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# Intrageneric and Intergeneric Interactions Developed by Oral Streptococci: Pivotal Role in the Pathogenesis of Oral Diseases

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**Abstract**

Oral streptococci are among the most abundant genera present in the oral cavity. They are usually the first colonizers of oral surfaces and they develop extensive microbial interactions, playing a fundamental role in the pathogenesis of oral diseases such as dental caries and periodontitis. In addition to physical adherence, streptococcal cells also exchange messages with cells from another *Streptococcus spp.* and other microorganisms in the form of metabolites and signaling molecules. In this review, we focused on these intrageneric and intergeneric interactions, and their association with oral diseases.

## Introduction

### Dental biofilms, microbial interactions and polymicrobial diseases

As we have known so far, human oral cavity contains diverse range of microorganisms that exist as biofilms on dental and mucosal surfaces (Marsh, 2016). Dental plaque is one of the most widely studied biofilms. It is a complex system, not merely a simple sum of its bacterial components, but a sophisticated microbial community which may result in novel functions other than the ones of planktonic cells. These novel functions are essential for the biofilm architecture and microbial physiology (Kolenbrander et al., 2002; Marsh, 2005). Notably, dental biofilms are not formed by random simultaneous colonization. The process of colonization is selective, reproducible and sequential (Diaz et al., 2006). Along with *Actinomyces spp.* and a few other genera, oral streptococci are present in high numbers and serve as pioneer colonizers in dental biofilm development by binding to complementary salivary receptors in the acquired pellicle coating the tooth surface (Jakubovics et al., 2014; Parashar et al., 2015; Ichinosawa et al., 2017). Later inhabitants, such as *Porphyromonas gingivalis* and other pathogenic species, are capable of binding to the antecedent organisms. All of these microorganisms are embedded in a self-produced matrix of hydrated extracellular polymeric substances (EPS) that form their immediate environment, where they are protected against environmental threats such as antibiotics, and develop an advantage over planktonic bacteria (Flemming and Wingender, 2010; Marsh, 2016).

Throughout the process of biofilm formation, adherent bacteria can sense their neighbors and give appropriate responses (Parashar et al., 2015). It is generally accepted that synergistic, mutualistic, and antagonistic interactions occur

between microorganisms and contribute to the development of polymicrobial biofilm communities (Kuramitsu et al., 2007). Traits such as high species diversity, physical contact between adjacent cells and large metabolic activity all make the oral microbial community a typical model for studying microbial interactions (Guo et al., 2014).

Oral microbial communities are in a dynamic equilibrium with their environment, offering certain benefits to the host by protecting the epithelial cells from damage and enhancing the digestion of some substrates (Vasudevan, 2017). However, under some circumstances, microbial communities may have negative effects on the host. The etiology of oral diseases such as dental caries, went through a paradigm shift from Koch´s postulates focusing on pathogen isolation, to the concept of a polymicrobial disease (Simónsoro and Mira, 2015; Marsh, 2016). Dysbiosis of a mixed-species community is prone to break down the synergistic relationship between host and microbiota.

The overall incidence of caries and periodontal diseases in the population has not significantly decreased in multiple decades. They continue to be among the most common human diseases worldwide (Kassebaum et al., 2015). Interactions among different oral microorganisms may influence the balance between health and dysbiosis (Thompson et al., 2016). Thus, understanding these interactions is of great importance to evaluate the cause of these diseases.

In the present review, we aim to provide an overview of the intrageneric, and intergeneric interactions developed by oral streptococci, and the consequent influence on caries and periodontitis pathogenesis.

## Interactions in the microbial community

*Coaggregation and coadhesion*

Coaggregation is a specific cell-to-cell recognition and binding reaction that occurs between genetically distinct bacterial cells. It is one of the most critical mechanisms for the temporary retention and eventual colonization of bacteria on dental surfaces, and contributes to dental biofilm formation (Hojo et al., 2009). Coaggregated partners are both suspended in the planktonic phase, whereas coadhesion usually refers to one microorganism immobilized on a surface while the other is suspended (Ruhl et al., 2014). Coaggregation and coadhesion among oral microorganisms play an important role in the development of biofilms and formation of microbial communities. Either of the processes can be synergistic, since one microorganism may generate a niche and facilitate the retention of the other, which may be a pathogenic microorganism. Notably, some "bridging" species represented by *Fusobacterium nucleatum* can coaggregate with both early colonizers and late colonizers, serving as a coordinator that allows connections of species that are not coaggregation partners (Kolenbrander et al., 2002; Denes and Barraud, 2016). Extensive coaggregation and coadhesion allow a close cell-to-cell contact, facilitating metabolic communication, signal transmission and reception, and genetic exchange (Hojo et al., 2009).

Coaggregation and coadhesion between distinct microorganisms involve the specific recognition of macromolecules on the surface of one cell by macromolecular surface components of a partner organism (Jakubovics et al., 2014). Bacterial surfaces are rich in adhesins, some of which are proteins while

others are lectins (Marsh, 2016). Antigen (Ag) I/II polypeptides are the best characterized adhesins expressed by most indigenous streptococci and are involved in binding a wide range of host receptors, mediating biofilm formation and coaggregating with oral microbial partners (Back et al., 2015; Ito et al., 2017). AgI/II proteins of oral streptococci have a molecular mass of approximately 160–180 kDa and have a conserved linear structure consisting of several clearly defined domains (Jakubovics et al., 2014). Notably, distinct domains mediate adherence to various species, making the recognition of interacting partner species-specific. Representative AgI/II proteins such as *S. gordonii* SspA and SspB are important in microbial interactions. These proteins differ in binding specificities and can coaggregate with distinct groups of actinomyces (Egland et al., 2001). Not only AgI/II, some streptococci also harbor other adhesins such as CshA and CshB which were discovered in *S. gordonii DL1* (Mcnab et al., 1999). The CshA polypeptide is a structural and functional component of fibrils and CshA-like fibrillar protein also occurs on the surfaces of other members of the oral *Streptococcus mitis* group (Elliott et al., 2003). Interestingly, many AgI/II proteins require accessory adhesins to enable coaggregation. For instance, the AgI/II family adhesion SpaP participates in binding to certain actinomyces when expressed in *S. gordonii*, but this interaction also requires the presence of CshA (Guo et al., 2016).

