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The Interleukin-23 axis and innate immunity in the airways

Akademisk avhandling

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av Marit Stockfelt

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Avhandlingen baseras på följande delarbeten

I. Hansson M, Silverpil E, Lindén A, Glader P. Interleukin-22 produced by alveolar macrophages during activation of the innate immune response. Inflammation Research 2013. Jun;62(6):561-9.

II. Silverpil E, Wright AK, Hansson M, Jirholt P, Henningsson L, Smith ME, Gordon SB, Iwakura Y, Gjertsson I, Glader P, Lindén A. Negative feedback on IL-23 exerted by IL-17A during pulmonary inflammation. Innate Immunity 2013 Oct; 19(5):479-92.

III. Smith ME*, Stockfelt M*, Tengvall S, Bergman P, Lindén A, Qvarfordt I. Endotoxin Exposure Increases LL-37 – but Not Calprotectin – in Healthy Human Airways. Journal of Innate Immunity. 2017. *Joint first authorship.

IV. Stockfelt M, Christenson K, Andersson A, Björkman L, Padra M, Sun J, Levänen B, Ganguly K, Asgeirsdottir H, Qvarfordt I, Bylund J and Lindén A. Neutrophil activation and associated cytokines before and after extravasation into the airways of smokers with and without COPD. Manuscript in preparation.

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The Interleukin-23 axis and innate immunity in the airways

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Abstract

The Interleukin-23 (IL-23) axis is a communication system that integrates innate and adaptive immunity. When triggered by microbial stimuli, antigen presenting cells can secrete the cytokine IL-23, leading to the production of IL-17 and IL-22. These cytokines facilitate the recruitment of neutrophils that can eliminate microbes, but may also cause epithelial damage through extensive inflammation. At the same time, the IL-23 axis protects the epithelium through the production of antimicrobial peptides.

The protective role of the IL-23 axis for local epithelial defence led us to ask whether inflammatory cells of the airway epithelium can produce IL-22, a cytokine associated with the IL-23 axis. We showed that airway macrophages responded to IL-23 and a bacterial stimulus with the secretion of IL-22. This constitutes a local and accessible source of IL-22 during activation of the innate arm of pulmonary host defence.

The IL-23 axis leads to neutrophil recruitment which risks damaging epithelial tissue. Therefore, a strict regulation of the production of these cytokines is necessary. We showed that IL-17 exerts a negative feedback effect on IL-23, thus decreasing its own production. Further, the IL-17 receptor was present on macrophages demonstrating a prerequisite to this response.

The airway epithelium is protected by antimicrobial peptides functioning as innate antibiotics, several of which are regulated by the IL-23 axis. We demonstrated the expression of two antimicrobial peptides, calprotectin and LL-37, in healthy human airways. Of these, only LL-37 was induced by the gram-negative bacterial stimulus endotoxin in this setting. This demonstrates the involvement of LL-37 in the innate immune response against gram-negative bacteria.

Finally, we quantified cytokines associated with the IL-23 axis in smokers with and without chronic obstructive pulmonary disease. Airway IL-17 did not differ significantly between the groups, but plasma IL-22 was increased in smokers, demonstrating a smoking induced systemic effect on the IL-23 axis. Neutrophils in the airways displayed signs of activation and could be further activated by TNFα, indicating that the local microenvironment can affect neutrophil activation.

Keywords: IL-23, IL-22, IL-17, airway, LL-37, neutrophil, macrophage

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