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Profibrotic function of pulmonary group 2 innate lymphoid cells is controlled by regnase-1

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Regnase-1 controls the proliferation and activation of ILC2, which thereby attenuates lung fibrosis in mice. In humans, lower regnase-1 level correlates with more abundant ILC2 number, which potentially associates with the prognosis of IPF patients. https://bit.ly/3c3GhKo

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ABSTRACT Regnase-1 is an RNase critical for post-transcriptional control of pulmonary immune homeostasis in mice by degrading immune-related mRNAs. However, little is known about the cell types Regnase-1 controls in the lung, and its relevance to human pulmonary diseases.

Regnase-1-dependent changes in lung immune cell types were examined by a competitive bone marrow transfer mouse model, and group 2 innate lymphoid cells (ILC2s) were identified. Then the associations between Regnase-1 in ILC2s and human diseases were investigated by transcriptome analysis and a bleomycin-induced pulmonary fibrosis mouse model. The clinical significance of Regnase-1 in ILC2s was further assessed using patient-derived cells.

Regnase-1-deficiency resulted in the spontaneous proliferation and activation of ILC2s in the lung. Intriguingly, genes associated with pulmonary fibrosis were highly upregulated in *Regnase-1*-deficient ILC2s compared with wild-type, and supplementation of *Regnase-1*-deficient ILC2s augmented bleomycin-induced pulmonary fibrosis in mice. Regnase-1 suppresses mRNAs encoding transcription factors *Gata3* and *Egr1*, which are potent to regulate fibrosis-associated genes. Clinically, Regnase-1 protein levels in ILC2 negatively correlated with the ILC2 population in bronchoalveolar lavage fluid. Furthermore, idiopathic pulmonary fibrosis (IPF) patients with ILC2s >1500 cells·mL^{-1} peripheral blood exhibited poorer prognosis than patients with lower numbers, implying the contribution of Regnase-1 in ILC2s for the progression of IPF.

Collectively, Regnase-1 was identified as a critical post-transcriptional regulator of the profibrotic function of ILC2s both in mouse and human, suggesting that Regnase-1 may be a novel therapeutic target for IPF.