

Streptococcus Mutans and Dental Caries: Biofilm Formation, Virulence Mechanisms and Emerging Preventive Strategies

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Abstract- Dental caries is one of the major chronic infectious diseases that continue to affect individuals worldwide in large numbers. The disease is closely related to various microorganisms that form biofilm on the surfaces of teeth, resulting in dental caries due to the metabolism of microorganisms present in dental plaque. Among these microorganisms, Streptococcus mutans is commonly associated with dental caries development, considering its virulence factors that enable it to adhere to tooth surfaces, synthesize exopolysaccharides, and metabolize carbohydrates to produce organic acids. These virulence factors enable S. mutans to dominate other microorganisms in dental plaque, resulting in dental caries through enamel demineralization in an acidic environment. Recent advances in microbiology have indicated that dental caries is a polymicrobial infection that is caused by imbalances in the ecological system of microorganisms in the mouth. Preventive measures that have been effective in controlling dental caries are fluoride therapy, antimicrobial agents, probiotics, and natural bioactive agents. This article focuses on the role of S. mutans in dental plaque biofilm development, its molecular pathogenesis, and recent advances in its prevention and control of dental caries.

Keywords: Dental Caries, Streptococcus Mutans, Dental Plaque, Biofilm, Antimicrobial Agents, Probiotics, Prevention.

I. INTRODUCTION

One of the most common chronic diseases, dental caries, occurs in both children and adults across the world. It is a common oral health issue that, despite increased awareness and preventive measures, still remains a significant burden on healthcare systems globally. Dental caries is a pathological process involving the progressive loss of dental hard tissues, i.e., enamel and dentin, as a result of acid production by microorganisms present in dental plaque biofilms

[1]. This occurs as a result of microbial fermentation of dietary carbohydrates, resulting in organic acids that can dissolve minerals on the surface of the tooth. The human oral cavity is inhabited by a complex microbial community that comprises over 700 different species of bacteria. Normally, these bacteria live in a balanced environment and contribute to the maintenance of oral homeostasis. However, changes in the balance of these bacteria, which can be caused by the regular consumption of sugars and poor oral hygiene practices, can result in the overgrowth of acidogenic and aciduric bacteria that can cause dental caries [2,3]. Among the diverse array of microbes found in dental plaques, Streptococcus mutans has been identified as one of the major cariogenic pathogens involved in the initiation of the caries process. This pathogen harbors a number of virulence factors that allow it to adhere to the surfaces of the teeth and maintain its presence in dental biofilms. Some of the virulence factors of S. mutans include its high adhesive capacity, production of extracellular polysaccharides, tolerance to low pH, and capacity to ferment sugars to organic acids [4,5]. This allows the pathogen to generate a suitable environment that can promote the initiation of the caries process. Recent studies have highlighted that dental caries is no longer caused by a single microorganism but rather by a complex biofilm-mediated process involving interactions between different microbial species. The ecological plaque hypothesis suggests that environmental changes such as an increase in sugar consumption can lead to an imbalance in the oral microbial biofilm and induce a cariogenic biofilm dominated by acid-producing bacteria [6,7].

The mechanisms by which Streptococcus mutans causes dental caries need to be understood for the

development of effective measures for prevention and treatment. The review article highlights the role of *Streptococcus mutans* in the causation of dental caries and its involvement in the formation of dental biofilm in caries prevention and treatment.

