



Innate-like Lymphocytes and Innate Lymphoid Cells in Asthma

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Abstract

Asthma is a chronic pulmonary disease, highly associated with immune disorders. The typical symptoms of asthma include airway hyperresponsiveness (AHR), airway remodeling, mucus overproduction, and airflow limitation. The etiology of asthma is multifactorial and affected by genetic and environmental factors. Increasing trends toward dysbiosis, smoking, stress, air pollution, and a western lifestyle may account for the increasing incidence of asthma. Based on the presence or absence of eosinophilic inflammation, asthma is mainly divided into T helper 2 (Th2) and non-Th2 asthma. Th2 asthma is mediated by allergen-specific Th2 cells, and eosinophils activated by Th2 cells via the secretion of interleukin (IL)-4, IL-5, and IL-13. Different from Th2 asthma, non-Th2 asthma shows little eosinophilic inflammation, resists to corticosteroid treatment, and occurs mainly in severe asthmatic patients. Previous studies of asthma primarily focused on the function of Th2 cells, but, with the discovery of non-Th2 asthma and the involvement of innate lymphoid cells (ILCs) in the pathogenesis of asthma, tissue-resident innate immune cells in the lung have become the focus of attention in asthma research. Currently, innate-like lymphocytes (ILLs) and ILCs as important components of the innate immune system in mucosal tissues are reportedly involved in the pathogenesis of or protection against both Th2 and non-Th2 asthma. These findings of the functions of different subsets of ILLs and ILCs may provide clues for the treatment of asthma.

Keywords Th2 asthma · Non-Th2 asthma · Innate-like lymphocytes (ILLs) · Innate lymphoid cells (ILCs) · Pathogenesis · Protection

Introduction

Asthma is a chronic inflammatory disease of the respiratory system. Patients with asthma may experience repeated bouts of wheezing, chest tightness, shortness of breath, and even risk of death [1]. Together with the high treatment cost, asthma poses a serious burden on individual, family, and society. Over the past few decades, asthma has become increasingly prevalent and now affects about 300 million people worldwide [2]. The current understanding of the pathogenesis of asthma is

still limited; however, it is widely accepted that the disease is heterogeneous and highly associated with immune disorders [3]. Several components of the innate and adaptive system have been reported to contribute to or protect against different types of asthma. Recently, innate lymphocytes have attracted extensive attention, owing to the identification of new subpopulations of ILCs and their functions in the development of asthma [4, 5]. The ILCs comprise a group of innate immune cells, which lack the T cell receptor (TCR) and B cell receptor (BCR), and can rapidly secrete various cytokines in response to stimulation. According to the latest nomenclature, ILCs are classified into five subpopulations, i.e., ILC1s, ILC2s, ILC3s, natural killer (NK) cells, and lymphoid tissue-inducer (LTi) cells [6]. In addition to ILCs, several subpopulations of T or B cells that express invariant TCRs or BCRs but function as innate immune cells have been identified, and are referred to as ILLs [7, 8]. The ILLs include NKT cells, $\gamma\delta$ T cells, mucosa-associated invariant T (MAIT) cells, B-1 cells, and marginal zone B (MZB) cells [9]. Except for their differences in expressing TCRs and BCRs, ILCs and ILLs have many similarities, e.g., relatively fewer in number, they both lack antigen-specificity, are tissue-resident, and preferentially

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located at mucosal sites, where infection and inflammation frequently occur [10]. As the second-largest mucosal surface in the human body, the respiratory tract is also colonized by ILL and ILC subpopulations (Fig. 1). Numerous studies have shown that both ILLs and ILCs are involved in the pathogenesis of or protection against asthma. Potential strategies targeting ILLs and ILCs for the treatment of asthma have been proposed.

Heterogeneity of Asthma

Before the early 2000s, asthma was widely believed to be a Th2 cell-mediated eosinophilic disease, which we now call allergic asthma or Th2 asthma. Th2 asthma shows an effective response to corticosteroid treatment [11]. However, clinical trials have found that some patients show an ineffective response to corticosteroids [12, 13]. Furthermore, non-Th2 asthma with little eosinophilic inflammation has also been documented. Currently, Th2 asthma and non-Th2 asthma are considered as the two major types of asthma. Each type can be further subdivided into several subtypes based on disease onset, pathogenesis, clinical features, and physiological features, even though there may be some overlap among these features [14, 15] (Table 1). Thus, asthma is a heterogeneous disease that is more complicated than we first thought. Therefore, proper knowledge of the etiology of various types of asthma is necessary, before a discussion about the function of ILLs and ILCs in asthma.

