

Streptococcus Adherence and Colonization

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INTRODUCTION

The *Streptococcus*, although not named, was first recorded in 1683 in van Leeuwenhoek's drawings of microscope images of

the material removed from between his teeth. The main entry of streptococci into history was in 1879, when Louis Pasteur was studying puerperal fever. This was causing high mortality rates in maternity wards. Within the bodies of diseased women, he found rounded granules (microorganisms) arranged in the form of chains or strings of beads. He was convinced, and it was later proven, that this was the cause of infections in women after childbirth. Thus, streptococci were one of the first mi-

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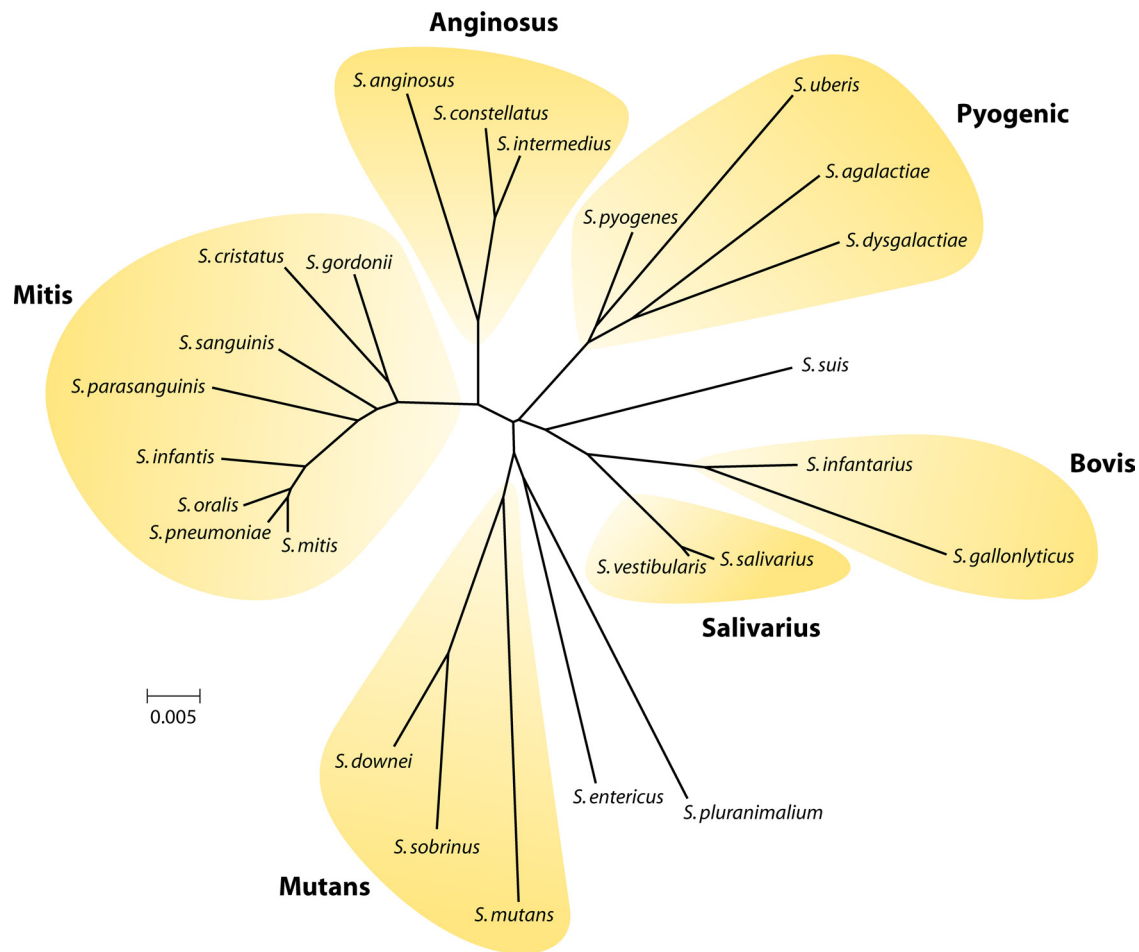


FIG. 1. Taxonomic relationship tree for *Streptococcus* based on 16S rRNA gene sequence comparisons showing positions of selected species. A number of species are not included to simplify the figure, and a full description may be found in a review by Kilian (295). (Courtesy of Mogens Kilian, Aarhus University, Denmark, reproduced with permission.)

crobes to be identified as causing contagious disease, and their existence led to the introduction of hygiene and aseptic practices into hospital wards. *Streptococcus* comes from the Greek strepto (twisted) and coccus (spherical). There are now over 100 recognized species of *Streptococcus*. Historically, the classification of streptococci was based on the Lancefield scheme, which groups streptococcal strains according to the carbohydrate composition of cell wall antigens (331). Such antigens, known as group-specific antigens or C substances, are either polysaccharides (as in groups A, B, C, E, F, and G), teichoic acids (as in groups D and N), or lipoteichoic acid (as in group H) (505). This approach has proved successful for the more pathogenic streptococci, but its widespread application is hindered by the fact that group-specific antigens for other species may be absent or shared between distinct taxa. The streptococci may also be organized into six groupings (Fig. 1) based on 16S rRNA gene sequences (295). The pyogenic group includes *Streptococcus pyogenes* (Lancefield group A), *S. agalactiae* and *S. uberis* (group B), and *S. dysgalactiae* (group C, G, or L) (Fig. 1). *S. equi* (group C) and *S. iniae* are also in this group but are not shown in Fig. 1. These organisms are involved mainly in the colonization of humans and other mammals (although *S. iniae*

colonizes fish). They are associated with a range of diseases including tonsillitis, pharyngitis, impetigo, mastitis, and sequelae such as rheumatic fever, glomerulonephritis (*S. pyogenes*), and neonatal sepsis (*S. agalactiae*). *S. dysgalactiae* is a major organism associated with bovine mastitis, while *S. equi* causes strangles in horses. The mitis group (Fig. 1) comprise species almost all of which may be isolated from the human oral cavity or nasopharynx. *S. oralis*, *S. mitis*, *S. gordonii*, and *S. pneumoniae* are highly related, and because of extensive horizontal gene transfer, the delineation of strains into these species is often blurred. *S. pneumoniae* is a major pathogen associated with otitis media, bronchitis, sinusitis, meningitis, and pneumonia. Colonization by *S. pneumoniae* will not be addressed in detail in this article, and the reader is referred to recent excellent reviews of adherence and virulence factors (43, 284). Other groupings include the anginosus and salivarius groups, which contain mainly human and animal oral cavity microbes, and the bovis group (Fig. 1). Mutans group streptococci comprise the least related organisms. They include a range of bacteria colonizing the oral cavities of humans (*S. mutans* and *S. sobrinus*), macaques (*S. downei*), rats (*S. rattii*), and hamsters (*S. criceti*) that are all associated with the devel-

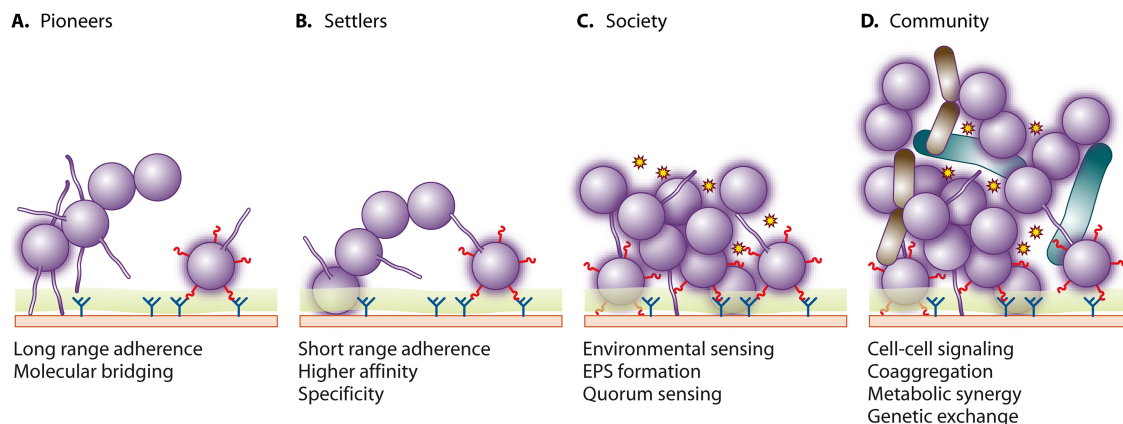


FIG. 2. Temporal sequence of adherence and colonization by streptococci. (A) Pioneer streptococcal species associate with a conditioned surface (green), utilizing longer-range interactions, e.g., pili, which can penetrate mucus, or shorter-range interactions. (B) Some of the pioneers form stronger bonds with the surface molecules (blue) engaging multiple adhesins (red). (C) Nutritional adaptation, intermicrobial signaling (stars), and extracellular polymeric substance (EPS) production result in the formation of societies. (D) Incorporation of other microorganisms, including intergeneric coaggregation and cell-cell signaling, leads to the development of complex communities. These communities contain specific microbial associations within metabolic networks, ensuring more efficient utilization of nutrients and reduced susceptibility to antibiotics and immune surveillance.

opment of dental caries (tooth decay). Oral cavity microbes are often cited as viridans group streptococci because colonies cause greening of blood agar. This is referred to as alpha-hemolysis and is indicative of hydrogen peroxide production. The pyogenic group of organisms is beta-hemolytic, producing true hemolysis on blood agar.

Colonization Attributes

This article focuses on the adherence and colonization properties of selected members of the genus *Streptococcus*, particularly from the perspective of community development. Bacteria in the natural environment often grow upon surfaces, and it is thought that many species of streptococci that colonize mammals exist naturally within communities of bacteria growing as biofilms. Different streptococci vary in their propensities to form biofilm communities, but in all cases, biofilm formation depends first upon the adherence of cells to a surface. Cell division and multiplication then occur to produce a society (clonal), and the integration of other microorganisms within the society leads to the formation of a community (mixed species) (Fig. 2). Environmental conditions such as pH, temperature, oxygen availability, and organic metabolites, etc., influence the development of these communities, and signaling molecules for cell-cell communication are integral to population control (Fig. 2). The coverage of this review is summarized diagrammatically in Fig. 3. Surface and secreted proteins are mediators of adherence and virulence, membrane transporters are central to the import of nutrients and the export of small signaling molecules, and two-component signal transduction systems (TCSS) enable environmental sensing, sampling, and cellular responses. All of these surface components contribute to colonization processes, biofilm formation, and microbial community development.

Studies of the structure and function of proteins in streptococci have been crucial to an understanding of pathogenesis ever since the *S. pyogenes* M protein was first purified from the group A *Streptococcus* (GAS) cell surface (121). Cell surface

proteins are responsible for initial interactions of streptococci with the host. These interactions may include adherence to host cells or tissues, e.g., salivary pellicle on teeth; binding of soluble factors, e.g., lactoferrin at mucosal surfaces, or of plasma proteins, e.g., immunoglobulins (Igs); and stimulation of host responses, e.g., cytokine production. Similarities between cell surface proteins produced by various species of streptococci enable the delineation of proteins into families in which sequences and overall structures are relatively well conserved. Horizontal gene transfer between strains of streptococci and duplication of genes encoding surface proteins have generated mosaics of structure and function. Despite high genetic identities of strains within species, it is clear that different isolates may express different complements of cell surface proteins. This results in considerable phenotypic heterogeneity between strains with respect to their abilities to adhere to surfaces, develop biofilms, and colonize the host.

From a single cell deposited onto a surface in the human body, a mixed-species community may be developed within 24 h (Fig. 2). The processes involved in colonization have been difficult to study *in vivo*. However, the advancement of molecular methods to determine the composition and spatial arrangement of microorganisms within communities has led to studies of oral biofilm development *in situ* (89). Also, with the introduction of live-animal imaging, it is possible to monitor the temporal and spatial course of colonization and infection (561). Adherence and colonization attributes have of course been studied mainly in the laboratory. Here, new technologies involving the use of flow cells to generate biofilms (58, 110) and multilayer differentiated host cell systems will enable fundamental studies of the role of cell surface proteins in adherence and host cell interactions. Some of these proteins may turn out to be candidates or provide epitopes for incorporation into new vaccines. In addition, since biofilm formation is in many instances associated directly with the development of infections and disease, new agents that interfere with or disrupt biofilms may be important for therapy or prevention.

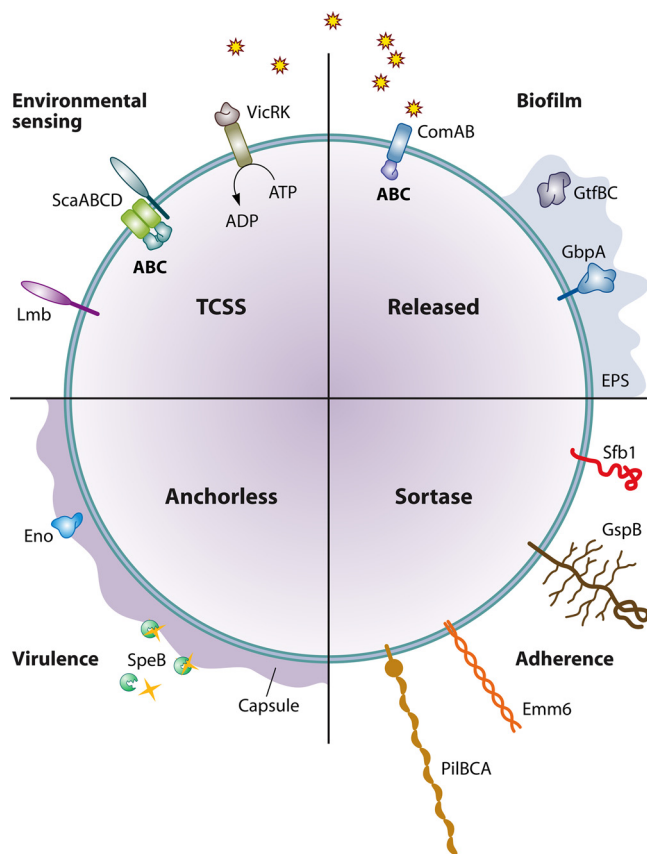


FIG. 3. *Streptococcus* colonization depends upon adherence, signaling, nutritional adaptation, and host modulation. Adhesins include cell wall-anchored polypeptides, e.g., SfbI, and anchorless proteins, e.g., Eno, which mediate attachment and possibly also host cell modulation. Secreted polypeptides may be synthetic, e.g., GtfBC producing polysaccharides, or degrade host proteins, e.g., SpeB, and supply additional nutrients. Extracellular polymeric substance (EPS) (blue shading) and capsular material (purple shading) contribute to a developing ECM. Secreted peptides, and possibly other signaling molecules, e.g., AI-2 (stars), and environmental stimuli, e.g., pH, may be sensed by TCSS, with an ensuing modulation of transcription. ABC transporters, e.g., ScaABCD, ensure nutritional homeostasis as well as a possible involvement in regulating adherence, directly or indirectly. The quadrants are labeled to indicate the processes of adherence, environmental sensing, biofilm formation, and virulence that may be orchestrated by the expression of surface-bound or secreted proteins. These processes are not, however, exclusive to those molecules in each quadrant. For example, cell wall-linked proteins (south-east quadrant) may also contribute to virulence, while transporters (north-west quadrant) may contribute to adherence.

STREPTOCOCCUS ADHERENCE

Cell Surface Components

Adherence studies have featured throughout the research life of *Streptococcus*. From the early days of dental research, it was acknowledged that the attachment of *S. mutans* to oral surfaces, which are usually coated with salivary molecules, was an initial event in the development of dental caries. Likewise, it was observed that *S. pyogenes* cell surface molecules, including proteins and lipoteichoic acid (LTA), were important for the adherence of these organisms to cultured human cells (34) and to extracellular matrix (ECM) proteins such as fibronectin (Fn). One of the first oral streptococcal surface protein anti-

gens shown to be an adhesin was antigen I/II (AgI/II) (515). The nomenclature for this protein family is confusing and arose because two cell surface antigens, designated AgI and AgII, were initially identified and thought to be the products of distinct genes. However, AgII was found to be a breakdown product of the larger AgI (291). The breakdown of streptococcal surface proteins into discrete fragments is a typical property and continually hinders functional analysis in the laboratory. As interest in the molecular biology of *Streptococcus* extended, it became established that adherence was mediated principally by surface proteins. LTA plays a part in streptococcal interactions with human tissue components (116, 239) and indeed triggers Toll-like receptor 2 (232, 532, 536), but the precise mechanism by which LTA might be involved in adherence is still not entirely clear. In *S. mutans*, the production of insoluble extracellular polysaccharides is essential for biofilm formation. However, glucan polysaccharides do not mediate the initial adherence to the tooth surface unless glucan-binding proteins (GBPs) are present within the salivary pellicle (26).

Adhesin-Receptor Interactions

Streptococci colonize different sites in the human body because they express multiple adhesins. These are usually proteins that recognize specific receptors, often sugars or oligosaccharides, expressed at various body sites. The keratinized epithelial cells at the buccal mucosal surface display different receptors from, for example, those present within the salivary pellicle formed on the tooth surface. This provides selectivity for the adherence of different streptococcal species (272). Following initial adherence processes (Fig. 2), bacteria will grow and survive only if the physical and chemical environment, e.g., pH, oxygen levels, and redox potential, is conducive. It is sometimes forgotten that adherence is a dynamic process. It may be advantageous for bacteria to detach from a surface if the growth conditions become unfavorable. As a result, streptococci have evolved methods for detachment as well as attachment.

In the development of a community, the initial adherence of single cells gives rise to microcolonies (Fig. 2). This results in the formation of what has been termed a linking film (80). Cell division leads to the generation of a small society with the concomitant incorporation and accumulation of other bacterial cells to establish a community (Fig. 2). In a dental plaque community, there may be over 100 different kinds of bacteria present (1). Multiple adhesive and metabolic interactions occur between bacterial cells in these communities. Appendages such as fimbriae (or pili), made up of multiple protein subunits (polymeric), are present on the surfaces of some streptococcal cells (see "Pili" below). These extended structures allow long-range adhesion to occur, sometimes across 5 μm , and may confer the ability to penetrate mucus or slime layers present on the surfaces of tissues. Shorter-range adherence processes occur through interactions of protein monomers or oligomers attached to the bacterial cell wall or membrane with host glycoproteins, e.g., integrins, or ECM proteins, e.g., Fn (431). Very close interactions between microbial cells and surfaces are mediated by hydrophobic or electrostatic forces. Collectively these can be quite strong, but generally they have low affinity (431).

Adhesins may be proteins that are linked directly to the cell surface or components of surface structures, e.g., pili projected away from the confines of the cell wall. The protein subunits of pili may themselves mediate adherence, or they may carry the adhesins along their lengths or at their tips. The specificity of microbial adherence is often associated with protein-carbohydrate (lectin-like) reactions. Common sugars (saccharides) that are recognized include galactose (Gal), *N*-acetyl-galactosamine (GalNAc), sialic acid (neuraminic acid [NeuNAc]), fucose (Fuc), *N*-acetyl-glucosamine (GlcNAc), and glucose (Glu). The recognition of Gal-containing carbohydrate chains or oligosaccharides is a common feature in oral microbial community development (306). On the other hand, the cell wall-anchored Hsa and GspB polypeptides in *S. gordonii* recognize NeuNAc residues on human cells (590), while the GBPs expressed by *S. mutans* attach to dextrans (26). Adherence processes may lead to one or more outcomes: commensal bacterial colonization, superficial infection of tissues, or intracellular invasion by pathogens and systemic spread.

Adherence Forces

It is thought that the streptococcal cell surface presents a vast spectrum of proteins to the host environment. Complex arrays of molecules are present upon host surfaces, e.g., salivary pellicle and epithelia, etc., with which streptococcal cells interact. Therefore, adhesin-receptor interactions between *Streptococcus* and the host will be multiply mediated. Interactions may be lectin-like (as described above), but they may also involve protein-protein or carbohydrate-carbohydrate recognition events. Adherence may involve ionic or Coulombic interactions, hydrogen bonding, the hydrophobic effect, or coordination involving divalent metal ions. These interactions differ quite considerably in their ranges and intermolecular forces. Van der Waals forces can play important roles in protein-protein recognition when complementary shapes are involved. This is the case for adhesin-receptor recognition, where a lock-and-key fit yields extensive Van der Waals attractions. Hydrophobic side chains of proteins can closely associate and are shielded from interactions with solvent H₂O. The force generating a hydrophobic bond is approximately 20 pN (488), while the forces required to maintain stereospecific lectin-CHO binding range from 50 to 120 pN (608). With the development of force spectroscopy, forces between cells or purified adhesins and individual molecules can be reasonably accurately determined (609). This methodology provides a new means for comparative analyses of adhesin-receptor interactions. Measurements of forces between microbial cells and their receptors, or of bacterial cell softness or viscoelasticity, provide novel biomechanical information on bacterial adhesins and cellular functions (619).

