IL-1 receptor blockade skews inflammation towards Th2 in a mouse model of systemic sclerosis

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IL-1 dampens collagen production of lung structural cells and balances pro-fibrotic actions of the immune system. Blockade of IL-1 signalling in Fra-2 TG mice worsens lung function by increased Th2 inflammation and collagen production in the lung.

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ABSTRACT The interleukin (IL)-1 family of cytokines is strongly associated with systemic sclerosis (SSc) and pulmonary involvement, but the molecular mechanisms are poorly understood. The aim of this study was to assess the role of IL-1α and IL-1β in pulmonary vascular and interstitial remodelling in a mouse model of SSc.

IL-1α and IL-1β were localised in lungs of SSc patients and in the fos-related antigen-2 (Fra-2) transgenic (TG) mouse model of SSc. Lung function, haemodynamic parameters and pulmonary inflammation were measured in Fra-2 TG mice with or without 8 weeks of treatment with the IL-1 receptor antagonist anakinra (25 mg·kg⁻¹·day⁻¹). Direct effects of IL-1 on pulmonary arterial smooth muscle cells (PASMCs) and parenchymal fibroblasts were investigated in vitro.

Fra-2 TG mice exhibited increased collagen deposition in the lung, restrictive lung function and enhanced muscularisation of the vasculature with concomitant pulmonary hypertension reminiscent of the changes in SSc patients. Immunoreactivity of IL-1α and IL-1β was increased in Fra-2 TG mice and in patients with SSc. IL-1 stimulation reduced collagen expression in PASMCs and parenchymal fibroblasts via distinct signalling pathways. Blocking IL-1 signalling in Fra-2 TG worsened pulmonary fibrosis and restriction, enhanced T-helper cell type 2 (Th2) inflammation, and increased the number of pro-fibrotic, alternatively activated macrophages.

Our data suggest that blocking IL-1 signalling as currently investigated in several clinical studies might aggravate pulmonary fibrosis in specific patient subsets due to Th2 skewing of immune responses and formation of alternatively activated pro-fibrogenic macrophages.

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