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Implications of salivary protein binding to commensal and pathogenic bacteria

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Abstract

An important function of salivary proteins is to interact with microorganisms that enter the oral cavity. For some microbes, these interactions promote microbial colonization. For others, these interactions are deleterious and result in the elimination of the microbe from the mouth. This paper reviews recent studies of the interaction of salivary proteins with two model bacteria; the commensal species *Streptococcus gordonii*, and the facultative pathogen *Staphylococcus aureus*. These organisms selectively interact with a variety of salivary proteins to influence important functions such as bacterial adhesion to surfaces, evasion of host defense, bacterial nutrition and metabolism and gene expression.

Keywords

Saliva; microbial adhesion; biofilm; oral diseases

Dental plaque, a complex and dynamic microbial biofilm, forms on subgingival and supragingival tooth surfaces, the surfaces of restorations, as well as on soft tissue surfaces such as the tongue, oral mucosa, and periodontium [1, 2]. This habitat is extraordinarily diverse, with over 1000 microbial species described in the oral cavity [3-5]. In normal healthy humans, the oral microflora is dominated by commensal bacteria such as streptococci, actinomyces and Veillonella species[1].

On the other hand, under some circumstances, pathogenic bacteria that are not normally part of the commensal microflora can colonize the oral cavity [6-8]. For example, *Helicobacter pylori*, which is known to cause stomach diseases such as gastritis and gastric adenocarcinoma, has been detected in dental plaque and saliva [9-11]. By utilizing 16S rDNA analysis, it has been shown that *Staphylococcus epidermidis*, *Haemophilus parainfluenzae*, *Micrococcus luteus* and other systemic bacteria colonize the subgingival plaque in periodontally healthy people [12]. Furthermore, respiratory pathogens including *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Staphylococcus*

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aureus have been found in supragingival plaque from both healthy subjects and more so in those at risk for lung infections [13-16]. It is not clear if colonization of the mouth by systemic pathogens is persistent or transient, but it has been proposed that the oral cavity may function as a reservoir for systemic pathogens [17-19]. That pathogens of the oral cavity are often closely associated with several systemic diseases including gastrointestinal, cardiovascular and respiratory diseases supports this notion [10, 19-21].

Saliva is ubiquitous in the oral cavity and serves a vital role in the innate immune defense system [22, 23]. In order to maintain the equilibrium within the oral microbial complexes in the mouth, saliva plays a key role as a defender against invading pathogens [24-26]. Various antimicrobial peptides in saliva can inhibit bacterial growth or directly kill microorganisms [27-30]. For example, lysozyme is a well-known antimicrobial enzyme that lyses bacteria by catalyzing the hydrolysis of cell wall polysaccharides [31]. Histatins are multifunctional peptides having fungicidal, bactericidal, and anti-inflammatory properties in addition to neutralization of noxious substances and inhibition of cytokine induction [25, 32, 33]. Similarly, lactoferrin has been shown to have fungicidal, bactericidal, anti-inflammatory, anti-biofilm and immunomodulatory activities [34, 35]

The purpose of this review is to provide a brief update regarding the potential role of salivary components in bacterial colonization of the oral cavity. For illustrative purposes, interactions of salivary components with two species are described: *Streptococcus gordonii*, an example of common oral commensal species, and *Staphylococcus aureus*, a pathogenic species which can colonize the mouth, especially in individuals at high risk for lung infections.

General aspects of the interaction of salivary proteins with bacteria

Many studies have demonstrated that bacteria can adhere to surface immobilized salivary proteins, and that, conversely, salivary components can bind to the bacterial surface to facilitate either bacterial colonization to oral surfaces or their clearance from the oral cavity [24, 36-43]. Based on these *in vitro* studies, it has been speculated that in healthy individuals, certain salivary components may be responsible for the agglutination of bacteria thereby preventing them from colonizing the oral cavity. Subsequently, these clumped bacteria may be cleared from the oral cavity by swallowing or expectoration. Thus, binding of salivary proteins to pathogens is thought to play an important role in preventing systemic infections. However, this function may be compromised in situations when salivary flow is impeded, such as in patients under medication or in hospitalized settings [44].

