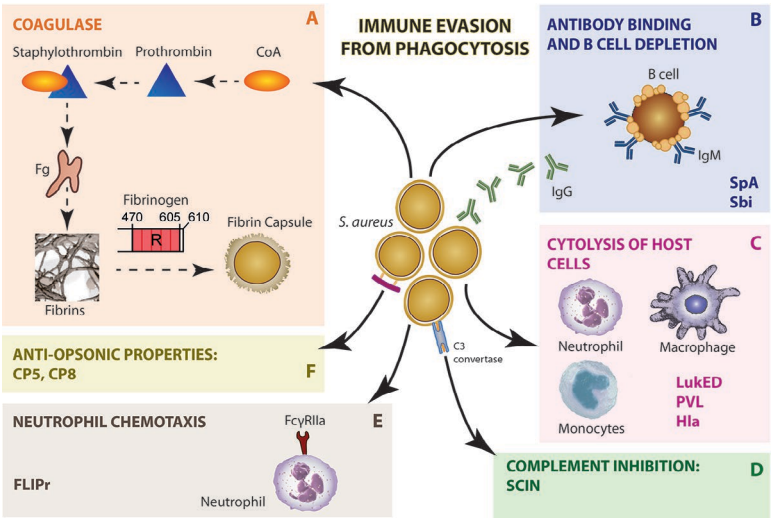
Staphylococcus aureus coagulase R domain, a new evasion mechanism and vaccine target

Insight from (left to right) Clarissa Pozzi, Fabio Bagnoli, and Rino Rappuoli

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 FCγRIIa blocking neutrophils activation and chemotaxis; (F) Capsule (CP) protects the bacterium from opsonophagocytosis by masking other surface-exposed antigens.

The authors of this study describe how the conserved C-terminal repeat domain of Coa directs fibrinogen to the bacterial surface generating a protective fibrin shield that resists opsonophagocytic clearance. The authors showed that a monoclonal antibody toward the R domain reduced bacterial burden in blood of human volunteers. This observation was obtained using a whole blood assay (WBA), which might represent an interesting alternative to the standard opsonophagocytosis assay (OPA) most commonly used as functional readout both in preclinical and clinical studies for vaccine development. Importantly, in the former assay no addition of exogenous and heterologous sources of constituents are needed. In addition, it can be performed using human blood, as in the study commented herein, which also contains the proper native environment potentially needed for protection against the pathogen such as cytokines and different leukocytes.

Altogether this study sheds new light on the importance of Coa for *S. aureus* pathogenesis and immunoevasion showing for the first time functional mechanisms associated with the R domain. Given that the R domain is important for the function of Coa and is conserved across different strains, it represents a promising vaccine candidate to be added to antigens in development that so far include 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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