Review Article

Crosstalk between ILC2s and Th2 CD4⁺ T Cells in Lung Disease

Lan-lan Mi ⬤ **and Wei-wei Guo** ⬤

Department of Neonatology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence should be addressed to Wei-wei Guo; viviguo_0578@163.com

Cytokine secretion, such as interleukin-4 (IL-4), IL-5, IL-9, IL-13, and amphiregulin (Areg), by type 2 innate lymphoid cells (ILC2s) is indispensable for homeostasis, remodeling/repairing tissue structure, inflammation, and tumor immunity. Often viewed as the innate cell surrogate of T helper type 2 (Th2) cells, ILC2s not only secrete the same type 2 cytokines, but are also inextricably related to CD4⁺T cells in terms of cell origin and regulatory factors, bridging between innate and adaptive immunity. ILC2s interact with CD4⁺T cells to play a leading role in a variety of diseases through secretory factors. Here, we review the latest progress on ILC2s and CD4⁺T cells in the lung, the close relationship between the two, and their relevance in the lung disease and immunity. This literature review aids future research in pulmonary type 2 immune diseases and guides innovative treatment approaches for these diseases.

1. Introduction

The lung is a fragile organ, sensitive to temperature variation (cold and heat), constantly exposed to the external environment, and consequently susceptible to pathogen invasion. Thus, the lung is protected by a complex network of highly specialized immune cells and their mediators to support tissue homeostasis and prevent extensive tissue damage. The resting lung is prominently immune-tolerant, despite a plethora of leukocytes including B, T, and myeloid cells (macrophages, monocytes, dendritic cell subsets, neutrophils, and eosinophils), which numbers and proportions changing dramatically during infection and inflammation.

Recently a small subset of other immune cells was identified in the lung, namely, innate lymphoid cells (ILCs), which are distinct from T and B lymphocytes. ILC1s, ILC2s, and ILC3s act as the innate counterparts of the traditional Th (CD4⁺T helper) 1, Th2, and Th17 T cell effector subsets, respectively [1]. Furthermore, ILCs and traditional T cells also share a common ontogeny [2–4]. Interestingly, ILC2s and Th2 cells not only share the same cytokine and transcription factor expression profile [5], but also co-regulatory signals. The homeostasis of both ILCs and T cells is supported by IL-7 and IL-15 [6, 7]. ILC2s and Th2 cells both secrete type 2 cytokines under the stimulation of epithelial factors, such as interleukin-33 (IL-33) [8] and thymic stromal lymphopoietin (TSLP) [8, 9]), and both can be activated by other factors such as GATA3 [10, 11], inducible co-stimulatory molecules (ICOS) [12], and TL1a [13, 14]. In addition to common stimulators, ILC2s and Th2 cells also share inhibitors, such as cyclosporin A (CSA) [15] and Rora [16]. However, the same factor may have different effects. IL-10 hinders T cell activation and Treg inhibition while increasing ILC2s levels [17]. Maresin 1 (MaR1) reduces lung inflammation in ILC2s but mediates the proliferation of Treg and the interaction between Treg and ILC2s [18]. Thus, ILC2s and CD4⁺T cells, especially their counterpart Th2 cells, share common stimulators and suppressors, as summarized in Figure 1.
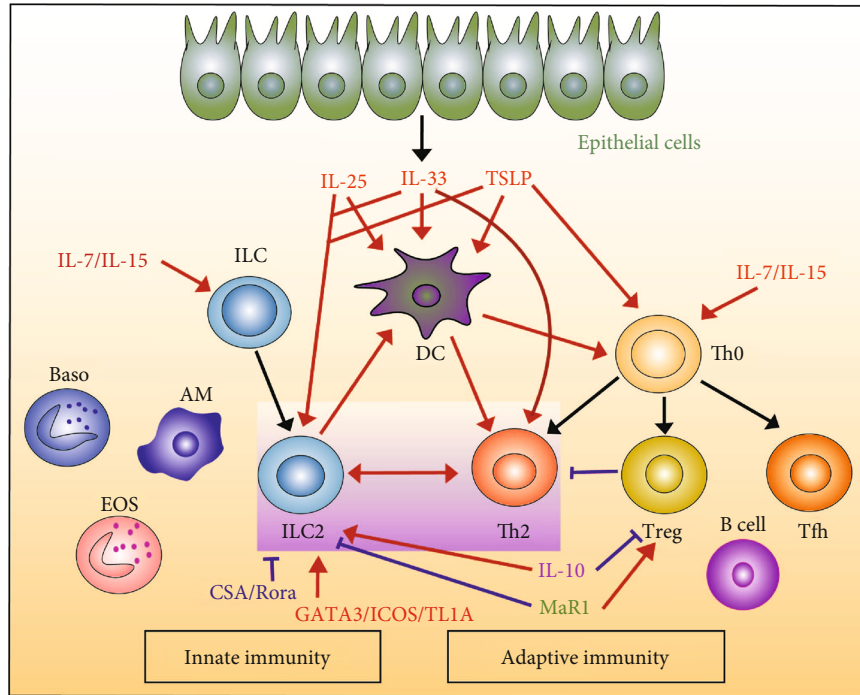
FIGURE 1: Co-stimulatory factors of ILC2s and CD4^{+}T cells and their roles in innate and adaptive immunity.

Compared to CD4^{+}Th cells, ILCs also have a unique and nonredundant genetic organization in terms of kinetics, fine-tuning, and spatial organization of the immune response [19]. Here, we will summarize the latest research progress on ILC2s and CD4^{+}T cells in the lung and how their interaction participates in the immune regulation and lung homeostasis and will explore how their dysregulation can lead to lung diseases.

2. ILC2s in Lung Homeostasis

The ILC2 is a tissue-resident population and the major helper type ILCs in the steady-state lung of mice [20, 21]. During homeostatic conditions, this tissue-resident population is self-renewed in the lung parenchyma and is virtually absent from circulation [22]. Tissue microenvironment strongly shapes ILC2s phenotype, strikingly heterogeneous across different mucosa, and specialized modulators of regional immune responses [23]. Natural ILC2s (nILC2s) produce type 2 cytokines, while plastic inflammatory ILC2s (iILC2s) can produce both type 2 cytokines and IL-17 [24], which are considered as transient progenitor cells of ILCs and develop into nILC2s in vitro and in vivo [25]. Increased IL-25 levels, either through experimental administration or after worm infection, can trigger local proliferation and activation of intestinal ILC2s, the precursor of iILC2s, which can then reach the lungs through blood circulation [26]. Some iILC2s can differentiate into nILC2s and reside in the lung, while others home back to the small intestine [26], suggesting that ILC2s, just like adaptive T lymphocytes, are locally activated with distant effector function [26, 27]. Another

study showed that ILC2s increase not only by local proliferation, but also by delivery from circulation to the lungs [28]. A new subgroup derived from ILC2s, the regulatory ILC (ILCreg) subgroup, was recently identified by the production of IL-10, therefore distinctive from activated IL-10^{−}ILC2s and IL-10^{+}Treg cells [29]. This population contracts after cessation of inflammatory stimulation in vivo, but can be restimulated upon new stimulus, similar to the Tl effector and memory cells [29].

Lung ILC2s are activated by the alarmins IL-33 [30], IL-25 [31], and TSLP [32] that is released from various immune and nonimmune cell types in response to different stimulation. After being activated, ILC2s mediate innate and adaptive type 2 immunity through rapid release of effector cytokines including IL-4, IL-5, IL-9, IL-13, and amphiregulin (Areg) and expression of co-stimulatory ligands that influence Th2 cells [33]. There are many other regulatory factors of lung ILC2s. Leukotriene cooperates with IL-33 to induce ILC2s during lung inflammation [34]. Cysteinyl leukotriene not only directly enhances IL-33 stimulated purified ILC2s to produce IL-5 and IL-13, but also promotes leukotriene-C4- and IL-33-co-induced-ILC2s activation and lung inflammation [35]. ILC2s can concurrently express ICOS and ICOS ligand, and ICOS: ICOSL signaling pathway promotes ILC2s function and homeostasis [36]. Finally, leukotrienes [37], miR-155 [38], and arginase 1 [39] can also act as key positive regulators of ILC2s.

However, the inherent defect of programmed death 1(PD-1) signaling in KLRG1^{+}ILC2s could lead to uncontrolled proliferation and activation of these cells [40]. The innate immune response triggered by immunogenic

extracellular RNA has a strong inhibitory effect on the proliferation and function of ILC2s *in vivo* [41]. Basophil recruitment is a hallmark of type 2 inflammation and can directly enhance the expression of neuropeptide neurotransmitter B receptor on ILC2s, which is an effective inhibitor of ILC2s [42], and androgen [43], endogenous neuropeptide calcitonin gene-related peptide [44, 45], prostaglandin E [46], and interferon-γ [47] are key negative regulators of ILC2s.