Th2 Asthma

The subtypes of Th2 asthma include early-onset, late-onset, and exercise-induced asthma. The age at which the first asthma attack occurs distinguishes early-onset from late-onset asthma [24, 42]. Early-onset asthma usually occurs in early childhood or preadolescence, but the exact age cut-off has not been clearly defined.

Early-onset Asthma

Early-onset asthma usually presents as a moderate syndrome, which is generally milder than that of late-onset asthma. However, the levels of allergen-specific immunoglobulin E (IgE) are much higher in early-onset asthma; thus, it is also referred to as early-onset allergic asthma. Genome-wide association studies (GWAS) have shown that some genes are highly associated with early-onset asthma, e.g., IL-4R α , IL-13, IL-33, and GATA3 [16, 17]. Therefore, this disease shows genetic susceptibility. In addition to genetic risk factors, some environmental factors, e.g., endotoxins and peptidoglycan in bacteria or air pollutants, also contribute to early-onset asthma [18]. Front-line treatment of early-onset asthma is non-specific corticosteroid therapy, which targets several biomarkers of the Th2 response, including IL-4, IL-13, IgE, and eosinophils. In addition, since 2003, IgE-specific antibody (Omalizumab) has been approved for the treatment of asthma and works well in patients with early-onset asthma [19, 20]. Furthermore, anti-IL-4R α treatment has been shown to improve the physiological state of patients. Strategies targeting IL-33/ST2 signaling could be a potential therapy, but anti-IL-5 or anti-IL-13 treatment have shown little efficacy in patients with early-onset asthma [12, 13, 21–23].

Late-onset Asthma

Late-onset asthma is more eosinophilic and less allergic, i.e., higher numbers of eosinophils can be observed in the sputum, bronchus, and blood, compared with that observed in early-onset asthma [25]. Thus, late-onset asthma is also referred to as late-onset eosinophilic asthma. Biomarkers of late-onset asthma include IL-13, IL-5, 15-lipoxygenase-1, 15-hydroxyeicosatetraenoic acid, inducible nitric oxide synthase (iNOS), and eotaxin, but exclude IgE [26, 27]. Late-onset asthma is corticosteroid-refractory [24]. Corticosteroids play a role in promoting the apoptosis of eosinophils. However,

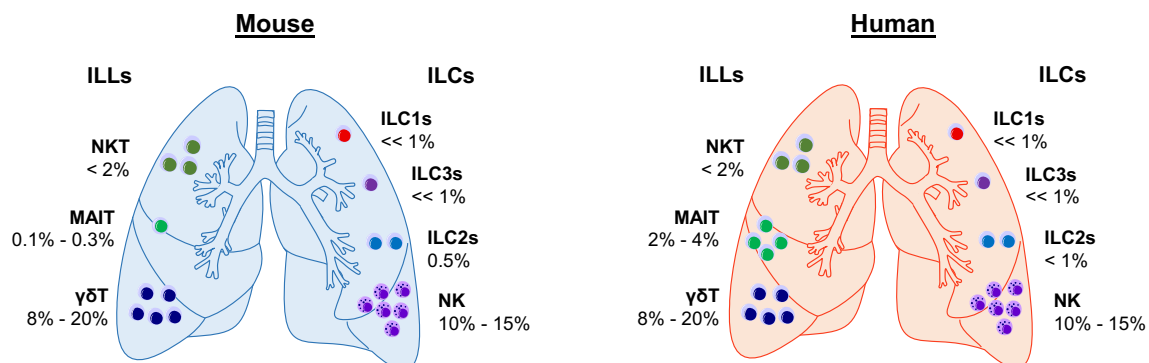


Figure 1. Distribution of ILLs and ILCs in mouse and human lungs. The lungs of mice and humans are colonized by several subpopulations of ILLs and ILCs. Among the subpopulations of ILLs, γδT cells are most frequent, which is followed by MAIT cells and NKT cells. Among the

subpopulations of ILCs, NK cells are most frequent, followed by other ILCs with low frequencies. % indicates the percentage of the cells in lymphocytes.

