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Review

The regulatory function of T_H2 and ILC2 in asthma

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ABSTRACT

Asthma is one of the most prevalent chronic diseases worldwide, affecting approximately 10% of adults and an even greater proportion of children. Type-2 innate lymphoid cell (ILC2)- and type 2 helper T cell (T_H2)-driven type 2 inflammation is a critical contributor to the pathogenesis of this disease. Various triggers, such as protease allergens, helminth parasites, fungi and influenza virus, can stimulate epithelial cells to release alarmins such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) to drive ILC2s and T_H2 activation. In this review, we provide some latest advances in our understanding of the role of ILC2s and T_H2 in asthma. With regard to T_H2, we focus on transcriptional factors, ubiquitination, Notch signaling pathway and clinical research. In the case of ILC2s, we concentrate on transcriptional factors, co-stimulatory molecules, epigenetic and metabolic pathways in a cell-intrinsic way and on cell-cell interaction in a cell-extrinsic way. The questions in this field are also addressed.

KEYWORDS: ILC2, T_H2, asthma, therapeutic target.

1. Introduction

Asthma is one of the most prevalent chronic diseases worldwide, affecting approximately 10% of adults and an even greater proportion of children [1]. As a chronic inflammatory disease of the conducting airways, asthma is characterized by bronchial hyper-reactivity (BHR), mucus overproduction, airway wall remodelling and airway narrowing [2]. Type-2 innate lymphoid cell (ILC2)- and type 2 helper T cell (T_H2)-driven type 2 inflammation is a critical contributor to the pathogenesis of this disease.

ILC2s, which were first described in mice in early 2001 as non-B/non-T cells that secrete IL-4, IL-5 and IL-13 in response to IL-25 [3], have important roles in helminth expulsion, wound healing, tissue repair after virus infection [4], obesity [5] and thermogenesis [6, 7]. Various triggers, such as protease allergens [8, 9], helminth parasites, fungi [10] and influenza virus [4, 11], can stimulate epithelial cells to release alarmins such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) [12-15] to drive ILC2 activation. ILC2s are found in various anatomical sites, such as adipose tissue, liver, mesenteric lymph nodes (LNs), the small intestinal lamina propria and lung. The common features of these cells, such as their cytokine receptor expression profiles, secretion of characteristic cytokines, and characteristic transcription factors, became apparent based on early studies. Although all ILC types can be found on the mucosal surface of the small intestine, ILC2 is the major ILC population in the lungs in the steady-state condition [16], and there is abundant evidence for the role of ILCs, especially ILC2s, in asthma based on various mouse models of allergic airway inflammation as well as clinical observations [17].

Compared to ILC2s, the study of T_H2 cells began earlier. T_H2 cells typically produce interleukin-4 (IL-4), IL-5, IL-9 and IL-13, and these cytokines are also produced by ILC2s [18]. IL-4 drives B cell proliferation and immunoglobulin class-switching to immunoglobulin E(IgE) [19], and eosinophils are recruited to lung tissue *via* IL-5 [20, 21]. IL-13 induces goblet cell hyperplasia and mucus production [22] and is also a potent mediator of fibrosis and airway hyperresponsiveness (AHR), a hallmark of allergic asthma [23].

In this review, we focus on the recent research progress of T_H2 and ILC2s in asthma, especially with regard to the role of ILC2s in lung inflammation and asthma.

2. T_H2 cells

Some recent studies on the mechanism of asthma mediated by T_H2 cells are introduced below separately as molecular mechanism and clinical research.

