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Communication

Biological Control of Cariogenic Bacteria and Periodontal Pathogens by Antimicrobial Peptides

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Abstract

The oral cavity is the second most diverse microbial ecosystem providing residency to AMP producers which play a significant role in shaping the community structure and preserving the delicate equilibrium between the host and the residential microbial flora. The integration of AMPs in the microbial membranes can disrupt the membrane structure, eventually causing cellular death. On the other hand, the permeabilization of the membrane allows for AMP leakage into the cytoplasm, where it can bind to nucleic acids and cellular components to disrupt the normal functioning of the microbial metabolism. Production of bacteriocins among oral bacteria has been commonly found in of the genera *Streptococcus*, *Lactobacillus*, *Fusobacterium*, and *Prevotella*. Furthermore, many of these have probiotic potential. Bacteriocins have been explored as alternatives to antibiotics for combating cariogenic species. For instance, the lantibiotic nisin has shown effectiveness in vitro against mono-species biofilms of *Streptococcus mutans*. Among the late colonizers studied, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans* were particularly sensitive to nisin. Furthermore, when cultured in the presence of nisin, multispecies biofilms showed a reduction in biomass and thickness. Through further advancements and collaborations between researchers, healthcare professionals, and industry partners, we can harness the power of these naturally occurring molecules to develop innovative therapies that effectively combat infections and enhance human health.

Keywords: antimicrobial peptides; bacteriocins; *Streptococcus mutans*; *Porphyromonas gingivalis*

Biological Control of Cariogenic Bacteria and Periodontal Pathogens by Antimicrobial Peptides

Maintaining a delicate balance between normal flora and the host's metabolic and immune activities is crucial for overall health. To achieve this, humans produce naturally occurring antimicrobials in every ecosystem or microhabitat. Antimicrobial peptides (AMPs) are a type of natural antimicrobial that targets pathogenic microbes. Through the disruption of biofilms and modulation of bacterial populations, phages may help mitigate the inflammatory responses that drive cancer progression. In multicellular organisms, the production of AMPs is referred to as host defense peptides, while AMPs produced by bacteria are commonly known as bacteriocins. Bacteriocins can be categorized into several subclasses, with lantibiotics, produced by lactic acid bacteria, being the most extensively studied [1]. Research has shown that AMPs produced by humans specifically target harmful microbes and help maintain ecological balance in the gut [2]. Additionally, bacteriocins play an important role in providing ecological advantages by eliminating competing bacteria, which in turn increases the availability of nutrients in their environment [1].

AMPs are ubiquitous and do short, frequently post-translationally modified polypeptides comprise 12-50 amino acids, synthesized via the ribosomal pathway. These peptides have varied

structures that modulate their mode of action. The formation of pores in microbial membranes is the most common bactericidal mechanism of AMPs. Additionally, targeting of intracellular components has also been reported [1,3]. AMPs are usually constituted by a C-terminal domain, responsible for pore formation in bacterial membranes, connected to an N-terminal domain, responsible for the binding to bacterial surface receptors. The integration of AMPs in the microbial membranes can disrupt the membrane structure, eventually causing cellular death. On the other hand, the permeabilization of the membrane allows for AMP leakage into the cytoplasm, where it can bind to nucleic acids and cellular components to disrupt the normal functioning of the microbial metabolism [3,4]. Production of bacteriocins among oral bacteria has been commonly found in of the genera *Streptococcus*, *Lactobacillus*, *Fusobacterium*, and *Prevotella*. Furthermore, many of these have probiotic potential [5]. Most of the studies on isolated bacteriocins for therapeutic approaches have been based on the subclass lantibiotics [6]. AMPs have been presented as alternatives to antibiotics to treat microbial infections in humans for their selectivity towards microbial cells and less expected tendency to induce resistance. The AMPs accepted or approved by the FDA and already on the market are polymyxins B and E (colistin) and daptomycin [1]. Other natural AMPs have been tested as therapeutics in vitro, and some are currently undergoing in vivo assays and clinical trials.

The production of human antimicrobial peptides (AMPs) occurs in the oral cavity, specifically within the salivary glands, oral mucosa, and dental pulp. Some AMPs have also been detected in gingival crevicular fluid (GCF) [7,8]. There are three main types of AMPs identified in the oral context. Defensins can be expressed either constitutively in salivary glands or in response to bacterial-induced inflammatory signals [7]. They exhibit antimicrobial activity against bacteria, fungi, and viruses.[7,8]. Human β - (hBDs) can be released by the host's immune cells defensins and have been found in various oral mucosal surfaces and epithelial tissues [7]. Histatins are another type of AMP present in human salivary glands. These are cationic, histidine-rich peptides with antibacterial and antifungal properties. They are effective against proteases and adhesins from both host and microbial sources, and they can inhibit bacterial-induced cytokine production by binding to the outer membrane proteins of pathogens.[7]. Lastly, LL-37 is the only member of the cathelicidins that has been identified in the human oral environment. This peptide is produced by both epithelial cells and neutrophils and possesses antibacterial properties. Additionally, LL-37 has immunomodulatory effects, as it can bind to inflammatory molecules of microbial origin and attract immune cells to sites of infection. Histatins are another type of AMP present in human salivary glands. These are cationic, histidine-rich peptides with antibacterial and antifungal properties. They are effective against proteases and adhesins from both host and microbial sources, and they can inhibit bacterial-induced cytokine production by binding to the outer membrane proteins of pathogens.

