**Secretion Systems, Adhesins, and Invasins**

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**Staphylococcus aureus** Pathogenesis

**SECRETION SYSTEMS**

Precursor proteins formed by the bacterial cell for diverse functions need to be transported to their correct cellular destinations while undergoing structural changes. Secretion systems direct these events. In bacteria, the majority of precursor proteins are integrated into or transported across membranes by the Sec pathway.

The bacterial Sec system consists of a membrane complex that forms a translocation channel (SecYEG) through which polypeptides pass, a cytosolic ATPase and a chaperone protein (SecB) which binds and a chaperone protein (SecB) which binds to the polypeptide and aids in the initial translocation steps. Certain features of the synthesized protein will determine its final location. For example, a cell-wall retention signal results in covalent attachment of the protein to the cell wall while a transmembrane-spanning domain leads to insertion of the protein into the cell membrane. If these features are absent, the protein is secreted into the extracellular space as in the case of enterotoxins and hemolysins.

The SecA component of the Sec system is essential for bacterial survival and there is no human analogue. Thus, SecA is an attractive target for development of novel antimicrobials. Small synthetic inhibitors that block the SecA enzymatic function have been identified and can be used to further study protein transport in bacteria and may, in the future, be developed into antimicrobial agents.

**ADHESINS**

Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) are cell wall-anchored proteins secreted via the Sec system. MSCRAMMs are involved in attachment of *S. aureus* to host cells or extracellular matrix as a first step in the development of infection. MSCRAMMs have a common cell wall sorting signal LPXTG motif through which they are covalently anchored to the cell wall peptidoglycan by sortase A.

MSCRAMMs were identified by their ability to bind extracellular matrix proteins such as fibrinogen (ClfA, ClfB), fibronectin (FnbpA, FnbpB), and collagen (Cna). A total of 21 MSCRAMMs have been identified but many host protein(s) to which these MSCRAMMs bind remain unknown. Certain MSCRAMMs, such as CiaA and SdrC are found in virtually all clinical *S. aureus* strains screened, whereas others, such as Cna and SdrD, are present only in a subset of strains.

There is redundancy in the MSCRAMM family with regards to host-bacterial protein recognition; many host proteins have the ability to bind more than 1 MSCRAMM and certain MSCRAMMs can bind to multiple host proteins. Multiple MSCRAMMs contribute to nasal colonization, including ClfB, which binds cytokinin-10 in nasal epithelial cells, SdrA, SdrD, and SdrF. Colonization of the nares and

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other body sites such as the perineum and pharynx has been detected in up to 50% of the population and is a risk factor for S. aureus infection in both adults and children.19

Previous attempts to use anti-MSCRAMM antibodies as passive immunization for the prevention of staphylococcal disease in neonates13 or treatment of staphylococcal disease in adults12 have been unsuccessful. However, encouraging results from animal studies will likely spur continued research and development of MSCRAMM-containing vaccines. In particular, MSCRAMMs IsdA, IsdB, SdrD, and SdrE were identified as protective in a murine model of abscess formation.13 Current active immunization protocols include a study using IsdB (available at: www.clinicaltrials.gov identifier NCT00518687) and one using 3 unspecified MSCRAMMs (available at: www.clinicaltrials.gov identifier NCT01018641) as antigens.

Another recently recognized adhesin group is the SERAMs (Secretable Expanded Repertoire Adhesive Molecules). SERAMs are not structurally related, but share a common functionality; their role in infection is unclear. The SERAM Eap binds multiple matrix proteins, including fibrinogen, fibronectin, prothrombin, and vitronectin and, after secretion, can rebind to S. aureus and mediate adhesion by acting as a bridge between bacteria and host cell.14

**INVASINS**

*S. aureus* is generally thought of as an extracellular pathogen, but it can be internalized by a variety of cell types in vitro (e.g., fibroblasts, osteoblasts, keratinocytes, and endothelial cells15) and in animal models (endothelial cells16 and osteoblasts17). This process may be important in systemic spread of infection, escape from antibiotic pressure and evasion of the host immune system.15 In vitro and animal model data suggest the chronic and recurrent nature of endocarditis and osteomyelitis may, in part, be due to intracellular bacteria. Internalized *S. aureus* have been described in chronic, recurrent infections in humans. Focal intracellular reservoirs of *S. aureus* have been reported in nasal mucosal cells in adults with recurrent rhinosinusitis18 and tonsillar tissue in children and adults with recurrent pharyngitis.19

Several MSCRAMMs are recognized as invasins. FbpA and B bind fibronecin which interacts with the host cell integrin α5β1.20 Integrins cluster and initiate a signaling pathway causing rearrangement of the host cell actin cytoskeleton and bacterial uptake. CIFA-mediated *S. aureus* attachment to murine heart valves in an endocarditis model, but disease progression from colonization of fibrin clots to endothelial invasion and subsequent systemic spread required fibronecin binding proteins.16 Internalization as a mechanism for antibiotic evasion was studied in cell culture models. In mouse osteoblasts, *S. aureus* demonstrated decreased susceptibility to antibiotics with good intracellular penetration (clindamycin, erythromycin, and rifampin). An associated alteration in the bacterial cell surface also was noted, although the precise nature of this alteration remains unclear.21

**SUMMARY**

*Staphylococcus aureus* is a complex pathogen with numerous classes of virulence factors. Protein secretion principally occurs via the Sec system and is required to render many virulence factors functional. Compounds which selectively block bacterial protein secretion while leaving the host system unaffected may lead to novel antimicrobial therapies.

Adherence to host tissues involves MSCRAMMs which are redundant and overlapping. MSCRAMMs continue to be targets of interest for vaccine development, although no current immunization studies involve children. The role of vaccines in combating *S. aureus* disease and the identification of populations which should be targeted for immunization strategies are questions yet to be resolved.

The importance of *S. aureus*’ capability to invade and replicate in nonprofessional phagocytic cells is unclear; intracellular persistence with subsequent decreased antibiotic exposure could, in the future, impact decisions of drug choice and therapy duration for infections such as endocarditis and osteomyelitis.

An improved understanding of protein secretion, tissue adherence and internalization in *S. aureus* pathogenesis carries the promise of identification of new targets for novel therapies for preventing and treating both acute and chronic *S. aureus* infections.

**REFERENCES**