A REVIEW OF THE ORAL MICROBIOME

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Summary

The oral cavity contains a complex environment consisting of biofilms on teeth and soft tissues of the gums. The balanced oral microbiome provides colonization resistance, nutrient metabolism, and immune function when the balance is intact. The condition of dysbiosis refers to when the oral microbiome becomes out of balance. During dysbiosis, the metabolic activities of pathogenic microorganisms (microbes) and pathogenic host increase, which can lead to dental caries and periodontal disease (Rajasekaran et al., 2024). This review paper will provide an overview of the ecology of oral biofilms, discuss roles for the specific microorganisms *Streptococcus mutans* and *Porphyromonas gingivalis* in the disease development of caries and periodontitis, and discuss the connections of the oral microbiome to larger systemic effects. The current diagnostic modalities, including 16S rRNA sequencing and shotgun metagenomics, and identify options for treatment of dysbiosis, including probiotics, arginine and fluoride formulations, and other targeted options will then be highlighted.

Background

The oral microbiome is one of the most diverse microbial ecosystems in the human body and significantly impacts on the body's oral and systemic health. The human oral microbiome contains more than 700 different species of bacteria, in addition to species of fungi, archaea, and viruses that coexist in biofilms on both hard and soft tissues within the mouth (Rajasekaran et al., 2024). These microorganisms, more commonly referred to as microbes, collectively form the oral microbiome which contributes to chemical food digestion and immune defense.

The balance of the oral microbiome can be triggered by dietary, behavioral, or environmental factors, such as disturbances in pH, oxygen, or nutrient availability, to become out of equilibrium, reaching an unbalanced state referred to as dysbiosis. This unbalanced state of dysbiosis can lead to the development or progression of oral diseases such as dental caries and periodontitis (Rajasekaran et al., 2024). Two microorganisms that have a significant impact on the balance of the oral microbiome include *Streptococcus mutans* and *Porphyromonas gingivalis,* which contain metabolic mechanisms that play significant roles in biofilm formation and immune interaction (Sedghi et al., 2021).

The composition of microbial communities varies throughout the oral environment due to variation in the microhabitat. The unique environments of the tongue, teeth, gingiva, and saliva foster distinct microbial communities that are shaped by local ecological and chemical gradients. The differences in pH, oxygen availability, salivary film velocity, nutrient flow, and tooth morphology and positioning collectively create selective pressures that determine which microbes can thrive in each habitat, forming unique microbial communities. These communities are further influenced by factors such selection, diversification, drift, dispersal (Proctor et al., 2020).

Over time, these selective and ecological pressures drive organized patterns of microbial dispersion and colonization on oral surfaces throughout the oral microbiome. The process of colonization begins with the establishment of pioneer species that adhere to available surfaces, creating the foundation for complex interactions between microbial species and biofilm development (Proctor et al., 2020). Examples of common early colonizing microbes include *Streptococcus* and *Actinomyces*, which attach to the thin film surrounding the oral cavity called the salivary pellicle using surface adhesins (Proctor et al., 2020). Examples of later colonizer

microbes include *Fusobacterium* and *Porphyromonas*, which then bind together using a method called coaggregation to form complex three-dimensional biofilms (Jakubovics, 2015). Within these biofilms, metabolic interactions, such as lactate cross-feeding between *Streptococcus* and *Veillonella bacteria* support microbial succession and stability to create the diverse oral microbiome.

Oral Microbiome and Disease

Caries Development

Dental caries, more commonly referred to as cavities, are the most common chronic oral disease throughout the world. Caries develop from an ongoing cycle of enamel demineralization and remineralization regulated by a variety of microbe metabolism and other environmental host factors. Bacteria metabolize fermentable carbohydrates into organic acids (Zhang et al., 2022). Saliva buffers and provides antimicrobial functions to maintain microbial equilibrium by providing bicarbonate and phosphate ions to neutralize acids and immunoglobulin A (IgA) to suppress the overgrowth of bacteria (Zhang et al., 2022). Decreases in salivary flow due to dehydration, medications, or systemic illness reduces the buffering capacity of saliva. The reduced buffering capacity of saliva can support certain acidogenic, or acid favoring, microbial species such as *Streptococcus mutans* and *Lactobacillus* within the oral microbiome which increases the risk of developing caries (Zhang et al., 2022).

