Innate lymphoid cells and asthma

Sanhong Yu, PhD,[a] Hye Young Kim, PhD,[b] Ya-Jen Chang, PhD,[c] Rosemarie H. DeKruyff, PhD,[a] and Dale T. Umetsu, MD, PhD[d] *Boston, Mass, Seoul, Korea, Taipei, Taiwan, and South San Francisco, Calif*

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List of Design Committee Members: Sanhong Yu, PhD, Hye Young Kim, PhD, Ya-Jen Chang, PhD, Rosemarie H. DeKruyff, PhD, and Dale T. Umetsu, MD, PhD

Activity Objectives

1. To be able to describe the role of innate lymphoid cells (ILCs) in response to both allergic and nonallergic asthma.
2. To be able to discuss the 3 distinct ILC subpopulations and factors that regulate the differentiation and activation of these cells.

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Asthma is a complex and heterogeneous disease with several phenotypes, including an allergic asthma phenotype characterized by T_H2 cytokine production and associated with allergen sensitization and adaptive immunity. Asthma also includes nonallergic asthma phenotypes, such as asthma associated with exposure to air pollution, infection, or obesity, that require innate rather than adaptive immunity. These innate pathways that lead to asthma involve macrophages, neutrophils, natural killer T cells, and innate lymphoid cells, newly described cell types that produce a variety of cytokines, including IL-5 and IL-13. We review the recent data regarding innate lymphoid cells and their role in asthma. (J Allergy Clin Immunol 2014;133:943-50.)

Key words: *Airway hyperreactivity, innate lymphoid cells, natural killer T cells, allergy, asthma, influenza*

Abbreviations used

AHR:	Airway hyperreactivity
CRTH2:	Chemoattractant receptor–homologous molecule expressed on T_H2 cells
ILC:	Innate lymphoid cell
ILC1:	Type 1 ILC
ILC2:	Type 2 ILC
ILC3:	Type 3 ILC
iNKT:	Invariant natural killer T
NK:	Natural killer
NKT:	Natural killer T
ROR:	Retinoic acid receptor–related orphan receptor
T-bet:	T-box transcription factor
TSLP:	Thymic stromal lymphopoietin

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For several decades, asthma has been thought of as an immunologic disease mediated by T_H2 cells and adaptive immunity.[1] Indeed, allergen-specific T_H2 cells play a critical role in asthma because they produce IL-4, a switch factor for IgE; IL-5, a growth and differentiation factor for eosinophils; and IL-13, which can directly cause airway hyperreactivity (AHR), a cardinal feature of asthma, by directly affecting airway epithelial cells and airway smooth muscle cells.

From [a]the Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston; [b]the Department of Medical Science, Seoul National University College of Medicine, Seoul; [c]the Institute of Biomedical Sciences, Academia Sinica, Taipei; and [d]Genentech, South San Francisco.

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Corresponding author: Dale T. Umetsu, MD, PhD, Genentech, One DNA Way, South San Francisco, CA 94080. E-mail: umetsud@gene.com.

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TABLE I. Properties of ILCs

1.	ILCs are non-T, non-B lymphocytes present in mucosal and lymphoid tissues.
2.	ILCs are not antigen specific.
3.	ILCs secrete a variety of cytokines, including IFN-γ, IL-5, IL-9, IL-13, IL-17, and IL-22.
4.	ILCs rapidly respond to environmental factors.
5.	ILCs are involved in tissue homeostasis, lymphoid tissue organogenesis, resistance to infection, control of the composition of commensal microbiota, and pathology at mucosal surfaces.
6.	ILC2s might be involved in atopic diseases by producing IL-5, IL-9, and IL-13 and by interacting with mast cells, NKT cells, T_H2 cells, eosinophils, epithelial cells, and macrophages.

HETEROGENEITY OF ASTHMA

However, although T_H2 cells and eosinophils can explain many of the features of asthma, it has become very clear over the past 5 years that asthma is much more than T_H2 cells and eosinophils and that asthma is in fact a very heterogeneous and complex trait with at least several distinct phenotypes.[2] There is an allergic asthma phenotype triggered by exposure to allergens and associated with eosinophils in the airways and with allergic sensitization and adaptive immunity. There are also nonallergic asthma phenotypes associated with exposure to environmental factors, such as air pollution, including ozone, cigarette smoke, and diesel particles; associated with exercise, viral infection, stress, and obesity[2]; and often associated with neutrophils in the airways and innate immunity independent of T_H2 cells.[3-6] There might also be intrinsic forms of asthma and possibly other forms as well. This heterogeneity in asthmatic patients suggests that other factors and components of immunity, in addition to allergy and T_H2 cells, must be involved in regulating and shaping the inflammation seen in asthmatic patients.[2] Indeed, recent studies suggest innate lymphoid cells (ILCs) mediate several nontraditional, non-T_H2 cell pathways that regulate asthma. In this review we will discuss the potential role in asthma of ILCs, which produce a striking array of cytokines similar to the wide variety of cytokines produced by adaptive T cells.[7]

