A crosstalk between type 2 innate lymphoid cells and alternative macrophages in lung development and lung diseases (Review)

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Abstract. Type 2 innate lymphoid cells (ILC2s) are important innate immune cells that are involved in type 2 inflammation, in both mice and humans. ILC2s are stimulated by factors, including interleukin (IL)-33 and IL-25, and activated ILC2s secrete several cytokines that mediate type 2 immunity by inducing profound changes in physiology, including activation of alternative (M2) macrophages. M2 macrophages possess immune modulatory, phagocytic, tissue repair and remodeling properties, and can regulate ILC2s under infection. The present review summarizes the role of ILC2s as innate cells and M2 macrophages as anti-inflammatory cells, and discusses current literature on their important biological significance. The present review also highlights how the crosstalk between ILC2s and M2 macrophages contributes to lung development, induces pulmonary parasitic expulsion, exacerbates pulmonary viral and fungal infections and allergic airway diseases, and promotes the development of lung diseases, such as pulmonary fibrosis, chronic obstructive pulmonary disease and carcinoma of the lungs.

Contents

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1. Introduction

Lung development initiates in utero and continues until infancy, and involves a complex process regulated by different types of cells, factors and mediators, such as macrophages, dendritic cells and lymphocytes (1). Abnormal lung development can be harmful to respiratory health, which may result in bronchopulmonary dysplasia, neonatal respiratory distress syndrome, asthma and chronic obstructive emphysema (2-4). Type 2 immune response is important for pulmonary development and several types of pulmonary diseases, such as asthma, lung infection and pulmonary fibrosis (5-7).

Interleukin (IL)-4, IL-5, IL-9 and IL-13 are important cytokines that play key roles in type 2 immunity, and are usually involved in allergic diseases or during helminthic parasitic infections (8,9). Th2 cells and certain myeloid cells are considered the primary source of these type 2 cytokines (10,11); however, recent studies have reported that a rare subpopulation of innate lymphocytes are the predominant source (12-14). Type 2 innate lymphoid cells (ILC2s), which were first discovered as non-T and B cells (15,16), play a defensive role in the initial stage of helminthic infestation (17), and are considered a major component of type 2 immunity in lungs (18,19).

Several types of cells, including eosinophils, mast cells, basophils and alternative (M2) macrophages, activated by IL-4 and IL-13 that are involved in type 2 immune response, also regulate the repair response following tissue injury (20). M2 macrophages initiate different responses to parasites, tissue remodeling, angiogenesis and allergic diseases (21-23). Therefore, it may be hypothesized that M2 macrophages can crosstalk with ILC2s during pulmonary development and in different pulmonary diseases.

2. ILC2s

ILCs are innate immune cells that regulate mucosal immune response (24). ILCs are important effector cells in the innate immune system (25). In addition to acting as first-line defense against pathogen invasion and infection, ILCs are also involved in lymphoid organ formation, tissue repair and mucosal homeostasis (26).

ILC2s are a subset of ILCs, and activation of these produce several Th2 cytokines, including IL-4, IL-5, IL-9

and IL-13, and/or dual-regulatory proteins, such as amphiregulin (AREG) (27). ILC2s depend on transcription factors, GATA binding protein 3 and retinoid acid receptor related orphan receptor α, for their development and function, but lack antigen-specific receptors (28,29). ILC2s are distributed throughout the body and are abundant on mucosal surfaces, such as the lungs, gastrointestinal tract and skin, in both humans and mice (30). ILC2s account for a major proportion in mouse pulmonary innate lymphocytes, and <3% of human lung innate lymphocytes (31,32).

Lung ILC2s are rapidly activated when exposed to epithelial-derived alarmin proteins and other inflammatory mediators, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) (33). A previous study demonstrated that IL-25 reactive lung ILC2s can change into IL-33 reactive lung ILC2s, both *in vivo* and *in vitro* (34). IL-33 and IL-25 both promote the enrichment of ILC2s in lung *in vivo*; however, only IL-33 can directly induce the migration of ILC2s *in vitro* (35). Similar effects of IL-33 are observed in skin (36), while TSLP and IL-25 exhibit relatively poor chemotaxis, although they can be detected at high concentrations in lungs (37,38).

Although ILC2s secrete IL-9, autocrine IL-9 maintains homeostasis of pulmonary ILC2s (37,38). IL-2 was the first cytokine reported to promote the secretion of IL-9 by ILC2s (39). IL-2 is also important for activating and culturing ILC2s *in vitro* (39,40). Another study demonstrated that IL-4 can increase IL-9 expression by stimulating ILC2s (41). Suppression of IL-9 production inhibits IL-33-induced eosinophilic airway inflammation, highlighting its role in effectively proliferating and activating ILC2s (42). In addition, the synergistic effects of TSLP and IL-33 markedly effect the production of IL-9 via ILC2s (37).