Table 1 The heterogeneity of asthma

	Subtypes	Onset	Severity	Molecular biomarkers	Treatment	Main references
Th2 asthma	Early-onset	Childhood	Mild to severe	High IgE; High Th2 cytokines; High FeNO	Corticosteroid-sensitive; IgE-specific antibody; Anti-IL-4R α treatment	[12, 13, 16–23]
	Late-onset (including AERD)	Adult	Severe; Persistenteosinophilia; Frequentexacerbation	High IL-5; High FeNO	Corticosteroid-sensitive; Anti-IL-5 antibody; Leukotriene modifiers for AERD	[24–31]
	Exercise-induced	Childhood	Mild; Bronchoconstriction after exercise	HighTh2 cytokines	Cysteinylleukotrienemodifiers; Anti-IL-9 antibody	[32–34]
Non-Th2 asthma	Neutrophilic	Adult	Generally severe	Neutrophilia in sputum; MMP9	Corticosteroid-refractory; Macrolide antibiotics	[35–38]
	Paucigranulocytic	Adult	Severe	–	Corticosteroid-refractory	[39]
	Obesity-related	Adult	Severe	HighIL-6 in serum	Weight loss; Antioxidants treatment; Hormonal therapy	[11, 28, 40, 41]

about 50% of patients with late-onset asthma have persistent eosinophilia in the lung and blood following corticosteroid treatment [28]. Mepolizumab, a humanized IL-5 antagonist, has been approved by the US Food and Drug Administration (FDA) for the treatment of late-onset asthma [29, 30]. Furthermore, clinical studies have shown that patients with late-onset asthma (particularly, patients with high levels of periostin) could show improvement following anti-IL-13 therapy and may derive additional benefits when such therapy is combined with anti-IL-4 therapy [31].

Exercise-induced Asthma

Exercise-induced asthma is a form of bronchial hyperreactivity, which is triggered by exercise and mediated by Th2 immune response but characterized by lower levels of eosinophilic inflammation. Although exercise-induced asthma has been identified for many years, no specific genetic factors or biomarkers currently exist for this disease. In therapy, antagonizing cysteinyl leukotrienes or blockade of IL-9 reportedly improves the physiological state of the patients with exercise-induced asthma [32–34].

Non-Th2 Asthma

Non-Th2 asthma was first described in 1999 [43]. However, its precise definition and biological mechanisms are yet undetermined. Non-Th2 asthma occurs mainly in severe asthmatic patients. In contrast to Th2 asthma, non-Th2 asthma lacks typical Th2 biomarkers and shows greater resistance to steroids. Non-Th2 asthma includes neutrophilic asthma, paucigranulocytic asthma, and obesity-related asthma.

Neutrophilic Asthma

Neutrophilic asthma is characterized by a large number of neutrophils in the sputum, accounting for 40 to 76% of the sputum cells [35]. The levels of neutrophils in the sputum are determined by disease severity, corticosteroid insensitivity, and chronic air-flow obstruction [35]. Patients with neutrophilic asthma account for 10 to 15% of those diagnosed with severe asthma. Because neutrophilic asthma usually displays a mixed Th1/Th17 cytokine milieu, Th1 cytokines (e.g., IL-1 and tumor necrosis factor (TNF)- α) and Th17 cytokines (e.g., IL-22, IL-17A, and IL-17F) were previously considered potential targets for the treatment of neutrophilic asthma. However, treatments targeting IL-17 and IL-25 with anti-IL-17RA receptor antibody or targeting TNF- α with blocking antibody have shown poor effects on asthma outcome [36, 37]. Unexpectedly, treatment with macrolide antibiotic, clarithromycin, reportedly improves the quality of life in patients by reducing the expression of neutrophilic markers [38]. Macrolide antibiotic treatment mainly influences the composition of respiratory microbiota. Thus, respiratory microbiota may participate in the development of neutrophilic asthma, but the underlying mechanism is still unclear.

Paucigranulocytic Asthma

Paucigranulocytic asthma is caused by hypertrophy of the airway smooth muscle tissue, a process that is independent of the immune response. Thus, the numbers of eosinophils and neutrophils are not typically increased in the sputum and blood of patients with paucigranulocytic asthma. In addition, anti-inflammatory therapy is ineffective for the treatment of the condition [39].