Interestingly, ILC2s are amateur antigen-presenting cells (APC) that can cooperate with dendritic cells (DCs) to maintain type 2 immune response [48]. ILC2s not only mediate neonatal lung development [49], but also play a role in lung diseases caused by developmental abnormalities, such as bronchopulmonary dysplasia [50]. The phenotypes of ILC2s in different models of airway inflammation are different, as manifested by ILC2s-specific expressed genes stimulated by house dust mites. These participate in adaptive immune regulation through the interaction of B cells and T cells, while the ILC2s stimulated by IL-33 express high levels of cytokine and proliferation-related genes [51]. This study indicates that lipid metabolism is required for pathogenic ILC2s response, and ketogenic diet is an effective intervention strategy for the treatment of airway inflammation [52]. However, the cognition of lung ILC2s characteristics and function is mostly based on mouse studies due to easy access to lung tissue, abundant inflammatory diseases models, and genetic impairment of ILC function.

In humans, ILC2s accumulate in fetal lungs at 10-fold higher levels than adult lungs [53]. Another study also detected ILC2s in fetal and adult lungs, which accounted for more of the total ILC in adult lungs [54]. A recent study with human blood, bronchoalveolar lavage fluid (BALF), and the lungs successfully identified ILC2s in human lung tissue and found a previously unrecognized human ILC2s population with new surface markers, such as CD30 and tumor necrosis factor receptor 2 (TNFR2), which may drive asthma [55]. However, none of the above studies directly prove the existence of human lung ILC2s by using multi-immunohistochemistry stain. Due to the presence of ILC2s in human blood, it cannot be excluded that ILC2s isolated from fragment of the human lung tissue came from contaminated blood. In other words, the existence of ILC2s in human lungs is based on suggestions rather than conclusive evidence. Better understanding of human lung ILC2s may come from less evasive samples such as human umbilical cord blood [53]/peripheral blood, or sputum and BALF [56–58], or humanized mice models [59]. Therefore, further study on human lung ILC2s, preferably directly, is needed for a better understanding of their characteristics and functions.

3. CD4+T Cells in Lung Homeostasis

CD4+T lymphocytes are a key element of adaptive immunity, and their role is to direct and enhance innate cell function [60]. Naive CD4+T cells proliferate and differentiate into several possible effector subpopulations, including traditional T helper effector cells (Th1, Th2, and Th17), T regulatory cells (Treg), and T follicular helper cells (Tfh) [60]

that can support B cells [61]. Lung CD11b+DCs have a self-maturation process, promoting Th17 differentiation at partial maturation and Th2 differentiation at maturation [62]. These cells contribute to the maintenance of normal immune homeostasis in the face of changing microorganisms in the environment.

Early Th2 cells tilt susceptibility to allergies and are often seen as remnants of fetal maternal symbiosis [63]. Dopamine signals through specific dopamine receptors to promote Th2 differentiation and cooperates with IL-4 to enhance Th2 inflammation in the lungs of young rather than adult mice [64]. The risk of allergic asthma in infants is higher than that of adults because infants fail to induce TNF-α [65]. TNF-α migrating upregulate T-bet transcription factor in CD11b+DCs inducing IL-12 secretion which in turn prevents the Th2 cells differentiation [65]. It has also been found to be caused by underdeveloped Treg cells [66]. Additionally, neonatal BCG vaccination can inhibit allergic airway inflammation, by promoting T-regulatory immune response through enhanced expression of toll-like receptor 2 and 4 and PD-L1 on DC [67].

Fasting can inhibit the proliferation of Th2 cells in the lung and downregulate the level of Th2 cytokines [68]. The percentage of Th17.1, Tfh, and Tfh2 was higher in severe allergic asthma patients, while the percentage of Breg cells and Treg was significantly lower than in the control group [69]. This immune imbalance was restored after omalizumab treatment [69]. Anti-F4/80 treatment of OVA-induced asthmatic mice inhibited alternately activated macrophages and also attenuated Th2 cell response in lung tissue [70]. Similarly, reducing the levels of IL-4, IL-5, and IL-13 in the lung and the number of Th2 cells in mediastinal lymph nodes, while increasing the number of Treg cells in mediastinal lymph nodes, can alleviate allergic airway inflammation [71]. Acupuncture also seems to reduce airway inflammation and airway hyperreactivity (AHR) in asthmatic patients by correcting the imbalance of CD4+T lymphocyte subsets (Th1/Th2 and Treg/Th17) [72].

Fluoxetine can inhibit cancer cell proliferation in cancer patients with depression [73]. Fluoxetine increases CD4+Th cells while decreasing CD25+FOXP3+Treg. Additionally, fluoxetine promoted Th differentiation to Th1 cells while inhibiting Th2 and Th17 differentiation [73]. Major depressive disorder promotes the production of Th2- and Th17-related cytokines in patients with allergic rhinitis and asthma, which could be inhibited by 5-hydroxytryptamine treatment. Mechanistically, IL-5 and IL-17 levels are strongly correlated with the severity of depressive and anxiety symptoms [74].

4. Crosstalk between ILC2s and CD4+T Cells

There are two main mechanisms of crosstalk between ILC2s and CD4+T cells (Table 1). During the transition to adaptive T cell-mediated immunity, a closed loop is formed between ILC2s and CD4+T cells, and crosstalk between the two contributes to their mutual maintenance, expansion, and cytokine production [75, 76], as summarized in Figure 2.

TABLE 1: Crosstalk mechanism between ILC2s and CD4+T cells.

Effects of ILC2s on CD4+T cells	Effects of CD4+T cells on ILC2s
CD80 and CD86 on ILC2s [75]	Acting on major histocompatibility complex class II (MHCII) expressed on ILC2s [75]
IL-13 [77, 78] and IL-9 [79] secreted by ILC2s	
Regulation DCs to promote Th2 polarization [48, 80, 81]	IL-4/IL-13 secreted by CD4+T [82]
Contact through PD-L1:PD-1 [83] and OX40L:OX40 [84]	IL-2 secreted by CD4+T [76]
High mRNA expression of serine protease inhibitor B3 and B4 mRNA [85]	Contact through ICOSL:ICOS [86]
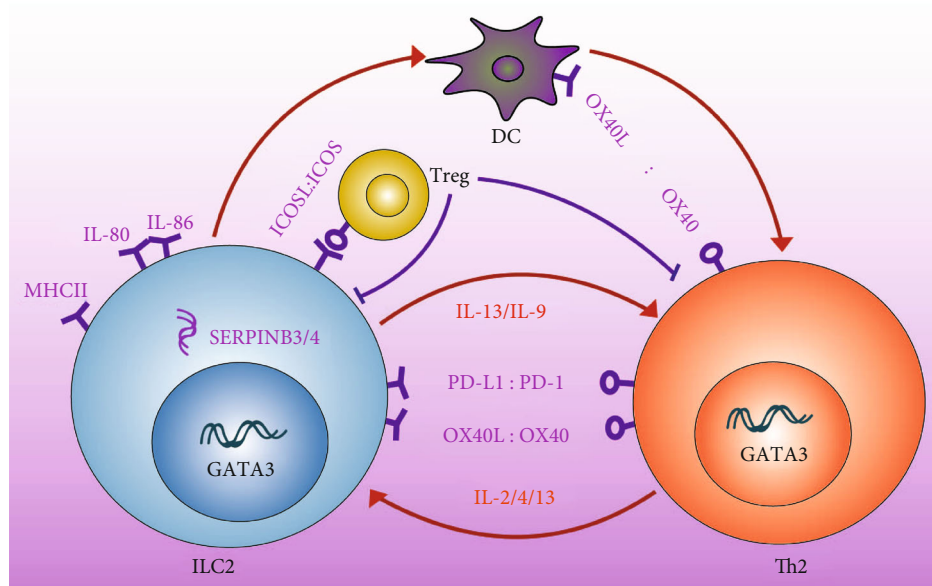
FIGURE 2: Crosstalk between ILC2s and CD4+T cells during type 2 immune response.

5. Crosstalk between ILC2s and CD4+T Cells in Lung Diseases

The crosstalk between ILC2s and CD4+T cells, particularly with Th2 cells, plays an important role in a variety of lung diseases (Figure 3).

5.1. Pulmonary Parasitosis. Several parasites spread to other parts of the human body via blood circulation and often reside in the lungs (pulmonary parasitosis) causing pathological changes [87]. During helminth infection, ILC2s play a protective role by secreting IL-13 [75]. In the absence of ILC2s, Th2 cell response is impaired, which no longer produce IL-2 required for ILC2s proliferation and IL-13 production [75]. This feedback is crucial during helminth immunity and essential for helminth clearance. Thus, ILC2s with conditional deletion of PD-L1 inhibit early Th2 polarization and cytokine production, resulting in delayed excretion of helminth during infection with gastrointestinal helminth [83].