A model for initial attachment envisages first a weak association of the microbial cell with substratum. For *S. pyogenes*, it has been suggested that LTA may counteract the electrostatic repulsion between bacteria and host surfaces. Alternatively, longer-distance first-attachment events (Fig. 2) may be mediated through surface appendages such as fimbriae (or pili). The initial attachment events are dynamic in that they demonstrate an on-off kinetic effect. They may be rather weak electrostatic or ionic forces or strong hydrophobic interactions

and involve multiple molecular forces (117). A second stage might then involve more specific and irreversible interactions occurring, e.g., lectin-carbohydrate or protein-protein interactions, which could be of higher affinity or high complexity and involve multiple adhesins. A two-step model has been proposed for the interaction of GAS with human cells (223). The first step would involve a weak hydrophobic interaction between LTA and potential binding domains on the host cell surface, while the second step might involve protein adhesins such as M protein, Fn-binding proteins, and laminin-binding proteins, etc., depending upon the receptors available. In general, the adherence mechanisms for streptococci follow the general paradigms for adherence in other bacteria quite closely. However, it should be emphasized that streptococci, like other gram-positive bacteria, present a potentially more vast and complex surface proteome than gram-negative bacteria. This highly advanced surface protein repertoire enables multiple interactions with different host components, and so streptococci have versatility when it comes to occupying adherence sites and evading immune recognition. This property of streptococci to engage multiple adhesin-receptor interactions with various affinities is one reason for the difficulties that have been encountered in the characterization of adhesins. For example, single-gene knockouts may reveal very little about adherence mechanisms, and antibodies generated to specific surface proteins may have little or no effect on streptococcal adherence.

Surface Fibrillar Structures

When viewed under an electron microscope, there are at least two types of filamentous structures that may be seen extending away from the streptococcal cell surface: fibrils and pili (otherwise known as fimbriae). Fibrils were first visualized in the 1970s and appeared as thin flexible rods of various lengths from 40 nm to about 400 nm. These structures have been best described for oral streptococci, including *S. sanguinis* and *S. salivarius*, and exhibit either a peritrichous (hair-like, all around the surface) distribution or localized distribution as tufts (214, 215). Clearly, the surface structures are important for growth and survival in the oral cavity because all freshly isolated streptococci show some form of surface structure (215). However, the composition of these structures remained unknown for many years, and precisely what controls their surface topography is still not explained. Recent evidence supporting a concept that there may be specific sites for the secretion of proteins through the cell membrane of streptococci (490, 506) might provide a future basis for understanding the lateral distribution of fibril tufts, composed of glycoproteins, observed in some strains of *S. cristatus* and *S. mitis* (265). Surface fibrils have been implicated in mediating adhesion to host cells and to ECM and salivary components (217), although direct evidence has been lacking because mutants have been hard to generate and because fibrillar proteins have been difficult to purify. Fibrils have also been implicated in facilitating interbacterial coaggregation (215, 217, 333, 650), but the composition and assembly of most of these fibrillar structures remain unknown. However, the CshA polypeptide (259 kDa) produced by *S. gordonii* has been identified as the structural and functional component of one fibril type (394) (Table 1).

TABLE 1. Cell wall-anchored or surface-associated adhesins

Protein group	Protein(s)	Species	Cell surface linkage ^b	Function(s) and/or substrate(s)	Reference(s)	
AgI/II family ^a	SpaP/PI/PAC/Sr/AgB	<i>S. mutans</i>	LPxTz	Coaggregation; multiple substrates	291	
	SpaA/PAG	<i>S. sobrinus</i>	LPxTz		335	
	SspA, SspB	<i>S. gordonii</i>	LPxTz		240, 271, 328, 329	
	Pas	<i>S. intermedius</i>	LPxTz		271	
	Spy1325	<i>S. pyogenes</i>	LPxTz		667	
	PAaA, PAaB	<i>S. criceti</i>	LPxTz		596, 598	
	PAh	<i>S. downei</i>	LPxTz		597	
	Ssp-5	<i>S. agalactiae</i>	LPxTz		604	
Serine-rich repeat family ^a	GspB, Hsa	<i>S. gordonii</i>	LPxTz	Multiple substrates	39, 41, 587	
	Fap1	<i>S. parasanguinis</i>	LPxTz		652, 653	
	SrpA	<i>S. sanguinis</i>	LPxTz		460	
	SrpA	<i>S. cristatus</i>	LPxTz		216	
	Srr-1, Srr-2	<i>S. agalactiae</i>	LPxTz		520, 539	
	PsrP	<i>S. pneumoniae</i>	LPxTz		509	
Alp family ^a	α Protein	<i>S. agalactiae</i>	LPxTz	Host glycosaminoglycans	49	
	Rib/R4	<i>S. agalactiae</i>	LPxTz		556, 572	
	R28/Alp3	<i>S. pyogenes, S. agalactiae</i>	LPxTz		332, 571	
	Alp2	<i>S. agalactiae</i>	LPxTz		326	
	R proteins (R1–R4)	<i>S. pyogenes, S. agalactiae, S. dysgalactiae</i>	LPxTz		167, 649	
Pili/fimbriae/fibrils ^a	PI-1, PI-2a, PI-2b	<i>S. agalactiae</i>	LPxTz	Coaggregation, biofilm formation, phagocyte resistance; multiple substrates	336, 512	
	PI-1, PI-2	<i>S. pneumoniae</i>	LPxTz		23, 342	
	PI	<i>S. pyogenes</i>	LPxTz		157, 412	
	Fap1	<i>S. parasanguinis</i>	LPxTz		652, 653	
	SrpA	<i>S. cristatus</i>	LPxTz		216	
	HAF	<i>S. salivarius</i>	Unknown		213	
	AgB, AgC	<i>S. salivarius</i>	Unknown		639, 640	
	CspB	<i>S. salivarius</i>	LPxTz		347	
	CshA-like	<i>S. oralis</i>	LPxTz		148	
	CshA-like	<i>S. sanguinis</i>	LPxTz		148, 213	
	CshA	<i>S. gordonii</i>	LPxTz		240, 394	
	GspB, Hsa	<i>S. gordonii</i>	LPxTz		39, 41, 587	
	Uncharacterized	<i>S. intermedius, S. mutans, S. mitis, S. constellatus</i>			170, 346, 650, 658	
	Saliva-binding proteins	AgI/II family ^a	<i>S. mutans, S. sobrinus, S. gordonii, S. oralis, S. intermedius</i>		LPxTz	Salivary components (gp340, salivary glycoproteins, proline-rich proteins) gp340
Pili, fimbriae, fibrils ^a		<i>S. pyogenes, S. parasanguinis, S. intermedius, S. salivarius, S. gordonii</i>	LPxTz	145, 153, 217, 489, 641		
SsaB		<i>S. sanguinis</i>	LXXC/XXGC	Salivary components	176, 178	
FimA		<i>S. parasanguinis</i>	LXXC/XXGC	Salivary components	436	
AbpA, AbpB		<i>S. gordonii</i>	LPxTz (AbpA)	α-Amylase	92, 138, 351, 501	
Uncharacterized		<i>S. mitis, S. salivarius, S. cristatus, S. anginosus, S. parasanguinis</i>		α-Amylase	69, 529	
EP-GP binding protein		<i>S. salivarius</i>	Unknown	Extra parotid glycoprotein	531	
Fn-binding proteins	SfbI/PrtF1 ^a	<i>S. pyogenes</i>	LPxTz	Fn	219, 443, 592	
	FbaA ^a	<i>S. pyogenes</i>	LPxTz		601	
	FbaB/PFBP/PrtF2	<i>S. pyogenes</i>	LPxTz		257, 480, 603	
	SOF/SfbII ^a	<i>S. pyogenes</i>	LPxTz		311, 314, 479	
	SfbX	<i>S. pyogenes</i>	LPxTz		269	
	Fbp54 ^a	<i>S. pyogenes</i>	Anchorless		Fn	114
	ScpA (C5a peptidase) ^a	<i>S. pyogenes</i>	LPxTz		Fn	94, 96, 106
	GAPDH/SDH ^a	<i>S. pyogenes</i>	Anchorless		Fn	447
	M proteins ^a	<i>S. pyogenes</i>	LPxTz		Fn	120
	M-like proteins ^a	<i>S. pyogenes</i>	LPxTz		Fn	120
	Shr ^a	<i>S. pyogenes</i>	Anchorless		Fn	165
	FnbA	<i>S. dysgalactiae</i>	LPxTz		Fn	358, 359
	FnbB	<i>S. dysgalactiae</i>	LPxTz		Fn	358, 359
	GfbA	<i>S. dysgalactiae</i>	LPxTz		Fn	300
	SmFnB	<i>S. mutans</i>	Anchorless		Fn	406
	FBP-130 ^a	<i>S. mutans</i>	Unknown		Fn	99
	PavA-like ^a	<i>S. mutans</i>	Anchorless		Fn	407
	ScpB (C5a peptidase) ^a	<i>S. agalactiae</i>	LPxTz		Fn	96, 100
	FbsA, FbsB ^a	<i>S. agalactiae</i>	LPxTz (FbsA)		Fn	207, 535
	PavA-like/GBS1263 ^a	<i>S. agalactiae</i>	Anchorless		Fn	407
	PavA ^a	<i>S. pneumoniae</i>	Anchorless		Fn	241
	FbpA	<i>S. gordonii</i>	Anchorless		Fn	102
	CshA	<i>S. gordonii</i>	LPxTz		Fn	396
	CshA-like ^a	<i>S. sanguinis</i>	LPxTz		Fn	530
	AgI/II family ^a	<i>S. mutans, S. intermedius</i>	LPxTz		Fn	36, 455, 456

Continued on following page

TABLE 1—Continued

Protein group	Protein(s)	Species	Cell surface linkage ^b	Function(s) and/or substrate(s)	Reference(s)	
Glucan-binding proteins	GbpABCD	<i>S. mutans</i>	LPxTz (GbpC)	Dextran-dependent aggregation; glucan	26, 517, 527, 544, 558	
	Gbp2–Gbp5, Dei	<i>S. sobrinus</i>	Unknown		26, 559, 580	
Collagen-binding proteins	Cpa	<i>S. pyogenes</i>	LPxTz	Collagen	313	
	WapA	<i>S. mutans</i>	LPxTz	Collagen	162, 210	
	Cnm	<i>S. mutans</i>	LPxTz	Collagen	525	
	AgI/II family ^d	<i>S. mutans</i> , <i>S. gordonii</i>	LPxTz	Collagen	272, 368	
Plasminogen-binding proteins	Enolase	<i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>S. oralis</i> , <i>S. anginosus</i> , <i>S. mutans</i> , <i>S. salivarius</i> , <i>S. sanguinis</i>	Anchorless	Plasminogen, plasmin	44, 76, 180, 298, 302, 448, 450, 648	
	M protein ^d	<i>S. pyogenes</i>	LPxTz	Plasminogen	500	
	PAM	<i>S. pyogenes</i>	LPxTz	Plasminogen	42, 651	
	GAPDH/Plr ^d	<i>S. oralis</i> , <i>S. anginosus</i> , <i>S. agalactiae</i> , <i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>S. gordonii</i> , <i>S. dysgalactiae</i>	Anchorless	Plasminogen, plasmin	45, 179, 277, 366, 540	
	CbpE	<i>S. pneumoniae</i>	CBD	Plasminogen	22	
	Streptokinase (Ska)	<i>S. pyogenes</i>	None	Plasminogen	28	
Laminin-binding proteins	Lbp ^d	<i>S. pyogenes</i>	LXXC/XXGC	Laminin	602	
	Lsp	<i>S. pyogenes</i>	LXXC/XXGC	Laminin	149	
	SpeB	<i>S. pyogenes</i>	Anchorless/none	Laminin	251	
	Lmb ^d	<i>S. agalactiae</i> , <i>S. pyogenes</i>	LXXC/XXGC	Laminin	567, 631	
	AgI/II family ^d	<i>S. mutans</i> , <i>S. intermedius</i>	LPxTz	Laminin	81, 272, 456	
	PLBP	<i>S. anginosus</i>	LXXC/XXGC	Laminin	10	
	Cnm	<i>S. mutans</i>	LPxTz	Laminin	525	
	145-kDa protein	<i>S. gordonii</i>	Unknown	Laminin	563	
	Uncharacterized	<i>S. mitis</i>		Laminin	584	
	Fibrinogen-binding proteins	M protein ^d	<i>S. pyogenes</i>	LPxTz	Fibrinogen	245
SOF/SfbII ^d		<i>S. pyogenes</i>	LPxTz	Fibrinogen	113	
Fbp54 ^d		<i>S. pyogenes</i>	Anchorless	Fibrinogen	114	
Mrp ^d		<i>S. pyogenes</i>	LPxTz	Fibrinogen	290	
DemA/Emm ^d		<i>S. dysgalactiae</i>	LPxTz	Fibrinogen	183, 623	
FbsA, FbsB ^d		<i>S. agalactiae</i>	LPxTz (FbsA)	Fibrinogen	207, 535	
CspA		<i>S. agalactiae</i>	LPxTz	Fibrinogen (cleavage)	221	
SpaP/P1/PAc/Sr/AgB		<i>S. mutans</i>	LPxTz	Fibrinogen	36	
Uncharacterized		<i>S. gordonii</i> , <i>S. sanguinis</i> , <i>S. mitis</i> , <i>S. oralis</i>		Fibrinogen	338	
Ig-binding proteins		Sfbl/PrtF1 ^d	<i>S. pyogenes</i>	LPxTz	IgG	401
		Sib35	<i>S. pyogenes</i>	Anchorless	IgG	289
	SibA	<i>S. pyogenes</i>	None	IgG, IgA, IgM	154	
	Protein H	<i>S. pyogenes</i>	LPxTz	IgG	8, 196	
	Arp	<i>S. pyogenes</i>	LPxTz	IgA	48, 576, 577, 606	
	Sir	<i>S. pyogenes</i>	LPxTz	IgA, IgG	577	
	Enn protein	<i>S. pyogenes</i>	LPxTz	IgA	47	
	M protein ^d	<i>S. pyogenes</i>	LPxTz	IgG, IgA	120	
	M-like proteins ^d	<i>S. pyogenes</i>	LPxTz	IgG, IgA	120	
	Mrp ^d	<i>S. pyogenes</i>	LPxTz	IgG	61, 105, 576	
	FcRA	<i>S. pyogenes</i>	LPxTz	IgG	227	
	Lzp	<i>S. pyogenes</i> , <i>S. agalactiae</i>	Anchorless	IgG, IgA, IgM	434	
	Bac/β antigen ^d	<i>S. agalactiae</i>	LPxTz	IgA	229, 275, 276	
	Protein B	<i>S. agalactiae</i>	Unknown	IgA	158	
	Protein G/SpG ^d	<i>S. dysgalactiae</i>	LPxTz	IgG	155, 205, 438	
	FOG	<i>S. dysgalactiae</i>	LPxTz	IgG	425	
	MAG, MIG ^d	<i>S. dysgalactiae</i>	LPxTz	IgG	282, 283	
	DemA/Emm ^d	<i>S. dysgalactiae</i>	LPxTz	IgG	623	
	CbpA/SpsA/PspC/PbcA/Hic ^d	<i>S. pneumoniae</i>	CBD	IgA	209	
	Platelet-binding proteins	GspB, Hsa	<i>S. gordonii</i>	LPxTz	Platelets (adhesion)	41, 589
SspA, SspB		<i>S. gordonii</i>	LPxTz	Platelets (aggregation)	261	
SrpA		<i>S. sanguinis</i>	LPxTz	Platelets	460	
PAAP		<i>S. sanguinis</i>	Unknown	Platelets	233	
PblA, PblB, PblT		<i>S. mitis</i>	Unknown	Platelets	40	
Complement-binding proteins	M protein ^d	<i>S. pyogenes</i>	LPxTz	Factor H, factor H-like protein 1	243, 308	
	M-like proteins ^d	<i>S. pyogenes</i>	LPxTz	Factor H, factor H-like protein 1	294	
	FbaA ^d	<i>S. pyogenes</i>	LPxTz	Factor H, factor H-like protein 1	451	
	CbpA/SpsA/PspC/PbcA/Hic ^d	<i>S. pneumoniae</i>	CBD	Factor H	266	
	CbpA/SpsA/PspC/PbcA/Hic ^d	<i>S. pneumoniae</i>	CBD	Complement C3	95	

Continued on following page

TABLE 1—Continued

Protein group	Protein(s)	Species	Cell surface linkage ^b	Function(s) and/or substrate(s)	Reference(s)
	ScpB ^a	<i>S. agalactiae</i>	LPxTz	Complement C5a	106
	Bac/β antigen ^a	<i>S. agalactiae</i>	LPxTz	Factor H	19
	PspA	<i>S. agalactiae</i>	CBD	Inhibits complement C3 deposition; lactoferrin	407, 613
Host cell-binding proteins	BibA ^a	<i>S. agalactiae</i>	LPxTz	C4-binding protein	524
	ScpA ^a	<i>S. pyogenes</i>	LPxTz	Complement C5a	94, 645
	BibA ^a	<i>S. agalactiae</i>	LPxTz	Epithelial cells	524
	FbsA ^a	<i>S. agalactiae</i>	LPxTz	Epithelial/endothelial cells	534
	ScpB ^a	<i>S. agalactiae</i>	LPxTz	Epithelial cells	96
	Lmb ^a	<i>S. agalactiae</i>	LXXC/XXGC	Endothelial cells	600
	Spb1	<i>S. agalactiae</i>	LPxTz	Epithelial cell invasion	4
	6PGD ^c	<i>S. pneumoniae</i>	Anchorless	Epithelial cells	127
	PsaA ^a	<i>S. pneumoniae</i>	LXXC/XXGC	Epithelial cells	504
	PsrP	<i>S. pneumoniae</i>	LPxTz	Epithelial cells	509
	RrgA	<i>S. pneumoniae</i>	LPxTz	Epithelial cells	422
	PavA ^a	<i>S. pneumoniae</i>	Anchorless	Epithelial/endothelial cells	465
	CbpA/SpsA/PspC/PbcA/Hic ^a	<i>S. pneumoniae</i>	CBD	Epithelial cells	510
	PclA	<i>S. pneumoniae</i>	LPxTz	Epithelial cells	452
	Shr ^a	<i>S. pyogenes</i>	Anchorless	Epithelial cells	165
	ScpA ^a	<i>S. pyogenes</i>	LPxTz	Epithelial cells	471
	Lbp ^a	<i>S. pyogenes</i>	LXXC/XXGC	Epithelial cells	602
	R28	<i>S. pyogenes</i>	LPxTz	Epithelial cells	571
	M protein ^a	<i>S. pyogenes</i>	LPxTz	Epithelial/endothelial cells (α ₅ β ₁ integrin, Fn bridge)	118, 147
	SfbI/PrtF1 ^a	<i>S. pyogenes</i>	LPxTz	Epithelial/endothelial cells (α ₅ β ₁ integrin, Fn bridge)	219, 442, 591
	SclA, SclB (Scl1, Scl2)	<i>S. pyogenes</i>	LPxTz	Epithelial cells (α ₂ β ₁ , α ₁₁ β ₁ integrins)	86, 248, 369, 483, 484
	FBP-130 ^a	<i>S. mutans</i>	Unknown	Endothelial cells	99
	GtfG	<i>S. gordonii</i>	None	Endothelial cells	618
	HAF ^a	<i>S. salivarius</i>	Unknown		213
	Alp family ^a	<i>S. agalactiae</i>	LPxTz	Epithelial cells	30, 60, 571
	Pili, fimbriae, fibrils ^a	<i>S. agalactiae</i> , <i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>S. salivarius</i>	LPxTz	Epithelial/endothelial cells	2, 23, 139, 217, 377, 459
	AgI/II family ^a	<i>S. mutans</i> , <i>S. gordonii</i>	LPxTz	Epithelial/endothelial cells (α ₅ β ₁ integrin)	12, 427
Enzymes	HtrA	<i>S. mutans</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i>	Anchorless	Serine protease	131, 371, 537
	GAPDH, α-enolase, PGK, PGM, TPI ^{a,c}	<i>S. pyogenes</i> , <i>S. oralis</i> , <i>S. anginosus</i>	Anchorless	Glycolytic enzymes	298, 447
	GAPDH/SDH ^a	<i>S. pyogenes</i>	Anchorless	Lysozyme, cytoskeletal proteins, CD87/uPAR	277, 447
	PulA	<i>S. pyogenes</i>	LPxTz	Pullulanase	250
	SAP	<i>S. agalactiae</i>	LPxTz	Pullulanase	523
	SpuA	<i>S. pneumoniae</i>	LPxTz	Pullulanase	621
	Neuraminidase (NanA, NanB)	<i>S. pneumoniae</i>	LPxTz (NanA)	Breaks down <i>N</i> -acetyl neuraminic acid	247, 381
	Hyal1	<i>S. pneumoniae</i>	LPxTz	Hyaluronidase	46
	StrH	<i>S. pneumoniae</i>	LPxTz	β- <i>N</i> -Acetylhexosaminidase	104
	GlnA	<i>S. agalactiae</i>	LPxTz	Glutamine synthetase	583
	FruA	<i>S. mutans</i>	LPxTz	β-D-Fructosidase	77
	Dex, DexA	<i>S. mutans</i> , <i>S. sobrinus</i>	LPxTz	Dextranase	254, 632
Other adhesins	CbpA/SpsA/PspC/PbcA/Hic ^a	<i>S. pneumoniae</i>	CBD	Polymeric Ig receptor	665
	PsaA ^a	<i>S. pneumoniae</i>	LXXC/XXGC	E-cadherin	16
	Srr-1	<i>S. agalactiae</i>	LPxTz	Keratin	520
	ScaA	<i>S. gordonii</i>	LXXC/XXGC	Coaggregation	15, 305
	GRAB	<i>S. pyogenes</i>	LPxTz	α ₂ -Macroglobulin; protects against proteolysis	485
	Protein G/Spg ^a	<i>S. dysgalactiae</i>	LPxTz	α ₂ -Macroglobulin, serum albumin	7, 413
	MAG, MIG ^a	<i>S. dysgalactiae</i>	LPxTz	α ₂ -Macroglobulin, serum albumin (MAG)	281–283
	PhtA, PhtB, PhtD, PhtE	<i>S. pneumoniae</i>	LXXC/XXGC	Unknown	3
	Sip	<i>S. agalactiae</i>	Anchorless	Unknown	67
	BPS	<i>S. agalactiae</i>	LPxTz	Unknown	152

^a Protein appears more than once in the table due to multiple binding specificities.

