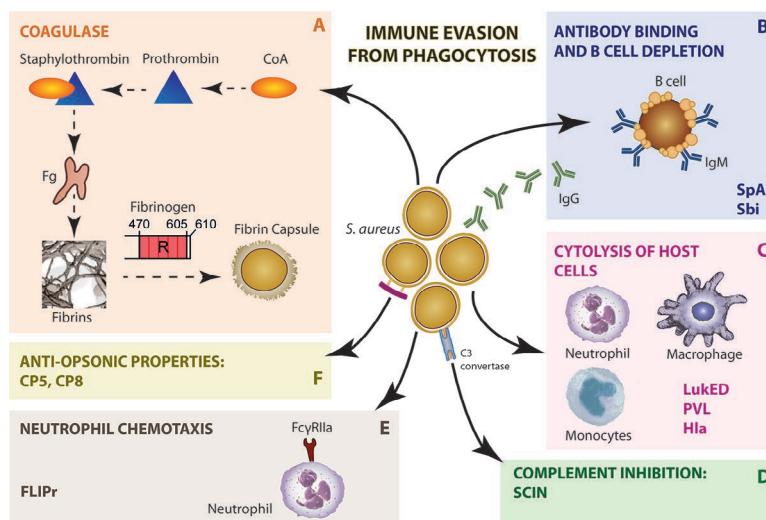


Staphylococcus aureus coagulase R domain, a new evasion mechanism and vaccine target

Staphylococcus aureus has a tremendous unmet medical need, is impressively fast in acquiring antibiotic resistance, and there are no licensed vaccines on the market yet. Unfortunately, lack of known mechanisms of protection against *S. aureus* in humans is hindering development of efficacious vaccines.

Several types of staphylococcal immune evasion mechanisms dampen effective humoral and cellular response. Indeed, *S. aureus* produces immune evasion factors that inhibit antibody deposition (e.g., SpA, Sbi, CP5, and CP8 in Fig. 1, B and F), complement proteins and neutrophil chemotaxis (e.g., SCIN and FLIPr in Fig. 1, D and E), and secrete several cytolytic toxins (hemolysins and leukocidins) that kill monocytes, macrophages, and neutrophils (Fig. 1 C).

In this issue, Thomer et al. provide unprecedented observations on an immune evasion mechanism mediated by coagulase (Coa) that the bacterium uses to escape phagocytic killing (Fig. 1 A). Coa is known to activate host prothrombin and generates fibrin fibrils that promote clotting of human plasma and protect the pathogen against phagocytosis by immune cells. Activation of prothrombin is mediated by the N-terminal D1-D2 domain of Coa. However, this domain is highly variable and does not elicit cross-protective immune responses. By contrast, the fibrinogen C-terminal repeats region is well conserved across *S. aureus* strains.



Mechanisms by which *S. aureus* subverts opsonophagocytosis. (A) Coagulase associates with human prothrombin to form enzymatically active staphylothrombin, which in turn cleaves fibrinogen generating fibrin fibrils. The R domain of Coa drives the formation of the bacterial fibrin shield that protects bacteria from phagocytosis. (B) Staphylococcal protein A (SpA) and staphylococcal IgG-binding protein (Sbi) binds Fc domains of IgGs impeding neutrophil-mediated opsonophagocytosis; SpA also inhibits antibody response to infection by binding VH3-type IgM on the surface of B cells; (C) Cytolytic toxins (e.g., α -hemolysin [Hla], leukocidin ED [LukED], and Panton-Valentine leukocidin [PVL]) mediate lysis of immune host cells; LukED and Hla target neutrophils and macrophages; Hla also lyses monocytes; PVL kills neutrophils and monocytes; (D) Staphylococcal complement inhibitor (SCIN) associates with C3 convertase impairing the production of C3a, C3b, and C5a and interfering with complement activation; (E) Formyl peptide receptor-like 1 inhibitory protein (FLIPr) associates with Fc γ RIIa blocking neutrophil activation and chemotaxis; (F) Capsule (CP) protects the bacterium from opsonophagocytosis by masking other surface-exposed antigens.

clude recombinant proteins (Als3, SEB, Hla, FhuD2, Csa1A, EsxAB, ClfA, MntC, and LukS-PV) as well as CP5 and CP8 glycoconjugates. Indeed, preclinical data published by several authors show that vaccine combinations can be more efficacious and protect against a broader array of *S. aureus* isolates and disease manifestations as compared with single antigens.

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