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Invited review article

Group 2 innate lymphoid cells and asthma

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Abbreviations:
α-GalCel, α-galactosylceramide; BAL, bronchoalveolar lavage; BCL3, B-cell lymphoma 3; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; CSF-1, colony-stimulating factor 1; CysLT1R, Cysteinyl leukotriene receptor 1; FALC, fat-associated lymphoid cluster; FPR2, formyl peptide receptor 2; GATA3, GATA-Binding protein 3 GM-CSF, granulocyte macrophage colony-stimulating factor; Ih2 cells, innate helper type 2 cells; ILC2s, group 2 innate lymphoid cells; iILC2s, inflammatory ILC2s; LTD_4, leukotriene D_4; MPP type 2 cells, multipotent progenitor type 2 cells; NH cells, natural helper cells; OVA, ovalbumin; PBMC, peripheral blood mononuclear cells; PGD_2, prostaglandin D_2; RORα, Retinoic acid receptor-Related orphan receptor α; TL1A, TNF-Like ligand 1A; TSLP, thymic stromal lymphopoietin

ABSTRACT

Group 2 innate lymphoid cells (ILC2s) are recently identified cell populations that produce type 2 cytokines such as IL-5 and IL-13 in response to epithelial cell-derived cytokines. Although ILC2s were initially reported to play a key role in the anti-helminth innate immunity, we now have greater interest in their role in asthma and other allergic diseases. In various asthma mouse models, ILC2s provoke eosinophilic inflammation accompanied by airway hyperresponsiveness independent of acquired immunity. Moreover, recent mouse studies show that ILC2s also promote acquired immunity and Th2 polarization, and various cytokines and lipid mediators influence the functions of ILC2s. Although ILC2s have also been identified in humans, studies on the role of human ILC2s in asthma are very limited. Thus far, human studies have shown that there is a slight difference in responsiveness and production of cytokines between mouse and human ILC2s, and it has been suggested that ILC2s are involved in allergic-type asthma and the exacerbation of asthma. In this review, we focus on mouse and human ILC2s, and discuss their role in asthma.

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Introduction

Asthma is an airway disease characterized by bronchial hyperresponsiveness, reversible airflow limitation, and airway inflammation. Classically, acquired immunity and antigen-specific Th2 cells, which secrete type 2 cytokines such as IL-4, IL-5, and IL-13, have been considered to play pivotal roles in the pathogenesis of asthma.[1] IL-5 induces development, recruitment, and activation of eosinophils,[2] whereas IL-13 promotes hyperproduction of mucus and airway remodeling.[3] Hence, antibodies against these cytokines are expected as a new treatment of asthma.[4]

Innate immunity, which refers to a nonspecific defense mechanism against numerous pathogenic microbes, provides immediate recognition and response to pathogens. Relatively little was known about the role of innate immunity in the pathology of asthma until the recent discovery of innate lymphoid cells that produce large amounts of type 2 cytokines upon stimulation by epithelial cell-derived cytokines, now termed group 2 innate lymphoid cells (ILC2s).[5–8] Mouse studies have suggested that ILC2s are major sources of IL-5 and IL-13, and that ILC2s might have a role in the pathophysiology of asthma.[9] However, studies of the role of human ILC2s in asthma are currently very limited; moreover, there are slight differences between mouse and human ILC2s. In this review, we will review the characteristics of mouse and human ILC2s, and discuss their role in asthma.

Discovery of ILC2

In 2010, groundbreaking studies from three independent researchers reported the identification of cell populations involved in type 2 innate immunity. Moro *et al.* were the first to identify the fat-associated lymphoid cluster (FALC), a previously unrecognized lymphoid structure in mouse and human mesenteric adipose tissue.[5] In addition, they noted a novel cell population in FALC, and named them natural helper (NH) cells. NH cells produce large amounts of IL-5 and IL-13 in response to IL-33 or a combination of IL-2 and IL-25, and they express Sca-1, c-Kit, IL-33 receptor, IL-2 receptor, Thy1, and IL-7 receptor, but lineage markers (CD3, CD4, CD5, CD8, CD19, B220, NK1.1, Gr-1, FcεRIα, CD11b, CD11c, TER119) are not expressed. Following this report, Neill *et al.* reported that IL-25 or IL-33 administered to IL-13 reporter mice led to the accumulation of a lineage-negative IL-13-positive population, named nuocytes, in the mesenteric lymph nodes, spleen, and bone marrow.[6] Similarly, Price *et al.* identified a population of lineage-negative IL-13-positive cells, which were named innate helper type 2 (Ih2) cells,[7] using IL-4 or IL-13 reporter mice. All of these lymphoid cells have no antigen-specific receptors and cause nonspecific immune responses, as well as natural killer cells and lymphoid tissue-inducer cells. Hence, these cells were collectively termed innate lymphoid cells.