ILC FAMILY

ILCs represent an emerging family of non-T, non-B effector cells that have conserved effector cell functions and play crucial roles in tissue homeostasis, repair, and remodeling and in innate immunity to pathogenic and nonpathogenic microorganisms (Table I).[8] Unlike adaptive immune cells, ILCs lack rearranged antigen-specific receptors and therefore are antigen nonspecific but react promptly to a wide range of innate signals. Given the amount and variety of cytokines produced by ILCs and their potential importance in immune regulation, it is surprising that ILCs were not discovered earlier, but this might be due to the initial focus of immunologists on adaptive immune cells, particularly $CD4^+$ T cells producing IFN-γ and IL-4 (eg, T_H1 and T_H2 cells).

The specific characteristics and features of ILCs are not fully defined, but a classification scheme has been developed.[9] The prototypic ILC is the natural killer (NK) cell (studied for many years), which produces IFN-γ and expresses T-box transcription factor (T-bet) and cytolytic activity.

Type 1 ILCs (ILC1s) are related to NK cells in that they both express T-bet and IFN-γ, but ILC1s do not appear to express perforin, granzyme B, or killer-cell immunoglobulin-like receptors and respond primarily to IL-7 rather than IL-15 (Fig 1).[10] Human ILC1s have been shown to expand in the intestines in patients with Crohn disease.

Type 2 ILCs (ILC2s; previously called natural helper cells or nuocytes),[7] which produce IL-13, IL-5, and IL-9, were initially described in the gut in the context of helminth infection. ILC2s require the transcription factor retinoic acid receptor–related orphan receptor (ROR) α[11,12] and the GATA transcription factor Gata3.[13] ILC2s have been shown to mediate eosinophilia and goblet cell hyperplasia, both of which are critical for antihelminth responses and for allergic diseases. Recently, ILC2s have been shown to exist in the lungs and to have a role in the pathophysiology of asthma and allergic inflammation,[14] as described in the sections below.

Type 3 ILCs (ILC3s) have also been described and require the RORγt and GATA3 transcription factors for development.[15-17] ILC3s include at least 3 different subtypes: (1) lymphoid tissue inducer cells required for lymphoid organogenesis and producing IL-17 and IL-22[18]; (2) IL-22–producing ILC3s participating in host defense in the skin, lungs, and gut; and (3) IL-17–producing ILC3s, which express CCR6 and are active in the gut in patients with some forms of colitis[19] and in the lungs in some models of asthma.[20] Together, ILCs define a universe of cells that is parallel to the universe of CD4 adaptive T cells, which includes T_H1 cells (comparable with ILC1s/NK cells), T_H2 cells (comparable with ILC2s), and T_H17 and T_H22 cells (comparable with ILC3s). Like CD4 helper cells, which arise from a common precursor cell, ILCs are also thought to arise from a common precursor cell characterized by expression of the transcription factor inhibitor of DNA binding 2.[12,21,22] The existence of these parallel universes of adaptive and innate cells, both of which are associated with the production of a wide variety of cytokines, blurs the lines between innate and adaptive immunity.

ILC2s

Cells with the characteristics of ILC2s were first described in 2001 as non-T, non-B cells that expanded on administration of IL-25[23,24] and were associated with a T_H2-like immune response with increased serum IgE levels and eosinophilic infiltrates in the lungs and digestive tract. Similar non-T, non-B lymphocytes producing IL-5 and IL-13 were described in the lungs of asthmatic patients, but their specific function was unclear.[25] In 2010, 3 different groups characterized a mouse non-T, non-B cell ILC type that produced large quantities of IL-5 and IL-13 in response to IL-25 and IL-33.[26-28] These cells expanded and mediated protection during helminth infection and were found in lymphoid structures associated with adipose tissue and in gut-associated lymphoid tissue. The initial reports of ILC2s described cell types with slightly different cell-surface markers and function,[24,27-29] but a consensus nomenclature panel renamed all of these type 2 ILCs because these cells secreted IL-5 and IL-13.[7] Although there are subtle differences between the cells described in these reports, in general, mouse ILC2s

