Modulatory role of IL-17 in airway inflammation

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IL-17 orchestrates the accumulation of neutrophils to sites of infection and the release of microbicidal substances, and therefore plays a critical role in the innate immune response to infection. IL-17 is also involved in certain chronic inflammatory diseases in which dysfunctional control of neutrophil accumulation and turnover constitutes an important pathogenic factor. This pro-inflammatory potential of IL-17 in host defence and in inflammatory diseases has been studied extensively. However, there is now also published evidence that IL-17 has more complex actions, including inflammation-resolving potential under certain conditions. With this in mind, the aims of this thesis were to investigate endogenous and exogenous methods to regulate the production of IL-17 and to elucidate the role that IL-17 plays in resolving ongoing inflammation. More specifically, we looked at whether the cells in the lung produce IL-17 after exposure to lipopolysaccharide (LPS) from the Gram-negative *Escherichia coli* bacteria, and whether anti-inflammatory pharmacotherapies could be used to regulate the production of IL-17 in these cells. We also examined whether IL-17 contributes to neutrophil turnover through the regulation of macrophage phagocytosis of apoptotic neutrophils. Finally, we investigated whether IL-17 down-regulates the release of the upstream regulator IL-23.

We found that LPS induced sustained IL-17 production and release from T cells that reside in lung tissue and that are recruited to the bronchoalveolar space in a mouse model of acute inflammation *in vivo*. In addition, population of cells other than T cells contributed to IL-17 production in the lung tissues and in the bronchoalveolar space. LPS-induced IL-17 production from T cells in lung tissues and in the bronchoalveolar space was inhibited by the anti-inflammatory drug dexamethasone. Furthermore, we found that IL-17 stimulated macrophage phagocytosis of apoptotic neutrophils and particles, and induced neutrophil apoptosis in an *in vitro* study on isolated murine and human cells. Finally, we found that that IL-17 inhibited the release of the upstream regulator IL-23, both in the bronchoalveolar space in mice *in vivo* and in isolated human cells of the monocyte lineage.

A major finding is that the production of IL-17 can be regulated exogenously by anti-inflammatory drugs and endogenously by an IL-17-induced feedback loop, which, in turn, may protect against excessive, IL-23-induced IL-17 signalling. In addition, we demonstrate that IL-17 has both pro-inflammatory and inflammation-resolving actions; IL-17 accumulates neutrophils after stimulation with LPS, while it also induces the phagocytosis of apoptotic neutrophils, thereby controlling the total turnover of neutrophils. That IL-17 induces the apoptosis of neutrophils and increases the phagocytosis of these cells indicates a potentially valuable strategy to mitigate conditions in which necrotic neutrophils are an important contributor to severe and sometimes life-threatening conditions, such as chronic lung allograft rejection and acute respiratory distress syndrome.

Key words: IL-17, IL-23, phagocytosis, apoptosis, neutrophils, macrophages, airways

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