*Streptococcus spp.* effectively utilizes dietary sucrose to synthesize extracellular polysaccharides as a scaffold for its biofilm (Lei et al., 2015). These extracellular polysaccharides can mediate coaggregation interactions. The receptor polysaccharide (RPS) recognizes lectin-like adhesins found on actinomyces, veillonellae and other streptococci (Hsu et al., 1994; Cisar et al., 1997). For

instance, *S. mutans* is capable of effectively converting dietary sucrose into acids and producing extracellular glucans using exoenzymes termed glucosyltransferases (Gtfs) (Bowen and Koo, 2011). Specifically, insoluble glucans produced by glucosyltransferase B (GtfB) provide bacterial binding sites and form the core of the extracellular matrix of cariogenic dental plaque biofilm *in vivo*. Besides, the enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expressed on the surface of streptococcal cells is also responsible for a number of interactions (Jakubovics et al., 2014), predominantly participating in the interactions between streptococci and *P. gingivalis* (Enersen et al., 2013; Wright et al., 2014).

*Metabolic communications*

In addition to the physical attachment mentioned above, microbial metabolites play important roles in the establishment of stable oral biofilm communities. Metabolic communications may occur where the excretion of a metabolite by one organism is used as a nutrient by other organisms, or breakdown of a substrate by enzymatic activity of one organism creates available substrates for different organisms (Hojo et al., 2009). A good example is represented by oral streptococci producing short-chain fatty acids, which are an essential carbon source for certain oral bacteria. Furthermore, the production of acids can lower the pH in dental biofilm and inhibit the growth of less aciduric microorganisms. Therefore, short-chain fatty acids have a role in competitive and/or mutualistic interactions and bacterial communication. They could even take a part in quorum sensing (Yuce et al., 2017).

To compete for restricted nutrient supply and limited foothold with other bacteria,

oral streptococci produce a plethora of general and specific antimicrobial agents (James, 2014). Bacteriocins are defined as proteinaceous bactericidal substances and their production is controlled by many genetic and environmental factors such as cell density, pH, nutrient source and oxygen (Hojo et al., 2009; Merritt and Qi, 2012). Unlike traditional antibiotics, bacteriocins have a narrow killing spectrum. Competition through bacteriocins commonly occurs and these activities enable bacteria to select their neighbors, promote the establishment of a community with specific bacterial species, and influence the ecological balance of the oral ecosystem. In addition, bacteriocins exert autolytic cell destruction and release of DNA to transform or stabilize the biofilm matrix (Jakubovics et al., 2014). Among all oral bacteria, streptococci possess the greatest bacteriocin production. *S. mutans* produces several bacteriocins named mutacins, including lantibiotics and nonlantibiotics, which inhibit the growth of other bacteria in close proximity such as *S. sanguinis* (Merritt and Qi, 2012). Lantibiotics contain either a lanthionine or methyllanthionine ring structure as well as dehydrated amino acids, while nonlantibiotics are unmodified peptides (Mohammad Shahnoor and Indranil, 2011). *S. salivarius* also has strains that are able to release lantibiotics in large amounts to eliminate harmful bacteria (Burton et al., 2013).

Another thing to note is that oral streptococci are able to produce growth-inhibiting amounts of hydrogen peroxide ($H_2O_2$) as byproduct of aerobic metabolism (Zhu and Kreth, 2012). Actually, it is more than a simple byproduct and functions in several aspects of oral bacterial biofilm ecology. Many species such as *S. sanguinis* and *S. gordonii* produce $H_2O_2$ as a weapon to compete over other species by limiting their carbon source availability and causing oxidative

stress . The activities thereby help these species in structuring the initial biofilm on tooth surfaces. Furthermore, $H_2O_2$ can serve as a signaling molecule to regulate gene expression, as shown by *Aggregatibacter actinomycetemcomitans* (Stacy et al., 2014). However, $H_2O_2$ production depends on the presence of oxygen. When these microorganisms are grown in an anaerobic environment, the lack of oxygen will lead to diminished $H_2O_2$ production (Kreth et al., 2008). As a result of $H_2O_2$ action, extracellular DNA released from cells is crucial in the biofilm development and stabilization. It also serves as the source for horizontal gene transfer between oral streptococci (Zhu and Kreth, 2012).

A selected group of oral bacteria produce ammonia ($NH_3$) via the arginine deiminase system (ADS) to increase intracellular pH and the pH of oral biofilms (Nascimento and Burne, 2014; Huang et al., 2015). Typically, the expression of ADS genes is inducible by arginine and is sensitive to carbohydrate catabolite repression. The gene expression can be highly variable within and between species due to both constitutional and environmental differences (Huang et al., 2015; Huang et al., 2017). It can be enhanced by conditions such as low pH and anaerobic environments. Other than inhibiting tooth demineralization by neutralizing glycolytic acids and by suppressing the emergence of a cariogenic pathogens (Nascimento and Burne, 2014), more recently arginine has been shown to influence the architecture and physicochemical properties of the biofilm matrix (He et al., 2016).

*Quorum sensing*

Quorum-sensing (QS) is the ability to detect and respond to population density by regulating gene expression through a sophisticated intercellular chemical

signaling pathway (Ng and Bassler, 2009; Basavaraju et al., 2016). As bacteria grow, they produce and release a series of molecules called autoinducers (AI) into the external environment at a low basal level (Mashima and Nakazawa, 2015). While the bacterial cells assess cell density until the population reaches a certain scale, accumulated molecules reach a certain threshold level. Subsequently, different sets of target genes are activated to allow bacteria adaptation to environmental changes. By means of QS, pathogens can regulate many aspects, including their virulence factor production, virulence-related behaviors, biofilm formation and motility (Vendeville et al., 2005; Irie and Parsek, 2008; Plančak et al., 2015). QS can be briefly described as a bacterial synchronizing behavior on a community-wide scale through communication.

QS systems in bacteria are generally divided into at least three classes (Sudheer et al., 2015): (1) LuxI/LuxR-type QS in Gram-negative bacteria, using acyl-homoserine lactones as signal molecules; (2) oligopeptide-two-component-type QS in Gram-positive bacteria, using small peptides as signal molecules; and (3) LuxS-encoded AI-2 QS in both Gram-negative and Gram-positive bacteria. There are two types of QS systems in Streptococci. One is ComCDE system that generates competence stimulating peptide (CSP), which is synthesized in the cell and released into the extracellular medium, enabling intraspecies cell-to-cell communication and modulating the expression of many genes in the same bacterial species (Li et al., 2001; Parashar et al., 2015).The other is LuxS/AI-2 system, which acts as a universal signaling molecule that can mediate interspecies interactions in the multispecies plaque community (Xiao et al., 2017).

