The findings of glucosyltransferase enzymes derived from oral streptococci

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Abstract

Glucosyltransferase enzymes (Gtfs) distribute among some streptococcal species in oral cavity and are known as key enzymes contributing to the development of oral biofilm such as dental plaque. In 18 streptococcal species, 45 glucosyltransferase genes (gtf) are detected from genome database. Gtfs catalyze the synthesis of the glucans, which are polymers of glucose, from sucrose and are the main component of oral biofilm. Especially, the Gtfs from Streptococcus mutans are recognized as one of dental caries pathogens since they contribute to the formation of dental plaque and the establishment of S. mutans in the tooth surface. Therefore, Gtfs has been studied particularly by many researchers in the dentistry field to develop the anti-caries vaccine. However, it is not still accomplished. In these days, the phylogenetic and crystal structure analyses of Gtfs were performed and the study of Gtfs will enter new situation from the technique in the past old viewpoint. The findings from those analyses will affect the development of the anti-caries vaccine very much after this. In this review, we summarize the findings of oral streptococcal Gtfs and consider the perspectives of the dental caries prevention which targeted Gtf.

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1. Introduction

The genus Streptococcus comprises many species of Gram-positive bacteria living in human or animal oral cavity and/or alimentary tract and sometimes associated with pathogens that have a severe influence on human health [1,2]. According to the phylogenomic analyses, the genus Streptococcus divided into eight monophyletic groups, Mitis
group, Sanguinis group, Anginosus group, Pyogenic group, Bovis group, Mutans group, Downei group, and Salivarius group [3,4].

Among these groups, some streptococcal species produce glucosyltransferases (Gtfs), which catalyze the synthesis of the glucans, polysaccharide, from sucrose as a substrate [5-7]. The produced glucans play an important role in developing oral biofilm [8]. Therefore, acquisition of the ability to produce polysaccharide from sucrose, i.e., the gtf gene encoding Gtf, is the key evolutionary event enabling dental biofilm formation by streptococci [9-11]. Especially, the glucan biofilms produced by the Gtfs from Streptococcus mutans are recognized as main components of cariogenic plaque and those enzymes are known as one of dental caries pathogens since those enzymes play an important role in the formation of dental plaque and the establishment of S. mutans on the tooth surface [12-14]. Thus, many researchers in the dentistry fields have studied streptococcal Gtfs to prevent dental caries [15-19].

On the other hand, immunization of S. mutans whole cells was attempted as the primary etiologic agent in rhesus monkeys to develop a vaccine against dental caries and were successfully prevent dental caries [20,21]. However, it was reported that the antibodies induced by S. mutans whole cells showed cross-reactivity with the human heart muscle [22,23]. Thus, GtfB and Pac (protein antigen c) from S. mutans were adopted on another occasion [24,25] since the components derived from S. mutans were used as the targets of anti-caries vaccine to prevent induction of the antibodies that cross-reacted with human tissue. Pac, a protein antigen on the cell surface of S. mutans would be more important factor as the antigen against anti-caries vaccine. However, we will be focused on GtfB since this review summarizes the Gtfs derived from oral streptococci. Moreover, GtfB was truncated to the catalytic region (CAT) and the glucan-binding domain (CBD), and these were employed as antigenic components [26,27]. These components were combined with the cholera toxin B subunit [28] or both [29] to further enhance immunogenicity. In spite of those successful reports, the anti-caries vaccine which targets to GtfB as antigen has not yet been put to practical use. One reason might be that CAT and CBD were employed as vaccine targets. These were selected due to their association with enzyme function [30,31]. However, there are no studies that the immunogenicity of CAT and CBD is verified by immunological, biochemical, or bioinformatic methods. Mora et al. (2018) suggested that effective screening for candidate vaccine antigens should include in silico analysis followed by in vitro and in vivo evaluations of antigenicity to reduce time and cost [32]. Those methods should be adopted also in the development of anti-caries vaccine against GtfB.

During this decade, in silico approaches have been clarified the necessity of reevaluation in the immunogenicity region of GtfB [33] and the phylogenetic relationships among streptococcal Gtfs and/or glycosyl hydrolyase family 70 enzymes from lactic acid bacteria [9-11]. Crystal structure analysis of Gtf180-AN from Lactobacillus reuteri 180 [34] was performed and then Crystal structure of Gtf-SI (GtfC) was analyzed [35]. Thus, the 3D-structure and domains of streptococcal Gtfs has been estimated [36]. Those findings would be available for the development of anti-caries vaccine or other caries prevention measure.