^b LPxTz, sortase motif; LXXC/XXGC, lipoprotein consensus sequence; CBD, choline binding domain.

^c PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; TPI, triosephosphate isomerase; 6PGD, 6-phosphogluconate dehydrogenase.

The fibrils composed of CshA mediate attachment to immobilized Fn and to other oral bacteria. CshA-like proteins have also been found on the surfaces of *S. oralis* and *S. sanguinis* (148), on which they possibly function in a similar capacity.

Also, serine-rich repeat (Srr) proteins have been characterized for several *Streptococcus* species (*S. gordonii*, *S. sanguinis*, *S. parasanguinis*, *S. cristatus*, and *S. pneumoniae*) (Table 1). The Hsa (Srr) polypeptide forms surface fibrils in *S. gordonii* (588),

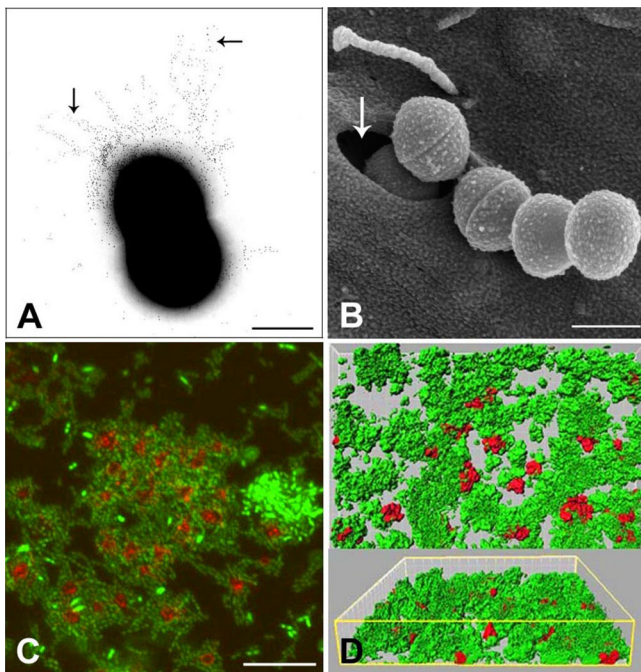


FIG. 4. *Streptococcus*-host interactions. (A) Pili (arrows) of GBS immunogold labeled with antibody generated to the backbone subunit of PI-2a. Bar, 0.5 μm . (B) Internalization of GAS by cultured epithelial cells showing formation of caveolae (arrow) containing a streptococcal cell being engulfed. Bar, 1 μm . (Image courtesy of Manfred Rohde, GBF-German Research Centre for Biotechnology, Braunschweig, Germany, reproduced with permission.) (C) Aggregation of human platelets (red) (phalloidin stained) by *S. sanguinis* (green) (fluorescein isothiocyanate stained). Bar, 20 μm . (Image courtesy of Steve Kerrigan, Royal College of Surgeons in Ireland, reproduced with permission.) (D) Flow cell biofilm (24 h) showing xy perspective and three-dimensional projection by confocal imaging of *S. gordonii* (green) and *Veillonella atypica* (red) growing in human saliva. Under salivary flow conditions, *V. atypica* is unable to form monospecies biofilms, but it is able to form mixed-species biofilms with *S. gordonii*. (Image courtesy of Rob Palmer, National Institute of Dental and Craniofacial Research, NIH, Bethesda, MD, reproduced with permission.)

while SrpA has been shown to comprise long (400-nm) fibrils in *S. cristatus* and to confer coaggregation capabilities (216). Because these fibrillar structures presumably confer a selective advantage to streptococci colonizing the host, perhaps initially by mediating adherence interactions, they are important to consider as potential targets for inhibitors or vaccines. Unfortunately, it has repeatedly proved technically challenging to identify the genes necessary for the production of these structures, except for the few instances described above. However, sequencing of *Streptococcus* genomes has thrown up a considerable number of surprises, not the least being the identification of pilus islands (PI) in the pyogenic group and recently in *S. sanguinis*. Studies of pili have been more fulfilling and provide much promise for the development of new protein vaccines.

Pili

Pili are thicker (3 to 10 nm in diameter) and longer appendages than fibrils, typically extending 1 to 3 μm from the bacterial cell surface (Fig. 4A). Interestingly, while they have been

reported for just two species of oral streptococci, *S. parasanguinis* and *S. salivarius* (166, 214), they have been found in the three major streptococcal human pathogens, namely, *S. agalactiae* (336), *S. pyogenes* (412), and *S. pneumoniae* (29) (Table 1). The precise composition of *S. salivarius* pili remains to be defined, but the structural component of *S. parasanguinis* pili has been identified as a serine-rich repeat protein, designated Fap1 (652, 653). The genes encoding pili of the pathogenic streptococci are found in discrete loci, termed PI. To date, three PI have been identified for *S. agalactiae* (512), two have been identified for *S. pneumoniae* (23), and nine have been identified for *S. pyogenes* (157), with the latter occurring within the Fn-binding, collagen-binding, T-antigen (FCT) region that forms part of the Lancefield T-serotyping system. While the exact composition varies, each PI comprises genes that encode LPxTz family proteins, which are linked to cell wall peptidoglycan precursors via sortase cleavage between T and z (see below). These form the physical structure of the pilus and can be divided into the “backbone” subunit, which forms the shaft of the pilus, and one or two “ancillary” subunits, which appear intermittently. There are also genes encoding transpeptidase enzymes of the sortase C subfamily that function to polymerize the protein subunits (see reference 469 for a detailed model of pilus assembly). Much attention has recently been given to such pili, as the protein subunits have been shown to elicit protective immunity against the corresponding pathogen in mouse models of infection, making them potential vaccine candidates (187, 376, 412). Such strategies have particular promise for *S. agalactiae*, where pilus protein conservation across a large number of clinical isolates has been shown to be relatively high (383).

Pili have also been implicated as putative virulence factors. Using recombinant protein subunits or whole bacterial cells, pili have been associated with mediating adhesion to a wide variety of host epithelia including cells derived from the lungs, cervix, nasopharynx, tonsils, and intestine (2, 23, 139, 459). In addition to mediating cell attachment, pili of *S. agalactiae* (group B *Streptococcus* [GBS]) have been shown to promote the invasion of human endothelial cells (377) and may facilitate paracellular translocation across the epithelial barrier (459). Immunomodulatory capabilities have also been associated with pili. Those of *S. pneumoniae* have been shown to promote inflammatory cytokine release (29), while *S. agalactiae* pili confer resistance to phagocytic killing (378). The pili of *S. pyogenes* promote bacterial aggregation via binding to the salivary component gp340, a process that may lead to increased bacterial clearance (145). Similarly, pili of *S. parasanguinis* were shown to bind salivary molecules adsorbed onto the surface of hydroxyapatite, an in vitro model of the tooth surface (153, 653).

Because of the inherent difficulties associated with their dissociation and purification, relatively little is known about the actual structures of pili. There have, however, been some recent breakthroughs. Advanced microscopy techniques, including atomic force and cryo-electron microscopy, have been utilized to visualize pneumococcal pili (156, 237). From these data, a model has been proposed in which protofilaments of backbone protein organize into coiled-coil structures to which “clusters” of ancillary proteins are attached intermittently (237). An ancillary protein component of *S. agalactiae* pili was

crystallized (320) and was shown to have an IgG-rev fold. Such a conformation has been found in microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) of other gram-positive bacteria and contributes to the adhesive capabilities of these proteins. The crystal structure of a backbone subunit from *S. pyogenes* has also been resolved (287). From these data, backbone subunits were shown to organize into filamentous structures supported by sortase-catalyzed intermolecular bonds and by self-generated intramolecular isopeptide bonds. This organization has been proposed to stabilize the thin pilus structures, enabling them to withstand the tensile forces associated with adhesion to host tissues. Interestingly, sequence comparisons have identified similar intramolecular isopeptide bonds in other surface adhesins, including PFBP of *S. pyogenes*, FnbB of *S. dysgalactiae*, and Cna of *Staphylococcus aureus* (287).

Backbone and ancillary subunits from each PI have been shown to elicit protective immunity against GBS in a neonatal mouse model of immunization (376, 383, 512), and a recent analysis of pilus distribution and conservation found that 94% of 289 clinical isolates expressed pili on their surface. Those studies also showed that a vaccine comprising just three pilus protein subunits could confer protection against 94% of GBS strains currently found in the United States and Italy (383). A pilus-based vaccine, therefore, has great potential for development as an effective universal vaccine against GBS disease.

Sortases

Many streptococcal surface proteins are attached to the bacterial cell wall by membrane-associated transpeptidases of the sortase family (comprehensively reviewed in reference 384). These enzymes function by cleaving target proteins at a C-terminal cell wall sorting signal (CWSS), typically LPxTz, to form an acyl enzyme intermediate. This is then resolved by the nucleophilic attack of amino groups, often provided by the lipid II precursor of peptidoglycan, which is subsequently incorporated into the cell envelope via the transglycosylation and transpeptidation reactions of cell wall synthesis. Target proteins of sortases are initially expressed in a precursor form bearing at least two topogenic sequences: an N-terminal signal peptide and the C-terminal CWSS. The signal sequence directs the protein for translocation across the plasma membrane, typically via the Sec secretion system, until the CWSS is reached. At this point, the protein is held in the membrane by a stretch of hydrophobic amino acids immediately downstream of the CWSS. The CWSS is then available for cleavage by the membrane-bound sortase, resulting in a protein that is exposed on the bacterial surface while securely embedded within the cell envelope.

Sortases have been found in virtually all gram-positive bacterial genomes available to date. Based on phylogenetic analyses, two recent studies have proposed their classification into either four (subfamilies A to D) or five (SrtA, SrtB, and families 3 to 5) subfamilies (109, 140). The sortase A (SrtA) subgroup contains the archetypal SrtA from *Staphylococcus aureus*, and virtually all gram-positive bacteria analyzed to date possess a single *srtA* gene. Often referred to as the "house-keeping" sortase, this enzyme typically anchors the majority of surface proteins with a CWSS expressed by a given bacterium.

As such, SrtA target proteins are abundant and functionally diverse. The genes encoding SrtA-type enzymes are never proximal to their substrates, and SrtA enzymes show a preference for an LPxTG CWSS motif. Members of the sortase B (SrtB) subgroup can be found in a small number of gram-positive bacilli and cocci. The prototype SrtB is from *S. aureus* and acts upon IsdC, a protein involved in heme-iron acquisition. Similarly, the genes encoding other SrtB members occur in the same operon as their target proteins and are involved in iron uptake. SrtB enzymes possess three amino acid regions that are not present in SrtA, and the CWSS motifs recognized by SrtB include NPQTN (*S. aureus*), NPKSS (*Listeria* species), and NPKTG (*Bacillus anthracis*). The sortase C (SrtC) subgroup (or subfamily 3) has the highest number of members. Multiple copies of genes encoding SrtC are often found per genome, and they are frequently located adjacent to their substrates. As for SrtA, SrtC enzymes recognize the LPxTG CWSS motif, often followed by a second G residue, but act upon a much smaller group of proteins than SrtA. Furthermore, while SrtA has an N-terminal stretch of hydrophobic amino acids, similar to type I membrane proteins, SrtC enzymes have a hydrophobic C terminus that could act as the membrane anchor, as for type II membrane proteins. Members of this subgroup have recently been found in pathogenic streptococci including *S. pyogenes*, *S. pneumoniae*, and *S. agalactiae*. In these genomes, the *srtC* genes occur within loci that encode pili, putative virulence factors, and function to covalently link pilus protein subunits to form the filamentous pilus structure. Subfamily D sortases (or subgroups 4 and 5) have been found in bacilli, clostridia, and actinomycetales. Their target proteins often have enzymatic functions and are characterized by atypical CWSS motifs, including LPxTA and LxATG.

Despite extensive knowledge of the biochemical reactions that result in the covalent linkage of secreted polypeptides to the cell wall peptidoglycan, the control mechanisms operating on sortase-catalyzed linkage and on surface protein localization are not well understood. There is evidence for a membrane microdomain in *S. pyogenes*, enriched in anionic phospholipids, within which proteins such as SpeB (cysteine protease) are secreted and folded (507). This microdomain, termed the ExPortal, was suggested to be the primary cellular site for protein secretion, accumulating high concentrations of translocons of the general secretion (Sec) pathway in addition to accessory proteins, e.g., HtrA, necessary for postsecretion folding (506). Since, however, the localization patterns of surface proteins are quite distinct, there must be additional signals that play a role in targeting polypeptides to discrete sites. One such signal appears to be the leader peptide (signal sequence), which, in *S. pyogenes*, directs the secretion of proteins to different subcellular regions. The signal sequence of M protein directs secretion at the division septum, whereas that of PrtF preferentially promotes the secretion of this polypeptide at the old pole (85). In those studies, SecA was shown to be distributed throughout the periphery of *S. pyogenes*, thus arguing against evidence for a single ExPortal. More recently, evidence has been obtained to show that sortase is distributed to the new division septum, colocalizing with areas of M protein anchoring (490). This supports the notion that the sorting process is dynamic and linked closely with cell division. The control of sortase activity is also of interest, and it was suggested that the

C-terminal peptide that remains as a result of sortase-catalyzed cleavage may play a subsequent role in modulating the expression or secretion of other proteins (J. Kreth, A. Khammanivong, Y. Lei, Y. Zhang, and M. C. Herzberg, presented at the International Association for Dental Research 85th General Session, New Orleans, LA, 21 to 24 March 2007). Overall, this area of study is of significant interest since the regulation of surface protein expression is closely linked to the ability of streptococci to colonize and invade tissues.

STREPTOCOCCUS ADHESINS

There are three ways in which streptococcal proteins may be held at the cell surface. First, they may be covalently anchored through the C terminus to the cell wall peptidoglycan. Second, they may be tethered to the cell membrane through N-terminal modifications with lipid (lipoproteins). Third, they may be retained on the cell surface, or bound back to the cell surface, through noncovalent interactions with cell surface components such as other proteins or polysaccharides. Many of the polypeptides listed in Table 1 belong to the superfamily of gram-positive bacterial proteins that are linked to the cell wall. These contain a C-terminal motif, the consensus for which is LPxTz, followed by a hydrophobic region and a charged tail. The motif is recognized by sortase A, for which there is one gene on the streptococcal chromosome. Since it is thought that all C-terminal protein linkage to the cell wall peptidoglycan occurs through the activity of SrtA (see above), there must be strong evolutionary selection against mutation within *srtA*. Streptococci appear to differ considerably in the numbers of LPxTz proteins produced on their cell surfaces. Genomic analyses show that whereas there are 33 genes encoding potential cell wall-anchored proteins in *S. sanguinis* SK36, *S. mutans* UA159 has only 6, *S. pyogenes* M1 has 13, *S. gordonii* CH1 has 20, and *S. agalactiae* NEM316 has 21 (161, 194, 657). However, there is always some redundancy in cell wall protein genes, and within the 33 genes in *S. sanguinis*, there are 9 paralogous genes across three families (657). These observations underscore the notion that streptococci utilize different complements of adhesins in order to successfully colonize the host.

Cell Wall-Anchored Polypeptides

Most of the adhesins listed in Table 1 are of the LPxTz superfamily. These adhesins come in many sizes, designs, and potential conformations (e.g., α -helical, coiled coil, and β -sheet). Within the superfamily, there are proteins that seem to be assembled, at least in part, from a relatively defined range of modules that are related in primary sequence and in adherence functions. An overriding feature of these polypeptides is that they contain amino acid repeat blocks or motifs. These may be short sequences, for example, the five blocks of 14 amino acid (aa) residues making up the A repeats of the M6 protein (Fig. 5), or highly repeated motifs, such as the 113 repeats of SASTSASVSASE in the *S. gordonii* Hsa protein (Fig. 5). Alternatively, they may comprise much larger repeats, for example, the 13 repeat blocks of 101 aa residues within *S. gordonii* CshA (398). The genes encoding these polypeptides are highly subject to intragenic recombination, intergenic recombination, gene duplication, and point mutation as a result

of host selective pressures. For example, 34 distinct alleles of the Fn-binding protein SfbI (Fig. 5) have been found in 54 strains of *S. pyogenes* (610) as a result of horizontal gene transfer. The N-terminal aromatic-amino-acid-rich domain has a high degree of sequence variability, while the deletion or duplication of repeat units has resulted in variable numbers of proline-rich (P) repeats (1 to 11 repeats) and Fn-binding (Fnb) repeats (1 to 5 repeats) (Fig. 5). This generates antigenic variation and also variable functional capabilities. Different lengths of repeat blocks also elicit different antibody repertoires (199), so lower-repeat-number variants with fewer epitopes might be able to escape antibodies generated to higher-repeat-number variants.

The structures of seven streptococcal cell wall-anchored proteins are depicted in Fig. 5. They have been selected to cover many of the different design features of streptococcal proteins. Each of the precursor proteins carries a leader (signal) peptide, usually about 30 to 40 aa residues in length but much longer (up to 90 aa residues) for some polypeptides, e.g., Hsa (Fig. 5). These leader sequences direct the respective proteins to the primary Sec secretion apparatus or to an accessory secretion system (Sec2) dedicated to exporting specific subsets of proteins (499, 670).

M proteins. GAS species are classified into 180 *emm* types based on the sequence of the hypervariable (N-terminal) region of the M protein. M protein typically consists of four repeat regions (Fig. 5), the A repeats of which are hypervariable and the B repeats of which are semivariable. Physicochemical studies suggested that M proteins form entirely α -helical coiled-coil dimers and are in an extended conformation on the cell surface as hair-like projections (424). Secondary structure predictions indicated that the N-terminal regions are stabilized by antiparallel interactions, so this may contribute to cell-cell aggregation (174). Many of the hypervariable repeat regions from different M proteins bind human C4b-binding protein (C4BP), a plasma protein that inhibits complement activation (17), plasminogen, IgA, IgG, and factor H (389). The B repeats bind fibrinogen, human serum albumin (HSA), and IgG, while the C repeats bind factor H, HSA, and the membrane cofactor protein CD46 (188, 433). Different M proteins have the ability to interact only with various subsets of the human plasma proteins specified, and A and B repeats vary in most of the known GAS serotypes. Strong sequence similarities to the C repeats are found in Arp polypeptides (M-like proteins), but the so-called B repeats in Arp are not similar to those in M6 or other serotypes (Table 1). Structural irregularities and instabilities throughout the coiled-coil structure of the M1 protein enhance fibrinogen binding, thus promoting proinflammatory and antiphagocytic activities (399). Soluble M1 protein released from *S. pyogenes* is a potent inducer of T-cell proliferation and the release of Th1-type cytokines. This leads to the suggestion that it is also a novel streptococcal superantigen contributing to excessive T-cell activation and inflammatory responses during invasive streptococcal infections (445). The pathological inflammatory response is believed to be enhanced by IgG antibodies to the C repeats (Fig. 5), complexing with fibrinogen and activating Fc γ II receptors on neutrophils to release heparin-binding protein, resulting in vascular leakage (285).

