Nature Reviews Immunology | AOP, published online 11 April 2014; doi:10.1038/nri3668

INNATE LYMPHOID CELLS

Breathing into allergic inflammation

Exposure to allergens leads to the production of the epithelial cell-derived cytokines interleukin-25 (IL-25), IL-33 and thymic stromal lymphopoietin (TSLP), which promote a type 2 immune response; however, the mechanisms behind this response are poorly defined. Now, two studies published in *Immunity* show that group 2 innate lymphoid cells (ILC2s) in the lungs are crucial for a robust type 2 immune response after inhalation of allergens.

Chitin, a polysaccharide found in the cell wall of fungi and the exoskeleton of arthropods, induces a type 2 immune response that is associated with the production of IL-5 and IL-13, and an accumulation of eosinophils and alternatively activated macrophages in the lungs. Van Dyken *et al.* showed that the numbers of eosinophils and alternatively activated macrophages were decreased in the lungs of mice that lacked expression of IL-13 compared with control animals following intranasal administration of chitin. Furthermore, using IL-13 reporter mice, the authors found that IL-13 was only expressed by lung ILC2s.

> “ILC2s are crucial for the differentiation of naive CD4$^+$ T cells into T_H2 cells”

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Next, the authors examined the role of IL-5 in response to chitin. The expression of IL-5 was increased in lung ILC2s, but not in any other immune cells, and the serum levels of IL-5 were also increased following chitin treatment. Furthermore, mice that lacked either IL-5- or IL-13-producing ILC2s that were challenged with chitin had similar numbers of lung ILC2s to mice with a defect in ILC2 development. Thus, inhaled chitin stimulates the production of IL-5 and IL-13 by ILC2s, which results in the accumulation of eosinophils and alternatively activated macrophages in the lungs.

Finally, the authors investigated the role of IL-25, IL-33 and TSLP in the activation of ILC2s in response to chitin. Single and combined deficiencies of these cytokines showed that they have a non-redundant role in activating ILC2s. Furthermore, in response to chitin, mice that were deficient in all three of these cytokines had almost no ILC2 cytokine secretion, and eosinophils and alternatively activated macrophages did not accumulate in the lungs of these mice. However, the recruitment of neutrophils to the lungs was normal in these mice due to the increased activation of IL-17A-producing γδ T cells.

In the second study, Halim *et al.* investigated the type 2 immune response that is induced by the plant-derived proteinase papain. Similar to Van Dyken *et al.*, they found that ILC2s had a crucial role in mounting this response. After papain challenge, mice lacking ILC2s had decreased numbers of eosinophils and neutrophils, as well as lower levels of type 2 cytokines, in the lungs and mediastinal lymph nodes compared with control mice. Furthermore, papain-challenged mice that lacked ILC2s showed lower numbers of T helper 2 (T_H2) cells that expressed IL-5 and IL-13 compared with control mice, which indicates that ILC2s are crucial for the differentiation of naive CD4$^+$ T cells into T_H2 cells.

Next, the authors investigated the role of IL-13 in the differentiation of T_H2 cells as they found that ILC2s expressed large amounts of this cytokine after papain challenge. Indeed, intracellular cytokine staining showed that ILC2-derived IL-13 was crucial for the differentiation of T_H2 cells. Interestingly, the IL-13 receptor was detected on activated dendritic cells (DCs) but not on naive CD4$^+$ T cells. Indeed, in response to papain, ILC2-derived IL-13 promoted the migration of activated DCs from the lungs to the draining mediastinal lymph nodes where they stimulated the differentiation of naive CD4$^+$ T cells into T_H2 cells.

Together, these studies show that ILC2s are required to induce innate and adaptive type 2 immune responses following the inhalation of allergens. This suggests that ILC2s have an important role in T_H2 cell-mediated inflammatory diseases such as asthma.

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ORIGINAL RESEARCH PAPERS Van Dyken, S. J. *et al.* Chitin activates parallel immune modules that direct distinct inflammatory responses via innate lymphoid type 2 and γδ T cells. *Immunity* **40**, 414–424 (2014) | Halim, T. Y. F. *et al.* Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity* **40**, 425–435 (2014)