In 2013, the classification of innate lymphoid cells was proposed on the basis of their phenotypical and functional characteristics, and innate lymphoid cells were classified into three groups: Group 1 (producing IFN-γ), Group 2 (producing IL-5 and IL-13), and Group 3 (producing IL-17 and/or IL-22).[8] NH cells, nuocytes, and Ih2 cells are able to produce IL-5 and IL-13 in response to IL-25 or IL-33; these cells depend on the transcription factors GATA3 and RORα for their development and function.[10–15] Therefore, they are all classified as ILC2s by virtue of these common features.

Characteristics of mouse ILC2

As mentioned above, the most notable feature of ILC2s is their ability to secrete IL-5 and IL-13 in response to epithelial cell-derived cytokines such as IL-33 and IL-25. These epithelial cell-derived cytokines are released from epithelial cells, endothelial cells, and other immune cells during cellular damage or allergen exposure.[16] However, the responsiveness to these cytokines differs depending on the ILC2 subset. NH cells proliferated and produced large amounts of IL-5 and IL-13 when they were cultured in the presence of IL-33 or a combination of IL-2+IL-25 *in vitro*.[5] Surprisingly, NH cells produced ~1 pg/cell of IL-5 and IL-13 after stimulation with IL-33 for 96 h[12] On the other hand, nuocytes isolated from spleens of IL-25-administered mice did not proliferate when they were cultured with IL-25 or IL-33 alone, whereas nuocytes proliferated robustly in a combination of IL-33 and IL-7.[6] In addition, differences in cell-surface markers have been noted among NH cells, nuocytes, and Ih2 cells (Table 1). Therefore, it has been considered that distinct cell subsets might be present in a population of ILC2s, or some ILC2s might have phenotype plasticity.[17] In fact, IL-25-responsive ILC2s, expressing large amounts of KLRG1 and IL-25 receptor but not IL-33 receptor, have recently been discovered.[18] This cell population was named "inflammatory ILC2s" (iILC2s), and appeared in lung, spleen, and mediastinal lymph nodes at early time points after IL-25 administration or helminth infection. Further investigation revealed that iILC2s quickly acquired the expression of the IL-33 receptor and responsiveness to IL-33 *in vitro* and *in vivo*. Therefore, this finding confirmed that ILC2s might change their phenotype, including their expression of cell surface markers and responsiveness to cytokines.

Furthermore, ILC2s were identified in many organs and tissues (lung, skin, brain, heart, intestine, and liver),[19] and their responsiveness to cytokines slightly differed depending on the tissue. In lungs, the IL-33 receptor expression of lung ILC2s was lower than that of NH cells,[20–22] and there was a synergistic effect on the proliferation or production of type 2 cytokines when lung ILC2s were cultured with a combination of IL-33 and STAT5 activators such as IL-2, IL-7 or thymic stromal lymphopoietin (TSLP) compared to IL-33 alone.[20–22] In addition, it was recently reported that IL-4 also enhanced the responsiveness to IL-33 in lung ILC2s.[23]

ILC2s have been shown to be activated by some other cytokines or lipid mediators. TL1A (TNFSF15) belongs to the tumor necrosis factor (TNF) family of cytokines and it is produced by activated myeloid cells and stressed epithelial and endothelial cells.[24] Although TL1A is known to regulate acquired immune responses in the gut and lungs, recent studies have shown that TL1A is able to directly stimulate ILC2s to produce type 2 cytokines independent of IL-25 or IL-33.[25,26] As for lipid mediators, ILC2s express cysteinyl leukotriene receptor 1 (CysLT1R), the high-affinity receptor for leukotriene D_4 (LTD_4).[27] Cysteinyl leukotrienes are generated by mast cells, eosinophils, macrophages, and dendritic cells, and cause contractions of smooth muscle cells and inflammation in asthma and allergic rhinitis.[28] LTD_4 induces the production of IL-5 and IL-13 from lung ILC2s in a CysLT1R-dependent manner. Intriguingly, although IL-33 or IL-25 stimulation does not induce IL-4 production from ILC2s, LTD_4 induces IL-4 production from ILC2s.[27] IL-4 is an important cytokine leading to Th2 cell polarization and class switching of the immunoglobulins synthesized by B cells.[29] This finding suggests that ILC2s possibly promote acquired immune responses as well as innate immune responses. Likewise, some ILC2s also express OX40L and MHC class II,[30–32] and are able to activate CD4 T cells. Furthermore, IL-13 produced by ILC2s promotes dendritic cell migration to the draining lymph nodes to stimulate Th2 polarization.[33]

Finally, mouse ILC2s produce not only IL-5 and IL-13, but also IL-6, IL-9, and amphiregulin. NH cells produce IL-6, which promotes IgA production in combination with IL-5.[5] In the presence of IL-2, lung ILC2s produce IL-9, a pleiotropic cytokine that contributes to mast cell accumulation, airway eosinophilia, and mucus production.[34] IL-9 also acts as an autocrine factor that promotes the