

Review

The context-dependent role of group 2 innate lymphoid cells in lung diseases

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Abstract

Group 2 innate lymphoid cells (ILC2s), a subset of innate lymphoid cells (ILCs) lacking antigen-specific receptors and functionally mirroring T helper 2 (Th2) cells, are indispensable components of the innate immune system that lack antigen-specific receptors but phenotypically and functionally mirror T helper 2 (Th2) cells, particularly in their expression of the transcription factor GATA3 and the secretion of type 2 cytokines for mediating type 2 immune responses. ILC2s are tissue-resident cells in mucosal tissues, including the lung, where they play crucial roles in maintaining tissue homeostasis and regulating immune responses. ILC2s are poised to respond to environmental signals such as IL-25, IL-33, and TSLP, which activate and expand ILC2s. Their functions are highly context-dependent and influenced by interactions with other immune cells. In this review, we summarize recent findings on the roles of ILC2s in lung diseases, highlighting their typical characteristics and their responsiveness to environmental signals in the context of pulmonary pathology. We also discuss potential therapeutic strategies targeting ILC2s, which may offer new avenues for the treatment of inflammatory lung diseases. Understanding the mechanisms by which ILC2s contribute to lung disease progression will provide valuable insights for the development of novel diagnostic (e.g., ILC2 phenotypic markers) and therapeutic approaches (e.g., targeting ILC2 plasticity or alarmin-ILC2 signaling axes).

Key words group 2 innate lymphoid cell (ILC2), lung diseases, type 2 cytokines, alarmins, therapeutic targeting

Introduction

Group 2 innate lymphoid cells (ILC2s) are tissue-resident innate lymphocytes characterized by the absence of antigen-specific receptors (e.g., TCR/BCR) and the expression of lineage markers such as CCR2, ST2 (IL-33 receptor), and GATA3 (master transcription factor). Developmentally, ILC2s originate from common lymphoid progenitors (CLPs) in the bone marrow, where they differentiate into ILC2 progenitors (ILC2Ps) under the regulation of transcription factors, including GATA3 and ROR α . ILC2s in most tissues are established during the perinatal period. In adulthood, ILC2s in the lungs, small intestine, and fat are replaced less frequently by circulating ILC2s and are maintained more through self-renewal. ILC2s in the bone marrow and skin are replaced more quickly by *de novo* ILC2s [1]. However, under conditions of parasitic, fungal, or allergen infection, circulating ILC2s of small intestine and bone marrow origin are recruited to the lungs [2–4]. In the lungs, tissue-resident ILC2s preferentially accumulate in areas

surrounding larger airways and blood vessels [5,6]. Functionally, ILC2s respond to epithelial-derived alarmins (IL-25, IL-33, and TSLP) to secrete type 2 cytokines (IL-4, IL-5, and IL-13) and tissue repair factors (Amphiregulin and Areg). Additionally, ILC2s interact with other immune cells (e.g., Th2 cells, eosinophils) and neuroendocrine signals (e.g., dopamine, NMU) to regulate immune homeostasis and inflammation.

Under physiological conditions, ILC2s contribute to tissue repair and host defense, particularly against helminth infections, through amphiregulin production [7,8]. However, dysregulated ILC2 activation contributes to pathological inflammation in certain diseases. In asthma [9], it induces airway hyperresponsiveness (AHR), whereas in pulmonary fibrosis [10,11], it exacerbates collagen deposition and disease progression.

Despite the growing interest in ILC2s, existing reviews often focus on their development or their roles in a specific disease. The complex roles of ILC2s in various lung diseases have not been

comprehensively compared and discussed. In this review, we aim to summarize the current advances in understanding the role of ILC2s in various lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, lung infections (helminths, viruses, bacteria, protozoans), acute lung injury and lung cancer. This review also provides an improved understanding of the mechanisms that regulate ILC2 functions and their interactions with other immune cells and tissues in different lung diseases (Figure 1). Understanding the versatile role of lung ILC2s is crucial for developing effective therapeutic strategies for lung diseases.

ILC2s in Asthma

Asthma is a common chronic inflammatory disease worldwide that affects the quality of life of approximately 300 million people. Asthma is typically characterized by chronic airway inflammation, AHR, a hallmark of asthma characterized by excessive airway narrowing in response to stimuli such as allergens or cold air, and airway remodeling. Asthmatic patients often present with wheezing, chest tightness, and coughing. Allergen exposure, viral infection, and other environmental factors may cause innate or

adaptive immune responses, leading to allergen sensitization, asthma occurrence and exacerbation. Asthma is a heterogeneous disease with multiple subtypes [12,13]. On the basis of the characteristics of airway inflammatory cell infiltration, four subgroups of adults with asthma have been identified: eosinophilic asthma (40%–50%), neutrophilic asthma (10%–20%), paucigranulocytic asthma (30%–50%) with neither asthma nor asthma, and mixed granulocytic asthma with both sputum eosinophils and neutrophils. Recently, asthma has been further classified into two main endotypes: type2 (T2)-high asthma and T2-low asthma. T2-high asthma is characterized by increased airway and systemic eosinophilia, whereas T2-low asthma may be characterized by increased neutrophil counts [14].

Type 2 immune response plays a key role in the pathogenesis of T2-high asthma. T2-high asthma is characterized by increased type 2 cytokines, such as IL-4, IL-5, and IL-13, and elevated immunoglobulin E (IgE), eosinophil and mast cell infiltration. The main sources of type 2 cytokines are ILC2s and Th2s. In lung tissue, allergens such as house dust mites and pollen cause damage to airway epithelial cells. These damaged cells, in turn, activate ILC2s

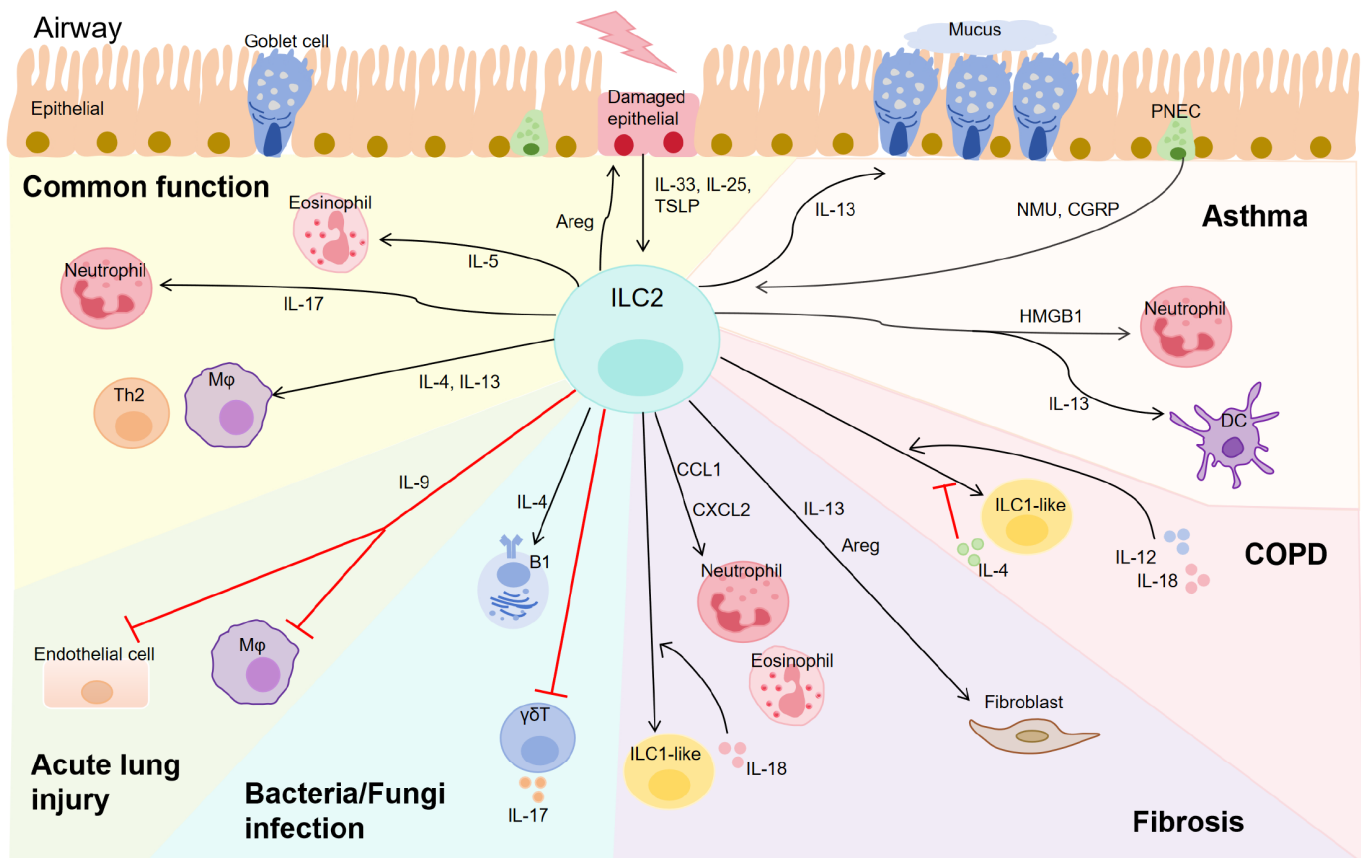


Figure 1. Regulatory network of ILC2s in lung diseases In response to infection, allergen exposure or injury, lung epithelial cells release alarmins such as IL-33, IL-25, and TSLP, activating the immune response of ILC2s and producing various cytokines. Conventionally, activated ILC2s promote IL-5-mediated eosinophil recruitment, IL-13- and IL-4-induced differentiation of M2 and Th2 cells, IL-17-promoted neutrophil recruitment, and Areg-mediated epithelial repair. In asthma, neuroepithelial cells coactivate alarmins to induce ILC2s to secrete IL-13/HMGB1. IL-13 promotes mucus secretion and DC migration to lymph nodes, thereby activating Th2 cells. HMGB1 promotes neutrophil recruitment. In COPD, ILC2s are transformed into ILC1s under the influence of IL-12 and IL-18 signals in the microenvironment. In pulmonary fibrosis, IL-13 and Areg secreted by ILC2s directly interact with fibroblasts, promoting their differentiation and collagen production. CCL1/CXCL2 also mediates the recruitment of eosinophils and neutrophils. ILC1s, which are transformed from ILC2s, promote fibrosis by secreting TGFβ. During bacterial and fungal infections, IL-4 secreted by ILC2s regulates B1-cell antibody production. γδ T cells are inhibited by ILC2s and reduce IL-17 secretion. In acute lung injury, IL-9 inhibits macrophage apoptosis and endothelial cell pyroptosis. PNEC, pulmonary neuroendocrine cell; DC, dendritic cell; M, macrophage.