In this review, we summarize the findings of oral streptococcal Gtfs, the distribution in the genus Streptococcus, phylogenetic relationships, and the immunogenicity based on 3D-structure analysis. Then, we make a survey of the development possibility of the anti-caries reagent and/or vaccine which targeted Gtf from S. mutans.

2. Gtfs among streptococcal species

2.1. Distribution of Gtfs in the genus Streptococcus

As early studies of Gtfs, it was reported that three different Gtfs, GtfB, GtfC, and GtfD, were identified from S. mutans GS-5 [37-39].

From Streptococcus sobrinus and Streptococcus downei, four different Gtfs, GtfA, GtfE, GtfF, and GtfU were reported [40-44]. GtfG, GtfR, and GtfP, which synthesize water soluble glucan, were identified from Streptococcus gordonii, Streptococcus oralis, and Streptococcus sanguinis, respectively [45-47]. In Streptococcus salivarius, four different Gtfs, GtfJ, GtfK, GtfL, and GtfM were identified [48,49]. Among those streptococcal species that produce Gtfs, the Mutans and Downei groups are known as caries-promoting species [50] and Gtfs from these groups contain water insoluble glucan (WIG) synthesizing Gtfs, GtfB, GtfC, and Gtf (Table 1). These WIG-synthesizing Gtfs are recognized as a pathogen of initial caries since those play an important role in the colonization of Mutans and Downei group streptococci on tooth surface [51]. In this point, the role of the Gtfs may be limited in the initial formation of dental caries. However, it would be important that the biochemical, molecular biological, and immunological characters of WIG-synthesizing Gtfs were studied since the obstruction of dental plaque formation in the early stage was most effective in the prevention of dental caries. Other than those WIG-synthesizing Gtfs, S. salivarius GtfJ and GtfL are also responsible for synthesizing WIG. However, they are not actually closely related to the WIG synthesizing Gtfs of Mutans and Downei groups [11].

Previously, by the sequence of 16 S rRNA, the genus Streptococcus was divided into 6 groups, Mitis group, Anginosus group, Pyogenic group, Bovis group, Mutans group, and Salivarius group [52]. By phylogenomic analysis, Sanguinis and Downei group was separated from Mitis and Mutans group, respectively, and the genus Streptococcus was divided into eight monophyletic groups [3,4]. Among these eight groups, Gtfs were detected in 7 groups except Anginosus group. Xu et al. (2018) surveyed 37 streptococcal species from the genome sequences on the NCBI (National Center for Biotechnology) Microbial Genomes resource site (http://www.ncbi.nlm.nih.gov/genome/microbes/) and 18streptococcal species that possess gtf genes and their 45 Gtfs were picked up [11] (Table 1). The Gtfs derived from human alimentary tract and oral cavity of horse, ruminants, rodents, and monkeys were additionally joined in the list of those Gtfs. Thus, it was suggested that Gtf enzymes were distributed among the genus Streptococcus.

2.2. Purification of WIG synthesizing Gtfs from S. mutans

To the induction of antibody and the crystal structure analysis, the purification of target protein is indispensable. Purification of oral streptococcal Gtfs was performed by many researchers [8,53-57]. It was also reported that WIG synthesizing Gtfs, GtfB or GtfC from S. mutans was successfully purified [17,37,58], it was practically difficult. This is one of reasons that the development of the anti-caries vaccine against GtfB has been delayed. Although we succeeded in the purification of GtfB and GtfC [33], the purified product was small amount and low concentration. Only about 0.5 mg of purified product was recovered from the whole cell collected from 5 L of S. mutans culture. In this study, it was revealed that GtfB from S. mutans was easy to aggregate by concentrating. It was thought that the character was disadvantageous to crystal structure analysis since it needs the purity and density of tested protein.

