Department of Neuroscience

The Physiological and Microbiological Response to Renal UPEC Infection

AKADEMISK AVHANDLING
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ABSTRACT

The pathological outcome of a bacterial infection depends on the interplay between the host's defences and the virulence arsenal of the pathogen. Appreciation of this interplay is crucial to the understanding of pathogenesis and the development of efficient clinical treatments. In this thesis we wanted to study the dynamics of the early stages of renal bacterial infection. While sacrificial models and *in vitro* experimentation has given us a wealth of information, they lack the spatial and temporal resolution required to follow the crucial first hours of infection. To overcome this we developed a multiphoton based live animal infection model which allows for the visualization of infection progression in real-time. This model allows for cellular resolution visualisation of events occurring in the live kidney with the influences of the all physiological factors such as the blood, nervous, hormonal and immune systems intact. Our model utilizes micropuncture techniques to directly infuse bacteria into the renal tubules allowing for a well defined time-frame of infection.

What we achieved was a unique insight into the rapid physiological responses to infection. Physiological responses described in this thesis include ischemic and obstruction injuries. These injuries are both related to dynamic physiological functions for which real-time live imaging is particularly suitable. Within 3-4 hours of the first bacterial interaction, epithelial signalling lead to activation of the clotting cascade and shut-down of local peri-tubular capillaries. The clotting response was shown to be crucial to isolate the infection and prevent sepsis. A rapid and dramatic drop in local tissue oxygen tension was also recorded with the combination resulting in a local ischemic injury. This infection-induced ischemia resulted in the characteristic cellular actin and integrin re-arrangements, but lacked a re-perfusion stage, instead resulting in localised tissue damage. We also investigated the effect of bacterial infection on renal filtration, revealing total nephron obstruction within 8 h. Other physiological responses seen include the infiltration of immune cells including both neutrophils and other unidentified mononuclear cells. This work shows that the full pathophysiology of pyelonephritis is a combination of numerous physiological injuries.

Investigating the microbiological response to infection revealed that certain virulence factors affected the kinetics of both bacterial colonisation and the host response. Expression of the exotoxin α- haemolysin was shown to induce a more rapid host vascular response. A synergistic interaction between the adhesion factors P and Type-1 was shown to facilitate optimal kidney colonisation. P fimbriae were important for bacterial-epithelial interaction and in withstanding the sheer stress of filtrate flow, while Type 1 fimbriae expression becomes pertinent as the bacterial community expands into the lumen. This heterogeneous population allowed for the formation of an epithelial anchored biofilm which contributes to renal obstruction.

Our work reveals new findings from both the physiological and microbiological responses to renal UPEC infection. These findings were made possible by the development and utilisation of the multiphoton based live-animal imaging model. It is hoped that as these types of live models become more integrated into infection biology awareness of these dynamic interplays will allow for improved treatment regimes.