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Oral streptococci: modulators of health and disease

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Streptococci are primary colonizers of the oral cavity where they are ubiquitously present and an integral part of the commensal oral biofilm microflora. The role oral streptococci play in the interaction with the host is ambivalent. On the one hand, they function as gatekeepers of homeostasis and are a prerequisite for the maintenance of oral health - they shape the oral microbiota, modulate the immune system to enable bacterial survival, and antagonize pathogenic species. On the other hand, also recognized pathogens, such as oral *Streptococcus mutans* and *Streptococcus sobrinus*, which trigger the onset of dental caries belong to the genus *Streptococcus*. In the context of periodontitis, oral streptococci as excellent initial biofilm formers have an accessory function, enabling late biofilm colonizers to inhabit gingival pockets and cause disease. The pathogenic potential of oral streptococci fully unfolds when their dissemination into the bloodstream occurs; streptococcal infection can cause extra-oral diseases, such as infective endocarditis and hemorrhagic stroke. In this review, the taxonomic diversity of oral streptococci, their role and prevalence in the oral cavity and their contribution to oral health and disease will be discussed, focusing on the virulence factors these species employ for interactions at the host interface.

KEYWORDS

biofilm, host interaction, oral diseases, *Streptococcus* sp., virulence factors

1 Introduction

Streptococcal species accompany us throughout our life – in the oral cavity, they are the first colonizers after birth and, onwards, they shape the establishment of a complex microbiota in health and disease (Abranches et al., 2018; Klein, 2022). Their interactions with the human host range from highly beneficial – influencing, as commensal species, proper immune system development (Lang et al., 2010) and preventing pathogen colonization - to detrimental, when dissemination in the blood stream occurs, potentially leading to no less than infective endocarditis (IE), purulent infections, brain hemorrhage, intestinal inflammation, autoimmune diseases, and bacteremia, among others (Yumoto et al., 2019). This review focuses on oral streptococci, their taxonomic diversity and roles within their ecological niche, and, first and foremost, their interaction with the host, within the oral habitat and beyond.

Complementary to this review, methods and tools for the detection, identification, characterization, and spatial localization of oral streptococci have been summarized in a recent book chapter (Klein, 2022).

2 Taxonomic overview of oral streptococci

Streptococci are facultative anaerobic, Gram-positive bacteria. Historically, species within the genus *Streptococcus* were classified according to their hemolytic potential on blood agar plates as fully (β -)hemolytic, partially (α -) hemolytic and non- (γ -) hemolytic (Sherman, 1937). β -hemolytic streptococci were further subcategorized according to the carbohydrate composition of the antigens present in their cell wall (Lancefield groups) as Group A *Streptococcus* (GAS), such as the highly pathogenic *Streptococcus pyogenes*, or as Group B *Streptococcus* (GBS), such as *Streptococcus agalactiae* (Facklam, 2002; Abranches et al., 2018).

With the advent of 16S rRNA sequencing techniques, the genus *Streptococcus* was further categorized into eight distinct groups based on phylogenetic relationships between its members; these are the *mitis*, *sanguinis*, *anginosus*, *salivarius*, *downei*, *mutans*, *pyogenic*, and *bovis* groups (Abranches et al., 2018). While the *mitis* group constitutes the largest group with 20 members detected in the oral cavity, oral streptococci – also often referred to as *viridans* streptococci – cluster in all groups except for *bovis* and *pyogenic* (Abranches et al., 2018). Between these groups as well as species within the same group, differences in virulence and pathogenicity can be observed (Sitkiewicz, 2018). For instance, members of the *mutans* group, e.g., *Streptococcus mutans* and *Streptococcus sobrinus*, have been identified as species with high cariogenic potential (Richards et al., 2017). *Mitis* group streptococci (MGS) such as *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus gordonii*, *Streptococcus infantis*, *Streptococcus sanguinis*, and *Streptococcus parasanguinis*, on the other hand, are associated with oral health (Richards et al., 2017). Notably, especially the first three species have recently been identified as causative agents in the development of IE, after the occurrence of a blood stream infection (Chamat-Hedemand et al., 2020). Among others, *S. mitis* as well as *S. oralis* have recently been classified as members of the core oral microbiota, i.e., they belong to a group of oral bacteria that is ubiquitously present within the oral cavity (Hall et al., 2017). When it comes to their pathogenic potential, MGS as well as *Streptococcus anginosus* Group (SAG) members have long been considered as commensals integrated in a healthy human microbiota, however, they have more and more frequently been recognized to elicit significant health problems in humans (Mitchell, 2011; Kuryłek et al., 2022; Pilarczyk-Zurek et al., 2022).

3 The oral cavity: habitat for complex polymicrobial communities in health and disease

The oral cavity is a unique and multifaceted bacterial habitat with distinct ecological niches, resulting from the presence of different

surfaces for colonization and varying conditions due to considerable fluctuations in oral environmental parameters such as temperature, pH, redox potential and nutrient availability, which, in combination with behavioral aspects of the human host (e.g., dental hygiene, diet, smoking) as well as genetic predisposition and the general health status, shape the composition of the resident microbial consortia (Mark Welch et al., 2020). The non-shedding surfaces of the teeth, the dorsal and lateral surfaces of the tongue, the periodontal pockets, and the remaining epithelial surfaces of the oral mucosa offer sites for colonization by distinct microbes. Streptococci have been found to be present at all of these sites and to be the dominant genus in supra- and subgingival plaque and on soft tissues (Mager et al., 2003; Aas et al., 2005; Huse et al., 2012; Mira, 2018). As primary/pioneer colonizers, they are the first species to colonize the oral surfaces and allow for the establishment of other species such as *Actinomyces*, *Veillonella*, *Fusobacterium*, *Prevotella*, and *Neisseria*, initializing the process of microbial succession and establishment of a complex microbial consortium (Sampaio-Maia and Monteiro-Silva, 2014; Gomez and Nelson, 2017). Recent investigations revealed a new understanding of how the oral biofilm is formed from bacterial aggregates serving as nuclei for the development of a strong biofilm embedded in the extracellular matrix. Regarding the presence of streptococci, an interesting observation was made concerning their localization; in addition to early colonization at the biofilm basis, these were detected radially in the outermost layer of the biofilm providing a microenvironment for strict anaerobes by consuming present oxygen (Simon-Soro et al., 2022).

Formation of dental plaque on the non-shedding surfaces of the teeth is one of the best characterized multispecies biofilm community activities; dental plaque is present in healthy individuals, but it is also associated with the development of oral diseases, including caries, gingivitis and periodontal diseases (Marsh and Zaura, 2017).