*Genetic exchanges*

Gene exchanges certainly occur between oral streptococci and other microorganisms due to the easy contact among neighboring cells. Extracellular DNA can be released from cells as a result of lysis or active secretion, and it may contribute to the structural integrity of the biofilm (Jakubovics et al., 2013; Okshevsky and Meyer, 2015). Conjugation, transduction and transformation are the 3 basic ways for possible exchange of DNA among bacterial cells. This section will be amply discussed in another chapter.

**Interactions between oral streptococci and caries-associated microorganisms.**

In the human oral cavity, certain streptococci such as *S. mutans* are associated with the onset and progression of caries. *S. mutans* shows multiple virulences such as the capacity to produce large quantities of organic acids (acidogenicity), the ability to tolerate low pH in the environment (aciduricity), and the ability to synthesize multiple secreted proteins and water-insoluble glucan exopolysaccharides (Lemos et al., 2013; Huang et al., 2017). However, despite its important role in caries pathogenesis, *S. mutans* is not an etiologic factor in caries (Giacaman et al., 2015). To understand the dysbiosis of the biofilm, not only should we focus on selected caries-associated species, but modulation of the biofilm as a whole, including species in the core community and species that can balance the acid production after normal dietary intakes of carbohydrates (Tanner et al., 2018). Thus, the microbial interactions involving caries pathogenesis is of great significance.

*Intrageneric interactions among oral streptococci*

In terms of intrageneric interactions among oral streptococci, the relationship between *S. sanguinis* and *S. mutans* associated to their coexistence and competition is considered as a pertinent model. Both species share the same ecological niche and are similar in metabolic requirements, thus one may inhibit the other and compete for tooth colonization. The cycle of early colonization by *S. sanguinis* likely occurs in every human after tooth eruption or extensive cleaning (Kreth et al., 2016). It is worth noting that high levels of *S. sanguinis* in the mouth is associated to a delayed colonization by *S. mutans* and similarly, *S. mutans* teeth colonization is associated to low levels of *S. sanguinis* (Caufield et al., 2000). A recent study using next-generation sequencing approach also confirmed the opposite relationship between these two species (Richards et al., 2017). Clinically, the predominance of *S. sanguinis* over *S. mutans* in the dental biofilm may be associated with lower caries prevalence in both children and adults (Ge et al., 2008; Giacaman et al., 2015), and *S. sanguinis* seems to be among the species that are more prevalent in subjects with periodontal health (Mason et al., 2015).

As previously reported, oxygen availability is a crucial factor in the intrageneric competition. *S. sanguinis* can outcompete *S. mutans* via production of $H_2O_2$, since *S. mutans* does not produce significant amounts of $H_2O_2$ itself and is highly susceptible to the $H_2O_2$ antimicrobial activity. Valdebenito et al. speculated that the competitive advantage of *S. sanguinis* over *S. mutans* is mainly attributed to its glutathione peroxidase and capacity to undergo gluconeogenesis, as demonstrated by in silico analysis (Valdebenito et al., 2017). Glutathione peroxidase endows *S. sanguinis* with the capacity to resist its own $H_2O_2$ production, while gluconeogenesis occurs under low-nutrient conditions to allow

continuous production of *S. mutans*-toxic peroxide. Interestingly, the inhibitory effect of *S. sanguinis* over *S. mutans* is accompanied by an inhibition of several *S. mutans* genes related with virulence. Therefore, $H_2O_2$ may be implicated not only in direct killing, but also in modulating the expression of *S. mutans* virulence genes (Wen et al., 2010). Importantly, ammonia production via arginine metabolism is another strategy used by many oral streptococci including *S. sanguinis* to compete with *S. mutans* and survive the acidification of oral biofilms (Huang et al., 2017). However, in retaliation, the acidogenicity of *S. mutans* can help lower the environmental pH to the point of inhibition of the growth of *S. sanguinis*. Under conditions where bacterial cells have enough energy to compete but not enough food for optimal growth, *S. mutans* produces mutacins I and IV that inhibit *S. sanguinis* (Kreth et al., 2005).

*S. gordonii* is also an ADS-positive bacterium, producing alkali in the form of ammonia that neutralize glycolytic acids and create an environment which is compatible with dental health (Nascimento and Burne, 2014). Besides, *S. gordonii* produces $H_2O_2$ that effectively affects *S. mutans* survival (Kreth et al., 2008). Unlike $H_2O_2$ production by *S. sanguinis*, *S. gordonii* producing $H_2O_2$ seems to be inversely correlated with carbohydrate availability (Zhu and Kreth, 2012). By contrast, the production of challisin is a more recognized feature of *S. gordonii*. Some strains of *S. gordonii* utilize this protease to reduce mutacin production and biofilm colonization of *S. mutans* by reducing the levels of the stimulating factor CSP (Kuramitsu et al., 2007; Wang et al., 2011). However, *S. gordonii* is sensitive to the mutacins produced by *S. mutans* , especially mutacin IV which is specifically active against members of the mitis group of oral streptococci (Kuramitsu et al., 2007).

Another species that needs attention is *Streptococcus oligofermentans*. Discovered in caries-free subjects, *S. oligofermentans* show relatively specific inhibitory effect on *S. mutans* without causing collateral damage to other streptococci due to its $H_2O_2$ production from lactic acid produced by *S. mutans* through lactate oxidase (Tong et al., 2007). The inhibition on *S. mutans* is available in biofilms at both neutral pH and cariogenic conditions (Bao et al., 2015). *S. oligofermentans* is thereby considered as a prominent probiotic candidate to compete against *S. mutans* at sites prone to caries.

*Oral streptococci interactions with Actinomyces spp.*

Several *Actinomyces spp.* have the cariogenic ability of acid production and acid tolerance (Tanner et al., 2018), and are implicated as pathogens of root surface caries (Dame-Teixeira et al., 2016). Nevertheless, actinomyces such as *Actinomyces naeslundii* metabolize carbohydrates into relatively weak acids (such as acetate) under aerobic conditions and also degrades lactate produced by other cohabitants into weak acids, thereby neutralizing dental biofilm pH (Oliveira et al., 2015).

