

Stamps-smart Bombs To Streptococcus Mutans



Dr. V.V. Subba Reddy
Principal & Head



Dr. Sathyajith Naik
Professor



Dr. R. Krishnakumar
Professor



Dr. S. Srinivasan
Reader

Department of Pedodontics and Preventive Dentistry
College of Dental Sciences

Department of Periodontics,
Rajah Muthiah Dental College and Hospital
Annamalai University

Abstract:

Plaque on the surface of the tooth consists of a bacterial film that produces acids as a by-product of its metabolism. To be specific, certain bacteria within the oral diseases, such as dental caries and periodontal disease, should be considered as consequences of ecologically driven imbalances of oral microbial biofilms. The ecological disruption resulting from antibiotic treatment frequently results in secondary infections or other negative clinical consequences. To address this problem, researchers have recently developed a new class of pathogen-selective molecules, called specifically (or selectively) targeted antimicrobial peptides (STAMPs), and based on the fusion of a species-specific targeting peptide domain with a wide-spectrum antimicrobial peptide domain.

Key Words: Biofilm- Specifically Targeted Antimicrobial Peptides; Streptococcus Mutans

Introduction:

Dental caries (tooth decay) is one of the most prevalent and costly diseases in the United States and throughout the world (Evans and Kleinman, 2000). Although the ultimate manifestation of the disease is the dissolution of tooth structure, the biological nature of the disease is a microbial infection caused primarily by the cariogenic bacterium *Streptococcus mutans* (S. mutans).¹

Dental plaque as a microbial biofilm is defined as the diverse community of micro-organisms found on the tooth surfaces, embedded in an extra cellular matrix of host and microbial polymers. The streptococci are the pioneer strains in plaque formation and mutans streptococci are the main etiological agent of dental plaque and caries.² During dental plaque formation, some oral bacteria are early colonizers that express biochemical components allowing them to adhere effectively to specific tissues (teeth or periodontal tissue). The later colonizers often contain components that enable them to adhere to the early colonizers, bringing competitive advantages. Within an established dental plaque, specific bacterial species are often found located adjacent to each other or mixed together to form unique structures that may confer adherence or growth advantages.³

In complex biofilms, it is not merely the presence of a single organism, but the interactions between and among the biofilm residents that are crucial and determine the properties of a biofilm. As an example, in the presence of nearby base-producing bacteria, S. mutans in dental plaque may not be pathogenic. Thus, for dental caries, it is now recognized that this disease results not solely because of the presence of S. mutans or any single organism in dental plaque. Rather, it is the interaction of multiple acid-producing organisms such as S. mutans with other biofilm residents (Kleinberg, 2002; Marsh, 2005)³

Most current dental therapies are focused on eradicating the entire dental plaque via mechanical removal or broad-spectrum antimicrobial treatments. However, the improved understanding of oral microbial ecology, especially the importance of the balance between oral pathogens and commensal residents, has prompted interest in novel approaches focused on selective pathogen inhibition and modulation of the microbial composition of dental plaque to control pathogenesis.¹

Stamps:

A new class of targeted antimicrobials, called specifically (or selectively) targeted antimicrobial peptides (STAMPs), constructed from short peptides that can be chemically synthesized with high yields in vitro studies. STAMPs have increased killing potency, selectivity, and kinetics against targeted bacteria.⁴

A typical STAMP molecule consists of two functionally independent moieties conjoined in a linear peptide sequence: a non-specific antimicrobial peptide serves as the killing moiety while a species-specific binding peptide comprises the targeting moiety that provides specific binding to a selected pathogen and facilitates the targeted delivery of the attached antimicrobial peptide. STAMPs have shown effective elimination of S. mutans from a mixed-species environment without affecting closely related non-cariogenic oral streptococci.¹

Sources Of Stamps:

A number of derivatives from natural products, such as cranberry constituents, plant lectins, crude extracts of

Morusalba leaves, and fractions of barley coffee, have been shown to be effective against biofilm formation of *S. mutans*. These substances can regulate the activities of surface-anchored virulence factors glucosyltransferase and fructosyltransferase. Numerous small molecules, including anthraquinones, apigenin, tt-farnesol, chitosan, and 7-epiclusianone, have been characterized and shown to have antibiofilm activity toward *S. mutans*. However, none of them were reported to possess selectivity against *S. mutans* biofilms. The prevention and treatment approaches based on these existing methods tend to disturb the ecological balance between pathogens and commensal residents in the oral cavity, which may lead to more severe infections. Therefore, it is necessary to develop a new approach which can selectively inhibit pathogenic bacteria and biofilms. To achieve this selectivity goal, pursuit of small molecules based upon nitrogen-dense marine alkaloids, have designed numerous derivatives of marine natural products based primarily on the 2-aminoimidazole (2-AI) scaffold and have shown that these compounds are potent inhibitors of biofilm formation by both Gram-positive and Gram-negative bacteria albeit the underlying mechanisms of biofilm inhibition/ dispersion are still under investigation.⁵