3.1 Dental caries

Streptococci are the predominant species to initially adhere to the salivary pellicle (Diaz et al., 2006). In supragingival plaque, predominantly the dietary intake of sugars promotes the formation of extracellular polymeric substances (EPS) and acidic metabolites causing the resident microflora to shift towards aciduric and acidogenic species (Lamont et al., 2018). If persistent, this leads to the acidification of the biofilm microenvironment and, ultimately, to the demineralization of dental enamel and the development of carious lesions (Lamont et al., 2018). The role of *mutans* streptococci (MS), i.e., *S. mutans* and *S. sobrinus*, as cariogenic agents has long been recognized (Conrads et al., 2014; Hajishengallis et al., 2017). The cariogenic potential of MS stems from three characteristic traits – the species' ability to synthesize large quantities of extracellular glucan from sucrose, their ability to metabolize a wide range of carbohydrates into organic acids, i.e., their acidogenicity, and their tolerance towards environmental stress conditions such as low pH, i.e., their aciduric nature (Lemos et al., 2019). Extracellular glucans form essential building blocks of the EPS as part of the extracellular biofilm matrix, which confers to the bacteria protection from shear forces and resistance

to antimicrobials, influences the diffusion of oxygen, nutrients, quorum sensing signals and metabolites, and creates an acidic microenvironment in which commensal bacteria are outcompeted by cariogenic species (Bowen et al., 2018).

3.2 Pulpitis and endodontic infections

Carious lesions or other factors that damage the tooth's integrity can reach the dental pulp, which is principally encased in the root canal system, exposed to the bacteria present in the oral cavity. Bacterial colonization elicits inflammation and necrosis of the dental pulp as well as inflammation of the periapical region, finally leading to bone resorption and the formation of granulomas or cysts (Graves et al., 2011). Oral streptococci, such as *S. oralis*, *S. anginosus*, *S. mitis*, *S. sanguinis* (Chávez de Paz et al., 2005; Narayanan and Vaishnavi, 2010), and *S. mutans* (Lima et al., 2020) are frequently among the species detected in root canal infections. In the dental pulp, bacterial pathogen associated molecular patterns (PAMPs) are recognized by macrophages, dendritic cells (DCs), odontoblasts and endothelial cells, and elicit an immune response leading to the recruitment of specialized immune cells and the initiation of bacterial clearance (Khorasani et al., 2020). The inflammatory response mechanisms, cytokine networks as well as pulpal disease pathogenesis are the focus of other reviews (Hahn and Liewehr, 2007a; Farges et al., 2015; Khorasani et al., 2020; Galler et al., 2021).

3.3 Periodontal diseases

The onset of gingivitis and emergence of periodontal diseases is caused by the shift in the composition of the resident oral microbiota from commensal to dysbiotic (Hajishengallis and Lamont, 2012). In a healthy individual, bacteria in the subgingival crevice exist in a balanced state with the host immune system, under controlled, low-level inflammation keeping bacterial growth in check (Hajishengallis and Lamont, 2016). This symbiotic state can be disrupted if certain risk factors, such as disadvantageous host genetics or lifestyle, or systemic diseases apply, or if keystone pathogens are present (Loos and Van Dyke, 2020). Dysbiosis is characterized by an increase in bacterial mass and the prevalence of Gram-negative, anaerobic species, leading to chronic inflammation (Hajishengallis et al., 2020). Particularly, the emergence of inflammophilic species such as *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans* or *Filifactor alocis* (Haffajee et al., 2008; Könönen et al., 2019), their modulation of the immune response and interaction with the resident polymicrobial community support an exacerbation of inflammation and bacterial overgrowth (Hajishengallis et al., 2012). Periodontal pathogens are capable of evading (Hajishengallis, 2011; Bloch et al., 2018, 2019) and subverting (Hajishengallis and Lamont, 2014; Hajishengallis and Diaz, 2020) the host immune response and thereby dysregulate immune homeostasis. A detailed description of immune mechanisms in the context of periodontal diseases can be found

in several excellent reviews (Hajishengallis, 2014; Ebersole et al., 2017; Könönen et al., 2019).

3.4 Oral streptococci and their balancing act between health and disease

Oral streptococci regulate the structure and function of the oral microbiome in a way that is beneficial to human health (Baty et al., 2022). However, *Streptococcus* was determined by metagenomic analyses as the predominant genus in patients with gingivitis (Park et al., 2015). As pioneer colonizers, streptococci not only enable later colonizers and pathogenic species to co-adhere, they also can be considered as accessory pathogens, as is the case for *S. gordonii* whose interaction with *P. gingivalis* and *A. actinomycetemcomitans* was found to substantially elevate these species' pathogenicity (Kuboniwa et al., 2006; Daep et al., 2011; Ramsey et al., 2011). In pathogen-free mice, inoculation with *P. gingivalis* led to a massive increase in streptococcal cell numbers (Hajishengallis et al., 2011) and in an *in vitro* subgingival biofilm model, omission of the periodontal pathogen from the community resulted in invasion of gingival epithelial cells by *S. oralis* instead (Thurnheer et al., 2014). On the other hand, *P. gingivalis* failed to cause periodontal disease in germ-free mice in the absence of the commensal core microbiome –which in fact was capable of causing modest bone loss in germ-free mice on its own putting oral streptococci in the spotlight as modulators of oral immune responses (Hajishengallis et al., 2011; Abusleme et al., 2013). These findings highlight the central role oral streptococci play in the balancing act between the maintenance of host-microbiome homeostasis during health and immunomodulatory effects in disease. In the following sections, the factors employed by these bacteria to tip this balance towards a healthy or diseased state will be discussed.

4 Immunomodulatory effects exerted by commensal oral streptococci

Maintenance of homeostatic control of infection and inflammation is crucial to oral health. As dominant members of the resident oral microflora, streptococci exert essential functions in this process (Figure 1). In a study by Myers and coworkers, 30% of streptococci isolated from supra- and subgingival plaque samples were found to exhibit anti-inflammatory properties, specifically by downregulation of IL-8 production in epithelial cells (Myers et al., 2021). Operating as an oral commensal, *S. gordonii* can suppress the secretion of IL-6 and IL-8 in epithelial cells, which contrasts with *Fusobacterium nucleatum*, an important bridging bacterium in oral biofilms that is regarded as a potential pathogen and was examined in the same study (Hasegawa et al., 2007). Other species such as *S. salivarius* or *S. mitis* contribute to a balanced immune status by attenuating pro-inflammatory immune responses towards themselves as well as towards pathogenic species (Cosseau et al., 2008; Eberhard et al., 2009; Sliopen et al., 2009a). Furthermore, *S. mitis* induces the release of the antimicrobial cationic peptide

