IL-17A from innate and adaptive lymphocytes contributes to inflammation and damage in cystic fibrosis lung disease

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ABSTRACT

Background: Elevated levels of interleukin (IL)-17A were detected in the airways of patients with cystic fibrosis (CF), but its cellular sources and role in the pathogenesis of CF lung disease remain poorly understood. The aim of this study was to determine the sources of IL-17A and its role in airway inflammation and lung damage in CF.

Methods: We performed flow cytometry to identify IL-17A-producing cells in lungs and peripheral blood from CF patients and β-epithelial Na^+ channel transgenic (*Scnn1b*-Tg) mice with CF-like lung disease, and determined the effects of genetic deletion of *Il17a* and *Rag1* on the pulmonary phenotype of *Scnn1b*-Tg mice.

Results: T-helper 17 cells, $CD3^+CD8^+$ T-cells, γδ T-cells, invariant natural killer T-cells and innate lymphoid cells contribute to IL-17A secretion in lung tissue, lymph nodes and peripheral blood of patients with CF. *Scnn1b*-Tg mice displayed increased pulmonary expression of *Il17a* and elevated IL-17A-producing innate and adaptive lymphocytes with a major contribution by γδ T-cells. Lack of IL-17A, but not the recombination activating protein RAG1, reduced neutrophilic airway inflammation in *Scnn1b*-Tg

mice. Genetic deletion of *Il17a* or *Rag1* had no effect on mucus obstruction, but reduced structural lung damage and revealed an IL-17A-dependent macrophage activation in *Scnn1b*-Tg mice.
Conclusions: We identify innate and adaptive sources of IL-17A in CF lung disease. Our data demonstrate that IL-17A contributes to airway neutrophilia, macrophage activation and structural lung damage in CF-like lung disease in mice. These results suggest IL-17A as a novel target for anti-inflammatory therapy of CF lung disease.