Like oral streptococci, actinomyces are early colonizers of the tooth surface. Either physical or metabolic interactions between the two genera have profound influence on early plaque development and subsequent bacterial adhesion. Xiao et al. discovered that, the presence of *A. naeslundii* can enhance the expression of *gtfB/gtfC* genes in *S. mutans*, mediating the establishment of an EPS-rich matrix and forming more biomass (Jin Xiao, 2012). Thus, there is a potential interaction between *S. mutans* and *A. naelsundii*, which affects biofilms' glucose metabolism.

Lectin-like interactions between actinomyces and streptococci occur in both directions. *Actinomyces oris* provides both adhesins and receptors for coaggregation with oral streptococci. The type 2 fimbriae expressed by actinomyces target on streptococci cell wall phosphopolysaccharides containing the linkages GalNAcb1-3Gal or Galb1-3GalNAc (the principal mechanism of these intergeneric bindings), while the polysaccharide receptor on *A. oris* is recognized by *S. sanguinis* (Yang et al., 2014; Back et al., 2015)

Mutual assistance has been demonstrated between these early colonizers. Sialidase activity in *A. naeslundii*, along with the glycolytic and proteolytic activities in *S. gordonii*, provide nutrients supply for each other (Bradshaw et al., 1994). $H_2O_2$ secreted by *S. gordonii* probably serve as a key factor influencing interaction dynamics between these two species. As has been previously noted, *S. gordonii* can produce $H_2O_2$ at concentrations sufficient to kill many oral bacteria, but it cannot produce catalase to tolerate $H_2O_2$. *A. naeslundii* may help remove $H_2O_2$ from coaggregate cultures, protecting *S. gordonii* from oxidative damage (Jakubovics et al., 2008). Another problem is that $H_2O_2$ production is likely to deplete the intracellular arginine pool in *S. gordonii* and increase its requirement for arginine. Coaggregation with *A.naeslundii* can stabilize arginine biosynthesis in *S. gordonii*, overcoming the requirement and enabling the growth of *S. gordonii* in the absence of arginine (Jakubovics et al., 2008). In exchange, the ability of *A. naeslundii* to bind to *S. gordonii* contributes to its retention in biofilms under flowing saliva (Jr et al., 2001).

*Oral streptococci interactions with Veillonella spp.*

Oral *Veillonella spp.*, especially *V. parvula*, is associated with caries and intraradicular infections (Mashima and Nakazawa, 2015). Veillonellae are among the most predominant species in the oral cavity and coaggregate with many initial, early, middle and late colonizers. They are considered as bridging species similar to oral fusobacteria (Zhou et al., 2015), and usually coexist with their streptococcal coaggregation partners in specific parts of the mouth. Their coaggregation and the subsequent metabolic cooperation are of major importance in biofilm formation, and are also key elements in facilitating the succession of species in developing dental plaque (Periasamy and Kolenbrander, 2010).

Veillonellae were unable to establish monoinfections. Mcbride et al discovered that when rats were monoinfected by *S. mutans* firstly and subsequently infected with veillonellae, the number of veillonellae in coinfected animals' teeth increased significantly (Mcbride and Van der Hoeven, 1981). This experiment demonstrated that veillonellae and oral streptococci are metabolically linked. Although veillonellae are unable to ferment sugars, streptococcal fermentation of sugars to lactic acid can serve as a favored carbon source for them. A food chain can thus be developed between these bacteria with the end-product of one organism serving as the energy source for the other (Egland et al., 2004; Chalmers et al., 2008).

The synergistic relationship between veillonellae and oral streptococci was demonstrated early in the 1970s, consequently resulting in reduced caries activity and enamel demineralization (Van der Hoeven et al., 1978). But an

opposite conclusion was made in later studies. A convincing reason could be that, although veillonellae form propionic and acetic acids (weaker than lactic acid) from metabolism of lactic acid, and propionic and acetic acids less likely dissolve the enamel of the teeth, veillonellae have been detected in high proportions in progressing incipient lesions (Milnes and Bowden, 1985). Consistent results acquired by molecular identification methods, demonstrated that significantly more veillonellae in dentinal lesions were detected than at any other site (Becker et al., 2002). More recently, significantly higher levels of veillonellae were detected in subjects with caries than those free of caries (Xu et al., 2014a; Thuy et al., 2015). Numerous findings indicated a strong association between *Veillonella spp.* and dental caries, thus the *Veillonella spp.* level in an individual is considered as a sensitive biologic indicator and early warning sign of dental caries. Gross et al. stated that, among children without history of caries, the presence of veillonellae helped to foresee a possible development of caries (Gross et al., 2012). Clinical data also demonstrated high *Veillonella spp*. levels are in association with more caries (Lima et al., 2011; Tanner et al., 2011).

The combination of veillonellae and *S.mutans* leads to more acid production and greater demineralization than the production and demineralization by *S. mutans* alone, as shown in an *in vitro* study (Noorda et al., 1988). The elevated acid production is probably facilitated by the lactate removal from the environment by veillonellae, creating a higher pH microenvironment (Marsh, 1994). An *in vivo* study showed that *Veillonella spp.* can mitigate the inhibitory effects of *S. gordonii* on *S. mutans* sugar metabolism, suggesting a specific interaction between *S.mutans* and *Veillonella spp.* that may be more complex than pH (Kreth et al., 2009; Liu et al., 2011). Promotion of acid production ensures better

nutrition supply for veillonellae. In return to the utilization of lactic acid, *Veillonella spp.* also provides protection to *S. mutans*. Luppens et al. reported that *S. mutans* grow in a dual-species biofilm together with *V. parvula* is subjected to a physiological change, and acquires an advantage in its ability to survive under antimicrobial treatment (Luppens et al., 2008).