through the secretion of alarmins. In animal models, type 2 cytokines secreted from ILC2s promote Th2 activation, eosinophil infiltration, airway smooth muscle contraction, and increased goblet cell mucus secretion [15], leading to pathological changes such as AHR and airway remodeling [9]. In addition to allergens, ILC2s are highly sensitive to other stimuli in the lung tissue microenvironment. Neurotransmitters, lipid mediators, nutrients and various hormones affect the activity of ILC2s and subsequently participate in regulating the lung immune response. ILC2s therefore play a critical role in the early response to and maintenance of asthma [16–19].

In the process of asthma, ILC2s not only promote the initiation of airway inflammation but also have complex interactions with other immune cells [20]. In a papain-induced asthma model, ILC2s can produce IL-13 to promote the differentiation and activation of Th2 cells by stimulating dendritic cell (DC) migration to mesenteric lymph nodes (mLNs). Moreover, IL-4 secreted by Th2s can further activate ILC2s, and there is positive feedback between ILC2s and Th2s, which exacerbates asthma [21–23]. ILC2s can also interact with eosinophils, neutrophils, macrophages, mast cells and other immune cells to promote the development of asthma [9,16,24,25]. Other studies have shown that the neuroendocrine system can also regulate the function of ILC2s and thus participate in the pathogenesis of asthma. Dopamine, an important neurotransmitter, inhibits mitochondrial oxidative phosphorylation and ATP synthesis by acting on dopamine receptor 1 on ILC2 surface, inhibiting ILC2 activation and function *in vitro*, and the existence of the dopamine-DRD1 axis represents a protective mechanism in controlling airway inflammation in an asthma model [26]. Ultraviolet B (UVB) radiation has also been shown to promote the secretion of the endogenous neuroendocrine hormone α -melanocyte-stimulating hormone (α -MSH) via the pituitary-lung axis, thereby inhibiting lung ILC2 function [27]. Pulmonary neuroendocrine cells (PNECs) regulate ILC2 function via calcitonin gene-related peptide (CGRP). Notably, CGRP has been shown by three independent studies to inhibit ILC2 proliferation and IL-13 secretion in allergic lung inflammation [28–30], which contrasts with its previously reported proallergic role in other models—highlighting that CGRP-ILC2 interactions depend on the disease microenvironment [31,32]. In addition, neuronal activation following allergen exposure releases the neuropeptide neuromedin U (NMU), which activates ILC2s via NMU receptor 1 (NMUR1), amplifying the effects of ILC2-driven allergic lung inflammation. Furthermore, sex hormones may play important roles in regulating ILC2s [33,34]. Female mice exhibit a greater number of ILC2s and produce higher levels of type 2 cytokines compared to their male counterparts. Research has shown that androgen signaling suppresses ILC2 function, thereby attenuating the severity of HDM-induced allergic asthma [35]. Some ILC2s survive long after inflammation and have “memory-like” properties. These memory ILC2s exhibit similar gene expression patterns to those of memory T cells. ILC2s that have experienced allergens have a stronger response to unrelated allergens than unstimulated ILC2s do, leading to more severe allergic inflammation. This finding might explain why asthma patients tend to be sensitive to multiple allergens [36]. Many studies have shown an association between ILC2s and asthma patients. In patients with asthma, the number of ILC2s in their blood, sputum and bronchoalveolar lavage fluid (BALF), a fluid sample collected from the lung alveoli via bronchoscopy to assess inflammatory cell

infiltration and cytokine levels, is significantly increased, especially in patients with T2-high asthma. ILC2s in asthmatic patients are more active and produce higher levels of IL-5 and IL-13 than those in healthy individuals [37,38]. van der Ploeg *et al.* [39] demonstrated that compared with those in healthy controls, circulating ILC2s in asthmatic patients exhibit increased migratory capacity toward lung-derived chemokines (e.g., CCL17 and CCL22). This increased migration correlates with worse lung function decline during asthma exacerbations, suggesting that circulating ILC2s may serve as biomarkers for asthma severity and targets for preventing exacerbations. However, the association between the number of ILC2s and asthma severity varies across different studies [40].

However, some T2-low asthmatic patients, especially those with late-onset and severe asthma, lack type 2 markers (such as eosinophilia in blood and sputum and elevated FeNO levels). These diseases are characterized by neutrophil infiltration and significantly increased IL-17A. These patients are usually associated with the use of high-dose corticosteroids, older age, smoking, irritant exposure, and obesity. A common feature of these patients is their poor response to the main asthma treatment drug, corticosteroids. Studies have shown that T2-low patients exhibit the presence of neutrophils in sputum, caspase-1 activation, and high levels of IL-1 β , which is consistent with the activation of the inflammasome pathway [41,42]. Compared with that of eosinophilic asthma, the pathogenesis of neutrophilic asthma is more complex and involves the interaction of multiple immune cells and cytokines. Although ILC2s are considered key cells involved in promoting eosinophilic asthma, recent studies have shown that ILC2s might play a certain role in neutrophilic asthma. ILC2s have significant plasticity and can be reprogrammed into IFN γ -producing ILC1-like cells or IL-17-producing ILC3-like cells under certain conditions [43]. It possibly contributes to nonallergic, neutrophilic asthma. In addition, ILC2s can also induce neutrophil infiltration into the BALF via IL-33. Mechanically, ILC2s release HMGB1-loaded lipid droplets into the extracellular environment, activating neutrophil chemotaxis [44]. ILC2s also modulate neutrophil infiltration in an IL-17A-dependent manner during allergic inflammation. In other words, IL-33 synergizes with leukotrienes to promote IL-17 secretion in ST2 $^{+}$ ILC2s via NFAT signaling. IL-17 promotes neutrophil recruitment into the BALF, and IL-17 $^{+}$ ILC2s play a pathogenic role in asthma [45]. In addition, researchers have identified an intermediate ILC2 population in severe asthma patients with mixed granulocyte inflammation. These cells express both characteristic markers of ILC2s (such as CRTH2, IL-5, and IL-13) and markers of ILC3s (such as c-kit and IL-17A) [46]. These findings suggest that ILC2s may be involved in the pathogenesis of T2-low asthma by altering its functional properties under certain conditions.

The pathogenesis of asthma is complex. ILC2s can integrate signals from epithelial cells, immune cells and the neuroendocrine system, subsequently coordinating the functions of downstream effectors. Further study of the characteristics and functions of ILC2s can improve the understanding of the pathogenesis of asthma and provide new ideas for clinical treatment. Targeting ILC2s will hopefully lead to better outcomes in the future.

ILC2s in Chronic Obstructive Pulmonary Disease (COPD)

COPD is a common inflammatory lung disease with high morbidity and mortality worldwide. Long-term exposure to cigarette smoke is

a major risk factor for the development of COPD. However, other environmental factors, such as indoor air pollution, other irritants, and individual genetic factors, are also important causes of COPD and promote disease exacerbation. The disease is usually progressive and characterized by persistent airflow restrictions that are difficult to reverse, resulting in air retention, shortness of breath, and difficulty with physical activity [47]. The main types of COPD are clinically recognized as chronic bronchitis and emphysema. The former is characterized mainly by increased mucus secretion, thickening and remodeling of the airway wall, whereas the latter is characterized mainly by permanent abnormal expansion at the end of the bronchioles, extensive destruction and collapse of the alveolar wall. The pathogenesis of COPD involves complex mechanisms, including abnormal innate and adaptive immune responses induced by smoking or pollutant exposure, proteinase-antiprotease imbalances, and oxidative stress [48].

Traditionally, neutrophils, macrophages, Th1 cells, and Th17 cells predominantly mediate immune responses during the course of COPD. In clinical studies, an increase in the number of macrophages and neutrophils in sputum can also be detected in most COPD patients, possibly reflecting increased secretion of chemotactic mediators in lung tissue that promote monocyte and neutrophil recruitment. However, there is increasing clinical evidence of significant heterogeneity in COPD: some COPD patients have significant type 2 inflammatory response characteristics, such as increased eosinophils in sputum and a response to hormone therapy, suggesting the increasing importance of type 2 immune pathways (mainly composed of ILC2s and Th2s). The pathological process of COPD involves a complex inflammatory immune response. Owing to the tissue-resident characteristics of ILC2s in the lung that rapidly respond to the microenvironment and the function of secreting type 2 cytokines to recruit inflammatory cells, ILC2s play a critical role in the complex immune and inflammatory responses in COPD pathogenesis and have gradually received increasing attention [49].