II. ROLE OF STREPTOCOCCUS MUTANS IN DENTAL CARIES

Streptococcus mutans is a Gram-positive bacterium that is a facultative anaerobe. This bacterium is classified as a member of the mutans streptococci. This bacterium is generally considered to be one of the most significant microorganisms that cause dental caries due to its ability to metabolize carbohydrates [4,8]. One of the important characteristics of *S. mutans* is that it has a high acidogenic potential. When it is given a source of carbohydrates such as sucrose, glucose, and fructose, it rapidly metabolizes these carbohydrates to produce lactic acid. The presence of lactic acid causes the dissolution of hydroxyapatite crystals in the tooth enamel due to the low pH that is caused by the presence of the organic acids [9]. In addition to the production of acids, *S. mutans* is capable of tolerating acids in the environment. The bacteria can survive and multiply in environments that have low pH levels. The capability of the bacteria to survive in such environments gives them a competitive advantage over other bacteria that cannot survive in such conditions. The capability is known as aciduricity. The virulence factor makes the bacteria dominant in caries biofilms [10]. Another virulence factor associated with *S. mutans* is the capability of the bacteria to produce extracellular polysaccharides. The bacteria produce extracellular polysaccharides through the action of glucosyltransferases. The extracellular polysaccharides produced by the bacteria have the capability to bind bacteria to the tooth surface. The capability of the extracellular polysaccharides to bind bacteria to the surface makes them useful in the formation of dental biofilms. The extracellular polysaccharides also make the bacteria resistant to environmental factors [8,11]. Recent studies have shown that several genes influence the virulence factors of *S. mutans*. The virulence factors include adhesion, biofilm formation, and stress tolerance. The genetic regulatory mechanisms enable

the bacterium to adapt to changing conditions in the oral environment and retain its virulence potential [12].



Figure 1

III. DENTAL PLAQUE AND BIOFILM FORMATION

Dental plaque is a microbial community that adheres to the surface of the teeth. The formation of dental plaque is the key to the formation of dental caries. Biofilms are complex microbial communities in which microorganisms are embedded in an extracellular matrix that is self-produced [2,37]. This matrix is made up of polysaccharides, proteins, and nucleic acids [2]. The formation of dental plaque is initiated with the adsorption of salivary proteins on the surface of the teeth. This layer is known as the acquired pellicle.



Figure 2

This layer acts as a substrate for the adhesion of microorganisms. Early-adhering microorganisms, such as *Streptococcus* species, adhere to the acquired pellicle with the help of adhesion molecules. After that, a number of microorganisms co-aggregate with the adhering microorganisms to form a highly structured microbial community [13,14]. In the

biofilm of dental plaque, microorganisms are found to interact with each other through metabolic cooperation and cell-to-cell communication mechanisms. Such interactions are advantageous for the formation of a stable microbial community capable of adapting to changing environments. However, the regular consumption of fermentable carbohydrates favors the growth of acidogenic bacteria like *S. mutans*. This leads to the formation of cariogenic biofilms with lower pH levels and increased demineralization of tooth enamel [15,16]. Current studies have also revealed that interactions between fungal and bacterial species can increase the pathogenicity of dental biofilms. For example, synergistic interactions between *S. mutans* and *Candida albicans* have been found to increase biofilm biomass and the formation of severe carious lesions [17].

IV. EMERGING PREVENTIVE AND THERAPEUTIC STRATEGIES

Prevention of dental caries involves a complex strategy that addresses both the biological activities of microbes and environmental risk factors.



Figure 3

Fluoride therapy is one of the most potent methods for the prevention of dental caries due to its capacity for enamel remineralization and the inhibition of bacterial metabolism [21-23]. In addition to fluoride therapy, scientists have also investigated the effectiveness of natural antimicrobial agents that are usually extracted from plants. These antimicrobial agents have bioactive molecules that are capable of inhibiting the growth of *S. mutans* and interfering with biofilm development. Polyphenolic compounds, flavonoids, and other natural molecules extracted

from plants have shown promising results in the reduction of acid production and interference in glucosyltransferase activities, thus hindering the development of extracellular polysaccharides in dental plaque [24-26]. Another promising approach is the use of probiotics to achieve a balanced microbiota composition in the oral cavity. Probiotics such as *Lactobacillus* and *Streptococcus salivarius* have the ability to control the growth of pathogenic bacteria causing dental caries by competing for adhesion sites on the tooth surfaces. Probiotics have the capacity to produce antimicrobial substances called bacteriocins [27-29]. These organisms have the potential to maintain a balanced microbiota composition in the oral cavity to control dental caries.

Recent advances in nanotechnology have resulted in the production of nanoparticles as antimicrobial agents to target biofilm-forming bacteria. These nanoparticles have the capacity to penetrate the biofilm matrix to deliver antimicrobial substances directly to the target bacteria [30-33]. Moreover, innovative strategies that include gene editing technologies and quorum sensing inhibitors are also being explored for their ability to target the virulence factors of *Streptococcus mutans* selectively. Even though these technologies are still in their experimental stages, they are likely to revolutionize the prevention of dental caries through the development of specific therapeutic agents [34-36].