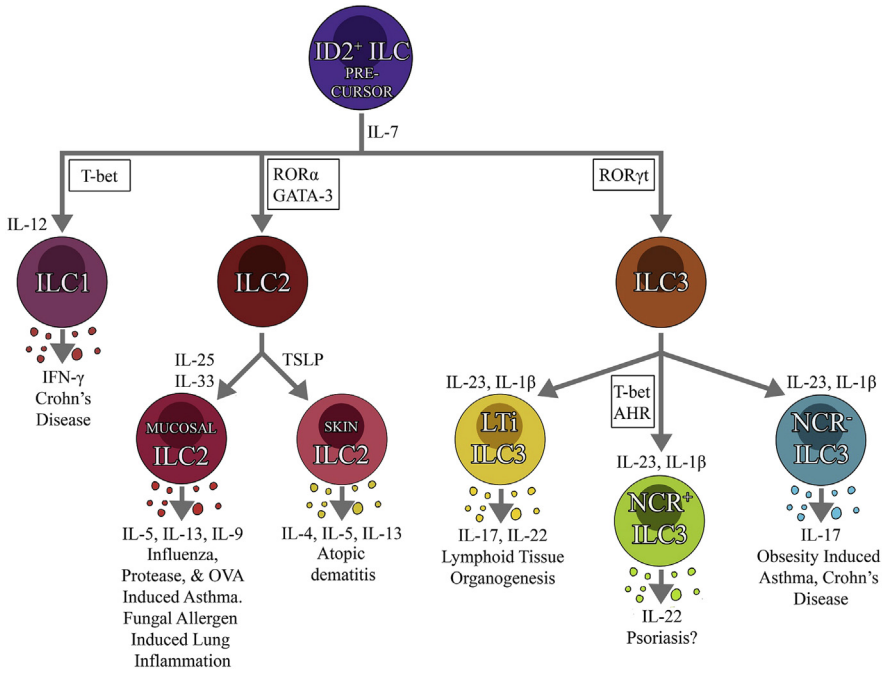

FIG 1. Development and function of ILCs. All ILCs develop from a common precursor cell characterized by expression of the transcriptional repressor inhibitor of DNA binding 2 *(ID2)*, expression of the common cytokine receptor γ chain (not shown), and dependence on IL-7 for development. ILC1s produce IFN-γ on stimulation with IL-12, depend on T-bet for their development, and are involved in the pathogenesis of Crohn disease. ILC2s depend on the transcription factors GATA3 and RORα for their development. They produce IL-5, IL-13, and IL-9, although skin ILC2s are reported to produce IL-4, IL-5, and IL-13. ILC2s are activated by stimulation with IL-33, IL-25, and IL-2 and participate in the development of some forms of asthma. Different from mucosal ILC2s, the skin ILC2 response is elicited by TSLP and promotes atopic dermatitis. ILC3s require the transcription factor RORγt for their development and respond to IL-23 and IL-1β. ILC3s include 3 different subsets: lymphoid tissue inducer *(LTi)* ILC3s, natural cytotoxicity receptor *(NCR)*$^+$ ILC3s, and NCR$^-$ ILC3s. LTi ILC3s play an important role in lymphoid tissue organogenesis and produce IL-17 and IL-22. NCR$^-$ ILC3s express CCR6, produce IL-17 and sometimes IL-22, and are critical in the development of obesity-induced asthma and inflammatory bowel disease. NCR$^+$ ILC3s produce IL-22 and also depend on the aryl hydrocarbon receptor *(AHR)* and T-bet for their function. Some ILC3s downregulate RORγt and transform into ILC1s. NCR$^+$ ILC3s might contribute to the development of psoriasis. *OVA*, Ovalbumin.

express CD25 (IL-2 receptor α), CD90 (Thy1), variable amounts of CD117 (c-Kit), and CD127 (IL-7 receptor α) and mediate the type 2 immunologic responses underlying helminth host defense and asthma/allergy. Additionally, ILC2s express variable amounts of CD278 (inducible costimulator), ST2 (IL-33 receptor), and IL-17RB and are IL-25 responsive (IL-17E) and IL-33 responsive, such that these cells proliferate and expand in response to IL-25 and IL-33 and in response to pathogens, including helminths, viruses, and fungi.[24,27-29] It should be noted that ILC2s have subtle differences depending on the mouse strains, the organ in which the cell resides, and its activation state. ILC2s appear to require IL-7 and IL-33 for their development and the transcription factors inhibitor of DNA binding 2, RORα, and GATA3, as well as Notch signaling.[11,12,21] In addition, the transcription factor Gfi1 also controls the development and activation of ILC2s by directly activating *Il1rl1*, which codes for the IL-33 receptor ST2, which favorably regulates the responsiveness of ILC2s to IL-33 but not IL-25 and inhibits the expression of IL-17.[30] The role of ILC2s in patients with lung disease is being defined, and recent studies of lung inflammation and development of asthma are discussed in next section.