ILC2s can regulate cigarette smoke-induced airway remodeling and emphysema. In ILC2-deficient mice exposed to cigarette smoke, the expression of IL-33 and IL-13 is increased, accompanied by increased collagen deposition, and appears to have a protective effect against cigarette smoke-induced emphysema [50]. In COPD patients, the contents of IL-33, IL-5 and IL-13 are significantly increased, and the proportion of ILC2s in the peripheral blood is significantly increased. Furthermore, the expression of ST2 in ILC2s is increased in COPD patients. IL-5⁺ and IL-13⁺ ILC2s in the sputum are also significantly increased, and the presence of eosinophils is positively correlated with the number of ILC2s ($R = 0.846$) in the sputum [51,52]. IL-33 may promote the proliferation and activation of ILC2s, leading to increased type 2 cytokine secretion by ILC2s, which participate in regulating the immune response in the process of COPD [52]. Elevated ILC2s in the peripheral blood of COPD patients coexist with their phenotypic and functional plasticity. Studies have shown that when ILC2s are exposed to COPD-related stimuli such as cigarette smoke, viruses, and bacterial infections, the expression of ST2 and GATA3 is significantly downregulated, whereas the expression of ST2 on NK cells and macrophages is increased [53]. In addition, reduced expression of characteristic ILC2 molecules is accompanied by an increase in the number of T-bet⁺IFN- γ ⁺ subsets that express IL-12R and IL-18R *in vitro* (Figure 2). Moreover, adoptive transfer experiments with ILC2s have shown

that ILC2s are plastic and promote the transformation of ILC2s into “ILC1-like” cells in response to local IL-12 and IL-18 signals [54]. A significant increase in ILC1 expression of IFN- γ has also been detected in the lung tissue of patients with COPD. *In vitro* cytokine stimulation experiments indicated that IL-12 can induce the transdifferentiation of ILC2s toward an IFN- γ -producing phenotype. While a type 1 inflammatory microenvironment can drive ILC2 transdifferentiation toward an ILC1-like phenotype, this plasticity is counteracted by IL-4 signaling, which restores ILC2 homeostasis [55]. Increased ILC1 subsets can also be found in COPD patients, and the increased ratio of ILC1s to ILC2s is also related to a decline in lung function and the severity of COPD [56]. The inflammation of mixed neutrophils and eosinophils in the sputum of patients with COPD is associated with an increase in IL-17A⁺ ILC2s. Thus, the presence of IL-17A⁺ ILC2s may predict the severity of COPD [57].

In mouse models of cigarette smoke-induced COPD, ILC2 depletion reduces airway remodeling and emphysema [50]; in human COPD patients, elevated ILC2 frequencies in peripheral blood and sputum correlate with eosinophilic inflammation, suggesting that ILC2s may contribute to COPD pathogenesis [52]; thus, the quantity and function of ILC2s are closely related to the severity of COPD. Modulating the function of ILC2s may provide new strategies for the treatment of COPD. For example, targeting ILC2s or their associated cytokines may help reduce airway inflammation, improve airway remodeling, and promote tissue repair in COPD patients. However, the application of ILC2s in the treatment of COPD is still in the research stage, and future studies need to explore the specific mechanism of ILC2s in COPD. Furthermore, its potential as a therapeutic target should be evaluated.

ILC2s in Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an immune-mediated interstitial lung disease arising from the recurrent inhalation of specific antigens (e.g., bacterial, fungal, or animal-derived proteins) in genetically predisposed individuals [58]. The pathogenesis involves a complex immune network, and mouse models have demonstrated that ILC2s play a key role in driving the Th2 immune deviation process, and elevated type 2 cytokines detected in patients' peripheral blood suggest a promoting effect on fibrosis. Acute HP is characterized by immune complex-mediated neutrophilic infiltration, which is characterized by high titers of antigen-specific IgG and respiratory bursts, whereas the subacute and chronic phases are driven predominantly by Th1/Th17-mediated delayed-type hypersensitivity reactions. Histopathologically, HP manifests as bronchiolocentric granulomatous inflammation, with chronic stages potentially advancing to pulmonary fibrosis [59].

While granuloma formation is traditionally attributed to Th1-dominant responses (e.g., IFN- γ , TNF- α), emerging evidence implicates Th2 skewing (elevated IL-4, IL-13) in chronic HP, potentially accelerating fibrogenesis [60,61]. ILC2s contribute significantly to this process by secreting IL-13 to promote Th2 differentiation and amplify Th2 signaling via alarmins such as IL-33 released upon epithelial injury [62,63]. However, the role of ILC2s remains debated, as murine models deficient in ILC2s retain intact Th1/Th17 responses, suggesting their dispensability in initiating core immune reactions [63]. The potential involvement of ILC2s in HP remains unclear, and the potential contribution of ILC2s to the

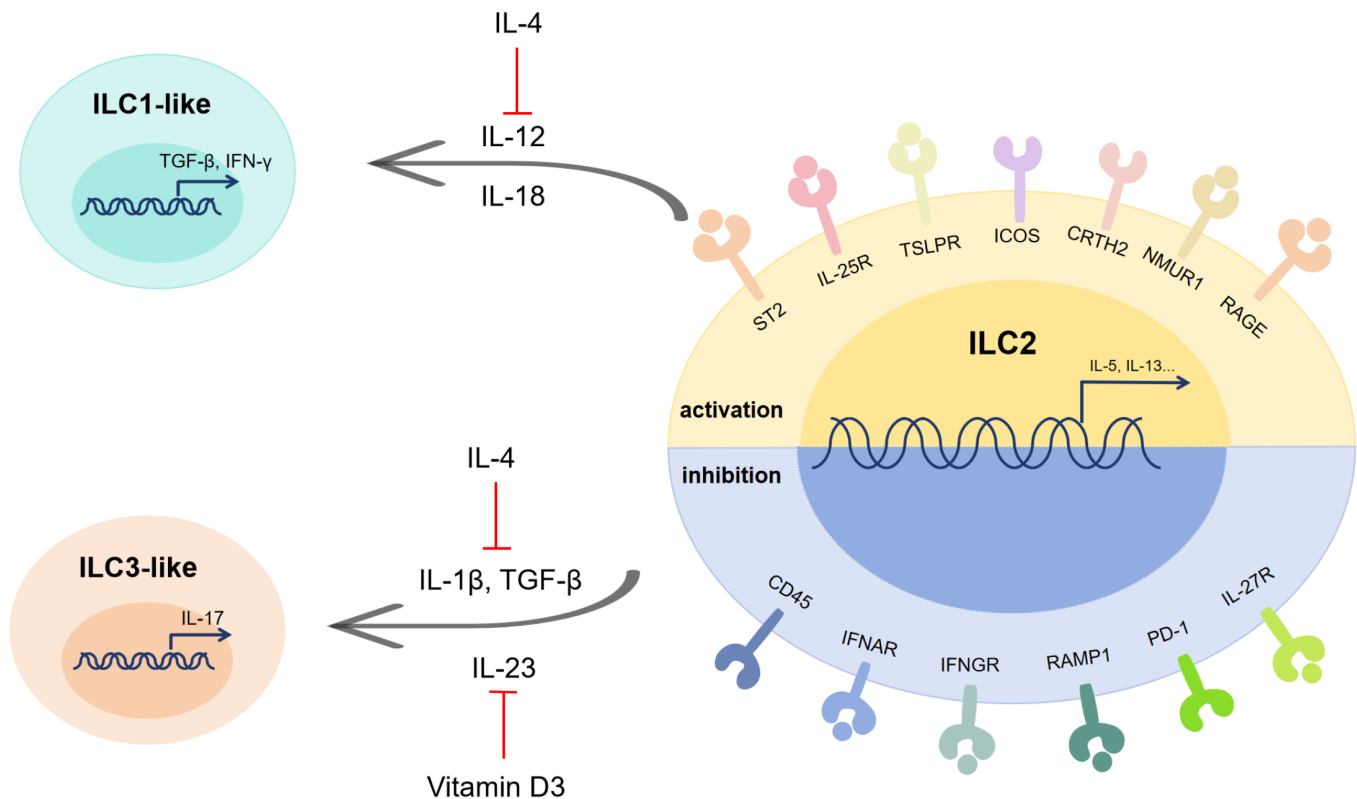


Figure 2. Factors modulating ILC2 activation and phenotypic plasticity Activating receptors [7], inhibitory receptors (bottom), and their regulation of ILC2s are indicated. Under conditions of lung inflammation, IL-12 and IL-18 promote the conversion of ILC2s into ILC1-like cells, which are characterized by the production of IFN- γ and TGF- β . ILC2-to-ILC1 conversion can be reversed by IL-4. Furthermore, the ILC2 subpopulation can be converted into ILC3-like cells, which produce IL-17 in response to IL-1 β , IL-23 and TGF- β . The transdifferentiation of ILC2s into IL-17-producing ILCs induced by IL-1 β and TGF- β is inhibited by IL-4, and the IL-23 signaling pathway is inhibited by vitamin D3.

chronic, Th2-driven fibrotic phase of the disease requires further investigation. Future research should explore inhibitory pathways that regulate ILC2s in the HP, such as the dopamine-DRD1 axis. This axis was recently shown to suppress ILC2 mitochondrial oxidative phosphorylation and ATP synthesis [64], thereby attenuating type 2 inflammation in allergic lung disease, raising the possibility that it may similarly constrain ILC2-driven fibrogenesis in chronic HP

ILC2s in Pulmonary Infections

Respiratory viral infections

In clinical practice, respiratory infections are triggered primarily by viral pathogens, including rhinovirus (RV), respiratory syncytial virus (RSV), influenza virus and SARS-CoV-2, and are characterized predominantly by type I immune responses. Although type 2 immune responses do not play a dominant role in direct viral clearance, the number and function of ILC2s are increased in mouse viral infection models and patient peripheral blood, suggesting that ILC2s participate in viral immune responses and induce pathological changes.