Recent studies of the relationship between sugar consumption and dental caries demonstrate that sugar exposure alone does not entirely determine caries development. A study of adolescent caries development found that individuals with low sugar consumption but active caries had plaque microbiomes with increased acidogenic bacteria, including species such as

Lactobacillus and *Streptococcus mutans*. The study also found that the individuals with low sugar consumption but caries had an increased expression of genes involved in sugar transport and metabolism, such as phosphotransferase systems and two-component response regulators (Pang et al., 2022). These increased gene functions enhanced the bacteria's ability to uptake and ferment minimal amounts of available sugar after consumption, leading to an acidic microenvironment in the oral microbiome which promotes demineralization of the enamel. Alternatively, the study found that individuals without active caries and higher sugar consumption had more balanced microbial communities. These more balanced communities had increased amounts of *Capnocytophaga gingivalis* and *Porphyromonas gingivalis*, microbes that are predicted to have antagonistic effects on cariogenic species, working to stabilize pH within the plaque and prevent enamel breakdown and caries development (Pang et al., 2022). This study helps conclude that sugar frequency or quantity alone does not predict dental caries development or progression, and the ecological balance and pre-existing conditions of the oral microbiome also influence caries risk. Environmental factors such as saliva composition, pH, and oxygen gradients further impact the development and variety within microbial communities, often favoring the support of facultative anaerobes like *Streptococcus* in oxygenated regions along the gumline and obligate anaerobes in deeper regions below the gumline that are not oxygenated (Proctor et al., 2020). These results suggest that dental caries is a multifactorial disease primarily caused by the imbalance of microorganisms, in causing the process of enamel demineralization powered by the enhanced metabolic adaptability of the biofilm rather than consumption of sugar alone.

Streptococcus mutans

Streptococcus mutans (*S. mutans*) is a Gram-positive facultative anaerobic bacteria within the oral microbiome that plays a significant role in the development of dental caries. *Streptococcus mutans* is mostly found within dental plaque biofilms, where it contributes to the demineralization of enamel by metabolizing dietary carbohydrates into organic acids, most commonly lactic acid (Lemos et al., 2019). These acids lower the pH of the enamel surrounding the bacteria, dissolving hydroxyapatite crystals and initiating progression of caries development. *Streptococcus mutans* bacteria exhibit several virulence traits that support its ability to grow and survive in the oral cavity, including acidogenicity and the ability to synthesize extracellular glucans using glucosyltransferase enzymes such as gtfB and gtfC. These extracellular glucans form a sticky matrix that enhances the bacteria's ability to adhere to tooth surfaces and trap acids within the biofilm, which creates a localized acidic microenvironment. Quorum-sensing systems, such as ComCDE, also contribute to biofilm formation and genetic competence by linking microbial population density with the expression of virulence genes (Lemos et al., 2019).

S. mutans are also able to contribute to the development of caries through its metabolic flexibility and ecological adaptability that enable it to thrive under acidic conditions to promote enamel demineralization. Studies comparing the genomes of various *S. mutans* strains have shown significant genetic and phenotypic heterogeneity, or diversity, among strains, with the complete genome containing approximately 3,300 genes and a core genome of 1,490 genes (Cornejo et al., 2012). This genome diversity allows for variation in biofilm formation, acid tolerance, and oxidative stress response, which could lead to differences in virulence between bacteria. Historical population genomic studies suggest that *S. mutans* population significantly expanded between 3,000 and 10,000 years ago, which is associated with the rise of agricultural development and an increase in carbohydrate consumption in the human diet (Lemos et al.,

2019). This shift in humans' diets likely favored strains with enhanced acidogenic and aciduric traits, meaning strains that produce more acid or are more capable of growing in acidic environments, further amplifying their role in caries development. Although *S. mutans* is not the only bacteria in the oral microbiome responsible for the development of caries, its ability to create a polysaccharide-rich and low-pH environment further promotes the growth of other acid-tolerant species, contributing to a dysbiotic or unbalanced biofilm community within the oral microbiome (Lemos et al., 2019).