ILC2s in asthma

Although IL-25 administration led to the discovery of ILC2s in several model systems, IL-33 has greater effects on ILC2 function, allowing ST2$^{-/-}$ mice (mice lacking the IL-33 receptor) to help define specific roles for ILC2s in various models. For example, ST2$^{-/-}$ mice, although having near-normal AHR responses after sensitization and challenge with allergen, have greatly reduced AHR after infection with influenza.[14] This suggested that in mice ILC2s play a critical role in influenza-induced AHR and less of a role in allergic asthma. Indeed, ILC2s were shown to be present in the lungs, particularly during influenza infection, and mediated the AHR response associated with influenza infection.[14] During influenza infection, the virus infects alveolar macrophages, which then release IL-33, which expands and activates ILC2s to secrete IL-13 and IL-5. Furthermore, the activation of ILC2s by influenza infection was confirmed by other studies showing that IL-5 production by ILC2s during influenza infection resulted in progressive accumulation of eosinophils after viral clearance.[31]

An important role for ILC2s during influenza virus infection might help to explain the mechanisms by which viral infection cause asthma, which until now have been very poorly

understood. Viral respiratory tract infections precipitate most of the hospitalizations in asthmatic patients, but previous paradigms of asthma have focused on how viral infections worsen T_H2/allergen-induced lung inflammation and AHR.[32] However, viral infections can precipitate symptoms in virtually all patients with asthma, regardless of the presence of allergy, suggesting that non-T_H2 mechanisms for asthma must be activated by viral infection. Thus acute infection of mice with influenza A virus rapidly induced AHR, even in the total absence of adaptive immunity, in *Rag2*$^{-/-}$ mice. However, the response depended on IL-33, its receptor ST2 (*Il1rl1*), and ILC2s expressing c-Kit, Sca-1, Thy1.2 (CD90), and ST2, and did not occur in ST2$^{-/-}$ mice.[14] Influenza-induced AHR was dependent on IL-13, and adoptive transfer experiments demonstrated that IL-13–secreting ILC2s were capable of restoring AHR in IL-13$^{-/-}$ hosts. Furthermore, depletion of ILC2s by treatment of *Rag2*$^{-/-}$ mice, which have ILC2s, with anti-Thy1.2 (CD90) mAb abolished the influenza-induced AHR response. This reliance on IL-13 is similar to the situation observed in models of allergic asthma, although in patients with allergic asthma, the IL-13 is produced by allergen-specific T_H2 cells and natural killer T (NKT) cells.[33]

In another study influenza infection was shown to also activate ILC2s, but in this case the ILC2s produced amphiregulin, which was required for restoring lung-tissue homeostasis after influenza infection. By depleting CD90.2-expressing ILC2s in *Rag1*$^{-/-}$ mice, the authors found increased airway damage, suggesting that ILC2s played a key role in the maintaining epithelial cell integrity and improving lung function after viral infection.[22] The homeostatic function of ILC2s was independent of IL-13 and IL-22, although a more recent study suggests that IL-22 is essential for lung epithelial repair after influenza infection.[34]

Thus these studies show that ILC2s can both promote inflammatory lung disease and restore airway epithelial cell integrity after injury. Although these 2 functions of ILC2s might appear contradictory, these roles could reflect the homeostatic versus pathologic role of ILC2s similar to the contrasting roles that have been observed with many other immune cell types. For example, T_H1, T_H2, and T_H17 cells each have evolutionarily conserved salutary effects (in resistance to intracellular, helminth, and fungal infections, respectively), as well as pathologic effects (in causing autoimmunity or allergy). Therefore the context in which ILC2s are activated determines whether their function is beneficial (enhancing epithelial cell integrity) or dysregulated and detrimental (causing airway inflammation and AHR). ILC2s might have evolved to repair lung injury, as in influenza-infected mice. However, when overactivated without opposing constraints, ILC2s might cause airway inflammation and AHR. On the other hand, in the context of helminth infection, ILC2s are also rapidly activated and essential for the initial T_H2-like response, which enhances an effective adaptive response associated with eosinophilia and increased mucus production needed for worm expulsion. Alternatively, it is possible that subsets of ILC2s might exist, such that some ILC2 subsets produce more IL-13 and less amphiregulin and cause airways disease, whereas others produce more amphiregulin and less IL-13 and reverse airway injury. Further investigation into the characteristics of ILC2s and possible subsets will help to resolve this issue.

