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Review article

Potential applications of antimicrobial peptides and their mimics in combating caries and pulpal infections

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ABSTRACT

Antimicrobial peptides (AMPs) are short cationic host-defense molecules that provide the early stage of protection against invading microbes. They also have important modulatory roles and act as a bridge between innate and acquired immunity. The types and functions of oral AMPs were reviewed and experimental reports on the use of natural AMPs and their synthetic mimics in caries and pulpal infections were discussed. Natural AMPs in the oral cavity, predominantly defensins, cathelicidins and histatins, possess antimicrobial activities against oral pathogens and biofilms. Incomplete debridement of microorganisms in root canal space may precipitate an exacerbated immune response that results in periradicular bone resorption. Because of their immunomodulatory and wound healing potentials, AMPs stimulate pro-inflammatory cytokine production, recruit host defense cells and regulate immuno-inflammatory responses in the vicinity of the pulp and periapex. Recent rapid advances in the development of synthetic AMP mimics offer exciting opportunities for new therapeutic initiatives in root canal treatment and regenerative endodontics.

Statement of Significance

Identification of new therapeutic strategies to combat antibiotic-resistant pathogens and biofilm-associated infections continues to be one of the major challenges in modern medicine. Despite the presence of commercialization hurdles and scientific challenges, interests in using antimicrobial peptides as therapeutic alternatives and adjuvants to combat pathogenic biofilms have never been foreshortened. Not only do these cationic peptides possess rapid killing ability, their multi-modal mechanisms of action render them advantageous in targeting different biofilm sub-populations. These factors, together with adjunctive bioactive functions such as immunomodulation and wound healing enhancement, render AMPs or their synthetic mimics exciting candidates to be considered as adjuncts in the treatment of caries, infected pulps and root canals.

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1. Introduction

Antimicrobial peptides (AMPs), a wide-ranging class of host-defense molecules, have attracted much attention in clinical medicine due to their potent antimicrobial activities against a broad spectrum of microorganisms and their low bacterial resistance [1–4]. Natural AMP molecules are present in the oral cavity and possess antimicrobial activities against oral pathogenic bacteria and biofilms [5]. These small cationic peptides also play important roles in the development of innate immunity and possess immunomodulatory functions [6–11]. Because intracanal pathogens may evade chemomechanical debridement [12], elimination of persistent pathogens and effective control of chronic immuno-inflammatory responses represent important targets for development of novel therapeutic initiatives in root canal therapy, potentially through the use AMP-mimicking peptides [13]. Hence, the objectives of the present review are to clarify the function of oral AMPs and their peptidomimetics, and to highlight their potential applications in combating caries and pulpal infections.

2. Classification and overall functions

Since the discovery of lysozyme, the first natural antibiotic isolated from the human body a century ago, a plethora of molecules with antimicrobial activities have been identified from animals, insects, plants and bacteria that have revolutionized clinical medicine [14]. According to the most recent antimicrobial peptide databases [15–17], > 4000 AMPs have been discovered to date.

Natural AMPs are highly heterogeneous in length, sequence and structure, but the majority are small, cationic and amphipathic. Three important classes of AMPs are present in humans: defensins, cathelicidins and histatins [18]. Alpha-defensins and β-defensins are cationic, non-glycosylated peptides containing six cysteine residues that form three intramolecular disulfide bridges, resulting in a triple-stranded β-sheet structure. Histatins are small, cationic, histidine-rich peptides present in the saliva. They adopt a random coil conformation in aqueous solvents and form α-helices in non-aqueous solvents. Only one cathelicidin, LL-37, is identified in humans. This peptide is cleaved from the C-terminal end of the human CAP18 protein. Similar to histatins, the LL-37 molecule adopts a random coil conformation in a hydrophilic environment, and forms an α-helical structure in a hydrophobic environment.

Human AMPs exhibit broad spectrum activities against Gram-positive and Gram-negative bacteria, yeasts, fungi and enveloped viruses. The innate immune system augments the physical and chemical barriers of the human body (e.g. skin and mucous membranes) by producing AMPs [19]. These natural peptides have pleiotropic functions; they not only kill microbes but also control host physiologic functions such as inflammation, angiogenesis and wound healing. Their activities include chemotactic functions, cytokine production, histamine release, lipopolysaccharide-binding and other immunomodulatory activities that, in concert, result in activation of the adaptive immune response [20].

Recent advances in the understanding of AMPs have been associated with their abnormal production in dermatological disorders such as psoriasis, atopic dermatitis and rosacea [20]. Expression of AMPs is also associated with viral infectious diseases such as mollusca contagiosm, condyloma acuminatum and verruca vulgaris [21,22], as well as autoimmune diseases such as cutaneous lupus erythematosus [23]. These examples illustrate how AMP induction or suppression may be adopted for management of autoimmune diseases and inflammation [24]. Commercialized AMP products are available with the potential to treat osteoporosis, diabetes, HIV, prostate, breast and bone cancer, heart failure, multiple sclerosis, neuroendocrine tumors, hereditary angioedema, pain, and idiopathic thrombocytopenic purpura [25].

2.1. Selective cytotoxicity of AMPs to microbes

Antimicrobial peptides may be described as natural microbicides that are selectively cytotoxic to bacteria, while exhibiting minimal cytotoxicity toward mammalian cells of the host organism. The selective cytotoxicity of AMPs toward microbes is due to the fundamental differences in composition and structure of the host cells, compared to those of pathogenic bacteria and yeasts, as well as the differential expression and localization of AMPs that prevent unwanted interactions with vulnerable host cells [26]. These peptides act by their relatively strong electrostatic attraction to the negatively-charged bacterial cells and relatively weak interaction to the eukaryote host cells; the latter are usually less negatively-charged than prokaryotes [27]. Regardless of their origin, AMPs share many common properties such as having net positive charges, being amphipathic and, in most cases, are membrane active [28].

The cell membranes of most pathogenic bacteria comprise mostly hydroxylated phospholipids such as phosphatidylglycerol, cardiolipin, and phosphatidylserine, which render them very electronegative. By contrast, mammalian cell membranes are rich in phosphatidylethanolamine, phosphatidylcholine or its analog, sphingomyelin. This makes the mammalian cell membranes neutral in terms of net charges [29,30]. In addition, cholesterol and other sterols such as ergosterol are abundantly found in eukaryotic cell membranes, but are seldom identified in prokaryotic membranes. These molecules are generally neutrally-charged [29] and increase the rigidity of membranes, which can reduce the insertion of AMPs. Differences in membrane symmetry, saturation of phospholipid bilayers, and compositional stoichiometry will influence the membrane's fluidity and phase transition [31]. This significant difference in transmembrane electrochemical potential may be another factor that enables AMPs to distinguish between host and target cells [27].

Previous studies suggest that the dynamic and/or inherent conformations of AMPs contribute to their selective cytotoxicity [27,32,33]. Moreover, AMPs may undergo conformational transition, self-association or oligomerization within the target pathogen