Experimental infection studies in humans and mice have shown that rhinoviruses can invade the lower respiratory tract and exacerbate allergic airway diseases. ILC2s may exacerbate this process [65]. In a neonatal mouse model of rhinovirus (RV) infection (not coupled to an asthma model), ILC2-driven inflammatory features are closely related to the duration and severity of viral infection. A neonatal mouse model of RV infection demon-

strated a significant increase in the epithelial-derived alarmin IL-25, which promotes cytokine secretion by ILC2s. Administration of an IL-25 neutralizing antibody reduced the expansion of IL-13⁺ ILC2s and alleviated airway reactivity, confirming the role of type 2 immune responses in viral infection [66]. Further studies revealed that IL-25 production is dependent on lung tissue IL-33/TSLP levels and similarly leads to an increase in IL-13-producing ILC2s, ultimately leading to mucus metaplasia and AHR [67]. In contrast, RV can also activate the NLRP3 inflammasome in lung macrophages. This process promotes pro-IL-1 β transcription and caspase-1-dependent IL-1 β maturation in macrophages and inhibits epithelial-derived IL-33/IL-25 expression, thereby negatively regulating ILC2 proliferation and the type 2 immune response *in vivo* [68].

Similarly, RSV represents a predominant viral etiology of acute lower respiratory tract infections in infants and young children. Nasal aspirate samples from patients have shown that ILC2 frequencies are highly similar to those of IL-4/IL-13 and correlate with disease severity, highlighting the role of ILC2s and type 2 cytokines in RSV [69]. In mouse models, neonatal RSV infection induces lung IL-33, which primes ILC2s for proliferation, and the level of IL-33 during primary RSV infection determines disease severity after reinfection [70]. Consistent with the core activation mechanism mentioned in the Core Biological Characteristics of Lung ILC2s, RSV-induced epithelial TSLP secretion drives IL-13⁺ ILC2 expansion to induce goblet cell metaplasia and AHR [71]. During RSV infection, the STAT1 signaling pathway is essential for

regulating the number and function of ILC2s [72]. Increased uric acid levels in lung tissue after infection can further activate the IL-1 β /CCL-2/IL-33 cascade, reinforcing the activation state of IL-13⁺ ILC2s [73]. IL-1 β has dual effects on ILC2s in viral infections: in RV infection, macrophage-derived IL-1 β activates the NLRP3 inflammasome, which inhibits epithelial IL-33/IL-25 secretion and thereby suppresses ILC2 proliferation [68]; in RSV infection, increased lung uric acid levels increase the IL-1 β /CCL-2/IL-33 cascade, which reinforces ILC2 activation [73]. These disparities may arise from differences in viral tropism (RV targets the airway epithelium, whereas RSV targets alveolar cells) and the local cytokine microenvironment (e.g., concurrent type I interferon levels). Pneumonia virus of mice (PVM) is a virus that causes respiratory illness similar to human respiratory syncytial virus (RSV). In the PVM-infected model, ILC2s regulate the migration of immune cells from the lung to the lymph nodes. Mechanistically, LIF produced by ILC2s induces pulmonary lymphatic endothelial cells to produce CCL21 and promotes plasmacytoid dendritic cells (pDCs), a type of immune cell primarily known for its role in antiviral immunity by secreting large amounts of type I interferon (IFN) in response to viral infection, to upregulate the expression of CCR7, thereby facilitating the migration of pDCs from the lungs to the lymph nodes. While the reduced secretion of IFN- γ by pDCs in the lung microenvironment increases the viral load, the absence of ILC2-derived LIF results in impaired generation of acquired immunity to the PVM and failure to overcome a secondary reinfection challenge [74].

ILC2s exhibit differential functions and impacts on diseases caused by different influenza viruses. In the H3N1 model, alveolar macrophage-derived IL-33 activates ST2⁺ natural helper cells to secrete IL-5 and IL-13, driving AHR, mucus hypersecretion, and the type 2 inflammatory response in an adaptive immunity-independent manner. The profile of natural helper cells is the same as that of ILC2s, suggesting that ILC2s may be necessary for promoting AHR with influenza virus [75]. During influenza A virus infection, ILC2s increase the secretion of amphiregulin (Areg) and promote the repair of AT2 cells after injury by accepting chitin, thereby restoring lung stability [76]. Nevertheless, type I interferon deficiency can lead to aberrant activation of ILC2s and an increased type 2 immune response, aggravating lung damage. *In vitro*, IFN- β inhibits the proliferation and cytokine release of both mouse and human ILC2s through the STAT1/STAT2/IRF9-dependent signaling pathway. In addition, IFN- γ and IL-27 have been shown to antagonize type 2 immune responses mediated by ILC2s [77].

The CA04 virus infection model further revealed that IFN- γ selectively suppressed the secretion of IL-5 and Areg by ILC2s but had no significant effect on IL-13. IL-5 derived from ILC2s plays a key regulatory role in reducing host susceptibility to viruses [78]. In the PR8 respiratory virus infection model, ILC2s in mouse lung tissue specifically aggregate through the IL-33/ST2 signaling axis. Although depletion of lung ILC2s does not affect viral replication, it significantly impairs airway epithelial repair capacity and adaptive immune responsiveness to influenza virus. Mechanistic studies have shown that ILC2s maintain epithelial integrity by secreting Areg rather than IL-13 [79].

The ongoing coronavirus disease 2019 (COVID-19) pandemic is caused by highly contagious and pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proportion of total ILC2s in the peripheral blood of COVID-19 patients is significantly

lower than that in the peripheral blood of healthy controls and further decreases in severe patients compared with moderate patients. However, ILC2s from severe patients show an increase in the level of the activating receptor NKG2D and a significant decrease in the levels of the inhibitory receptors CD25 and KLRG1 [80]. In contrast, increased levels of IL-6 and IL-10 in the serum positively correlate with accumulated CD69⁺ ILC2s in the circulation, suggesting that the inflammatory status of these patients could be a driver of ILC activation [81]. Moreover, the decreased proportion of CCR6⁺ ILC2s in the peripheral blood of patients is accompanied by an increase in the CCL20 concentration, suggesting that ILC2s migrate to lung lesions and participate in the fibrosis process. The proportion of CD117^{low} ILC2s is increased, suggesting that more type 2 cytokines may be secreted to promote fibrosis [81]. After SARS-CoV-2 papain-like protease (PLpro) is administered to the lungs of mice, an increased number of IL-5-secreting ILC2s are also observed [80].

In a murine model of murine gammaherpesvirus 4 (MuHV-4) infection (which mimics human EBV infection), IFN- γ -dependent inhibition of ILC2 type 2 cytokine secretion alleviated asthma disease responses induced by subsequent HDM exposure (referred to as “combined asthma and viral infection”). However, under conditions of MuHV-4-induced alveolar microenvironment exhaustion, GM-CSF derived from ILC2s is essential and sufficient for the differentiation of monocyte-derived alveolar macrophages (Mo-AM), a type of macrophage that originates from circulating monocytes and is recruited to the lungs in response to infection or injury and the inhibition of the M2 phenotype, and can reduce the susceptibility of the host to allergic reactions in the long term [82].

Collectively, these studies reveal the dual role of ILC2s in viral respiratory infections (Table 1). They maintain host homeostasis through epithelial repair functions and immune regulation but can also lead to pathological inflammation via excessive activation. Targeting the functional plasticity of ILC2s and their interactions with epithelial alarmins, interferons, and metabolic signaling may provide a new direction for the precise intervention of infection-related respiratory diseases.

Bacterial and fungal infections

In addition to viruses, bacteria and fungi are also important pathogens of respiratory tract infections. ILC2s have shown significant regulatory effects on immune responses in different bacterial and fungal infection models in mice, and more activated ILC2s in the peripheral blood of patients with bacterial infections suggest that they may have an impact on disease development. In fungal-related models, ILC2s reportedly increase and promote the recruitment of eosinophils. Chitin, a fungal polysaccharide component, can induce lung epithelial cells to release IL-25, IL-33, and TSLP and then activate ILC2s to promote the secretion of IL-5 and IL-13, thereby driving eosinophil infiltration and the aggregation of alternative activated macrophages.