2.3. Three Gtfs from S. mutans and other streptococcal Gtfs in glucan biofilm formation

Ooshima et al. (2001) reported that three Gtfs, GtfB, GtfC, and GtfD, contributed cooperatively to adherence of S. mutans cells to smooth surface by reconstitution experiment of sucrose-dependent adherence using the resting cells and its three recombinant Gtfs (rGtf) and that the highest level of sucrose-dependent adherence was found at the ratio of 20 rGtfB:1 rGtfC:4 rGtfD in both the resting cells of Gtf-deficient mutants and insoluble glucan synthesized by
rGtfs [59]. And then, Fujiwara et al., (2002) indicated that the mRNA expression ratios of gtfB:gtfC:gtfD in the early-, middle-, and late-exponential phases were 16:1:10, 15:1:12, and 69:1:25, respectively, by real time RT-PCR analyses of mRNA expression of three gfts from S. mutans [60]. For these reasons, it was suggested that the presence of all three Gtfs at the optimum ratio was necessary for sucrose-dependent adherence of S. mutans, and that GtfC and GtfD might play significant roles in the synthesis of adhesive and insoluble glucan from sucrose.

On the other hand, the effects of GtfR from S. oralis, which is a member of the human oral microbiota and an early-colonizing microorganism in human oral cavity, on the sucrose-dependent adhesion of S. mutans resting cells was verified experimentally [8]. As the results, it was revealed that the addition of a small amount of GtfR (1 mU/ml) resulted in firm adhesion of the S. mutans resting cells and that the adhesion was as strong as that of the S. mutans growing cells in sucrose-containing medium, although the cells incubated without GtfR adhered to smooth surface only loosely. Thus, it was suggested that other streptococcal Gtfs containing GtfR would play a significant role as a substitute for GtfD in glucan biofilm formation.

### 3. Evolution of Gtfs in the genus Streptococcus

#### 3.1. Phylogenetic analysis of Gtfs

At first, in order to test for evidence of recombination between the four gtf alleles, gtfA, gtfB, gtfC, and gtfD of S. salivarius, the phylogenetic tree was constructed among the 12 oral streptococcal Gtfs.
containing \textit{S. mutans}, \textit{S. sobrinus}, and \textit{S. salivarius} \cite{5,49}. Then, Streptococcal Gtf and their homologs in the genus \textit{Leuconostoc} and \textit{Lactobacillus}, which are belonging to the glycoside hydrolase family 70 (GH70), were analyzed and the phylogenetic tree was constructed \cite{9}. As the results, it was suggested that all Streptococcal Gtfs share a common ancestor and that the ancestral Streptococcal Gtf gene was likely acquired from a lactic acid bacteria via horizontal gene transfer. Thereafter, more Gtf genes from various Streptococcal species became available, and a phylogeny covering 39 Gtf sequences from 16 Streptococcal species was carried out \cite{10}. As the result, it was revealed that Streptococcal Gtfs had diverged into two major clades, with one clustering only Gtfs synthesizing WIG and the other including mainly Gtfs synthesizing WSG. Moreover, Xu et al., \cite{2018} surveyed a total of 872 Streptococci genomes covering 37 species to detect Gtf genes and 45 sequences from 18 species to establish the updated Gtf gene phylogenetic tree \cite{11}. This report supported that Streptococcal Gtfs indeed share a common ancestry among all 45 sequences formed a monophyletic group and that the phylogeny includes two major clades, one WIG clade and the other WSG clade. In addition, the tree indicated that Clade I included gtf genes from nine caries-promoting species from the Mutans and Downei groups and that Clade II contained the gtf genes from all 18 species, which are mainly responsible for synthesizing WSG.

### 3.2. Alteration of glucan coupling by evolution of Gtf

It was reported that streptococcal Gtf came to produce soluble glucans as the result of the displacement of amino acids in the catalytic domain and/or a decrease in the number of repeating units in the glucan-binding domain \cite{42,61}. Thus, Hoshino et al. suggested that streptococcal Gtf evolved to synthesize WSGs and that the ability to synthesize WIGs would only be acquired if the ancestral character was strongly retained and highly specialized \cite{9}. The result phylogeny of Xu et al. \cite{2018} also indicated that WIG Clade (I) existed in the upper stream of WSG Clade (II) \cite{11}. Thus, streptococcal Gtfs would become mainly responsible for synthesizing WSGs by evolution.

