P-19

Influence of S. aureus coagulases on bacteria-vessel wall interactions in infective endocarditis

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Introduction: Staphylococcus aureus (S. aureus) is one of the major pathogens causing infective endocarditis (IE). Its high propensity to adhere to endothelial cells (ECs) and to spread via the bloodstream is associated with a high mortality. Von Willebrand factor (VWF) mediates shear-dependent platelet-vessel wall interaction. S. aureus binds VWF under shear stress, however, the mechanisms are incompletely understood. Furthermore, S. aureus activates the coagulation by staphylothrombin, a complex of S. aureus coagulases and prothrombin.
Aim: Given the key role of coagulase activity and VWF binding in the initiation and pathogenesis of intravascular infections, we aim to investigate if S. aureus von Willebrand factor binding protein (vWbp) is a key factor in mediating these two functions.
Methods: Experiments were performed in a parallel flow chamber under shear stress of 10 dynes/cm2. By using either pharmacological coagulase inhibition, targeting both coagulases (staphylocoagulase and vWbp), or by using mutant strains lacking either staphylocoagulase, vWbp or both, we studied the contribution of VWF binding and coagulase activity in shear-dependent S. aureus adhesion. The effect of S. aureus mediated thrombin activity on EC activation, EC fibrin deposition and bacterial EC adhesion was studied in vitro. Furthermore, we evaluated the interaction of S. aureus Newman and staphylocoagulase- and vWbp-deficient mutants with activated ECs in vivo by using real-time fluorescence videomicroscopy in mesenteric vessels.
Results: We found that in contrast to thrombin, staphylothrombin does not directly activate ECs. However, S. aureus-mediated fibrin deposition increased bacterial retention to ECs in vitro. Furthermore, both coagulases induced the formation of circulating microthrombi in vivo. Staphylothrombin-mediated microthrombus formation and VWF binding both contributed to S. aureus adhesion to activated ECs suggesting a unique dual role for vWbp in bacteria-vessel wall interaction. Pharmacological inhibition of coagulases reduced bacterial adhesion to ECs in vivo. In the mouse IE model, genetic absence of coagulases increased survival.
Conclusion: S. aureus vWbp is a key factor in mediating coagulase activity and VWF binding and might serve as a target for alternative treatment strategies in S. aureus IE.