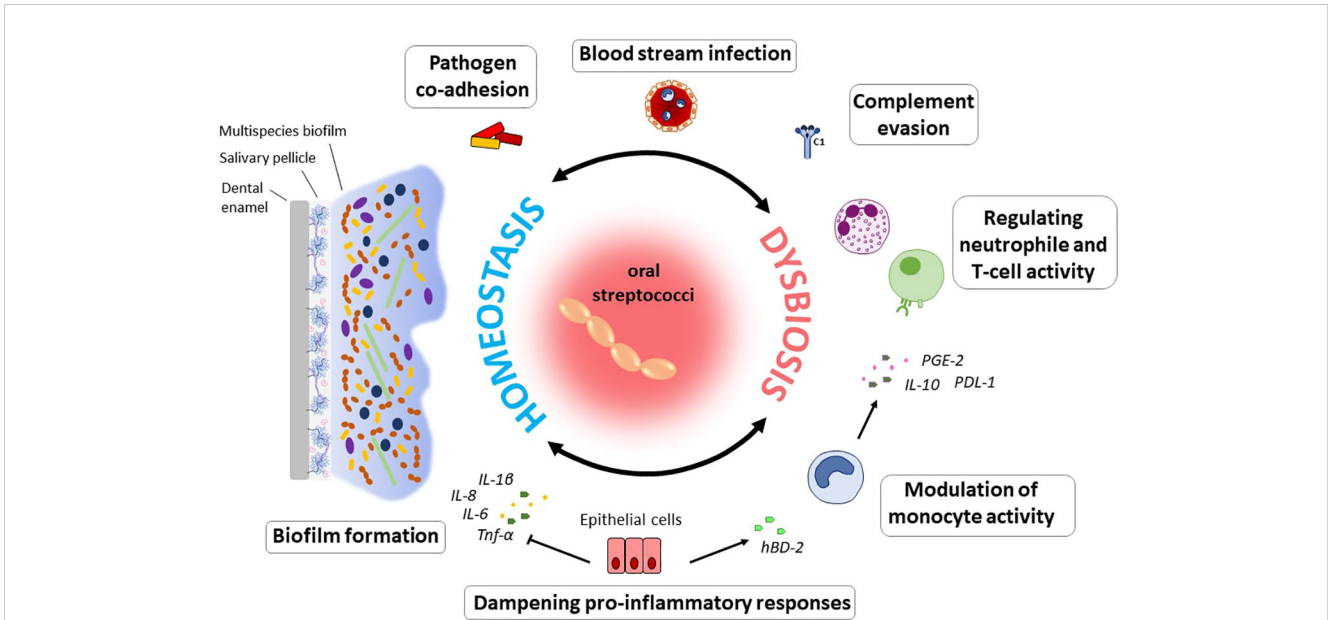


FIGURE 1

Immunomodulatory effects of oral commensal streptococci. The ability to form biofilms on numerous substrates can be regarded as a hallmark of oral streptococci. From within oral biofilms, streptococci interact with immune and epithelial cells, enable pathogens to co-adhere, and can disseminate into the blood stream. Modulation of the immune response to the bacterial biofilm challenge enables their persistence and survival in the host and determines the balance between immune homeostasis and dysbiosis. Specifically, through the downregulation of pro-inflammatory immune responses, oral streptococci contribute to a balanced immune status. Induction of hBD-2 released e.g., by *S. mitis* counteracts colonization by pathogenic species. This commensal was also found to induce a pro-inflammatory immune response in monocytes, while at the same time inhibiting neutrophil activity and T cell proliferation through the action of IL-10, PD-L1 and PGE2. In the context of systemic disease, it is beneficial for many streptococcal species that they can evade complement mediated immunity and thereby remain under the radar. Especially in periodontal disease, the role of oral streptococci to adhere to numerous substrates as primary colonizers and biofilm builders makes them a contributing factor to disease development, since they enable colonization of pathogenic species.

human β -defensin 2 (hBD-2) which is not harmful to *S. mitis* itself, but affects other bacteria (Eberhard et al., 2009; Mitchell, 2011) and thereby antagonizes oral colonization by pathogenic species. Expression of hBD-2 has been found to be upregulated in gingival epithelial cells in response to commensals, e.g., *F. nucleatum*, but not to pathogenic species, such as *P. gingivalis*, and is produced in the gingiva also in a non-inflamed state (Krisanaprakornkit et al., 2000). Apart from bacterial killing, hBD-2 can also inhibit bacterial biofilm formation at nanomolar concentrations, as was shown for, e.g., *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Parducho et al., 2020). In response to *S. mitis* challenge, monocytes produce chemotactic as well as pro-inflammatory mediators and at the same time increase the secretion of interleukin-10 (IL-10) and prostaglandin E2 (PGE2) and expression of programmed cell death protein ligand 1 (PD-L1), inhibiting neutrophil activity and T cell proliferation (Engen et al., 2018). *S. mitis* can, thus, trigger the recruitment of immune cells to the site of infection, while at the same time dampening the inflammatory response and thereby promote commensal bacterial tolerance and survival on site. Certain MGS and *sanguinis* streptococci, especially those associated with systemic infections, even display immune evasion mechanisms being less susceptible to complement opsonization and thereby escape immune surveillance (Alves et al., 2019). In *S. mutans*, complement resistance as well as uptake by neutrophils is controlled by the orphan response regulator CovR, a repressor of virulence factor expression

(Negrini et al., 2012; Alves et al., 2016). Specifically, CovR regulates the expression of genes involved in cell wall biogenesis and surface interactions with EPS and impacts not only susceptibility to complement opsonization and survival in blood, but also the formation of cariogenic biofilms on the tooth surface (Alves et al., 2016).

5 Streptococcal adhesion and initial colonization

The salivary pellicle that forms on the tooth and mucosal surfaces constitutes the primary substrate for streptococcal colonization *via* specialized adhesins, which can bind to albumin, proline-rich proteins, glycoproteins, mucins, and sialic acid (Sia) (Abranches et al., 2018). Other structures that oral streptococci are able to adhere to include glucan, collagen, plasminogen, laminin, and fibrinogen (Nobbs et al., 2009). Streptococcal adhesion and colonization has been reviewed in detail by Nobbs et al. (Nobbs et al., 2009) and will be briefly discussed here.

Anchoring of streptococcal cell surface proteins typically occurs *via* their Leu-Pro-x-Thr-Gly (LPxTG) motif and is facilitated by sortases that catalyze the attachment of the proteins to the cell wall (Okahashi et al., 2022). The cell-wall anchored antigens I/II (AgI/II) – also named P1, SpaB, AgB, or Pac – belong to a family of adhesins that is present in most oral streptococci, and recognizes multiple host

proteins thereby facilitating sucrose-independent biofilm formation, platelet aggregation, invasion of tissues, and interaction with the host immune system (Koga et al., 1990; Brady et al., 2010; Abranches et al., 2018). AgI/II proteins have been found to bind to fibronectin, salivary glycoproteins and proline-rich proteins, collagen, laminin, fibrinogen, platelets and $\alpha_5\beta_1$ integrin on epithelial and endothelial cells (Nobbs et al., 2009). *S. gordonii* AgI/II proteins SpaA and SpaB have also been shown to facilitate interaction with oral *Actinomyces* species (Jenkinson et al., 1993) and *P. gingivalis*, enabling invasion of dentinal tubules by the periodontopathogen (Love et al., 1997), contributing to the bacterium's role in the development of periodontal disease (Lamont et al., 1994). Also, in fungal-bacterial communication AgI/II proteins play a pivotal role; specifically, this includes the interaction between *S. gordonii* SspB and the *C. albicans* hyphal cell wall protein Als3, which is relevant to biofilm formation (Silverman et al., 2010). Furthermore, AgI/II from *S. mutans* was shown to be important for the incorporation of *C. albicans* into a dual-species *S. mutans*-*C. albicans* biofilm and also required for increased acid production. Notably, this interaction is independent of the known streptococcal Als1 and Als3 receptors of *C. albicans* (Yang et al., 2018).