2.1. Molecular mechanism

2.1.1. Transcription factors

Transcription factor B cell lymphoma 11b (Bcl11b) is expressed by all T cells, starting from CD4/CD8 double-negative stage 2. However, the results of recent studies are controversial as to whether Bcl11b promotes T_H2 differentiation. For example, Difeng *et al*. found that Bcl11b is a negative regulator of T_H2 cell differentiation. Bcl11b represses GATA3 expression and interacts with the GATA3 protein to limit GATA3-mediated T_H2 cytokine IL-4, IL-5, and IL-13 production [24] (see Figure 1). In contrast, Kyle J. *et al*. found that Bcl11b promotes T_H2 differentiation, whereby mature T cells from Bcl11b-deficiency mice shows reduced T_H2 cytokines and GATA3 during T_H2 response, further causing reduced severity of asthma [25]. The role of Bcl11b in ILC2s has also been studied in asthma by considering the similarity between T_H2 and ILC2s and the strong expression of Bcl11b in ILC2s. Bcl11b acts directly upstream of Gfi1, a key ILC2

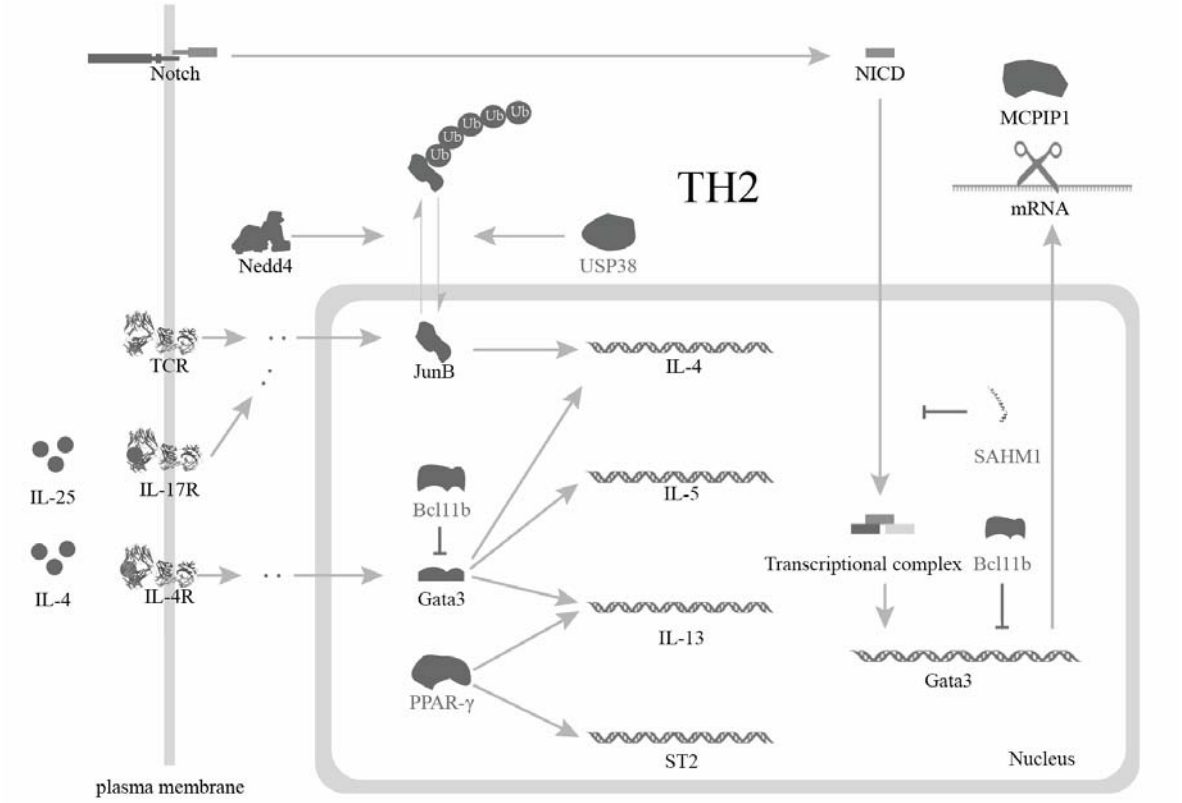

Figure 1. Recently proposed mechanism mediated by T_H2 in asthma. Bcl11b represses GATA3 expression and interacts with the GATA3 protein to limit GATA3-mediated IL-4, IL-5, and IL-13 cytokine production in T_H2 cells. PPAR-γ is considered an anti-inflammatory factor that regulates T_H2 effector function in an IL-33-dependent manner. USP38 is up-regulated after TCR stimulation and decreases the degradation rate of downstream JunB in T_H2-mediated allergic asthma. SAHM1 directly prevents assembly of the Notch transcription factor complex and decreases lung inflammation, including eosinophilic airway inflammation, T_H2 differentiation, and BHR, in an HDM-driven asthma model. MCPIP1 promotes GATA3 mRNA decay through the RNase domain and negatively regulates the Notch/Gata3 pathway to control the development and function of IL-5-producing T_H2 cells.

transcription factor, to maintain its expression in mature ILC2s [26].

Peroxisome proliferator-activated receptor-γ (PPAR-γ), a transcription factor expressed by adipocytes and macrophages, is considered to be an anti-inflammatory factor that regulates T_H2 effector function in an IL-33-dependent manner. CD4-Cre $Pparg^{fl/fl}$ mice exhibit a reduced type-2 inflammatory response, including reduced eosinophilia and mucus production, in both HDM- and OVA/Alum-induced asthma models [27] (see Figure 1), and similar results were reported for Lck-Cre $Pparg^{fl/fl}$ mice [28]. Furthermore, PPAR-γ is predominantly expressed in mouse T_H2 cells, rather than in T_H1 and T_H17 cells, and also in T_H2 cells of allergic patients [27]. Further study should focus on the role that PPAR-γ plays in ILC2s, which are also activated by IL-33.