Obesity-related Asthma

Obesity has been identified as a risk factor of asthma, which affects both Th2 and non-Th2 asthma [28]. Potential mechanisms have been proposed regarding the association between obesity and asthma. These include increased levels of adipose hormone α P2 induced by obesity, which has been found to contribute to chronic inflammation and induce obesity-related asthma [40]. Furthermore, shallow breathing in obese individuals can lead to chronic narrowing of the respiratory tract, which may promote the development of obesity-related asthma [41]. Obesity-related asthma can be improved through weight loss, as well as the administration of antioxidants and hormone therapy [11].

ILLs and ILCs in Asthma

As described above, asthma is an immune-mediated heterogeneous disease. Its complexity can be attributed to the interaction between host and environmental factors. Host factors include the genetic background, the type of immune cells involved in the disease, the different signaling pathways that are activated, and the different molecules involved [44]. Previous research studies have been focused mainly on adaptive immune responses associated with asthma. However, with the discovery of non-Th2 asthma and the involvement of ILCs in their pathogenesis, innate immune responses have now become the focus of attention in asthma research. Several subpopulations of ILLs and ILCs are involved in the pathogenesis of, or protection against asthma (Fig. 2), and this involvement depends on the subtype of asthma (Table 2).

ILLs in Asthma

The ILLs are subsets of lymphocytes that express TCRs or BCRs with limited diversity, and which tend to recognize self-

antigen and the simple molecular structure of foreign pathogens. The ILLs usually colonize non-lymphoid tissues, and compared with conventional lymphocytes, have a faster and more robust response to antigen stimulation [130]. Innate-like T cells include $\gamma\delta$ T cells, NKT cells, and MAIT cells, and innate-like B cells include B-1 cells and MZB cells.

$\gamma\delta$ T Cells

The $\gamma\delta$ T cells are unique innate-like lymphocytes that belong to the lineage of T cells. Unlike $\alpha\beta$ T cells, $\gamma\delta$ T cells recognize endogenous soluble and non-protein antigens without antigen processing and MHC presentation [45]. The $\gamma\delta$ T cells are abundantly enriched in mucosal tissues, e.g., in the respiratory, digestive, and reproductive tracts. Approximately 8–20% of resident lymphocytes in the lung are $\gamma\delta$ T cells, which maintain lung tissue homeostasis [46]. The $\gamma\delta$ T cells seem to play contradictory roles, as they both drive and suppress allergic immune responses through different mechanisms, which depend on the different mouse models under study, as well as the different types and stages of asthma.

The CD1-restricted $\gamma\delta$ T cells recognize mucosal allergens presented by CD1⁺ dendritic cells (DCs) and initiate an allergic response [47], and the V γ 1⁺ $\gamma\delta$ T cells can promote the ovalbumin (OVA)-specific IgE response in the mouse model of OVA/alum-induced asthma [48]. In humans, V γ 9⁺V δ 2⁺ $\gamma\delta$ T cells, which are similar to mouse V γ 1⁺ cells, can also secrete the Th2 cytokines IL-4, IL-5, and IL-13 to mediate IgE responses against cypress pollen [49]. Furthermore, $\gamma\delta$ T cells can also potentially promote asthma by influencing other cells. The $\gamma\delta$ T cells in lymphoid tissues express CXCR5, ICOS, and CD40L, produce IL-21, and regulate B cell differentiation and Ig switching, similar to T follicular helper (Tfh) cells [48, 50–52].

In addition, $\gamma\delta$ T cells protect against asthma under certain conditions. Immune tolerance induced by long-term allergen challenge can be abolished by depletion of $\gamma\delta$ T cells in asthma

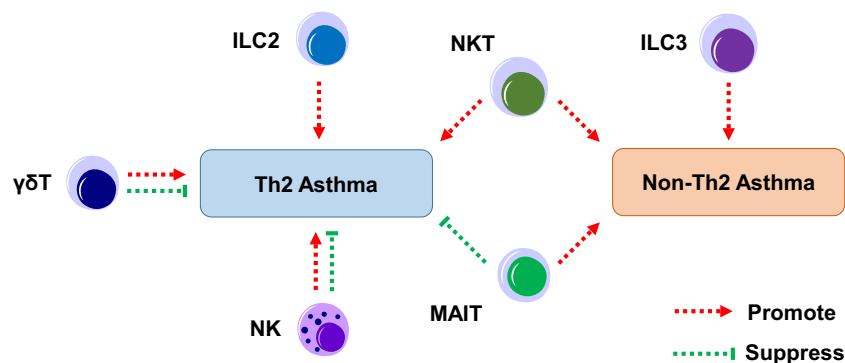


Figure 2. Overview of the functions of ILLs and ILCs in Th2 and Non-Th2 asthma. Asthma is an immune-mediated heterogeneous disease. Some subpopulations of ILLs and ILCs are involved in the pathogenesis and/or protection of both Th2 and non-Th2 asthma. Furthermore, some

cells play contradictory roles, as they both drive and suppress allergic immune responses, which depend on the different mouse models, as well as the different types and stages of asthma.