ILC2s express corresponding receptors, including suppression of tumorigenicity 2 (ST2), IL-25R (IL-17RB), TSLPR and AREG receptor, as well as toll-like receptors (TLRs) 2 and 4 (28,29,43-45). Upon activation, excluding Th2-type cytokines and/or AREG, ILC2s also secrete other factors, including granulocyte-macrophage colony stimulating factor (GM-CSF), IL-6 and IL-10 (46-48). In addition to stimulators, there are also inhibitors of ILC2s. For example, the neuropeptide calcitonin gene-related peptide and its receptor can inhibit the secretion and enrichment of pulmonary ILC2s and Th2 cytokines driven by alarmin, both *in vitro* and *in vivo* (49).

Elevated numbers of ILC2s in patients with asthma and chronic sinusitis suggest that ILC2s are detrimental to chronic inflammation (50). However, intrahepatic ILC2s can exacerbate fibrosis in liver diseases by secreting AREG (51). Thus, the roles of ILC2s vary in different tissues and diseases, and involve complex molecular mechanisms.

Recently, ILC2s have become the research focus in different tissue and organ diseases. It has been reported that intestinal helminthic infection induces activation of ILC2s, proliferation of IL-13 dependent goblet cells and increases mucin production at distal sites, including the lungs (52). In severe cases, increased mucus secretion via alveoli and the lungs inhibits lung metastasis (52). This suggests that the innate immunity of ILC2s is not only limited to certain tissues, but also influences and interacts with different organs. According to a previous study, aging influences innate immunity (53). ILC2s in elderly lungs are not uniform in transcription and function, and cannot produce cytokines during influenza infection and homeostasis *in vivo* (53). The transfer of ILC2s in the lungs of young mice strengthens the immunity of old mice to influenza infection (53). Notably, ILC2s in neonatal lungs involve distinct pro-inflammatory and tissue repair subgroups (54). Neonatal endogenous IL-33 stimulates ILC2s in the pulmonary, which may 'train' ILC2s for implantation into the lungs following birth, thus becoming resident cells that respond more effectively to future challenges (55). Thus, by secretion of a plethora of mediators, ILC2s play vital roles in inducing and supporting type 2 immune responses in lung tissues.

3. M2 macrophages

Macrophages, which act as myeloid cells, are among the first cells that respond to pathogens and tissue damage (56). They not only have innate immune function, which acts by phagocytizing and killing pathogens directly to exert innate immunity, but also initiate adaptive immunity by presenting pathogens to T lymphocytes (57,58). Tissue macrophages, which are important immune cells, are produced by yolk sac or fetal liver and their function is guided by resident tissues (59). Thus, it is important to study the macrophages that reside in the lung to understand the role of macrophages in lung diseases. There are two subtypes based on anatomical position of pulmonary resident macrophages, alveolar macrophages (AMs) and interstitial macrophages (60).

AMs, which are the most important resident macrophages in the lung, act as immune barriers in the alveoli against several pathogens of the respiratory tract (61). Alveolar macrophages are highly heterogeneous and exhibit unique phenotypes and functions in the complex microenvironment of the body (62). They are non-polarized under normal conditions (63). However, macrophages are induced and polarized into classical activation (M1) or alternate activation (M2) phenotypes under the stimulation of inflammation or in different immune development stages (64,65). These also play a role in producing different chemokines and cytokines in the local microenvironment (66).

M2 macrophages are predominantly induced by cytokines, including IL-4, IL-10 and IL-13, glucocorticoids and immune complexes TLRs (67). Similar to ILC2s, they can also induce typical Th2 cytokines to decrease inflammatory response by promoting angiogenesis, tissue repairing, remodeling and wound healing (68). In addition, excessive tissue repair and remodeling results in fibrosis, which can aggravate the condition (69). M2 macrophages highly express type I arginase encoding genes (arginase-1, Arg1) and mannose receptor (CD206), and thus the expression and activity of Arg1 and CD206 are used to identify M2 macrophages (70). Under the induction of memory Th2 cells, M2 macrophages, which are important immune effector cells, can scavenge pathogens, which is associated with Arg1 activity (71). M2 macrophages have a weak antigen-presenting capacity compared with M1 macrophages, and downregulate the immune response by secreting inhibitory cytokines, such as IL-10 and/or tumor growth factor β (TGF-β) (72). A different type of M2 macrophage exists in the tumor site, which can be induced by IL-10 and is affected by chemokines, including CCL2, M-CSF and vascular endothelial growth factor (58).