In mice with single or combined deficiencies in TSLPR, IL-25, and IL-33R, chitin administration does not affect the expansion of lung ILC2s, but the ability to secrete cytokines is completely suppressed. Genetic deletion of ILC2s results in significant upregulation of the proinflammatory cytokines IL-1 β , TNF- α and IL-23, accompanied by increased expression of IL-17A by $\gamma\delta$ T cells, which leads to persistent neutrophilic airway inflammation. These results indicate a dual role for ILC2s in fungal infection. They promote type 2

Table 1. Comparison of ILC2 functions in viral and helminth infections

Pathogen	Infection type	ILC2 signals	Key effectors	ILC2 function	Ref.
Rhinovirus	Viral	IL-25, IL-33, TSLP	IL-13	Promotes mucus metaplasia and AHR; NLRP3 inflammasome inhibits ILC2	[66–68]
Respiratory syncytial virus	Viral	IL-33, TSLP	IL-13	Promotes goblet cell metaplasia and AHR	[71–73]
Influenza virus (H3N1)	Viral	IL-33	Areg, IL-5, IL-13	Epithelial repair (Areg); active type 2 inflammatory	[75]
Influenza virus	Viral	Chitin	Areg	Epithelial repair	[76,77]
Influenza virus (CA04)	Viral	IFN- β	IL-5, IL-13	Inhibits type 2 inflammatory	[78]
		IFN- γ	IL-5, Areg	Reduces host susceptibility	
Influenza virus (PR8)	Viral	IL-33	Areg	Epithelial repair	[79]
SARS-CoV-2	Viral	IL-6, IL-10	IL-5, CD69	Promotes fibrosis	[80,81]
MHV-68	Viral	IFN- γ	GM-CSF	Inhibits M2 polarization	[82]
Nippostrongylus brasiliensis	Helminth	IL-33, TSLP (from ASC), PGD2	IL-5, IL-13, IL-9, Ach, Areg	Recruits eosinophil, promotes mucus production and barrier recovery	[5,83–85]

ASC, fibroblast-like adventitial stromal cell; Ach, acetylcholine; PGD2, prostaglandin D2. Red, activating signals; blue, inhibitory signals.

immune responses and eosinophil recruitment but negatively regulate $\gamma\delta$ T cell-mediated neutrophilic inflammation [86]. Further studies have revealed that *Aspergillus*-derived fungal-associated proteases (FAPs) can specifically induce the generation of IL-33 in alveolar epithelial cells through the protease-activated receptor 2 (PAR-2) signaling axis rather than the TLR2/TLR4 pathway. During fungal infection, protease-activated receptor 2 (PAR-2) on epithelial cells is activated by serine proteases of allergens, triggering epithelial cells to secrete IL-33 precursors (pro-IL-33) into the extracellular space [87]. The extracellular precursors are then cleaved by proteases released by fungal allergens (such as *Alternaria*) to form mature IL-33 [88], which provides a mechanistic link between fungal proteases and ILC2 activation. FAP-induced IL-33 activates ILC2s to secrete more IL-5, IL-13 and IL-4 to promote the accumulation of airway eosinophils, but this process also depends on the presence of IL-25/TSLP [87]. Similarly, *Alternaria* serine proteases activate PAR-2, induce IL-33 secretion, and trigger the activation and accumulation of ILC2s as well as eosinophil infiltration in the lungs. TSLP and IL-33 are essential for the activation of ILC2s stimulated by *Alternaria* extract [89]. Moreover, the reconstitution of ILC2s in ILC2-deficient mice and exposure to *Alternaria* extract significantly increase the levels of IL-5 and IL-13 secreted by ILC2s and promote increased eosinophil infiltration [90]. Taken together, these results demonstrate that different types of fungal infections have a powerful ability to mediate type 2 inflammation by regulating the activation of lung ILC2s after promoting the secretion of alarmins by epithelial cells.

In bacterial infection, the biological behavior of ILC2s shows pathogen-specific differences. Compared with that in normal individuals, the number of ILC2s in the peripheral blood of tuberculosis [47] patients is increased [91]. The expression of the antiapoptotic molecule BCL-2 and the activation marker CD25 on the surface of ILC2s in patients is significantly upregulated, suggesting that these cells maintain the stability of the circulating pool through antiapoptotic mechanisms. Mouse *Mycobacterium tuberculosis* (*Mtb*) models revealed that ILC3s rapidly aggregate in lung tissues in the early stage of infection, while ILC1s do not

change significantly, and the later stage is characterized by ILC2 accumulation [92]. Activated ILC2s in mice perform unique functions, such as phagocytosis of *Streptococcus pneumoniae* and the formation of extracellular traps to trap bacteria [93]. Oral administration of OM-85, a standardized lysate of human airway bacteria, can suppress allergic asthma in all models. OM-85 administration dampens allergen-induced type-2 airway responses through the epithelium/IL-33/ILC2 axis [94]. Research on the regulation of the gut microbiota-lung axis has revealed that disorders associated with gut dysbiosis promote increases in the protein levels of IL-33 and IL-25 in the lungs. Among them, *Proteobacteria* induce intestinal IL-33 and CXCL16 secretion, prompting nILC2s to upregulate CXCR6 expression, thereby mediating their directional migration to lung tissue. The IL-25/CCR9 axis is crucial for the accumulation of inflammatory ILC2s (iILC2s) [95]. Two distinct ILC2 subsets are involved: natural ILC2s (nILC2s), which are tissue-resident, express the IL-33 receptor ST2 and maintain tissue homeostasis [96], and iILC2s, which are recruited from the circulation, express the IL-25 receptor IL-17RB, and are activated early in infection [97]. Both types of ILC2s have a certain protective effect on CLP-induced lung injury [95]. Moreover, short-term cohousing experiments revealed that the response of lung ILC2s to *A. alternata* extract could be attenuated by remodeling the gut microbiota. The mechanism may involve the inhibition of ILC2 function via the activation of the interferon receptor signaling pathway. However, the ability of ILC2s to produce a type 2 immune response to pathogens is not completely suppressed during long-term cohousing; rather, it is delayed [98]. Furthermore, pulmonary ILC2s induced by dysbiosis can produce high levels of IL-4 when IL-33 is inhaled. These expanded and activated ILC2s promote the proliferation of B1 cells and the production of IgE in an IL-4-dependent manner, thereby exacerbating allergic inflammation. This phenomenon is primarily induced by the absence of short-chain fatty acid (SCFA)-metabolizing bacteria [99].

In summary, as a key regulator of mucosal immunity, the functional status of ILC2s is finely regulated by pathogen type, epithelial-stromal signaling, and the microbiota-metabolic network.

These genes play pivotal roles in the type 2 immune response and antimicrobial defense and provide new molecular targets for the immunotherapy of infectious diseases.

Helminth infections

Helminth infection represents a significant global health concern. It is estimated that over a billion people worldwide are infected with various helminth parasites, which can lead to malnutrition, growth disorders, cognitive deficits, and chronic immune system diseases. Helminth infection is caused by various helminth parasites that enter the host body through different routes, such as oral ingestion and skin contact. Helminths can parasitize human hosts and reproduce within tissues, causing progressive pathological changes such as lung injury (during larval migration) and malnutrition (in chronic infections). Common helminth infections include ascariasis, hookworm infection, and schistosomiasis. Many helminths need to migrate through lung tissue in the larval stage. This process can cause significant immune responses, and the innate immune system and adaptive immune system synergistically form a line of defense against pathogen infection [100]. Among them, ILC2s, as important resident innate immune cells in lung tissue, can rapidly respond to environmental signals and regulate immune responses by secreting specific cytokines, which play a significant role in regulating the host immune response to helminth infection. Therefore, the role of ILC2s in host resistance to helminth infection has gradually attracted increasing attention in recent years. The activation mechanism of ILC2s involves the coordinated function of multiple signaling pathways. During helminth infection, parasites or their products can stimulate host tissues to produce a series of inflammatory mediators and cytokines, such as IL-33, IL-25, and TSLP. These inflammatory mediators and cytokines can directly bind to receptors on the surface of ILC2s, thereby activating ILC2s and promoting the secretion of type 2 cytokines [101]. ILC2s are essential sources of early type 2 cytokines in helminth infections to induce protective type 2 responses. In addition, the interaction between neurons and immune cells plays an important role in regulating ILC2 function [102–104].

The course of disease in mice infected with *Nippostrongylus brasiliensis* (*N. brasiliensis*) is very similar to that in humans infected with hookworms. Therefore, *N. brasiliensis* is a commonly used model for studying the immune response. In this system, the infected larvae (L3) invade the host through the skin. Once inside the body, the larvae enter the bloodstream and migrate through the vascular system to the lungs within a day, causing hemorrhagic lung injury within 1 to 3 days after infection. The larvae are coughed out and then swallowed by the host along the esophagus, where they enter the digestive system. Eventually, the larvae will remain in the intestine and mature into adults. During the migration of larvae through lung tissue, various alarm signals are triggered by mechanical damage and the secretion of excretions, rapidly activating pulmonary ILC2s. Activated ILC2s significantly drive the early type 2 immune response and coordinate antiparasitic effects and tissue repair. The core protective role of pulmonary ILC2s in antiparasitic infection is beyond doubt. In ILC2-deficient mice, after infection with *N. brasiliensis*, eosinophil infiltration in the lungs completely disappears, with a lower frequency than that in uninfected mice, while the proportion of Th2 cells remains unchanged [7]. Overall, mucus secretion is reduced in ILC2-deficient mice, and larval clearance ability is severely impaired,

resulting in a greater parasite load and more severe pathological damage [83,105]. These findings indicate that ILC2s are essential for triggering type 2 immune responses to resist parasite infection and promote parasite expulsion.

