

## REGULATION OF INFLAMMATION BY IL-4 RECEPTOR SIGNALING

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The importance of the IL-4 receptor in regulating T cells to become TH2 cells in a murine model of allergic lung disease has been well documented. Furthermore, numerous studies have indicated the IL-4R $\alpha$  expressed on lung epithelium is necessary for goblet cell differentiation and mucus hypersecretion. However, the IL-4R $\alpha$  is expressed on many cell types that could contribute to the overall pathology and severity of asthma. The relative role of the Type I and Type II IL-4 receptors on these cells has not yet been fully delineated. To clarify the role the IL-4R $\alpha$  plays in the development of asthma-like symptoms, we used a bone marrow transfer approach that allowed us to specifically analyze the relative contribution of IL-4R $\alpha$  expression on hematopoietic cells vs. non-hematopoietic cells in a murine model of airway inflammation. We found that in the absence of IL-4R $\alpha$  in recipient mice, there was no goblet cell metaplasia or mucus hypersecretion, even in the presence of IL4R $\alpha$ <sup>+</sup> hematopoietic cells, TH2 cells, and substantial eosinophilic inflammation. Furthermore, we found that expression of the IL-4R $\alpha$  on a non-lymphocytic, BM-derived CD11b<sup>+</sup> cell correlated with the severity of inflammation and mucus production.

CD11b<sup>+</sup> macrophages can respond to either IL-4 or IL-13 by differentiation into alternatively activated macrophages (AAM) that express a characteristic set of genes. Using primary bone-marrow-derived macrophages from WT mice, we found that IL-4 is dramatically more potent than IL-13 in inducing the tyrosine phosphorylation of the insulin receptor substrate 2 adaptor and a subset of genes characteristic of AAM (Arginase I, FIZZ1, YM1), even using concentrations of cytokine that elicited similar levels of STAT6 activation. This was not true for all AAM genes since both cytokines induced expression of macrophage mannose receptor and Sphk1 similarly. These enhanced responses were dependent on expression of the  $\gamma$ C-containing Type I receptor complex.

To directly test the contribution of IL-4R $\alpha$ <sup>+</sup> macrophages on the severity of allergic lung inflammation, we transferred CD11b<sup>+</sup> cells isolated from IL-4R $\alpha$  positive or negative mice in the presence of exogenous TH2 cells to IL-4R $\alpha$ xRAG2KO recipient mice. Strikingly, the presence of IL-4R $\alpha$ <sup>+</sup> CD11b<sup>+</sup> macrophages greatly enhanced allergic lung inflammation in IL-4R $\alpha$ xRAG2KO recipient mice. These macrophages were detected in the lung tissue and were YM-1 positive. These cells significantly enhanced the percentage of eosinophils found in the lavage fluid. Taken together, these results suggest that IL-4 and IL-13 contribute to the development of asthma-like symptoms by a complex interplay between several IL-4R $\alpha$ <sup>+</sup> cell types of both hematopoietic and non-hematopoietic origin, and that signaling by IL-4 on macrophages directly impacts the severity of allergic lung inflammation. This contribution could be due to the production of AAM-specific genes or the production of other cytokines/chemokines. [Supported by PHS AI38985, AI59775]

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