ILC2s in allergic airway disease

Allergen-induced innate IL-13–producing ILC2s in lungs. In addition to having a role in the lung during influenza infection, the production of IL-13 and IL-5 by ILC2s suggests that ILC2s could play an important role in allergic asthma. Indeed, several studies have shown that ILC2s are associated with allergic asthma. First, in a mouse model in which mice were sensitized to ovalbumin and challenged through the airways to induce allergic inflammation, Kearly et al[35] showed persistent AHR correlated with the continued presence of T_H2 cells, but not eosinophils, in the lungs. In their study they found the ST2–IL-33 pathway was important because treatment with blocking antibodies against ST2 reduced IL-4 and IL-13 secretion, allergic inflammation, and AHR. However, they concluded that T_H2 cells were the primary cell type that causes AHR, although ILC2s, which also rely on the ST2–IL-33 pathway, might contribute to type 2 allergic airway inflammation. Similarly, studies by Barlow et al[36] using $Il4^{+/eGFP}Il13^{+/Tomato(Tom)}$ dual-reporter mice showed that ovalbumin-induced ILC2s provide significant IL-13 in the lung. They found that CD4$^+$ T cells infiltrating the lung almost exclusively express IL-13 and not IL-4, whereas T cells in the draining lymph nodes produce primarily IL-4. Therefore both T cells and ILC2s expand in the allergic lung and are highly biased toward IL-13 production. Furthermore, intranasal administration of recombinant IL-25 or IL-33 induces the expansion of IL-5– and IL-13–producing ILC2s in the lungs, bronchoalveolar lavage fluid, and mediastinal lymph nodes.[36-39] In another study, Klein Wolterink et al[40] showed that both ILC2s and T_H2 cells produce large amounts of IL-5 and IL-13, which contribute to house dust mite–induced or ovalbumin-induced allergic asthma.[40]

Several groups have explored the mechanisms by which ILC2s become activated by allergens. First, Wilhelm et al[41] found that papain, an allergen with protease activity expressed by many potent allergens, activated ILC2s, particularly those producing IL-9. This process required IL-2 and IL-33 (but not IL-25), and blockade of IL-9 resulted in reduced expression of IL-5 and IL-13, suggesting that ILC2s might initially produce IL-9 and then mature in an autocrine fashion to produce IL-5 and IL-13. Second, Halim et al[42] extended the study of protease-containing allergens in ILC2 activation and showed that protease activity itself damaged airway epithelial cells, which released IL-33 and in turn activated ILC2s. This group showed that intranasal administration of papain to *Rag1*$^{-/-}$ mice, but not *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice (ILC2s are present in *Rag1*$^{-/-}$ mice but not *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice), rapidly caused lung eosinophilia, mucus hypersecretion, and an increase in bronchoalveolar lavage fluid IL-5 and IL-13 levels (AHR was not examined). Furthermore, depletion of ILC2s in *Rag1*$^{-/-}$ mice by anti-CD25 mAb injection significantly reduced lung eosinophilia and mucus secretion on papain administration, and adoptive transfer of ILC2s into *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice reconstituted these symptoms. Similar results were obtained with the allergen from *Alternaria alternata*, which also has protease activity, and induced IL-33 and IL-25 production from airway epithelial cells and the expansion of lung Lin$^-$CD25$^+$CD44^{hi} ILC2s.[37] This suggested that ILC2s are a critical early source of IL-5 and IL-13 in protease allergen–induced lung inflammation and that this occurs in a T cell–independent manner. Although all of these studies suggest that ILC2s expand and are present during

allergen-induced airways disease, none have shown that ILC2s are actually required for the development of allergen-induced AHR. Further study of this important question is necessary to more precisely understand the ILC2 requirement in patients with allergic lung disease.