After being infected with *N. brasiliensis*, fibroblast-like adventitious stromal cells (ASCs) in mouse lungs activate ILC2s by producing IL-33 and TSLP. These activated ILC2s are located mainly in the adventitial cuff close to IL-33⁺ ASCs, then induce a type 2 immune response and promote the expulsion of the larvae. Moreover, IL-13 derived from ILC2s promotes ASC proliferation and IL-33 secretion. ASCs support the survival, proliferation, and cytokine production of ILC2s [5]. During infection with *N. brasiliensis*, the recruited ILC2s affect prostaglandin D2 (PGD2) and chemokine receptor-homologous molecule expressed on Th2 cells (CRTH2). Additionally, *N. brasiliensis* infection significantly increases the level of choline acetyltransferase [77] in ILC2s, which is responsible for the biosynthesis of acetylcholine (ACh). ACh acts through binding to the ACh receptors expressed on ILC2s, leading to increased levels of IL-5 and IL-13 production by ILC2s. This biological process enhances the expansion of eosinophils and goblet cells, thereby accelerating the expulsion of *N. brasiliensis*. When ILC2s are deficient in ChAT expression or have an impaired ability to synthesize ACh, this leads to a reduction in the number of ILC2s and insufficient production of type 2 effector factors, resulting in a defect in the ILC2 response against *N. brasiliensis* and impaired immune function [84]. During *N. brasiliensis* infection, ILC2s can also produce more IL-9 in an autocrine manner, which is 5 to 10 times greater than that of CD4⁺ IL-9-producing T cells. ILC2s promote their own expansion via IL-9, which is crucial for the production of IL-9, IL-5, and Areg [85]. This process acts upon the epithelium, promoting mucus production, smooth muscle over-contraction, and barrier recovery, thus playing a protective role during helminth infection. When IL-9R is ablated, deficiency of IL-9 signaling significantly reduces the expansion of ILC2s and CD4⁺ T cells in the lungs during *N. brasiliensis* infection and significantly reduces the immune response and cytokine production of effector cells. This results in weakened lung tissue repair, delayed worm clearance, and exacerbated and slow recovery of lung function.

The interaction between ILC2s and T cells contributes to their maintenance, expansion, and cytokine production during *N. brasiliensis* infection. Lung ILC2s upregulate the costimulatory molecule OX40L under the induction of IL-33, which enhances communication with OX40⁺ T cells. It is also necessary for the proliferation of Th2 cells and Tregs. The deficiency of OX40L in mice infected with *N. brasiliensis* leads to impaired Th2 and Treg immune responses, resulting in reduced activation and weakened function of M2 macrophages [106]. Furthermore, ILC2s can express MHC-II and present antigens. In *in vitro* culture, ILC2s and T cells work together in an MHC-II-dependent manner, leading to cell interactions through dialog. Among them, the IL-2 produced by T cells promotes the proliferation of ILC2s and the production of IL-13. IL-13 produced by ILC2s can facilitate the migration of dendritic cells to draining lymph nodes and enhance the activation and polarization of T cells [107].

Two types of ILC2s enter the bloodstream during *N. brasiliensis* infection. On day 5 post infection, ILC2s mainly originate from the intestine and express the IL-25 receptor (IL-17RB), whereas on day 12 post infection, ILC2s mainly originate from the lung and express the IL-33 receptor (ST2). When stimulated by IL-25, ILC2s

expressing IL-25R in the lamina propria of the small intestine enter the blood circulation and lymph circulation via chemotaxis mediated by sphingosine-1-phosphate (S1P) and are further transferred to lung tissue to participate in the clearance of helminths and tissue damage repair [97]. These iILC2s are activated in the early stage of *N. brasiliensis* infection, earlier than the proliferation of nILC2s residing in the lung, and finally transform into nILC2s during the infection process. The basic leucine zipper ATF-like transcription factor (BATF) is a transcription factor necessary for the differentiation of iILC2s. BATF-deficient mice cannot generate iILC2s during helminth infection but can maintain nILC2s. The reduced number of IL-13⁺ ILC2s, accompanied by delayed expulsion of *N. brasiliensis*, indicates that iILC2s play a key role in antihelminth immunity. In addition, tryptophan hydroxylase 1 (TPH1), a rate-limiting enzyme for serotonin biosynthesis, is upregulated in iILC2s after infection. Mice lacking TPH1 have a delayed response to *N. brasiliensis* infection.

In conclusion, helminth infection can cause changes in the quantity and function of ILC2s in lung tissue, and ILC2s also play important roles in immune regulation (Table 1). Future research will reveal the interactions between ILC2s and other immune cells, as well as their specific mechanisms in regulating immune responses and tissue repair. In addition, targeted therapeutic strategies for ILC2s will provide new insights for the prevention and treatment of helminth infection.

Protozoan infections

Protozoan infection has revealed that succinate, a metabolite of the gut microbiota, drives the migration of iILC2s to the lung by upregulating the expression of S1P receptors. In this process, OX40-mediated IL-2 secretion by T cells and ICOSL expression by B cells jointly maintain the antigen-independent accumulation of iILC2s and synergistically regulate pulmonary eosinophilia. Studies in *Toxoplasma gondii*-colonized mice have demonstrated enhanced ILC2 activation and eosinophil infiltration. Moreover, clinical observations have revealed a positive correlation between the detection rate of pathogenic protozoa in airway samples and disease severity in certain asthma patients. These findings suggest that specific intestinal microbial characteristics, including the presence of protozoan organisms such as *T. gondii*, may contribute to exacerbated type 2 inflammation in a certain group of asthma patients [108].

ILC2s in Pulmonary Fibrosis

Certain chronic or severe infections, if not completely eliminated or recurrent, may become important causes of pulmonary fibrosis. Clinically, pulmonary fibrosis can be divided into secondary and idiopathic types according to the cause. Bleomycin-induced lung fibrosis, a common model, can mimic the pathogenesis of idiopathic pulmonary fibrosis via the inflammation-fibrosis transition and downstream fibrotic pathways. Cystic fibrosis and silicosis are considered secondary pulmonary fibrosis. ILC2s drive the inflammation-fibrosis cascade through multidimensional mechanisms.

In pulmonary fibrosis, ILC2s exhibit a profibrotic effect, as demonstrated in multiple mouse models. In a bleomycin-induced model, adoptive transfer of ILC2s has accelerated lung inflammation and fibrosis [109], whereas depletion of ILC2s with an anti- α -Thy1.2 antibody has reduced pulmonary collagen deposition. In an *S. mansoni* egg-induced pulmonary granuloma model, compared

with wild-type (WT) mice, ILC2-deficient *Rora*^{sg/sg} mice presented no increase in pulmonary collagen deposition [10]. Furthermore, in *Ifngr1*^{-/-}*Rag2*^{-/-} mice, which spontaneously develop PF, elimination of ILC2s by neutralizing antibodies can prevent fibrosis [11]. This evidence strongly indicates that ILC2s are pulmonary fibrosis-promoting factors.

In IPF and bleomycin mouse models, both microenvironmental factors and endogenous signaling pathways can regulate ILC2 function collaboratively. In IPF patients, the concentrations of IL-25 and IL-33 are significantly increased in both bronchoalveolar lavage fluid (BALF) and lung tissue homogenates, and bleomycin treatment also enhances the protein production of IL-33 and IL-25 in lung tissue. IL-33, a primary activator of ILC2s, binds to its receptor ST2 (IL-1RL1) and recruits the adaptor protein MyD88, leading to activation of the IRAK4-IRAK1-TRAF6 signaling cascade. This cascade leads to the phosphorylation of the I κ B kinase (IKK) complex, resulting in the degradation of I κ B α and the nuclear translocation of NF- κ B (p65/p50 heterodimer), thereby enhancing type 2 immunity. Interleukin-25 binding to its receptor, IL-17RB, can activate NF- κ B and promote type 2 cytokine production in ILC2s [110]. Genetic deficiency of ST2 or IL-25 suppresses ILC2 activation, thereby alleviating pulmonary fibrosis [10,109]. Mechanically, the function of ILC2s is regulated by different endogenous signals under these microenvironmental activation factors. There is a significant negative association between Regnase-1 expression levels and the number of ILC2s in the BALF of IPF patients. Genetic deficiency of Regnase-1 suppresses the number of ILC2s and the function of type 2 cytokine production via a cell-intrinsic pathway through reducing ICOS expression and inhibiting STAT5 phosphorylation. This pathway defines a Regnase-1-ICOS axis that is critical for controlling the profibrotic activity of ILC2s in bleomycin-induced fibrosis [111]. The expression of neuropilin 1 (Nrp1), a tissue-specific marker of lung ILC2s, is induced and sustained by the TGF- β -induced phosphorylation of Smad2/Smad3. The cell-intrinsic effect of the TGF- β -Nrp1 axis subsequently enhances ILC2 function via ST2 upregulation to promote pulmonary fibrosis [112]. In addition, alcohol may inhibit the activation of ILC2s in the bleomycin-induced fibrosis process through the CGRP-Ramp1 signaling pathway, reduce the secretion of type 2 cytokines, and thus alleviate the process of pulmonary fibrosis induced by alcohol consumption [113].

Type 2 cytokines secreted by ILC2s promote diseases by acting on surrounding immune and nonimmune cells. IL-13 secreted by ILC2s can induce periostin expression and promote collagen synthesis in the lung fibroblasts of IPF patients in a TGF- β -independent manner [114]. ILC2-derived IL-5 and IL-13 can induce monocytes to differentiate into profibrotic monocyte-derived alveolar macrophages (Mo-AMs) and drive disease progression [115]. CD45, as a cell-intrinsic negative regulator of ILC2s, restricts the proliferation and activation of ILC2s by inhibiting glycolysis. Consequently, genetic deficiency of CD45 in ILC2s leads to increased expression of the type 2 cytokine ICOS and high expression of the type 2 cytokines Ccl1 and Cxcl2, accelerating fibrosis through the recruitment of eosinophils and neutrophils [116]. CRTH2, which is upregulated on ILC2s in the bleomycin model, is responsible for the recruitment and migration of CHI3L1-induced ILC2s in the lungs. ILC2-derived Aregs act on EGFR⁺ primary fibroblasts to stimulate their proliferation and α -SMA expression, thus playing a profibrotic role [117]. Clinical studies have shown that ILC2s in the peripheral blood of IPF

patients present a characteristic phenotype of upregulated *IL1RL1* expression and suppressed *IFNGR1* expression. In *Ifngr1^{-/-}Rag2^{-/-}* mice, *Ifngr1* deficiency in ILC2s rather than its deficiency in other types of cells results in spontaneous pulmonary fibrosis. In addition, these ILC2s, which upregulate the expression of IL-33 receptors, increase in the fibrotic area and directly promote increased collagen deposition in lung fibroblasts [11].