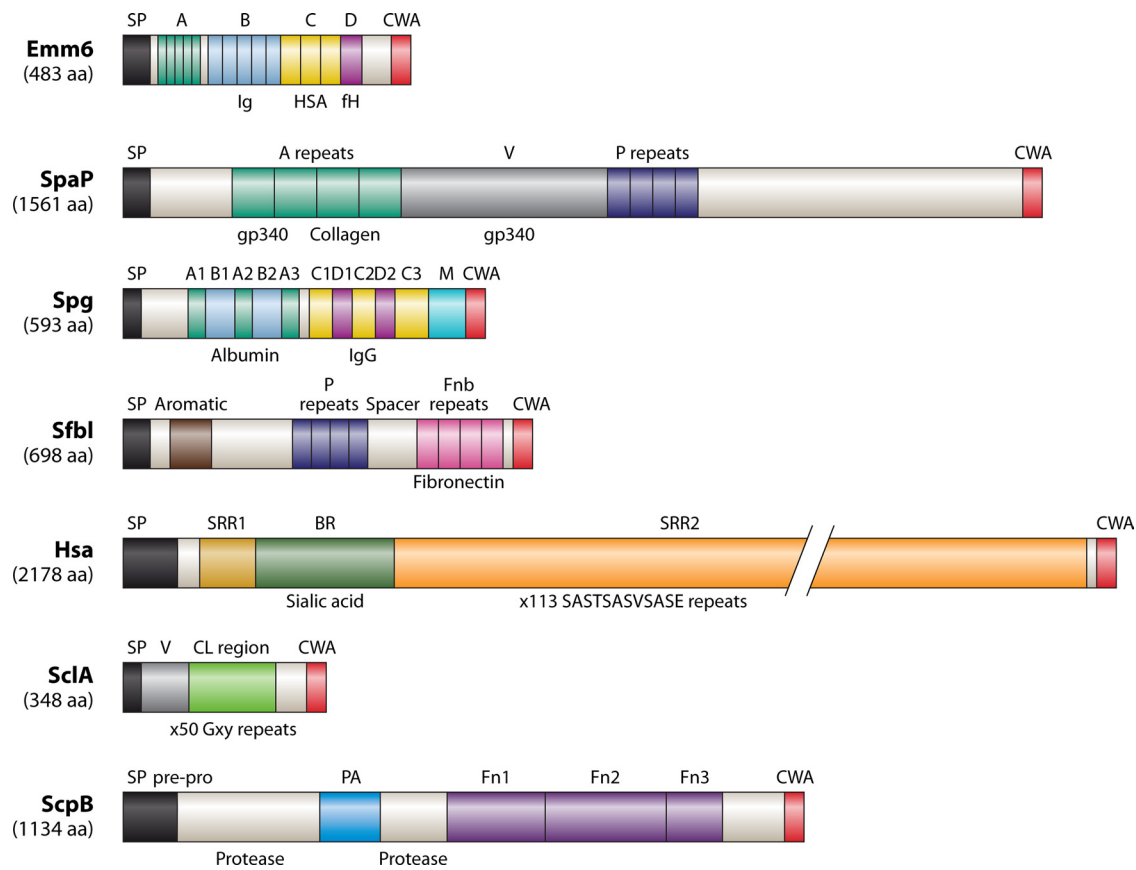


FIG. 5. Structural features of seven streptococcal cell surface proteins that function in adherence and colonization. Emm6, *S. pyogenes*; SpaP, *S. mutans*; Spg, *S. dysgalactiae*; SfbI, *S. pyogenes*; Hsa, *S. gordonii*; SclA, *S. pyogenes*; ScpB, *S. agalactiae*. Precursor polypeptides are drawn N terminal (left) to C terminal (right), and all of the proteins are thought to be held at the cell surface through covalent cell wall anchorage (CWA) via a specialized C-terminal motif (see text). Leader (signal) peptides (SP) are cleaved at conventional sites by signal peptidase I. Specific structural features and amino acid residue repeat block regions are indicated (see descriptions in the text). Like-shaded regions across the different proteins indicate only similarities in amino acid composition or predicted secondary structure, e.g., α -helical coiled coil, and not sequence homologies. Conversely, amino acid residue repeat blocks within a polypeptide, e.g., SpaP, are highly conserved. Some of the substrates bound by the polypeptides, and the approximate locations of the binding sites, are indicated below each structure. fH, factor H; gp340, cysteine-rich scavenger protein (salivary agglutinin).

AgI/II polypeptides. Most indigenous streptococci found in the oral cavity express cell surface polypeptides of the AgI/II family. These have been shown to interact with multiple host environmental receptors such as collagen, Fn, laminin, and other oral microorganisms, e.g., *Actinomyces naeslundii*, *S. oralis*, *Porphyromonas gingivalis*, and *Candida albicans* (271). It was suggested, therefore, that these proteins contribute to initial adherence as well as to microbial community development. A major receptor for AgI/II family proteins is gp340, a highly glycosylated (~25% carbohydrate) innate defense molecule produced at mucosal surfaces (466) and involved in the regulation of cellular immune responses (59) and epithelial differentiation (288). In the fluid phase, gp340 promotes bacterial aggregation and clearance, but when surface immobilized, it provides a receptor for streptococcal adherence (62). AgI/II polypeptides interact with gp340 oligosaccharides and with peptide backbone sequences (52, 263). The AgI/II polypeptides from oral streptococci contain between 1,310 and 1,653 aa residues, while the genes present in some strains of *S. pyogenes* and in *S. agalactiae* encode polypeptides in the range of 863 to 1,352 aa residues. The overall structure of AgI/II

polypeptides from different streptococci is conserved, with ligand-binding domains assigned to alanine-rich (A) and central (V) regions and to a C-terminal region downstream of the proline-rich (P) region (Fig. 5). The N-terminal region including the A repeats is predicted to form α -helical coiled-coil structures similar to M protein. The V region (approximately 370 aa residues in SpaP) is predicted to carry a lectin-like trench for carbohydrate binding (611). The P region carries repeats of 39 aa residues rich in proline and is essential for the secretion and stability of AgI/II (541). Adhesive and immunodominant epitopes of AgI/II have been identified and enabled the development of pilot synthetic peptide inhibitors of bacterial adherence. One of these, a synthetic 20-aa-residue peptide designated p1025, comprising 1,025 to 1,044 aa of AgI/II from *S. mutans*, blocks the binding of streptococci to gp340 (292). Epitopes within the A and P regions are in close proximity in native AgI/II (622), and so it is believed that the A and P regions interact to orientate the V region to bind oligosaccharides. AgI/II-binding domains for *P. gingivalis* are discussed below (see Community Development).

Ig-binding proteins. A number of Ig-binding proteins (Table 1) contribute to the ability of GAS to escape detection by the immune system. The proteins include M protein; the M-like proteins Enn, Mrp, and protein H; IgA receptor protein (Arp); streptococcal Ig receptor (Sir); streptococcal Ig-binding protein from GAS (SibA); and SfbI. All of these proteins contain leucine zipper motifs that consist of leucine residues spaced 6 or 7 aa residues apart. The Lzp protein is found in GAS and GBS and is a 66-kDa protein with 24 leucine zipper motifs and a signal peptide but no LPxTz motif. It reacts with light chains of human IgG and IgA and heavy chains of IgG and IgM. Protein H, SfbI, and Mrp bind only IgG, while Arp, Sir, and SibA bind IgA and IgG. Protein H has the highest affinity for IgG (1.6×10^{-9} M), while the affinity of Lzp for IgG is 5.5×10^{-8} M. Lzp binds several isotopic IgGs with high affinity and also binds to itself and forms multimers on the cell surface. Like protein H (173), Lzp binds a wide range of proteins (434). Protein G (Spg) (Fig. 5) (57) and FOG (425) contribute to the accumulation of IgG on the surfaces of group C and group G streptococci. FOG has no homology to the IgG-binding sequences of protein G. Protein G binds all four IgG subclasses, while FOG does not bind IgG3. The interaction with protein G ablates the ability of IgG to bind C1q, thus preventing the activation of the classical pathway of complement. The alanine-rich E region of Spg (Fig. 5) binds α_2 -macroglobulin, which is a protease inhibitor and immunoregulator. This occurs independently of IgG binding, and of HSA binding, to the three- α -helix-containing B1B2 region (Fig. 5). The IgG-binding region of Spg is similar in sequence to the IgG-binding regions of the MIG and MAG proteins, but there is no homology toward the N terminus.

The *S. equi* M protein is known as fibrinogen binding protein and binds to the interdomain region of IgG Fc (350). The same regions are recognized by staphylococcal protein A and by protein G. The unrelated IgA-binding proteins Sir22 (GAS), beta-protein (GBS), and SSL27 from *S. aureus* all bind the Fc domain interface in human IgA (481).

Fn-binding proteins. Fn-binding proteins are expressed by all streptococci (Table 1), but the proteins differ in their binding affinities. Some are able to bind soluble Fn with high affinities in the nM range, while others appear not to be able to bind soluble Fn and attach only to Fn immobilized onto a surface (396). Most of the Fn-binding proteins are anchored to the cell wall peptidoglycan through the LPxTz motif (Table 1), although some are classed as anchorless adhesins (see below). The Fn-binding proteins attach bacteria to the ECM, which acts as a bridge between streptococci and host cells. There are at least 11 Fn-binding proteins in *S. pyogenes* (310), including SfbI (PrtF1) (Fig. 5), protein F2 (PrtF2/FbaB/PFBP), serum opacity factor (SOF/SfbII), FbaA (601), and several different M proteins. The expression of Fn-binding proteins is highly regulated in response to environmental factors (312). The binding of Fn by these proteins is associated mainly with sequences within the amino acid repeat blocks toward the C-terminal end of the polypeptide (Fig. 5). The numbers and sizes of these blocks vary between different proteins. SfbI contains four blocks of 37 aa residues, and they each contain the core consensus sequence ED(T/S)(X,7-10)GG(X,4)(I/V)(D/E)(F/I/T) for binding Fn, which is also found in many of the other proteins with Fn-binding repeats (Table 1). However, regions

upstream of the repeat blocks have been shown to be involved secondarily in binding Fn, and in SfbI, the upstream spacer region (Fig. 5) is able to bind Fn when expressed as a separate polypeptide (593). The N-terminal aromatic domain of SfbI (Fig. 5) may provide some specificity in the recognition of glycosylated receptors or carbohydrate repeat structures. The region has homology to an aromatic sequence comprising YG repeat blocks of approximately 20 aa residues found within the C-terminal repeating unit of glucosyltransferases (GTFs) (190). The YG repeats are also found in *S. mutans* GBPs (25), *Clostridium difficile* toxin, and the *S. pneumoniae* autolysin LytA. Polypeptides such as *S. gordonii* CshA, which bind only to immobilized Fn, do not contain the core consensus sequence (398). In addition, C5a peptidases of *S. pyogenes* (ScpA) and *S. agalactiae* (ScpB) (Fig. 5) are able to bind Fn with high affinity (96, 595), but this is not associated with the protease cleavage site or with Fn-binding repeats (the repeats shown in Fig. 5 are Fn type III domains). There is therefore still much to be learned about the molecular mechanisms involved in interactions of cell surface proteins with Fn and other ECM molecules.

Serine-rich repeat polypeptides. Serine-rich repeat (Srr) glycoproteins have been found in oral streptococci, pathogenic streptococci, staphylococci, and lactobacilli (Table 1). These are characterized by containing multiple serine-rich repeats running through approximately 75% of the polypeptide. A unique N-terminal region is thought to be held out from the cell surface via a stalk-like structure generated by the O-glycosylated repeats (587). The Hsa polypeptide from *S. gordonii* DL1 (Fig. 5) is one of two alleles encoding Srr proteins in this species, the other being GspB (41). Like all Srr proteins, Hsa contains two repeat regions, with the smaller repeat region at the N terminus being flanked by two nonrepeated regions. The latter are diverse, and the nonrepeat II region may be basic (Fig. 5) or acidic (pI < 6.0). The pI value may be important in directing this region to binding host receptors. The B region in Hsa, GspB, and SrpA directs the recognition of sialic acid oligosaccharides (39, 460) found on epithelial cells, platelets, and salivary glycoproteins. Isogenic mutants in Srr protein genes are correspondingly deficient in adherence to host cells (261) and the salivary pellicle (653). The Srr protein genes are found at loci containing additional genes encoding glycosylation enzymes and an alternative secretion system. There is a core region of seven genes that are conserved in every genome that contains an Srr protein gene (670). The rest of the locus contains genes encoding glycosyltransferases, but these genes may also be at other sites on the chromosome. The diversity of glycosyltransferases produced across streptococci ensures that glycolytic modifications to these proteins are structurally and antigenically distinct. The presence of an alternative secretion system (SecA2) has also sparked interest in novel export functions, with evidence that the glycosylation of Fap1 in *S. parasanguinis* is linked to secretion and that the Sec2 system in *Listeria monocytogenes* is associated with the secretion of virulence factors and of proteins like superoxide dismutase that do not possess conventional signal sequences (18, 499). Interestingly, while genes encoding Srr proteins have been identified for a wide range of streptococci (Table 1), they have not yet been found for *S. pyogenes*. Clearly, the selection pressures for the retention of a locus of approximately 20 kb encoding a

surface protein and a dedicated secretion and modification system must be high, suggesting that the expression of Srr polypeptides by oral streptococci and GBS must be critical to their successful colonization.

Collagen-like proteins. Collagen-like proteins are characterized by carrying a conserved collagen-like region and a hyper-variable N-terminal portion (484). There are two genes encoding collagen-like proteins in *S. pyogenes*, designated SclA (Scl1) and SclB (Scl2) (Table 1). The transcription of *sclA* is upregulated by the transcriptional regulator Mga, while *sclB* is downregulated. In addition, slipped-strand mispairing at sites containing pentanucleotide noncoding repeats leads to phase variation of SclB (483). Orthologs of these genes have not been found in any of the *Streptococcus* genomes sequenced to date, except *S. equi* (closely related to *S. pyogenes*). The collagen-like sequences are comprised of Gxy triplet amino acid residue motifs, and there are 50 of these contiguous repeats in SclA (Fig. 5) (369). The noncollagenous globular domain of SclA binds factor H (87) and apolipoprotein B, a component of low-density lipoprotein (210). The collagen-like region has the functional properties of human collagen, interacting with $\alpha_2\beta_1$ integrin and activating intracellular signaling pathways (248). Interestingly, proteins containing the collagen-like sequences (Gxy triplet motif) are found in *S. pneumoniae*, *Clostridium perfringens*, and *Haemophilus* species. This suggests that this is a well-conserved sequence distributed widely across bacteria, possibly providing extension, flexibility, and additional functionality to surface protein modules.

Peptidases. A number of hydrolytic enzymes such as glycanases, glycosidases, proteinases, and peptidases are secreted by streptococci. Some of these carry the LPxTz motif for covalent cell wall anchorage, and some do not and are released into the environment (Tables 1 and 2). A dipeptidase from *S. gordonii* is secreted and released but carries no signal peptide (195). Clearly, there is still a limited understanding of the molecular mechanisms of protein secretion in streptococci. Also, it is apparent from genomic sequencing data that there are numerous genes encoding LPxTz polypeptides with potential proteolytic activities based on homology searches, which are yet to be characterized. However, GAS and GBS both produce a C5a peptidase (Scp), a cell wall-anchored LPxTz protein that specifically inactivates complement factor C5a (Fig. 5). This factor is normally a chemotactic peptide that attracts polymorphonuclear neutrophils, which are critical for phagocytosis. Scp is a subtilisin-like protease with a 68-aa-residue prosequence that must be removed to produce active Scp (Fig. 5). The PA domain is shared by other proteases such as the *Lactococcus* cell wall-associated protease, and there are three Fn type III repeats in the C-terminal region. It is thought that the Pro- and Gly-rich sequences within these repeats are α -helical and could push the protein and active-site region out from the cell surface. Two RGD (integrin recognition) sequences could interact with cellular receptors and increase Scp activity through conformational changes (70).

Anchorless Adhesins

The majority of streptococcal surface proteins anchor through their C termini via an LPxTz motif. There are, however, a small group of proteins that bind to the cell surface but

possess no recognized anchor. Such proteins also frequently lack an N-terminal signal sequence. The mechanism by which these so-called “anchorless adhesins” are exported from the cytoplasm to the cell surface is not understood. However, many can be removed by chaotropic agents (129), implying that they are likely bound to the cell surface through less-defined charge or hydrophobic interactions.

The anchorless adhesins have not been grouped together as a family in Table 1 because they are structurally and functionally diverse and have a wide range of adherence properties. A large proportion of the anchorless adhesin family comprises proteins with enzymatic functions. Five of the streptococcal anchorless adhesins identified to date are glycolytic enzymes typically found in the cytosol, namely, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), α -enolase, phosphoglycerate kinase, phosphoglycerate mutase, and triosephosphate isomerase (298, 447). Of these, GAPDH and α -enolase are the best characterized. α -Enolase is the major plasmin- and plasminogen-binding protein of streptococci (Table 1), although it has also been associated with binding to mucin MG2 for *S. mutans* (180). Plasminogen can be converted following cleavage by plasminogen activators to the serine protease plasmin. This in turn can degrade ECM proteins. Thus, surface-associated plasmin has been proposed to facilitate bacterial invasion and dissemination through epithelial barriers.

GAPDH (variously named SDH and Plr in GAS) has been described for several species of *Streptococcus* (Table 1) and exhibits binding to a broad spectrum of extracellular targets, including the matrix proteins plasmin, plasminogen, Fn, and fibrinogen. Given its multiple binding specificities, GAPDH is therefore likely to make a significant contribution to the colonization capabilities of streptococci. Furthermore, GAPDH has been shown to interact with the pharyngeal cell cytoskeletal proteins actin and myosin (447, 540) and with urokinase plasminogen activator receptor (277), factors that may contribute to the modulatory effects of GAPDH in triggering host cell internalization by GAS (as described elsewhere). In addition to their adhesive and glycolytic functions, another interesting property of the five anchorless enzymes described above is that they function as a complex in the production of ATP (164). This has important implications for host modulatory effects, as extracellular ATP is able to bind P2X₇ receptors on the surface of immune and epithelial cells and induce apoptosis (135, 660). Thus, an ability to produce extracellular ATP on the cell surface provides an opportunity for streptococci to manipulate host cell behavior and, potentially, the progression of infection.

Other enzymes within the anchorless adhesin family include GtfG, SpeB, and HtrA. GtfG of *S. gordonii* is a GTF responsible for the synthesis of α -1,3- and α -1,6-linked glucans. Similar to GTFs of other streptococci (Table 2), GtfG is secreted, but a proportion of this protein has been shown to bind back to the cell surface via its C terminus (626). The regulator Rgg (see below) controls *gtfG* transcription, and levels of cell-associated GtfG have been shown to influence *S. gordonii* adhesion to host surfaces and dispersal (626). SpeB is a potent cysteine protease known to play a significant role in GAS virulence, being able to degrade host proteins and activate interleukin-1 β (IL-1 β). Originally identified as a secreted product, SpeB was also found to become associated with the cell surface, possibly via its propeptide moiety (251). In this form, SpeB mediates

TABLE 2. Secreted factors and transporters

Protein group	Protein(s)	Species	Function(s) and/or substrate(s)	Reference(s)
Glucosyltransferases (secreted)	GtfB, GtfC, GtfD	<i>S. mutans</i>	Glucan synthesis	26, 533, 659
	GtfB, GtfP	<i>S. sanguinis</i>		244, 657
	GtfG	<i>S. gordonii</i>		628
	GtfI, GtfS, GtfT, GtfU	<i>S. sobrinus</i>		192, 211, 212, 420, 519
	GtfR	<i>S. oralis</i>		175
	GtfJ, GtfK, GtfL, GtfM	<i>S. salivarius</i>		189, 191, 553
Fructosyltransferases (secreted)	SacB/Ftf	<i>S. mutans</i>	Fructan synthesis	6
	Ftf	<i>S. salivarius</i>		487
Hemolysins (secreted)	Hemolysin III	<i>S. mutans</i>	Erythrocytes	6, 407
	CyIE	<i>S. agalactiae</i>		468
	SLO, SLS	<i>S. pyogenes, S. dysgalactiae</i>		13, 51, 575
Other degradative enzymes (secreted)	DNase A–DNase D	<i>S. pyogenes</i>	DNA	13
	Hyaluronidase	<i>S. pyogenes, S. pneumoniae</i>	Hyaluronic acid	236, 482
	EndoS	<i>S. pyogenes</i>	Endoglycosidase, IgG	108
	SpeB	<i>S. pyogenes</i>	IgG (cleavage)	108
Toxins (secreted)	SMEZ, SMEZ-2, SMEZ-3	<i>S. pyogenes</i>	Superantigens	182, 286, 470
	SSA	<i>S. pyogenes</i>		14, 410
	SpeA, SpeC, SpeG, SpeH, SpeI, SpeJ, SpeK, SpeL, SpeM	<i>S. pyogenes</i>		14, 407, 470
	NADase	<i>S. pyogenes</i>	NAD ⁺ -glycohydrolase; promotes survival and proliferation	66
	Pneumolysin	<i>S. pneumoniae</i>	Cytolysis	107
Other secreted factors	Streptokinase (Ska)	<i>S. pyogenes, S. dysgalactiae</i>	Plasminogen	379, 407
	Mac	<i>S. pyogenes</i>	Inhibits opsonophagocytosis; CD11b, CR3	339, 407
	SIC	<i>S. pyogenes</i>	Inhibits complement-mediated lysis	9
	Sg-xPDPP	<i>S. gordonii</i>	X-prolyl dipeptidyl-peptidase	195
Transporters	PiuBCDA/PiaABCD	<i>S. pneumoniae</i>	Fe	71, 73
	FhuBDGC	<i>S. pneumoniae</i>	Fe	467
	PitADBC	<i>S. pneumoniae</i>	Fe	72
	FtsABCD	<i>S. pyogenes</i>	Fe	218
	SiaABC/HtsABC	<i>S. pyogenes</i>	Fe	32, 340
	SiuADBG	<i>S. pyogenes</i>	Fe	411
	SsaCBA	<i>S. sanguinis</i>	Fe	177, 270
	PsaABCD	<i>S. pneumoniae</i>	Mn	522
	MtsABC	<i>S. pyogenes, S. agalactiae</i>	Mn, Fe, Zn, Cu	63, 267, 268
	ScaCBA	<i>S. gordonii</i>	Mn	303, 304, 647
	FimCBA	<i>S. parasanguinis</i>	Mn	160, 270, 430
	SloABCR	<i>S. mutans</i>	Mn, Fe	299, 446
	AdcRCBA	<i>S. pneumoniae, S. gordonii, S. pyogenes, S. agalactiae, S. mitis, S. mutans</i>	Mn, Zn	134, 365
	CopYAZ	<i>S. gordonii, S. mutans, S. pneumoniae, S. agalactiae, S. pyogenes, S. sobrinus, S. mitis</i>	Cu	408, 494, 624
	PstSCAB	<i>S. pneumoniae</i>	Phosphate	429
	FruRKI	<i>S. mutans, S. gordonii, S. pneumoniae, S. pyogenes, S. agalactiae, S. mitis</i>	Fructose	38, 364
	FxpABC	<i>S. mutans, S. pyogenes, S. pneumoniae</i>	Fructose, xylitol	38
	LacABCDFE	<i>S. mutans</i>	Lactose	511
	ScbCBA	<i>S. cristatus</i>	Unknown	111
	BfrCD, BfrEFG	<i>S. gordonii</i>	Biofilm formation	669
	BfrCD, BfrXY	<i>S. sanguinis</i>	Biofilm formation	669
	SilDE	<i>S. pyogenes</i>	Virulence	151, 235
	OppABCDF	<i>S. pyogenes</i>	Virulence	461, 637
HppABCDF	<i>S. gordonii</i>	Adhesion, coaggregation	397	

adhesion to glycoproteins and the ECM component laminin, functions that may promote the colonization capabilities of GAS. HtrA is also a protease and has been found in a number of streptococci (Table 1). Unlike SpeB, however, HtrA is thought to be anchored to the cell membrane via a single, hydrophobic transmembrane domain located near the N terminus (463). HtrA is a serine protease, and homologs in other bacteria serve to degrade abnormal exported proteins in re-

sponse to environmental stresses (297). A similar role is proposed for streptococci, as the deletion of *htrA* in *S. mutans* altered its ability to withstand environmental stresses (temperature, pH, and oxidative stress) (131), while in GAS, the biogenesis of secreted virulence factors was affected (371).