A group of streptococcal serine-rich repeat (Srr) glycoproteins can bind to sialoglycans present on salivary mucin MG2/MUC7, platelet glycoproteins (Takamatsu et al., 2005; Bensing et al., 2016) and polymorphonuclear neutrophils (PMNs) (Ruhl et al., 2000), and induce maturation and activation of DCs (Ko et al., 2017). Among these Srr glycoproteins are Gsp and Hsa of *S. gordonii* (Takahashi et al., 2002; Urano-Tashiro et al., 2016), the major fimbrial subunit Fap1 of *S. parasanguinis* (Wu et al., 2007) and *S. oralis* (Singh et al., 2017), SrpA, SrpB and SrpC of *S. salivarius* (Couvigny et al., 2017) and SrpA of *Streptococcus cristatus* (Handley et al., 2005) and *S. sanguinis* (Plummer et al., 2005; Deng et al., 2014). The interaction of these Sia-binding proteins with platelets may contribute to the pathogenesis of IE and potentially renders oral streptococci more virulent (Deng et al., 2014; Bensing et al., 2016).

S. gordonii additionally expresses short fibrils constituted by the CshA polypeptide on its cell surface (McNab et al., 1996). CshA as well as CshA-like fibrils present on the cell surface of other MGS such as *S. oralis* and *S. sanguinis* bind to other bacteria as well as salivary proteins (Fachon-Kalweit et al., 1985; Handley et al., 1987; Weerkamp et al., 1987; Ray et al., 1999) and immobilized fibronectin (McNab et al., 1996), thereby contributing to the establishment of the bacteria in the multispecies biofilms and colonization of various sites within the host. Other structures that oral streptococci are able to adhere to include glucan, collagen, plasminogen, laminin, and fibrinogen (Nobbs et al., 2009).

6 Streptococcal cell wall-associated virulence factors

6.1 AgI/II adhesin protein family

AgI/II adhesins are widely distributed among oral streptococci and constitute an important factor in the bacteria's pathogenicity and ability to colonize oral sites (Jenkinson and Demuth, 1997) (see

5.). The AgI/II proteins consist of several structural regions, with the intertwined A- and P-regions presenting the globular, less conserved V-domain on the cell surface for ligand interaction (Manzer et al., 2020). *Viridans* streptococci reportedly induce the expression of proinflammatory cytokines IL-8 and IL-6 in endothelial and IL-8 in epithelial cells; in the case of *S. mutans* OMZ175, this is facilitated through the binding of AgI/II (as well as rhamnose-glucose polysaccharide (RGP) – see 7.3.) to glycoproteins present at the host cell surface through lectin-type interactions (Vernier et al., 1996). IL-8 stimulation occurs through binding of AgI/II to $\alpha_5\beta_1$ integrin and subsequent activation of MAPK signaling (Al-Okla et al., 1999). In primary human coronary artery endothelial cells, cellular binding of AgI/II was furthermore shown to stimulate the expression of the adhesion molecules E-selectin, ICAM-1 and VCAM-1 and thereby stimulate trans-endothelial migration of neutrophils and contribute to the exacerbation of inflammatory responses to the bacterial burden (Vernier-Georgenthum et al., 1998). Also, binding of AgI/II to monocytes occurs *via* a lectin-type interaction with Sia and fucose residues exposed on host cell surface-glycoproteins and results in an increased production of the proinflammatory cytokines TNF- α , IL-1 β and IL-6 (Soell et al., 1994; Chatenay-Rivauday et al., 1998, 2000). Induction of pro-inflammatory cytokines in synovial cells suggests that AgI/II might even play a role in rheumatic disease, its initiation and perpetuation (Gourieux et al., 2001). Stimulation of TNF- α in THP-1 cells by the extended V-region of AgI/II was observed not only for *S. mutans* strains, but also for *S. gordonii* and the SAG members *S. anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*, highlighting the universal role the AgI/II protein family plays in streptococcal adhesion and virulence (Chatenay-Rivauday et al., 2000).

6.2 Cnm cell surface glycoprotein

Another factor contributing to *S. mutans*' success not only within but also outside its ecological niche is the cell surface glycoprotein Cnm which exhibits collagen- and laminin-binding capability. Cnm is present in 10-20% of all isolated strains of *S. mutans* (Nakano et al., 2010) and was most extensively studied in the *S. mutans* strain OMZ175. Cnm was found to be vital for the invasion of human coronary artery endothelial cells (HCAEC) and virulence in a *Galleria mellonella* infection model (Abranches et al., 2011; Aviles-Reyes et al., 2014). In the oral cavity, Cnm promotes *S. mutans*' invasion of oral keratinocytes and fibroblasts and enhances binding of the bacterium to collagenated surfaces, as well as dentin and root tissues contributing to its cariogenicity (Miller et al., 2015). Furthermore, Cnm was found to influence bacterial cell permeability and therefore might play a role in the susceptibility to antimicrobial agents (Naka et al., 2022).

Together with AgI/II, Cnm plays a crucial role in the aggravation of non-alcoholic steatohepatitis (NASH) (Naka et al., 2014, 2016, 2018); it is directly involved in and a potential risk factor for hemorrhagic stroke (Nakano et al., 2011) and IE (Nomura et al., 2013) and therefore can be considered as an indispensable virulence factor in the onset and progression of systemic diseases such as IE

elicited by Cnm-positive *S. mutans* strains. Cnm is most frequently found in strains with serotype *f* (see 7.3.), such as *S. mutans* OMZ 175, which in contrast to serotype *c* strains, is not most common in dental plaque, but has been specifically implicated in the pathogenesis of systemic disease (Abranches et al., 2011).