Cystic fibrosis (CF) is a genetic disorder characterized by abnormal mucus secretion and recurrent bacterial infections and is distinct from pulmonary fibrosis (a disease characterized by excessive collagen deposition). However, ILC2s contribute to CF pathogenesis by promoting type 2 inflammation and fibrotic remodeling. For example, CFTR-deficient mice infected with *Aspergillus* exhibit ILC2-derived IL-9 secretion, which activates mast cells to produce profibrotic TGF- β . Elevated IL-9 levels are observed in the sputum of patients with cystic fibrosis. In CFTR-deficient mice with *Aspergillus* infection, ILC2s produce IL-9 after being stimulated with IL-33, activating mast cells to produce IL-2 and TGF- β . The former leads to the expansion of CD25⁺ ILC2s, which secrete more IL-9 and promote Th9 cell activation to amplify the inflammatory response, whereas the latter promotes the process of fibrosis [118]. Clinical cohort studies have shown that CCR6⁺ ILC2s in the peripheral blood of CF patients are significantly reduced, which is significantly associated with more severe disease and advanced pulmonary failure. In the BALF of corresponding CF patients, elevated levels of the CCR6 ligand CCL20 have been detected. Mechanistically, human ILC2s in humanized mice are recruited to the lung injury area through the CCL20/CCR6 axis and promote fibrotic remodeling by secreting IL-4/IL-13 to induce fibroblasts to secrete type VI collagen and eosinophil/neutrophil infiltration [119]. In CF patients with nasal polyps (CFwNPs), the nasal polyp microenvironment contains high levels of IL-1 β , IL-23, and TGF- β . In *in vitro* culture, these cytokines drive STAT3- and SMAD2/3-dependent transcriptional reprogramming of ILC2s, converting them into an IL-17A⁺ proinflammatory subset (while suppressing type 2 cytokine secretion). IL-17A then promotes epithelial IL-8 secretion, which recruits neutrophils and exacerbates CF-related airway inflammation, highlighting the unique role of ILC2 plasticity in CF complications. IL-4 can inhibit the responsiveness of ILC2s to IL-1 β and TGF- β by downregulating the expression of IL-1R1 (IL-1 β receptor) and TGFBR1 on ILC2s. This reduces the binding affinity of IL-1 β and TGF- β to their receptors. Moreover, vitamin D3 inhibits the process of ILC2 transformation to the IL-17⁺ phenotype by inhibiting the IL-23 signaling pathway [120].

ILC2s can adjust their response to different pathogenic stimuli by changing their own characteristics and inducing plasticity in different microenvironments (Figure 2). In the silica-induced silicosis model, the expression level of characteristic ILC2 markers and the secretion of type 2 cytokines decrease, and ILC2s gradually transform into ILC1s. This process depends on the regulation of IL-18 produced by mechanically activated fibroblasts through the Notch3 signaling pathway. ILC1s exacerbate pulmonary fibrosis by increasing the secretion of TGF- β [121].

In summary, ILC2s contribute significantly to the development of pulmonary fibrosis. Targeting the ILC2-associated pathway has emerged as a novel antifibrotic therapeutic strategy. However, their functional heterogeneity and tissue-specific regulatory mechanisms require further elucidation.

ILC2s in Pulmonary Hypertension

Pulmonary hypertension (PH), a fatal progressive disease, is pathologically characterized by pulmonary vascular remodeling and progressive right heart failure. Under various conditions, pulmonary blood vessels undergo abnormal contraction, inflammation, excessive cell proliferation and vascular remodeling, leading to thickening of the vascular walls, narrowing of the lumen and even occlusion. Pulmonary vascular resistance and pressure continue to increase, eventually causing the right ventricle to be overwhelmed and fail [122]. Recent studies indicated that ILC2s play a significant role in the pathogenesis of various types of PH by mediating type 2 immune responses. In infection-associated pulmonary arterial hypertension (PAH), such as schistosomiasis, activation of the IL-33/ST2 signaling pathway triggered by egg embolism markedly promotes pulmonary ILC2 proliferation [123]. It has been confirmed that activated ILC2s secrete large amounts of type 2 immune cytokines. In a mouse model, ILC2-derived IL-13 recruits Ly6c⁺ monocytes and promotes monocyte-derived thrombospondin-1 (TSP-1) secretion, thereby activating the TGF- β /Smad2/3 signaling pathway and ultimately leading to significant pulmonary vascular remodeling. Clinical studies have also revealed aberrant activation of the IL-13/IL-4R α /phosphorylated STAT6 signaling pathway in the lung tissue of patients with schistosomiasis-associated PAH, further confirming the importance of this mechanism [124,125]. In connective tissue disease-associated PAH, the pathogenic role of ILC2s is equally prominent. Significantly elevated IL-13 levels in the lung tissue and peripheral blood of systemic sclerosis patients with PAH may exacerbate disease progression by activating the monocyte/macrophage system [124,126]. Animal experiments confirmed that IL-13 overexpression can directly stimulate vascular smooth muscle cell proliferation via the IL-13R α 2/Arg2 pathway, inducing a pulmonary hypertension phenotype [127].

Although direct evidence for ILC2s in chronic lung disease-associated PH requires further substantiation, on the basis of their role in chronic airway diseases, it is hypothesized that ILC2s may participate in the vascular remodeling process of hypoxic PH by secreting cytokines such as IL-13 to recruit eosinophils and polarize macrophages or by secreting amphiregulin to promote lung fibroblast activation.

These findings provide novel insights into the immunotherapy of PH. Intervention strategies targeting ILC2s and their downstream effector molecules, such as blocking IL-33/ST2 signaling, applying IL-13/IL-4R α neutralizing antibodies (e.g., dupilumab), and inhibiting amphiregulin, all show potential translational value. Future research needs to further elucidate the dynamic changes in ILC2s across different PH subtypes and their interactions with other immune cells, laying the foundation for developing precise immunotherapeutic strategies. As ILC2s are key nodes connecting immune dysregulation and vascular remodeling, in-depth research on ILC2s holds promise for opening new avenues in PH treatment.

ILC2s in Acute Lung Injury

Acute lung injury (ALI) is a severe pulmonary syndrome characterized by widespread inflammation and increased permeability in the lungs, leading to fluid leakage into the lung tissue and alveolar spaces, thereby impairing gas exchange. Studies on the immune regulatory mechanisms of ALI induced by different models have shown that the dynamic changes in ILC2s in the lung microenvironment and their functional heterogeneity have complex regulatory

effects on the disease process. The accumulation of functional ILC2s is observed in the lungs of patients with sepsis. In a mouse sepsis model induced by cecal ligation and puncture (CLP), lung ILC2s expand significantly. Signaling molecules derived from various types of cells in the tissue microenvironment participate in ILC2 activation. IL-33 can promote the proliferation and activation of ILC2s, and a continuous increase in protein levels was detected in CLP lungs. In the context of the IL-33/ST2 signaling pathway, ILC2ps in the bone marrow promote the migration of ILC2ps to lung tissue by increasing GRK2-mediated endocytosis of the membrane receptor CXCR4 [128]. Notably, although IL-25 expression in lung tissue is increased in the CLP model, the classical pathway of intestinal iILC2 migration to the lungs mediated by IL-25 is not activated. Evidence shows that the circulating IL-25 level and the number of lung iILC2s did not change significantly in this model, suggesting that nILC2s constitute the main effector subpopulation of sepsis ALI [129,130].

In the CLP model, ILC2-derived IL-5 expression increases and alleviates CLP-related lung injury by enhancing macrophage cytokine secretion, activation, and phagocytosis, and this process is independent of eosinophils [131]. Concurrently, IL-5 promotes the recruitment of neutrophils to the lungs, and neutralizing IL-5 with antibodies significantly reduces neutrophil infiltration and the severity of ALI in the CLP model [132]. In contrast, ILC2-mediated IL-9 exerts a protective effect through a dual mechanism: on the one hand, it inhibits macrophage mTOR pathway-dependent apoptosis and the conversion of macrophages to M1 inflammatory macrophages [132]. On the other hand, it reduces caspase-1-mediated pyroptosis in lung endothelial cells [133]. A study revealed that ILC2-deficient mice have a greater survival rate after CLP surgery, suggesting that ILC2s have different functions in this disease [130].

The functional phenotype of ILC2s is spatiotemporally dependent. Sustained stimulation with IL-33 induces ILC2s to secrete IL-4 and IL-13, which promotes M2 macrophage polarization and IL-10 production and then activate the immunosuppressive microenvironment mediated by regulatory T cells (Tregs) [134]. In the early stage of CLP, ILC2s upregulate the inhibitory receptor PD-1, which, together with IL-33/ST2 signaling, regulates the level of IL-13 production. In the late stage of CLP, the level of IL-13 secreted by ILC2s mainly depends on IL-33/ST2 signaling [129]. Emerging research reveals the critical role of the neuroimmune regulatory network in ALI. In the CLP sepsis model, the expression of neuromedin U (NMU), a neuropeptide secreted by activated neurons, increases. NMU binds to NMUR1 on ILC2s, promoting ILC2 secretion of IL-9. IL-9 then acts on $\gamma\delta$ T cells to increase their production of IL-17A, which reduces mortality and is correlated with increased neutrophil recruitment and less severe bacteremia. This sequential signaling between neurons, ILC2s, and $\gamma\delta$ T cells forms a protective “neuro-ILC2- $\gamma\delta$ T cell axis” [135].