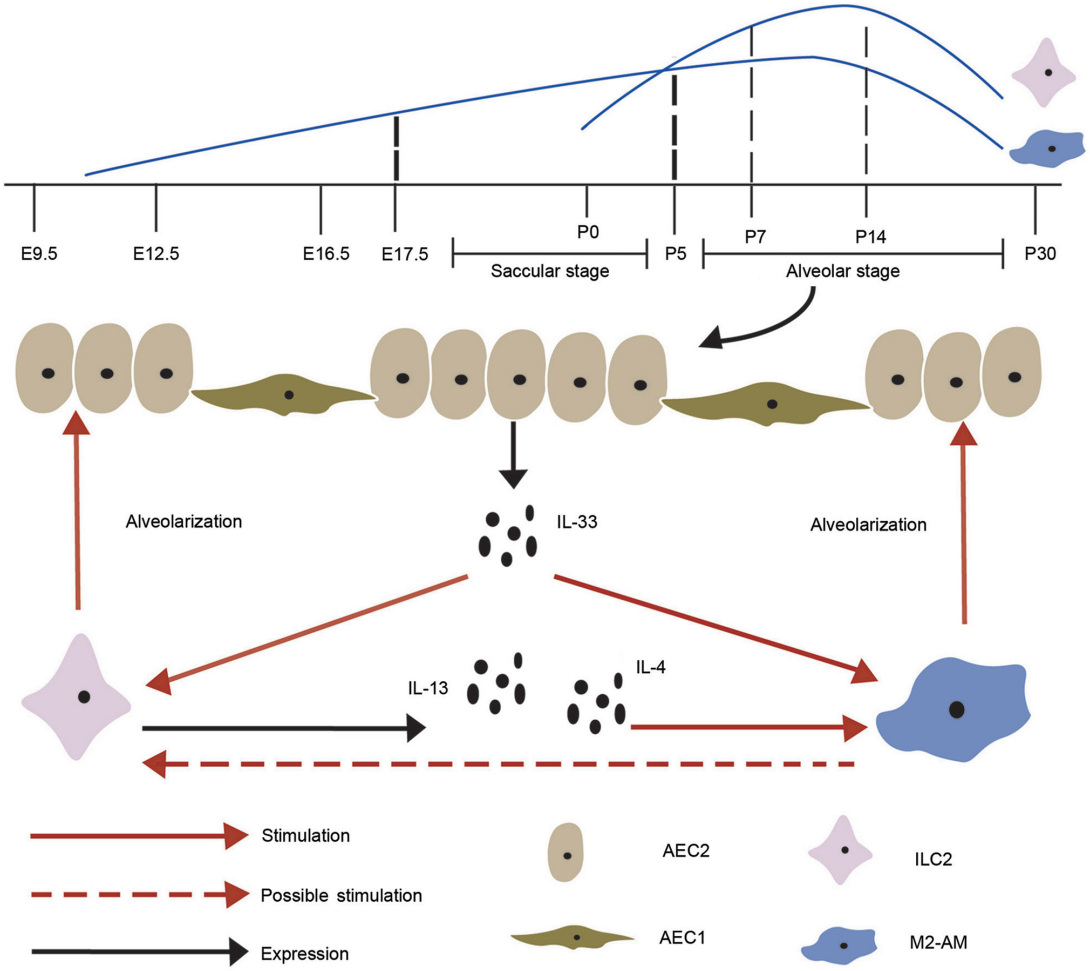

Figure 1. Quantitative changes of ILC2s and M2 macrophages in lung development and the effect of crosstalk on alveolarization. ILC2, type 2 innate lymphoid cell; M2-AM, alternative macrophage; IL, interleukin; AM, alveolar macrophage; AEC1, type 1 alveolar epithelial cell; AEC2, type 2 alveolar epithelial cell.