Aside from enzymatic capabilities, other members of the anchorless adhesin family share an ability to bind ECM proteins and so promote adhesion to host tissues via an ECM

protein bridge. One of the first such adhesins to be reported was Fn/fibrinogen-binding protein Fbp54 in GAS (114). Homologs in a number of other streptococci have since been discovered, exhibiting high percent identities: FbpA in *S. gordonii* (81%), PavA in *S. pneumoniae* (70%), and SmFnB in *S. mutans* (70%). All have been shown to adhere directly to immobilized Fn (Table 1), although FbpA also exerts its effects through the modulation of CshA expression, another Fn-binding adhesin of *S. gordonii* (102). The role of these adhesins in streptococcal colonization is implied by the fact that an N-terminal fragment of Fbp54 can impair GAS adhesion to buccal epithelial cells (112), while PavA was shown to be essential for virulence in a mouse model of pneumococcal sepsis (241). A further Fn-binding anchorless adhesin identified in GAS is Shr (165). Unlike Fbp54, this 145-kDa protein bears an N-terminal signal peptide and is predicted to be anchored to the cell membrane via a transmembrane domain at its C terminus. Shr binds myoglobin and hemoglobin and is thought to mediate heme acquisition through the ATP-binding cassette (ABC)-type SiaABC transporter (32). Shr also binds laminin and Fn but does not contain Fn-binding repeat blocks or the Fn-binding consensus motif (see above).

Two further anchorless adhesins of GAS that adhere to Igs have been described, Sib35 and Lzp. Both possess an N-terminal signal sequence, but whereas Lzp has five C-terminal hydrophobic regions that are predicted to hold it within the cell membrane, no such domains exist in Sib35. Sib35 exhibits adhesion to human IgG, IgA, and IgM (289) and has been shown to act as a mitogen, triggering proliferation and differentiation of mouse B cells (435).

In summary, the anchorless adhesins complement the functions of cell wall-anchored adhesins because they provide positional as well as functional flexibility. They have the potential to act as scouts in the inevitable battle between bacteria and host defenses. They could be released from the cell surface to sense the environment and may be bound back to the cell surface, perhaps in complex with their ligands. The possibility exists, therefore, that they may represent a mechanism for feeling the environmental waters, interacting with host molecules at a distance and with a surface dispensability that cannot be achieved through activities of cell wall-anchored adhesins.

Host Cell Modulation

Receptor recognition by bacterial surface adhesins is an essential step in mediating attachment to host tissues. It is increasingly evident, however, that these events can also trigger host cell signaling cascades and so modulate host cell behavior. In many cases, the precise sequence of signaling events triggered by streptococci remains to be defined. Nonetheless, the outcomes of streptococcal host cell modulation can be grouped into three general categories: (i) internalization of streptococci by host cells, (ii) induction of cytokine release, and (iii) induction of apoptosis.

Internalization. A common property shared by host cells and a number of streptococcal adhesins is the ability to bind ECM proteins. For mammalian cells, this is often facilitated by integrin receptors. Integrins are a large family of $\alpha\beta$ heterodimeric glycoproteins that regulate diverse cellular processes including cell migration, proliferation, and adhesion. To

date, 18 α and 8 β subunits that combine to form 24 distinct heterodimers, each with various affinities for ECM proteins, have been identified (249). Using common ECM protein ligands as bridging molecules, several streptococci have been found to interact with integrins and exploit their signaling pathways to promote their own adhesion, colonization, and invasion. One of the best-characterized examples of this is signaling via Fn-binding integrin $\alpha_5\beta_1$ by GAS, a process that leads to GAS internalization by nonprofessional phagocytic cells. Two Fn-binding adhesins of GAS are principally associated with this process, SfbI and M protein, and trigger distinct uptake mechanisms (refer to reference 426 for a comprehensive review of this process). SfbI interacts with the N terminus of Fn, which in turn binds integrin $\alpha_5\beta_1$ via its RGD motif. Interactions with multiple Fn molecules leads to integrin clustering and the formation of focal complexes and focal adhesions, which contain numerous signaling and structural components linked to the host cytoskeleton. These are the sites of activation for two independent signaling pathways. One requires tyrosine phosphorylation of focal adhesion kinase (FAK) and paxillin and involves the Src kinases Src, Yes, and Fyn. The second requires the recruitment and activation of the GTPases Rac and Cdc42. These pathways then ultimately converge to trigger the formation and fusion of caveolae beneath the attached bacteria, resulting in large invaginations via which GAS species are internalized (441) (Fig. 4B).

M protein also interacts with integrin $\alpha_5\beta_1$ via a Fn bridge, but the subsequent downstream signaling events differ from those triggered by SfbI. The reason for this variation is not fully understood, but as SfbI and M protein interact with different domains of Fn, it has been postulated that this may affect the way in which Fn binds to integrin, which in turn may influence subsequent signaling events. For M protein, major cytoskeletal rearrangements are triggered, and this is dependent upon the activation of phosphatidylinositol 3-kinase (472). This activates a classic endocytotic pathway, the result of which is the recruitment and fusion of microvilli around the streptococcal cells and their uptake via a zipper-like mechanism (137). Rather than caveolae, bacteria ingested by this pathway ultimately enter phagolysosomes, as characterized by the lysosomal marker LAMP-1 (137). Similar entry mechanisms are also utilized by GBS (79, 620) and *S. dysgalactiae* (82).

It should be noted, however, that adhesins that bind ECM proteins are not the only mediators of streptococcal host cell invasion. GAS strain A8, which lacks Fn-binding capabilities, has been shown to trigger its uptake in a Fn- and $\alpha_5\beta_1$ integrin-independent manner (409), although details of the surface proteins and signaling networks in this process remain to be defined. Furthermore, both SDH (GAPDH) (Table 1) and hyaluronic acid capsular polysaccharide (CPS) have been shown to promote GAS internalization. SDH-mediated invasion triggers a series of signaling events following adhesion to two pharyngeal membrane proteins, one outcome of which is the phosphorylation of nuclear core histone H3 (449). In contrast, CPS signals via keratinocyte receptor CD44 to induce membrane ruffling, a process that requires the activation of Rac1 and the cytoskeleton linker protein ezrin (123). Rather than leading to direct host cell invasion, the latter mechanism disrupts intercellular junctions, allowing the passage of GAS to underlying tissues via a paracellular route. This alternative

method of promoting streptococcal dissemination has also been described for GBS and is associated with pilus expression (459, 564).

Invasion may enable bacteria to translocate or disseminate to other parts of the host, but there is growing evidence that an ability to enter nonphagocytic cells may also provide bacteria with an increased opportunity for survival. Once internalized, bacteria are protected against host innate immune defenses and antibiotic therapies, and this is thought to explain, at least in part, the recurrence of some GAS infections (439). The notion of host cells as a reservoir of bacteria has implications not only for pathogens but also for commensal microorganisms. Rudney et al. (514) demonstrated that an extensive polymicrobial flora can be found within buccal epithelial cells, a large proportion of which corresponds to commensal streptococci. This implies that commensals are also able to become internalized, and the commensal *S. gordonii* was shown to trigger its internalization by HEp-2 epithelial cells via an interaction of its SspA and SspB (AgI/II family polypeptides) with integrin $\alpha_5\beta_1$ (427).

Cytokine release. Proinflammatory responses resulting from de novo or increased cytokine synthesis are a frequent outcome of streptococcal interactions with a range of host cells. These can significantly influence the progression of disease by affecting a number of processes including immune cell infiltration, tissue inflammation, and tissue damage. In some cases, the streptococcal triggers are known and include both cell-bound adhesins and secreted factors. One powerful inducer of inflammation is the GAS M protein. This has been shown to trigger the release of the cytokines IL-6, IL-1 β , and tumor necrosis factor alpha (TNF- α) following recognition by Toll-like receptor 2 on the surface of monocytes (444). In *S. mutans*, rhamnose glucose polymers, GTFs, and AgI/II polypeptides have been shown to induce IL-6 and IL-8 release from epithelial, endothelial, and T cells (12, 97, 625). For the AgI/II proteins, this process is associated with binding to integrin $\alpha_5\beta_1$ and the activation of FAK, paxillin, and phospholipase C γ , fundamental components of the mitogen-activated protein kinase signaling pathways (12). In contrast, *S. gordonii* was found to inhibit the release of IL-6 and IL-8 from epithelial cells (222), a phenomenon that may contribute to the ability of this organism to persist in the oral cavity as a commensal. Interestingly, *S. gordonii* and other oral streptococci were also shown to suppress the IL-8 release normally induced by the opportunistic periodontopathogen *Fusobacterium nucleatum* (664), providing insight into how the presence of such commensals might promote a "healthy" oral environment (273). Aside from proinflammatory effects, cytokine release may also influence mechanisms such as streptococcal invasion, as described above. Interactions of GAS with epithelial cells and tonsillar fibroblasts have been shown to trigger the production of transforming growth factor β_1 (635). This is a multifunctional cytokine and a positive regulator of integrin signaling, upregulating several proteins including FAK, paxillin, and phosphatidylinositol 3-kinase. GAS-mediated transforming growth factor β_1 release was found to upregulate integrin α_5 expression (635). Thus, GAS is able to manipulate host cytokine production to increase levels of expression of target receptors and so promote its own adherence and internalization.

Apoptosis. Apoptosis is often considered a host strategy for clearance of infection by eliminating infected cells and removing potential targets for adhesion and internalization. However, the ability to induce apoptosis may be beneficial to bacteria, enabling escape from phagocytic activity or damaging host tissues and so promoting deeper penetration and dissemination. There are two main pathways via which mammalian cells commit to apoptosis. The first results from the deregulation of mitochondrial function. Cytochrome *c* is released from mitochondria into the cytoplasm, where it binds APAf-1 and cleaves procaspase-9 to form the apoptosome, which in turn activates caspase-3 (intrinsic apoptosis). Alternatively, the ligation of death receptors such as CD95 and TNF receptors on the cell surface leads to the cleavage of procaspase-8. This then cleaves procaspase-3, leading to DNA fragmentation and cell death (extrinsic apoptosis). Bacterial components with proapoptotic effects can be broadly differentiated into four groups: (i) superantigens, (ii) pore-forming toxins, (iii) nonenzymatic structural components, and (iv) metabolic end products (comprehensively reviewed in reference 614). Knowledge of apoptosis regulation by streptococci is limited but has been best studied for pathogenic species, including GAS and GBS.

GAS induces apoptosis in a variety of cell types, including neutrophils (301), macrophages (323), and epithelial cells (416, 417, 612), and can activate both pathways. Extrinsic apoptosis can be attributed in part to the activities of SpeB, which has been shown to activate matrix metalloproteinases on the surface of mammalian cells and trigger TNF- α and Fas ligand release (594). Alternatively, interactions of GAS with epithelial cells induce caspase-9 activation, cytochrome *c* release, and Bax translocation to the mitochondria (416, 417). These events are associated with intrinsic apoptosis and are dependent upon SfbI-mediated internalization (416), as described previously. The GAS-secreted toxin NADase has also been shown to promote the apoptosis of keratinocytes in conjunction with the hemolysin streptolysin O (SLO). SLO forms pores in the cell membrane, and NADase enters the cell through these pores and exerts its effects (66). Similarly, the hemolysin CylE of GBS triggers the apoptosis of macrophages, but the mechanism is not yet understood (163). It should be noted, however, that not all modulatory effects lead to enhanced host cell apoptosis. For example, GBS infection of HeLa cells has been shown to trigger prosurvival signaling events and protection against caspase-3 cleavage (79). It seems, therefore, that a delicate balance exists between the pro- and antiapoptotic effects of streptococci upon host cells and that this can significantly influence disease progression. By promoting apoptosis, bacteria can escape phagocytic killing and enhance their dissemination, while apoptosis inhibition can allow bacteria to create an intracellular refuge and so persist in the host.

Platelet Interactions

The adherence of streptococci to platelets is thought to be crucial for the colonization of damaged heart valves, which may result in the life-threatening condition infective endocarditis (IE). Streptococci that can induce platelet activation, and the resulting thrombus formation, are believed to play a role in disseminated intravascular coagulation by causing increased platelet and clotting factor consumption (Fig. 4C). Interactions

of streptococci with platelets usually occurs by direct binding to platelets via streptococcal surface proteins (293). It may also occur indirectly via streptococci binding a plasma-bridging molecule, such as fibrinogen (171), engaged with a platelet surface receptor. Bacteria may activate platelets or simply adhere to them, suggesting that platelet adherence and activation are separate events that are perhaps mediated by different bacterial and platelet components.

Viridans group streptococci including *S. sanguinis*, *S. oralis*, *S. mutans*, *S. mitis*, *S. parasanguinis*, and *S. gordonii* (31) have long been recognized as major etiological agents of IE. They gain entry to the vascular system via the oral cavity, and their adherence to platelets is thought to be pivotal to pathogenic potential (234). Components of streptococci involved in colonization and virulence in IE include lipoproteins, polysaccharides, and LPxTz-anchored proteins. The lipoproteins shown to be virulence factors in IE are FimA from *S. parasanguinis* and SloC from *S. mutans*. These are divalent metal ion-binding proteins of ABC transport systems for the uptake of Mn^{2+} or Fe^{2+}/Fe^{3+} (430, 446). *S. mutans* mutants that do not produce extracellular glucan show decreased virulence in rat models of endocarditis (414). Moreover, the serotype-specific cell wall polysaccharides from *S. mutans* comprised of rhamnose-glucose polymers induce platelet aggregation in the presence of plasma (98).

The Srr proteins (see above) SrpA (460) and GspB/Hsa (39) have been identified as recognizing sialyl-T antigen found on platelet integrin GPIIb/IIIa. GspB/Hsa are strain specific to *S. gordonii* and have been shown to induce platelet adherence by interacting with sialic acid residues on the sialomucin core and the N terminus of GPIIb/IIIa, respectively (39, 588). They act in concert with the AgI/II polypeptides SspA (172 kDa) and SspB (164 kDa) (427) to aggregate platelets (261). The M1 protein of *S. pyogenes* triggers thrombus formation by forming complexes with fibrinogen, which, in the presence of IgG against M protein, engage the Fc receptor on platelets and activate them (545). This leads to platelet aggregation and the formation of platelet-rich thrombi. Streptococci thus utilize a range of different components and mechanisms for adherence to, and activation of, platelets. It is important to decipher further the molecular mechanisms involved in *Streptococcus*-induced thrombus formation so that potential new targets for the prevention of IE or disseminated intravascular coagulation may be identified.

STREPTOCOCCUS SOCIETY DEVELOPMENT

After the first encounter of *Streptococcus* with a surface, and adherence to that surface, the bacterial cells may begin to multiply if the environmental conditions are favorable. A small society of streptococci can then form, sometimes referred to as a linking film, and provides a new surface onto which other bacteria may deposit (Fig. 2). Alternatively, some species may attach but become internalized before a linking film can develop. Within the society, cell-cell signaling ensures coordinated growth and development, while the production of extracellular hydrolytic enzymes provides new nutrients, and polysaccharide formation promotes the retention and accumulation of streptococci (Fig. 2). All these activities occurring within the society are central to the overall colonization pro-

cesses, which may then lead to carriage, to the formation of mixed-species communities, or on to infection.

Biofilm Formation

Dental plaque, comprising many hundreds of bacterial species, is the best example of a natural biofilm in the human body. Complex biofilms are also formed on the intestinal linings and on the mucosal surfaces of the vagina, but these biofilms are conceptually different for this article because they do not generally incorporate commensal streptococci. Single-species biofilms (biofilm societies) may occur in some instances in nature, such as in the colonization of prosthetic implants by *Staphylococcus epidermidis* or of the middle ear by *S. pneumoniae*. However, many studies of single-species biofilm formation, although providing information on the growth of the organisms as sessile societies, do not truly represent the biofilm communities encountered in vivo, where there is intense competition as well as metabolic synergism among many microbial species. *S. mutans*, *S. gordonii*, and other oral streptococci readily form single-species biofilms in the laboratory on a variety of surfaces, and biofilm formation is dependent upon activities of multiple genetic loci (Fig. 6), as discussed below. Thus, mutations in genes encoding components of quorum-sensing systems, e.g., *comCDE* (354); TCSS, e.g., *vicRK* (543); GBPs (370); and metal ion permeases (503) can impair *S. mutans* biofilm formation. Optimal biofilm formation by *S. gordonii* and *S. sanguinis* also requires multiple gene products including sortase (428) and proteins involved with β -glucoside metabolism and carbon catabolite control (296, 364), nucleotide biosynthesis (181), oxidative stress (322, 363), and environmental sensing and signaling (193). The growth of non-mitis-group streptococci as biofilms is only just beginning to be studied, but the complexities of M serotypes, capsular serotypes, and the expression of pilus types and antigenically variable surface proteins will probably make interpretations of the molecular pathways involved extremely difficult. Already, it is clear that strains of *S. pyogenes* encompassing clinically important serotypes behave very differently and quite unpredictably in biofilm formation (341). Pili (382), M protein, and streptococcal protective antigen (Spa) (115) are some factors that have been implicated, but the complements of surface components required for biofilm development may turn out to be strain and serotype specific. Interestingly, the inactivation of the regulator Srv in *S. pyogenes* results in the upregulation of the cysteine protease SpeB and a significant decrease in biofilm formation (136). Thus, it is possible that the production of SpeB may be associated with a transition from a colonizing to an invasive phenotype.