Table 2 Features and functions of ILLs and ILCs in asthma

Subtypes	Antigen receptors	Major distribution	Functions in asthma	Mechanism	Main references
ILLs $\gamma\delta$ T cells	TCR γ and δ ; $V\gamma 9V\delta 2$ in human	Gut, lung, skin, and reproductive tracts; low in blood and lymphoid organs	Promotive or protective roles, depending on the different models, types, and stages of asthma	1. CD1-restricted recognition of allergen 2. Promote IgE response via IL-4, -5, and -13 3. B cell differentiation and Ig class-switching 4. $V\gamma 4\gamma\delta$T cells suppress AHR via IFN-γ 5. Suppress rhinovirus-induced asthma via IL-17A and IFN-γ Promote the AHR of Th2 and Non-Th2 asthma via IL-4, -5, and -13 or IL-17A	[45–54]
NKT cells	TCR α and β ; $V\alpha 14$ in mouse; $V\alpha 24$ in human	Liver, lung, and spleen; low in blood and lymphoid organs	Promote both Th2 and non-Th2 asthma in mouse; unclear function in human	1. Resist Th2 asthma via increasing Th1 response	[55–71]
MAIT cells	TCR α and β ; $V\alpha 19$ in mouse; $V\alpha 7.2$ in human	Lung, gut, and liver in human; low in mouse	Resist Th2 asthma; promote non-Th2 asthma	2. Promote non-Th2 asthma via producing IL-17A	[72–75]
B-1 cells	BCR (IgM high, IgD low)	Peritoneal and pleural cavity; low in other tissues	Promotive roles	Produce anti-hapten IgM antibody to mediate AHR	[76–81]
MZB cells	BCR (IgM high, IgD low)	Spleen; rare in the other tissues	No report	No report	[82, 83]
ILCs NK cells	Absent	Lung, liver, spleen, and blood; low in other organs	Promotive or protective roles, depending on the different models, types, and stages of asthma	1. Produce Th2-type cytokines	[84–98]
ILC1s	Absent	Intestinal intraepithelial compartment; low in other organs	No report	2. Express granzyme B/NKG2D	
ILC2s	Absent	Gut, lung, skin, tonsils, and fat-associated lymphoid clusters	Promotive roles	3. Mediate predisposition across generations	
ILC3s	Absent	Gut and skin; low in other organs	Promotive roles	4. Prevent disease by limiting ILC2s	[6, 99–103]
LTi cells	Absent	Fetal intestines; low in other organs	No report	No report	
				1. Produce Th2-type cytokines	[6, 100, 104–120]
				2. Promote Th2 polarization and function via IL-13 and OX40L, respectively	
				3. Antigen presentation	[100, 101, 121–124]
				Facilitate obesity-associated non-Th2 asthma via IL-17A	
				No report	[6, 125–129]

ILLs innate lymphoid cells, *ILLs* innate-like lymphocytes, *AHR* airway hyperresponsiveness, *NK* natural killer, *MAIT* mucosa-associated invariant T, *MZB* marginal zone B, *LTi* lymphoid tissue-inducer, *TCR* T cell receptor, *BCR* B cell receptor

therapy. This means that $\gamma\delta$ T cells play a role in the induction or maintenance of immune suppression [53]. In addition, $V\gamma 4^+$ $\gamma\delta$ T cells from allergen-challenged mice can suppress AHR in a mouse model of acute OVA/alum asthma after adoptive cell transfer, and this suppression is dependent on interferon (IFN)- γ . Other studies have found that both mouse and human $\gamma\delta$ T cells can suppress rhinovirus-induced asthma exacerbations by secreting IL-17A and IFN- γ [54]. Thus, the different roles of $\gamma\delta$ T cells in asthma depend mainly on the type of cytokines that they produce. Further studies on the mechanisms that regulate various cytokines in $\gamma\delta$ T cells could provide more evidence for the treatment of asthma.