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2.1. AMP Against Cariogenic Bacteria

Bacteriocins have been explored as alternatives to antibiotics for combating cariogenic species. For instance, the lantibiotic nisin has shown effectiveness in vitro against mono-species biofilms of *Streptococcus mutans* [6]. However, when nisin was tested against a three-species biofilm composed of *S. oralis*, *S. gordonii*, and *A. naeslundii*, no significant antibiofilm activity was observed, and its antimicrobial effect was only moderate.[9].

In contrast, promising results have been reported using the iron-free form of lactoferrin on dual-species biofilms formed on saliva-coated surfaces. Lactoferrin significantly reduced the biofilm formed by *S. gordonii* and *Fusobacterium nucleatum*, as well as that formed by *S. gordonii* and *Porphyromonas gingivalis* [10]. Furthermore, a peptide known as 1018 nearly completely eliminated biofilm formation from supragingival plaque samples cultured in vitro [11]. These findings suggest

that antimicrobial peptides (AMPs) could be a promising approach for controlling cariogenic biofilms.

2.2. AMP Against Periodontal Pathogens

Periodontitis is an inflammatory disease of the periodontium with polymicrobial aetiology and commonly seen in oral cancer patients. [12–16]. Some antimicrobial peptides (AMPs) may help prevent the attachment and development of microorganisms related to periodontal disease into a biofilm. Nisin, which has already been shown to inhibit oral streptococci, was found to suppress the growth of both early and late colonizers in saliva-derived biofilms formed in vitro [17]. Among the late colonizers studied, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans* were particularly sensitive to nisin. Furthermore, when cultured in the presence of nisin, multispecies biofilms showed a reduction in biomass and thickness. Notably, the effect of nisin on oral epithelial cells was evaluated in vitro, and no toxicity was observed at concentrations that displayed antimicrobial and anti-biofilm activities.[17].

A characteristic of periodontal diseases is the inflammation that is common to all of them. The potential of AMPs as a strategy against these dysbiotic states partly stems from their immunomodulatory activities. Lactoferrin, which has been proposed for caries prevention, has also demonstrated significant anti-inflammatory effects due to its ability to sequester bacterial lipopolysaccharides [18]. In fact, lactoferrin is a component of several products designed for oral health maintenance, with beneficial effects confirmed in multiple clinical trials.[19].

A key concern during the development of engineered phages is their potential impact on the oral microbiome. Although these phages are genetically modified, they are designed to specifically target only pathogenic bacteria that contribute to disease states, such as those associated with tumor progression. This is achieved by using selective gene-editing tools that limit infection by pathogenic species like *Fusobacterium nucleatum* while leaving commensal bacteria unharmed [20].

Despite their potential, several challenges must be addressed before phage-based strategies can be fully integrated into clinical practice. Significant hurdles to the widespread adoption of phage therapy include phage resistance, immune system clearance, and regulatory barriers. Additionally, the complex interactions between bacteriophages, host immunity require further investigation to optimize both therapeutic efficacy and safety. Advancing research on bacteriophages in the context of oral diseases could revolutionize current treatment paradigms, offering more targeted, efficient, and patient-friendly alternatives to conventional therapies. By harnessing the natural specificity and adaptability of bacteriophages, clinicians and researchers can develop innovative approaches to combat oral diseases, ultimately improving patient care and clinical outcomes.

In conclusion, AMPs denote a promising avenue for combating infectious diseases and addressing the growing issue of antibiotic resistance. These small molecules, derived from natural sources, have shown potent antimicrobial activity against a wide range of pathogens, including bacteria, fungi, and even some viruses. Continued research and innovation in this field will pave the way for new and effective strategies in combating infections and improving patient outcomes. In conclusion, antimicrobial peptides against pathogens of oral infectious diseases offer a compelling solution to the global challenge of antimicrobial resistance. Through further advancements and collaborations between researchers, healthcare professionals, and industry partners, we can harness the power of these naturally occurring molecules to develop innovative therapies that effectively combat infections and enhance human health.

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