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# *In Silico* Analysis of Possible Surface associated Proteins of the Oral Pathogen *S. mutans*

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**Abstract**

*Streptococcus mutans* is a gram-positive pathogen associated with dental caries in humans, thereby posing a significant strain on public health. Bacterial surface associated proteins are important for virulence and pathogenesis. Since these proteins are likely to be targets of the host's immune defense, they could also be important for vaccine development.

In this study three different protein prediction algorithms (PSORTb, CELLO and LocTree) were used to identify possible cell-surface associated proteins of *S. mutans* UA159. This *in silico* approach allowed the prediction of 48 potential surface-associated proteins. The data reported here might help to identify possible candidates for development of diagnostic agents, drugs and vaccines against *S. mutans*.

**Keywords:** Subcellular protein localization (SCL) programs; Surface associated proteins; *Streptococcus mutans*; Biofilm formation

## Introduction

Whilst oral biofilms, which can consist of up to 700 different species, are closely linked to oral disease, several specific pathogens and their surface proteins have been associated with playing major roles in oral biofilm formation and disease development [1]. Interactions between these species play significant roles in pathogenesis [2]. There is particular interest in the key pathogen involved in caries, *Streptococcus mutans*, which is thought to be a major global health burden [3-5]. *S. mutans* is known to play a leading part in the development of cariogenic lesions, and is frequently found in biofilms extracted from carious dentin [6-8].

Bacterial surface-associated proteins are important for virulence and pathogenesis [9]. Several known virulence factors of *S. mutans* are extracellular, may it be cell-surface associated or secreted. For example, *S. mutans* is able to build extracellular glucanpolymers from saccharose using glucosyltransferases, allowing it to adhere to tooth enamel, and establish biofilm formation [10]. Some strains of *S. mutans* produce proteases which can de-activate IgA-antibodies in saliva and thus weaken the host's immune defense [11]. Since surface proteins are likely to be targets of the host's immune defense, they could also be important for vaccine development [12].

The aim of this study was to identify possible cell-surface associated proteins of *S. mutans* UA159 which could be potential new diagnostic, drug and vaccine targets. An *in silico* approach using three different protein prediction algorithms (PSORTb, CELLO and LocTree) was applied to search for candidate proteins. A literature research was conducted to verify the predicted subcellular localization or function of these proteins where possible.

## Materials and Methods

### *In silico* analysis

In this analysis Subcellular Protein Localization (SCL) programs were employed to identify potential cell-surface associated proteins of *S. mutans* UA159 [13]. Three programs, with high prediction coverage (>75%) and accuracy in Gram-positive bacteria, were specifically selected: PSORTb Version 3.0, Cello v.2.5. and LocTree3 [14-18]. The whole genomic sequence of *S. mutans* UA159 [13] was analyzed in the PSORTdb using the PSORTb Version 3.0 algorithm [14,19]. From the PSORTb prediction results proteins within the predicted localization categories "cell wall", "extracellular" and "unknown/ multiple localization" were short-listed as being possibly surface associated. FASTA sequences of these short-listed proteins were then run through the CELLO v.2.5 and the LocTree3 programs [15-18].

A review of the literature available to date on the short-listed proteins was carried out using the PubMed NCBI database (www.ncbi.nlm.nih.gov/pubmed). Keywords used were the locus tag and/ or the definition of the shortlisted proteins, as well as the terms "*Streptococcus mutans*". In case the search yielded no published data on the protein in *S. mutans*, search terms "streptococcus", or "bacterial" were used. Where applicable, studies relating to the protein's function, experimentally verifying or implying an extracellular, cell wall or surface associated localization in either *S. mutans*, streptococci or other bacterial species were included. In the case of no or sparse available literature pertaining to function or localization (for example hypothetical proteins), studies showing their up- or down regulation under certain conditions were included where possible.

## Results

Assuming that cell-surface associated proteins could be found in several localizations proteins included in the following predicted categories of localization by PSORTb were short-listed: extracellular, cell wall, and multiple localizations. The resulting 48 candidates for potential cell-surface associated proteins, their predicted subcellular localization by CELLO and LocTree, and the literature available on their putative localization are listed in Table 1.




