Bacteria – host interplay in Staphylococcus aureus infections

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I. Kwiecinski J, Josefsson E, Mitchell J, Higgins J, Magnusson M, Foster T, Jin T, Bokarewa M. Activation of plasminogen by staphylokinase reduces the severity of *Staphylococcus aureus* systemic infection. *J Infect Dis* 2010; 202: 1041-1049.

II. Kwiecinski J, Jacobsson G, Karlsson M, Zhu X, Wang W, Bremell T, Josefsson E, Jin T. Staphylokinase promotes the establishment of Staphylococcus aureus skin infections while decreasing disease severity. *J Infect Dis* 2013, in press.

III. Kwiecinski J, Jin T, Josefsson E. Surface proteins of Staphylococcus aureus play an important role in experimental skin infection in mice. *Manuscript.*

IV. Kwiecinski J, Rhost S, Löfbom L, Blomqvist M, Månsson JE, Cardell SL, Jin T. Sulfatide attenuates experimental *Staphylococcus aureus* sepsis through a CD1d dependent pathway. *Infect Immun* 2013; 81: 1114-1120.

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ABSTRACT

Bacteria – host interplay in Staphylococcus aureus infections

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Staphylococcus aureus infections are a major healthcare challenge and new treatment alternatives are needed. The key to new therapies is understanding the interplay between bacterial virulence factors and host immune response, which decides on disease outcome. *S. aureus* produces numerous virulence factors. Among them are the surface proteins and soluble factors, like staphylokinase (Sak) – a protein activating host plasminogen. Recently characterized subset of leukocytes, the natural killer T-cells (NKT) respond rapidly to bacterial challenge and link innate and adaptive immunity. Activation of NKT cells might possibly affect the outcome of *S. aureus* infections.

In this thesis, I explored the role of certain bacteria components (surface proteins, Sak) and host factors (NKT cells, plasminogen) during infectious process. Various mouse infection models (*S. aureus* skin infections, septic arthritis, and sepsis), as well as in vitro models and collections of clinical bacterial isolates were used.

Staphylococcal surface proteins were crucial for establishment of abscess-like skin infection in mice. Activation of host plasminogen by Sak was an important element for staphylococcal invasion into the skin and establishment of new infectious sites. However, once infection was established, Sak diminished the infection severity and reduced the damage. Benifical effect of plasminogen activated by Sak was also observed in *S. aureus* systemic infection. On the host side, the NKT cells were involved in experimental *S. aureus* sepsis, but they didn't appear to have a significant impact on the disease outcome. However, sulfatide treatment activating the type II NKT cells significantly reduced mortality in experimental *S. aureus* sepsis.

Staphylococcal infection is a complex process, regulated by various staphylococcal factors interacting with host: both by surface proteins and by secreted proteins like Sak. Those bacterial factors might be potential future treatment targets for limiting disease severity. Another potential treatment strategy is to activate type II NKT cells, which downregulates exaggerated immune response in *S. aureus* sepsis, leading to less tissue damage and better survival.

Key Words: *Staphylococcus aureus*, staphylokinase, NKT cells, surface proteins

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