4. Crosstalk between ILC2s and M2 macrophages during lung development

The developmental process of lungs involves complex steps in humans/mice, and is subdivided into five stages, embryonic, pseudoglandular, canalicular, saccular and alveolar (73). Among these, the vesicle [Embryo day(E)16-E266/E17.5-Postnatal day (P)5] and alveolar (E252-2 years/P5-P30) stages are important as they affect the development and maturity of lungs (Fig. 1) (73). Macrophages first appear on day 10 of pregnancy and can be continuously detected during fetal lung development (74), which then increases with alveolarization (75,76). The perinatal period is a critical window for transferring and distributing congenital immune cells to all the tissues and organs during lung development (77). ILC2s, which are similar to tissue macrophages, also appear during pregnancy, but at a later stage, and most of the peripheral ILC2 pools are produced *de novo* following birth (77). Several studies have confirmed that rapid amplification and activation of ILC2s in pulmonary occur during the early postnatal period (78-80). Pulmonary resident ILC2s are minimal at birth, increase during alveolarization, reach peak at 7-14 days and subsequently decrease in adulthood, similar to AMs (76,81-83). Thus, the interactions between ILC2s and macrophages most likely occur during the vesicle and alveolar stages. Gradually, fewer ILC2s in lung tissues are replaced by newly generated ILC2s, but the expanded ILC2s during the early postnatal period account for the majority of adult lung ILC2s (77).

From the very start, the lung is exposed to the external environment (84). The microenvironment of the lung undergoes a notable change within a short period of time and requires rapid regulation to avoid inflammatory response caused by environmental stimulation (84). After being stimulated during labor, IL-33 rapidly increases and activates ILC2s in the fluid filled lung and begins to promote the formation of type 2 immune environment in pulmonary tissues (76). Type 2 immunity involves type 2 cytokines, eosinophilia, mucogenesis, IgE and M2 macrophages (85). The presence of AMs is consistent with that of IL-13-secreting ILC2s, which exhibit IL-13 dependent anti-inflammatory M2-type in the early stage of lung development (76). It has also been reported that IL-4 receptor α (IL-4R α), including IL-4 and IL-13, can promote AMs to polarize into M2 macrophages, suggesting that the crosstalk between ILC2s and M2 macrophages plays a role in regulating type 2 immunity (86,87). Another study demonstrated that the addition of ILC2s can make AMs express more M2 macrophages-related markers *in vitro* (88). Postnatal adaptation to breathing depends on pulmonary surfactant being synthesized and secreted by type 2 alveolar epithelial cells (AEC2) (89). Promoted by M2 macrophages,

AEC2 continuously proliferate and differentiate to accelerate alveolar formation (90).

A previous study revealed that M2 macrophages are enriched in lung tissues and AEC2 proliferated rapidly following pneumonectomy (91). ILC2s increase and become the main source of IL-13, which induces AMs to differentiate into M2 phenotype (91). Both IL-4R α-expressing ILC2s and M2 macrophages, which are necessary for optimal lung regeneration, promote the regeneration of lung tissues by stimulating the growth of AEC2 (91). Rindler *et al* (92) reported that M2 macrophages are clustered together and localized in the site of AEC2 multiplication during regeneration.

It has been reported that activation of IL-33 can promote type 2 immunity in pulmonary development by amplifying and activating ILC2s during the perinatal period (81). IL-4, IL-5 and IL-13 exhibit upregulation after activation of ILC2s, which constitutively express ST2. In addition to activating ILC2s, IL-33 also stimulate the expression and polarization of AMs by basophils during alveolar formation (93,94). Thus, it is hypothesized that IL-33 promotes proliferation and activation of ILC2s and M2 macrophages during lung development, and crosstalk between ILC2s and M2 macrophages promotes alveolarization. This is consistent with the IL-33-ST2 axis regulating regeneration of epithelial through activation of monocyte differentiation into reparative M2 macrophages and ILC2s-mediated M2 macrophages (95). In summary, ILC2s promote the polarization of M2 macrophages via IL-4/13. In addition to IL-4/13, there may be other associations between ILC2s and M2 macrophages in the complex process of embryonic development, which have not been fully investigated. Thus, future studies are required to determine how M2 macrophages directly affect ILC2s, and how their crosstalk promotes fetal and preterm lung development.

5. Crosstalk between ILC2s and M2 macrophages in lung diseases

The arrest of alveolar development or disruption of alveolar structure is not only associated with neonatal respiratory distress syndrome, bronchopulmonary dysplasia and persistent pulmonary hypertension, but also chronic lung diseases, such as asthma, allergic diseases and chronic obstructive pulmonary emphysema (2-4). Pulmonary epithelial barrier dysfunction is an important pathological component of lung injury, which is mainly caused by damage of epithelial cell migration (96). ILC2s participate in the regulation of AEC2 and different lung diseases (37). M2 macrophages are a subgroup of macrophages whose polarization is important for AEC2 regulation and inflammatory response (97). Thus, the crosstalk between increased ILC2s and upregulated M2 macrophages may regulate lung development, and modulate the processes of several lung diseases (Fig. 2).

