Plasminogen Activators in Staphylococcal Arthritis

Tao Jin
Department of Rheumatology and Inflammation Research, Göteborg University
Guldhedsgatan 10 A,41346 Göteborg, Sweden

Staphylococcus aureus (*S. aureus*) is a dangerous human pathogen being a major cause of community- and hospital- acquired infections that may be associated with hemostatic abnormalities. However, it is unclear how fibrinolytic system is involved in pathogenesis of staphylococcal infections. The current study aims to dissect the interplay between human protective immunity and plasminogen activators including both staphylokinase (SAK) expressed by *S. aureus* and endogenous urokinase (uPA), one of major host plasminogen activators.

S. aureus strain LS-1 was genetically modified by the insertion of the *sak* gene into its chromosome using single copy integration vector. Murine model of staphylococcal arthritis demonstrated that SAK^+ *S. aureus* strains developed more severe arthritis. *In vitro*, we observed a direct binding between alpha-defensins (HNPs) and SAK, which resulted in complete abrogation of bactericidal effect of HNPs. Moreover, it was shown by bacterial killing assay that SAK producing staphylococcal strains were less sensitive to HNPs than SAK mutants. HNPs injected intra-articularly together with live staphylococci alleviated joint destruction. In contrast, injection of HNPs together with SAK gave rise to significantly worse outcome. Would uPA, expressing similar fibrinolytic properties as SAK, bind to HNPs thereby interfering with SAK/HNPs interaction? To this end, ELISA was used to analyse direct interaction between these three molecules. We observed that high molecular weight (HMW) uPA has the ability to bind to both HNPs and SAK. Biological consequences of such a complex formation were analysed by its bactericidal properties. HMW uPA killed *S. aureus* at relatively high doses through serine protease domain of the molecule. Importantly, as a result of the binding between HMW uPA and SAK, the latter molecule was totally deprived of its neutralizing properties with respect to HNPs. In murine infection model, uPA treatment alleviated staphylococcal sepsis by inhibiting bacterial growth.

In conclusion, SAK enhances the development of arthritis, and neutralizes bactericidal properties of HNPs, which might be of importance during *S. aureus* infections. uPA, an endogenous plasminogen activator, inhibits *S. aureus* growth *a)* directly by cytolysis and *b)* indirectly by abrogation of neutralizing properties of SAK on bactericidal activities of HNPs. Thus, plasminogen activators affect the outcome of staphylococcal infection by a network of well defined interactions.

Key words: *Staphylococcal aureus*, staphylokinase, urokinase, human neutrophil peptides, mice

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