Various surface molecules and the streptococcal transcription factor catabolite control protein A are required for the interspecies interaction between *S. gordonii* and *Veillonella atypical* (Johnson et al., 2009). The adhesins and/or transcription factors may also involve in the interaction and biofilm formation of other veilloella-streptococcal pairs, as suggested by Mashima et al. (Mashima and Nakazawa, 2014). They also stated that, signaling molecules between bacterial cells should be considered as an important way of communication, in that *Veillonella tobetsuensis* promoted *S. gordonii* biofilm formation to the greatest extent without intergeneric coaggregation (Mashima and Nakazawa, 2014). They hypothesized that a small molecule such as AI produced by *V. tobetsuensis* may stimulate *S. gordonii* biofilm formation. In a following study, AI-1 and AI-2 were detected in the culture supernatants of *V. tobetsuensis* and the researchers concluded that these molecules (mainly AI-2) may play key roles in facilitating biofilm formation of *S. gordonii* (Mashima and Nakazawa, 2015). Besides, Zhou et al discovered that Hag 1, a multivalent hemagglutinin in *V.atypica*, is involved in its adherence to oral streptococci, *P. gingivalis* and human oral buccal cells (Zhou et al., 2015).

*Oral streptococci interactions with Candida Albicans*

*Candida Albicans* is able to survive as a commensal in several anatomically

distinct sites. However, under certain circumstances, *C. albicans* can cause infections that range from superficial infections of the skin to life-threatening systemic infections (Mayer et al., 2013). *C. albicans* can exhibit two forms under different environmental conditions. The yeast form colonizes predominantly surfaces, whereas the hyphal form confers invasiveness to *C. albicans*, which can thus cause serious damages to human tissues (Gow et al., 2012; Ashkanane et al., 2017). Moreover, the hyphal form can provide structural integrity to biofilms (Banerjee et al., 2013). Oral candidiasis usually includes pseudomembraneous stomatitis, erythematous stomatitis and hyperplastic lesions.

*C. albicans* can coaggregate with a variety of oral commensal bacteria, especially in the range of oral streptococci. Oral streptococci were once believed to protect humans against oral candidiasis (Liljemark and Gibbons, 1973). However, with the development of research, the streptococcal species considered as avirulent can show its pathogenicity when coaggregated with *C. albicans*. Within the biofilms, fungal and bacterial cells use metabolites or cell contact-mediated signals to communicate with each other, further influencing gene expression, host responses and progression of the disease (Xu et al., 2017).

Interactions between *C. albicans* and commensal oral streptococci are bidirectional and generally considered as mutualistic beneficial. The synergistic relationship has been demonstrated in several aspects. In addition to providing adhesion sites, streptococci can also excrete lactate as a carbon source for yeast growth. In turn, yeast cells can reduce the oxygen tension to more

preferable levels for streptococci, providing growth stimulatory factors for them (Diaz et al., 2012; Metwalli et al., 2013). In practical terms, *C. albicans* promotes the ability of streptococci to form biofilms in oral environment, and oral streptococci in turn enhances the growth of *C. albicans* biofilm and oral mucosa invasion (manifested by enhanced hyphal production and increased biomass) (Bamford et al., 2009).

*S. gordonii* cell wall-associated polypeptides SspA, SspB, CshA, and EPS-mediated interactions play important roles in binding to *C. albicans* (Xu et al., 2014b). Along with the secretion and/or modulation of QS molecules, these mechanisms together lead to synergism for their survival as mixed species biofilms (Diaz et al., 2012). *S. gordonii* provides an adherent surface to *C. albicans* thus facilitating its colonization on oral tissues. Moreover, *S. gordonii* can prevent *C. albicans* from detecting farnesol, a quorum sensor produced by the fungus that functions as a self-restriction signal (Bamford et al., 2009). The inhibition of farnesol detection leads to production of more robust biofilms, increasing pathogenicity and higher levels of antimicrobial resistance (Daniel et al., 2016).This aspect is of clinical significance particularly for immunocompromised individuals, because this synergism can subsequently develop into a fungal infection.

In another study focused on *S. oralis*, the introduction of *C. albicans* enhances mucosal biofilm formation by *S. oralis* (which lacks the ability to form robust mucosal biofilms), and the co-infection significantly increases the frequency and size of the oral thrush lesions in mice (Xu et al., 2014c). Xu et al. demonstrated that this synergism can activate host enzymes that cleave epithelial junction

proteins, increasing fungal invasion (Xu et al., 2016).

The correlation between *C. albicans* and dental caries has also been highlighted. Indeed, high candidal presence in dental plaque and saliva are correlated with caries experience and severity (De-La-Torre et al., 2016; Fragkou et al., 2016; Moraga et al., 2016). With regard to caries etiology, in addition to the ability of *C. albicans* to produce and tolerate acids, much of the attention has focused on the relationship between *S. mutans* and *C. albicans* (Falsetta et al., 2014; Ellepola et al., 2017; Pereira et al., 2017a). A symbiotic relationship between these two species has been demonstrated to enhance the virulence of cospecies plaque biofilms, ultimately amplifying the severity of caries (Falsetta et al., 2014). As have been shown in an animal model, coinfection of rats with *S. mutans* and *C. albicans* enhances the colonization and carriage of both organisms *in vivo* and dramatically amplifies the virulence of plaque biofilms formed on rodent dentition, leading to the development of rampant carious lesions (Falsetta et al., 2014).

Unlike the binding mechanism between *S. gordonii* and *C. albicans*, which is sucrose-independent, *S. mutans* poorly binds to the fungal surface without sucrose. Gtf-derived EPS is a key mediator of cospecies biofilm development (Hwang et al., 2015; Ellepola et al., 2017), and it binds to the mannan layer of *C. albicans* independent of hyphae or other known major cell surface adhesins (Hwang et al., 2017). Moreover, Kim et al. discovered that bacterial-fungal derived metabolites increases the growth of *S. mutans* and its Gtf activity, furtherly altering the biofilm architecture into enlarged and densely packed bacterial cell-clusters (Kim et al., 2017). Co-cultivation with *C. albicans* also influences carbohydrate utilization by *S. mutans*, as was revealed by He et al. via

RNA sequencing demonstrating that the majority of up-regulated genes are related to carbohydrate transport and metabolic/catabolic processes (He et al., 2017).

Some streptococci exert an inhibition on fungal growth. *S. sanguinis* has an antagonistic effect on *C. albicans* growth due to its production of *S. sanguinis* bacteriocin. The bacteriocin can change the cell shape of *C. albicans*, increase the fungal cell membrane permeability, and reduce its adhesion ability (Ma et al., 2014; Ma et al., 2015; Ma et al., 2017) .