V. DISCUSSION

Currently, dental caries is understood as a complex biofilm-mediated disease resulting from ecological imbalances in the oral microbiome, as opposed to a pathogenic infection caused by a specific microorganism. However, *Streptococcus mutans* remains widely accepted as one of the main microorganisms involved in dental caries, especially in its initiation and progression, as a result of its unique virulence factors, such as acidogenicity, aciduricity, and production of extracellular polysaccharides, which play a crucial role in biofilm formation [1-4]. The ecological plaque hypothesis proposes that dietary sugars, especially sucrose, stimulate the growth of acid-producing microorganisms, such as *S. mutans*, leading to a

decrease in plaque pH and, consequently, enamel demineralization [5-7].

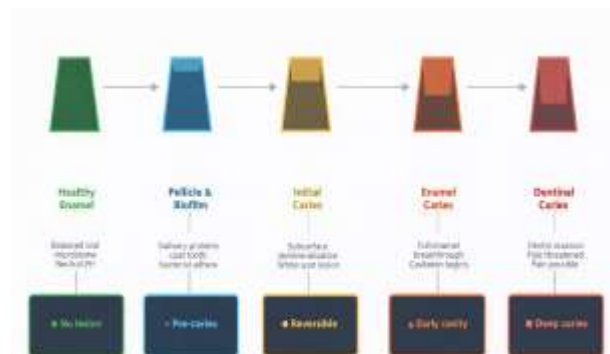


Figure 4

A major virulence factor that makes *S. mutans* cariogenic is its ability to synthesize glucans that are external in nature through glucosyltransferase enzymes encoded by genes *gtfB*, *gtfC*, and *gtfD*. These glucosyltransferases are responsible for converting sucrose into water-insoluble glucans that enable *S. mutans* adhesion to tooth surfaces, thus providing strength to dental plaque biofilms [8-10]. The glucans not only enable *S. mutans* aggregation but also provide a protective shield that makes them resistant to various antimicrobial agents and environmental changes. This makes it possible for the biofilm community to create an acidic microenvironment that favors enamel dissolution [8-11]. In recent times, several studies have revealed genetic regulatory systems involved in the regulation of biofilm formation in *S. mutans*. The genetic systems, such as *vicRK*, *liaSR*, and other two-component systems, are well documented for their involvement in stress response, synthesis of extracellular polysaccharides, and bacterial adherence [9-12]. These genetic systems play a significant role in adapting to changing environmental conditions in the oral cavity, such as variations in nutrient availability and pH levels. These genetic systems are of significant importance in developing novel therapeutic targets for interfering with cariogenic biofilm without affecting other oral flora. Another key feature in the pathogenesis of dental caries is the polymicrobial biofilm component. Though *S. mutans* is a key player in the development of dental caries, the disease process is a complex interplay between

different species of microbes, which include *Lactobacillus*, *Actinomyces*, *Veillonella*, etc. These microbes are known for their capacity for metabolic synergy in dental plaque biofilms that facilitate the development of dental caries [13-16]. In addition, synergy between *Streptococcus mutans* and fungi like *Candida albicans* has also been shown. This synergy has a synergistic effect on the biomass of the biofilm, thus leading to a virulent disease process [17]. Recent advances in the microbiome field have further confirmed that the formation of caries is associated with microbiome dysbiosis rather than the presence of a particular microorganism. The changes in the diversity of the microflora, the environment, and the host all contribute to the appearance of a cariogenic microbiome [18-20,39]. This has resulted in a new paradigm in caries research that focuses on the development of new strategies for the restoration of the balance of the microflora rather than the elimination of the pathogenic microorganisms. The classical approach to the prevention of dental caries has been based on the application of fluoride-containing products and the mechanical removal of dental plaque. Fluoride is considered one of the most effective caries-preventive agents due to its ability to stimulate the remineralization of the enamel tissue and block the metabolism of the microorganisms [21-23]. Recent studies have confirmed that the application of fluoride-containing varnish and the use of fluoride-containing toothpaste can effectively prevent dental caries. However, the recent emergence of antimicrobial resistances and the inability of conventional antimicrobial agents to combat oral pathogens have prompted researchers to seek alternative therapeutic options. Natural products have been found to exhibit promising results against *S. mutans*. Resveratrol and polyphenol have been found to inhibit the production of acids, the synthesis of extracellular polysaccharides, and the formation of biofilm [24-26]. The above results have shown promising effects of natural products as an adjuvant therapy for the prevention of oral caries. Probiotic therapy has also been found to be promising in recent years for the maintenance of oral microbial balance. Probiotic bacteria, including *Lactobacillus* and *Streptococcus salivarius*, have been found to inhibit the growth of oral pathogens by producing bacteriocins and competing for adhesion to tooth