6.3 Rhamnose-glucose polysaccharide

S. mutans decorates its cell surface with a rhamnose-glucose polysaccharide (RGP), a major cell wall antigen whose composition determines the strain serotype (*c*, *e*, *f*, and *k*) and which has distinct functions in cell division and morphology (Rijn and Bleiweis, 1973; Nakano and Ooshima, 2009; De et al., 2017). Also, in colonization of tooth surfaces - as well as heart muscle and kidney tissues - serotype *f* RGP plays a role as a putative adhesin (Stinson et al., 1980; Engels-Deutsch et al., 2003). The RGP's contribution to adhesion was also demonstrated for THP-1, dental pulp and periodontal ligament cells, which upregulated the production of IL-6 and IL-8 in response to bacterial challenge dependent on the presence of RGP as well as AgI/II on the cell surface (Engels-Deutsch et al., 2003). RGP binds to human monocytes in a CD14-dependent manner and induces the release of TNF- α and other pro-inflammatory cytokines (Benabdelmoumene et al., 1991; Soell et al., 1995) as well as the up-regulation of RfC γ (Benabdelmoumene et al., 1991). RGP derived from *S. mutans* OMZ175 binds epithelial as well as endothelial cells in a dose-dependent manner and stimulates the release of IL-8 and IL-6 (Vernier et al., 1996). In rat model studies, RGP was found to render *S. mutans* more virulent in the induction of IE (Nagata et al., 2006) and stimulate nitric oxide synthase activity linking it to the genesis of septic shock induced by Gram-positive bacteria (Martin et al., 1997). Furthermore, the hydrophilic nature of RGP might play a role in the resistance of *S. mutans* to phagocytosis by PMNs and thereby contribute to the bacteria's defiance of immune response mechanisms and survival within the host (Tsuda et al., 2000).

6.4 Lipoteichoic acid

In Gram-positive bacteria, teichoic acids - wall teichoic acids (WTA) anchored to the cell wall peptidoglycan and lipoteichoic acids (LTA) anchored to membrane glycolipids - constitute a major part of the cell envelope and play vital roles in bacterial physiology, surface attachment, as well as interspecies and host interactions (Silhavy et al., 2010). Depending on the chemical structure, LTAs can be classified into five types (I-V) (Percy and Gründling, 2014). Type I, present e.g., in *S. mutans* and *S. gordonii*, is comprised of repeating polyglycerolphosphate units coupled with D-alanine and glucose (Lima et al., 2019); type II LTA as present in *S. oralis*, is composed of polyribitolphosphate repeating units (Hong et al., 2014a).

In the context of cariogenesis, LTA plays a vital role in conferring adhesive properties to bacterial cells and hydration of the cariogenic plaque in concert with streptococcal derived glucan (Rølla et al., 2009). When provided with high amounts of sucrose, *S. mutans* upregulates not only its glucan production, but also produces higher amounts of LTA (Rølla et al., 2009). *S. mutans* LTA

furthermore induces apoptosis in pulpal cells from deciduous teeth indicating its involvement in the development to pulpitis (Wang et al., 2001), which has been reviewed elsewhere (Hahn and Liewehr, 2007b). In monocytic, dental pulp and periodontal ligament cells, *S. mutans* LTA is a less potent inducer of proinflammatory cytokines than RGP and AgI/II (Engels-Deutsch et al., 2003). In a murine macrophage cell line, LTA from both *S. mutans* and *S. sanguinis* induced the production of TNF- α and release of nitric oxide (NO) potentially contributing to septic shock elicited by these bacteria in immunocompromised patients (English et al., 1996; Hong et al., 2014a).

When analyzing *S. mutans* LTA-binding proteins in saliva of caries-free and caries-active subjects, Hong and coworkers found differences in protein profiles dependent on the health status, with histone H4, neutrophil defensin-1 and profilin-1 being associated with health, and cystatins and lysozyme, among others, predominantly present in saliva from caries patients (Hong et al., 2014b). In the case *S. sanguinis*, LTA was shown to antagonize recognition of lipopolysaccharide (LPS) on gingival fibroblasts in a CD14-dependent manner, thereby potentially dampening the cells' immune response to Gram-negative periodontal pathogens and contributing to commensalism (Sugawara et al., 1999). LTA in contrast to LPS also stimulates expression of hepatocyte growth factor/scatter factor in gingival epithelial cells (Sugiyama et al., 1996). When stimulated with an LTA-deficient strain of *S. gordonii*, human dendritic cells reacted with a stronger immune response, i.e., increased phagocytic activity and production of proinflammatory markers and T-cell activation, than those treated with the corresponding parent wild-type strain, indicating an immune evasive role of LTA (Kim et al., 2023). In this context it is interesting to note, that *S. gordonii* cell wall lipoproteins, but not LTA have been shown to stimulate IL-8 production in periodontal ligament cells in a TLR2-dependent fashion (Kim et al., 2017; Park et al., 2020) and, in the case of lipoprotein PpiA, to suppress phagocytosis by macrophages (Cho et al., 2013).

6.5 Glycosyltransferases

Colonization of the oral cavity by oral streptococci depends on the production of extracellular glucans that to a large part make up the ECM of streptococcal biofilms (Nobbs et al., 2015; Bowen et al., 2018). *S. mutans* produces several dietary sucrose-hydrolyzing enzymes producing fructose and glucose, which are the building blocks of α -1,2- and β -1,6-linked glucans formed by the subsequent action of secreted (GtfD) and cell-wall associated (GtfB, GtfC) glucosyltransferases (Gtfs) (Nobbs et al., 2015; Bowen et al., 2018). In cariogenic biofilms, these sugars contribute to the acidification of the biofilm microenvironment and the shift to a dysbiotic microbiota, since these are catabolized along fermentative pathways leading to acid production (Bowen et al., 2018; Lamont et al., 2018). The secretion and action of Gtfs is not a specific trait of *S. mutans*, in which these enzymes have been most extensively studied; many oral streptococci employ Gtfs for colonization, adhesion, cohesion, and interbacterial interactions (Nobbs et al., 2009; Abranches et al., 2018). GtfB, GtfC and GtfD adhere to the salivary pellicle on the tooth surface as well as to other

microorganisms including bacteria and *Candida albicans*, essentially converting them to glucan producers contributing to the build-up of EPS and biofilm formation (Falsetta et al., 2014; Bowen, 2016). Furthermore, glucan binding proteins (Gbps) expressed by MS are prerequisites for successful biofilm formation, facilitating binding to dextrans and accumulation of MS in the biofilms (Nobbs et al., 2009). Streptococcal Gtfs can be regarded as immunogenic; a humoral immune response with anti-Gtf-specific immunoglobulin G (IgG) in serum or IgA in saliva naturally occurs in human populations (Chia et al., 1997). A Gtf-inhibitory factor (GIF) was found as an innate defense factor present in human saliva, specifically binding to the glucan binding domain of Gtfs and inhibiting Gtf function (Jespersgaard et al., 2002). Gtfc and Gtfd influence T-cell proliferation and modulate the immune response by monocytes, with a higher response elicited by Gtfd than Gtfc (Chia et al., 2001). *S. mutans* Gtfs furthermore robustly induce the production of IL-6 by T-cells *in vitro* as well as *in vivo* in an experimental rat model of endocarditis – pinpointing their contribution to disease development outside the oral cavity, since IL-6 levels were found to be elevated in patients with IE (Chia et al., 2001). In the same experimental model, it was also shown that *S. mutans* Gtfs induce the production of IL-6 in endothelial cells in infected heart valves, specifically during the acute stage of infection (Shun et al., 2005). In *S. gordonii*, a Gtf contributes to the bacterium's capability to cause IE, being a prerequisite for the adhesion to endothelial as well as epithelial cells *in vitro* (Vacca-Smith et al., 1994).