In addition to its role in the development of dental caries, *Streptococcus mutans* has been found to play a significant role in systemic diseases such as infective endocarditis, cerebral microbleeds, and IgA nephropathy, which demonstrates its broader pathogenic potential. Environmental factors such as saliva composition, fluoride exposure, and behavioral habits like smoking and vaping influence the activity of *Streptococcus mutans* within the oral microbiome (Pandarathodiyil et al., 2021). Fluoride is protective against caries development by forming a mineral called fluorapatite, which is more resistant to acid dissolution. Fluoride is also able to protect the teeth against caries development through inhibiting bacterial glycolysis (Nassar & Brizuela, 2023). Alternatively, tobacco and e-cigarette use have been found to support caries development through increasing lactate dehydrogenase levels and reducing the ability for saliva to buffering the acidity of the environment, conditions that further support acidogenic and anaerobic bacteria such as S. mutans (Ranjan & Lenton, 2019). These findings support the conclusion that *S. mutans* contributes to caries through a multifactorial process involving environmental modification, such as the presence of certain enhancing microbes such as lactate dehydrogenase or inhibiting microbes such as fluoride within the oral cavity environment.

Periodontal disease

Periodontal disease is a chronic inflammatory disease that affects the supporting tissues of teeth, including the gingiva, more commonly referred to as the gums, periodontal ligament, and alveolar bone. Periodontal disease begins as gingivitis, which is inflammation of the gingiva that can be reversed, but when left untreated can progress to periodontitis. Periodontitis is irreversible tissue destruction and alveolar bone loss that results from advanced and untreated gingivitis (Berezow & Darveau, 2010). The transition from a healthy state of oral health or minor gingivitis to the development of periodontal disease involves a shift in the oral microbiome population from Gram-positive facultative anaerobes to Gram-negative obligate anaerobes. This shift in microbial population favors the growth of species that break down proteins, referred to as proteolytic, and inflammatory species, that thrive in oxygen-deprived pockets in the gums and contribute to tissue degradation and trigger inflammation (Marsh, 1994). Biofilms that cause periodontal disease often contain key species within the "red complex bacteria" such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, that help advance the development of periodontal disease by promoting inflammation and altering the microbiome (Sedghi et al., 2021).

The development of periodontal disease is influenced by both microbial and environmental factors. The shift in the oral microbiome to favor anaerobic bacteria that break down proteins results in an increased release of enzymes and toxins that break down gingival tissues and stimulate a chronic inflammatory response (Kim et al., 2022). In response to this inflammation, host immune cells such as neutrophils and macrophages release cytokines that further support inflammation. These inflammatory cytokines, such interleukin-1β and tumor necrosis factor-α, further contribute to the degradation of connective tissue and resorption of alveolar bone, worsening the condition of periodontal disease. Lifestyle factors such as smoking,

diabetes, and poor oral hygiene can then exacerbate this imbalance of the oral microbiome by impairing the function of immune responses and promoting anaerobic conditions within the mouth. Studies comparing the genomes of healthy individuals and patients with periodontitis have shown significant differences between microbiome profiles. Patients with periodontitis have been specifically found to exhibit increased abundance of pathogenic bacteria and reduced microbial diversity within the oral microbiome (Kim et al., 2022). These findings emphasize the variety of factors that influence the microbial imbalance leading to periodontal disease.

Porphyromonas gingivalis

Porphyromonas gingivalis (*P. gingivalis*) is a type of Gram-negative obligate anaerobic bacteria that influences the development and progression of periodontal disease. *P. gingivalis* has the ability to manipulate immune responses and reshape the oral microbial community in favor of dysbiosis, or lack of balance in the microbiome (Hajishengallis & Lamont, 2014). *P. gingivalis* expresses a variety of virulence factors that aid in its manipulation of host immune responses, such as fimbriae, lipopolysaccharides and cysteine proteases called gingipains. Specific cysteine proteases called gingipains are capable of degrading host structural proteins such as collagen and immunoglobulins, interfering with complement activation, and promoting inflammation by stimulating cytokine release (Septiwidyati & Bachtiar, 2020). These virulence mechanisms enable *P. gingivalis* to maintain its presence within gingival tissues to contribute to the chronic inflammation of periodontal disease.

In addition to its direct pathogenic effects, *P. gingivalis* impacts the surrounding oral biofilm by altering microbial interactions and weakening host defenses. It suppresses antimicrobial peptides, disrupts epithelial barrier integrity, and modulates the activity of immune cells such as neutrophils and macrophages, which contributes to immune evasion and sustained

inflammation. Even in low abundance, *P. gingivalis* can initiate a shift in the microbial community toward a more pathogenic biofilm structure, amplifying tissue destruction and promoting disease progression (Miller et al., 2019). Its ability to invade epithelial cells and persist intracellularly further complicates immune detection and clearance. Studies have shown that *P. gingivalis* can alter host cell transcriptional activity and stimulate a pro-inflammatory microenvironment that supports chronic disease development (Darveau, 2009; Septiwidyati & Bachtiar, 2020). These findings emphasize the ecological and immunological influence of *P. gingivalis* within the oral microbiome and support its role as a key contributor to the chronic inflammation and tissue degradation observed in periodontitis.