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**Table 1:** Putative cell-surface associated proteins of *S. mutans*. PSORTdb predicted 48 proteins with either extracellular (Ex), cell wall (Cw) or multiple localization sites (Mls). CELLO predicted additional locations in the cytoplasm (Cy), membrane (Mb). LocTree also assigned secreted (Sec), periplasmic (Peri), fimbrial (Fim), inner membrane (Imb) locations. Definition, MW and amino acid length was based on the data available in the NCBI genome and protein database for *S. mutans* UA159.

| Locus Tag (SMU_) | Definition | MW (kDa) | Protein length (aa) | PSORT db | CELLO | Loc Tree | Reference |
|---|---|---|---|---|---|---|---|
| 1004 | GtfB | 165.88 | 1476 | Ex | Ex | Sec | [10,21] |
| 1005 | GtfC | 162.99 | 1455 | Ex | Ex | Sec | [10,21] |
| 910 | GtfD | 163.42 | 1462 | Ex | Ex | Sec | [10,21] |
| 2112 | GbpA | 63.14 | 565 | Ex | Ex | Sec | [22,23] |
| 22 | GbpB/SagA | 44.64 | 431 | Ex | Ex | Sec | [23-25] |
| 1396 | GbpC | 63.36 | 583 | Cw | Ex | Sec | [22,23] |
| 772 | GbpD | 79.8 | 726 | Ex | Ex | Sec | [22] |
| 1915 | ComC/CSP | 5.21 | 46 | Ex | Ex | Sec | [26-29,31] |
| 299c | BsmE | 7.74 | 72 | Ex | Ex | Sec | [29,30] |
| 836 | LytF | 60.3 | 544 | Ex | Ex | Sec | [32] |
| 704c | autolysin; amidase | 37.63 | 327 | Ex | Ex | Sec | [33] |
| 629 | Fe/Mn-SOD SodA | 22.63 | 203 | Ex | Ex | Sec | [35] |
| 862 | permease | 47.73 | 444 | Ex | Ex | Sec | [37] |
| 2028 | SacB | 87.4 | 795 | Ex | Ex | Sec | [38] |
| 395 | PepX | 86.76 | 758 | Ex | Cy | Sec | [39] |
| 963c | PgdB | 33.37 | 299 | Ex | Mb | Sec | |
| 1590 | Amy | 56.47 | 486 | Ex | Cy | Sec | [42] |
| 78 | FruA | 158.69 | 1423 | Cw | Ex | Sec | [43] |
| 79 | FruB | 58.57 | 519 | Cw | Ex | Sec | |
| 610 | SpaP | 170 | 1562 | Cw | Ex | Sec | [45] |
| 2042 | DexA | 94.5 | 850 | Cw | Ex | Sec | [47-49] |
| 196c | transfer protein | 39.9 | 365 | Cw | Ex | Sec | [50] |
| 1169c | thioredoxin family | 20.92 | 187 | Cw | Ex | Peri | |
| 1874 | signal peptidase I | 22.43 | 195 | Cw | Mb | Imb | |
| 987 | WapA | 48.91 | 453 | Cw | Ex | Imb | [53,54] |
| 1091 | WapE | 55.07 | 507 | Cw | Ex | Sec | [55] |
| 550 | FtsQ/DivIB | 42.52 | 374 | Cw | Ex,Mb,Cy | Cy | |
| 255 | OppA | 60.24 | 549 | Cw | Ex,Mb | Peri | |
| 1213c | 5'-nucleotidase | 75.47 | 704 | Cw | Mb | Peri | |
| 683 | ATP-binding protein | 126.56 | 1137 | Cw | Ex,Mb,Cy | Sec | - |
| 76 | N-acetyl-muramidase | 21.89 | 195 | Mls | Mb | Peri | [32] |
| 1093 | ABC transporter | 53.26 | 502 | Mls | Mb | Imb | [60] |
| 1024c | transposase fragment | 6.49 | 53 | Ex | Ex | Sec | - |
| 1358 | transposase fragment | 4.17 | 33 | Ex | Ex | Sec | - |
| 616 | hypothetical protein | 8.03 | 82 | Ex | Ex | Sec | - |
| 1752c | hypothetical protein | 6.12 | 56 | Ex | Ex | Sec | - |
| 1882c | hypothetical protein | 12.74 | 117 | Ex | Ex | Sec | [61] |
| 2048 | hypothetical protein | 5.82 | 50 | Ex | Ex | Sec | [67] |
| 2076c | hypothetical protein | 5.21 | 42 | Ex | Ex | Sec | [63] |
| 2146c | hypothetical protein | 21.04 | 201 | Ex | Ex | Sec | - |
| 63c | hypothetical protein | 63.97 | 613 | Cw | Ex | Sec | [64] |
| 520 | hypothetical protein | 49.94 | 443 | Cw | Cy | Peri | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 739c | hypothetical protein | 53.75 | 518 | Cw | Ex. Mb | Fim | [60] |
| 984 | hypothetical protein | 18.91 | 166 | Cw | Ex | Sec | [64] |
| 2147c | hypothetical protein | 30.48 | 288 | Cw | Ex | Sec | [62] |
| 367 | hypothetical protein | 22.47 | 211 | Mls | Ex | Sec | [65] |
| 689 | hypothetical protein | 107.22 | 979 | Mls | Ex | Sec | [66] |
| 752 | hypothetical protein | 17.12 | 145 | Mls | Ex | Cy | - |