Gastrointestinal helminth infection can cause local proliferation and accumulation of ILC2s in the lungs, which is promoted by IL-4/IL-13 secreted by Th2 cells [82]. This occurs during acute type 2 immune response and is inseparable from the fact that signal transducers and activators of transcription 6 promotes the communication between Th2 cells and ILC2s in an antigen-dependent manner [82]. IL-33 mediates the activation of ILC2s and Treg cells in tissues after worm infection, and the Treg cell accumulation *in vivo* required ILC2s activation, which was independent of ILC2s secreted cytokines but partially dependent on direct co-stimulatory interactions via ICOSL:ICOS [88]. IFN-γ inhibits the activation of ILC2s and aggregation of Treg cells by IL-33 in infected tissues, and this inhibitory effect is enhanced with age and high-fat diet-induced obesity [88].

During helminth infection, adventitial stromal cell depletion impairs the accumulation and function of lung ILC2s and Th2 cells partially dependent on adventitial stromal cells-derived IL-33, thus impairing the effect of expelling helminth [89]. After hookworm infection, CD4+T cells and ILC2s cooperate to quickly expel worms within 48 hours [90]. This report shows that ILC2s plays a protective role during hookworm infection, which can be maintained by CD4+T cells, so as to ensure the rapid activation and maintenance of IL-13-dependent M2 macrophages immunity in the lung [90]. It should be noted that these observations
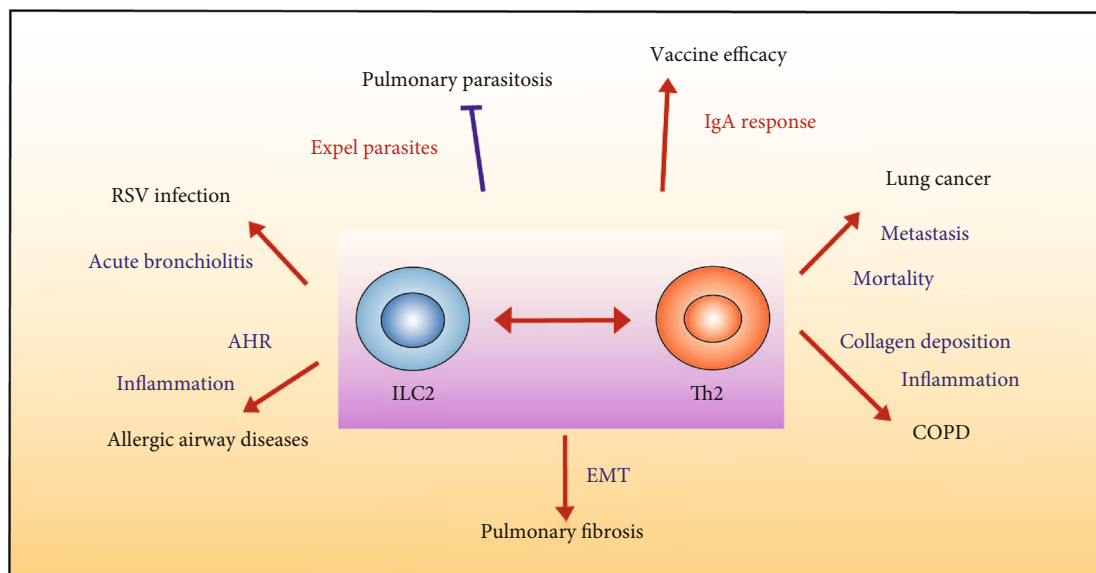
FIGURE 3: The relevance of ILC2s and Th2 cells crosstalk in lung disease.

are restricted to mouse models, and these crosstalk mechanisms between ILC2s and CD4+T cells require further confirmation in human pulmonary parasitosis.

5.2. Respiratory Syncytial Virus (RSV) Infection. RSV infection is a major cause of bronchiolitis and pneumonia, especially in infants and young children [91]. After treatment of RSV-infected mice, a decrease in lung mucus was observed, accompanied by a significant decrease in the number of ILC2s and macrophages, and a decrease in IL-33 in bronchoalveolar lavage fluid [92]. Similarly, during RSV infection, Th2 cell deletion can inhibit ILC2s activation and secretion of type 2 cytokines, to reduce the severity of the disease [76]. RSV infection can expand and activate CD4+T cells in the lungs of mice [84]. Adoptive transfer of lung ILC2s can not only increase the number of CD4+T cells, but can also increase the cytokine production by CD4+T cells, which is dependent on direct contact between them [84]. NF-B/IL-33/ST2 axis mediated the level of Th2 cytokines and the number of bronchoalveolar lavage fluid cells induced by RSV [93], and NF-B/IL-33/ST2 inhibition during RSV infection alleviated acute bronchiolitis in mice [93]. Thus, in the process of RSV infection, ILC2s and CD4+T cells aggravate disease by promoting each other's proliferation and activation in mice.

Human primary bronchial epithelial cells infected with rhinovirus can induce IL-33, and the culture of human T cells and ILC2s with its supernatant can strongly induce type 2 cytokines [94]. Viral infection is thought to cause chronic pulmonary interstitial inflammation and pulmonary fibrosis [95], which is described in detail next.

5.3. Allergic Airway Diseases. Allergic airway diseases are characterized by sneezing, itching, wheezing, chest tightness, airway obstruction, and hyperresponsiveness [96]. After allergen exposure, the number of CD4+T cells and ILC2s

in the lung increases dramatically, with the significant increase of IL-33 expression in the lung [97]. ILC2s and CD4+T cells (rather than each cell population) can induce strong airway inflammation and antigen-specific type 2 immune response [97]. IL-5 and IL-13 in BALF and lung tissue mainly come from ILC2s and Th2 cells [98]. Thus, strengthening GATA3 expression is sufficient to increase the susceptibility to allergic airway inflammation by enhancing Th2 and ILC2s activity [98]. In the alveolar phase, house dust mites exposure also leads to a clear increase of IL-33, which promotes the production of cytokines in ILC2s and activates DCs, thereby promoting Th2 cell tilt [63]. IL-9 secreted by ILC2s has a similar effect [79].

Both T cells and ILC2s contribute to the deterioration of influenza-induced allergic airway inflammation, but the dynamics are different [99]. Specifically, ILC2s secreted less type 2 cytokines in the early stage of influenza-induced acute exacerbation, and became the main source after virus clearance, while T cells showed increased production of IL-4 and IL-5 in the early stage [99]. It is easy to sensitize and aggravate the degree of asthma by promoting ILC2s amplification and Th2 differentiation [100]. Blocking T cell activation and Treg inhibition and promoting the increase of ILC2s could lead to severe Th2 immune response and airway inflammation [17]. Repeated exposure to antigen preferentially triggered the increase of Ag-specific CD4+Th2 cells, which synergized with ILC2s, resulting in the deterioration of murine allergic airway diseases with prominent eosinophilia [101].

Thus, by reducing the number of ILC2s or CD4+T cells, the effect of inhibiting both can be achieved, to reduce the pulmonary inflammation of asthmatic mice [15, 102, 103]. In mice with allergic airway inflammation treated with anti-CD127 monoclonal antibody, airway resistance was significantly reduced, and lung histology was improved, accompanied by significant reduction of Th2 cytokines (IL-4, IL-5,

and IL-13) in lung tissue and BALF. This also leads to a reduction of total leukocytes and specific leukocyte subsets in BALF and lung tissue, such as eosinophils, macrophages, lymphocytes, T lymphocytes, and ILC2s [104]. The regulatory DC marker C1q is as effective as dexamethasone-reducing AHR, eosinophil, and ILC2s infiltration in BALF, as well as allergen-specific Th2 cells in lung [105]. As an important regulatory cluster in T cells, Treg cells play a unique role in ILC2s. In the asthma model, the induced peripheral expansion of Treg cells effectively inhibits the proliferation of ILC2s, which may become a promising target for treatment [86].

Similar findings have been found in human. A prospective study found that Th2 cells were high during asthma exacerbation and returned to baseline levels (similar to those of stable asthma patients) after aggressive treatment, suggesting that Th2 cells may be a biomarker of impending exacerbation in asthma patients [106]. Pediatric severe asthma with fungal sensitization resulted in an increase in the number of IL-33-mediated ILC2s, Th2 cells, and steroid-resistant AHR [107]. Recently, it has been found that human umbilical cord blood-derived mesenchymal stem cells can also reduce lung type 2 (Th2 and ILC2s) inflammation [108]. Glucocorticoid is an effective drug for the treatment of asthma [109]. One study has shown that IL-13$^+$ILC2s are more resistant to this therapy in humans than Th2 cells and are closely related to asthma control status [109]. Interestingly, retinoic acid stimulates human ILC2s to secrete IL-10, and this cell population is named ILCregs, which inhibit the activation of CD4$^+$T cells and ILC2s [110].