2.1.2. Ubiquitin regulation of T_H2 cells

T_H2-specific cytokine expression and allergen-induced airway inflammation depend on the transcription factor JunB [29], and JunB-mediated regulation of the ubiquitin degradation pathway plays an important role in asthma. Nedd4 family-interacting protein-1 (Ndfip1) binds to Nedd4, a HECT-type E3 ubiquitin ligase, leading to ubiquitination of JunB [30]. In 2014, Heikamp *et al*. found that serum- and glucocorticoid-regulated kinase 1 (SGK1) phosphorylates and inhibits Nedd4-2 to prevent degradation of JunB in an mTOR-dependent manner, which promotes the differentiation of T_H2 cells [31]. In 2018, Chen *et al*. found that ubiquitin-specific protease 38 (USP38) was up-regulated after TCR stimulation and decreased the degradation rate of downstream JunB in T_H2-mediated allergic asthma [32] (see Figure 1). Grail, an E3 ubiquitin ligase, specifically targets signal transducer and activator of transcription 6 (STAT6), but not JunB, for ubiquitination and degradation in T_H2 cells. Grail deficiency results in more severe type 2 inflammation in OVA-induced asthma models [33].

2.1.3. Notch signaling pathway

IL-4 induces the differentiation of naïve T cells towards the T_H2 direction through the IL-4 receptor (IL-4R) and signal transducer and activator of transcription 6 (STAT6). In addition, the Notch signaling pathway mediates T_H2 differentiation, and its important role in asthma has recently been discovered. There are four Notch proteins (Notch1-Notch4) and two distinct families of Notch ligands, known as Delta-like ligands (consisting of DLL1, DLL3 and DLL4) and Jagged ligands (Jagged1 and Jagged2). Delta-like ligands induce T_H1, whereas Jagged induces the alternate T_H2 fate independent of IL-4/STAT6 [34]. Notch ligands on antigen-presenting cells induce the release of the Notch intracellular domain (NICD), which then translocates from the cytosol to the nucleus. NICD recruits mastermind-like (MAML) proteins and RBPJ and forms a transcriptional complex, resulting in the activation of target genes [35, 36]. Notch signaling in T cells is essential for inducing T_H2-mediated allergic airway inflammation in the HDM-driven asthma model. In 2017, Tindemans *et al*. found that mice deficient for RBPJκ, a downstream transcription factor of the Notch pathway, failed to develop allergic airway inflammation [37].