Interaction between ILC2s and other innate and adaptive cells

As an innate cell type, ILC2s likely interact with many other cell types. First, ILC2s have been shown to synergize with T_H2 cells in the gut for the expulsion of metazoan helminths.[27] ILC2s respond early during helminth infection (presumably to IL-33, IL-25, and thymic stromal lymphopoietin [TSLP] released by damaged gut epithelial cells). However, effective elimination of helminths also requires adaptive T_H2 cells, which develop later during infection. Interestingly, the sustained presence of ILC2s in the gut during helminth infection required adaptive immunity,[27] presumably because of production by the adaptive cells of IL-2, which might also increase IL-9 production by ILC2s.[43]

Interaction between ILC2s and NKT cells. ILC2s also appear to interact with invariant natural killer T (iNKT) cells. iNKT cells are innate-like T cells that recognize glycolipid antigens presented by CD1d, rapidly produce large quantities of cytokines, and are thought to have an important role in regulating the development of asthma.[44] The interaction between iNKT cells, airway epithelial cells, and macrophages might be mediated by bacterial or fungal glycolipids that directly activate iNKT cells. For example, in several airway models iNKT cells activated by these glycolipids induced IL-33 production in airway epithelial cells and macrophages, leading to activation of ILC2s and rapid induction of AHR.[45] The glycolipids studied included those from *Sphingomonas* species,[45] which are present in the lungs of patients with chronic asthma,[46] and from *Aspergillus fumigatus*,[47] which is frequently associated with severe steroid-resistant asthma.[48,49] These AHR responses were blocked with anti-ST2 mAb, which is greatly reduced in $ST2^{-/-}$ mice, and restored by adoptive transfer of IL-13–producing ILC2s.[45] It might be that the environment is replete with iNKT cell–activating glycolipids, such as from plant pollens,[50] house dust,[51] some bacteria, and fungi, allowing iNKT cells to interact with ILC2s to greatly enhance the development of AHR and asthma through mechanisms involving an IL-33–ST2–IL-13 axis.

ILC2s, eosinophils, and mast cells. Because ILC2s produce IL-5, they also appear to control eosinophil homeostasis in the lung, small intestine, and peripheral blood. In naive mice ILC2s represent the majority of IL-5–producing cells in the peripheral tissues, and ILC2s turn over more slowly compared with IL-5-producing $CD4^+$ T cells.[52] ILC2s thus maintain serum IL-5 levels in mice. In addition, ILC2s release IL-5 in response to vasoactive intestinal peptide, which is released after feeding. This relationship between IL-5 release and feeding appears to explain eosinophil circadian cycling by regulating eosinophilopoiesis and eosinophil tissue accumulation. Similar interactions between ILC2s and eosinophils occur in visceral adipose tissue, where ILC2s promote the accumulation of eosinophils and maintain alternatively activated macrophages.[53]

In the skin of mice, ILC2s have been shown to be abundant and require IL-7 for survival.[54] These cells produced IL-13 constitutively (and possibly IL-9) and interacted with cutaneous mast cells, which are known to produce IL-33.[55] This suggests that the recognition of allergens by IgE on mast cells might lead to increased secretion of IL-33 and to activation of ILC2s, which then secrete IL-5, to enhance eosinophil accumulation. Thus once allergen-specific IgE is present, this innate pathway involving mast cells/ILC2s/IL-33/IL-9 and releasing IL-13 and IL-5 could dominate the persistence of an allergic type of inflammation.

ILC2s in human disease

As with many new discoveries in the immune system, the initial studies of ILC2s were all performed in mice. Subsequently, however, multiple studies suggest that ILC2s are also important in human subjects, particularly in the human respiratory tract, although much more investigation is required to understand their role in human disease. First, Allakhverdi et al[25] reported that non-T, non-B cells producing IL-13 and IL-5 with characteristics of ILC2s were present in the sputum of asthmatic subjects but not in that of healthy subjects. These investigators found that the non-T, non-B $CD34^+$ cells expressed receptors for TSLP and IL-33 and responded to these cytokines by rapidly producing high IL-13, IL-5, and chemokine levels. In addition, numbers of these cells increased in response to specific allergen inhalation challenge. Although Allakhverdi et al did not further characterize this subset, their findings suggest that ILC2s might play an important role in asthma. The source of the IL-33 and TSLP was not clear, although airway epithelial cells and airway smooth muscle cells might be the source of IL-33 in asthmatic patients.[56]

The second area of investigation suggesting an important role for ILC2s and the ILC2 axis in asthmatic patients is observations in genome-wide association studies identifying the genes for IL-33, ST2, and RORα as very important susceptibility genes for human asthma.[57]