NKT Cells

The NKT cells express a limited TCR repertoire, which mainly recognizes self-antigens and foreign lipid antigens presented by MHC-like molecule, CD1d. They share common morphological and functional features with $\alpha\beta$ T cells and NK cells [55]. The NKT cells can be found in almost all tissues and account for $\sim 7\%$ of T lymphocytes in the lung [56]. In mouse models, NKT cells reportedly participate in the pathogenesis of Th2 and non-Th2 asthma associated with viral infections and air pollution [57]. The NKT cells are associated with the induction of AHR in asthma. This finding is supported by significantly lower levels of AHR and inflammation after challenge in NKT cell-deficient mice. The NKT cells exert their effects by secreting cytokines IL-4, IL-5, IL-13, and IL-17 [58–60]. In some cases, the functions of NKT cells in asthma depend on the type of antigens involved. Although NKT cells alone are unable to induce an allergen-specific response to protein antigens, lipids from pollens and glycolipids or their counterparts from microorganisms can activate NKT cells and thereby induce asthma in mice lacking adaptive immunity [61, 62]. In humans, a series of investigations have been conducted following reports that NKT cells consist of about 60% of the $CD4^+$ T lymphocytes in the bronchoalveolar lavage fluid (BALF) of patients with asthma [63–67]. However, subsequent studies have shown divergent results [68–71]. Thus, the function of NKT cells in human asthma is still unclear.

MAIT Cells

The MAIT cells comprise a subset of $\alpha\beta$ T cells that express a semi-invariant TCR α -chain, and which recognize MHC-related molecule 1 (MR1)-presented bacterially-produced vitamin B metabolites. As their name suggests, MAIT cells are preferentially located in mucosal tissues. They account for 1–3% of $CD3^+$ cells in the lung of the mouse, but they comprise 20–40% of $CD3^+$ cells in the lung of humans [72]. A comprehensive analysis of T cells in the bronchus and blood of asthmatic adults showed that a reduced number of MAIT cells can

be found in the sputum and blood of asthmatic patients, particularly those with severe asthma, implying that MAIT cells may play a crucial role in the protection against asthma [73]. Indeed, another study about childhood asthma found that a higher MAIT cell frequency at the age of 1 year is negatively associated with the risk of asthma at the age of 7 years because of an increased number of IFN- γ^+ Th1 cells [74]. This finding suggests that the protective function of MAIT cells against asthma might be associated with a tendency of the immune profile toward the Th1 response. However, MAIT cells are reportedly correlated with the severity of asthma symptoms in children, owing to a higher frequency of IL-17-producing MAIT cells [75].

B-1 Cells

The B-1 cells are innate-like B cells that secrete natural IgM and IgA antibodies in the absence of antigenic stimulation [76]. In mice, B-1 cells primarily reside, and account for 70% of the B cells, in the peritoneal cavity [77]. They can rapidly respond to non-specific inflammatory or mucosal microbial stimulation and migrate from various cavities to secondary lymphoid tissues [77]. Human B-1 cells were identified much later than those in mice because of a lack of specific surface markers and controversy regarding their tissue distribution [78, 79]. The B-1 cells reportedly exhibit regulatory properties by secreting the anti-inflammatory cytokine, IL-10, following activation, and are involved in maintaining immune homeostasis and preventing autoimmune disease [80]. However, in the mouse model of asthma induced by haptens, B-1 cells reportedly produce anti-hapten IgM antibodies, which subsequently activate complement and mediate AHR [81].

MZB Cells

The MZB cells comprise another subpopulation of innate-like B cells. Like B-1 cells, MZB cells are natural IgM-producing cells. The MZB cells reside in the marginal zone of the spleen, where bloodborne antigens are filtered through the marginal zone sinus [82]. They account for 5% of the splenic B cells and protect against bloodborne microbes and antigens through rapid proliferation and producing antibodies [83]. However, their role in asthma has not been reported.

ILCs in Asthma

The ILCs are innate immune cells that lack TCRs and BCRs, but can rapidly produce various cytokines in response to stimulation. The ILCs are classified into five subpopulations, including ILC1s, ILC2s, ILC3s, NK cells, and LT α i cells. Similar to the ILLs, ILCs preferentially reside in mucosal tissues. They are involved in the maintenance of mucosal

homeostasis, tissue repair and remodeling, and innate immunity against infection.