The hydrocarbon-stapled peptide SAHM1 directly prevents assembly of the Notch transcription factor complex [38] (see Figure 1), and KleinJan *et al*. reported in 2018 that the SAHM1 peptide decreased lung inflammation, including eosinophilic airway inflammation, T_H2 differentiation, and BHR, in an HDM-driven asthma model [36]. Monocyte chemotactic protein–induced protein 1 (MCPIP1) negatively regulates the Notch/Gata3 pathway to control the development and function of IL-5-producing T_H2 cells. In 2018 Peng *et al*. demonstrated that MCPIP1-deficient mice spontaneously developed severe lung inflammation, and it was observed that MCPIP1-deficient OVA- and HDM-specific T cells lead to more severe T_H2-mediated airway inflammation in OVA- and HDM-induced asthma models [39]. Furthermore, ultra-fine particles induce Jagged1 expression on lung alveolar macrophages, which in turn activates Notch4 signaling in allergen-specific T cells and promotes their differentiation into T_H2/T_H17 cells [40].

2.2. Clinical research

Due to the complexity of asthma, many studies divide the disease into different subtypes in efforts to find an ideal treatment for different subtypes. However, there is no clear and systematic classification. Recently, because of the availability of sputum as a sample, many scientists have distinguished different asthma patients based on this material, with significant progress. For instance, by analysing sputum cell transcriptomics, Kuo *et al*.

defined three transcriptome-associated clusters (TACs) from 104 moderate- to severe asthmatic subjects and 16 non-asthmatic subjects. TAC1 showed the highest enrichment of gene signatures for T_H2 cells and ILC2s, with also the highest sputum eosinophilia rate. The TAC2 group displayed the highest sputum neutrophil counts, serum C-reactive protein levels and prevalence of eczema. TAC3 had normal to moderately high sputum eosinophil counts and better preserved forced expiratory volume in 1 s [41]. Thus, asthma patients with different subtypes can be selected for suitable treatment based on sputum analysis. It has been confirmed that patients with high levels of mast cell CPA3 expression in sputum will have poor lung function and that blood eosinophils poorly respond to oral corticosteroid treatment [42]. Regardless, many questions remain such as why the relative number of eosinophils in the blood and sputum is not consistent [43].

Inhaled corticosteroids are mainly used to suppress type 2 inflammation in the treatment of asthma, with the addition of long-acting β2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) in patients with moderate to severe disease. Recently, key cytokines, including IL-4, IL-5, IL-13, IL-33 and TSLP, have been selected as attractive targets for the treatment of severe asthma, with some progress in clinical studies [1]. Although antibodies against IL-4R [44] and TSLP [45] have achieved good results, including reduced exacerbation, fewer symptoms and increased FEV1, antibodies against or inhibitors of IL-5 [46, 47], IL-5Rα [48, 49], and IL-13 [50] are not as effective as expected. Overall, asthma is a complex disease, and blocking one cytokine or certain cytokines only effective in specific subtypes of asthma may not be successful. Nonetheless, targeting upstream cytokines, such as IL-25 and IL-33, may constitute a good direction, and theoretically blocking the release of more downstream cytokines, including IL-4, IL-5 and IL-13, would be efficient. For a more detailed overview of the cytokine targeting therapy, we refer the reader to the review written by Barnes [1].

3. ILC2s

Below, we focus on the mechanism of ILC2s in asthma and separately introduce recent research on cell-intrinsic and cell-extrinsic ILC2 pathways.

3.1. Cell-intrinsic pathway

3.1.1. Transcription factors

Several transcription factors, including GATA3 [51-53], GFI1 [54], TCF1 [55] and RORα [56], have been identified as being critical for the differentiation of ILC2 subtypes (see Figure 2).GATA3 plays a variety of roles in T cell differentiation, such as promoting the generation of the earliest T cell progenitor cells and the differentiation of thymocytes and subsequently participating as an important driving factor of T_H2 cell polarization. As expected, GATA3 plays a crucial role in the differentiation of ILC2s [57]. GATA3 activates type 2 cytokine transcription [58], which is necessary for the function and survival of mature ILC2s. GFI1 promotes ILC2 development by maintaining GATA3, and it represses the expression of the ILC3 cytokine IL-17 [54].