surfaces [27-29]. Probiotics have also been found to stimulate the immune system of the host for the maintenance of oral microbial balance. Research is also emerging on other therapeutic agents, including quorum-sensing inhibitors, enzyme inhibitors of glucosyltransferases, and nanoparticles that are used as antimicrobial agents. These agents are aimed at selectively interfering with virulence factors of *S. mutans* without affecting other beneficial microorganisms in the mouth [30-33]. In this regard, recent studies have focused on identifying agents that are capable of inhibiting glucosyltransferase enzyme functions, thus preventing the production of polysaccharides that are required for biofilm stability [10]. Gene-targeting therapy is also another area of interest that is showing immense potential in the control of biofilm-related infections, including dental caries, through CRISPR technology that is aimed at eliminating cariogenic bacteria. This is still in its experimental stages but is likely to be a major breakthrough in the control of biofilm-related infections [34-36]. Despite these advances, there are still a number of challenges that exist in the development of efficient anti-caries therapies. For instance, the biofilm's complexity and the dynamic balance of the oral microbiome make it challenging to target a specific microorganism without interfering with the balance of the whole microbiome. In addition, the results observed in the laboratory must be extensively tested in clinical trials for safety, efficacy, and outcomes. In general, the present research has shown a shift from the traditional pathogen-elimination paradigm to a more ecological approach that seeks to reestablish the balance between microorganisms and reduce the virulence of cariogenic pathogens. A combination of traditional methods and modern microbiome-based therapies may be a better option for the management and control of dental caries.

VI. FUTURE PERSPECTIVES IN DENTAL CRIES RESEARCH

With the recent developments in the fields of oral microbiology and molecular biology, the understanding of dental caries as a complex disease has been greatly improved. The future of dental caries research is expected to be focused on the

exploration of the complex interactions between host factors, environmental factors, and the oral microbiome that may contribute to the progression of dental caries. The classical approach to the understanding of dental caries as an infection caused primarily by *Streptococcus mutans* is gradually replaced with a new approach based on the ecological/microbiome model of dental caries that focuses on the concept of microbial imbalance in dental plaque biofilms [3, 20]. This new approach to the understanding of dental caries underlines the necessity for the development of new strategies for the promotion of the balance of the oral microbiome rather than the elimination of the microorganisms that are considered to be cariogenic. A promising area of caries research is related to the application of sophisticated microbiome analysis methods, including metagenomics, transcriptomics, and metabolomics. These methods would enable caries researchers to study the microbiota of the oral ecosystem in unprecedented ways. The application of high-throughput sequencing methods has provided evidence that dental plaque is comprised of complex microbiological networks where various species of bacteria are in close interaction with each other in the development of caries [13,41,42]. Such interactions may help in the identification of new markers of caries detection, including aspects related to personalized approaches of prevention. Another significant area for further investigation is the creation of targeted antimicrobial agents that selectively interfere with virulence factors of cariogenic pathogens. Instead of killing all the microbes in the oral cavity, these agents are designed to interfere with key virulence factors like biofilm development, production of extracellular polysaccharides, or quorum sensing in *Streptococcus mutans* [31,32]. This may help control the virulence of dental biofilms without eliminating beneficial microbes. Recent developments in the field of nanotechnology have also paved the way for the development of new strategies for the prevention and treatment of dental caries. The results of the applications of nanoparticle-based antimicrobial materials, such as silver nanoparticles and bioactive nanomaterials, in the prevention of dental caries are encouraging. The materials show significant results in the inhibition of the formation of dental biofilms as