Pulmonary parasitic infection. Several parasites, namely pulmonary parasitic diseases, spread to other parts of the human body via blood circulation, and often reside in the lungs, causing pathological changes (98). The host cells of helminth mega parasites are involved in type 2 immune response, including Th2 cells and type 2 cytokines (IL-4, IL-5, IL-9 and IL-13), which are required to fight these pathogens (99,100). Recently, it has been reported that the relative abundance of these macrophages and the rare ILC2s have a swift and strong response to helminth antigen and helminth induced injury, activating damaged epithelial cells and recruiting other effector factors (101). Immunocompromised larvae of helminths have a significant morphological defect, which is affected by aggregation of IL-13-secreting ILC2s and $CD4^+$ T cells, and the polarization of M2 macrophages (102). Application of IL-2 or IL-33 can bypass the requirement of T cells, resulting in proliferation of IL-13 and secretion of ILC2s and death of larvae, and exhaustion of ILC2s inhibits larval death in mice by transferring IL-2 (102). Thus, it is not surprising that ILC2s are the key factor during infection and are maintained by $CD4^+$ T cells, which not only ensure rapid activation of IL-13 dependent M2 macrophages, but also maintain their immune function in lung tissues (102).

Amp activated protein kinase (AMPK) is a significant driving factor of cellular energy, which exists in AMs (103). Deletion of AMPK decreases the secretion of IL-13 and impairs the expansion of ILC2s in lung tissues from mice that are selectively deprived of α 1 subunit, thereby exacerbating lung injury following ancylostoma infection (103). Surfactant protein D (SP-D) is an important epithelial product (104). Increased levels of pulmonary SP-D before infection can enhance parasite excretion and type 2 immune response, including the increase of IL-13-producing ILC2s, M2 macrophages and the cytokines, IL-4 and IL-13 (104). Thus, it is speculated that AMs and ILC2s assist in coordinating the regulation of mucosal tissue damage through metabolic enzyme function (103,104).

Pulmonary viral and fungal infections. Several studies have confirmed that the intensity of infection is affected by type 1 immune response and polarization of M1 macrophages, while type 2 immunity and polarization of M2 macrophages are closely associated with disease progression and adverse outcomes (105-107). In infected lungs, the number of ILC2s significantly increase following induction of type 2 response (108). ILC2-deficient mice exhibit a notable declination in type 2 immune response 14 days after infection, which is characterized by decreased expression levels of IL-4, IL-5 and IL-13, as well as the number of M2 macrophages (108).

The change in polarization of pulmonary macrophages in ILC2-deficient mice is frequently associated with better control of fungi and prolongation of survival time of infected mice (108). Rhinovirus (RV) infection also induces IL-25, IL-33, IL-4, IL-5, IL-13 and ILC2s expansion, mucus metaplasia and airway hyperresponsiveness (109). IL-1 β of pulmonary macrophages inhibits type 2 inflammation and mucus metaplasia following RV infection by decreasing ILC2s and cytokines (109).

Group V phospholipase A2 (Pla2g5) is a lipid-producing enzyme that is required for macrophage functioning in lung inflammation (110). Macrophages also assist in regulating IL-33 induction and free fatty acids (FFAs)-driven ILC2s activation via Pla2g5, significantly contributing to type-2 immunity (110). In addition, mass spectrometry analysis demonstrated significant reduction of FFAs in Pla2g5 deficient lung tissues and BM-macrophages in Alternaria-exposed wild-type mice (110).