RORα, a member of the nuclear hormone receptor superfamily [59], is highly expressed by multiple ILC subsets, though its deletion results in selective defects in the number of ILC2s, especially in bone marrow [60, 61]. Bcl11b was previously considered to be specific to T cells, maintaining the key ILC2 transcription factor GFI1 and limiting transcription factors necessary for ILC3s, thereby maintaining the genetic and functional processes of peripheral ILC2s [62].

In addition, the transcription factor ETS1, which regulates Id2 transcription in NK cells [62], was confirmed as having a role in cytokine-induced lung ILC2 amplification and its production of IL-5 and IL-13. Moreover, it was suggested that ETS1 is an early regulatory factor in the transcriptional network that controls the appearance and function of ILC2s [63].

3.1.2. Epigenetic regulation

G9a (Ehmt2 and Kmt1c) is a lysine methyltransferase that is responsible for dimethylation of histone H3 lysine 9 [64]. G9a, but not its methyltransferase activity, is necessary to promote the differentiation of T_H2 cells [65]. Furthermore, G9a-mediated suppression of ILC3-related genes is critical for the optimal development of ILC2s. This was the first evidence of the epigenetic regulation pathway in ILC2s, and G9a-dependent H3K9me2 is identified as the key inhibitory mechanism regulating ILC2 development [66] (see Figure 2).

