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Group A streptococcal CXC chemokine-protease cleaves the human antimicrobial cathelicidin peptide LL-37 resulting in the loss of immunomodulatory functions of the peptide

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Statement of the Problem: Severe-soft tissue infections caused by group A streptococci (GAS) are characterized by a rapid dissemination of GAS followed by massive necrosis and tissue destruction. The human antimicrobial peptide, LL-37, is expressed during invasive GAS infections. It is believed that LL-37 antibacterial activity limits GAS spreading, since mice deficient of the LL-37 murine analog, CRAMP, is more sensitive than wild type mice to subcutaneous GAS challenge. LL-37 also directly recruits neutrophils to the site of infection and stimulates interleukin-8 (IL-8) production by keratinocytes. Thus, the immunomodulatory activity of LL-37 is aimed to exacerbate neutrophil response that is crucial for eradication of GAS from soft-tissue. Yet, analysis of debrided human soft-tissue samples revealed the coincidence of LL-37 along with viable GAS.

Methodology & Theoretical Orientation: The GAS CXC-chemokine protease ScpC plays a central role in virulence through IL-8 cleavage preventing recruitment of neutrophils to the site of infection and reducing the production of neutrophil extracellular trap. Because of its immunomodulatory activities, we hypothesized that LL-37 may also serve as a substrate for ScpC. Functional significance of ScpC-mediated cleavage of LL-37 was studied *in vitro* and verified in vivo in the mouse model of human GAS soft-tissue infections.

Findings: Here, we demonstrate that immunomodulatory activity of LL-37 is crucial for controlling GAS spreading in soft-tissue. We found that GAS CXC-chemokine protease ScpC degrades and inactivates IL-8 as well as LL-37. ScpC cleaves the first 8 amino acids from the N-terminal of LL-37. This results in loss of its capacity to recruit neutrophil and stimulate IL-8 production by keratinocytes. In summary, the capacity of ScpC to shut down recruitment of neutrophils that is mediated through both IL-8 and LL-37 as well as inactivate LL-37-mediated IL-8 production by keratinocytes reflects a perfect adaptation of GAS to its human host.

Fig 1. A schematic model depicting several mechanisms by which ScpC contributes to GAS virulence

Biography

Debabrata Biswas completed his PhD in the field of Cell Biology while working on Arsenic Toxicity in blood. He shifted his interest to the study of pathogen biology and infectious disease during his Post-doctoral study at Hebrew University of Jerusalem. He joined the laboratory of Prof Emanuel Hanski, working on the mechanism of pathophysiology of group A streptococcal soft tissue infection. His present work in Microbiology department of National University of Singapore deals with bacterial virulence factors and various strategies that might be designed against the disease based on the mechanism of actions of these factors. He is currently investigating molecules in the host inflammatory and immune signaling cascade that might act as the potential targets of the bacterial serine protease ScpC, which is a major virulence factor in soft tissue infections.

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