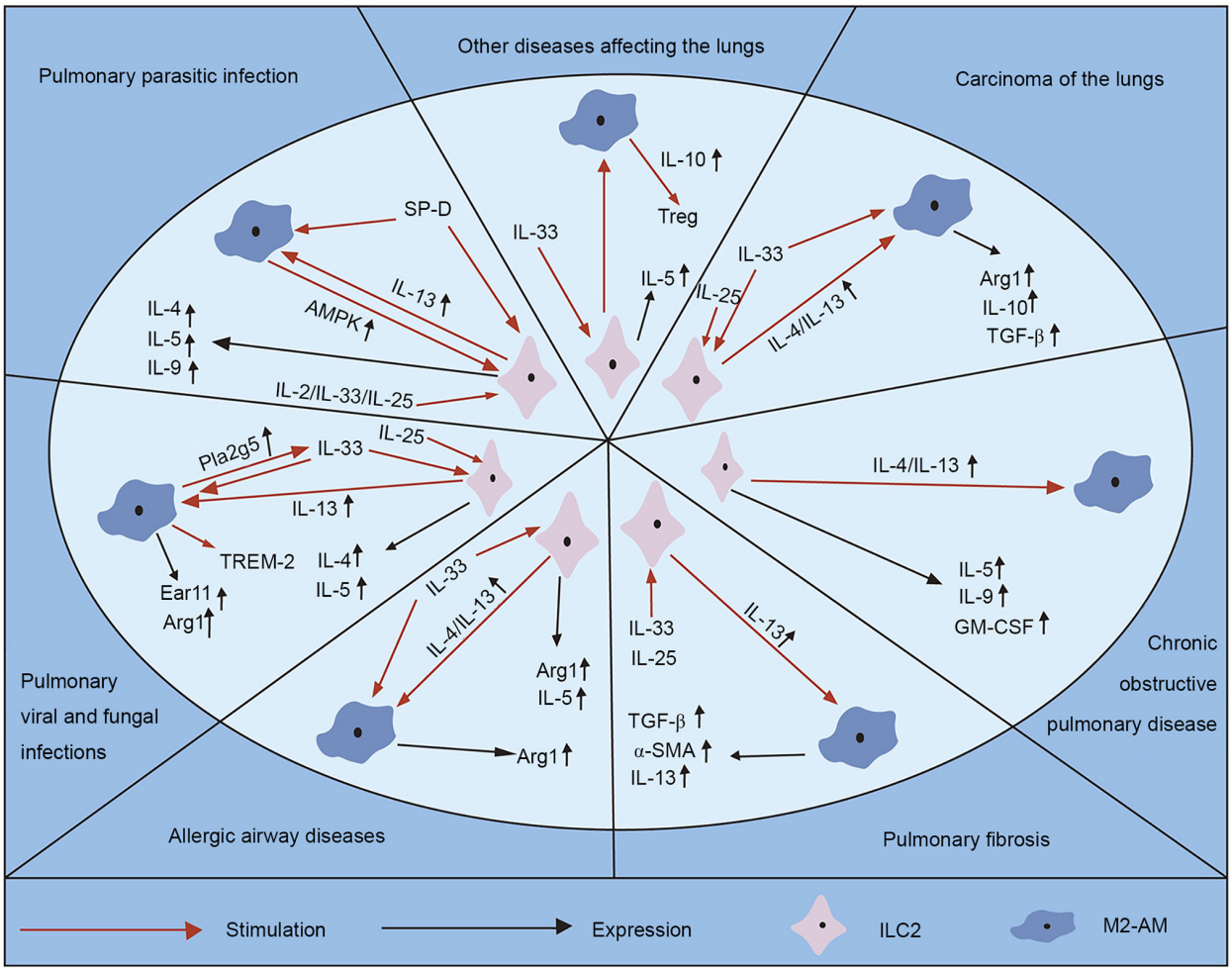

Figure 2. Crosstalk between ILC2s and M2 macrophages regulates type 2 immune response in lung diseases. ILC2, type 2 innate lymphoid cell; M2-AM, alternative macrophage; IL, interleukin; AMPK, Amp activated protein kinase; SP-D, surfactant protein D; TGF-β, tumor growth factor β; TREM-2, triggering receptors on myeloid cell 2; Pla2g5, group V phospholipase A2; Ear11, eosinophil-associated ribonuclease 11; GM-CSF, granulocyte-macrophage colony stimulating factor.

Another study reported that type 2 immunoregulatory neutrophil infiltration is influenced by mouse eosinophil associated ribonuclease 11, and is secreted by M2 macrophages downstream of ILC2s that are stimulated by IL-25 (111). Furthermore, neutrophils can promote type 2 immune response without aggravating inflammation (111).

Chronic post viral disease is characterized by excessive airway mucus formation and multiplication of M2 differentiated pulmonary macrophages, requiring expression of macrophages for triggering receptors on myeloid cell 2 (TREM-2) (112). With increasing levels of IL-13, virus replication increases the levels of macrophages and TREM-2 in the lung tissues, preventing macrophage apoptosis in acute diseases (112). Following infection clearance, IL-13 promotes cleavage of TREM-2 into the soluble form, STREM-2, which prevents macrophage apoptosis (112). These results may explain how crosstalk between ILC2s with M2 macrophages in acute infection results in chronic inflammatory diseases.