### 3.3. Gene transfer of gtf genes among streptococcal species

Homologues can be acquired through gene duplication (paralogs) or horizontal gene transfer (orthologs) \cite{62,63}. In our previous study, it was assumed that evidence exists to support both methods of acquisition also in the GH70 genes. As evidence of horizontal gene transfer, it was shown that transposase encoding gene upstream or downstream of the gtf gene in both \textit{Lactobacillus reuteri} and \textit{Lactobacillus sakei} and that a sequence highly homologous to streptococcal transposase genes was also found downstream of \textit{S. oralis gtfR} \cite{9}. It was reported that intra-and interspecies genomic variation in streptococcal species was associated with transposase and that the bacterial population was a flexible gene pool \cite{64}. Thus, it was suggested that the streptococcal gtf was acquired through horizontal gene transfer via transposons, while periodic extinguishing of transposable elements might explain their absence around the gtf in some species of bacteria \cite{65}. Later, Wu et al. estimated it as follows. If one assumes that the ancestral Gtf gene originated in the common ancestor of the monophyletic clade secondarily constructed with the Salivarius group, the Downei group, the Mutans group, the Bovis group, the Pyogenic group in the phylogenomic tree of the genus Streptococcus, then the GtfR from \textit{S. oralis}, GtfP from \textit{S. sanguinis}, GtfG from \textit{S. gordonii}, and Gtf from \textit{S. cristatus} would more likely have been acquired secondarily from a Salivarius group species \cite{11}.

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**Fig. 1.** Outline of phylogenetic analysis among 45 streptococcal gtf genes. The outlined phylogenetic tree was built with the Maximum-Likelihood method using the aligned homologous sequences (~3.9 kb) of gtf genes. WIG or WSG refers to in which Gtf are mainly responsible for synthesizing water-insoluble glucan or water-soluble glucan. The phylogenetic tree is constructed of WIG clade (I) and three WSG subclades (IIA, IIB, and IIC). (adapted from Xu et al. 2018 \cite{11}).

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### 4. Antigenic prediction of GtfB from \textit{S. mutans} by in-silico and crystal structure analysis

#### 4.1. Antigenic propensity of catalytic domain (CAT), glucan binding domain (CBD), and N-terminal region of GtfB by in-silico analyses

GtfB is roughly divided into 4 regions as follows: a ca. 40-amino-acid conserved signal sequence; a ca. 360-amino-acid variable region with unknown function that is species specific and not conserved among the other Gtfs; a ca. 500-amino-acid catalytic region that contains conserved amino acids that are necessary for sucrose hydrolysis \cite{54,66,67}; a series of 6 direct repeats that function in glucan binding \cite{16,42,54} (Fig. 2). Since antigenicity prediction of these 4 regions from GtfB by using Kolaskar’s method \cite{68} estimated that primary catalytic site (DSIR DAVNVDALLIQAGDYLKA) and glucan-binding site (repeat of NGQHLYFRANGQVKG) were included in the group of highly antigenic candidates \cite{33}, two functional domains, CAT and CBD were employed as potential vaccine target regions in previous studies to develop a component vaccine against GtfB \cite{69}, owing to their association with enzyme function. CAT has the high degree of amino acid sequence conservation among streptococci (Fig. 3). Since this high homogeneity would induce cross-reactive antibodies among Gtfs of \textit{S. mutans} and those of \textit{S. sobrinus}, it was thought that the cross-reactivity was more effective in the prevention of dental caries \cite{26}. Moreover, to make up for antigenicity, the diepitopic antigen consisting of both the CAT and GBD has not been put to practical use yet. For this reason, we...
reevaluated the antigenic region of GtfB by the other in-silico predictions identified by the Parker’s [71] and Welling’s [72] methods by using the ANTHEPROT software [73] in our previous study [33] (Fig. 2). As the results, it was suggested that the antigenicity of the primary catalytic site and the glucan binding site would be predicted to be low that the N-terminal variable region of GtfB was immunodominant, because of many antigenic peaks compared with those of CAT and GBD. On the other hand, because of high homogeneity in the catalytic site as shown in Fig. 3., the antibodies induced by this site would cross-react not only between Gtfs of S. mutans and S. sobrinus but also among Gtfs of other oral streptococci. If the antibodies induced by the catalytic site have a sufficient effect, the establishment of other commensal streptococci in oral cavity will be inhibited. Since the healthy oral microbiota would be destroyed by this hypothesis, it was thought that the species-specific component should be adopted as a vaccine target.