Besides, Ishijima et al. found that *S. salivarius* is effectively working against *C. albicans* growth and exerts a protective effect against candidiasis, as shown in a candidiasis model (Ishijima et al., 2012). *S. salivarius* is able to directly bond candida cells, thus inhibiting the adhesion of *C. albicans* to a plastic Petri dish and reducing *C. albicans*' ability to maintain its blastospore shape. MacDonald also showed that two strains of *S. salivarius* do not reduce yeast growth but inhibit its hyphae formation and adhesion to surfaces (Macdonald, 2015). The inhibition effect is likely to be attributed to protein secretion of *S. salivarius* (Fairiska et al., 2017).

**Interactions between oral streptococci and periodontal pathogens**

Periodontitis is a common infection worldwide and affects a large population (Kassebaum et al., 2014). This disease not only compromises the integrity of the tooth supporting tissues (gingiva, periodontal ligament and alveolar bone), but it is also associated with severe systemic conditions such as coronary artery disease, rheumatoid arthritis, and diabetes (Hajishengallis, 2015). Oral

streptococci can develop extensive communication with periodontal pathogens. *S. gordonii* is metabolically compatible with definite periodontal pathogens such as *P. gingivalis*, *F. nucleatum* and *A. actinomycetemcomitans*. It has been proposed as one of the "Helper Pathogens Facilitating the Formation of Periodontal Disease" (Whitmore and Lamont, 2011). Unlike *S. gordonii*, some *Streptococcus spp.* such as *S. sanguinis* is often found in subgingival biofilm. It is correlated with a delay in colonization by periodontal pathogens, and it antagonizes a variety of periodontal pathogens (Lee, 2015; Herrero et al., 2016). In the following part several representative periodontal pathogens were selected and their relationships with oral streptococci were discussed.

*Oral streptococci interactions with Porphyromonas gingivalis*

*P. gingivalis* is a major pathogenic species involved in gingivitis and periodontitis. It has been designated as a "keystone pathogen" which induces dysbiosis through the manipulation of the host innate immune response, leading to uncontrolled inflammation and tissue damage (Hajishengallis and Lamont, 2014; Kalia et al., 2017). A high level of *P. gingivalis* in the subgingival oral biofilm is attributed to its extensive interactions with other gram-negative obligate and facultative anaerobes, such as *F. nucleatum*, *Treponema denticola* and *Tannerella forsythus* (Daep et al., 2008). However, its initial colonization in the oral cavity is in the supragingival biofilm (Wright et al., 2013). The fimbriae of *P. gingivalis* can attach to streptococci and both major and minor fimbriae are involved. The major fimbria (FimA) of *P. gingivalis* is linked to GAPDH located on the surface of streptococci, and the minor fimbria (Mfa) engages streptococcal cell surface protein SspA/B (Enersen et al., 2013; Wright et al., 2013; Wright et al., 2014).

Adherence of *P. gingivalis* to *Streptococcus spp.* such as *S. gordonii* is considered as an initial event that facilitates *P. gingivalis* colonization in the oral cavity (Wright et al., 2013; Kalia et al., 2017). Interbacterial coaggregation or coadhesion between *P. gingivalis* and *S. gordonii* enhances the colonization of both species in a biofilm model, where *S. gordonii* outcompetes *P. gingivalis* for attachment sites in the salivary pellicle, and substantial mixed bacterial biofilms develop on saliva-coated glass slides only when *S. gordonii* cells are plated to provide an attachment substrate for *P. gingivalis* (Cook et al., 1998). The synergistic interaction between *S. gordonii* and *P. gingivalis* is multifaceted, and metabolic interchanges between the two species have also been characterized. *S. gordonii* may deplete oxidants to allow the survival of *P. gingivalis*, and *P. gingivalis* secretes several proteases that may breakdown peptides for *S. gordonii* metabolism (Jenkinson, 2011). The proteolytic activity of *P. gingivalis* is increased when *S. gordonii* is present, and a community composed of *P. gingivalis* and *S. gordonii* is more pathogenic in animal models of periodontal diseases compared to each species alone (Daep et al., 2011; Whitmore and Lamont, 2011). Therefore, this synergy may play an important role in the development of bacterial populations associated with the onset and progression of severe periodontal disease forms (Forsgren et al., 2010).

In addition to an increased periodontal pathogenicity of the biofilm, the coadhesion of *P. gingivalis* with streptococci such as *S. gordonii* and *S. mutans* is important in the invasion of dentinal tubules, inducing infections of the root canal system (etiology of pulpal and periapical diseases) (Love et al., 2000). The recognition of collagen type I present within the tubules by streptococcal antigen

I/II polypeptides is essential for the bacterial invasion and for the intratubular growth (Love et al., 1997). Although *P. gingivalis* can also bind to collagen type I deposited onto hydroxylapatite surfaces (Naito et al., 2010), its ability to bind type I collagen within dentinal tubules alone is not sufficient to promote the invasion of tubules. The binding of *P. gingivalis* to intratubular collagen just probably help the invasion process (Love et al., 2000). Due to its noninvasive nature, *P. gingivalis* is able to penetrate tubules only after coadhering to the invasive partner streptococci.

A synergy in biofilm formation between *P. gingivalis* and *S. oralis*, another species of the mitis group, has also been uncovered by Maeda et al. via proteomic and transcriptional analysis. They observed an overexpression of *P. gingivalis* FimA and *S. oralis* GAPDH in mixed-biofilm and concluded that *S. oralis* regulates the transcriptional activity of *P. gingivalis luxS* (Maeda et al., 2015).

Not all *Streptococcus spp.* seem to offer help when confronted with this pathogen. Known that *S. sanguinis* have measures to limit the overgrowth of *P. gingivalis* via its aforementioned $H_2O_2$ production ability, the study conducted by Ma et al. also showed significant inhibitory effects on *P. intermedia* exerted by intracellular proteins extracted from *S. sanguinis* (Ma et al., 2014). Besides, Lee demonstrated that *S. sanguinis* peptidoglycan inhibited the cytokine expression triggered by lipopolysaccharide in *P. gingivalis* and may alleviate inflammatory responses (Lee, 2015).