PSORTb predicted 24 proteins with an extracellular localization. These include the glucosyltransferases GtfB, GtfD and GtfC; the glucan-binding protein GbpA; the secreted antigen GbpB/SagA;the glucan-binding protein GbpD; the competence stimulating peptide (CSP) ComC; the bacteriocin peptideBsmE;the autolysin LytF; an autolysin/amidase (SMU_704c); the manganese-type superoxide dismutase SodA; a permease (SMU_862); the β-D-fructosyltransferaseSacB; thex-prolyl-dipeptidylaminopeptidasePepX;a peptidoglycan-deacetylase PgdB; two transposase fragments (SMU_1024c and SMU_1358); the cytoplasmic α-amylase Amy; and 4 hypothetical proteins (SMU_616, SMU_1752c, SMU_1882c, and SMU_2048). The predicted extracellular or secreted localization concurred with the CELLO and LocTree results for all but 3 proteins (Table 1). CELLO predicted PepX to be cytoplasmic, PgdBto be located in the membrane, and Amy to be cytoplasmic. In contrast to this, LocTree assigned all 3 a secreted localization, in agreement with the PSORTb result (Table 1).

PSORTb predicted 19 proteins to be located in the cell wall. These include the glucan-binding protein GbpC; the exo-β-D-fructosidases FruA and FruB; the cell surface antigen SpaP; the dextranase DexA; a transfer protein (SMU_196c); a thioredoxin family protein (SMU_1169c); a signal peptidase I (SMU_1874); the cell wall-associated protein WapA; the cell wall protein, WapE; the cell division protein FtsQ/DivIB; the oligopeptide ABC transporter substrate-binding protein OppA; a 5'-nucleotidase (SMU_1213c); an ATP-binding protein (SMU_683); as well as 5 hypothetical proteins (SMU_63c, SMU_520, SMU_739c, SMU_984 and SMU_2147c) (Table 1). There were differing predictions from this localization for 8 of these proteins (Table 1). The thioredoxin family protein (SMU_1169c) was found to be extracellular by CELLO, but periplasmic by LocTree. Both programs predicted the signal peptidase I (SMU_1874) to be (inner) membrane associated. WapA was predicted to be extracellular by CELLO and to be located in the inner membrane by LocTree. FtsQ was found to be extracellular or membrane associated by CELLO, and to be cytoplasmic by LocTree. OppA was predicted to be extracellular or membrane associated by CELLO, and to be periplasmic by LocTree. The 5'-nucleotidase (SMU_1213c) was placed in a membrane associated position by CELLO, and in the periplasm by LocTree. The hypothetical protein SMU_520 was predicted cytoplasmic (CELLO) and periplasmic (LocTree). The hypothetical protein SMU_739c was assigned an extracellular or membrane associated position by CELLO, and to be part of the fimbrium by LocTree.

PSORTb found 5 proteins to be associated with multiple locations. These include an N-acetyl-muramidase (SMU_76), an ABC transporter permease (SMU_1093) and 3 hypothetical proteins (SMU_367, SMU_689 and SMU_752) (Table 1). Both CELLO and LocTree predicted 2 of the hypothetical proteins (SMU_367 and SMU_689) to be extracellular/ secreted. The N-acetyl-muramidase was predicted to be localized in the membrane by CELLO, and supposedly localized in the periplasm according to LocTree. The ABC transporter permease (SMU_1093) was predicted to be a membrane protein by CELLO, and to be an inner membrane protein by LocTree. These two programs also gave differing localizations for the hypothetical protein SMU_752, which was predicted extracellular by CELLO, and cytoplasmic by LocTree (Table 1).

## Discussion

Computational/*in silico* SCL prediction methods require only sequence data and state of the art SCL predictors have been shown to exceed the accuracy of common high-throughput laboratory approaches [20]. Our *in silico* analysis yielded a list of 48 candidate proteins with a potential cell-surface associated localization (Table 1).

