2 and -3 are inducible in response to bacterial lipopolysaccharides (LPS), proinflammatory mediators (Interleukins [IL-1β], tumor necrosis factors [TNF-α], interferons [IFN-γ]) and are more effective against almost all pathogens (Krisanaprakornkit et al., 1998). These peptides are in low concentration in the gingival crevicular fluid. Immunohistochemistry has been carried out in tissues sample from radicular cyst, lichen planus, leukoplakia and candida leukoplakia suggesting that hBD-2 is forcefully induced by lichen-planus related inflammation and plays role in protecting *Candida albicans* (Abiko et al., 2002). Zhao et al. reported that the location of human genes for α-defensins and β-defensins is adjacent to loci on chromosome 8p22-p23 (Liu et al., 1997).

3.2. 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 50–425 μg/ml in healthy adults (de Sousa-Pereira et al., 2013). They are 7–38 amino acid residues in length with at least 12 histidine residues, hence called as *histidine rich proteins*. Histatins are predominantly antifungal and comprise of three main members (His-1, His-3 and His-5) with other members being generated from the proteolytic cleavage of these (Table 3) (MacKay et al., 1984; Troxler et al., 1990). Along with the capability of inhibiting the growth of *Candida* species, they have other functions such as regulating oral hemostasis and bonding of metal ions in saliva (Bercier et al., 1999; Oudhoff et al., 2009). Histatins have high affinity for enamel surfaces and play a role in the formation of acquired enamel pellicle (Richardson et al., 1993). Their antifungal mechanism has a few phases: bonding to the specific membrane, transport through membrane, inhibition of mitochondrial respiration by forming reactive oxygen species, entering the cell by mobilization of ions (K^+, Mg^{2+}) and causing cell death (Xu et al., 1991).

Oral candidiasis is a common infection in the human oral cavity associated with trauma or in immunocompromised patients due to low salivary flow (Sjogren's syndrome). In these situations, histatins play an active positive role. *In-vitro*, Hst-5 has been shown to inhibit *Candida* species (*Candida albicans, Candida glabrata, Candida krusei, and Cryptococcus neoformans*) at physiological concentration (15–30 μM) (Raj et al., 1990). Another study demonstrated that Hst M (middle portion of Hst-3) has the same candida-cidal activity as the full length molecule and this indicates the potential future use of short length antifungal peptides for oral ointments (Raj et al., 1990). Common cause of biofilm in dental prosthesis is by colonization of *Candida* and Hst-5 has showed potent limiting effect on biofilm in comparison with chlorhexidine (Pusateri et al., 2009). A promising antimicrobial peptide appears to be the histatin 5 12-mer P113 (Demegen) which works as a mouth rinse for oral candidiasis in patients with human immuno deficiency virus HIV (Gorr, 2009, 2011).

3.3. Cathelicidins (LL-37)

Cathelicidins (LL37) are AMPs from the family of α-helical peptides without cysteine and located at the carboxyl terminus of a 15–18 kDa highly conserved cathepsin-L-inhibitor (cathelin)-like domain (Lehrer and Ganz, 2002; Kosciuczuk et al., 2012). Cathelicidins only have one delegate in humans in the oral cavity and respiratory tract which is known as human cationic antimicrobial peptide (hCAP18) (Murakami et al., 2002; Tecle et al., 2010). They are synthesized and stored in cells as 2-domain proteins and when required are split by proteases to produce a cathelin protein and an antimicrobial peptide. They derive their name from the first two residues at the N-terminus (**L**eucine, **L**eucine) and contain 37 amino acids (Zanetti et al., 2002). LL37/hCAP18 has the function of stimulation of monocytes, neutrophils, mast cells and T-cells. Various studies have demonstrated the capability of LL37/hCAP18 as a potent antimicrobial against many gram-negative and positive bacteria, fungi, viruses and parasites (Tanaka et al., 2000; Isogai et al., 2003b; López-García et al., 2005). LL37/hCAP18 neutralizes bacteria very quickly by forming ionic channels in the cell membranes of the microorganisms and by ability to bind LPS of bacterial membranes (Zanetti et al., 2002). Turner, Cho et al. reported minimal inhibitory concentration (MIC) of LL37/hCAP18 range of less than 10 μg/ml against microorganisms (Turner et al., 1998). Another study demonstrated the stronger killing action of LL37/hCAP18 derived synthetic peptides against *Streptococcus sanguis* (isolated from Behcet's disease) (Isogai et al., 2003a). In addition, Ouhara et al. chemically

Table 3 Histatin family with their proteolytic fragments.