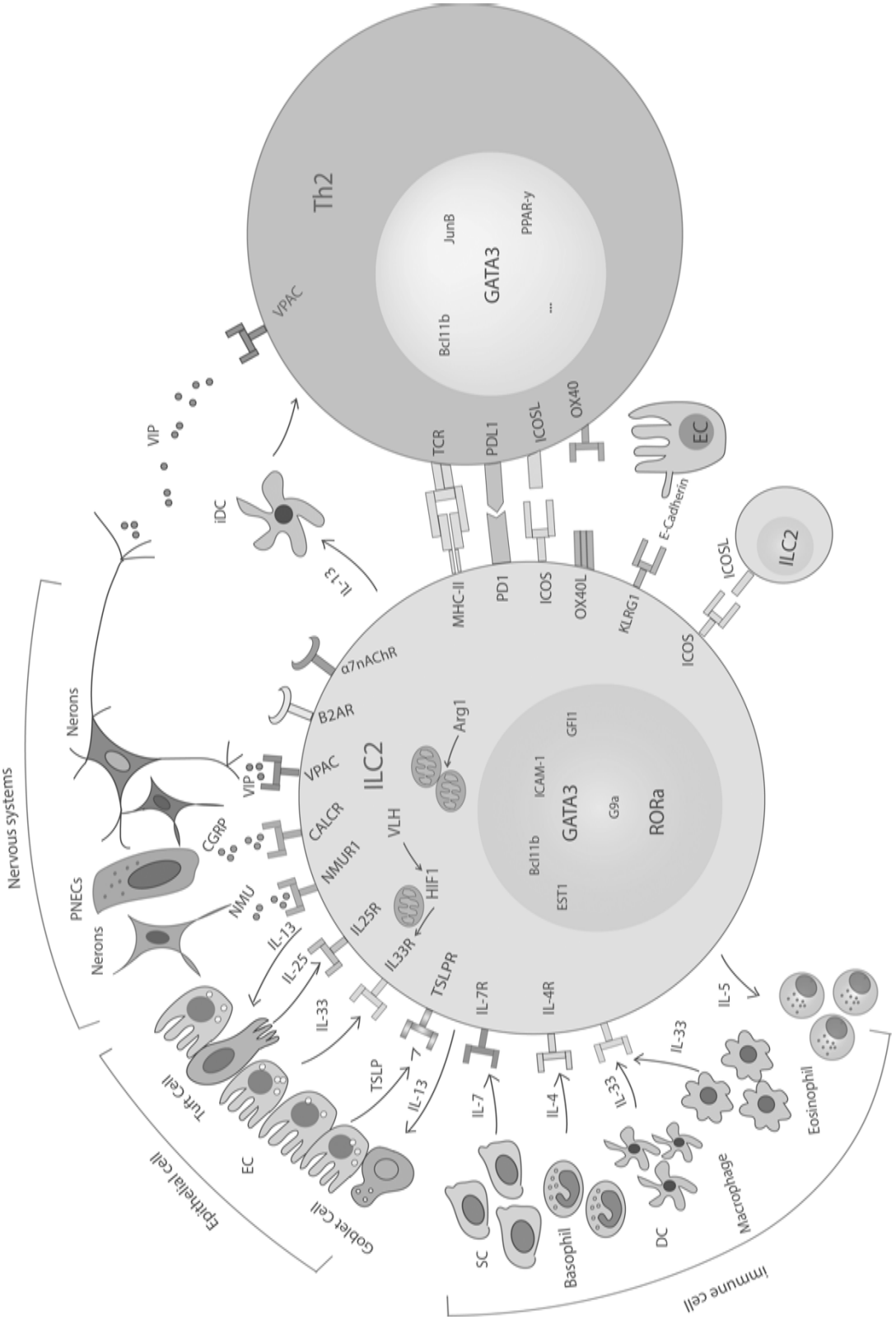

Figure 2. Recent research progress on cell-intrinsic and cell-extrinsic ILC2 pathways. ILC2s can be regulated by several transcription factors, including GATA3, GFI1, TCF1, and RORα as well as by recently revealed Bcl11b, EST1 and co-stimulatory molecule ICAM1. Arg1 and VHL can regulate the metabolic pathways that control the function of ILC2s. ILC2s express various surface molecules that interact with ligands on other cells, e.g., ICOS-ICOSL, PD1-PDL1, KLRG1–E-cadherin, MHCII-TCR and OX40-OX40L. ILC2s can also be influenced by the nervous system and epithelial cells, such as tuft cells.

3.1.3. Metabolic pathways

ILC2s modulate tissue inflammation and repair *via* extrinsic cytokines, such as host-derived cytokines. However, the metabolic pathways that control the function of ILC2s are poorly understood. Arginase-1 (Arg1) metabolizes L-arginine to produce urea and ornithine, which is further metabolized into the proline and polyamines that drive collagen synthesis and biological energy pathways crucial for cell proliferation [67]. Absence of Arg1 affected the proliferation of ILC2s, though apoptosis was not altered, and this may have led to differences in the proportion of ILC2s in the pulmonary inflammatory response. The authors found that Arg1 was involved in ILC2 glycolysis and that disruption of Arg1 activity led to internal metabolism disorder in ILC2s (see Figure 2), which may have caused the observed decline in their proliferation [68].

The VHL protein is the core of an E3 ubiquitin ligase complex that contains elongin C, elongin B, cullin2, and RING-box protein RBX1. Hypoxia-inducible factor a-subunit (HIFa) is the most important substrate for the VHL E3 complex [69, 70], and the transcription factor HIF has an important function in controlling immune cell metabolism, lymphocyte differentiation and the immune response [71]. Conditional deletion of VHL in innate lymphoid progenitor cells results in a decrease in the number of mature ILC2s in peripheral non-lymphoid tissues and a decreased type 2 immune response. VHL deficiency also leads to accumulation of hypoxia-inducible factor 1a (HIF1a) and reduced expression of the interleukin-33 (IL-33) receptor ST2, a process that can be reversed by HIF1a ablation or inhibition (see Figure 2). In addition, expression of the HIF1a-driven glycolytic enzyme pyruvate kinase M2 down-regulates expression of ST2 and suppresses ILC2 development induced by IL-33 through epigenetic modification. These results indicate that the VHL-HIF-glycolysis axis is necessary for the late maturation and function of ILC2s through the IL-33-ST2 pathway [72].