For 8 of the predicted extracellular proteins, many of which seem to play a role in virulence or biofilm formation, the predicted subcellular localizations have been confirmed in previous studies. Streptococcal glucosyltransferases are important extracellular virulence factors, mediating adhesion to tooth enamel and thus enabling biofilm formation [10]. Kopec and colleagues have researched the effect of antibody-mediated inhibition of GtfD, GtfB and GtfC on biofilm formation, verifying their extracellular location [21]. The glucan binding proteins GbpABCD of *S. mutans* are already known cell-surface associated proteins involved in biofilm formation. GbpA and GbpD are extracellular proteins particularly important for biofilm architecture [22,23]. GbpB (previously described as secreted antigen SagA) appears to be crucial for maintenance of cell wall integrity. Given that it is also a dominant *S. mutans* antigen, reacting with antibodies found in human saliva, an extracellular location seems plausible [24,25]. GbpC (included here for completion) is known to be cell-bound, supporting the cell wall localization predicted by PSORTb as opposed to extracellular/secreted [22].The extracellular competence stimulating peptide (CSP) ComC appears to play a role in quorum sensing as well as in biofilm formation [26,27]. Furthermore, it has not only been shown to influence biofilm structure, but also to play a role in bacteriocin expression, some of which, such as ImmB, play a role in resistance to antimicrobial agents such as sodium fluoride, chlorhexidine and ampicillin or the establishment of genetic competence [28,29]. The expression of bacteriocin BsmE, which has been hypothesised to play a role in the defense against other organisms, does not appear to be regulated by CSP [29]. Both CSP and bacteriocins have been shown to be extracellular streptococcal proteins [30,31].

The exact subcellular locations remains to be confirmed for the other 8 candidates classed as extracellular by PSORTb. However, according to the literature available on their function or similar proteins from other streptococci, an extracellular localization appears

highly likely for 7 of them. LytF, which is also regulated by CPS, has been shown to be a self-acting peptidoglycan hydrolase, believed to be important for *S. mutans* cell death under stress conditions [32]. The autolysin/amidase SMU_704c, which is upregulated under heat stress, could also play a role in stress survival [33].There is currently no information available on the subcellular localization of this particular protein. However, autolysins, such as the virulence factor LytA of Streptococcus pneumoniae, can be found both intra- and extracellularly [34]. SodA has been shown to play a role in growth with competing streptococci, such as S. sanguinis [35]. It is highly likely to be an extracellular protein, for example SodA of Streptococcus pyogenes is a known extracellular enzyme, believed to play a role in immune evasion [36].There is limited data available on the permease SMU_682, and it is possibly regulated by MbrC, which in turn is involved in resistance to bacitracin. This mechanism appears to be mediated by substrate transport across the cell surface, making a permease a putative candidate for involvement [37]. Another gene involved in biofilm formation is SacB. It seems to be associated with sucrose dependent adhesion and is upregulated when grown with sucrose or xylitol [38].

The *in silico* analysis revealed conflicting localizations for three proteins, PepX, PgdB, and Amy (Table 1). PepX was predicted to be cytoplasmic by CELLO, and to be extracellular/secreted by PSORTb and LocTree. Since PepX is a known extracellular protein in S. gordonii, which might play a role during in pathogenesis, an extracellular location in *S. mutans* appears likely [39]. There is currently no published research on PgdB, predicted extracellular/ secreted by PSORTb and LocTree, and membrane located by CELLO. However, PgdA is a cell-surface enzyme mediating bacterial interaction with salivary agglutinin [40]. Furthermore, PgdA is a pneumococcal virulence factor, and a current target for novel drug development [41]. Thus, a similar role and subcellular location might be postulated for PgdB. The α-amylase Amy was predicted to be cytoplasmic by CELLO. This is likely to be the correct localization of this enzyme, which has been shown to be intracellular in *S. mutans* [42].

Some of the proteins predicted to have a cell wall location by PSORTb were predicted to be extracellular/ secreted by CELLO and LocTree. The latter seems to be the correct prediction for at least 7 of them, based on the available literature. FruA and FruB are most likely extracellular enzymes, since FruA has confirmed cell-surface localization and has previously been shown to be a mainly extracellular [43]. SpaP, is a surface protein of *S. mutans* involved in adhesion to host tissues and belongs to a family of antigen I/II proteins which are widespread in streptococci [44-46]. DexA is a known extracellular enzyme of *S. mutans* involved in dextran catabolism. It is believed to affect adhesion and its expression is upregulated during multi-species biofilm growth, supporting a role in cell surface remodeling [47-49]. The transfer protein (SMU196c) has previously been described to be "secreted and immunogenic" and is upregulated in *S. mutans* under acid- or acid- and hydrogen peroxide stress [50]. The thioredoxin family protein SMU_1169c has yet to be characterized in *S. mutans*. A surface associated localization could be plausible should it have a similar function to the surface exposed Etrxthioredoxin lipoproteins of S. pneumonia [51]. The signal peptidase I SMU_1874 could play a similar role to SipA of *S. pyogenes* which is hypothesized to process proteins secreted for pilus polymerization [52].

