It Takes 1 for Type 2: IL-1 Receptor Mediates Eosinophilia in Scnn1b Transgenic Mice

A major phenotype that is present in muco-obstructive lung diseases such as asthma and chronic obstructive pulmonary disease is eosinophilic inflammation. Eosinophils contribute to airway hyperresponsiveness, and eosinophil-generated oxidants may further promote mucus plug formation (1). Scnn1b-Tg mice overexpress a subunit of the epithelial sodium channel that results in ion transport imbalance, leading to airway surface dehydration, increased mucin concentration, and reduced mucociliary clearance. Together, these factors cause severe mucus obstruction.

In addition, Scnn1b-Tg mice exhibit prominent type 2 inflammation during the first weeks of life. Previous studies have linked IL-1 receptor (IL-1R) signaling to the recruitment of leukocytes in allergic models (2, 3). However, how IL-1R participates in spontaneous airway eosinophilia is still unknown. In this issue of the *Journal*, Brown and colleagues (pp. 300–309) provide insight into the role of IL-1R signaling in spontaneous airway eosinophilia and type 2 inflammation in juvenile Scnn1b-Tg mice (4).

Upon genetic deletion of the *Il1r* gene in Scnn1b-Tg mice, the authors found that eosinophil (and neutrophil) numbers partially decreased in BAL fluid obtained from the mice. A previous study by the same group demonstrated that hypoxic epithelial necrosis due to mucus obstruction causes sterile neutrophilic inflammation through IL-1R (5). However, the increase in eosinophilia in juvenile Scnn1b-Tg mice could be associated with transient type 2 airway inflammation (6). To examine this issue, Brown and colleagues measured transcript levels of the key type 2 cytokines *Il13* and *Il5* and the eosinophil chemoattractants *Ccl11* and *Ccl24*. Although there were small decreases in *Il13* and *Il5* at Postnatal Day 8 in Scnn1b-Tg mice lacking IL-1R, no significant changes were observed on subsequent days or in the transcript levels of *Ccl11* and *Ccl24*, suggesting that IL-1R eosinophil recruitment is independent of a stereotypical type 2 airway inflammation process.

In addition to recruitment by chemokines, eosinophils can exhibit a Siglec F^{high}/$CD11c^{low}$ phenotype and show enhanced recruitment to the airways during allergic inflammation. Indeed, the Scnn1b-Tg juvenile mice had a higher proportion of Siglec F^{high}/$CD11c^{low}$ eosinophils, but deletion of IL-1R in these mice did not decrease these numbers. The authors then evaluated whether the decrease in eosinophils could be explained by an increase in apoptosis, but they found no increase in annexin V surface expression upon deletion of IL-1R in Scnn1b-Tg juvenile mice.

Previous studies have linked IL-1R signaling with increased expression of ICAM-1 (intercellular adhesion molecule 1) to promote leukocyte transmigration (7). Because eosinophil numbers were also reduced in whole lung, Brown and colleagues examined the expression levels of ICAM-1 on endothelial cells by flow cytometry. ICAM-1 expression was decreased upon deletion of IL-1R in Scnn1b-Tg mice. Thus, IL-1R signaling may have a role in mediating the transendothelial migration of eosinophils into lung tissue in muco-obstructed airways.

Lastly, the authors evaluated the effect of deleting IL-1R on lung damage and distal airspace enlargement in Scnn1b-Tg mice. Scnn1b-Tg mice show emphysema-like lung damage primarily caused by neutrophil elastase, macrophage elastase, and cathepsin S secreted from activated neutrophils and macrophages (8–10); however, the authors hypothesized that eosinophil peroxidase plays a supportive role. To test the role of eosinophils in lung damage, the authors complemented their study by depleting eosinophils using an anti–IL-5 antibody. Lungs with no eosinophils present had a better conserved lung architecture with less structural damage, confirming a relationship between airway eosinophils and lung structure.

Collectively, these data may have important implications for innate and allergic lung remodeling. Of note, though, the changes seen here in juvenile mice may reflect lung development programs that are independent of mechanisms that evoke structural changes in older animals or humans. Thus, further investigation is needed to determine whether the mechanisms identified here apply to a later disease stage rather than a development-related transient rise in eosinophils.

In summary, Brown and colleagues provide new insight into how muco-obstructive lung disease leads to airway eosinophilia and a pathology that is similar to chronic obstructive pulmonary disease. They show that IL-1R could be acting through ICAM-1 to promote transendothelial migration of both neutrophils and eosinophils. Taken together, their findings indicate that IL-1R should be examined further as a potential novel therapeutic target for treating inflammatory sequelae of chronic muco-obstructive lung diseases. This may be especially important in eosinophilic inflammation settings that lack typical type 2 cytokine profiles. ■

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