ILC1s

The ILC1s express the transcript factor, T-bet, and produce IFN- γ . Because they share several common features, ILC1s and NK cells were previously classified as group 1 ILCs [6]. However, ILC1s and NK cells originate from different developmental precursors. The ILC1s originate from the innate lymphoid cell precursor (ILCP) and are generally non-cytotoxic, but NK cells originate from the NK cell precursor (NKP) and are highly cytotoxic [99]. Therefore, ILC1s are now considered as a group of independent ILCs that are different from conventional NK cells. In mice, ILC1s comprise the dominant ILC population in the intestinal intraepithelial compartment, which accounts for 25–50% of the total ILCs there. In other tissues, ILC1s account for less than 10% of the resident ILCs [100]. In humans, ILC1s account for less than 5% of the ILCs in all tissues [101]. The ILC1s mainly play a protective role against viral and bacterial infections in mucosal tissues by producing high levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IFN- γ [102, 103]. To our knowledge, no studies have yet reported on the involvement of ILC1s in asthma, which may be attributed to low cell numbers in the lung and limited methods for the specific deletion of ILC1s.

ILC2s

The ILC2s are characterized by the production of large amounts of IL-5 and IL-13 following stimulating with IL-25 and IL-33 [104]. Mouse ILC2s are mainly distributed in the skin, white adipose tissue, intestinal lamina propria, and lung, accounting for about 3%, 5%, 0.5–1.0%, and 0.2% of the CD45⁺ leukocytes, respectively [100]. Human ILC2s are low in number in all tissues, accounting for 0–0.1% of the CD45⁺ leukocytes [105]. Both IL-33 and IL-25 play critical roles in the development and activation of the ILC2s [106]. Interestingly, ILC2s are activated in different tissues through distinct surface receptors: gut ILC2s express IL-17RB (a subunit of the IL-25 receptor); skin ILC2s specifically express IL-18R; while lung ILC2s preferentially express T1/ST2 (a subunit of the IL-33 receptor) [107, 108]. The ILC2s are mainly responsible for protection against parasites and allergens, and tissue repair [6].

Furthermore, ILC2s have been widely reported to be involved in several types of asthma, e.g., OVA-, house dust mite (HDM)-, papain-, and *Alternaria alternata*-induced airway inflammation, and influenza A virus-induced AHR [109–115]. Lung ILC2s are the first and main source of IL-5 and IL-13 in airway inflammation [116]. In addition, ILC2s can act as antigen-presenting cells (APCs) that present antigen

epitopes *via* MHC-II, promote Th2 polarization by secreting IL-13, and promote the effector functions of CD4⁺ T cells by expressing the costimulatory molecules, OX40L [117–119]. The ILC2s are the most widely studied ILC subpopulation in humans. As they are in mice, human ILC2s are involved in asthma by producing IL-5 and IL-13 after IL-33 and thymic stromal lymphopoietin (TSLP) stimulation [105, 120]. Based on the above findings, we can expect that ILC2s would be an important therapeutic target for asthma treatment; however, more research on human ILC2s is needed.

ILC3s

Like Th17 cells, ILC3s require the transcription factor, retinoid-related orphan receptor γ t (ROR γ t). Under the stimulation of IL-23, IL-1 β , and aryl hydrocarbon receptor ligands, ILC3s activate and secrete the effector cytokines IL-17A, IL-22, and TNF- α [121, 122]. In mice, ILC3s are abundant in the lamina propria of the small intestine, accounting for more than 50% of the total ILCs [100]. They are also found in lower numbers in the mesenteric lymph nodes (LNs), inguinal LNs, lung, and liver. Human ILC3s are also distributed at lower levels in these tissues (less than 5% of the total ILCs) [101]. The ILC3s are involved in gut barrier homeostasis and mediating colitis through IL-22 and IL-17A, respectively [123]. The ILC3s reportedly participate in asthma, especially non-Th2 asthma. In a high-fat diet (HFD)-induced AHR model, which imitates obesity-associated non-Th2 asthma in humans, AHR is mediated by an increase in IL-17A⁺ ILC3s in the lung. Furthermore, adoptive transfer of IL-17A⁺ ILC3s can induce AHR in recipient mice lacking adaptive immunity. Mechanistically, the HFD activates macrophages to secrete IL-1 β , which subsequently promotes the proliferation of IL-17A⁺ ILC3s. This suggests that obesity-associated asthma is caused by IL-1 β /ILC3s/IL-17A axis-mediated inflammation [124]. More importantly, IL-17A⁺ ILC3s can also be detected in the lungs of patients with severe asthma, but not healthy donors [124]. This means that ILC3s could be a potential target for obesity-associated asthma therapy in humans.

