

Interleukin-17 in models of neutrophilic lung disease

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- I. Ivanov S., Palmberg L., Venge P., Larsson K., A. Lindén. Interleukin-17A mRNA and protein expression within cells from the human bronchoalveolar space after exposure to organic dust. *Respiratory Research* 2005 May 25; **6**: 44
- II. Sergejeva S., Ivanov S., Lötvall J., A. Lindén. IL-17 as a recruitment and survival factor for airway macrophages in allergic airway inflammation. *AJRCMB*. 2005; **33** (3): 248-253.
- III. Ivanov S., Bozinovski S., Bossios A., Valadi H., Vlahos R., Malmhäll C., Sjöstrand M., Kolls J.K., Anderson G.P., A. Lindén. Functional relevance of the IL-23-IL-17 axis in lungs *in vivo*. Submitted to *AJRCMB*.

Interleukin-17 in models of neutrophilic lung disease

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Several acute or chronic lung disorders like adult respiratory distress syndrome, acute severe asthma, chronic obstructive pulmonary disease, chronic lung allograft rejection and cystic fibrosis, are associated with signs of an excess innate response in the bronchoalveolar space. Neutrophils may play a pathogenic role in these lung diseases by contributing to non-specific bronchial hyper-responsiveness and bronchial hypersecretion, as well as to epithelial damage and tissue remodelling. Previous studies employing stimuli of Gram-negative bacteria in mice have shown that the T-cell cytokine Interleukin (IL)-17 (also named IL-17A) can contribute to accumulation of neutrophils within the bronchoalveolar space. The general aims of this thesis were to determine a cellular source of IL-17 in the human bronchoalveolar space *in vivo* and to further characterize the role of IL-17 and the IL-17-inducing cytokine IL-23 in neutrophilic lung disease.

In study one, severe neutrophilic inflammation in the human bronchoalveolar space was caused by exposure of healthy, non-smoking volunteers to organic dust. The exposure increased IL-17 messenger (m) RNA in bronchoalveolar-lavage (BAL) cells and, because of an intracellular expression of IL-17 protein in lymphoid BAL cells, IL-17 may originate from lymphocytes residing within the bronchoalveolar space. The increased IL-17 mRNA expression was associated with an increased percentage of matrix metalloproteinase (MMP)-9-expressing BAL neutrophils. This is compatible with IL-17 controlling the local proteolytic burden of tissue-degrading enzymes like MMP-9, via its neutrophil-accumulating effect.

In study two, sensitized and allergen-challenged mice were pre-treated with a specific anti-IL-17 antibody in order to block endogenous IL-17. We showed that endogenous IL-17 may contribute not only to the accumulation of BAL neutrophils but also to the accumulation of BAL macrophages. IL-17 may serve as a direct chemotactic factor for macrophage precursor cells and as a survival factor for macrophages within the bronchoalveolar space. In addition, we present evidence that IL-17 might control the local proteolytic burden, since blocking endogenous IL-17 decreased the percentage of MMP-9-expressing BAL neutrophils and macrophages.

In study three, we determined the impact of the antigen-presenting cells cytokine IL-23 in the innate response of the lungs utilizing stimulation with bacterial structural components as well as with recombinant IL-23 protein. We showed that both Gram-negative and Gram-positive bacterial components promoted the release of IL-23 in lung tissue and BAL fluid. We also demonstrated that short-term stimulation with recombinant IL-23 protein caused accumulation of macrophages and neutrophils in the bronchoalveolar space via endogenous production of IL-17. This production of IL-17 occurred locally in IL-23-responsive CD4 cells. In addition, IL-23 did not seem to markedly affect the Th1 or Th2 polarization of these CD4 cells. Finally, stimulation with recombinant IL-23 protein increased the local MMP-9 activity, which was generated by neutrophils mainly.

In conclusion, there are lymphocytes residing within the human bronchoalveolar space, which are capable of producing IL-17. In mice, IL-17 production takes place in IL-23-responsive bronchoalveolar CD4 cells and IL-17 may contribute to the accumulation of both macrophages and neutrophils to the bronchoalveolar space. Thus, the antigen-presenting cell cytokine IL-23 and the T-cell cytokine IL-17 seem to form a functional immunological axis in mouse lungs *in vivo*. This IL-23-IL-17 axis is involved in the early innate immune response to Gram-negative and Gram-positive bacteria. If similar mechanisms exist in humans, IL-23 and IL-17 may constitute potential pharmacotherapeutical targets in severe lung diseases associated with an excess innate response.

Keywords: Interleukin-17, Interleukin-23, matrix metalloproteinase-9, neutrophils, macrophages, CD4 cells, innate response, lungs

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