Oral microbiome and systemic health

The impact of the oral microbiome extends beyond the oral cavity, and many studies have found evidence connecting oral dysbiosis to greater systemic health conditions. Portions of biofilm fragments called bacterial metabolites and inflammatory mediators originating from oral sites can enter the bloodstream, which can then contribute to systemic inflammation and chronic disease progression. Transient bacteremia, meaning bacteria present in the bloodstream, can occur during routine activities such as tooth brushing or chewing, allowing oral microbes and their products to spread to the circulation and throughout the body (Lockhart et al., 2008). Studies have found the DNA of the periodontitis-linked *Porphyromonas gingivalis* bacteria in plaques of atherosclerosis, and elevated antibody levels against oral pathogens have been observed in patients with cardiovascular disease, suggesting a direct microbial contribution to pathology of the circulation (Li et al., 2022).

Studies have discovered specific proposed mechanisms responsible for the connection between oral dysbiosis and systemic disease, including cytokine-mediated inflammation,

molecular mimicry, and microbial translocation. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are released in response to oral inflammation and can circulate systemically and contribute to endothelial dysfunction and insulin resistance (Rajasekaran et al., 2024). Molecular mimicry is a process in which microbial antigens resemble host proteins to evade the immune system, which may trigger autoimmune responses and progress chronic inflammatory conditions (Hajishengallis & Lamont, 2014).

The oral microbiome has also been discovered to impact the development of certain metabolic syndromes, diabetes, and pregnancy complications. For diabetes specifically, dysbiosis in the oral cavity has been found to influence insulin resistance through systemic inflammation and altered lipid metabolism (Li et al., 2022). In pregnant individuals, the presence of periodontal pathogens has been associated to cause an increased risk of pre-term birth and low birth weight, likely due to inflammatory microbes crossing the placental barrier from the mother to the baby (Rajasekaran et al., 2024). These findings emphasize the importance of maintaining healthy oral microbial balance for both oral health and overall systemic health and well-being.

Microbiome-Based Diagnostics and Therapies

Diagnostic Techniques

New advancements in diagnostic technologies, including metagenomic sequencing, probiotics, and targeted interventions, show how advancements in microbiology can apply to personalized and prevention-based oral health. In particular, metagenomic sequencing has revolutionized modern-day understanding of the composition of the microbiome by allowing researchers to use techniques that identify what microorganisms are present and the genetic function of the microorganisms that specifically promote oral diseases. Using both 16S rRNA

sequencing and shotgun metagenomics, researchers are able to characterize microbial diversity and gene expression associated with metabolism, virulence and interactions in the oral microbial community (Jovel et al., 2016). Functional analyses of the communities of microorganisms indicate that dental biofilms are upregulated for certain genes associated with proteolytic activity and sulfur metabolism that progress the breakdown of gingival tissues and inflammation (Basic & Gunnar Dahlén, 2023). These modernized metagenomic technologies improve diagnostic capabilities of oral diseases and support the development of more targeted preventive strategies that focus on restoring microbial balance (Jovel et al., 2016).

Conclusion

The oral microbiome plays an important role in maintaining overall oral and systemic health through its complex balance of microorganisms and other host factors. When this microbial balance is disrupted, harmful shifts in microbiome composition of dysbiosis can lead to conditions such as dental caries and periodontal disease. The bacteria *Streptococcus mutans* and *Porphyromonas gingivalis* demonstrate how specific bacterial species contribute to oral disease through unique metabolic mechanisms, including acid production, biofilm formation, and tissue degradation. These metabolic processes highlight that oral diseases result from imbalances in the ecological and metabolic stability of the oral microbiome rather than isolated infections.

Recent advancements in microbiome-based research and technology have expanded the ability to diagnose and treat these dental diseases. Metagenomic sequencing allows for early identification of changes in microbial composition, while microbe-targeted therapies focus on restoring microbial balance. By using a more preventive and personalized approach using knowledge of the oral microbiome, dental professionals can improve oral health outcomes and reduce the long-term systemic effects of oral inflammation.

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