The PSORTb predicted cell wall localization is most likely correct for at least 3 of the proteins with conflicting predictions. WapA is a cell-wall associated protein know to affect cell surface structure and believed to be involved in biofilm formation and has already been investigated as a possible vaccine candidate [53,54]. WapE expression is upregulated during biofilm formation. Its role in stress survival and possibly cell wall biogenesis would support a cell-wall associated localization [55]. The cell division protein FtsQ/DivIB has been well characterized in *S. pneumoniae*, where it is hypothesized to play a role in cell wall synthesis [56]. In contrast to the PSORTb cell wall location, the periplasmic LocTree prediction for OppA is most likely to be accurate. OppA is the periplasmic binding protein of the opp cell wall transporter in group A streptococci (GAS), which is believed to be important for pathogenesis of GAS [57,58].

Given the lack of available literature and the clashing predictions, further studies are required to confirm the subcellular location of 2 of the PSORTb predicted cell wall proteins. Whilst there is currently no data available on the putative 5′-nucleotidase SMU_1213c, one might liken its function to the streptococcal 5'-nucleotidase S5nA, a virulence factor of *S. pyogenes* [59]. SMU_683 is a yet uncharacterized ATP-binding protein. PSORTb predicted multiple locations for the N-acetyl-muramidase SMU_76 and the ABC transporter permease SMU_1093. Again, a lack of available data calls for further studies to verify a possible surface associated localization of these proteins. The N-acetyl-muramidase SMU_76 is one of several putative autolysins (cell wall hydrolases) of *S. mutans*. Its exact function remains to be determined, although it does not appear to be involved in CPS induced cell death, a cell wall location should not be ruled out without further studies [32]. The ABC transporter permease SMU_1093 appears to be part of the CiaRHregulon, its exact function or subcellular location remains to be confirmed [60].

Sixteen of our candidate proteins are as yet uncharacterized transposase fragments (SMU_1024c and SMU_1358) or hypothetical proteins (SMU_616, SMU_1752c, SMU_1882c, SMU_2147c, SMU_2048, SMU_2076c, SMU_2146c, SMU_63c, SMU_520, SMU_739c, SMU_984, SMU_367, SMU_689, SMU_752). However, the molecular function of some of these proteins can be deferred from genetic experiments. SMU_1882c and SMU_2147care regulated by the global response regulator CovR [61,62]. SMU_2076c may be vital for natural transformation [63]. SMU_739cis regulated by the CiaRH two component systems, which regulate several stress responses [60]. SMU_984potentially plays a role in stress tolerance though affecting the CSP-inducible persistence phenotype [64]. SMU_367is involved in cell wall and cell envelope biogenesis [65]. SMU_689 is homologous to bacteriolytic Autolysin A [66]. Notably, SMU_2048 is argued to most likely not encode a protein at all as it lacks an obvious initiation codon, and it has no significant similarity to known genes [67]. The exact subcellular localization of these proteins remains to be established (Table 1).

Bacterial cell-surface associated proteins play an important role in host-pathogen interactions, pathogenesis, biofilm production and the host's immune response. An *in silico* approach, using the protein predication algorithms PSORTb, CELLO and LocTree, enabled the identification of 48 possible surface associated proteins. With a few

exceptions (notably Amy, and OppA), the subcellular localizations given by the PSORTb database appear to be mostly accurate, suggesting it to be a reliable program to search for possible surface associated proteins [68]. The putative surface associated location of the proteins identified needs to be verified. Furthermore, the existence of additional surface associated proteins, which may not have been included in the prediction due to a lack of certain cell-surface associated targeting motifs or structures, cannot be ruled out. Thus, additional studies are called for. For example, Severin and colleagues have recently demonstrated an elegant approach for subcellular localization confirmation for *S. pyogenes*. Following an *in silico* analysis, cell-surface associated proteins were verified by proteolytic digestion, MS-analysis, antibody-reactivity and targeted gene knock outs [69]. Identification of these proteins by means of a genome wide *in silico* analysis, and verification of their localization can provide new leads for vaccine development or novel targets for antibiotic therapy.

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