A Review on *Staphylococcus aureus* Pathogenesis

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**ABSTRACT**

Over the millennia, *Staphylococcus aureus* has evolved evasion strategies to overcome a myriad of chemical and environmental challenges, including antibacterial drugs and infections that are caused by antibiotic-resistant strains often occur in epidemic waves that are initiated by one or a few successful clones. Detailed mechanistic insights of the mechanisms by which such resistance could emerge will be helpful in development of strategies to minimize this potential problem. Using the data obtained through local strain genotyping there is a need for construction of a broad systems biology-based tool that could be used to predict virulence phenotypes from *S. aureus* genomic sequences.

**Introduction**

*Staphylococcus aureus* is a major human bacterial pathogen which causes a variety of community acquired and nosocomial infections ranging from skin infection to deep abscess and clinical syndromes such as pneumonia, osteomyelitis and endocarditis. *S. aureus* pathogenesis is linked with a broad range of virulence factors which include pore forming toxins (alpha-hemolysin, Panton-Valentine leukocidin), superantigens (enterotoxins, toxic shock syndrome-I), Phagocytosis inhibitors (polysaccharide capsule, Protein A) and immune evasion molecules (Chemotaxis inhibitory proteins, staphylokinase, aureolysin). This review focuses on these virulence factors and their possible roles as target in new drug ad vaccine development.

**Secretary System of *S. aureus***

In bacteria, the majority of precursor proteins are integrated into or transported across membranes by the secretary pathway. Precursor proteins formed by the bacterial cell need to be transported to their correct cellular destinations. The bacterial Sec system consists of a membrane complex that forms a translocation channel through which polypeptides pass, a cytosolic ATPase and translocase that acts as a motor to move the polypeptide through the channel, and a chaperone protein which binds to the polypeptide and aids in the initial translocation steps. If these features are absent, the protein is secreted into the extracellular space as in the case of enterotoxins and hemolysins. The secretory 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 translocase 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.

Contemporary studies provide wealth of information regarding the fact that intermediate levels of VAN resistance are rising among MRSA strains; these are designated VAN-intermediate *S. aureus* (VISA) strains. Mounting evidence suggested that *Staphylococcus aureus* has 17 chromosomally encoded two-component regulatory systems (TCRS). Overexpression of one TCRS (graRS) has been linked with the VISA phenotype and it has been shown that GraRS induces expression of the adjacent vraFG ABC transporter genes. It has been persuasively revealed that isogenic strains with mutations in genes encoding the GraRS TCRS and the VraFG ABC transporter are hypersensitive to vancomycin as well as polymyxin B.

Surprisingly, in a latest study it was indicated that after
30 days of vancomycin exposure, the strain was resistant to all antibiotics however reversion to vancomycin susceptibility occurred 21 days after removal.

Laboratory methodologies provide sufficient proof that inflammasomes are the major regulator of resistance and tolerance in mammalian cells and are comprised of a family of cytosolic receptors, called NOD-like receptors (NLR), that are involved in innate immune recognition of pathogen-associated molecular patterns as well as intracellular and extracellular damage-associated molecular patterns. It has recently been explored that different compounds can be administered to initiate a host defense mechanism via the NLRP3 inflammasome and are reported to induce clearance of either a Gram-positive or Gram-negative bacterium. It is relevant to mention that Staphylococcus aureus pore-forming toxin PVL activates the NLRP3 inflammasome, that is involved in caspase-1-dependent IL-1β processing in response to pathogens and endogenous danger signals.

MRSA Treatment: fresh from the pipeline

Comparative genomics and molecular genetics are being applied to produce lists of essential new targets for compound screening programmes and it has been shown that crude methanolic extract of Piper sarmentosum is effective against MRSA. It has recently been suggested that amino-terminated poly(amidoamine) dendrimers (PAMAM-NH2) are nonresistance-inducing antibiotic agent with relatively low toxicity. On a similar note, different novel 1,3-diphenyl-1H-pyrazoles functionalized with phenylalanine-derived rhodamine derivatives were reported to be effective against MRSA. Cynomoritiannin obtained from Cynomorium songaricum Rupr. was the most effective of the plant constituents against MRSA. It is noteworthy that liposomal encapsulation of vancomycin improves killing of MRSA in a murine infection model. Accumulating evidence reveals that aqueous extract of Psidium guineense Swartz in conjiation with beta lactamics antimicrobials has considerably enhanced antimicrobial activity. Combinatorial chemistry and structural biology are being applied to rapidly explore and optimize the interactions between compounds and their biological targets and it has been reported that Vancomycin-loaded nano-hydroxyapatite pellets effectively repaired bone defects and controlled infection in MRSA-induced chronic osteomyelitis.

Targeted therapy is gradually being appreciated for inhibition of MRSA biological activities. In accordance with this approach, it has been shown that blockade of the MecR1-MecI-MecA signalling pathway with an mecR1-targeted DNAzyme can restore the susceptibility of MRSA to existing beta-lactam antibiotics.

Summary

Protein secretion principally occurs via the Secretory 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. Microbial Surface Components Recognizing Adhesive Matrix Molecules continue to be targets of interest for vaccine development. 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

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