

Interleukin 15 and 17 in *Staphylococcus aureus* arthritis

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Staphylococcus aureus-induced arthritis leads to severe joint destruction and high mortality despite antibiotic treatment. Thus, there is a need to identify new treatment targets in addition to antibiotic therapy. Interleukin (IL)-15 has been implicated both in osteoclastogenesis and in bacterial clearance – two important issues in *S. aureus*-induced joint destruction. Interleukin-17A has been discovered as an important mediator of aseptic arthritis both in mice and men, while its function in *S. aureus*-induced arthritis is largely unknown. The aim of this thesis was to investigate the importance of IL-15 and IL-17A and in addition, the interaction between IL-17A and interleukin-23 in *S. aureus*-induced arthritis. Wildtype, IL-15 knockout and IL-17A knockout mice were inoculated (systemically or locally) with a defined number of toxic shock syndrome toxin-1 (TSST-1) producing *S. aureus*. At sacrifice, tissues were collected and further analysed. We found that mice genetically lacking IL-15 or treated with anti-IL-15 antibodies developed less severe and destructive arthritis compared with control mice. In neither situation the bacterial clearance was negatively influenced. Furthermore, the IL-15 knockout mice had fewer osteoclasts in the joints compared with wildtype mice. We suggest that due to IL-15 absence, the mice developed milder arthritis probably because of less bone and cartilage destruction. We observed that IL-17A was of minor importance in systemic *S. aureus* arthritis but played a major role in local *S. aureus* arthritis. In the systemic model of arthritis we found elevated levels of IL-17F in the IL-17A knockout mice, suggesting that IL-17F compensates for the absence of IL-17A and that IL-17F in a normal wildtype mice is inhibited by IL-17A. Furthermore we found that IL-17A regulates the production of IL-23, a cytokine that is known to regulate the production of IL-17A, in a negative feedback manner, which means that IL-17A may have regulatory properties. Thus, we have found that IL-15, but not IL-17A, could represent a promising treatment target along with antibiotics in *S. aureus*-induced arthritis, and that IL-17A negatively regulates its upstream inducer, IL-23.

Key words: IL-15, IL-17A, IL-17F, IL-23, arthritis, mice, osteoclasts, *S. aureus*.

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- I. **Louise Henningsson**, Pernilla Jirholt, Yalda Rahpeymai Bogestål, Tove Eneljung, Martin Adiels, Catharina Lindholm, Iain McInnes, Silvia Bulfone-Paus, Ulf H. Lerner and Inger Gjertsson.
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- II. **Louise Henningsson**, Pernilla Jirholt, Catharina Lindholm, Tove Eneljung, Elin Silverpil, Yoichiro Iwakura, Anders Lindén and Inger Gjertsson.
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