The increased number of ILC2s detected in the peripheral blood of haemorrhagic shock [119] patients is positively correlated with increased levels of HMGB1 in plasma and type 2 cytokines. In the mouse haemorrhagic shock model, ILC2s also increased significantly in lung tissue. ILC2s receive HMGB1 signals through the membrane receptor RAGE, which promotes proliferation while inhibiting apoptosis, causing excessive accumulation of ILC2s in the lungs, triggering type 2 cytokine storms and eosinophil infiltration, aggravating lung damage, and highlighting the functional heterogeneity of ILC2s in different pathological models [136].

In summary, the regulatory role of ILC2s in ALI is significantly model-dependent and stage specific, and their proinflammatory/anti-inflammatory balance may be dynamically regulated by multiple factors, such as microenvironmental cytokines, neural signal input, and metabolic reprogramming. This complexity poses significant challenges for developing precise immune intervention strategies.

ILC2s in Lung Cancer

Pulmonary tumors can be classified as primary or metastatic. These two types are quite different in terms of pathogenesis and pathological characteristics. However, current studies indicate that ILC2s play significant roles in both processes but show significant biological functional heterogeneity. Their dual ability to promote and suppress tumors is dynamically regulated by pathological background and microenvironmental signals.

In a lung metastatic melanoma model, ILC2s demonstrated antitumor effects. Adoptive transfer of ILC2Ps in *Rag*^{-/-}*IL2rg*^{-/-} mice significantly reduces tumor size. IL-33 can enhance ILC2-derived IL-5 and GM-CSF. These factors can promote eosinophil maturation, survival, and activation and facilitate tumor elimination [137,138]. However, IL-33 also triggers the expression of PD-1, an immune checkpoint molecule that inhibits ILC2 activity and suppresses ILC2 antitumor function. Combined treatment with IL-33 and an anti-PD-1 antibody enhances the antitumor effect of the ILC2-eosinophil axis. In the tumor environment, ILC2s reduce LKB1 phosphorylation levels and increase PD-1 expression through the ROS-NFAT signaling pathway in a cell-intrinsic manner, which inhibits ILC2 activation and weakens the secretion capacity of IL-5 and IL-13, thereby significantly increasing the number of lung tumor metastases [139]. Treatment with an anti- α -PD-1 antibody can restore ILC2 effector function and control lung tumor growth. Conversely, in the superimposed allergic inflammation model, ILC2s promote tumor metastasis under IL-33 or *Aspergillus* stimulation. Mechanistically, IL-33 activates ILC2s to secrete IL-5, and the induced eosinophils locally antagonize the secretion of IFN- γ and granzyme B by lung NK cells by regulating NK cell glucose metabolism (glucose restriction and enhanced glycolysis), thereby promoting tumor metastasis and spread in the airway [140]. ILC2s play a significant role in non-small cell lung cancer (NSCLC). Clinical data indicate that the number of ILC2s infiltrating the peripheral blood and tumors of patients with non-small cell lung cancer (NSCLC), especially lung adenocarcinoma, is significantly greater than that of healthy controls. Mechanistically, tumor-infiltrating ILC2s highly express the immune checkpoint molecule PD-1 and drive the polarization of M2 macrophages via IL-4 and IL-13 production, fostering a proangiogenic and immunosuppressive microenvironment that accelerates tumor progression [141].

In the Lewis lung cancer (LLC) model, IL-33 expression levels are increased, and genetic deficiency of IL-33 inhibits tumor development [142]. ILC2s upregulate GPR35 and increase IL-5 and IL-13 secretion under IL-33 stimulation. IL-13 promotes tumor growth by inducing the accumulation of myeloid-derived suppressor cells (MDSCs) [143]. Furthermore, the increase in M2 macrophages, ILC2 counts, and type 2 cytokine secretion in tumor tissues depends on the negative regulation of vitamin A and is correlated with increased tumor burden and decreased survival rates [144]. These results demonstrate that the type 2 immune response of ILC2s plays a tumor-promoting role in LLC.

In the TC1 lung adenocarcinoma model, single-cell transcriptomic analysis revealed the differentiation of ILC2 functional subsets: some subsets activated cytotoxic T lymphocyte (CTL) responses through the expression of antigen presentation-related genes (such as MHC-II) and Th1-type cytokines. This may indicate an antitumor effect in ILC2s [145].

In summary, ILC2s are implicated in the development of a variety of pulmonary tumors. This evidence highlights the importance of the “double-edged sword” characteristics of ILC2s in tumors. These results provide potential application value for subsequent ILC2-based tumor-targeted therapy.

ILC2s in Lung Transplantation

Lung transplantation, a critical treatment for end-stage lung diseases, faces dual constraints on its clinical efficacy because of primary graft dysfunction (PGD), a serious form of acute lung injury causing progressive hypoxemia and chronic lung allograft dysfunction (CLAD), a range of pathologies characterized by a persistent, progressive, and largely irreversible decline in lung function. Research indicates that ILC2s play a complex and pivotal role in immune regulation post-lung transplantation, although their functions vary across different phases.

In the acute phase, ischemia-reperfusion injury (IRI) activates ILC2s through a dual mechanism. On the one hand, damaged lung tissue releases IL-33 to directly stimulate ILC2 activation [146]; on the other hand, mechanical changes induced by pulmonary edema promote the production of IL-33 by alveolar macrophages via the Piezo1-Ca²⁺-NFAT pathway [147]. This early activation of ILC2s has significant protective effects, with clinical observations revealing an inverse correlation between ILC2 abundance and PGD risk [148]. The underlying mechanism may involve IL-5-mediated eosinophil recruitment and the expansion of regulatory T cells [149,150], collectively maintaining an immune-tolerant microenvironment. However, in the later stages posttransplantation, persistently activated ILC2s may drive the development of bronchiolitis obliterans syndrome [33], a form of CLAD causing scarring and narrowing of the small airways in transplanted lungs, leading to progressive airflow obstruction and symptoms such as cough and breathlessness. By secreting large amounts of profibrotic factors such as IL-13 [151].

This seemingly paradoxical dual role highlights the dynamic function of ILC2s in lung transplantation. It plays a tissue protective role in the early stage, whereas long-term activation promotes chronic rejection. On the basis of this understanding, future therapeutic strategies may focus on precisely modulating the functional plasticity of ILC2s. For example, their immunoregulatory role during the acute phase is enhanced via the IL-33/ST2 axis, while the inhibition of profibrotic factors such as IL-13 in the chronic phase is targeted. Such time-specific intervention strategies hold promise for overcoming the current bottleneck in immune regulation for lung transplantation, offering novel therapeutic approaches to improve long-term patient outcomes.

Conclusions and Future Perspectives

ILC2s have emerged as vital components of the immune system and have significant implications for lung inflammation and disease outcomes. Their functions simultaneously encompass both beneficial protective responses (such as epithelial repair during viral infections and antiworm defense) and pathological inflammatory

responses (such as respiratory remodeling in asthma and fibrosis in pulmonary hypertension), highlighting the complexity of their functions and interactions within the lung microenvironment. Understanding the regulatory mechanisms that govern ILC2 activity and their crosstalk with other immune cells and tissues is crucial for developing targeted therapies for a range of lung inflammatory diseases.

The dynamic characteristics of ILC2s, including their ability to differentiate into other ILC subsets and interact with T cells through MHC-II and CD80 expression, underscore their plasticity and adaptability [152,153]. This plasticity is particularly evident in fibrotic conditions, where ILC2s are found alongside IL-33-positive fibroblasts, suggesting their involvement in tissue remodeling and fibrosis progression. Additionally, the context-dependent roles of ILC2s in cancer, such as their ability to either suppress tumor growth or exacerbate metastasis, highlight the need for a nuanced understanding of their functions in different disease contexts.

Future research should focus on elucidating the key signaling pathways and crucial transcription factors that regulate ILC2 differentiation, activation, and function in different microenvironments. Furthermore, the development of novel tools and techniques to precisely isolate and characterize ILC2 subpopulations will be essential for understanding their distinct functional characteristics and interactions with other cells in the lung microenvironment.

To further dissect ILC2-lung microenvironment interactions, lung organoids, the simplified *in vitro* models of the respiratory system, are promising for studying ILC2 function in tissue regeneration and disease. These organoids can be generated from adult lung stem cells and used to simulate ILC2 activation by epithelial alarmins (e.g., IL-33) or to screen therapeutic compounds targeting ILC2s. However, challenges remain, such as the incomplete differentiation of lung stromal cells and the use of complex culture media. Future research should refine organoid models to better mimic *in vivo* ILC2-niche interactions, facilitating mechanistic studies of ILC2s in lung disease.

In conclusion, the multifaceted roles of ILC2s in lung inflammation and disease highlight their potential as therapeutic targets. Future studies should aim to elucidate the regulatory mechanisms governing ILC2 function, their interactions with other immune cells and tissues, and their role in lung stem cell-mediated regeneration. Advances in these areas will not only deepen our understanding of the biology of ILC2s but also pave the way for the development of novel therapies for a range of respiratory diseases.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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