However, the number of ILC2s was only found to be statistically significant in the acute exacerbation state versus the stable state, and not in the acute exacerbation phase versus after treatment in one clinical study [106]. In this study, the absolute number or percentage of Th2 cells in CD4$^+$T was statistically significant in the stable state, in the acute exacerbation state, and after treatment, suggesting that Th2 cells can be used as a biomarker for acute exacerbations of asthma [106]. The inconsistency between clinical findings and basic studies regarding the role of ILC2s in asthma may be explained by the insufficient sample size of the clinical study, which means that larger longitudinal prospective studies are needed.

5.4. Pulmonary Fibrosis. Pulmonary fibrosis is the end-stage change in a large group of lung diseases characterized by damaged alveolar structure, the massive proliferation of fibroblasts, and deposition of extracellular matrix [111], which means that normal alveolar tissue is damaged and then abnormally repaired resulting in structural abnormalities (scar formation). Basic research confirmed that IL-13 is an important cytokine for epithelial mesenchymal transition (EMT) to promote pulmonary fibrosis [95]. Therefore, dexamethasone or anti-IL-13 can delay the progress of pulmonary fibrosis by preventing the progress of EMT[95]. In the lungs of WT mice, the frequency of IL-13$^+$ILC2s peaked on day 7, and the expression of such cells was approximately five times higher than IL-13$^+$CD4$^+$T cells [112]. This study in a pulmonary fibrosis mice model found that ILC2s

secreted IL-13 in an IL-25-dependent manner, which was independent of the antigen-specific immune responses mediated by CD4$^+$T cells [112]. Areg produced by IL-33-activated-Th2 cells guides eosinophils to develop airway fibrosis both in mice and human [113, 114], and human lung ILC2s also produce Areg [115], which as a driver of tissue fibrosis [116].

5.5. Chronic Obstructive Pulmonary Disease (COPD). COPD is an obstructive and progressive airway disease [117], which is characterized by severe chronic airway epithelial inflammation, leading to airway remodeling [118]. In COPD experimental model mice, T/B lymphocytes and ILC2s play a significant role in airway collagen deposition and fibrosis, but do not affect inflammation [119]. The consensus that cigarette smoking is a critical factor to induce and aggravate COPD has been confirmed in humans [120]. Reducing the number of CD3$^+$CD4$^+$T cells and regulating Th1/Th2 function can inhibit the progression of the COPD [120]. The increasing number of ILC2s during viral infection leads to the enhancement of inflammatory damage and, in some cases, the differentiation of ILC2s to pro-inflammatory ILC1s, resulting in acute exacerbation of COPD (AECOPD) [121, 122]. The proportion of Th2 and ILC2s was significantly increased in the peripheral blood of AECOPD patients [123]. In addition, ILC2s have the ability to mediate Th2 type adaptive immune responses in AECOPD by promoting Th2 cell differentiation through Notch-GATA3 signal pathway [123].

5.6. Lung Cancer. Lung cancer is one of the most lethal cancers in the world [124]. IL-33-driven activation of ILC2s inhibits IFN-γ production by natural killer cells, but not by CD4$^+$ and CD8$^+$ T cells, thereby suppressing natural killer cell-mediated intrinsic antitumor immunity and leading to increased cancer lung metastasis and mortality [125]. ILC2s promote lung metastasis of triple-negative breast cancer in a mouse tumor model [11]. They activate myeloid-derived suppressor cells by secreting IL-13, which may reduce the expansion of Tregs in the lungs of tumor-bearing mice, while promoting the proliferation of CD4$^+$T cells and CD8$^+$T cells [11]. IL-33 enhances T cell-mediated killing of tumor cells in primary and metastatic mouse lung tumors [126].

In lung cancer patients, low levels of stimulator of interferon genes (STING) are strongly associated with poor patient prognosis [127]. There was a positive correlation between STING cell levels and CD4$^+$/CD8$^+$T cell ratios and a negative correlation with Treg cell levels [127]. The low intratumoral T/Tregs ratio was associated with the early infiltration (3-6 months) of ILC2s in both primary and metastatic tumors, suggesting that Treg is involved in establishing lung immunosuppression together with ILC2s [127]. ILC2s express PD-1 which limited their intratumoral accumulation, proliferation, and antitumor effector functions [128–130]. This can be reversed by combining interleukin-33-driven ILC2s activation with PD-1 blockade [128]. Another study of patients with nonsmall cell lung cancer found that Th2 was the most abundant Th subgroup in

cancer tissue and tumor tertiary lymphoid structure, followed by Treg cells, and Th1 which was the most frequently detected Th subgroup in patient-matched noncancer lung tissue [131]. In summary, the crosstalk between ILC2s and CD4$^+$T seems to promote the occurrence of human primary lung cancer and mouse primary and metastatic lung cancer and its role in human metastatic lung cancer required further research.

5.7. Vaccine Efficacy. Vaccines are biological products made from various types of pathogenic microorganisms for immunization [132]. Vaccination induces a strong immune response to specific antigens, to prevent related diseases [132]. IL-25 and IL-33 cytokines, which regulate the activation and function of ILC2s, can differentially regulate the ILC spectrum at the vaccination site in a vaccine pathway dependent manner [133]. IL-25-binding protein can affect the quality and affinity of T cell immunity by affecting the level of IL-4/IL-13 at the vaccination site. The quality of vaccine specific T cell immunity can be improved by intramuscular injection [133]. Aluminum hydroxide salt has been added to inactivated vaccines as a safe and effective adjuvant to enhance vaccination efficacy [134].

It was found that IL-33 secretion induced by epithelial cells necroptosis initiates APC- and ILC2-mediated T cell activation, which facilitated alum-enhanced Ag-specific IgA antibody production [134]. IL-33-activated ILC2s may enhance vaccine efficacy in a Th2 cytokine-dependent manner by enhancing mucosal humoral immunity, especially IgA response [135]. Their role in establishing extensive protective and lasting humoral mucosal immunity against influenza suggests that it is helpful to develop a universal vaccine against a variety of influenza viruses [135]. The role of crosstalk between ILC2s and CD4$^+$T in human vaccines is still lacking and urgently needs to be further studied.

6. Conclusions

CD4$^+$T cells are the command center of the adaptive immune system, also known as the "helper" of the immune system, and ILC2s are important innate lymphoid cells that serve as a bridge between innate and adaptive immunity. As summarized in Figure 2, there is accumulating evidence suggesting that ILC2s and CD4$^+$T cells interact in various ways, especially Th2 cells which seem to mutually promote each other's activation, proliferation, and function. Similar to the biological role of Th2 cells, ILC2s are involved in the defense against pulmonary parasitosis, the exacerbation of RSV infection, the aggravation of airway hyperresponsiveness during allergic diseases, the induction of lung injury, the acute exacerbation of COPD, the increase of cancer lung metastasis and mortality, and the improvement of vaccine efficacy, as summarized in Figure 3. Importantly, future studies should focus on elucidating the unique aspects of these interactions between ILC2s and their adaptive Th2 counterparts, especially in human, which will be particularly important for developing novel therapeutic strategies to specifically targeting type 2 immunity in human disease.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Authors' Contributions

L.-L.M. designed the concept of the project and wrote the manuscript. All authors reviewed and approved the manuscript.

Acknowledgments

References

[1] Y. Akama, N. Satoh-Takayama, E. Kawamoto et al., "The role of innate lymphoid cells in the regulation of immune homeostasis in sepsis-mediated lung inflammation," *Diagnostics (Basel)*, vol. 10, no. 10, p. 808, 2020.

[2] L. Qian, S. Bajana, C. Georgescu et al., "Suppression of ILC2 differentiation from committed T cell precursors by E protein transcription factors," *The Journal of Experimental Medicine*, vol. 216, no. 4, pp. 884–899, 2019.

[3] V. Peng, C. Georgescu, A. Bakowska et al., "E proteins orchestrate dynamic transcriptional cascades implicated in the suppression of the differentiation of group 2 innate lymphoid cells," *The Journal of Biological Chemistry*, vol. 295, no. 44, pp. 14866–14877, 2020.

[4] S. B. Shin, B. C. Lo, M. Ghaedi et al., "Abortive γδTCR rearrangements suggest ILC2s are derived from T-cell precursors," *Blood Advances*, vol. 4, no. 21, pp. 5362–5372, 2020.