6.6 Nucleases

In the resolution of bacterial infection, neutrophils play a pivotal role, clearing and killing bacterial invaders through phagocytosis, granule release, oxidative burst, and neutrophil extracellular trap (NET) formation – the release of chromatin fibers carrying antimicrobial peptides (AMPs) ready for bacterial killing and prevention of bacterial spreading (Scott and Krauss, 2012; Chapple et al., 2023). In *S. sanguinis*, a streptococcal wall-anchored nuclease (SWAN) confers resistance to NET killing by digesting released NET DNA (Morita et al., 2014). Another *S. mutans* nuclease - DeoC - enables the bacteria to escape NETs and facilitates biofilm dispersal (Liu et al., 2017). Lacking the LPxTG sorting motif for cell wall anchoring, DeoC most likely acts during late stages of biofilm growth when cell autolysis and dispersal occur and aids in bacterial escape of entrapment in NETs by chromatin degradation (Liu et al., 2017).

7 Streptococcal small molecules at the host immune interface

7.1 Hydrogen peroxide

One characteristic trait of oral streptococci that has been getting attention for its relevance in the regulation of immune responses is the production of hydrogen peroxide as a by-product of aerobic

metabolism (Zhu and Kreth, 2012). Through the production of H₂O₂, oral streptococci like MGS inhibit other potentially pathogenic species, among them *S. mutans*, and thereby gain a competitive advantage over these species (Kreth et al., 2008). By triggering the release of eDNA, H₂O₂ production additionally facilitates the exchange of genetic material between the bacteria (Kreth et al., 2009). In the interaction with the host, H₂O₂ production shows the potential to be a vital contributor to disease pathogenesis. Bacterial species such as *S. sanguinis* and *S. oralis* induce the formation of foam cells, contributing to atherosclerosis, and cause lysosome dysfunction and cell death in macrophages as well as in epithelial cells through the action of ROS, *i.e.*, the release of H₂O₂ (Okahashi et al., 2011, 2013, 2014, 2016). Microarray studies of macrophages infected with *S. oralis* wild-type and a corresponding streptococcal pyruvate oxidase (*spx*)-deletion mutant deficient in H₂O₂ production showed that H₂O₂ suppresses the expression of proinflammatory mediators, especially NF-κB signaling, and cellular stress responses (Matsushima et al., 2017). Pyruvate oxidase SpxB catalyzes the conversion of inorganic phosphate and pyruvate to acetyl phosphate, carbon dioxide and H₂O₂ (Chen et al., 2011). Notably, SpxB is distinct from the *S. mutans* transcriptional regulator Spx, encoding two homologues, SpxA1 and SpxA2, involved in oxidative stress response and regulation of genes involved in cell division and cell envelope biosynthesis, respectively (Baker et al., 2020; Ganguly et al., 2020). *S. oralis* was furthermore found to inhibit the activation of inflammasomes through the release of H₂O₂ corroborating its contribution to the establishment and persistence of the oral commensal within the oral cavity and even in bloodstream infections (Erttmann and Gekara, 2019). In the context of periodontal disease, SpxB of *S. oralis* and *S. mitis* plays a vital role in enabling bacterial colonization and host homeostasis by inhibiting NF-κB signaling through the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) (Tang et al., 2022). Also, through the induction of cell death in periodontal ligament cells (PDLs) by H₂O₂ production, *S. gordonii*, *S. mitis*, *S. sanguinis* and *S. sobrinus* play their part in the development of apical periodontitis (Park et al., 2021). In *S. sanguinis*, Spx was a prerequisite for bacterial survival in blood and an *spx*-deletion mutant failed to induce cell death and NET formation in neutrophils (Sumioka et al., 2017). Through the release of H₂O₂, oral streptococci can additionally dampen the proinflammatory immune response to LPS and *F. nucleatum* thereby influencing overall plaque development (Tang et al., 2022).

7.2 Secondary metabolites

Genome mining studies have revealed an abundance of bacterial biosynthetic gene clusters (BGCs) in the oral microbiome producing small molecules and secondary metabolites that can function as signaling molecules and serve as language of interbacterial, interspecies and interkingdom communication (Donia and Fischbach, 2015; Liu et al., 2016; Aleti et al., 2019). Among these secondary metabolites are mutanobactins, mutanamide and mutanofactins - lipopeptides produced by *S. mutans* along a non-ribosomal peptide synthetase–polyketide synthase (NRPS–PKS) assembly line (Wu et al., 2010; Zvanich et al., 2015; Li et al., 2021).

Mutanobactins act as interkingdom signaling molecules by blunting hyphae formation and inhibiting biofilm formation by the opportunistic pathogen *C. albicans* and as interspecies communicator by inhibiting planktonic growth of other oral bacteria (Joyner et al., 2010; Wu et al., 2010; Wang et al., 2012; Pultar et al., 2021). Given that, co-infection with *S. mutans* and *C. albicans* not only resulted in a higher bacterial-fungal burden, but also increased biofilm virulence and led to more severe carious lesion in a rat model (Falsetta et al., 2014), hyphae blunting by mutanobactin represents only a small facet of this highly complex interkingdom interaction and the implications of this process *in vivo* have yet to be determined. Interestingly, Zvanich et al. attested to the mutanobactins also immunomodulatory properties, since in a murine macrophage cell line pre-stimulated with LPS, mutanobactin B upregulated IL-6 and IL-12 and downregulated MCP-1, G-CSF and TNF- α production (Zvanich et al., 2015). Another small molecule produced by *S. mutans* with the potential to inhibit competing oral bacteria, is the tetramic acid mutanocyclin (Tang et al., 2020). In a Matrigel plug assay, mutanocyclin was found to inhibit CD45⁺ leukocyte infiltration thereby exerting an anti-inflammatory role (Hao et al., 2019).

7.3 Competence stimulating peptide CSP-1

For the development of microbial communities, quorum sensing (QS) is an indispensable mechanism of bacteria to regulate inter- and intra-species interactions. *S. mutans* utilizes multiple QS systems to regulate biofilm formation, transfer of genetic material and stress tolerance responses; one of these systems relies on the competence stimulating peptide (CSP) encoded by the *comCDE* gene locus (Bernabè et al., 2022). Medapati and coworkers recently explored the possibility that *S. mutans* CSPs might be recognized by bitter taste receptors (T2Rs) - G-protein coupled receptors (GPCRs) involved in taste chemosensation and recognition of bacterial QS molecules – thereby participating in innate immune responses to bacterial colonization (Medapati et al., 2021). The researchers demonstrated binding of CSP-1 to T2R14 expressed in gingival epithelial cells (GECs) and mediating activation of IL-6, IL-8 and TNF- α production, thus, identifying a novel mechanism of host-QS interaction and a potential target for therapeutic intervention (Medapati et al., 2021).