Polysaccharide Production

The production of extracellular polysaccharides by oral streptococci plays a key role in the development of biofilms and dental plaque (Fig. 6). The accumulation of *S. mutans* is enhanced through the binding of extracellular glucans by cell surface-associated GBPs (Table 1). GTFs and fructosyltransferases are enzymes secreted by viridans group streptococci (Table 2) that are responsible for the synthesis of glucans and fructans. There are three genes encoding GTFs in *S. mutans*,

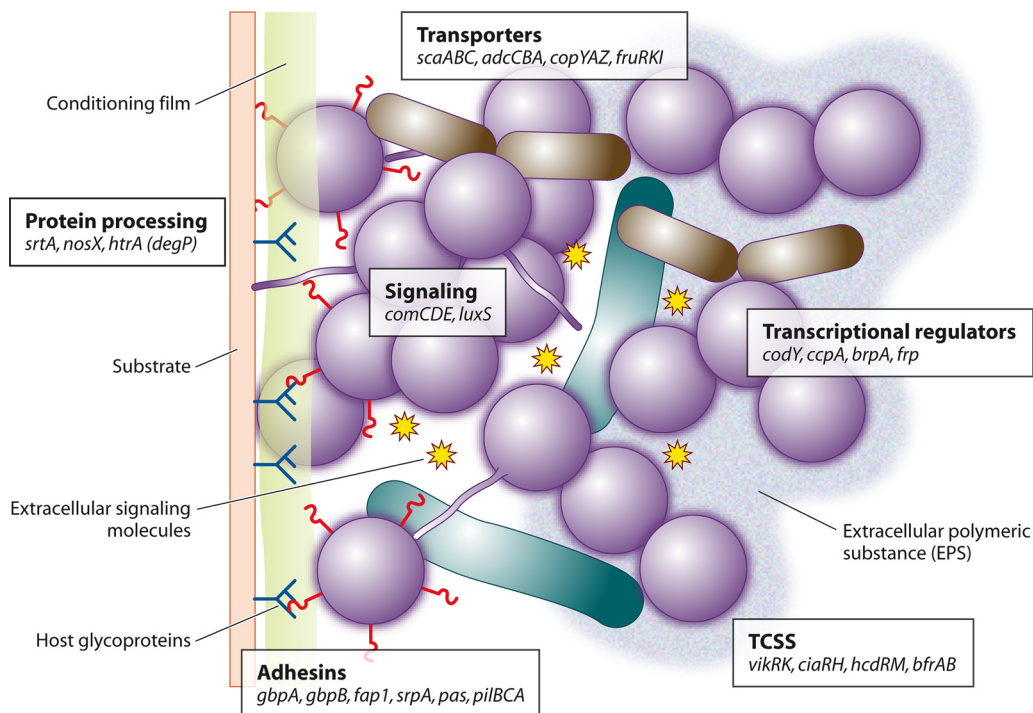


FIG. 6. Integration of adhesins, receptors, signals, adaptation, and nutrition in *Streptococcus* biofilm formation. The colonization process depends upon the expression of genes encoding adhesins (*gbpA* and *srpA*, etc.), transporters (*scaABC*, etc.), transcriptional regulators (*codY*, etc.), posttranslational processing (*htrA*, etc.), TCSS (*vikRK*, etc.), and cell-cell communication (pheromones and AI-2, etc.), with only a few selected examples shown.

designated *gtfB*, *gtfC*, and *gtfD*. The GtfB enzyme (162 kDa) synthesizes a water-insoluble glucan comprised of α 1-3-linked glucose (Glc) residues, GtfC (149 kDa) produces a low-molecular-mass partly water-soluble glucan, and GtfD (155 kDa) synthesizes a water-soluble glucan. Sucrose induces the expression of *gtfB*, while Glc and fructose repress it (246, 646) at acidic pHs, possibly through the activity of the RegM transcriptional regulator (similar to catabolite control protein A) (74). The GBPs help determine the architecture of the biofilm, with GbpC being the principal glucan receptor (370). The transcriptional regulator CovR represses *gbpC* (53) as well as *gtfB* and *gtfC* (55). The water-insoluble glucans contribute to adherence and society formation, while the water-soluble glucans are akin to trapped nutrient supplies, which are readily degraded into metabolizable sugars by extracellular or cell-bound dextranases (Fig. 6).

A large amount of work carried out over the last few decades has confirmed that colonization and dental caries production by *S. mutans* in rodents fed high-sucrose diets depend upon the synthesis of water-insoluble glucans. However, it is clear that the polysaccharide-synthesizing enzyme products of all four genes *gtfBC*, *gtfD*, and *ftf* are involved in eliciting dental caries (415). The GTFs secreted by oral streptococci contain a common four-domain structure: a signal (leader) peptide of 36 to 38 aa residues, followed by a nonconserved region (200 aa residues), a highly conserved catalytic domain (800 aa residues), and a C-terminal region of approximately 500 aa residues that binds glucans. The latter regions are composed of a series of YG repeats, each of which comprises a 21-aa-residue sequence with one or more aromatic residues (190). The YG

repeats are present in regular arrays within GtfB, GtfC, GtfD, and GtfI (*S. downei*), etc., and have arisen from multiple duplication events, with evidence for a functional selection of conserved residues for carbohydrate binding.

The virulence of *S. pyogenes* correlates closely with the expression of hyaluronic acid CPS. Heavily capsulated strains are spread more readily, while capsule production is repressed during carriage. The upregulation of capsule during systemic infection protects *S. pyogenes* from opsonophagocytosis and masks other immunogenic determinants on the cell surface, constituting a mechanism for the evasion of antigen-specific antibodies (133). The biosynthesis of the capsule is directed by the *hasABC* gene cluster (20), and there is evidence that the antimicrobial protein human cathelicidin LL-37, perhaps with other signals from the host, may trigger increased CPS production through the CsrRS TCSS (202).

A major factor contributing to the virulence of *S. agalactiae* is the polysaccharide capsule. It is composed of repeating units of Glc, Gal, GlcNAc, and NeuNAc (sialic acid), and variations in saccharide linkages and composition result in the designation of nine capsular serotypes to date. All GBS capsule types share a terminal NeuNAc that is similar to the sialic acid on human cells. It has been envisaged that this may play a role in resistance to complement-mediated killing by binding factor H, as well as binding CD33rSigslecs on neutrophils and macrophages to exert suppressive effects on the innate immune system (84). The oral streptococci *S. sanguinis*, *S. oralis*, and *S. gordonii* also express antigenically diverse cell wall polysaccharides on their cell surfaces that contain the host-like recognition motifs GalNAc β 1 \rightarrow 3Gal or Gal β 1 \rightarrow 3GalNAc (103).

These are receptor polysaccharides for the fimbrial lectins of *Actinomyces naeslundii* in the development of oral microbial communities, but the host glycoconjugate-like features of the receptor polysaccharides suggest that they may also be involved in the evasion of the secretory immune response by oral streptococci.

Two-Component Signal Transduction Systems

To successfully colonize and persist within the host, bacteria must adapt their gene expression profiles in response to environmental changes. Streptococci utilize two main types of transcriptional regulators: TCSS and stand-alone regulators (see below). TCSS (more formally known as histidine-aspartate phosphorelay systems) comprise two signaling proteins: a sensor kinase, which is anchored to the cell membrane, and a cognate response regulator found within the cytoplasm. Sensor kinases typically possess a highly variable N-terminal sensor region, containing one to several transmembrane domains, and a more conserved C terminus, containing the kinase and transmitter domains. Comparative analyses across the sensor kinase family have identified five amino acid motifs (or boxes) within the C-terminal region, named after the most conserved residue (H, N, D, F, and G). Response regulator proteins can be divided into an N-terminal region, which carries a highly conserved “receiver” domain, and the C-terminal “effector” domain, which often exhibits DNA-binding capabilities. Upon receipt of an appropriate stimulus, the sensor kinase is activated and autophosphorylates at the conserved histidine residue of the H box. The kinase then donates the high-energy phosphate group to an invariant aspartate residue within the receiver domain of the response regulator. This phosphorylation leads to structural changes in the regulator, enabling the modulation of gene expression or protein function.

Analyses of complete genomes have revealed 13 independent TCSS in GAS (161), *S. pneumoniae* (334, 605) and *S. mutans* (6), while 20 TCSS were found in GBS (194). TCSS are not, however, restricted to these species of streptococci and have been associated with the regulation of an array of cellular responses including pathogenesis, nutrient utilization, competence, and stress resistance (Table 3). Nonetheless, it should be noted that for many TCSS, the precise regulatory networks and functional roles are still not understood.

CsrRS. One of the best-characterized TCSS is CsrRS (capsule synthesis regulator), otherwise known as CovRS (control of virulence genes). As its names suggest, CsrRS was first shown to repress the expression of the capsule synthesis *has* operon in GAS (349) but has since been found to affect the expression of a wide range of genes associated with GAS colonization and virulence (159, 197). These include genes encoding surface adhesins (e.g., *lmb* and *scl2*), extracellular enzymes (e.g., *speB*, *ska*, and *sagA*), and stress response proteins (e.g., *dnaJK* and *grpE*). Furthermore, CsrRS regulates other TCSS (e.g., *ciaRH*, *ihk-irr*, and *trxSR*) and global regulators (e.g., *rgg* and RofA-like protein [RALP] family genes), thereby mediating indirect effects on the expression of a secondary set of genes (197, 337). Taken together, CsrRS influences the transcription of 15% of GAS chromosomal genes (197), and as the majority of these are downregulated, CsrRS is often referred to as a negative global regulator. Accordingly, mutants attenuated in *csrRS* exhibit increased virulence in mouse models of infection

(150). Gryllos et al. (201) found that CsrRS responds to the Mg^{2+} concentration, being repressed at low concentrations and becoming fully active only once concentrations of ≥ 10 mM are reached. As physiologic Mg^{2+} levels in body fluids such as mucosal secretions and blood are approximately 1 mM, this means that the expression of Csr-regulated virulence genes is maximal under conditions encountered during human infection.

Similar to GAS, a CsrRS homolog in *S. dysgalactiae* was shown to repress the expression of streptokinase and streptolysin S (SLS) (575). In contrast, CsrRS of GBS was found to upregulate almost as many genes (63 genes) as were repressed (76 genes), and a $\Delta csrRS$ mutant is attenuated for virulence in a neonate rat sepsis model (330). Such differences may reflect the adaptation of these pathogens to the specific environments encountered during the course of infection. *S. mutans* expresses an orphan regulator with homology to CsrR, known as GcrR/TarC (253, 526). This acts as a transcriptional repressor of GTF GtfD and GBP GbpC expression, thereby affecting *S. mutans* attachment to tooth surfaces and subsequent biofilm formation (253). GcrR has also been shown to upregulate the expression of genes required for the acid tolerance response, which enables *S. mutans* to survive at pHs as low as 3.0. Rather than responding directly to acidic pHs, however, the transcription of *gcrR* is itself regulated by the transcriptional repressor SloR, whose repression is relieved under manganese-depleted and acidic conditions (141).

VicRK. Another TCSS of *S. mutans* that affects GTFs and GBPs is VicRK (Table 3). This TCSS positively regulates the expression of GtfBCD, Ftf, and GbpB (543), thereby modulating glucan and fructan synthesis and sucrose-mediated bacterial aggregation. No environmental stimulus has been defined for VicRK, but a *vicK* mutant was found to form aberrant biofilms that were readily disrupted compared to the wild type, implying an important role for VicRK in *S. mutans* colonization of tooth surfaces (Fig. 6). VicRK was also implicated in competence development by *S. mutans*, indicating that it may act in conjunction with the TCSS ComED to promote genetic variation and the uptake of heterologous genes, including those associated with antibiotic resistance (543). *S. pneumoniae* and GAS possess VicRK homologs, and mutants in this TCSS are attenuated for virulence in mouse models of infection (360, 630). This is associated with the fact that for both pathogens, VicRK positively regulates the expression of PcsB, a murein hydrolase that is homologous to GbpB and that is required to maintain cell wall integrity (360, 423). VicRK in GAS has also been shown to modulate nutrient uptake, by the regulation of a carbohydrate transport system, and osmotic protection, by targeting the osmoprotectant transporter OpuA (360). Interestingly, VicK contains a PAS domain, a motif associated with proteins that detect oxygen and cytoplasmic redox potentials (630). It is possible, therefore, that the signal recognized by VicRK may originate from the cytoplasm.

CiaRH. CiaRH was the first TCSS to be identified in *S. pneumoniae* (203) and has since been reported for a number of streptococcal species (Table 3). For *S. pneumoniae*, mutations in *ciaRH* are associated with increased antibiotic resistance (186, 203, 386), a phenotype that is likely linked to the regulation of genes related to cell wall polysaccharide biochemistry (186, 386). In addition, CiaRH affects competence development by repressing the *comCDE* operon (143, 186, 203), and a

TABLE 3. TCSS

TCSS	Species	Homolog(s)	Function(s) and/or substrate(s) ^b	Reference(s)
CsrRS (CovRS)	<i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. dysgalactiae</i>	GcrR/TarC (<i>S. mutans</i>); orphan	Virulence, biofilm formation, negative global regulator	330, 349, 575
VicRK	<i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>S. mutans</i>		Virulence, stress resistance; ↑ GtfBCD, GbpB, Ftf; biofilm formation, competence, nutrient uptake	360, 543, 630
CiaRH	<i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>S. mutans</i> , <i>S. mitis</i> , <i>S. agalactiae</i> , <i>S. gordonii</i> , <i>S. sanguinis</i>		Virulence, competence, biofilm formation	5, 186, 203, 495
BfrAB	<i>S. gordonii</i> , <i>S. sanguinis</i>		Biofilm formation	668, 669
ComED	<i>S. mutans</i> , <i>S. pneumoniae</i> , <i>S. gordonii</i> , <i>S. oralis</i> , <i>S. anginosus</i> , <i>S. cristatus</i> , <i>S. sanguinis</i> , <i>S. mitis</i>		Competence (CSP), mutacin production, biofilm formation	122, 225, 352, 453
HdrRM	<i>S. mutans</i>		High cell density, bacteriocin production, biofilm formation, competence	404
HK11/RR11	<i>S. mutans</i>		Acid resistance, biofilm formation	353
TcbRK	<i>S. mutans</i>	SpiHR (<i>S. pneumoniae</i>)	Biofilm formation	50
TcdRK (TCS3)	<i>S. mutans</i>	ScnRK (<i>S. pyogenes</i>)	Mutacin production	50, 348
SpiHR	<i>S. pneumoniae</i>	TcbRK (<i>S. mutans</i>)	Bacteriocin production	491
BlpRH	<i>S. pneumoniae</i>		Bacteriocin production	130
ScnRK	<i>S. pyogenes</i>	TcdRK (TCS3) (<i>S. mutans</i>)	Lantibiotic production	393
SalKR	<i>S. salivarius</i>		Lantibiotic (SalA) production	617
LytRS	<i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. pneumoniae</i>		Virulence	197, 280, 607
Ihk-Irr	<i>S. pyogenes</i>		Polymorphonuclear neutrophil signal, virulence	629
FasBCA	<i>S. pyogenes</i>	FasCAX (<i>S. dysgalactiae</i>), RgfAC (<i>S. agalactiae</i>)	Local tissue destruction	309
TrxSR	<i>S. pyogenes</i>		Mga virulence regulon	337
SptRS	<i>S. pyogenes</i>		Carbohydrate uptake and utilization	549
SilAB	<i>S. pyogenes</i>		Virulence	151
PnpRS (TCS04)	<i>S. pneumoniae</i>		Phosphate regulation; ↑ PsaA; oxidative stress	334, 390, 429
VncRS	<i>S. pneumoniae</i>		Vancomycin resistance	429
MicAB	<i>S. pneumoniae</i>		Oxidative stress	144
CbpRS	<i>S. pneumoniae</i>		↓ pili	508
CpsXY	<i>S. pneumoniae</i>		Capsule expression	307
HK/RR03	<i>S. pneumoniae</i>		↓ pili	508
HK06/RR06	<i>S. pneumoniae</i>		Virulence (CbpA, PspA)	573, 574
TCS08	<i>S. pneumoniae</i>		Virulence, cellobiose metabolism	334, 392
RelRS	<i>S. mutans</i>		(p)ppGpp production	344
LiaSR	<i>S. mutans</i>		Virulence; ↓ Gbp; mutacin production	54, 101
LevRS	<i>S. mutans</i>		↑ FruA	663
LytTS	<i>S. mutans</i>		Autolysin regulation, cell division	91
TCS9	<i>S. mutans</i>		Competence	348
GcrR/TarC	<i>S. mutans</i>	CovR (<i>S. pyogenes</i>)	Acid tolerance response; ↓ GtfS, GbpC	141, 253
RgfAC	<i>S. agalactiae</i>	FasBCA (<i>S. pyogenes</i>)	Surface adhesins (↓ ScpB)	566
DltRS	<i>S. agalactiae</i>		LTA biosynthesis	464
FasCAX	<i>S. dysgalactiae</i>	FasBCA (<i>S. pyogenes</i>)	Streptokinase and SLS production	575
StkP/PhpP/RitR ^a	<i>S. pneumoniae</i>		Global; stress resistance, iron homeostasis	142, 615, 616
Stk1/Stp1/Cov ^a	<i>S. agalactiae</i>		Beta-hemolysin/cytolysin production, growth, virulence	477, 478

^a Serine/threonine kinase-phosphatase signaling via regulator.

^b ↑, gene/protein expression is upregulated; ↓, gene/protein expression is downregulated.

Δ*ciaRH* mutant failed to effectively colonize the mouse nasopharynx, a finding that is associated with a reduced level of expression of the anchorless protease HtrA (252, 537). Conversely, the inactivation of *ciaH* in *S. mutans* diminishes competence development and increases the level of expression of

HtrA, although the mutation does disrupt biofilm formation (5, 476). It is clear, therefore, that there has been a significant divergence in the function of this TCSS across streptococci, meaning that it influences their colonization capabilities in a variety of ways. This is further highlighted by the role of

CiaRH in GAS. As GAS is not naturally transformable, the mutation of *ciaH* has little effect on competence development. Rather, the mutant exhibits decreased levels of expression of sugar transport systems (495), implying a role in maintaining sugar homeostasis. CiaRH of GAS was also found to regulate the expression of some virulence factors, including the adhesins PrtF2 and SfbX, a function that influences GAS adhesion and the invasion of HEp-2 epithelial cells (495). As for the functions of CiaRH homologs, the environmental stimuli to which they respond also vary. For GAS, *ciaRH* transcription was shown to be altered in the presence of various concentrations of Co^{2+} , Cu^{2+} , and Zn^{2+} (495), while CiaRH of *S. pneumoniae* and *S. mutans* senses Ca^{2+} (186, 226). For *S. mutans*, a third gene of the operon has been found, CiaX, which encodes a double-glycine-containing peptide. This acts as a calcium signaling peptide, which, when bound by Ca^{2+} , undergoes a conformational change that prevents its activation of CiaRH (226).

BfrAB. In *S. gordonii*, the TCSS BfrAB is involved in biofilm development (666, 668). BfrAB regulates the expression of the *bfrCD* and *bfrEFG* operons, which encode two ABC transporters and a CAAX amino-terminal protease family protein. Interestingly, *bfrC* (*ccmA*) and *bfrG* are also required for the maturation of dual-species communities with *P. gingivalis* (322). As an organism that is predominantly in the biofilm mode of existence, *S. gordonii* may benefit from homotypic and heterotypic community-related genes being in relatively close proximity.

Other TCSS. Several other TCSS that are implicated in biofilm formation have been found in streptococci, including HdrRM, TcbRK, and HK11/RR11 of *S. mutans* (50, 353, 404). However, aside from ComED, a TCSS found in many streptococci that is associated with competence development and biofilm formation (see "Peptide-Mediated Signaling"), the regulatory networks of these TCSS remain to be defined.

A further function that can influence the ability of streptococci to colonize an environmental niche, and which TCSS often regulate, is the production of bacteriocins. Bacteriocins are proteinaceous toxins that inhibit the growth of closely related bacterial strains. Thus, by their production, streptococci can effectively compete with neighboring bacteria for a given site. Two types of bacteriocins are produced by streptococci, classified according to their posttranslational modifications: lantibiotics (class I) and nonlantibiotics (class II). Lantibiotics correspond to ribosomally synthesized and post-translationally modified peptides that contain lanthionine or β -methylanthionine. These can be further divided into class A lantibiotics, which have a linear structure, and class B lantibiotics, which have a more globular conformation. One such example is SA-FF22, a lantibiotic expressed by GAS. SA-FF22 production is regulated by the TCSS ScnRK (393), a homolog of which is found in *S. mutans*, designated TcdRK (50). Similarly, a second TCSS of *S. mutans*, TcbRK, is homologous to SpiHR of *S. pneumoniae* (50), which regulates the putative bacteriocin cluster comprised of PncA to PncM (491). No environmental signal has yet been determined for these TCSS. However, Guerra and Pastrana (204) showed that bacteriocin production was stimulated by acidic pHs in *Lactococcus lactis*, a model that may also be relevant for streptococci, particularly *S. mutans*. Another environmental stimulus associated with

bacteriocin expression is cell density. Thus, by expressing bacteriocins when cell numbers are high, bacteria are able to kill competing species when nutrients become limited. Such a strategy has been seen for *S. mutans* expression of the lantibiotic mutacin I, which acts against most gram-positive bacteria, and the nonlantibiotic mutacin IV, which targets predominantly mitis group streptococci and is associated with the LuxS/HdrRM and ComED regulatory systems, respectively (318, 402, 404). Interestingly, the coordination of mutacin IV and competence development has been proposed to be a mechanism for *S. mutans* to acquire DNA from bacteriocin-sensitive streptococci, thereby promoting genetic diversity (317). The production of the bacteriocin Blp in *S. pneumoniae* is also cell density dependent but, unlike *S. mutans*, is controlled independently of ComED by the TCSS BlpRH (130).

One final mechanism of bacteriocin production that has important implications for colonization and community development is interspecies signaling. This has been demonstrated for lantibiotic production by *S. salivarius* and GAS (617). *S. salivarius* expresses salivaricin A (SalA), regulated by the TCSS SalKR, which is active against GAS (513). GAS possesses a homologous *sal* locus that encodes the lantibiotic SalA1 and is effective against *S. salivarius* (555). In both cases, lantibiotic expression is autoregulated and provides increased immunity to the inhibitory effects of SalA and SalA1 compared to SalA/SalA1-negative strains. Of particular interest, however, is that although not identical, the TCSS of *S. salivarius* and GAS do not discriminate between SalA and SalA1 and are capable of sensing and responding to either one (617). As such, lantibiotic production by one species could be detected by another, inducing its own lantibiotic production. In this way, the outgrowth of a single streptococcal population could be restricted and, instead, a state of cocolonization could be promoted. By modulating the coexistence of streptococcal populations, such mechanisms are likely to have a significant influence on the development of polymicrobial community structures.