Another species which may hamper the pathogenesis of *P. gingivalis* is

*Streptococcus cristatus*. It has been reviewed that there is an opposite relationship between the number of *S. cristatus* and *P. gingivalis* in the dental plaque isolated from periodontitis subjects, suggesting that *S. cristatus* may be beneficial to the host by antagonizing the colonization and accumulation of *P. gingivalis* (Wang et al., 2009). The arginine deiminase of *S. cristatus* represses the expression of FimA in *P. gingivalis* (Christopher et al., 2010), and also represses the expression of several well-known virulence genes involved in the production of gingipains (Ho et al., 2017a, b).

*Oral streptococci interactions with Fusobacteria nucleatum*

Fusobacteria are the most frequent Gram-negative bacteria in dental plaque, binding to a diverse array of microbial species. Fusobacteria are present in both supragingival and subgingival plaque, and are predominantly involved in both caries and periodontal diseases (Haffajee et al., 2008; Lima et al., 2011; Aruni et al., 2015). Most worthy of mention is *F. nucleatum*, which is described as a “bridge” connecting early and late colonizers, making great contributions to biofilm formation and architecture (Denes and Barraud, 2016; Lima et al., 2017). Regarded as a periodontal pathogenic bacteria, *F. nucleatum* is consistently associated with, and increased in number in periodontitis sites (Signat et al., 2011).

Within dental plaque, *F. nucleatum* is often found with streptococci in “corncob” formations (Lancy et al., 1983). The outer membrane protein RadD and CmpA, two arginine-inhibitable adhesins, are major fusobacterial adhesins allowing the physical attachment to *S. sanguinis and S.gordonii* (Kaplan et al., 2009; Lima et al., 2017). By adhering to *S. sanguinis*, *F. nucleatum* is able to mask the surface

components and evade detection by antagonistic oral bacteria, thereby overcoming the colonization resistance (He et al., 2012). The adherence also triggers a specific cellular response by *F. nucleatum* and results in increased resistance to environmental stress (He et al., 2012). By this way, *F. nucleatum* integration into Gram-positive bacteria dominating supragingival microbial community is greatly facilitated.

In addition to physical contact mediated by the RadD and CmpA adhesins, in a more recent study, Sakanaka et al. discovered that *S. gordonii* arginine-ornithine antiporter-mediated ornithine efflux is indispensable for a successful colonization by *F. nucleatum*, where *F. nucleatum* utilizes the ornithine released by *S. gordonii* antiporter as a substrate of ornithine decarboxylase (Sakanaka et al., 2015). This leads to *S. gordonii-F. nucleatum* community development and finally result in the formation of a middle-stage periodontopathic biofilm.

Unlike the adhesion to *S. sanguinis* or *S. gordonii,* the specific interaction between *F. nucleatum* and *S. mutans* is mediated by the RadD-SpaP adhesin pair (Guo et al., 2016). The interaction can broaden the possibility of integration into oral streptococci biofilm, and is potentially beneficial, since *F. nucleatum* was found to have acid-neutralizing abilities (Takahashi et al., 1997), which may help decrease the risk of dental caries.

The binding of another early colonizer, *S.cristatus*, to *F. nucleatum*, which is mediated by the *S.cristatus* fibrillar tufts, arouse researchers' concern. Since *Fusobacteria spp.* can penetrate the epithelium (during periodontitis) while *S.cristatus* cannot, the adhesion to invasive *F. nucleatum* helps noninvasive *S.*

*cristatus* to enter epithelial cells (Edwards et al., 2006). As a consequence of that, *S. cristatus* attenuates the expression of a number of inflammatory cytokines induced by *F. nucleatum*, and upregulates several anti-inflammatory mediators, reducing the proinflammatory effect of *F. nucleatum* (Zhang and Rudney, 2011). This is of clinical significance because the mucosal hyporesponsiveness to invasive bacteria may also provide a possibility for these pathogens to later colonize the gingival crevice and remote locations (Zhang and Rudney, 2011), which is related to periodontal pathogenesis.

However, not all oral streptococci develop a mutualistic beneficial relationship with *F. nucleatum.* Jang et al. discovered that *F. nucleatum* AI-2 stimulated *S. gordonii* biofilm growth and aggregation of *F. nucleatum* with *S. gordonii*, while inhibited *S. oralis* biofilm growth and aggregation of *F. nucleatum* with *S. oralis*, indicating that initial colonizing streptococci affects sequential colonization of *F. nucleatum* in dental biofilms and enrichment of *S. oralis* in initial biofilm may reduce *F. nucleatum* attachment (Jang et al., 2013).

*Oral streptococci interactions with Prevotella intermedia*

*Prevotella intermedia* is strongly associated with the acute necrotizing ulcerative gingivitis and pregnancy-induced gingivitis (Chung et al., 1983). It also plays an important role in producing volatile sulfur compounds (Tanaka et al., 2004), causing halitosis.

*S. salivarius* is considered as a probiotic bacteria due to its ability to compete with the colonization of bacteria that increase volatile sulfur compounds (Burton et al., 2006a; Hyink et al., 2007; Burton et al., 2010). Therefore, its influence on *P.*

*intermedia* is of great clinical significance. The coaggregation between *S. salivarius* and *P. intermedia* is special. When tested by a fimbriae-negative mutant of *S. salivarius*, coaggregation is observed with *F. nucleatum* and with *P. gingivalis*, but not with *P. intermedia*. Only fimbriaed *S. salivarius* cells coaggregated with *P. intermedia*, suggesting that *S. salivarius-P. intermedia* coaggregation is mediated by *S. salivarius* fimbriae (Lévesque et al., 2003). *S. salivarius K12* showed an antibacterial effect against *P. intermedia* when exceeds a certain concentration (70%), leading to significant decrease of volatile sulfur compounds both *in vitro* and in human mouth (Burton et al., 2006b; Moon et al., 2016).

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*Oral streptococci interactions with Aggregatibacter actinomycetemcomitans*

*A. actinomycetemcomitans* can be found in healthy individuals as part of the normal flora, and it is the predominant pathogen associated with localized aggressive periodontitis (Gholizadeh et al., 2017; Vaniabella et al., 2017). The most prominent pathogenic traits of *A. actinomycetemcomitans* should be its role in the decline of host immune response and degradation of gingival epithelial attachment on periodontal tissues (Vaniabella et al., 2017). Aggregatibacteria and streptococci are found in plaque samples as dense aggregates at the tips of abundant hedgehog structures (Mark Welch et al., 2016). Similar to veillonellae, *A. actinomycetemcomitans* entirely depends on other oral microorganisms to grow in saliva (Kolenbrander, 2011).