Natural histatins present in saliva	Sequences
Histatin 1	DSpHEKRHHGYRRKFHEKHHSHREFPFYGDYGSNYLYDN
Histatin 3	DSHAKRHHGYKRKFHEKHHSHRGYRSNYLYDN
Histatin 5	DSHAKRHHGYKRKFHEKHHSHRGY
Proteolytic fragments in saliva	
Histatin 2	RKFHEKHHSHREFPFYGDYGSNYLYDN
Histatin 4	KFHEKHHSHRGYRSNYLYDN
Histatin 6	DSHAKRHHGYKRKFHEKHHSHRGYR
Histatin 7	RKFHEKHHSHRGY
Histatin 8	KFHEKHHSHRGY
Histatin 9	RKFHEKHHSHRGYR
Histatin 10	KFHEKHHSHRGYR
Histatin 11	KRHHGYKR
Histatin 12	KRHHGYK

synthesized human b-defensin-1 (hBD1), hBD2, hBD3 and LL37 (CAP18) for their antimicrobial activity against oral bacteria (*Streptococcus mutans*, *S. sanguinis*, *S. salivarius* and *S. mitis*) and demonstrated the high activity of LL37 against these pathogens (Ouhara et al., 2005).

3.4. Adrenomedullin

Adrenomedullin is a cationic amphipathic peptide with one disulfide bond. It is a proteolytically processed 185 amino acid protein initially that is C-terminally amidated to create the mature 52 amino acid adrenomedullin (Gorr, 2009). This AMP is present in the gingival crevicular fluid and saliva. Although adrenomedullin is in both glandular and whole saliva, it is in large concentrations in whole saliva (Gorr, 2009). This suggests that the oral epithelial cells donate to the salivary expression of adrenomedullin (Kapas et al., 2004). It has been observed that the quantity of adrenomedullin is almost double in periodontally compromised areas than in healthy areas (Lundy et al., 2006).

3.5. Statherin

Statherin is a 5.4 kDa peptide belonging to the histatin/statherin family. It is believed that statherin and a basic histidine-rich peptide might have developed from a common ancestral gene (Dickinson et al., 1987). Antimicrobial properties are observed in C-terminal peptide of the statherin (Kochanska et al., 2000). Statherin is found in saliva (Vitorino et al., 2004; Wilmarth et al., 2004; Denny et al., 2008) and the gingival crevicular fluid (Pisano et al., 2005). This AMP is secreted by the submandibular and the parotid glands and hinders the growth of anaerobic bacteria isolated from the oral cavity (Vitorino et al., 2004; Wilmarth et al., 2004; Denny et al., 2008). Statherin also restrains the crystallization of calcium phosphate and hence may have a protective role against plaque formation (Wilmarth et al., 2004; Denny et al., 2008). The proteomic analysis of saliva acquired from patients with high and low numbers for bacterial adhesion and agglutination has revealed the potential of statherin to be utilized as a biomarker for infections in oral cavity (Rudney et al., 2009).

3.6. C–C motif chemokine 28

This is a 128-amino acid peptide, which is principally expressed in a variety of epithelial cells, including salivary glands, and is observed in saliva (Denny et al., 2008). The C–C motif chemokine 28 acts both as a broad-spectral antimicrobial agent and as a chemokine (Gorr, 2009). A C-terminal 28 amino peptide has similarities with histatin 5 and this peptide is salt sensitive, and increases the permeability of cell membrane, as has been noted for other cationic AMPs (Hieshima et al., 2003).

3.7. Azurocidin

Human saliva proteomic analysis helped in the identification of azurocidin, which is a 37 kDa cationic antimicrobial protein expressed in azurophil granules of neutrophils 1(264,55). Azurocidin is a 251-amino acid protein which has strong antibacterial properties toward gram-negative bacteria due to having strong affinity for lipopolysaccharide (Gorr, 2009; Dhaifalah et al., 2014). The two cysteine residues in positions 52 and 68 are thought to be essential for the antibacterial activity (Soehnlein and Lindbom, 2009).

3.8. Neuropeptides

Gingival crevicular fluid contains the neuropeptides, calcitonin gene related peptide and substance P (Awawdeh et al., 2002). In addition to these peptides, the neuropeptide Y and vasoactive intestinal peptide are also expressed and present in salivary fluids (Dawidson et al., 1997). However, their antimicrobial role is extremely limited since their concentrations varying from 2 to 45 pg/ml are lower by several orders of magnitude than the minimum inhibitory concentrations required to be effective against *Candida albicans* and bacteria (El Karim et al., 2008).