Transporters

When streptococci deposit upon a surface, one of the first requirements is that they acquire nutrients in order to form a society. Streptococcal species differ considerably in their growth requirements, with oral species generally being far less fastidious than pyogenic group organisms (Fig. 1). The sugar transport systems in *S. mutans*, especially the phosphoenolpyruvate-dependent phosphotransferase systems, are critical for growth and for extracellular polysaccharide production. There have been 10 or more phosphotransferase systems identified within the *S. mutans* and other streptococcal genomes, with more than 50 putative carbohydrate transporters in *S. sanguinis* (657). The streptococci also have transporter systems for complex carbohydrates such as maltodextrins, e.g., Msm in *S. mutans*. Maltodextrin utilization is important for *S. pyogenes* growth in human saliva and for colonization of the oropharynx in an animal model (548).

Specific ABC transporters have been implicated in streptococcal colonization processes (Table 2). The oligopeptide permeases HppABCDF in *S. gordonii* and OppABCDF in *S. pyogenes* are involved in adherence and virulence, respectively. The Hpp transporter is necessary for the response of *S. gordo-*

nii to an extracellular factor that regulates the expression of the fibril adhesin CshA (397). Mutations in the genes encoding the oligopeptide permease in *S. pyogenes* lead to a reduced level of production of the cysteine protease SpeB (461) and cause less mortality and tissue damage in an air pouch model of virulence (637). Other permeases that have been specifically shown to influence adherence and biofilm formation are the ABC-type metal ion transporters (Fig. 6). The ScaA lipoprotein component of the ATP binding protein-dependent permease ScaABCD was first identified as being a putative adhesin mediating the binding of *S. gordonii* to *A. naeslundii* (304) in mixed-species community development. The orthologous FimA protein in *S. parasanguinis* was shown to adhere to salivary components (436). More recently, the PsaA protein ortholog from *S. pneumoniae* has been shown to bind E-cadherin (16). In addition to their putative roles in adherence, these proteins are substrate-binding components of transporters for Mn^{2+} ions (262) and possibly Fe^{3+} ions (430). Metal ion homeostasis in streptococci is crucial for many aspects of metabolism, particularly responses to oxidative stress (260). Therefore, the disruption of genes encoding these transporters has deleterious effects on the growth and survival of bacteria in vivo. In animal models of endocarditis, *S. parasanguinis* FimA⁻ mutants (78) or *S. mutans* Slo⁻ (Mn^{2+}/Fe^{3+}) permease mutants (446) are severely attenuated. The Adc permease, encoded by *adcRCBA*, is involved in Zn^{2+} and Mn^{2+} uptake in *S. gordonii*, and the inactivation of *adcR* results in a competence- and biofilm-defective phenotype (365). Downstream of the *adc* operon is a copper transport operon (*copYAZ*), which is involved in biofilm detachment (408). Taken collectively, these observations suggest that metal ion homeostasis in streptococci is central to their abilities to express adhesins for interacting with host surfaces, grow in the face of environments that may be limiting in essential metal ions such as Mn^{2+} or Fe^{2+}/Fe^{3+} , resist oxidative stress and host defenses, and form biofilm communities.

Iron is essential for most bacterial pathogens. The substrate-binding components of ATP-type transporters are able to bind Fe^{3+} , the ferric siderophore complex, or heme, and these are taken across the plasma membrane concomitant with ATP hydrolysis. *S. pyogenes* expresses three transporters, FtsABCD, HtsABC (SiaABC), and MtsABC (Table 2), that acquire ferric ferriochrome, heme, and Fe^{3+}/Mn^{2+} , respectively. *S. pyogenes* can utilize heme derived from human hemoproteins as a source of iron, but the affinity by which heme is bound to host proteins is extremely high. The acquisition machinery for heme must therefore be specialized and comprises the cell surface proteins Shr and Shp and HtsABC. Shp and HtsA are both able to bind heme, but Shp cannot acquire heme from methemoglobin. Instead, it was suggested that Shr acquires heme from host proteins and transfers this directly to Shp, which then relays the heme to the lipoprotein HtsA of the heme transporter (671). In this way, heme at infection sites is effectively sequestered from host proteins bound at the streptococcal cell surface and delivered to the uptake system sited at the plasma membrane.

Regulators

Streptococci are able to coordinate changes in their environment with the modulation of a given set of genes (regulon), thereby ensuring expression of the factors necessary for sur-

vival. One way in which this is achieved is through the activities of TCSS (see above). Alternatively, streptococci possess transcriptional regulators, both activators and repressors, for which the sensory element is unknown. These are the so-called "stand-alone" regulators. Multiple examples exist across the streptococci, regulating a vast range of genes (Table 4). However, the regulatory networks and functional roles have been defined in detail for relatively few of them, examples of which will be described here.

Mga. One of the first regulators to be studied in detail was the multiple-gene regulator of GAS, Mga, previously known as VirR (virulence regulator) (565) or Mry (M protein RNA yield) (83). Mga is ubiquitous in GAS and, due to its regulation of a vast array of genes implicated in GAS pathogenesis, is often referred to as a global regulator of virulence (see references 242 and 312 for comprehensive reviews). Such genes include those encoding adhesins associated with colonization (e.g., *emm*, *sclI*, *sof*, and *fba*) and immune evasion factors (e.g., *sic*, *scpA*, and *mvp*), along with *mga* itself. Located within a region of DNA closely linked to *mga*, these genes form part of the core regulon, and Mga binds directly to their promoter regions, although a consensus binding site has yet to be defined. Mga can also regulate genes outside of this region, which include sugar utilization and metabolic operons, although its control is thought to be indirect. The expression of the Mga regulon is maximal during exponential growth, while during stationary-phase growth, the regulators RofA/Nra and Rgg/RopB repress *mga* transcription. The activation of Mga also occurs in response to elevated CO₂ levels, normal body temperature, and iron-limiting conditions. Homologs of Mga have been identified for a number of streptococci, including DmgA/MgrC of *S. dysgalactiae* and MgrA of *S. pneumoniae*. Similar to Mga, DmgA was shown to regulate transcription of the *emm* homolog *demA* and is responsive to CO₂ (183, 623). MgrA represses the expression of PI-1 in *S. pneumoniae* (230) and was found to be essential for nasopharyngeal colonization of mice (224).

RofA. Another group of regulators, first identified in GAS, is the RALP family (Table 4). Four members have been found in GAS, of which RofA and Nra are the best characterized. These regulators modulate the expression of a variety of MSCRAMMS (e.g., SfbI and Cpa) and extracellular enzymes (e.g., SLS and SpeB), along with the regulator Mga, and are associated with the abilities of GAS strains to attach to and invade host cells and to persist intracellularly (312). The expression of Nra is maximal at early stationary phase (462), while the transcription of *rofA* has been shown to respond to changes in temperature and O₂ levels (168, 562). RALP family members have also been identified in GBS and *S. pneumoniae* and have been shown to regulate virulence mechanisms including pilus expression (139, 206, 224).

Rgg. Rgg family proteins are a group of regulators that control the expression of extracellular products. Rgg was first identified in *S. gordonii* and was shown to positively regulate the expression of the GTF GtfG (578, 579). Homologs of Rgg and GtfG were then found in strains of *S. sanguinis* and *S. oralis* (627), implying an important role for Rgg in regulating the expression of these colonization determinants in oral streptococci. An Rgg regulator has also been described for *S. mutans*, designated MutR, but rather than controlling Gtf expres-

TABLE 4. Stand-alone regulators

Protein family	Protein(s)	Species	Function(s) and/or substrate(s) ^a	Reference(s)
Mga	Mga/VirR/Mry	<i>S. pyogenes</i>	Virulence (↑ <i>emm</i> , <i>sof</i> , <i>scpA</i> , <i>mrp</i> , <i>arp</i> , <i>scl1</i> , <i>sic</i> , <i>fbaA</i> , <i>nra</i>)	83, 242, 312
	DmgA/MgrC MgrA	<i>S. dysgalactiae</i> <i>S. pneumoniae</i>	Unknown Virulence (↓ PI-1)	183, 623 230
RALP	Nra	<i>S. pyogenes</i>	Virulence (↓ <i>pfbp</i> , <i>cpa</i> , <i>speB</i> , <i>speA</i> , <i>sagA</i> , <i>mga</i>)	169, 462
	RofA	<i>S. pyogenes</i>	Virulence (↑ <i>sfbl</i> ; ↓ <i>speB</i> , <i>sagA</i> , <i>mga</i>)	35, 198
	RALP3	<i>S. pyogenes</i>	Virulence (↓ <i>sdal</i> , <i>speB</i> , <i>hasA</i> , <i>lsa</i> , <i>mga</i>)	325
	RALP4 RALP5/RlrA RogB	<i>S. pyogenes</i> <i>S. pneumoniae</i> <i>S. agalactiae</i>	Unknown Colonization, virulence (↑ PI-1) Virulence (↑ <i>fbsA</i> , PI-2a; ↓ <i>cpsA</i>)	198 198, 224 139, 206
Rgg	Rgg/RopB	<i>S. pyogenes</i>	Virulence (↑ <i>csrRS</i> , <i>fasBCAX</i> , <i>ihk-irr</i> ; ↓ <i>mga</i> , <i>sagA</i>)	93, 312
	RovS	<i>S. agalactiae</i>	Virulence (↑ <i>cylE</i> , <i>sodA</i> , <i>rogB</i> ; ↓ <i>fbsA</i>)	521
	MutR	<i>S. mutans</i>	↑ <i>mutA</i>	474
	Rgg	<i>S. gordonii</i> , <i>S. sanguinis</i> , <i>S. oralis</i>	↑ <i>gtfG</i>	578, 579, 627
LacI/GalR	CcpA	<i>S. pyogenes</i>	Carbon catabolite repression, virulence (↑ <i>mga</i>)	11
	CcpA/RegM	<i>S. pneumoniae</i>	Carbon catabolite repression, virulence (↑ <i>cps</i>)	185
	CcpA/RegG	<i>S. gordonii</i>	Carbon catabolite repression (↓ <i>abpA</i>)	502
	CcpA/RegM	<i>S. mutans</i>	Carbon catabolite repression	554
	CcpA	<i>S. salivarius</i> , <i>S. sanguinis</i>	Carbon catabolite repression	324
	RegR	<i>S. pneumoniae</i>	Competence, virulence (↑ <i>comDE</i> , <i>ciaRH</i> ; ↓ <i>hyl</i>)	90
	MalR	<i>S. pneumoniae</i>	Maltose utilization (↓ <i>malXCD</i> , <i>malMP</i>)	473
	ScrR ScrR, SusR	<i>S. mutans</i> <i>S. pneumoniae</i>	Sucrose utilization (↓ <i>scrAB</i>) Sucrose utilization, colonization (↓ <i>scrTKH</i> , <i>susTIT2X</i>)	238, 634 255, 256
DeoR	FruR	<i>S. mutans</i> , <i>S. gordonii</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. mitis</i>	Fructose utilization (↓ <i>fruRKT</i>)	38, 364
	FxpA	<i>S. mutans</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i>	Fructose and xylitol utilization (↓ <i>fxpABC</i>)	38
	LacR	<i>S. mutans</i>	Lactose utilization (↓ <i>lacABCDFE</i>)	511
DtxR	MtsR	<i>S. pyogenes</i>	Iron homeostasis, virulence (↓ <i>siaABC</i> , <i>shr</i>)	33
	PsaR	<i>S. pneumoniae</i>	Mn homeostasis, virulence (↓ <i>psaBCA</i> , <i>pcpA</i> , <i>rlrA</i>)	278
	SloR/Dlg	<i>S. mutans</i>	Mn homeostasis, virulence (↓ <i>sloABC</i> , <i>fimA</i> ; ↑ <i>ropA</i> , <i>spaP</i> , <i>comDE</i> , <i>sod</i> , <i>gbpB</i> , <i>gtfB</i> , <i>gcrR</i>)	141, 503
	ScaR AdcR	<i>S. gordonii</i> <i>S. pneumoniae</i>	Mn homeostasis (↓ <i>scaCBA</i>) Mn homeostasis, competence (↓ <i>adcCBA</i> , <i>phtA</i> , <i>phtB</i> , <i>phtD</i> , <i>phtE</i>)	262 134, 432
	AdcR	<i>S. gordonii</i>	Mn homeostasis, biofilm formation (↓ <i>adcCBA</i>)	365
	AdcR	<i>S. pyogenes</i>	Mn homeostasis, competence, biofilm formation (↓ <i>adcCBA</i> , <i>phiD</i> , <i>phY</i> , <i>rpsN2</i> , <i>lsp</i>)	65
	Fur	PerR	<i>S. pyogenes</i>	Iron and sugar homeostasis, peroxide and phagocytic killing resistance, virulence (↑ <i>sodA</i> , <i>mtsA</i> , <i>csp</i> , <i>czcD</i> ; ↓ <i>mrgA</i> , <i>pmtA</i>)
LysR	MtaR	<i>S. agalactiae</i>	Methionine utilization, virulence (↑ <i>metQINP</i> , <i>pdsM</i> , <i>artPQ</i> , <i>artGH</i> , <i>manB</i> , <i>cspA</i> ; ↓ <i>fbsB</i>)	75, 550

Continued on following page

TABLE 4—Continued

Protein family	Protein(s)	Species	Function(s) and/or substrate(s) ^a	Reference(s)
	MetR	<i>S. mutans</i>	Methionine utilization (↑ <i>metEF</i> , <i>atmBDE</i>)	568
Crp/Fnr	Srv	<i>S. pyogenes</i>	Virulence, biofilm formation (↑ <i>sic</i> , <i>mga</i> , <i>dpp</i> , <i>ropA</i> , <i>htrA</i> , <i>luxS</i> ; ↓ <i>speB</i>)	136, 492, 493
CodY	CodY	<i>S. pneumoniae</i>	Amino acid metabolism, colonization (↑ <i>pcpA</i> ; ↓ <i>ilvBNC</i> , <i>ilvA</i> , <i>ilvE</i> , <i>livJ</i> , <i>amiA</i> , <i>aliB</i> , <i>gdhA</i> , <i>fatD</i> , <i>acuB</i> , <i>asd</i> , <i>gapN</i>)	231
	CodY	<i>S. pyogenes</i>	Amino acid metabolism, virulence (↑ <i>pel</i> [<i>sagA</i>], <i>mga</i> , <i>dppA</i> , <i>prtS</i> ; ↓ <i>covRS</i> , <i>ropB</i> , <i>pyrR</i> , <i>graB</i> , <i>pncA</i>)	380
	CodY	<i>S. mutans</i>	Amino acid metabolism, acid tolerance, biofilm formation (↑ <i>feoA</i> ; ↓ <i>ilvC</i> , <i>livK</i> , <i>gdhA</i> , <i>hisE</i>)	345
AraC	MsmR	<i>S. pyogenes</i>	Colonization, cytolysin-mediated translocation (↑ <i>nra</i> , <i>cpa</i> , <i>prtF2</i> , <i>sclA</i> , <i>fbaA</i> , <i>scpA</i> , <i>sof</i> , <i>sfbX</i> , <i>hasA</i> , <i>nga</i> , <i>slo</i>)	419
	MsmR	<i>S. mutans</i>	Sugar metabolism (↑ <i>aga</i> , <i>dexB</i>)	518
	PblR	<i>S. mitis</i>	Unknown	40
Other regulators	Frp	<i>S. mutans</i>	Exopolysaccharide synthesis, biofilm formation, competence (↑ <i>fff</i> , <i>gtfB</i> , <i>gtfC</i> , <i>comC</i>)	551, 633
	BrpA	<i>S. mutans</i>	Biofilm formation, virulence (↑ <i>fruC</i> , <i>atpD</i> , <i>recA</i> ; ↓ <i>sod</i> , <i>nox</i> , <i>dpr</i>)	418, 642, 643
	RelA, RelP, RelQ	<i>S. mutans</i> , <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. dysgalactiae</i>	Stringent response [(p)ppGpp synthesis]	183, 343, 344, 400, 421
Alternative regulatory mechanisms	LacD.1	<i>S. pyogenes</i>	Class I tagatose-1,6-bisphosphate aldolase; virulence (↓ <i>speB</i>)	367
	LuxS	<i>S. mutans</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>S. anginosus</i> , <i>S. agalactiae</i> , <i>S. gordonii</i> , <i>S. oralis</i>	Acid and oxidative stress tolerance, carbohydrate metabolism, biofilm formation, virulence (AI-2 production)	220, 372, 395, 403, 440, 454, 497, 582

^a ↑, gene/protein expression is upregulated; ↓, gene/protein expression is downregulated.

sion, MutR regulates lantibiotic mutacin II (MutA). While these examples describe Rgg regulation of a single gene, Rgg (or RopB) and RovS of GAS and *S. pneumoniae*, respectively, have been shown to control the expression of multiple genes. In GAS, mutation of Rgg affects the transcription of a number of virulence factor genes, including *speB*, *mac*, *sagA*, and *slo* (312). However, rather than direct regulation, these effects are associated predominantly with Rgg modulation of other regulatory systems such as Mga, CsrRS, FasBCA, and Ihk-Irr (93). Conversely, RovS of *S. pneumoniae* was found to regulate the expression of FbsA, SodA, and CylE by binding directly to the promoter regions of their genes (521). Despite the implied importance of Rgg regulators to streptococcal colonization and pathogenesis, little is yet known about the stimuli to which they respond.

LacI/GalR. Efficient nutrient utilization is critical for bacterial survival. Consequently, the genes involved in these processes are tightly controlled, and many representative regulators can be found in Table 4. Of these, one of the largest protein families is the LacI/GalR family, which includes regulators of carbohydrate utilization. Streptococci, particularly those that colonize the oral cavity, must often survive under

conditions of carbohydrate starvation that alternate with periods of sugar excess. One mechanism that streptococci have developed to cope with this situation is carbohydrate catabolite repression. This enables bacteria to repress the metabolism of a complex sugar source in favor of one that is readily metabolizable and is controlled by the global regulatory protein CcpA (see reference 638 for a detailed review of this mechanism). Upon activation by glycolytic intermediates, CcpA binds catabolite response elements in the promoters of a specific set of genes associated with carbohydrate utilization, blocking their transcription. Interestingly, CcpA regulation has also been shown to contribute to streptococcal virulence (547). The mutation of CcpA (RegM) in *S. pneumoniae* resulted in reduced virulence in mouse models of bacteremia and nasopharyngeal colonization. This was associated with changes in the pneumococcal cell surface, including reduced levels of expression of polysaccharide capsule and enolase (185, 255). Similarly, in the absence of CcpA, GAS was significantly impaired in its ability to colonize the mouse oropharynx, and CcpA was found to modulate the expression of a number of virulence factors both via the regulator Mga and by direct promoter binding (11, 547). Given the widespread distribution of CcpA

homologs across streptococci, this may represent an important regulatory mechanism of streptococcal colonization.

Virulence Factors

Pyogenic streptococci produce an array of virulence factors (recently reviewed in references 437 and 599) that include extracellular enzymes, toxins, and surface proteins, all of which have the ability to modulate antibody recognition and immune cell function (119). The activities of some of these, e.g., M protein and C5a peptidase, have already been considered above. Those not already discussed and of notable relevance to adherence and the initiation of disease are SpeB, SLO, streptokinase, and superantigens. SpeB cysteine protease is a crucial virulence factor, which is able to modulate functions of *S. pyogenes* cell surface proteins in colonization and significantly contribute to tissue destruction in necrotizing fasciitis. SpeB can cleave host ECM proteins, e.g., Fn, as well as immune system components, e.g., the antimicrobial peptide cathelicidin LL-37, and activates matrix metalloproteinases to promote further tissue damage and the release of proapoptotic factors (594). SLO is a human-specific cytolysin (Table 2) with a range of properties, including the ability to form pores through which effector proteins, e.g., NAD⁺ glycohydrolase (SN), may be injected into the host cell cytoplasm (184). An important property of SLO in colonization is that it prevents the internalization of GAS by lysosomes, thus enhancing the intracellular survival of GAS within epithelial cells (208). This is believed to be a feature involved in the long-term carriage of not only GAS but also commensal oral streptococci (514), which may potentially survive for long periods within epithelial cells, partially protected from immune defenses and from antibiotics.

A common defense mechanism to prevent the systemic spread of infecting bacteria involves the encapsulation of bacteria within fibrin networks. The acquisition of plasmin at the bacterial cell surface circumvents this defense process. Streptokinase is a plasminogen-activating protein produced by GAS that combines with plasminogen to make functional plasmin. This can hydrolyze fibrin and promote the spread of GAS through tissues. Streptokinase is an important virulence factor that acts in concert with plasmin(ogen)-binding proteins (Table 1), and the reader is referred to a recent article for further information (388).

A significant feature of GAS and group C and group G *Streptococcus* is the production of a range of superantigens (Sags), with 11 found to date in GAS. Sags are released as toxins that can activate a large proportion of the T-cell population, eliciting an inflammatory response. The excessive uncoordinated release of cytokines such as IL-1, IL-2, IL-6, TNF- α , IFN- γ , and macrophage inflammatory protein 1 α , etc., overloads the body, resulting in rash, fever, organ failure, coma, and death. These effects are associated more with overt infection than with initial colonization and therefore will not be further advanced in this article, but the reader is referred to a recent detailed review (172).