[5] M. Messing, S. C. Jan-Abu, and K. McNagny, "Group 2 innate lymphoid cells: central players in a recurring theme of repair and regeneration," *International Journal of Molecular Sciences*, vol. 21, no. 4, p. 1350, 2020.

[6] M. L. Robinette, J. K. Bando, W. Song, T. K. Ulland, S. Gilfillan, and M. Colonna, "IL-15 sustains IL-7R-independent ILC2 and ILC3 development," *Nature Communications*, vol. 8, no. 1, p. 14601, 2017.

[7] C. E. Martin, D. S. Spasova, K. Frimpong-Boateng et al., "Interleukin-7 availability is maintained by a hematopoietic cytokine sink comprising innate lymphoid cells and T cells," *Immunity*, vol. 47, no. 1, pp. 171–182.e4, 2017.

[8] V. Soumelis, P. A. Reche, H. Kanzler et al., "Human epithelial cells trigger dendritic cell-mediated allergic inflammation by producing TSLP," *Nature Immunology*, vol. 3, no. 7, pp. 673–680, 2002.

[9] K. Tatsuno, T. Fujiyama, H. Yamaguchi, M. Waki, and Y. Tokura, "TSLP directly interacts with skin-homing Th2 cells highly expressing its receptor to enhance IL-4 production in atopic dermatitis," *The Journal of Investigative Dermatology*, vol. 135, no. 12, pp. 3017–3024, 2015.

[10] T. Hoyler, C. S. Klose, A. Souabni et al., "The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells," *Immunity*, vol. 37, no. 4, pp. 634–648, 2012.

[11] D. N. Kasal, Z. Liang, M. K. Hollinger et al., "A Gata3 enhancer necessary for ILC2 development and function," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 118, no. 32, 2021.

[12] D. Paclik, C. Stehle, A. Lahmann, A. Hutloff, and C. Romagnani, "ICOS regulates the pool of group 2 innate lymphoid cells under homeostatic and inflammatory conditions in mice," *European Journal of Immunology*, vol. 45, no. 10, pp. 2766–2772, 2015.

[13] A. C. Richard, C. Tan, E. T. Hawley et al., "The TNF-family ligand TL1A and its receptor DR3 promote T cell-mediated allergic immunopathology by enhancing differentiation and pathogenicity of IL-9-producing T cells," *Journal of Immunology*, vol. 194, no. 8, pp. 3567–3582, 2015.

[14] R. K. Singh, W. V. Perks, J. P. Twohig et al., "Death receptor 3 regulates distinct pathological attributes of acute versus chronic murine allergic lung inflammation," *Cellular Immunology*, vol. 320, pp. 62–70, 2017.

[15] F. Kudo, M. Ikutani, M. Iseki, and S. Takaki, "Cyclosporin A indirectly attenuates activation of group 2 innate lymphoid cells in papain-induced lung inflammation," *Cellular Immunology*, vol. 323, pp. 33–40, 2018.

[16] L. Haim-Vilmovsky, J. Henriksson, J. A. Walker et al., "Mapping Rora expression in resting and activated CD4+ T cells," *PLoS One*, vol. 16, no. 5, article e0251233, 2021.

[17] S. Y. Qu, X. Y. Ti, J. Zhang, and C. G. Wu, "Disruption of the notch pathway aggravates airway inflammation by inhibiting regulatory T cell differentiation via regulation of plasmacytoid dendritic cells," *Scandinavian Journal of Immunology*, vol. 91, no. 5, article e12865, 2020.

[18] N. Krishnamoorthy, P. R. Burkett, J. Dalli et al., "Cutting edge: maresin-1 engages regulatory T cells to limit type 2 innate lymphoid cell activation and promote resolution of lung inflammation," *Journal of Immunology*, vol. 194, no. 3, pp. 863–867, 2015.

[19] G. Ercolano, T. Wyss, B. Salomé, P. Romero, S. Trabanelli, and C. Jandus, "Distinct and shared gene expression for human innate versus adaptive helper lymphoid cells," *Journal of Leukocyte Biology*, vol. 108, no. 2, pp. 723–737, 2020.

[20] Y. R. Yu, E. G. O'Koren, D. F. Hotten et al., "A protocol for the comprehensive flow cytometric analysis of immune cells in normal and inflamed murine non-lymphoid tissues," *PLoS One*, vol. 11, no. 3, article e0150606, 2016.

[21] L. A. Monticelli, G. F. Sonnenberg, M. C. Abt et al., "Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus," *Nature Immunology*, vol. 12, no. 11, pp. 1045–1054, 2011.

[22] G. Gasteiger, X. Fan, S. Dikiy, S. Y. Lee, and A. Y. Rudensky, "Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs," *Science*, vol. 350, no. 6263, pp. 981–985, 2015.

[23] J. Qiu, J. Zhang, Y. Ji et al., "Tissue signals imprint Aiolos expression in ILC2s to modulate type 2 immunity," *Mucosal Immunology*, vol. 14, no. 6, pp. 1306–1322, 2021.

[24] K. Zhang, X. Xu, M. A. Pasha et al., "Cutting edge: notch signaling promotes the plasticity of group-2 innate lymphoid cells," *Journal of Immunology*, vol. 198, no. 5, pp. 1798–1803, 2017.

[25] Y. Huang, L. Guo, J. Qiu et al., "IL-25-responsive, lineage-negative KLRG1$^{\mathrm{hi}}$ cells are multipotential 'inflammatory' type 2 innate lymphoid cells," *Nature Immunology*, vol. 16, no. 2, pp. 161–169, 2015.

[26] R. N. Germain and Y. Huang, "ILC2s - resident lymphocytes pre-adapted to a specific tissue or migratory effectors that adapt to where they move?," *Current Opinion in Immunology*, vol. 56, pp. 76–81, 2019.

[27] Y. Huang, K. Mao, X. Chen et al., "S1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense," *Science*, vol. 359, no. 6371, pp. 114–119, 2018.

[28] M. R. Karta, P. S. Rosenthal, A. Beppu et al., "β_2 integrins rather than β_1 integrins mediate _Alternaria_ -induced group 2 innate lymphoid cell trafficking to the lung," *The Journal of Allergy and Clinical Immunology*, vol. 141, no. 1, pp. 329–338.e12, 2018.

[29] C. R. Seehus, A. Kadavallore, B. Torre et al., "Alternative activation generates IL-10 producing type 2 innate lymphoid cells," *Nature Communications*, vol. 8, no. 1, p. 1900, 2017.

[30] M. Zhang, J. L. Duffen, K. H. Nocka, and M. T. Kasaian, "IL-13 controls IL-33 activity through modulation of ST2," *Journal of Immunology*, vol. 207, no. 12, pp. 3070–3080, 2021.

[31] L. B. Roberts, C. Schnoeller, R. Berkachy et al., "Acetylcholine production by group 2 innate lymphoid cells promotes mucosal immunity to helminths," *Sci Immunol*, vol. 6, no. 57, 2021.

[32] C. Pelaia, G. Pelaia, F. Longhini et al., "Monoclonal antibodies targeting alarmins: a new perspective for biological therapies of severe asthma," *Biomedicine*, vol. 9, no. 9, p. 1108, 2021.

[33] M. J. Schuijs and T. Y. F. Halim, "Group 2 innate lymphocytes at the interface between innate and adaptive immunity [J]," *Annals of the New York Academy of Sciences*, vol. 1417, no. 1, pp. 87–103, 2018.

[34] T. Cai, J. Qiu, Y. Ji et al., "IL-17-producing ST2+ group 2 innate lymphoid cells play a pathogenic role in lung inflammation," *The Journal of Allergy and Clinical Immunology*, vol. 143, no. 1, pp. 229–244.e9, 2019.

[35] S. J. Lund, A. Portillo, K. Cavagnero et al., "Leukotriene C4 potentiates IL-33-induced group 2 innate lymphoid cell activation and lung inflammation," *Journal of Immunology*, vol. 199, no. 3, pp. 1096–1104, 2017.

[36] H. Maazi, N. Patel, I. Sankaranarayanan et al., "ICOS:ICOS-ligand interaction is required for type 2 innate lymphoid cell function, homeostasis, and induction of airway hyperreactivity," *Immunity*, vol. 42, no. 3, pp. 538–551, 2015.

[37] J. von Moltke, C. E. O'Leary, N. A. Barrett, Y. Kanaoka, K. F. Austen, and R. M. Locksley, "Leukotrienes provide an NFAT-dependent signal that synergizes with IL-33 to activate ILC2s," *The Journal of Experimental Medicine*, vol. 214, no. 1, pp. 27–37, 2017.