The interaction of salivary components with bacteria likely involves both specific and non-specific mechanisms. Generally, nonspecific interactions originate from physicochemical forces, and include Lifshitz-van der Waals, hydrogen bonding, ionic interactions, and hydrophobic interactions [45-48]. For example, salt bridges and/or electrostatic interactions occur between the positive charges of the ammonium groups and the negative charges of the acidic groups [45-47]. Hydrophobic interactions of non-polar amino acid side chains may contribute by stabilizing the tertiary structures in protein complexes [49-52]. In fact, it has been suggested that hydrophobic interactions may be the primary driving force for the adhesion of most pathogens [53]. It has also been suggested that hydrophobic interactions are the strongest of all long-range non-covalent interactions in biological systems [54].

In order to determine whether such nonspecific mechanisms are involved in salivary protein binding to bacteria, denaturing agents, including chaotropic agents (e.g. urea), or salts (e.g. NaCl), have been employed during saliva-bacteria binding assays. At high concentration (6 M), urea causes extensive unfolding of proteins or protein complex disassociation [49,

55-58]. Inhibition of the interaction between proteins and bacteria suggests a role for the secondary structure of proteins in binding. Sodium chloride can be used to study the role of electrostatic interactions that are strongly dependent on the ionic strength of the solution, though relatively weak at the physiological ionic strength (0.14 M NaCl) [59-61]. Thus, such nonspecific binding mechanisms have been suggested to guide the very early events of bacterial binding to salivary substrates. However, it is likely that nonspecific contributions are augmented by specific recognition [62]. Indeed, the two mechanisms appear to work together, since both interactions originate from the same, fundamental physico-chemical forces (Lifshitz-Van der Waals, electrostatic, and acid-base interaction)[62]. The summation of the relatively weak interactions between all atoms of an adherent bacterium and a substratum yields the final interaction force. Specific interactions, allowing for molecular recognition between ligand and receptor molecules, operate over spatially well-confined stereochemical regions, (up to several nanometers). Thus, both specific and nonspecific interactions likely act synergistically to maintain the three-dimensional integrity (secondary or tertiary) among or between salivary proteins and bacterial surface components [24, 63].

Specific mechanisms also help explain salivary component interactions with bacteria. Typically, specific interactions are mediated by proteins on the surfaces of bacteria that recognize the unique shapes of ligands presented by salivary components in much the same way as occurs between antibodies and antigens, or enzymes and their substrates [64]. Numerous microbial protein adhesins have been identified on the surfaces of oral bacteria [64]. A complete discussion of all oral microbial adhesins so far described is beyond the scope of this paper. However, a few descriptive examples are provided below.

Interaction of salivary components with *Streptococcus gordonii*

Streptococcus gordonii is a member species of the viridans group of streptococci that are numerous in the oral cavity and is used extensively as a model organism in studies of the interactions of salivary components and oral bacteria.

The adhesins Hsa [65, 66] or GspB [67] belong to the serine-rich repeat protein (SRRP) family that are found on the surface of *S. gordonii*. Serine-rich repeat proteins are exclusively in gram-positive bacteria, predominantly in oral streptococci, but also in other medically relevant streptococci such as the respiratory tract pathogen *Streptococcus pneumoniae* [68] and in the neonatal pathogen *Streptococcus agalactiae* [69]. These proteins are also found in *Staphylococcus aureus* [70], *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus hemolyticus*, *Lactococcus johnsonii*, and *Lactococcus reuteri* [71-73]. Serine-rich repeat proteins, although quite diverse in size and composition, generally consist of two serine-repeat regions, a short one and a longer one. The longer one forms a stalk-like structure that can protrude 600 nm or more from the bacterial surface and is decorated and stabilized by O-linked glycans [73]. Located between the long and the short serine-rich repeat domains are structurally highly diverse non-repeat domains that seem to be unique for each species and confer the adhesive properties to the molecule. The non-repeat domains of GspB, Hsa, and SrpA contain further subdomains that are each responsible for distinct adhesive properties [71]. The first subdomain shows structural similarity to the MSCRAMM family member Cna, found on staphylococci. The second subdomain resembles members of the sialic acid-binding immunoglobulin-like lectin (Siglec) family of proteins. Only GspB, but not Hsa and SrpA, contains a third, unique, subdomain of as yet unclear function. The genes for serine-rich proteins are arranged on genomic islands that contain also two or more glycosyltransferases, responsible for glycosylation of the serine-rich repeat domains, and a non-canonical Sec translocase (sec-Y2A2), responsible for export of the SRRPs to the bacterial surface [74].