Recruitment of neutrophils, eosinophils and inflammatory chemokines (KC, eotaxin-1, MIP1a and MIP1b), Th2 cytokines (IL-4/5), arginase-1 (M2 macrophage marker) and IL-33R+ ILC2s cells are significantly elevated in adenovirus Oncostatin M (OSM) mice, while these responses are significantly attenuated in IL-33-/- mice (113). *In vitro*, IL-33 upregulates OSM expression in RAW264.7 macrophage cells and bone marrow-derived macrophages (113). Thus, IL-33 is a key mediator of OSM-driven lung inflammation, induction of type 2 immune responses and M2 macrophages in mice, which contributes via activation of ILC2s (113).

Allergic airway diseases (AAD). In addition to the common tissue tropism, AAD also have obvious inflammatory patterns, including eosinophils, M2 macrophages, ILC2s, IgE secreting B cells and Th2 cells, and cytokines, including IL-33, IL-4, IL-5 and IL-13 (114,115). Reduction of Th2 cytokines (IL-4, IL-5 and IL-13), macrophages, ILC2s and other cells in lung tissues, and alveolar lavage fluid, can improve allergic airway inflammation in mice, which may be a potential way to treat allergic asthma (58,116).

Arg1, produced by M2 macrophages, can regulate asthma and allergic inflammation (117). A study demonstrated that compared with M2 macrophages expressing Arg1 after activation of STAT6 mediated by IL-4/13, ILC2s constitutively express Arg1 in a STAT6-independent manner (117). IL-33 can affect Arg1 in lung tissues by promoting the proliferation of ILC2s and indirectly activating macrophages via STAT6 (117). These results further highlight that ILC2s

and M2 macrophages have a synergistic regulatory effect on asthma and allergic inflammation via Arg1.

During allergic response, the selective depletion of E3 ligase VHL in innate lymphoid progenitor cells increases hypoxia inducible factor-1α (HIF-1α) expression, which in turn decreases ST2 and inhibits the development of ILC2s induced by IL-33 via epigenetic modification (118). HIF-1α affects glycolysis and phenotype of macrophages (119), suggesting that HIF-1α acts through the regulation of ILC2s and macrophages during allergic reaction.

Lung ILC2s exhibit an inverse correlation with MHC-II^{high} resident macrophages (M1), and a positive correlation with MHC-II^{low} resident macrophages (M2), and their contribution to AAD induced by HDM may also be affected by heredity (120). Notably, ILC2s, which are amateur antigen presenting cells (121), cooperate with macrophages to form and regulate adaptive immunity to allergens and helminth (121).

Pulmonary fibrosis. Idiopathic pulmonary fibrosis is characterized by fibroblast aggregation, collagen deposition and extracellular matrix remodeling, in which myofibroblasts are considered effector cells (72). In the pulmonary fibrosis model, AMs were recruited into the alveoli, and the phenotype involves M2 macrophages, which upregulates CD206 on the cell surface (72). *In vitro*, 264.7 cells treated with IL-4 were used as M2 macrophages, and the TGF-β levels in the supernatant significantly increased. α-SMA expression increased following co-culturing of lung epithelial cells (MLE-12) with M2 macrophages, suggesting that M2 macrophages regulate pulmonary fibrosis by inducing epithelial-to-mesenchymal transition (72).

In addition to the increase of M2 macrophages, the increase of IL-33, IL-13, TGF-β1 and inflammatory chemokines are also observed during pulmonary fibrosis (122). IL-13 and TGF-β1 are produced by M2 macrophages, and IL-13 is secreted by ILC2s, both *in vivo* and *in vitro*, and induced by IL-33 (122). As IL-13 can induce the polarization of M2 macrophages (123), a cycle where IL-13 can be produced by M2 macrophages and promotes polarization of M2 macrophages is formed. IL-33 sends signals through ST2, and recruits and guides inflammatory cell function in ST2- and macrophage-dependent manners, and enhances the generation of pro-fibrosis cytokines, thus promoting the occurrence and development of pulmonary fibrosis (122).

Zhao *et al* (124) reported that bone marrow-derived ILC2s accumulate in the fibrotic lung and activated fibroblasts to promote pulmonary fibrosis by inducing the IL-33/ST2 signaling pathway. In addition, ILC2s are induced by IL-25, which results in significant changes in the pathological process of pulmonary fibrosis through the production of IL-13 (125). Thus, the application of anti-IL-33 antibody and depletion of AMs or ILC2s may be potential therapeutic methods for pulmonary inflammation and fibrosis.

