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Review Article

Role of *Streptococcus mutans* surface proteins for biofilm formation

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Summary *Streptococcus mutans* has been implicated as a primary causative agent of dental caries in humans. An important virulence property of the bacterium is its ability to form biofilm known as dental plaque on tooth surfaces. In addition, this organism also produces glucosyltransferases, multiple glucan-binding proteins, protein antigen c, and collagen-binding protein, surface proteins that coordinate to produce dental plaque, thus inducing dental caries. Bacteria utilize quorum-sensing systems to modulate environmental stress responses. A major mechanism of response to signals is represented by the so called two-component signal transduction system, which enables bacteria to regulate their gene expression and coordinate activities in response to environmental stress. As for *S. mutans*, a signal peptide-mediated quorum-sensing system encoded by *comCDE* has been found to be a regulatory system that responds to cell density and certain environmental stresses by excreting a peptide signal molecule termed CSP (competence-stimulating peptide). One of its principal virulence factors is production of bacteriocins (peptide antibiotics) referred to as mutacins. Two-component signal transduction systems are commonly utilized by bacteria to regulate bacteriocin gene expression and are also related to biofilm formation by *S. mutans*.

Contents

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1. *Streptococcus mutans* and biofilm formation

Streptococcus mutans has been implicated as a primary causative agent of dental caries in humans [1] and one of its important virulence properties is an ability to form biofilm known as dental plaque on tooth surfaces [2]. The bacterium synthesizes adhesive glucan from sucrose by the action of glucosyltransferases (GTFs), then glucans mediate firm adherence of its cells to tooth surfaces [3]. *S. mutans* also produces multiple glucan-binding proteins (Gbp proteins), which are thought to promote adhesion [4]. Furthermore, the cell surface protein antigen c (PAc), a major surface protein of *S. mutans*, is correlated to its virulence in regard to development of dental caries, as it is known to participate in bacterial adherence to tooth surfaces via interaction with the salivary pellicle [5]. Together, these bacterial surface proteins coordinate to produce dental plaque, thus inducing dental caries.

1.1. Glucosyltransferases

S. mutans produces 3 types of GTFs (GTFB, GTFC, GTFD), whose cooperative action is essential for adherence of bacterial cells, with the highest level of sucrose-dependent cellular adhesion found at the ratio of 5:0.25:1 [6].

GTFB and GTFC, which mainly synthesize water-insoluble glucans rich in α-1,3-glucosidic linkages, are located on the cell surface, and encoded by the *gtfB* and *gtfC* genes, respectively [7,8]. On the other hand, GTFD, which synthesizes water-soluble glucans rich in α-1,6-glucosidic linkages, has been detected in culture supernatant and known to be encoded by the *gtfD* gene [9]. Each enzyme is composed of 2 functional domains, an amino-terminal catalytic domain (CAT), which binds and hydrolyzes the substrate of sucrose, and a carboxyl-terminal glucan-binding domain (GBD), which functions as an acceptor for binding glucan and also plays an important role in determining the nature of the glucan synthesized by a GTF [10–12]. In a previous study of anti-caries activities of oolong tea, high-molecular-weight polyphenols were found to have site-specific actions, thus an oolong tea fraction rich in polymeric polyphenols reduced glucan synthesis in a noncompetitive manner by targeting the *S. mutans* glucan-binding domains of GTFB and GTFD in the solution phase [13].

Simultaneous synthesis of glucans by GTFB and GTFC is essential for establishment of a matrix that enhances the coherence of bacterial cells and adherence to tooth surfaces, allowing for formation of high density biofilm [14–16]. It has been shown that the presence of highly adherent and insoluble glucans in situ increases mechanical stability by binding bacterial cells together, as well as to an apatite surface (Fig. 1). In addition to interactions with specific Gbps expressed by *S. mutans* and other oral microorganisms, these polymers are critical for maintaining the 3-dimensional structure of biofilm (Fig. 1), thereby playing a role in modulating development of cariogenic biofilm [15–17].

1.2. Glucan-binding proteins

Binding of *S. mutans* to glucans formed in situ is mediated by the presence of cell-associated GTF enzymes and non-GTF glucan-binding proteins (Gbps) [4]. This bacterial organism produces at least 4 glucan-binding proteins (Gbps); GbpA [18], GbpB [19], GbpC [20], and GbpD [21], which presumably promote its adhesion. GbpA, the first designated glucan-binding protein, contains carboxyl terminal repeats similar to the glucan-binding domain of GTF enzymes [21,22]. This protein is involved in cellular adherence to tooth surfaces, and has been shown to contribute to the cariogenicity of *S. mutans* both *in vitro* and *in vivo* [23].

GbpA contributes to development of optimal plaque biofilm, which minimizes stress on the bacterial population [24], while it also has an important role in binding proteins and exopolysaccharides for construction of biofilm and maintenance of a balanced environment, while the structure of biofilm and its tolerance to various types of stress is affected by its absence [25]. A deficiency of GbpA results in loose binding to the EPS matrix, resulting in a weak non-uniform biofilm structure (Fig. 2). Thus, GbpA has important roles as a protein for formation of firm and stable biofilm.

Alterations in biofilm structure cause harbored bacteria to be exposed to acid, making them susceptible to gene introduction, with the stress response proteins RecA, DnaK, and GroEL possibly related to that response, though the detailed mechanisms remain unclear [24,25].

GbpB has been purified and shown to be immunologically distinct from other Gbps expressed by *S. mutans* and *Streptococcus sobrinus* [19]. It was also found to be homologous with peptidoglycan hydrolases of other Gram-positive microorganisms, while results of a comparative genomic analysis of the *gbpB* region suggested a functional relationship between genes involved in cell shape and cell wall maintenance [26,27]. GbpB is considered to have some roles in the cariogenicity of *S. mutans*, as mucosal immunization has been found to induce protective immune responses against experimental dental caries [28,29].

GbpC is a cell-surface-associated protein involved in dextran-induced aggregation and is expressed only under stress conditions [20]. Although the glucan-binding domain of GbpC has not been identified, it is homologous with the AgI/II family of proteins [20]. GbpC (and possibly

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