[38] J. von Moltke, C. E. O'Leary, N. A. Barrett, Y. Kanaoka, K. F. Austen, and R. M. Locksley, "MicroRNA-155 is a critical regulator of type 2 innate lymphoid cells and IL-33 signaling in experimental models of allergic airway inflammation," *The Journal of Allergy and Clinical Immunology*, vol. 139, no. 3, pp. 1007–1016.e9, 2017.

[39] L. A. Monticelli, M. D. Buck, A. L. Flamar et al., "Arginase 1 is an innate lymphoid-cell-intrinsic metabolic checkpoint controlling type 2 inflammation," *Nature Immunology*, vol. 17, no. 6, pp. 656–665, 2016.

[40] S. Taylor, Y. Huang, G. Mallett et al., "PD-1 regulates KLRG1 + group 2 innate lymphoid cells," *The Journal of Experimental Medicine*, vol. 214, no. 6, pp. 1663–1678, 2017.

[41] L. She, H. H. Alanazi, L. Yan et al., "Sensing and signaling of immunogenic extracellular RNAs restrain group 2 innate lymphoid cell-driven acute lung inflammation and airway hyperresponsiveness," *PLoS One*, vol. 15, no. 7, article e0236744, 2020.

[42] J. M. Inclan-Rico, J. J. Ponessa, N. Valero-Pacheco et al., "Basophils prime group 2 innate lymphoid cells for neuropeptide-mediated inhibition," *Nature Immunology*, vol. 21, no. 10, pp. 1181–1193, 2020.

[43] C. Wang, Z. B. Xu, Y. Q. Peng et al., "Sex differences in group 2 innate lymphoid cell-dominant allergic airway inflammation," *Molecular Immunology*, vol. 128, pp. 89–97, 2020.

[44] A. Wallrapp, P. R. Burkett, S. J. Riesenfeld et al., "Calcitonin gene-related peptide negatively regulates alarmin-driven type 2 innate lymphoid cell responses," *Immunity*, vol. 51, no. 4, pp. 709–723.e6, 2019.

[45] H. Nagashima, T. Mahlakõiv, H. Y. Shih et al., "Neuropeptide CGRP limits group 2 innate lymphoid cell responses and constrains type 2 inflammation," *Immunity*, vol. 51, no. 4, pp. 682–695.e6, 2019.

[46] Y. Zhou, W. Wang, C. Zhao et al., "Prostaglandin E2 inhibits group 2 innate lymphoid cell activation and allergic airway inflammation through E-prostanoid 4-cyclic adenosine monophosphate signaling," *Frontiers in Immunology*, vol. 9, p. 501, 2018.

[47] D. Califano, Y. Furuya, S. Roberts, D. Avram, A. N. J. McKenzie, and D. W. Metzger, "IFN-γ increases susceptibility to influenza A infection through suppression of group II innate lymphoid cells," *Mucosal Immunology*, vol. 11, no. 1, pp. 209–219, 2018.

[48] M. J. Schuijs, H. Hammad, and B. N. Lambrecht, "Professional and 'amateur' antigen-presenting cells in type 2 immunity," *Trends in Immunology*, vol. 40, no. 1, pp. 22–34, 2019.

[49] S. Saluzzo, A. D. Gorki, B. M. J. Rana et al., "First-breath-induced type 2 pathways shape the lung immune environment," *Cell Reports*, vol. 18, no. 8, pp. 1893–1905, 2017.

[50] L. Mi, S. Zhu, J. Cai, S. Xu, Z. Xue, and H. Lu, "Tissue-resident type 2 innate lymphoid cells arrest alveolarization in bronchopulmonary dysplasia," *Journal of Immunology Research*, vol. 2020, 2020.

[51] B. W. S. Li, R. Stadhouders, M. J. W. de Bruijn et al., "Group 2 innate lymphoid cells exhibit a dynamic phenotype in allergic airway inflammation," *Frontiers in Immunology*, vol. 8, p. 1684, 2017.

[52] F. Karagiannis, S. K. Masouleh, K. Wunderling et al., "Lipid-droplet formation drives pathogenic group 2 innate lymphoid cells in airway inflammation," *Immunity*, vol. 52, no. 5, p. 885, 2020.

[53] G. Martins Costa Gomes, P. de Gouveia Belinelo, M. R. Starkey et al., "Cord blood group 2 innate lymphoid cells are associated with lung function at 6 weeks of age," *Clin Transl Immunology*, vol. 10, no. 7, article e1296, 2021.

[54] S. M. Bal, J. H. Bernink, M. Nagasawa et al., "IL-1β, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs," *Nature Immunology*, vol. 17, no. 6, pp. 636–645, 2016.

[55] C. A. Christianson, N. P. Goplen, I. Zafar et al., "Persistence of asthma requires multiple feedback circuits involving type 2 innate lymphoid cells and IL-33," *The Journal of Allergy and Clinical Immunology*, vol. 136, no. 1, pp. 59–68.e14, 2015.

[56] E. D. Gordon, L. J. Simpson, C. L. Rios et al., "Alternative splicing of interleukin-33 and type 2 inflammation in asthma," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 31, pp. 8765–8770, 2016.

[57] S. G. Smith, R. Chen, M. Kjarsgaard et al., "Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia," *The Journal of Allergy and Clinical Immunology*, vol. 137, no. 1, pp. 75–86.e8, 2016.

[58] S. Liu, K. Sirohi, M. Verma et al., "Optimal identification of human conventional and nonconventional (CRTH2– IL7Rα–) ILC2s using additional surface markers," *The Journal of Allergy and Clinical Immunology*, vol. 146, no. 2, pp. 390–405, 2020.

[59] B. P. Hurrell, D. G. Helou, P. Shafiei-Jahani et al., "Cannabinoid receptor 2 engagement promotes group 2 innate lymphoid cell expansion and enhances airway hyperreactivity," *The Journal of Allergy and Clinical Immunology*, 2021.

[60] Q. P. Nguyen, T. Z. Deng, D. A. Witherden, and A. W. Goldrath, "Origins of CD4(+) circulating and tissue-resident memory T-cells," *Immunology*, vol. 157, no. 1, pp. 3–12, 2019.

[61] C. Cui, J. Wang, E. Fagerberg et al., "Neoantigen-driven B cell and CD4 T follicular helper cell collaboration promotes anti-tumor CD8 T cell responses," *Cell*, vol. 184, no. 25, pp. 6101–6118.e13, 2021.

[62] G. Izumi, H. Nakano, K. Nakano et al., "CD11b$^+$ lung dendritic cells at different stages of maturation induce Th17 or Th2 differentiation," *Nature Communications*, vol. 12, no. 1, p. 5029, 2021.

[63] I. M. de Kleer, M. Kool, M. J. de Bruijn et al., "Perinatal activation of the interleukin-33 pathway promotes type 2 immunity in the developing lung," *Immunity*, vol. 45, no. 6, pp. 1285–1298, 2016.

[64] W. Wang, J. A. Cohen, A. Wallrapp et al., "Age-related dopaminergic innervation augments T helper 2-type allergic inflammation in the postnatal lung," *Immunity*, vol. 51, no. 6, pp. 1102–1118.e7, 2019.

[65] H. Bachus, K. Kaur, A. M. Papillion et al., "Impaired tumor-necrosis-factor-α-driven dendritic cell activation limits lipopolysaccharide-induced protection from allergic inflammation in infants," *Immunity*, vol. 50, no. 1, pp. 225–240.e4, 2019.

[66] R. Ouchi, T. Kawano, H. Yoshida et al., "Maternal separation as early-life stress causes enhanced allergic airway responses by inhibiting respiratory tolerance in mice," *The Tohoku Journal of Experimental Medicine*, vol. 246, no. 3, pp. 155–165, 2018.

[67] A. C. C. Gouveia, F. G. Braga, M. Mota et al., "Enhanced expression of PD-L1 and IFN-γ on dendritic cells is associated with BCG-induced Th2 inhibition," *Cytokine*, vol. 99, pp. 163–172, 2017.

[68] Y. Suzuki, T. Hayashi, R. Yokoyama et al., "Fasting impairs type 2 helper T cell infiltration in the lung of an eosinophilic asthma mouse model," *FEBS Open Bio*, vol. 11, no. 9, pp. 2619–2630, 2021.

[69] L. Bergantini, M. d'Alessandro, P. Cameli et al., "Follicular T helper and Breg cell balance in severe allergic asthma before

and after omalizumab therapy," *Molecular Diagnosis & Therapy*, vol. 25, no. 5, pp. 593–605, 2021.

[70] N. Deng, X. Guo, Q. Chen et al., "Anti-F4/80 treatment attenuates Th2 cell responses: implications for the role of lung interstitial macrophages in the asthmatic mice," *International Immunopharmacology*, vol. 99, article ???, 2021.