well as the delivery of antimicrobial substances to dental plaque microflora [33]. The materials exhibit strong physicochemical properties that enable them to penetrate the protective matrix of the dental biofilm. Probiotic therapy is another promising novel approach that is receiving increased attention for the prevention of caries. The beneficial effects of certain microorganisms such as *Lactobacillus* and *Streptococcus salivarius* have been proven to inhibit the growth of cariogenic pathogens by competitive exclusion and production of antimicrobial agents [27-29]. Further studies are needed to assess the long-term efficacy of probiotic therapy and to find the best microbial strain to favor oral microbial homeostasis. The recent advances in genetics and molecular sciences also offer great promises for the control of oral biofilm diseases. For example, the recent advances in the genetics of microbial pathogens have led to the identification of the CRISPR system as a promising approach for the selective elimination of oral pathogens [34-35]. Even though these technologies are still at their infancy, they have great promises for the control of biofilm-associated oral diseases with great precision without compromising the balance of the oral microbial community. Moreover, it is also believed that future advancements in preventive dentistry would be made to develop individualized oral care strategies based on risk profile and microbiome composition. Such an approach would enable healthcare practitioners to develop preventive care strategies that take into consideration the specific microbial and environmental components that are responsible for the progression of dental caries in each patient [38,40]. In conclusion, it is believed that the future of dental caries research would be based on an interdisciplinary approach that would encompass microbiology, biotechnology, materials science, and dentistry. Such an approach would be essential to develop novel preventive and therapeutic strategies to combat the global burden of dental caries.

VII. CONCLUSION

Dental caries is one of the most common chronic diseases afflicting the global population. This disease still remains a challenge to the global health community. Dental caries is a disease characterized

by the progressive loss of hard tissues on the teeth due to the metabolic activity of the microbes residing in the dental biofilm. Among the varied microbes found in the oral environment, *Streptococcus mutans* is one of the major microbes implicated as the causative agent of dental caries. The virulence of *S. mutans* is attributed to the unique virulence factors of the microbes. These virulence factors of the microbes include the capacity to metabolize sugars to produce organic acids, the capacity to withstand low pH environments, and the capacity to produce extracellular polysaccharides. The virulence factors of the microbes facilitate the formation of dental biofilm on the tooth surfaces. The formation of dental biofilm leads to the demineralization of the enamel tissue. In recent times, substantial advances have been made regarding the complex microbial ecology of dental plaque. Contemporary studies have confirmed that dental caries is a polymicrobial disease caused by ecological imbalances in the oral microbiome. Environmental factors like dietary habits, oral hygiene practices, and host susceptibility are also important for the microbial community and disease progression. Preventive measures are the best way to control dental caries. Fluoride therapy is still an important preventive treatment for controlling dental caries because of its ability to promote enamel remineralization and inhibit microbial metabolism. Apart from fluoride therapy, recent preventive measures like natural antimicrobial agents, probiotics, and nanotechnology-based therapy have also been found to have promising potential against microbial pathogens. These plant-derived natural compounds have shown antimicrobial activity against *S. mutans* by inhibiting the production of acids and interfering with biofilm formation. Probiotic therapy is another novel approach to the maintenance of a balanced microbiota in the oral cavity. This can be achieved by the administration of beneficial microbes that are capable of inhibiting the growth of pathogenic microbes. Recent advances in nanotechnology have led to the production of nanoparticles as antimicrobial agents. These nanoparticles have the capacity to penetrate biofilms to enhance the activity of antimicrobial agents.

The aforementioned advances are still in the experimental stages. Further studies are needed to

bridge the gap between the findings of such studies and the actual therapeutic benefits. The areas to be concentrated on are the interaction of microbes in dental plaques, the identification of novel targets for antimicrobial agents, and the production of personalized therapy to prevent caries. In conclusion, it is worth noting that dental caries is a multifactorial disease process that is subject to complex interplay among microbial agents, host factors, and environmental influences. A better understanding of the role of *S. mutans* in the process of biofilm formation would be essential for the design of innovative strategies to combat the global burden of this disease process.

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