NK Cells

The NK cells are the prototypical innate lymphoid cells, well known for their cytotoxicity to virus-infected and cancer cells [84, 85]. However, recent studies suggest that NK cells possess immune regulatory and memory properties of adaptive immunity [86–88]. The NK cells account for 10–15% of the lymphocytes in the tissues of both mouse and human lungs [84], and their roles in asthma have been widely studied. Like other cells mentioned above, NK cells can be either harmful or protective in asthma, which depends on the disease-causing agents and the phase of the disease (sensitization, challenge, or resolution phase) [89]. Experiments of antibody-mediated

depletion of NK cells suggest that NK cells play roles in the allergic sensitization phase of the mouse model of Th2 asthma to promote disease [90]. Similarly, increased NK cell activity and an increased number of IL-4⁺ NK cells can also be found in patients with asthma [91, 92]. Further studies based on NKG2D-deficient mice and cell adoptive transfer have revealed the pivotal role of NKG2D molecules and granzyme B expressed by NK cells in the pathogenesis of HDM-induced asthma [93]. In contrast, other studies have reported that NK cells can limit lung ILC2s and prevent the allergic inflammatory response to inhaled HDM or papain [94–96]. In addition, lipid Ag-specific CD4⁺ T cell-activated NK cells participate in the resolution of allergic inflammation [97]. Another study reported that constitutive or temporary genetic depletion of NK cells has no influence on HDM-induced asthma [98]. Therefore, further research is needed to clarify the precise functions of NK cells in asthma.

LTi Cells

As one of the earliest ILCs to be discovered, LTi cells together with ILC3s are classified as group 3 ILCs, because they both express the transcription factor, ROR γ t, and secrete cytokines, IL-17 and IL-22, after activation. However, their developmental paths and immune functions are quite different [6]. In contrast to other ILCs, LTi cells are abundant in the fetal intestine and participate in generating secondary lymphoid tissues [125]. Lymphotoxin and TNF from LTi cells can stimulate mesenchymal cells to produce chemokines and adhesion molecules, which are essential for lymphoid organogenesis, particularly for cryptopatches and isolated lymphoid follicles in the intestine [126]. However, it is still unclear whether embryonic-derived LTi could persist in the neonate and even in adults, although the LTi-like CCR6⁺ ILCs, which are phenotypically and functionally similar to embryonic-derived LTi cells, are found within the mesenteric and mediastinal LNs, lamina propria of the intestine, and spleen of adults [127–129]. To our knowledge, no previous reports about the involvement of LTi in asthma currently exist.

Conclusion

With the exploration and discovery of new subsets of ILLs and ILCs, we now have a better understanding of the innate immune system [131]. More importantly, research on these particular cell subsets has led to new insights into the development of immune-related diseases, such as infectious, autoimmune, and allergic diseases. Typically, asthma had been widely believed to be a Th2 cell-mediated immunological disease. However, over the past few years, with the advancement of detection techniques and a deeper understanding of

the immune system, asthma has been found to be a heterogeneous disease.

Research on ILLs and ILCs have extended the research areas of asthma. As described above, both ILLs and ILCs are significant sources of effector cytokines IL-5, IL-13, and IL-17, which can directly promote the development of different types of asthma. Furthermore, ILLs and ILCs can also affect other immune cells, e.g., macrophages and T cells, and regulate their functions in asthma. Therefore, an in-depth study of the role of ILLs and ILCs in asthma may help to identify new preventive and therapeutic targets of the disease.

However, although some studies have shown that ILLs and ILCs are associated with the occurrence and development of asthma, owing to the limitation of technologies and research materials, the detailed mechanisms underlying the effects of ILLs and ILCs on certain types of asthma remain unclear or controversial. Moreover, most of the conclusions about the functions of ILLs and ILCs in asthma are derived from experiments in mice, and only a few studies have been conducted in humans. Therefore, more precise studies are needed in humans before ILLs and ILCs can be considered as targets for the treatment of asthma.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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