Serine-rich repeat proteins are involved in adhesion to host surfaces and in intra- and inter-species adhesion. These proteins have also been associated with pathogenesis of oral infectious diseases, infective endocarditis, pneumonia, meningitis, and neonatal sepsis [71]. The non-repeat domains of GspB and Hsa bind preferentially to sialyl-T antigen [43, 65], although Hsa has less restricted binding specificity than GspB because it also binds to sialyllactosamine [43]. Streptococci carrying Hsa or GspB bind to sialic acid-containing glycoproteins on platelets, neutrophils, and also to salivary sialoglycoproteins such as MG2, salivary agglutinin, and secretory IgA that coat tooth surfaces [42, 43, 75]. Both GspB and SraP are also involved in biofilm formation [76] and it is assumed that recognition of glycoconjugates by serine rich repeat proteins may play a role in this process.

Another well-characterized bacterial protein adhesin commonly expressed on the surface of streptococci belongs to the antigen I/II (AgI/II) family of polypeptides [77]. The *Streptococcus mutans* AgI/II protein (also known as AgI/II, P1, SpaP, PAc, and AgB), is the prototype for this group of adhesins. AgI/II is produced by almost all oral streptococci, including *S. gordonii*, as well as by pathogenic streptococci. These adhesins interact with salivary components such as DMBT-1/glycoprotein-340 (formerly termed parotid or salivary agglutinin) [78] and this interaction may mediate bacterial agglutination and clearance from the oral cavity by swallowing. However, when the salivary protein is adsorbed to a host surface, it could mediate bacterial adhesion.

A third interesting example of a specific salivary-component bacterial interaction is that of salivary α -amylase binding to *S. gordonii* and a select group of other oral streptococcal species [79]. α -Amylase is an abundant enzyme produced primarily by serous cells of the parotid gland, but also by sublingual, submaxillary and minor glands. It catalyzes the hydrolysis of α -1,4-glucosidic bonds of starch, glycogen and other polysaccharides [80]. The enzyme not only binds to *S. gordonii*, but also to *Streptococcus mitis*, *Streptococcus cristatus*, *Streptococcus parasanguinis*, *Streptococcus salivarius*, and several other species [81-84], collectively referred to as the α -amylase-binding streptococci (ABS). To date, ABS have only been found to colonize animals that are able to secrete α -amylase in their saliva [85]. Thus, it is likely that the α -amylase-streptococcal interaction may have evolved with the host to play an important role in the ability of these bacteria to colonize the oral cavity.

ABS express several types of α -amylase binding proteins (APBs). Most strains produce multiple ABPs, typically a higher molecular weight form (> 60 kDa) and a lower molecular weight form (<30 kDa). There is considerable heterogeneity in the size of these components between species [86]. *S. gordonii* produces two ABPs; AbpA (20 kDa) and AbpB (82 kDa). AbpA is an extracellular cell wall associated surface protein that is maximally expressed during mid-log phase of bacterial growth [87]. AbpA appears to be essential for α -amylase binding to the bacterial surface since inactivation of AbpA entirely eliminates α -amylase binding to the bacterium [88]. While AbpB does not appear to be essential to amylase binding to the surface of *S. gordonii*, it does appear to possess proteolytic activity and shares sequence homology with a family of bacterial dipeptidases [89]. Interestingly, strains of *S. gordonii* defective in AbpB showed impaired colonization of teeth of starch-only-eating rats, but colonized rats if sucrose was added to the diet [90].

