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Grant Title: Analysis of molecular mechanisms of sugar allergen-induced allergic diseases.

(a) Abstract

1. Objective

Chitin, β-(1-4)-poly-N-acetyl-D-glucosamine, which is widely distributed in nature, is a common structural component in certain organisms: in the cell wall of pathogens such as bacteria and fungi, the sheath of parasitic nematodes, and the exoskeleton of crustaceans (crabs and shrimp) and insects. Chitin is also present in the exoskeleton of house dust mites, which is the most frequent and pervasive aeroallergen causing allergic diseases such as asthma and atopic dermatitis. It has been shown that inhalation of chitin in mice results in development of asthma-like airway inflammation accompanied by eosinophils and neutrophils. Chitin stimulates airway epithelial cells to produce cytokines such as IL-33 and TSLP, followed by production of IL-5 by group 2 innate lymphoid cells and Th2 cells to recruit eosinophils (1). On the other hand, the molecular mechanisms for airway neutrophilia induced by chitin still remain unclear. In the present study, we investigated it using mouse models.

2. Methods

Wild-type and gene-deficient mice on the C57BL/6 background were intranasally treated with chitin in saline or with saline alone once. One day after the inhalation of chitin or saline, the bronchoalveolar lavage (BAL) fluids were collected. The number of leukocytes in the BAL cells was counted with an automated hematology analyzer (XT-1800i; Sysmex, Japan).

3. Results

After chitin inhalation, the number of neutrophils in the BAL fluids was comparable between T and B cell-deficient Rag2-deficient（*Rag2*$^{-/-}$） mice and wild-type mice, but significantly reduced in *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice and *Rag2*$^{-/-}$ *Rorc*$^{-/-}$ mice, indicating that ILC3, but not T and B cells, were involved in chitin-induced airway neutrophilia. It is well known that IL-23, IL-1, IL-17C and IL-36 are key cytokines for activation of ILC3. After chitin inhalation, the number of neutrophils in the BAL fluids was significantly reduced in *Il23a*$^{-/-}$ mice, but normally observed in *Il17c*$^{-/-}$ and *Il36a*$^{-/-}$ mice, compared with wild-type mice, indicating that IL-23, but not IL-17C and IL-36α, is crucial for chitin-induced airway neutrophilia. Taken together, these observations suggest that chitin activates certain cells to produce IL-23, followed by activation of ILC3 to induce neutrophil recruitment in the lungs.

Reference

(1) Arae K. et al., Sci Rep, 11, 5913, 2021