*S. gordonii* excretes lactate acid as a carbon source for *A. actinomycetemcomitans* and in exchange, the latter detoxifies $H_2O_2$ that *S. gordonii* produces. Their mutual benefit is also shown in a murine abscess model,

where both species grow more virulent when they are together than when they are alone (Stacy et al., 2014; Stacy et al., 2016). Moreover, when cocultured with *S. gordonii* and senses the streptococcal metabolite $H_2O_2$, *A. actinomycetemcomitans* displays an enhanced resistance of being killed by the host innate immunity (Ramsey and Whiteley, 2009).

*A. actinomycetemcomitans* also interacts with *S. mutans*. In dual-species biofilms grown on artificial saliva, *A.actinomycetemcomitans* triggers the expression of the QS regulon of *S. mutans*, resulting in an up-regulation of the transformasome and mutacin related genes, and down-regulation of oxidative stress related genes (Szafrański et al., 2017). It can be concluded that *A. actinomycetemcomitans* protects *S. mutans* from oxidative stress possibly by the aerobic respiration. Simultaneously, *A. actinomycetemcomitans* grows in a highly virulent form but down-regulates genes important for its escape from the host immune response.

Not all *Streptococcus sp.* develop a synergistic relationship with *A. actinomycetemcomitans*. Species such as *S. sanguinis*, *S. mitis*, and *S. salivarius* show prominent inhibitory effects on *A. actinomycetemcomitans* recovery and colonization but without a bactericidal activity (Teughels et al., 2007), and the growth of tested streptococcal strains are also affected by *A. actinomycetemcomitans*. In a recent study, the inhibitory effect of *S. salivarius* on the growth of *A. actinomycetemcomitans* was further verified and the researchers proposed that the production of lactic acid and lantibiotics by *S. salivarius* should be the major cause (Vaniabella et al., 2017): The lactic acid produced by *S. salivarius* can increase the permeability of the outer membrane

of *A. actinomycetemcomitans* and thus increase its sensitization of lantibiotics.

## Conclusion and strategies for prevention and therapy regarding microbial interactions

Oral streptococci play a pivotal role in dental biofilms formation and interact with multiple microorganisms. These microbial interactions, either cooperative or competitive, may promote the establishment of a pathogenic community, causing problems such as dental caries and periodontal diseases. Ultimately, the goal of investigating these microbial interactions is to open the way for controlling oral diseases. Taking dental caries as an example, the removal of dental plaque and the application of fluoride and antimicrobial agents have always been the mainstay through the years. However, the fast accumulation of dental plaque, continual debate on the safety of fluoride use and increasingly severe antimicrobial resistance are problems we must face at this stage. There is an urgent need to develop new preventive and therapeutic methods against oral diseases. Since many oral diseases originate from the dysbiosis of dental biofilms, oral care strategies should place emphasis on maintaining the composition and activity of these biofilms at levels compatible with oral health rather than trying to eliminate them (Marsh, 2016). Microbial interactions within dental biofilms, as have been discussed in the present review, can help assembly and convert distinct bacterial cells to a pathogenic biofilm. Either utilizing or fighting against these interactions should be considered as feasible strategies to cure oral diseases.

One of the strategies being closely studied is the adoption of probiotics. Probiotics are defined as live microorganisms that, when administered in

adequate amounts, confer a health benefit on the host (Gruner et al., 2016). Probiotic bacteria can bind and compete with already coaggregated pathogenic bacteria for nutritive sources or produce chemical substances that inhibit the development of pathogenic bacteria, in order to promote oral health without negatively impacting the normal oral macrobiotic of the host (Burton et al., 2013; Zambori et al., 2016; Pereira et al., 2017b). A range of bacteria (most of them being acidogenic such as lactobacilli, streptococci or bifidobacteria) exert such effects (Gruner et al., 2016). Taking probiotic lactobacilli as an example, they coaggregate with *S. mutans* and other caries-associated strains, inhibiting the growth of these microorganisms (Lin et al., 2018). By comparing the efficacy of milk supplemented with *Lactobacillus rhamnosus* with standard milk in preschool children, a recent clinical trial demonstrated a significantly lower increment of caries in the study group than the control group after 10 months of intervention (Rodríguez et al., 2016). In addition, a probiotic blend containing *S. salivarius*, *L. reuteri* and *L. paracasei* is a useful adjunct to scaling and root planing in chronic periodontitis patients (Mani et al., 2017).

Another approach, which is the interference with the cell-cell communication system targeting the QS signaling pathways, has also been considered as a possible solution to oral diseases, especially in this time of increasing antibiotic resistance and treatment failures. Because of the significant role of signaling molecules in coordinating gene expression and promoting biofilm formation, there is an impetus to investigate the potential of inhibitory analogues to disrupt these networks, thereby providing mechanisms to control or influence the development of dental plaque (Parashar et al., 2015; Pérez et al., 2018).To date, QS inhibitors and quorum quenching enzymes have been investigated for their

QS interfering capabilities (Fong et al., 2018). furthermore, addition of exogenous CSP or QS-modifying compounds showed effects on maintaining a healthy microbial ecology in dental plaque (Philip et al., 2018).

The specifically targeted antimicrobial peptide (STAMP), a synthetic fusion peptide, is also an ecological approach. It is based on the addition of a targeting peptide to an existing broad spectrum antimicrobial peptide (AMP), making it selective for a particular bacterial species or strain (He et al., 2010). It specifically targets pathogens such as *S. mutans* from multispecies biofilms and show membrane-disrupting activities (Philip et al., 2018). As a result, not only the pathogens are eliminated, but a more benign oral microbial community is established (Guo et al., 2015). A clinical study demonstrated the efficacy of a mouth rinse containing a STAMP (C16G2) resulting in a significantly lower levels of *S. mutans* in the plaque and saliva samples after rinsing (Sullivan et al., 2011). Furthermore, this rinse is effective in preventing *S. mutans* regrowth in spite of frequent exposure to sugar.

As mentioned above, new strategies are emerging and changing the way of preventing oral diseases from widespread killing to mediation of microbial communications. We can say that we are embracing a new era with more effective disease control and better oral health.

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