COMMUNITY DEVELOPMENT

Left undisturbed, assemblages of adherent organisms develop into complex communities. Increases in biomass can

occur through growth and division or through the recruitment and retention of additional organisms from the fluid phase. Bacteria within these communities encounter higher cell densities than their planktonic counterparts. In consequence, community living involves adaptation to higher (and unevenly distributed) levels of metabolic by-products, secondary metabolites, and other secreted molecules, along with lower levels of nutrients and oxygen. Bacterial inhabitants of biofilms are known to both collaborate (e.g., through nutritional cross-feeding) and compete (e.g., through the production of bacteriocins) as they strive to optimize their adaptation to these environmental constraints. More recently, it has become apparent that bacteria can communicate with one another through a variety of sensing and response systems based on either cell-to-cell contact or the detection of soluble mediators. The signaling molecules are processed through transcriptional and posttranscriptional networks, and they allow bacterial inhabitants of biofilms to coordinate activities at a group or community level.

Peptide-Mediated Signaling

Many gram-positive bacteria utilize competence-stimulating peptide (CSP), such as the pneumococcal 21-aa-peptide pheromone, to trigger readiness for natural transformation (reviewed in references 542 and 581). CSP is also a quorum-sensing signal that is secreted into the milieu and initiates competence development throughout the bacterial culture after exceeding a threshold level. In the archetypal pneumococcal system, extracellular CSP binds to a sensor histidine kinase, ComD, which, with the response regulator ComE, forms a TCSS (Table 3) that initiates temporally distinct waves of transcriptional activity. First, there is an upregulation of the CSP precursor (*comC*), which, along with *comDE*, forms an operon. ComE also controls *comAB* and *comX*. ComA is an ABC transporter that, together with its accessory protein ComB, exports CSP following the removal of the leader peptide distal to a Gly-Gly motif (double-glycine leader) of the pre-CSP (453). ComX induces the second phase of gene regulation that includes components of the DNA uptake and integration systems (the late-competence genes) through the recognition of a *com* box (or *cin* box) consensus sequence in the upstream regulatory region of target genes. This is followed by an induction of the delayed class of stress-related genes and then by the repression of genes involved in protein synthesis. Many of the mitis group and anginosus group streptococci have a genetic arrangement similar to that of the pneumococci; however, in *S. mutans*, *comC* has a distinct promoter (581). The repertoire of genes controlled by the CSP system extends beyond competence and includes bacteriocin production, adaptation to low pH, virulence-associated properties, and biofilm formation.

In *S. mutans*, the loss of CSP results in biofilms with altered architectures, whereas mutants defective in *comD*, *comE*, or *comX* are deficient in adherence and form biofilms with reduced masses (354). The loss of ComA and ComB also attenuates biofilm formation (662). Collectively, these results indicate that multiple biofilm control pathways in *S. mutans* are influenced by CSP (Fig. 6). In addition, the TCSS HK/RR11 (Table 3) controls biofilm architecture, and HK11 may act as a second receptor for CSP (355). CSP-mediated communication has also been shown to be important for biofilm formation in

S. gordonii (362) and *S. intermedius* (457). Structure-function studies have revealed that *S. mutans* CSP possesses at least two functional domains. The C-terminal structural motif comprises polar hydrophobic charged residues and is required for the activation of the signal transduction pathway, while the core α -helical structure extending from residue 5 to the end of the peptide is necessary for receptor binding (585). Some strains of GAS possess a putative CSP-like communication system known as Sil (341). The *sil* locus encodes an ABC transporter comprised of SilD and SilE, a TCSS (SilAB), and two small converging overlapping open reading frames (SilC and SilCR). The CSP-like peptide is encoded by SilCR, whereas SilC encodes a signaling peptide. Together, SilC and SilCR form a novel regulatory circuit that controls the transcription of the *sil* locus (151). The deletion of *silC* drastically reduces biofilm accumulation by GAS (341). The aggregation of GAS into microcolonies is also dependent on AHP, a conserved 19-aa-residue peptide present in M protein and in protein H (174).

The evolutionary driving force that ties CSP to biofilm formation may be related to the ability of streptococcal cells in a biofilm to incorporate foreign DNA more efficiently than equivalent cells in suspension (352). Transcriptional upregulation of *comCDE* and *comX* has been demonstrated in actively growing biofilms of *S. mutans* and *S. gordonii* (21, 193, 354). Moreover, the production of bacteriocins and bacteriocin immunity proteins is coordinated by CSP through ComE binding to direct repeats in the promoter regions (315, 387). Along with the regulation of autolysis by the CSP system (315, 475, 666), these mechanisms will ensure the availability of DNA in biofilms. DNA may be used to increase genetic variability or as a nutrient source (570). In addition, however, DNA can comprise a major component of the ECM in *S. mutans* biofilms (458) and contribute to biofilm formation in a structural capacity.

Diffusible Signals and Environmental Factors

The close proximity of bacteria in biofilms provides an environment conducive to signaling through short-range diffusible mediators such as metabolites and autoinducers (Fig. 6). Oral streptococci, GAS, and GBS all produce autoinducer-2 (AI-2). While CSP signaling is species or strain specific, the AI-2 quorum-sensing system, originally identified in *Vibrio harveyi*, is considered to be not species specific and may function as a universal bacterial language (654). AI-2 is produced through the action of the LuxS enzyme, which cleaves *S*-ribosylhomocysteine to produce homocysteine and the AI-2 precursor 4,5-dihydroxy-2,3-pentanedione. This reaction is also a major component of the activated methyl cycle that recycles homocysteine from *S*-adenosyl methionine (220). AI-2 is more accurately a collective term for a group of structurally related molecules generated from the spontaneous cyclization of 4,5-dihydroxy-2,3-pentanedione (405, 569). In *V. harveyi*, AI-2 above a threshold concentration is detected by LuxPQ, which channel information to the phosphotransferase protein LuxU. LuxU, in turn, transfers the signal to LuxO, a σ^{54} -dependent transcriptional activator (37). Other bacterial species may process AI-2 by different mechanisms (546, 586), and indeed, AI-2 signaling is not always density dependent (264). In some cases,

AI-2 may have a physiological role related to the activated methyl cycle rather than a signaling role (220).

Many gram-positive bacteria, including streptococci, possess *luxS* and respond to AI-2, and this signaling has been associated with biofilm formation. However, despite intense study, a clearly defined role for AI-2 has not yet emerged, and the impact of AI-2 on streptococcal biofilm formation appears to be assay and growth condition dependent. For example, an early study with a *luxS* mutant of *S. mutans* reported no difference in the abilities of parent and mutant strains to form biofilms in microtiter plates (643). However, a subsequent microscopic visualization found architectural differences between biofilms of parent and *luxS* mutant *S. mutans* strains (403). The role of AI-2 in *S. mutans* biofilm structure has since been observed consistently (644, 661) and is dependent on the presence of sucrose in the growth medium (661). Sucrose dependence is related to the regulation of the GTF genes *gtfB* and *gtfC* by LuxS (661). In *S. mutans*, LuxS also controls the production of the lantibiotic bacteriocin mutacin I (which is not controlled by the CSP system) at the transcriptional level (402). In the absence of AI-2, the level of expression of the transcriptional regulator IrvA is increased, which leads to the repression of *mutA* (encoding mutacin I) and *mutR* (encoding a specific transcriptional activator of *mutA*) and reduced levels of mutacin I production. AI-2 also controls biofilm development by *S. gordonii*, and the inability to produce AI-2 is associated with an altered microcolony architecture (58). LuxS controls GTF activity, and indeed, AI-2 affects several aspects of carbohydrate metabolism in *S. gordonii*. The presence of AI-2 favors the utilization of sucrose by *S. gordonii*, whereas in its absence, lactose and other galactose-containing sugars are metabolized preferentially (395).

Many streptococcal biofilms in nature, particularly in the oral cavity, are polymicrobial, and AI-2 can play a role in the formation of these heterotypic communities. Mutualistic biofilm growth of *S. oralis* and *A. naeslundii* in flowing saliva is dependent upon the production of AI-2 by *S. oralis* (498). Furthermore, this effect is dependent on the AI-2 concentration, and heterotypic biofilm formation is suppressed above and below threshold concentrations. AI-2 is also required for the accumulation of mixed biofilms of *S. gordonii* with the periodontal pathogen *P. gingivalis* (395). Interestingly, the bacterial source of AI-2 is unimportant, as *luxS* mutants of either *S. gordonii* or *P. gingivalis* form biofilms in the presence of the wild-type partner organisms. Heterotypic communities do not accumulate, however, when AI-2 production is disrupted in both organisms.

Metabolic communication that extends beyond the provision of nutrients is a feature of high-density heterotypic biofilms. For example, oral streptococci coaggregate with *Veillonella atypica*, and these organisms are also metabolically compatible, as *S. gordonii* ferments carbohydrates to form lactic acid, which is a preferred fermentation substrate for *V. atypica* (Fig. 4D). In addition, however, a short-range diffusible signal is produced by *V. atypica* that induces expression of the α -amylase-encoding gene *amyB* in *S. gordonii* (146).

Related species of oral streptococci, in contrast, compete for space and resources. For example, under aerobic conditions, *S. sanguinis* and *S. gordonii* produce hydrogen peroxide more efficiently than *S. mutans* and, consequently, *S. mutans* is in-

hibited in mixed communities of these three species (319). Furthermore, in the presence of oxygen, *S. sanguinis* and *S. gordonii* release more DNA, which can stabilize biofilm structure, but may also be acquired by *S. mutans* cells that are more competent within biofilms (discussed above). In retaliation, *S. mutans* within biofilms increases the production of bacteriocins that target *S. sanguinis* and *S. gordonii* (316). The “arms race” escalates as *S. gordonii* in biofilms can interfere with bacteriocin production by *S. mutans* (636). The ongoing blows and counterblows struck by these organisms result in “competitive exclusion,” and hence, the establishment of *S. gordonii*/*S. sanguinis* or of *S. mutans* in a niche precludes colonization by the antagonistic species (316).

Cell-to-Cell Communication

Signaling mediated by surface contact is emerging as an important means of information transfer in bacteria. The streptococci dominate the densely packed biofilms that develop on supragingival tooth surfaces and will thereby be in direct contact with numerous other oral biofilm constituents. Signaling can ensue from adhesin-receptor binding or from the activation of surface proteins not associated with adherence. One of the best-studied examples is coadhesion and communication between *S. gordonii* and *P. gingivalis*. On the streptococcal surface, the AgI/II proteins SspA and SspB interact with short fimbriae (containing the Mfa major subunit protein) of *P. gingivalis* (273). The engagement of SspA or SspB with the short fimbriae initiates a signaling event within *P. gingivalis* cells that facilitates biofilm accumulation (68, 327). Structure-function analyses of the mechanism of the Mfa-SspB interaction identified a functional domain of SspB, designated BAR (SspB adherence region), spanning aa 1167 to 1193, that is fully conserved between SspA and SspB (68, 124). Within BAR, the N¹¹⁸² and V¹¹⁸⁵ of an NITVK motif are essential for the Mfa recognition of SspB, and these residues, along with T¹¹⁸⁴, are not conserved in SpaP, the *S. mutans* homolog of Ssp that does not bind to Mfa (124, 128). The substitution of basic amino acids or serine for N¹¹⁸² and the substitution of the hydrophobic residue Ile, Trp, or Phe for V¹¹⁸⁵ enhance the level of *P. gingivalis* binding to BAR, suggesting that both electrostatic and hydrophobic interactions contribute to BAR-Mfa binding. Furthermore, the substitution of the α -helix-breaking residue Pro or Gly is detrimental to *P. gingivalis* adherence, consistent with secondary structure playing a role in *P. gingivalis* adherence.

BAR also possesses a region resembling a known protein-protein-interacting motif, the eukaryotic nuclear receptor (NR) box (528). Interactions of NRs with their coactivating proteins are driven by the association of a hydrophobic α -helix of consensus sequence LXXLL, the NR box, with a hydrophobic pocket in the NR protein. This initial interaction is stabilized by electrostatic interactions that form with charged amino acids that flank LXXLL (528). The specificity of the coactivator interaction with a given NR is thus determined by the residues that reside on either side of LXXLL. The BAR peptide contains a predicted hydrophobic α -helix of the sequence VXXLL that is flanked on each side by positively charged lysine residues (125). This region resides immediately upstream from the NITVK motif. The introduction of amino

acids with the potential to disrupt the secondary structure of VXXLL reduced the specific binding activity of BAR, suggesting that the putative α -helical character of VXXLL is important for the interaction of BAR with Mfa (125). Furthermore, replacing the lysines that flank VQDLL with acidic amino acids also reduced the binding activity, indicating that the association of VQDLL with Mfa may be stabilized by a charge clamp. The outcome of SspB-Mfa binding is a shift in the metabolic activity of *P. gingivalis*, including an increase in levels of extracellular polysaccharide synthesis, which enhances structure and leads to the recruitment of additional *P. gingivalis* cells (375, 552).

Conversely, contact with *S. cristatus* propagates a signal in *P. gingivalis* that causes the downregulation of *fimA* expression, with a resultant reduction in the amount of long fimbriae (containing the FimA major subunit protein) on the surface of *P. gingivalis* and the failure of these organisms to develop a heterotypic biofilm (655). Signaling is mediated by arginine deiminase (ArcA) on the surface of *S. cristatus* (656). While ArcA is an enzyme involved in the arginine metabolism pathway that converts arginine to ornithine, ammonia, and CO₂, the signaling function of ArcA does not depend on enzymatic activity (356). Although *S. gordonii* also expresses ArcA, the ability of *S. cristatus* to repress FimA production is related to the elevated level of expression of *arcA* due to differences in the *cis* catabolite response elements of *arcA* and in the expression of *trans*-acting regulatory proteins (356).

Cell-to-cell communication in densely packed communities can also contribute to optimal metabolic activity in the participating organisms. Contact between *S. gordonii* and *A. naeslundii* induces the differential expression of genes involved in streptococcal arginine biosynthesis and transport (258). As a result, *S. gordonii* in a dual-species community is capable of aerobic growth when exogenous arginine is limited. Moreover, *A. naeslundii* produces catalase that can remove H₂O₂ from dual-species cultures and consequently decrease the level of oxidation of arginine residues in *S. gordonii* proteins (259). Interspecies interactions thus drive these organisms toward an ecologically balanced community.

CONCLUSION

Streptococcal adherence and colonization are complex multilevel processes that define the success or failure of the organism in human ecosystems. As such, streptococci devote considerable resources to ensuring the availability of an appropriate repertoire of effector molecules (Fig. 3) with sufficient redundancy to be robust in situations where one particular activity is unavailable or impeded by host or other bacterial factors. Moreover, these are not passive events; rather, streptococci are continuously monitoring the local environment and fine-tuning the expression of adhesins, communication systems, and metabolic pathways to optimize fitness under the prevailing conditions. The universal presence of streptococci in humans (and in many other animal hosts) reflects the success of these strategies. Paradoxically, the strengths of the streptococcal colonization mechanisms may also turn out to be weaknesses that can be exploited to develop new ways to control colonization and infection.

Vaccination against pathogenic species is very much a pre-

ferred strategy because it reduces the usage of antibiotics. These may be harmful, as in the case of application to pregnant mothers to act against potential GBS infection of neonates, or simply add to the ongoing problem of antibiotic resistance development. However, the vaccine route is fraught with difficulties, a major one being that the best protective (opsonic) antibodies are directed against cell surface components that are highly antigenically variable. A strategy being adopted for GAS is to string together multiple A regions of M proteins representing the most invasive serotypes and then use this as a polyvalent vaccine. This avoids the conformational regions of M protein that may generate cross-reactive antibodies to heart, brain, kidney, or joint cartilage and includes the opsonic epitopes. A 26-valent vaccine of this type has been shown to be well tolerated in human adult volunteers (126). However, the experience with pneumococcus conjugate vaccine comprised of seven or nine CPS serotypes is that the elimination of vaccine serotypes leads to serotype replacement and the emergence of new virulent strains. The careful construction of vaccine epitopes may go some way to reducing this, but nevertheless, the antigens to which protective antibodies have to be made are subject to immune selection. The many facets of GAS pathogenesis have been recently summarized in an excellent review (437), and the reader is referred to that article for detailed information about virulence factors.

The sialic acid-containing CPS has been a focus of most vaccine strategies for GBS to date, and clinical trials with conjugate vaccines covering five CPS serotypes have shown them to be safe and immunogenic (24). There are nine distinct CPS serotypes, but even a 9-valent vaccine would not protect against the increasing number of nontypeable isolates (24). A protein-based vaccine could, on the other hand, provide antigenic targets that are conserved across all GBS serotypes. Major surface proteins include the Alp family of proteins, e.g., α , Rib, R28, and Alp2 (357, 571, 572), that elicit protective immunity; ScpB C5a peptidase (96); β protein that binds IgA and factor H (373, 374); Lmb (228, 567); FbsA fibrinogen-binding protein (535); Sip (67, 385); LrrG (538); and CspA protease (221). Some of these proteins are promising vaccine candidates, but their potential for cross-protection is relatively unknown (279). More recently, the components of GAS and GBS pili have been a focus of vaccine design. Backbone and ancillary subunits from each GBS PI have been shown to elicit protective immunity against GBS in a neonatal mouse model of immunization (376, 383, 512). A vaccine comprising three selected pilus protein subunits could potentially confer protection against 94% GBS strains currently found in the United States and Italy (383).

Anti-dental-caries vaccines have been under study since it was first shown that antigens from *S. mutans* cells, such as Gtf, Gbp, and AgI/II, were protective against *S. mutans* colonization and caries in animal models (557). Clinical trials have tested the delivery of *S. mutans* antigens via the nasal route to utilize the inductive characteristics of nasally associated lymphoid tissue for secretory IgA and IgG antibodies. Immunization with Gtf or GbpB consistently produces high levels of salivary antibodies and reductions in experimental dental caries. The oral health impact on children would be huge, especially for those who are at high risk, if an effective dental caries vaccine were to be developed that was stable and could be

administered mucosally (560). There are many interesting strategies under development that could affect longer-term colonization patterns of bacteria on mucosal surfaces or hard surfaces, e.g., teeth, to promote health. It is thought that the early retention of some organisms, e.g., *S. salivarius* and *S. sanguinis*, within the oral cavity of infants may be beneficial to their future oral health (88). It is possible, then, that by supplementing the oropharynx or nasopharynx with selected streptococcal species shortly after birth and during infancy, less desirable bacterial species may be excluded. There is evidence that colonization of the tongue and throat by bacteriocin-producing *S. salivarius* may assist in reducing the incidence of GAS pharyngitis in children (132). Replacement therapy has been considered to have potential for controlling *S. mutans* levels. By introducing an engineered nonpathogenic strain of *S. mutans* with a selective advantage, it might be possible to replace pathogenic strains, but the efficacy when applied to human subjects remains to be established.

Biofilm formation occurs as a result of initial adherence, the growth of societies involving quorum sensing, and then community development associated with a range of intermicrobial communication reactions. In terms of preventing specific organisms from depositing onto surfaces or being incorporated into communities, promising results have been obtained by blocking the adherence of *S. mutans* to salivary pellicles with peptides that mimic the streptococcal AgI/II surface protein adhesin (292). Variable-F_c-chain antibodies to AgI/II expressed by lactobacilli have been shown to prevent *S. mutans* colonization and caries development in rodent models of infection (321). These observations suggest that there may be alternatives to vaccination and antibiotics for modulating *Streptococcus* colonization. However, in removing a component of the natural microflora, there is a potential for exposing a niche that could be colonized by another less desirable organism.

Although not yet tried with complex biofilm communities, inhibitors of quorum sensing have been shown to effectively impair normal biofilm formation. Bromofuranone interferes with AI-2 signaling pathways and inhibits the formation of single-species biofilms of *S. mutans* and *S. intermedius* (361). However, halogenated furanones show toxic side effects on human cells and possible carcinogenic properties that make them unsuitable for use as pharmaceuticals for humans (56). It is possible that nontoxic microbial signaling inhibitors (486) or biomimetics (391) that disrupt the interactions that occur between streptococci in establishing biofilms might be found.

It is clear that new approaches are required, informed by microbiology, immunology, and molecular biology, to control components of microbial communities that form on or in the human body. The increased use of DNA sequencing for the characterization of pathogens, commensals, and complex ecosystems such as the oral microbiome has led to new approaches in the study of host-bacterium interactions. The *in silico* prediction of streptococcal surface-exposed proteins (27) is of interest for the rational development of vaccines or new inhibitors. The continuing use of broad-spectrum antibiotics to resolve problems associated with streptococcal infections might not be sustainable in the future, with the increasing incidence of antibiotic resistance. Since streptococci need to colonize mucosal surfaces, mainly in the upper respiratory tract, to be

carried long-term or prior to causing infection, it seems crucial that nonantibiotic measures be developed in order to control colonization. The oropharynx and microflora therein provide an ideal system for experimental studies. The results of such studies might lead to an extension of methodologies to control the colonization of streptococci at other body sites.

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