8 Effect of oral streptococci on the host immune response to other oral bacteria

In multispecies communities, interactions between species – through synergistic or antagonistic effects - can be a decisive factor when it comes to survival and persistence within the host. In the context of periodontal disease, for instance, *P. gingivalis* can subvert the host immune responses through numerous mechanisms, enabling other members of the biofilm community to escape immune surveillance and increase in cell numbers (Hajishengallis and Lamont, 2014). *P. gingivalis* and other late biofilm colonizers require the presence of streptococci and *F. nucleatum* in order to

establish themselves within the biofilm community profiting from reduced oxygen tension and the provision of metabolites and nutrients by the antecedent colonizers (Kuboniwa and Lamont, 2010).

8.1 MGS and their interaction partners at the immune interface

Due to their co-adhesion with *P. gingivalis*, MGS can be classified as accessory pathogens and contribute to the formation of pathogenic oral communities (Whitmore and Lamont, 2011). The formation of heterotypic communities between the different species has been extensively studied for *S. gordonii* and *S. oralis* with *P. gingivalis*. Cohesion occurs through the binding between *P. gingivalis* fimbriae Mfa1 and FimA to the streptococcal surface antigens SspA/B and surface-expressed glyceraldehyde-3-phosphate dehydrogenase (GAPDH), respectively (Bergmann et al., 2004; Kuboniwa and Lamont, 2010). Upon binding, a signaling cascade is triggered in *P. gingivalis*, leading to the suppression of Mfa1 production and the expression of a protein tyrosine phosphatase Ltp1 which regulates protease activity and thereby influences the bacterium's pathogenic potential (Maeda et al., 2008; Kuboniwa and Lamont, 2010; Hajishengallis and Lamont, 2014).

Another species that *S. gordonii* is frequently associated with is *F. nucleatum* (Mutha et al., 2018). Co-aggregation not only results in transcriptional changes within both bacteria, but also affects their survival within macrophages and decreases the expression of pro-inflammatory cytokines and thereby influences bacterial virulence and host persistence (Liu et al., 2021). Also the commensal *S. cristatus* dampens the response to *F. nucleatum* infection by inhibiting NF- κ B and IL-8 production in oral epithelial cells (Zhang et al., 2008; Zhang et al., 2011).

Co-infection studies with *S. oralis* and *C. albicans* demonstrated that in an oral thrush mouse model, *C. albicans* augments streptococcal colonization and that, in turn, *S. oralis* contributes to the exacerbation of the immune response through TLR2 signaling and neutrophil recruitment causing more severe lesions than the opportunistic fungal pathogen alone (Xu et al., 2014). In epithelial tissues, the synergy between the two bacteria caused upregulation of pro-inflammatory markers (Martorano-Fernandes et al., 2023) and the disruption of epithelial barrier integrity through activation of calpain 1, a calcium ion-dependent cysteine protease specifically cleaving E-cadherin (Xu et al., 2016). Interaction with the allegedly harmless commensal *S. oralis* therefore seems to be a key contributor to *C. albicans* virulence and tissue invasion.

When oral keratinocytes were precultured with *S. cristatus*, *S. salivarius*, *S. mitis* or *S. sanguinis*, the presence of the oral streptococci inhibited keratinocyte colonization by *A. actinomycetemcomitans*, with *S. sanguinis* exerting the strongest inhibitory effect (Teughels et al., 2007; Sliepen et al., 2009b). In a similar experiment, adhesion of periodontal pathogens, including *P. gingivalis*, *Prevotella intermedia* and *A. actinomycetemcomitans*, to the surface of a parallel plate flow chamber was found to be reduced in the presence of a similar set of commensal streptococci, identifying antagonistic functions that could

render these bacteria suitable candidates as probiotics in the prevention of periodontal disease recurrence (Van Hoogmoed et al., 2008). Different strains of *S. salivarius* alone reduced the secretion of IL-6 and IL-8 by gingival fibroblasts, which is usually induced by *P. gingivalis*, *A. actinomycetemcomitans* and *F. nucleatum*, both in co-infection studies and when fibroblasts were pre-treated with the commensal before pathogen stimulation (MacDonald et al., 2021). Notably, the tested *S. salivarius* strains did not elicit enhanced pro-inflammatory cytokine secretion or microbiome alterations in healthy volunteers when administered in the form of a chewing gum and therefore might be interesting candidates for a probiotic therapy of periodontal disease (MacDonald et al., 2021).

The capacity of oral streptococci to modulate the tissue response to oral pathogens has also been discussed in the context of probiotic treatment of oral biofilm disease. Detected solely in samples from caries- and periodontitis-free patients, the rather recently discovered *Streptococcus dentisani* might be a potential candidate probiotic agent (Esteban-Fernández et al., 2019; Ferrer et al., 2020). *In vitro* studies showed that *S. dentisani* induced secretion of anti-inflammatory cytokine IL-10 in gingival fibroblasts, reduced the pro-inflammatory response to *P. gingivalis* and *F. nucleatum*, and inhibited growth as well as colonization of fibroblasts by these Gram-negative bacteria (Esteban-Fernández et al., 2019). This highlights the role of oral streptococci in maintaining oral health through their interaction with the host immune system and exertion of antagonistic effects towards pathogenic species.

9 Conclusions and future perspectives

Streptococci have a profound and life-long presence in humans, being the first colonizers in the oral cavity after birth and continuing to shape the intricate microbiota within our mouth throughout our life. *Streptococcus* species are commensal inhabitants, influencing the development of a properly functioning immune system and acting as barriers against the colonization of harmful bacteria – functions that are crucial for maintaining oral health and preventing disease. On the other hand, when things go awry, streptococci can become detrimental, potentially leading to serious infections and health complications, including infective endocarditis, purulent infections, brain hemorrhage, intestinal inflammation, autoimmune diseases, and bacteremia (Yumoto et al., 2019). A key characteristic in these processes is the ability of these species to adhere to numerous substrates present on host cell surfaces and within the dental pellicle and to form biofilms (Figure 1). This is facilitated through specialized surface proteins such as AgI/II, Srr proteins, Cnm and RGP formation through the action of Gtfs (Nobbs et al., 2009; Nakano et al., 2011) (Figure 2). Also, in the interaction with the host immune system these factors play a vital role by modulating the induction of proinflammatory immune responses, bacterial cell invasion and adhesion. In the context of therapeutic approaches to dental caries, the most researched virulence antigens of *S. mutans* are AgI/II, Gtfs and Gbps (Patel, 2020). RGP and LTA as constituents of the cell wall act as potent inducers of pro-inflammatory cytokine production and confer resistance to phagocytosis (Tsuda et al., 2000; Engels-