Third, recent studies have identified human ILC2s as important sources of IL-13 and IL-5. These studies include reports of ILC2s in fetal gut tissue, which were identified as Lin^-, IL-7 receptor α $(CD127)^+$ cells expressing chemoattractant receptor–homologous molecule expressed on T_H2 cells (CRTH2) and CD161,[58] in the pleural effusion of patients with primary spontaneous pneumothorax associated with the presence of IL-5, IL-33, and TSLP[59] in the lungs of healthy subjects (and responding to prostaglandin D_2, a ligand of CRTH2)[60] and in the skin of patients with atopic dermatitis identified as Lin^-CD127^+ cells dependent on TSLP rather than on IL-33 or IL-25.[61] These reports and studies of murine ILC2s suggest that the specific cell-surface markers of ILC2s might vary depending on the activation state and site of derivation (eg, lung, gut, or skin). Finally, ILC2s have been found in nasal polyp tissue from patients with chronic rhinosinusitis.[58] Because TSLP levels are increased in nasal polyps of patients with chronic rhinosinusitis[62] and because IL-33 and ST2 are increased in the serum and tissue of patients with allergic rhinitis,[63] ILC2s might play an important role in human subjects with allergic rhinitis. These studies together suggest that ILC2s likely play

a critical role in human subjects, both in the respiratory tract and in the skin.

ILC1s, ILC3s, and asthma

ILC1s and asthma. ILC1s or NK cells have not been studied extensively in the context of asthma in part because the tools for specifically ablating ILC1s or NK cells are limited. However, more than a decade ago, Korsgren et al[64] showed in a mouse model that NK cells might control the development of allergic eosinophilic airways inflammation. Depletion of innate cells (both NK and NKT cells) with anti-NK1.1 antibody greatly reduced eosinophilic infiltrates in the lung tissue and was associated with decreased IL-5 and IL-12 levels in the lung and reductions in allergen-specific IgE and IgG levels. Because NKT cell–deficient mice did not have reduced allergen-induced airway eosinophilia, the authors concluded that NK cells might have an important role in enhancing allergen-induced airway inflammation. However, because airway inflammation does not always correlate with AHR and because no assessment of AHR (a measure more related to asthma) was made in this model, determining the specific role of NK cells/ILC1s in asthmatic patients requires further study. Indeed, examination of ILC1s taken from the lungs of asthmatic patients suggested that ILC1s promoted eosinophil apoptosis and functioned to inhibit eosinophilic airway inflammation.[60]

ILC3s and asthma. The role of ILC3s producing IL-17A in asthmatic patients must of necessity relate to a role for IL-17A in asthmatic patients, which has been controversial because IL-17A was shown early on to either inhibit or exacerbate allergic asthma.[4,65] However, recent studies indicate that IL-17 can directly cause AHR,[66,67] although the source of IL-17 has been assumed to be T_H17 cells.

Given that IL-17 might be pathogenic in airways disease, a role for ILC3s producing IL-17A and causing AHR associated with obesity has been recently proposed.[20] Obesity, which is associated with type 2 diabetes mellitus, cardiovascular disease, liver disease, and some forms of cancer,[68] is also a major risk factor for the development of asthma,[69-71] particularly for a severe, therapy-resistant form of asthma distinct from allergic asthma.[72] In a mouse model of obesity-induced AHR, Kim et al[20] demonstrated that obese mice, which spontaneously had AHR, had significant numbers of IL-17–producing cells in their lungs and that the majority of these IL-17A–producing cells were $Lin^{-}Thy1.2^{+}Scal\text{-}1^{+}$ ILC3s. Unlike ILC2s, the ILC3s were $ROR\gamma t^{+}CD44^{+}CCR6^{+}$ and did not make IL-13. Moreover, $Rag^{-/-}$ mice treated with a high-fat diet also became obese and had AHR associated with an increase in IL-17–producing ILC3 numbers in their lungs, indicating that this pathway for AHR could occur in the absence of adaptive immunity. IL-17 was required for the obesity-induced AHR because $IL17^{-/-}$ mice fed the high-fat diet did not have AHR, even though these mice became obese. The development of IL-17–producing ILC3s in the obese mice required the NLRP3 inflammasome because $Nlrp3^{-/-}$ mice on the high-fat diet became obese but did not have AHR. NLRP3-mediated AHR developed through enhanced IL-1β production in the obese mice, particularly in lung macrophages, which converted from M2 to M1 macrophages, producing IL-1β. Moreover, blocking IL-1β signaling with a short treatment course of an IL-1 receptor antagonist (anakinra) abrogated development of AHR in the obese mice and greatly decreased the numbers IL-17–producing lung ILC3s. IL-1β mediated the development of IL-17–producing ILC3s because administration of IL-1β to $Rag^{-/-}$ mice or $Nlrp3^{-/-}$ mice directly induced AHR associated with a great increase in IL-17–producing IL-3 cell numbers in the lungs. Furthermore, adoptive transfer of IL-17–producing ILC3s to $Rag2^{-/-}Il2rg^{-/-}$ mice restored IL-1β–induced AHR, indicating that IL-17–producing ILC3s by themselves could induce AHR. Importantly, examination of the bronchoalveolar lavage fluid from a small group of patients with severe asthma demonstrated the presence of IL-17–producing ILC3s, particularly in the lungs of patients with more severe disease. This indicated that (1) ILC3s are present in the lungs of patients with asthma and (2) ILC3s might play an important role in some forms of human asthma.