3.1.4. Co-stimulatory molecules

Intercellular cell adhesion molecule-1 (ICAM-1 or CD54) is broadly expressed in many cell types, including T cells, B cells, neutrophils, endothelial cells, and epithelial cells [73]. High expression of ICAM-1 and its ligand LFA-1 has been detected in ILC2s and their progenitor cells. IL-33 stimulation enhances expression of ICAM-1 on mouse and human ILC2s, and lack of ICAM-1 impairs the development and function of ILC2s, which reduces allergic inflammation in the lungs. Further studies have revealed the underlying mechanism: ICAM-1 deficiency causes dysregulation of the GATA3 protein *via* the ERK pathway [74] (see Figure 2).

3.2. Cell-extrinsic pathway

3.2.1. Direct interaction with other cells

ILC2s express various surface molecules that may interact with ligands on other cells. To date, however, only a few of the possible cell-cell interactions of ILC2s with other lung cell groups have been studied, as discussed below.

3.2.1.1. ICOS–ICOS-L

Inducible T cell co-stimulatory molecules (CD278) are members of the CD28 family and play an important role in T cell signal transduction [75]. ILC2s display high expression of ICOS, and ICOS signaling in mice regulates ILC2 homeostasis independently of T cells and B cells by promoting the proliferation and accumulation of mature ILC2s in the lung and intestine. In a model of IL-33-induced airway inflammation, ICOS was found to control ILC2 activation and eosinophil infiltration in the lung [76]. ICOS deficiency in murine ILC2s and blocking the ICOS-ICOS-ligand interaction in human ILC2s reduces lung inflammation. ILC2s express both ICOS and ICOS-ligand, and the ICOS-ICOS-ligand interaction promotes cytokine production and survival in ILC2s through STAT5 signaling. Thus, the ICOS-ICOS-ligand pathway is critically involved in ILC2 function and homeostasis [77] (see Figure 2).

3.2.1.2. Programmed cell death 1 (PD-1)-PD-L1

Upon activation, the programmed cell death 1 (PD1) was induced to regulate T cells. PD1 plays an important role in balancing protective immunity and immunopathology, homeostasis and tolerance [78]. Indeed, recently developed PD1 pathway inhibitors have revolutionized cancer treatment for some patients, though the majority of patients do not show a complete response, and adverse events have been reported [78]. PD-1hiIL-25Rhi has been defined as an early checkpoint in ILC2 development

that can be abolished by the deficiency of the zinc-finger protein Bcl11b, but restored by IL-25R overexpression. Similar to T lymphocytes, PD-1 is up-regulated in activated ILCs [79]. PD-1 is also an important negative regulator of killer-cell lectin-like receptor G1 $(KLRG1)^+$ ILC-2s in both mice and humans, and an increase in $KLRG1^+$ ILC-2 cell numbers has been attributed to an intrinsic defect in PD-1 signaling, resulting in enhanced STAT5 activation. Upon immune challenge, including IL-33 stimulation, PD-1 and PD-L1 are up-regulated in ILC2s [80]. ILC2 interacts with PD-1 on T_H2 cells through PD-L1 and promotes its type 2 effector function, revealing another important regulatory mechanism of ILC2s and its adaptive counterpart, T_H2 cells. A novel PD-L1-controlled mechanism for type 2 polarization has been identified, whereby ILC2s mediate an innate checkpoint to control adaptive T helper responses, with important implications for the treatment of type 2 inflammation [81] (see Figure 2).

3.2.1.3. KLRG1–E-Cadherin

The co-inhibitory receptor KLRG1, which is expressed on NK cells and antigen-experienced T cells, has been proposed to serve as a marker of senescence. Although KLRG1 has frequently been employed as a marker of cellular differentiation, data are emerging indicating that KLRG1 has an inhibitory role and binds to cadherins (E, N, and R) [82]. The KLRG1–E-cadherin interaction may alter ILC2 function and act as a suppressive mechanism for dampening the ILC2 response *via* down-regulation of GATA3 [14]. In humans, E-cadherin loss and presence in sputum correlates with asthma severity [83]. Nevertheless, the exact mechanism and downstream signal transduction pathway in ILC2s after KLRG1 activation are poorly understood. Moreover, it remains elusive whether lung ILC2s can interact with N and R-cadherins expressed in the nervous system through KLRG1 induction (see Figure 2).