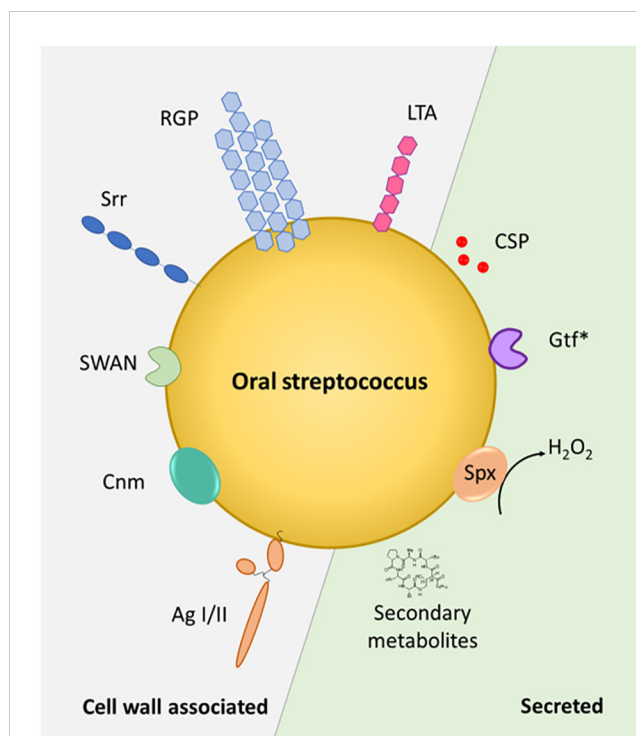


FIGURE 2
Streptococcal factors at the host interface. Cell wall-associated and secreted factors are depicted in the schematic representation of an oral *Streptococcus* sp. Gtf*, glycosyltransferases - GtfB and GtfC are cell wall associated, GtfD is secreted – Spx – streptococcal pyruvate oxidase. AgI/II – antigen I/II, Srr – serine-rich repeat protein, CSP – competence stimulating peptide, SWAN – cell-wall associated nuclease, RGP – rhamnose-glucose polymer, LTA – lipoteichoic acid, Cnm – surface glycoprotein Cnm with collagen- and laminin-binding capability.

Deutsch et al., 2003). In *S. sanguis* and *S. mutans*, SWAN confers resistance to NET killing and therefore enables these bacteria to evade immune defense mechanisms (Liu et al., 2017; Kim et al., 2023). Through the production of H₂O₂ commensal oral streptococci antagonize pathogens such as *S. mutans* or *A. actinomycetemcomitans* (Baty et al., 2022). While commensal streptococci such as *S. mitis* or *S. salivarius* can downregulate cytokine production in response to challenge with periodontal pathogens and thereby counteract gingival inflammation, others such as *S. gordonii* can be regarded as accessory pathogens and support colonization by periodontal pathogens.

For vaccine development and caries treatment, the identification of novel streptococcal virulence factors is a central prerequisite. Understanding virulence mechanisms and interactions within the microbial networks in oral biofilms will help to develop targeted therapeutic or preventative measures to decrease the burden of oral diseases. Promising results achieved with the use of health-associated streptococci as probiotics such as *S. salivarius* or *S. dentisani* highlight the importance of oral streptococci in oral microbial interaction networks (Ferrer et al., 2020; MacDonald et al., 2021). Streptococci are essential in the maintenance of homeostasis and controlling the composition of the oral microbiota, but their role in regulating host-microbiome interaction is still to be unraveled. The host response regulation

exerted by these bacterial species could be a key factor and future studies on this topic will allow a better understanding of oral streptococci and their roles in oral health and disease.

Author contributions

SB: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. FH-M: Formal Analysis, Writing – original draft, Writing – review & editing, Funding acquisition. OA: Writing – original draft, Writing – review & editing, Funding acquisition. CS: Writing – original draft, Writing – review & editing, Funding acquisition, Conceptualization, Formal Analysis, Project administration, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

A. <i>actinomycetemcomitans</i>	<i>Aggregatibacter actinomycetemcomitans</i>
Agl/II	antigen I/II
BGC	biosynthetic gene cluster
<i>C. albicans</i>	<i>Candida albicans</i>
CSP	competence stimulating peptide
DC	dendritic cell
ECM	extracellular matrix
eDNA	extracellular desoxyribonucleic acid
EPS	extracellular polymeric substance
<i>F. nucleatum</i>	<i>Fusobacterium nucleatum</i>
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GAS	Group A <i>Streptococcus</i>
Gbp	glucan binding protein
GBS	group B <i>Streptococcus</i>
G-CSF	granulocyte-colony stimulating factor
GEC	gingival epithelial cell
GPCR	G-protein coupled receptor
Gtf	glucosyltransferase
hBD-2	human β -defensin 2
ICAM-1	intercellular adhesion molecule 1
IE	infective endocarditis
IL	interleukin
LPS	lipopolysaccharide
LTA	lipoteichoic acid
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein 1
MGS	<i>mitis</i> group streptococci
MS	<i>mutans</i> streptococci
NASH	non-alcoholic steatohepatitis
NET	neutrophil extracellular trap
NO	nitric oxide
Nrf2	nuclear factor erythroid 2-related factor 2
NRPS-PKS	non-ribosomal peptide synthetase–polyketide synthase
<i>P. gingivalis</i>	<i>Porphyromonas gingivalis</i>
PAMPs	pathogen associated molecular patterns
PDL	periodontal ligament cell
PD-L1	programmed cell death protein ligand 1

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PGE2	prostaglandin E2
PMN	polymorphonuclear neutrophil
QS	quorum sensing
RGP	rhamnose-glucose polymer
ROS	reactive oxygen species
<i>S. anginosus</i>	<i>Streptococcus anginosus</i>
<i>S. cristatus</i>	<i>Streptococcus cristatus</i>
<i>S. dentisani</i>	<i>Streptococcus dentisani</i>
<i>S. gordonii</i>	<i>Streptococcus gordonii</i>
<i>S. mitis</i>	<i>Streptococcus mitis</i>
<i>S. mutans</i>	<i>Streptococcus mutans</i>
<i>S. oralis</i>	<i>Streptococcus oralis</i>
Srr	serine-rich repeat
Spx	streptococcal pyruvate oxidase
<i>S. salivarius</i>	<i>Streptococcus salivarius</i>
<i>S. sanguinis</i>	<i>Streptococcus sanguinis</i>
<i>S. sobrinus</i>	<i>Streptococcus sobrinus</i>
SAG	<i>Streptococcus anginosus</i> Group
Sia	sialic acid
SWAN	surface-associated nuclease
TLR	Toll-like receptor
TNF	tumor necrosis factor
VCAM-1	vascular adhesion molecule.