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Streptococcus pyogenes:
life within the macrophage

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ABSTRACT

Streptococcus pyogenes is a versatile human pathogen causing a wide array of diseases ranging from uncomplicated throat and skin infections to invasive life-threatening diseases with a mortality rate of up to 60%. It is ranked number nine on the list of worst infectious diseases world wide, causing 500 000 deaths yearly. The work presented in this thesis was initiated upon finding viable bacteria in tissue macrophages of patients with severe *S. pyogenes* infections. This intracellular bacterial reservoir was linked to prolonged bacterial persistence at the tissue site. It was therefore of interest to investigate how the bacteria could survive within professional phagocytes that has evolved for the specific purpose of degrading invading microbes. Hence, the overall aim of the thesis was to decipher streptococcal survival strategies in macrophages.

Certain bacterial serotypes are more efficient in causing invasive infections than others, as they are equipped with special tools to facilitate invasion and survival. We have identified the bacterial M1-protein as an important factor for intracellular survival in macrophages. Studies on entry and intracellular trafficking revealed that the bacteria are residing inside membrane-bound compartments, which do not fuse with the lysosomal compartments; thus enabling persistence and replication. Thereto, M1-protein was shown to suppress the host-inflammatory response upon *S. pyogenes* infection. Regulation of bacterial intracellular signaling is vital for bacterial survival and it also affects host responses. Data are supporting a role for the two-component gene regulatory system, Ihk/Irr, during adaption to the intracellular environment while another regulatory system, CovR/S, possibly facilitates infectivity of disseminating bacteria. In addition, we show that the arachidonic acid metabolite, prostaglandin E_2, which is produced by host cells upon infection, has a negative impact on macrophage bactericidal responses, thus enabling bacterial survival inside the host cell.

The studies comprised in this thesis contribute to a deeper understanding of the host-pathogen interplay during severe *S. pyogenes* infections, in particular with regards to mechanisms contributing to intracellular survival in host cells. The results demonstrate that *S. pyogenes* ability to persist within macrophages is enabled through distinctly regulated mechanisms involving both host and bacterial factors.

S. pyogenes used to be considered as an extracellular pathogen, however, it is becoming increasingly apparent that it is important to consider also an intracellular source; thus affecting choice of antimicrobial agents. In addition, work presented in this thesis has identified several novel targets, both on the bacterial and on the host side, which may be suitable candidates for intervention.

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