abpA-deficient mutants showed impaired ability to adhere to surface-adsorbed amylase as well as to form biofilm *in vitro* [88]. Mutation of *abpA* also impaired the ability of *S. gordonii* to grow with starch as the predominant carbon source [88]. These findings suggest that amylase binding could influence the ability of ABS to colonize the oral cavity. However, *abpA*-deficient mutants colonized teeth to a better extent than did the wild type strains in an experimental rat model [90]. These findings necessitated consideration of other functions for amylase binding. Indeed, microarray studies of gene expression of *S. gordonii*

following the binding of salivary α -amylase found a total of 33 genes differentially expressed following exposure to purified salivary α -amylase [91]. The greatest change in expression was observed for genes involved in fatty acid synthesis, which were also accompanied by changes in bacterial phenotype, including increased bacterial growth, increased resistance to low pH and increased resistance to the detergent triclosan. These findings suggest that α -amylase binding to AbpA initiates a signal resulting in differential gene expression. This may serve as an environmental sensing mechanism specific for the oral environment.

This is not the first example of saliva-induced differential gene expression in bacteria. In group A streptococci, several genes were found to be up-regulated in bacteria grown in saliva [92]. For example, *sptR* and *sptS* (*sptR_S*), which encode a two-component gene regulatory system, were upregulated by saliva. Furthermore, an isogenic nonpolar mutant strain (*sptR*) showed reduced persistence in saliva than the parental strain. It was also noted that these changes were accompanied by up-regulation of a variety of genes involved in carbohydrate metabolism and nutrient acquisition. These observations suggest that oral bacteria possess elaborate systems to recognize environmental cues in order to allow them to optimize their fitness.

***Staphylococcus aureus* in the oral cavity**

Staphylococcus aureus is a common cause of nosocomial and surgical infections [93, 94]. In humans, *S. aureus* can colonize multiple body sites either transiently or persistently, especially skin and mucosa [95]. In the hospital setting, *S. aureus* causes a number of systemic infections, which include endocarditis, septicemia, surgical wound infections and osteomyelitis [93, 94, 96-98]. This organism is also well known to demonstrate antibiotic resistance, with resistance to a variety of antibiotics increasing in prevalence [94].

S. aureus has been long known to colonize the oral cavity [99, 100] where it has been associated with oral diseases including periodontitis [101, 102], peri-implantitis [103, 104], refractory endodontic lesions [105], and osteomyelitis of the jaw [106]. Furthermore, *S. aureus* has also been frequently detected among the oral flora, and it may play an important role in both health and disease [107]. The prevalence of *S. aureus* in saliva or at the oral mucosa ranges from 4% [108] to 64% [109] in healthy populations to (41-68%) in the saliva of healthcare providers [110, 111]. In dental plaque of healthy adults, *S. aureus* was isolated with a frequency of 24 to 36% [112]. Also, some strains of methicillin-resistant *S. aureus* could be infrequently (<3% prevalence) detected in the dental plaque from healthy subjects [111, 113, 114].

Several studies have demonstrated frequent oral colonization of *S. aureus* in institutionalized individuals, including hospitalized and nursing home patients. Terpenning et al. isolated *S. aureus* in the saliva of 8 (16%) of 50 of study patients. It was notable that the presence of *S. aureus* significantly increased the risk for aspiration pneumonia, with an odds ratio of 8.3 [18]. *S. aureus* has also been detected in the supra-gingival plaque and oral mucosa of ~15% of patients in intensive care units [21], but rarely in the plaque of dental outpatients. Interestingly, in some patients undergoing antibiotic therapy, *S. aureus* was found to account for up to 100% of the cultivable aerobic flora [21].

The oral cavity may thus serve as an important reservoir of *S. aureus* infection. Molecular epidemiologic studies have shown that *S. aureus* recovered from the lungs of patients with ventilator-associated pneumonia were indistinguishable to those isolated from the oral cavity as demonstrated by pulse-field gel electrophoresis (PFGE) [19]. Also, the PFGE profiles from strains of the same species obtained from the same patient showed no differences in

band patterns over time. Collectively, these findings confirm that the oral cavity is a major portal for *S. aureus* in ventilated hospitalized patients.