3.9. Role of AMPs in oral diseases

The exposure of gingival epithelial cells with bacteria related to periodontitis results in the production of β-defensins and LL-37 (Gorr, 2009). Around twenty genetic disorders connected with periodontal disease have been identified to date (Hart and Atkinson, 2007). Some of these disorders are associated with alterations in the AMP expression, which potentially increases the susceptibility to bacterial infections (Gorr, 2009). It has been shown that conditions of sever congenital neutropenia (Morbus Kostmann disease) are associated with severe irreversible periodontitis (Putsep et al., 2002). These patients have insufficient LL-37 in neutrophils, saliva and plasma. Also the α-defensins are markedly reduced (to about 30% of normal) while the lactoferrin content in plasma remains normal (Putsep et al., 2002). Individuals suffering from Morbus Kostmann when treated with granulocyte–colony stimulating factor demonstrate regular neutrophil count but still lack LL-37 and continue to suffer from advanced periodontal disease (Carlsson et al., 1967; Putsep et al., 2002). It has been observed that bone marrow transplantation in a patient resulted in the restoration of both neutrophils and LL-37 to normal levels. While this proved that LL-37 is related to periodontal disease, normal levels were not enough to prevent or restore the periodontal disease alone (Bachrach et al., 2006; Gorr, 2009). Periodontal disease is also common in children with Down's Syndrome (Trisomy 21) (Orner, 1976). Mucin-7 and lactoferrin are other AMPs that are associated with periodontal disease. In A. actinomycetemcomitans-associated periodontitis, the levels of mucin-7 are decreased three fold when compared with disease free patients (Groenink et al., 1999). Lactoferrin levels are shown to be within normal ranges, but the protein is iron saturated, indicating a reduction in the antimicrobial properties in patients with periodontitis (Groenink et al., 1999).

Other oral diseases and infections have also exhibited relations to the levels of expression of AMPs. Low levels of variety of AMPs, including lactoferrin and β-defensins 1 and 2 are associated with oral candidiasis (Tanida et al., 2003). Remarkable variations in susceptibility to AMPs hBD3 and LL-37 have been noted between different species of oral bacteria and different strains of the same species (Ji et al., 2007).

A good example of this is the Streptococcus Gordonii M5 that is weakly susceptible to both AMP hBD3 and LL-37, while Streptococcus. Gordonii 10,558 is highly susceptible. *P. gingivalis* 33,277, by contrast, is less susceptible to LL-37 but greatly susceptible to death by hBD3 (Ji et al., 2007). Haim–Munk syndrome and the Papillon–Lefe'vre syndrome are induced by allelic mutations of the cathepsin C gene, CTSC 1 and identified by severe periodontitis and palmoplantar keratoderma (Hart, Hart et al., 2000). Although, patients with Papillon–Lefe'vre syndrome express normal levels of the cathelicidin precursor, very little is processed to the mature LL-37 peptide. Similar to Morbus Kostmann, it is plausible that the decreased levels of LL-37 result in occurrence of periodontitis in patients with Papillon–Lefe'vre syndrome (de Haar et al., 2006).

The interrelation of AMPs expression levels and occurrence of caries have been difficult to establish. Development of caries in children has been linked with the low-level expression of α-defensins (human neutrophil peptides 1–3) (Tao et al., 2005). However, due to the fact that caries is observed at broad variation in α-defensin expression levels, it cannot be definitely established whether α-defensin expression is accurately predictive of development of future caries (Dale et al., 2006). Also, salivary peroxidase and lactoferrin have not shown correlation with occurrence of caries in clinical studies carried out in children (Kirstila et al., 1998) and adults (Grahn et al., 1988). The wide variety and range of AMP expression levels between study subjects is possibly one of the strong reasons for the complication in relating single point analysis of AMPs with oral disease (Tenovuo et al., 1987). It is already known that salivary peptide levels between patients can differ about 100-fold (levels normalized to total salivary protein; Tao et al., 2005). This makes it very challenging to express exact or normal values for individual AMPs. A multiplex investigative and analytical approach toward antimicrobial protein expression in healthy and diseased individuals with the aim to recognize AMP signatures would potentially result in higher predictive/diagnostic power.

4. Conclusions

A wide range of AMPs with miscellaneous functions have been discovered in the oral tissues and secretions. The protective role played by these peptides against microbes entering the oral cavity results in effective fight against infections. The interest in the potential use of AMPs as a therapeutic regimen is due to their wide range of efficacy and low rates of induced resistance owing to the co-evolution of pathogens and the host AMPs. After reviewing the literature we can conclude that these AMPs have 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 designing effective oral microbial antibiotics.

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