In addition to caloric excess, other nutritional factors can affect the development of ILC3s. Thus vitamin A deficiency in mice resulted in greatly reduced numbers of IL-22– and IL-17–producing ILC3s,[73] which are normally abundant in the small intestine and protect against intestinal infection. Surprisingly, vitamin A deficiency was also associated with a significant reciprocal increase in ILC2 numbers, indicating that vitamin A drives the expansion of ILC3s but inhibits the growth of ILC2s. The imbalance of ILC2s and ILC3s during vitamin A deficiency resulted in a susceptibility to intestinal bacterial but protection against intestinal helminth infection. Moreover, treatment of vitamin A–deficient mice with all-trans retinoic acid restored the number of ILC3s to normal levels, whereas it reduced the number of ILC2s, confirming an important role of vitamin A in ILC homeostasis.

The mechanism by which ILC3s protect against bacterial infection is related to their capacity to produce IL-22 and soluble LTα3 and to express membrane-bound LTα3 (LTα1β2).[74-76] IL-22, production of which depends on aryl hydrocarbon receptor[75] and signal transducer and activator of transcription 3 signaling,[77] induces epithelial cells to secrete antimicrobial peptides, whereas soluble LTα3 regulates influx into the lamina propria of T cells that induce IgA production. In contrast, LTα1β2 controls the induction of IgA synthesis by $CD11c^{+}$ dendritic cells independent of T cells by enhancing inducible nitric oxide synthase production in dendritic cells. All of these functions are critical in controlling the composition of commensal and pathogenic intestinal microbiota.

Concluding remarks

The discovery of ILCs over the past several years has changed our understanding of the principles for immune regulation and shown how innate immunity profoundly shapes the development of asthma. In some situations ILCs appear to be as important as adaptive immune cells, greatly contributing to some forms of allergic disease and asthma. Although the unique cell-surface and intracellular markers of ILC2s and their interactions with other cell types are not fully understood and many additional questions regarding their function remain to be answered, studies of these ILC2s have opened a new area of investigation that might lead to much improved therapies for lung and allergic diseases.

What do we know?

- **ILCs comprise a newly described set of lymphocytes that produce an array of cytokines rivaling adaptive CD4$^+$ T cells.**
- **The role of ILCs in immunity is currently being defined, but they are likely to play important roles in regulating atopic diseases, including asthma.**
- **ILCs are activated in non–antigen-specific ways and, as innate cells, rapidly produce cytokines, including IL-5, IL-13, IFN-γ, and IL-17. These cytokines can direct the development of adaptive immunity or mediate immune responses independent of adaptive immunity.**
- **ILCs produce a broad array of cytokines, including IL-5, IL-13, and IL-17.**
- **ILCs respond in a non–antigen-specific fashion.**
- **ILCs can function independently of adaptive immunity but might also regulate adaptive immunity.**

What is still unknown?

ILCs have only recently been identified, and many of their functions and characteristics are still being determined. Among the numerous questions regarding ILCs that remain are:

- **How do ILC2 cells interact with adaptive immune cells?**
- **How do ILC3 cells interact with adaptive immune cells?**
- **Because ILCs are low frequency cells in the naive state, when and how do they expand in number? In what situations do they become critical in host defense against infection or in causing pathology?**
- **Are ILCs important in human disease, and if so, in which diseases? Are ILC2 and ILC3 cells required for the development of human asthma, as they are in some mouse models of asthma? Are they required for the development of atopic dermatitis or other atopic diseases?**
- **Are ILCs important in humans infected with helminths or other pathogens?**
- **Are ILC1 and ILC3 cells required for the development of human inflammatory bowel disease?**
- **Is targeting ILCs worthwhile in the treatment of disease?**
- **Will additional subsets of ILCs be discovered?**

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