The interactions of salivary proteins with *S. aureus*

Only a few studies have investigated the interactions of salivary proteins with *S. aureus* [115-117]. We have recently found that *S. aureus* rapidly and selectively binds a limited number of salivary proteins to its surface following exposure to saliva, many of which are associated with specific or innate immune defense [116] (Figure 1). By using fluorescently labeled saliva and proteomics techniques we demonstrated that *S. aureus* bound DMBT1^{gp-340}, mucin-7, secretory component, immunoglobulin A, immunoglobulin G, S100-A9 and lysozyme C. Biofilm-grown *S. aureus* bound fewer salivary components, particularly immunoglobulins. Staphylococcal protein A (SpA) was found responsible for mediating the binding of immunoglobulins, but not of non-immunoglobulin components, including mucin-7, indicating the presence of additional bacterial surface adhesive components. Interestingly, a recent study found that SpA, *Staphylococcus* SasA (SraP) binds to salivary agglutinin gp340 through recognition of *N*-acetylneuraminic acid [117].

It is not surprising that SpA binds salivary immunoglobulins to the staphylococcal surface, because it has been shown to bind the Fc fragment of IgG. SpA belongs to the MSCRAMM family of bacterial proteins [118], and was the first identified as a protein on the surface of *S. aureus* [119, 120]. SpA is produced by over 90% of *S. aureus* strains [121, 122] and accounts for ~ 7% of the *S. aureus* cell wall [123]. Among *S. aureus* strains, the molecular mass of SpA varies from 45 kDa to 57 kDa [124], and it has been well established that each domain can bind the Fc portion of IgG of mammals [125]. Furthermore, SpA can also bind to the Fab portion of immunoglobulins and it has been found that SpA specifically binds to the V region of the immunoglobulin heavy chain (V_H3) of the Fab domain of all immunoglobulin classes [126, 127]. Recent investigations have demonstrated that SpA can also bind various non-immunoglobulin molecules including von Willebrand factor (vWF) [128, 129], tumor necrosis factor receptor-1 (TNFR1) [130, 131], and epidermal growth factor receptor (EGFR) [132, 133].

These findings pose interesting questions regarding the role of saliva in the colonization of the oral cavity by *S. aureus*. What are the mechanisms responsible for the binding of non-immunoglobulin salivary components to *S. aureus*? Do these interactions modulate the adhesion of *S. aureus* to the host surface? Would interruption of these interaction help control the colonization of *S. aureus* in the host?

Conclusions

This brief review has summarized recent information regarding the interaction of salivary components with selected bacteria. A number of salivary components have been shown to interact with both commensal oral bacteria as well as with pathogenic bacteria that can influence their colonization of the oral cavity. Of course, the fact that hundreds of bacteria that colonize the mouth can interact with hundreds of salivary components results in an astronomical number of potential interactions. This underscores the notion that the mechanisms responsible for bacterial colonization of the mouth are extremely complex and difficult to ascertain. Additional research is necessary to dissect these interactions and ultimately to determine the interactions that are essential for oral colonization of both commensal and pathogenic species. Such knowledge may empower specific interventions to control infectious diseases that use the human mouth as their portal.

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Figure 1.

Differences in the profiles of salivary proteins bound to *S. gordonii* and *S. aureus*. Bacteria were exposed to salivary secretions and washed to remove unbound proteins. Bound proteins were eluted from the bacterial organisms and separated by SDS-PAGE. Protein and glycoprotein bands were revealed by a combination of Coomassie blue and periodic acid-Schiff staining. The salivary eluate from *S. gordonii* strain CH1 after exposure to whole saliva shows salivary amylase as the predominant component being bound. The salivary eluate from *S. aureus* strain 8325 shows several bands (ranging from high to low molecular weight: DMBT-1^{gp-340}, mucin-7, secretory component, immunoglobulin (Ig) α -chain, Ig γ -

chain, Ig κ - and λ -chains, lysozyme, and protein S100-A9; Note: In contrast to *S. gordonii*, *S. aureus* does not bind salivary amylase.) (116). Eluates from several clinical isolates of *S. aureus* [isolated strains 7, 15, 41, 59, 74 (19)] after exposure to saliva show a similar pattern as for the type strain 8325. For comparison, the range of protein bands present in whole saliva are shown (left lane). This figure is a modified version of a figure published (116).