[71] Y. Wu, Q. Yu, M. Zhang et al., "Hemin-primed dendritic cells suppress allergic airway inflammation through releasing extracellular vesicles [J]," *Journal of Leukocyte Biology*, 2022.

[72] H. Zhao, F. Dong, Y. Li et al., "Inhibiting ATG5 mediated autophagy to regulate endoplasmic reticulum stress and CD4$^+$ T lymphocyte differentiation: mechanisms of acupuncture's effects on asthma," *Biomedicine & Pharmacotherapy*, vol. 142, article ???, 2021.

[73] Z. Yang, Z. Li, Z. Guo et al., "Antitumor effect of fluoxetine on chronic stress-promoted lung cancer growth via suppressing kynurenine pathway and enhancing cellular immunity," *Frontiers in Pharmacology*, vol. 12, article 685898, 2021.

[74] H. A. A. Oyamada, M. Cafasso, C. M. Vollmer et al., "Major depressive disorder enhances Th2 and Th17 cytokines in patients suffering from allergic rhinitis and asthma," *International Archives of Allergy and Immunology*, vol. 182, no. 12, pp. 1155–1168, 2021.

[75] C. J. Oliphant, Y. Y. Hwang, J. A. Walker et al., "MHCII-mediated dialog between group 2 innate lymphoid cells and CD4+ T cells potentiates type 2 immunity and promotes parasitic helminth expulsion," *Immunity*, vol. 41, no. 2, pp. 283–295, 2014.

[76] X. Han, S. Bai, Y. Cui, W. Zhu, N. Zhao, and B. Liu, "Essential role of CD4+ T cells for the activation of group 2 innate lymphoid cells during respiratory syncytial virus infection in mice," *Immunotherapy*, vol. 11, no. 15, pp. 1303–1313, 2019.

[77] T. Y. Halim, C. A. Steer, L. Mathä et al., "Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation," *Immunity*, vol. 40, no. 3, pp. 425–435, 2014.

[78] T. Y. Halim, Y. Y. Hwang, S. T. Scanlon et al., "Group 2 innate lymphoid cells license dendritic cells to potentiate memory TH2 cell responses," *Nature Immunology*, vol. 17, no. 1, pp. 57–64, 2016.

[79] J. Wan, L. Huang, X. Ji et al., "HMGB1-induced ILC2s activate dendritic cells by producing IL-9 in asthmatic mouse model," *Cellular Immunology*, vol. 352, article 104085, 2020.

[80] F. Roan, K. Obata-Ninomiya, and S. F. Ziegler, "Epithelial cell-derived cytokines: more than just signaling the alarm [J]," *The Journal of Clinical Investigation*, vol. 129, no. 4, pp. 1441–1451, 2019.

[81] E. B. Brandt, P. E. Bolcas, B. P. Ruff, and G. K. Khurana Hershey, "IL33 contributes to diesel pollution-mediated increase in experimental asthma severity," *Allergy*, vol. 75, no. 9, pp. 2254–2266, 2020.

[82] C. Symowski and D. Voehringer, "Th2 cell-derived IL-4/IL-13 promote ILC2 accumulation in the lung by ILC2-intrinsic STAT6 signaling in mice," *European Journal of Immunology*, vol. 49, no. 9, pp. 1421–1432, 2019.

[83] C. Schwartz, A. R. Khan, A. Floudas et al., "ILC2s regulate adaptive Th2 cell functions via PD-L1 checkpoint control," *The Journal of Experimental Medicine*, vol. 214, no. 9, pp. 2507–2521, 2017.

[84] J. Wu, Y. Cui, W. Zhu, S. Bai, N. Zhao, and B. Liu, "Critical role of OX40/OX40L in ILC2-mediated activation of CD4$^+$T cells during respiratory syncytial virus infection in mice," *International Immunopharmacology*, vol. 76, article ???, 2019.

[85] M. H. Shamji, J. N. Temblay, W. Cheng et al., "Antiapoptotic serine protease inhibitors contribute to survival of allergenic T$_H$2 cells," *The Journal of Allergy and Clinical Immunology*, vol. 142, no. 2, pp. 569–581.e5, 2018.

[86] D. Rigas, G. Lewis, J. L. Aron et al., "Type 2 innate lymphoid cell suppression by regulatory T cells attenuates airway hyperreactivity and requires inducible T-cell costimulator-inducible T-cell costimulator ligand interaction," *The Journal of Allergy and Clinical Immunology*, vol. 139, no. 5, pp. 1468–1477.e2, 2017.

[87] S. I. Sersar, H. A. Elnahas, A. B. Saleh, S. A. Moussa, and W. A. Ghafar, "Pulmonary parasitosis: applied clinical and therapeutic issues," *Heart, Lung & Circulation*, vol. 15, no. 1, pp. 24–29, 2006.

[88] A. B. Molofsky, F. Van Gool, H. E. Liang et al., "Interleukin-33 and interferon-γ counter-regulate group 2 innate lymphoid cell activation during immune perturbation," *Immunity*, vol. 43, no. 1, pp. 161–174, 2015.

[89] M. W. Dahlgren, S. W. Jones, K. M. Cautivo et al., "Adventitial stromal cells define group 2 innate lymphoid cell tissue niches," *Immunity*, vol. 50, no. 3, pp. 707–722.e6, 2019.

[90] T. Bouchery, R. Kyle, M. Camberis et al., "ILC2s and T cells cooperate to ensure maintenance of M2 macrophages for lung immunity against hookworms," *Nature Communications*, vol. 6, no. 1, p. 6970, 2015.

[91] T. Zohar, J. C. Hsiao, N. Mehta et al., "Upper and lower respiratory tract correlates of protection against respiratory syncytial virus following vaccination of nonhuman primates [J]," *Cell Host & Microbe*, 2021.

[92] W. Fonseca, C. A. Malinczak, C. F. Schuler et al., "Uric acid pathway activation during respiratory virus infection promotes Th2 immune response via innate cytokine production and ILC2 accumulation," *Mucosal Immunology*, vol. 13, no. 4, pp. 691–701, 2020.

[93] L. Zhang, Y. Wan, L. Ma, K. Xu, and B. Cheng, "Inhibition of NF-kappaB/IL-33/ST2 axis ameliorates acute bronchiolitis induced by respiratory syncytial virus," *Journal of Immunology Research*, vol. 2021, 2021.

[94] D. J. Jackson, H. Makrinioti, B. M. Rana et al., "IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo," *American Journal of Respiratory and Critical Care Medicine*, vol. 190, no. 12, pp. 1373–1382, 2014.

[95] F. Zhang, L. Chen, Y. Zhou et al., "Dexamethasone prevents the Epstein-Barr virus induced epithelial-mesenchymal transition in A549 cells," *Journal of Medical Virology*, vol. 92, no. 12, pp. 3697–3708, 2020.

[96] M. J. Sun, Z. Teng, P. S. Fan, X. G. Chen, and Y. Liu, "Bridging micro/nano-platform and airway allergy intervention [J]," *Journal of Controlled Release*, vol. 341, pp. 364–382, 2022.

[97] L. Y. Drake, K. Iijima, and H. Kita, "Group 2 innate lymphoid cells and CD4+T cells cooperate to mediate type 2 immune response in mice," *Allergy*, vol. 69, no. 10, pp. 1300–1307, 2014.

[98] A. Klein Jan, R. G. K. Wolterink, Y. Levani et al., "Enforced expression of Gata3 in T cells and group 2 innate lymphoid

cells increases susceptibility to allergic airway inflammation in mice," *Journal of Immunology*, vol. 192, no. 4, pp. 1385–1394, 2014.

[99] B. W. S. Li, M. J. W. de Bruijn, M. Lukkes et al., "T cells and ILC2s are major effector cells in influenza-induced exacerbation of allergic airway inflammation in mice," *European Journal of Immunology*, vol. 49, no. 1, pp. 144–156, 2019.

[100] M. A. Ullah, C. T. Vicente, N. Collinson et al., "PAG1 limits allergen-induced type 2 inflammation in the murine lung," *Allergy*, vol. 75, no. 2, pp. 336–345, 2020.

[101] B. Liu, J. B. Lee, C. Y. Chen, G. K. K. Hershey, and Y. H. Wang, "Collaborative interactions between type 2 innate lymphoid cells and antigen-specific CD4+Th2 cells exacerbate murine allergic airway diseases with prominent eosinophilia," *Journal of Immunology*, vol. 194, no. 8, pp. 3583–3593, 2015.

[102] Y. Wu, W. Shi, H. Wang et al., "Anti-ST2 nanoparticle alleviates lung inflammation by targeting ILC2s-CD4(+)T response [J]," *International Journal of Nanomedicine*, vol. -Volume 15, pp. 9745–9758, 2020.