Antimicrobial Action:

It has been hypothesized that the rapid bactericidal activity of such peptides is based on an initial binding to lipopolysaccharide (LPS) from gram-negative bacteria⁶ although the details of this mechanism appear to vary widely. Previous observations have indicated the critical role of the general hydrophobic and cationic character of AMP function, including the significant contribution of aromatic Tryptophan and cationic Arginine residues found in many AMPs. Despite their small size (most are less than 50 amino acids), secondary structure also appears to play an important role in activity: certain linear AMPs can adopt an α -helical or β -strand confirmation upon interaction with hydrophobic environments such as detergents or lipid vesicles that mimic bacterial membranes, suggesting that these conformational changes are necessary for antimicrobial function.⁷

Stamps Clinical Implication:

Cariogenic organism *S. mutans* exhibits greatly reduced colonization in the presence of a preexisting saliva-derived biofilms containing no or a minimal amount of *S. mutans*. Evidence for the protective effect of a "normal" oral biofilm in concurrence with the proposed "window of infection" identified based on previous clinical studies (Caufield et al., 1993). *S. mutans* colonization mainly occurs between the second to the third year of life. Those who were infected during this crucial time period acquired persistent *S. mutans* colonization, while

uninfected individuals remained *S. mutans*-free until the eruption of secondary dentition provided new colonization opportunities. It is likely that these uninfected individuals formed a protective biofilm community void of *S. mutans*.¹

Kreth et al., 2008 demonstrated that the sequence of inoculation determines whether cariogenic streptococcus *mutans* or the health-associated *S. sanguinis* (Corby et al., 2005; Corby et al., 2007) compete or co-exist with one another. Both species can persist in a biofilm when inoculated at the same time, but given the chance to establish a biofilm first, either species can preclude colonization of the other. STAMP technology is a potentially useful method for removing *S. mutans* from saliva, thus establishing an oral flora that can help prevent or reduce further infection of *S. mutans*.¹

C16G2, a novel synthetic specifically targeted antimicrobial peptide with specificity for *S. mutans*. C16G2 consists of a *S. mutans*-selective 'targeting region' comprised of a fragment from *S. mutans* competence stimulation peptide (CSP) conjoined to a 'killing region' consisting of a broad-spectrum antimicrobial peptide (G2). In vitro studies have indicated that C16G2 has robust efficacy and selectivity for *S. mutans*, and not other oral bacteria, and affects targeted bacteria within seconds of contact. C16G2 rinse usage was associated with reductions in plaque and salivary *S. mutans*, lactic acid production, and enamel demineralization. The impact on total plaque bacteria was minimal.⁸

Other Choice Of Agents, Approaches

In addition to 'traditional' agents, new approaches have been initiated to keep the oral biofilm 'healthy'. Many efforts are devoted to extracts from plants and natural products (Koo et al., 2005). Also, photodynamic therapy has been developed, which combines a relatively inert dye that is photoactivated and then has bactericidal properties (Wood et al., 2006). Antimicrobial peptides in saliva and their synthetic analogues have promising potential (Helmerhorst et al., 1999).⁹

Replacement therapy has been researched for over 30 years, with cariogenic bacteria being modified to make them less acidogenic, while keeping their colonization-resistance properties (Hillman and Socransky, 1987). Much of this work was started in the period when most attention was given to the arch criminal of caries, *Streptococcus mutans*.⁹ Animal experiments involving lactate-dehydrogenase deficient and ureolytic *S. mutans* strains have shown promising results in caries prevention (Clancy et al., 2000). In the former case, the approach is directed against single microbial species. However, one should not disregard the role of other microorganisms, such as non-*mutans* acidogenic streptococci, in the caries process in humans.¹

The use of probiotics, very established in the treatment of intestinal diseases, is now also considered for oral diseases (Näse et al., 2001; Twetman and Stecksén-Blicks, 2008). Most attention is given to the lactobacillus species, in particular those that produce bacteriocins. Obviously, this should be done with great care, since lactobacilli also produce acids.

Biofilm research has disclosed that bacteria in a biofilm interact through peptides to regulate their metabolism. Quorum-sensing peptides are secreted, and when these exceed threshold concentrations, bacteria modify their physiology. Quorum-sensing peptide-like molecules have been tested to upset bacterial 'societies' (Aharoni et al., 2008). For each of these promising new approaches, the questions remain how agents can be made cost-effective and how they can be formulated into usable products.¹⁰

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