

 ASTHMA AND ALLERGY

An IFN γ bias in severe asthma

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Asthma is a phenotypically heterogeneous disease with ~10% of individuals having a severe form that is poorly controlled by corticosteroids. Recent evidence suggests that the type of immune response associated with severe asthma is distinct from the eosinophil-dominant type 2 inflammation associated with mild–moderate asthma. In this study, Raundhal *et al.* show that severe asthma is characterized by high levels of the T helper 1 (T_H1) cell cytokine interferon- γ (IFN γ) and low levels of secretory leukocyte protease inhibitor (SLPI) in both mice and humans.

An analysis of bronchoalveolar lavage (BAL) fluid showed that the percentage of IFN γ ⁺CD4⁺ T cells and IL-17⁺CD4⁺ T cells was higher in individuals with severe asthma

than in those with mild–moderate asthma. Furthermore, IFN γ levels were higher in samples from individuals with severe asthma, whereas interleukin-5 (IL-5) and IL-17 levels were similar between the two groups, and IL-13 production was enhanced only in individuals with mild–moderate asthma.

Next, the authors sought to develop a new mouse model of severe asthma. Bacterial airway infections have been linked with treatment-resistant severe asthma in humans and therefore, the authors hypothesized that the bacterial second messenger cyclic diguanylate (c-di-GMP), which induces T_H1 and T_H17 cell responses, could be used as part of a model of severe asthma. In this regard, mice were first sensitized and then challenged with house dust mite (HDM) allergen with or without c-di-GMP. Similar to severe asthma in humans, mice that received c-di-GMP had heightened airway hyperreactivity (AHR) and neutrophil-dominant airway inflammation, and these mice responded poorly to treatment with the corticosteroid dexamethasone. Furthermore, the lungs of these c-di-GMP-treated ‘severe asthma mice’ (SA mice) had high levels of IFN γ and IL-17.

By subjecting mice deficient in either IFN γ or IL-17 receptor A to the severe asthma model, the authors showed that IFN γ is required for the induction of AHR, whereas IL-17 promotes neutrophilic airway inflammation. These observations

suggest that IFN γ is the dominant cytokine associated with AHR in severe asthma and that airway inflammation and AHR may not always be linked.

Using computer-assisted pathway analysis tools to assess molecules that could link IFN γ with increased AHR, the authors identified an inverse correlation between IFN γ and SLPI expression in the lungs of SA mice. Furthermore, SLPI expression in bronchial epithelial brushings was inversely correlated with IFN γ levels in BAL cells from patients with severe asthma. Treatment of primary bronchial epithelial cells with IFN γ suppressed SLPI expression, and forced expression of SLPI in mice greatly reduced the induction of AHR. SLPI inhibits the function of mast cell serine proteases, so it is possible that increased protease activity in the presence of high IFN γ and low SLPI is involved in increased AHR.

Together, this study shows that high IFN γ levels in the airways promote AHR through the suppression of SLPI expression in bronchial epithelial cells and that this IFN γ -mediated immune response differentiates severe asthma from mild–moderate asthma in both humans and mice.

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ORIGINAL RESEARCH PAPER Raundhal, M. *et al.* High IFN- γ and low SLPI mark severe asthma in mice and humans. *J. Clin. Invest.* <http://dx.doi.org/10.1172/JCI80911> (2015)

FURTHER READING Fahy, J. V. Type 2 inflammation in asthma — present in most, absent in many. *Nat. Rev. Immunol.* **15**, 57–65 (2015)



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