[103] J. Yang, I. R. Moral, C. van't Veer et al., "Complement factor C5 inhibition reduces type 2 responses without affecting group 2 innate lymphoid cells in a house dust mite induced murine asthma model," *Respiratory Research*, vol. 20, no. 1, p. 165, 2019.

[104] H. L. Mai, T. V. H. Nguyen, G. Bouchaud et al., "Targeting the interleukin-7 receptor alpha by an anti-CD127 monoclonal antibody improves allergic airway inflammation in mice," *Clinical and Experimental Allergy*, vol. 50, no. 7, pp. 824–834, 2020.

[105] L. Mascarell, S. Airouche, N. Berjont et al., "The regulatory dendritic cell marker C1q is a potent inhibitor of allergic inflammation," *Mucosal Immunology*, vol. 10, no. 3, pp. 695–704, 2017.

[106] N. Shrestha Palikhe, Y. Wu, E. Konrad et al., "Th2 cell markers in peripheral blood increase during an acute asthma exacerbation," *Allergy*, vol. 76, no. 1, pp. 281–290, 2021.

[107] S. Castanhinha, R. Sherburn, S. Walker et al., "Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33," *The Journal of Allergy and Clinical Immunology*, vol. 136, no. 2, pp. 312–322.e7, 2015.

[108] J. W. Shin, S. Ryu, J. Ham et al., "Mesenchymal stem cells suppress severe asthma by directly regulating Th2 cells and type 2 innate lymphoid cells," *Molecules and Cells*, vol. 44, no. 8, pp. 580–590, 2021.

[109] Y. Jia, X. Fang, X. Zhu et al., "IL-13+ type 2 innate lymphoid cells correlate with asthma control status and treatment response," *American Journal of Respiratory Cell and Molecular Biology*, vol. 55, no. 5, pp. 675–683, 2016.

[110] H. Morita, T. Kubo, B. Rückert et al., "Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid," *The Journal of Allergy and Clinical Immunology*, vol. 143, no. 6, pp. 2190–2201.e9, 2019.

[111] L. Chen, J. Hou, X. Fu, X. Chen, J. Wu, and X. Han, "tPA promotes the proliferation of lung fibroblasts and activates the Wnt/β-catenin signaling pathway in idiopathic pulmonary fibrosis," *Cell Cycle*, vol. 18, no. 22, pp. 3137–3146, 2019.

[112] E. Hams, M. E. Armstrong, J. L. Barlow et al., "IL-25 and type 2 innate lymphoid cells induce pulmonary fibrosis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 1, pp. 367–372, 2014.

[113] Y. Morimoto, K. Hirahara, M. Kiuchi et al., "Amphiregulin-producing pathogenic memory T helper 2 cells instruct eosinophils to secrete osteopontin and facilitate airway fibrosis," *Immunity*, vol. 49, no. 1, pp. 134–150.e6, 2018.

[114] K. Hirahara, A. Aoki, Y. Morimoto, M. Kiuchi, M. Okano, and T. Nakayama, "The immunopathology of lung fibrosis: amphiregulin-producing pathogenic memory T helper-2 cells control the airway fibrotic responses by inducing eosinophils to secrete osteopontin," *Seminars in Immunopathology*, vol. 41, no. 3, pp. 339–348, 2019.

[115] E. K. van der Ploeg, K. Golebski, M. van Nimwegen et al., "Steroid-resistant human inflammatory ILC2s are marked by CD45RO and elevated in type 2 respiratory diseases," *Sci Immunol*, vol. 6, no. 55, 2021.

[116] L. Ding, T. Liu, Z. Wu et al., "Bone marrow CD11c+ cell–derived amphiregulin promotes pulmonary fibrosis," *Journal of Immunology*, vol. 197, no. 1, pp. 303–312, 2016.

[117] M. G. Alharbi, H. S. Kalra, M. Suri et al., "Pulmonary rehabilitation in management of chronic obstructive pulmonary disease," *Cureus*, vol. 13, no. 10, article e18414, 2021.

[118] H. Zhang, B. Liu, S. Jiang et al., "Baicalin ameliorates cigarette smoke-induced airway inflammation in rats by modulating HDAC2/NF-κB/PAI-1 signalling," *Pulmonary Pharmacology & Therapeutics*, vol. 70, article 102061, 2021.

[119] C. Donovan, M. R. Starkey, R. Y. Kim et al., "Roles for T/B lymphocytes and ILC2s in experimental chronic obstructive pulmonary disease," *Journal of Leukocyte Biology*, vol. 105, no. 1, pp. 143–150, 2019.

[120] Z. Chen, Q. Yan, Z. Zhang et al., "Immunomodulatory effects of hydrolyzed seawater pearl tablet (HSPT) on Th1/Th2 functionality in a mice model of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke," *Evidence-based Complementary and Alternative Medicine*, vol. 2020, 2020.

[121] J. S. Silver, J. Kearley, A. M. Copenhaver et al., "Inflammatory triggers associated with exacerbations of COPD orchestrate plasticity of group 2 innate lymphoid cells in the lungs," *Nature Immunology*, vol. 17, no. 6, pp. 626–635, 2016.

[122] M. Jiang, H. Liu, Z. Li et al., "ILC2s induce adaptive Th2-type immunity in acute exacerbation of chronic obstructive pulmonary disease," *Mediators of Inflammation*, vol. 2019, 2019.

[123] M. Jiang, R. Cai, J. Wang et al., "ILC2 cells promote Th2 cell differentiation in AECOPD through activated notch-GATA3 signaling pathway," *Frontiers in Immunology*, vol. 12, article 685400, 2021.

[124] G. Zhang and Z. Yan, "A new definition of pyroptosis-related gene markers to predict the prognosis of lung adenocarcinoma," *BioMed Research International*, vol. 2021, 2021.

[125] M. J. Schuijs, S. Png, A. C. Richard et al., "ILC2-driven innate immune checkpoint mechanism antagonizes NK cell antimetastatic function in the lung," *Nature Immunology*, vol. 21, no. 9, pp. 998–1009, 2020.

[126] I. Saranchova, J. Han, H. Huang et al., "Discovery of a metastatic immune escape mechanism initiated by the loss of expression of the tumour biomarker interleukin-33," *Scientific Reports*, vol. 6, no. 1, p. ???, 2016.

[127] K. Domvri, S. Petanidis, P. Zarogoulidis et al., "Treg-dependent immunosuppression triggers effector T cell dysfunction via the STING/ILC2 axis," *Clinical Immunology*, vol. 222, article ???, 2021.

[128] N. Jacquelot, C. Seillet, M. Wang et al., "Blockade of the co-inhibitory molecule PD-1 unleashes ILC2-dependent antitumor immunity in melanoma," *Nature Immunology*, vol. 22, no. 7, pp. 851–864, 2021.

[129] N. Jacquelot and G. T. Belz, "Type 2 innate lymphoid cells: a novel actor in anti-melanoma immunity [J]," *Oncoimmunology*, vol. 10, no. 1, p. 1943168, 2021.

[130] E. Howard, B. P. Hurrell, D. G. Helou et al., "PD-1 blockade on tumor microenvironment-resident ILC2s promotes TNF-α production and restricts progression of metastatic melanoma," *Frontiers in Immunology*, vol. 12, article 733136, 2021.

[131] A. Frafjord, L. Buer, C. Hammarström et al., "The immune landscape of human primary lung tumors is Th2 skewed," *Frontiers in Immunology*, vol. 12, article 764596, 2021.

[132] Q. Li, Z. Li, N. Deng, F. Ding, Y. Li, and H. Cai, "Built-in adjuvants for use in vaccines," *European Journal of Medicinal Chemistry*, vol. 227, article 113917, 2022.

[133] Z. Li, R. J. Jackson, and C. Ranasinghe, "A hierarchical role of IL-25 in ILC development and function at the lung mucosae following viral-vector vaccination," *Vaccine X*, vol. 2, article 100035, 2019.

[134] E. Sasaki, H. Asanuma, H. Momose, K. Furuhata, T. Mizukami, and I. Hamaguchi, "Nasal alum-adjuvanted vaccine promotes IL-33 release from alveolar epithelial cells that elicits IgA production via type 2 immune responses," *PLoS Pathogens*, vol. 17, no. 8, article e1009890, 2021.

[135] C. M. Williams, S. Roy, D. Califano, A. N. J. McKenzie, D. W. Metzger, and Y. Furuya, "The interleukin-33-group 2 innate lymphoid cell axis represents a potential adjuvant target to increase the cross-protective efficacy of influenza vaccine," *Journal of Virology*, vol. 95, no. 22, article e0059821, 2021.