Chronic obstructive pulmonary disease (COPD). A clinical study demonstrated that normal AMs are mainly nonpolarized (63). However, the polarization of M1 and M2 macrophages significantly enhances, and the co-expression of M1 and M2 markers in the same AMs also significantly increases, with the aggravation of smoking and COPD severity (63).

In human COPD, ILCs accumulate in lung tissues, with increasing signature cytokines, such as IL-5 and GM-CSF (126). The levels of neutrophil elastase and IL-5 increase in patients with acute exacerbation of COPD (127), and the levels of IL-13 mRNA in eosinophils and endothelial cells in the sputum also increase to about 30 times (128). In addition, Th2 cytokine IL-9 can also aggravate lung injury by activating STAT3 in COPD mice and increasing inflammation and oxidative stress (129).

For the interaction of STIP1 homology and U-box-1 (STUB1), IL-4R α is used as the target, which prevents IL-4 or IL-13 signal transduction via ubiquitination mediated proteasome degradation (130). In STUB1-deficient mice, spontaneous airway inflammation increases IL-4R α expression, STAT6 is continuously activated, M2 macrophages are activated and serum IgE increases (130). The level of STUB1 in the airway of patients with asthma or COPD increases, suggesting that upregulation of STUB1 may be an important feedback mechanism for inhibiting IL-4R signal transduction in airway inflammation (130).

Carcinoma of the lungs. In different tumors, type 2 immune responses induce polarization of M2 macrophages, which in turn enhances the invasion and migration of tumor cells by secreting Arg1, IL-10 and TGF-β (107,131,132). The progression of lung cancer is associated with poor patient prognosis and high mortality (133). The survival rate of tumor-bearing mice with vitamin A deficiency diet is low, and the tumor size increases with increasing number of type 2 cytokines, ILC2s and M2 macrophages in BALF of mice, suggesting that ILC2s and polarized M2 macrophages play a synergistic role in promoting cancer progression (133). This synergistic effect may be accomplished via two pathways, the co-promotion of ILC2s and M2-type macrophages by IL-33 (134-136), and the promotion of M2 macrophage polarization by type 2 cytokines (123,137), such as IL-4 and IL-13, secreted by ILC2s (138). This is consistent with the fact that both M2 subtype macrophages (M2a and M2b) and IL-25-stimulated ILC2s favor cancer progression (139). Notably, other substances that inhibit the polarization of M2 macrophages by IL-4/13 can change the tumor microenvironment (140). However, further studies are required to understand the crosstalk between ILC2s and M2 macrophages in lung cancer and determine their underlying molecular mechanisms.

Other diseases affecting the lungs. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (141). The lung is an extremely fragile organ that is prone to sepsis (142). In sepsis model with cecal ligation and puncture, IL-33 upregulates IL-5 in ILC2s, whereas IL-5 inhibits neutrophil and monocyte infiltration, suggesting that this axis is involved in lung injury early after sepsis (142). Survivors of sepsis will have chronically low immune functions (143). IL-33, which is produced following sepsis, activates ILC2s and promotes the polarization of M2 macrophages, thus accelerating the proliferation of Treg cells through IL-10 (143). Subsequently, increased ILC2s, M2 macrophages, IL-10 and Treg cells result in immunosuppression (143).

6. Conclusions and perspective

Lung resident ILC2s are important immunoregulatory cells that are involved in metabolism, tissue repair and multiple organ remodeling, outlining a previously unanticipated role of type 2 immunity in regulating basal homeostasis. Similarly, macrophages are a group of pluripotent and plasticity immune cells, that also regulate type 2 immune response. In lungs, AMs and interstitial macrophages differentiate into different cell phenotypes at different stages of development, including M1 and M2 macrophages.

The proliferation and activation of ILC2s and M2 macrophages are consistent, and are not only involved in lung development, but also in lung diseases. In addition, ILC2s and M2 macrophages interact to regulate the lung microenvironment, which is effective in pulmonary development and pulmonary diseases. The crosstalk between IL-4R α-expressing ILC2s and upregulated M2 macrophages produces remarkable effects in lung inflammation, allergy, tumor and fibrosis responses. Further studies are required to better understand the development, activation, turnover and interaction between ILC2s and M2 macrophages in lung tissues. Targeting the IL-33/ILC2s/M2-macrophage axis may be an effective novel approach for the treatment of several lung diseases.

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Authors' contributions

LLM and HYL conceived the present study and performed the literature review. LLM and YZ collected and reviewed the literature, and drafted the initial manuscript. All authors confirm the authenticity of all the raw data and critically revised the manuscript for important intellectual content. LLM and YZ produced the figures. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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