4.2. 3D-structure analysis of Gtf-SI from S. mutans and antigenicity of GtfB

In the recent review of structure–function relationship studies about GH70 family enzymes [36], it was shown that the 3D-structure of GTF180-ΔN from Lactobacillus reuteri 180 confirmed the hypothesis of the circular permutation [34] and revealed an organization in five distinct domains: the domains A, B and C, structurally close to those of the glycoside hydrolase 13 family enzymes [74,75], and the domains IV and V, unique to GH70 family enzymes (Fig. 4. A). Each domain is built of a non-contiguous chain except for domain C, which forms the base of the U-shape fold [34] (Fig. 4. B). Ito et al., (2011) crystallized recombinant Gtf-SI (GtfC) from S. mutans and clarified 3D-structure of that [35] (Fig. 4. C). GtfB would also take the 3D-structure like GtfC because of high homology between them.

Streptococcal Gtfs are members of the α-amylase superfamily and contain a circularly permuted (α/β)₈-barrel motif [76,77]. It was thought that the primary catalytic site existed in the (α/β)₈-barrel structure (Fig. 4. C) would be difficult to be recognized as an antigen for the immune system although low-molecular-weight sucrose was able to pass through this structure as an enzyme substrate. Previously, function of the N-terminal region in Gtfs was thought to be unknown as described above. However, it was clarified that this N-terminal region contained domains IV and V by the U-shape fold formation (Fig. 4. B). Domains IV and V are unique to GH70 Gtfs [78]. Domain IV was positioned next to domain B in the Gtf-SI (GtfC) structure. Domain V is thought to be composed of sequences upstream of domain IV and/or downstream of domain IV, which
implies that it is located next to domain IV. Although domains IV and V are not essential for the enzymatic activity of Gtfs [79], domain IV may serve as a hinge, swinging glucan-binding domain V toward and away from the catalytic domains to facilitate glucan extension [35]. For this reason, it would suppress the enzyme activity to assume then-terminal region of GtfB with a target of vaccine. In our previous study, it was shown that antibody against the N-terminal region of GtfB suppress glucan production [33].

5. Future perspectives and conclusions

The dental plaque is the oral biofilm which is the pathogen associated with periodontal disease e. g. dental caries and periodontitis, and systematic disease e. g. infective endocarditis and aspiration pneumonia [1,2]. Since oral streptococcal Gtfs play an important role by producing glucan that is main constituents of this oral biofilm, the biochemical, molecular biological, phylogenetic, and immunological studies of Gtfs lead to discover biofilm-formation inhibitor as a result. Especially, 3D-structure analysis of Gtf would be available for the discovery of the molecular inhibitor that could reduce glucan-producing activity as well as the development of anti-caries vaccine.

By the way, an outbreak of COVID-19 in these days is extremely a serious problem. However, the RNA and DNA vaccine were recognized by this outbreak [80–83]. These techniques would be effective in the development of the anti-caries vaccine and were adopted in the development of anti-caries vaccine [84,85]. Especially, in the case that the large-scale purification of antigen protein such as GtfB from S. mutans may be difficult, the method of vaccine application would be updated. Moreover, antigenic prediction of GtfB from S. mutans by in-silico and crystal structure analysis would give the new idea of anti-caries vaccine development different from

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**Fig. 3.** Homologous region in catalytic site of Gtfs among the streptococci in human oral cavity. The rubric amino acid residues agree on all the selected Gtfs. Black and green characters indicate the amino acid residues of majority and minority, respectively.

**Fig. 4.** Schematic representation of the U shape fold formed by the various domains of GTF-SI from S. mutans and the active site which sucrose substrate is bound in. A. Five distinct domains of GH70 family enzyme. B. The U-shape fold formation. The colors in the 3D structure indicate red: domain V; yellow: domain IV; green: domain B; blue: domain A; and purple: domain C, respectively. C. 3D-structure of GTF-SI from S. mutans. The magenta circle indicates the catalytic site.

(adapted from Vujčić-Žagar et al., 2010 [34], Ito et al., 2011 [35], and Molina et al., 2021 [36])
the measures that have been performed so far. Especially, in the future developmental study of anti-caries vaccine, the placement of the three-dimensional amino acid residues which seem to be recognized as the actual immunogen in vivo would come to be selected although the past vaccine development was performed by employing the two-dimensional amino acid sequence as antigen based on function.

Conflicts of interest

We declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported on this paper.

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