



A human fibrinogen variant with impaired *Staphylococcus aureus* binding function promotes host survival during septicemia in mice.

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*Staphylococcus aureus* is a common gram-positive bacterium and a major public health threat. An important mechanism that contributes to *S. aureus* virulence is the ability of this pathogen to bind fibrin(ogen) and other host factors through an array of membrane bound bacterial virulence proteins. Our previous studies, using Fib  $\gamma^{\Delta 5}$  mice that express a fibrinogen mutant lacking the binding motif for clumping factor A (ClfA) indicated that binding to this site is a major mechanism of pathogen virulence during acute septicemia. We hypothesized that the naturally occurring human fibrinogen  $\gamma'$  variant would have similar properties to fibrinogen  $\gamma^{\Delta 5}$  mutant in that it would (i) lack *S. aureus* ClfA binding function and (ii) confer protection to acute septicemia in *S. aureus* infected hosts. Under stationary phase conditions, ClfA was the primary fibrinogen binding receptor whereas under exponential growth conditions binding was largely independent of ClfA. Surprisingly, both the ClfA dependent and independent binding to fibrinogen was almost completely abolished when using the human fibrinogen  $\gamma'$  variant (hFib  $\gamma'$ ). Fibrinogen-dependent 'clumping' in solution was completely eliminated when analyzed using hFib  $\gamma'$  and was fully dependent on ClfA in both stationary and exponentially growing *S. aureus*. Reconstitution of fibrinogen-deficient mice or WT mice with hFib  $\gamma'$  provided a significant prolongation in host survival relative to mice reconstituted with hFib  $\gamma$ , indicating that hFib  $\gamma'$  confers protection alone and in combination with other fibrinogen species. These findings provide the proof-of-concept that naturally occurring fibrinogen variants could offer significant therapeutic potential against infection and potentially other diseases.

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