3.2.1.4. MHC-II–TCR

ILC2s have been reported to express or up-regulate MHC-II upon activation [84]. MHC-II expression on ILC2s can be elicited in response to IL-25 or IL-33, but ILC2s from lung tissue exhibited a considerably lower frequency of MHCII expression compared with small intestinal ILC2s [85]. It has been demonstrated that the T_H2 cell response is impaired in the absence of ILC2s. Moreover, ILC2s expressing MHC-II interact with antigen-specific T cells, with T cells secreting IL2 to promote ILC2 proliferation and IL-13 production [86]. However, absence of MHC-II fails to cause ILC2s to produce IL-13 to effectively induce expulsion of *Nippostrongylus brasiliensis*. Therefore, during the immune transition to adaptive T cells, crosstalk between ILC2s and T cells contributes to their mutual maintenance, amplification and cytokine production. Furthermore, this interaction appears to augment dendritic cell-induced T cell activation and identifies a previously unappreciated pathway in the regulation of type-2 immunity [85] (see Figure 2).

3.2.1.5. OX40-OX40L

Binding of OX40L by OX40, encoded by the genes Tnfsf4 and Tnfrsf4, respectively, provides an important signal for the expansion or survival of T_H2 cells [87, 88]. Although expression of OX40L in many immune cells has been reported, the most marked expression occurs in professional antigen presenting cells such as dendritic cells (DCs), defining a critical role for DC-derived OX40L in the induction and development of T_H2 responses [89]. A recent study showed that local expansion of T_H2 and Treg cells in response to the alarmin IL-33 is dependent on expression of the co-stimulatory molecule OX40L by ILC2s (see Figure 2), uncovering a central role for the IL-33-ILC2-OX40L pathway in the orchestration of type 2 immunity [90].

3.2.2. Regulation of ILC2 by neurons

Over the past two decades, it has been found that the nervous system plays an important role in regulating immune balance and inflammation. Indeed, increasing attention has been paid to the interaction between the nervous and immune systems in terms of injury or disease course. For example, primary and secondary immune organs, such as the bone marrow and lymph nodes, are innervated by afferent and efferent nerves. The brain regulates immune function through the autonomic nervous system, and sympathetic innervation regulates lymphocyte proliferation, macrophage activity and cytokine production [91] (see Figure 2).

3.2.2.1. Neuromedin U (NMU)

Three recent reports have demonstrated that neuropeptide NMU is an effective activator of ILC2s in the digestive and respiratory tracts [92-94]. In

the mouse gastrointestinal tract, ILC2s co-localize with cholinergic neurons that express the neuropeptide neuromedin U (NMU). In contrast to other hematopoietic cells, ILC2s selectively express NMU receptor 1 (NMUR1). These studies suggest that the signaling circuit of NMU-NMUR1 neurons provides a selective mechanism by which the intestinal nervous system and the innate immune system are integrated to promote a rapid type 2 cytokine response, which can induce antimicrobial activity, the inflammatory response and the tissue protective type 2 response at mucous sites [93, 94]. Another study used single-cell RNA sequencing to analyse mouse lung resident ILCs at steady states and after stimulation by alarmin cytokines IL-25 and IL-33 *in vivo*. ILC2s display transcriptional heterogeneity after activation, and subsets are distinguished by proliferation, homeostasis and effector gene expression. The neuropeptide receptor Nmur1 was preferentially expressed by ILC2s in both the steady state and after IL-25 stimulation. These findings demonstrated that NMUR1 signaling promotes lung inflammatory ILC2 responses, highlighting the importance of neuro-immune crosstalk in allergic inflammation at mucosal surfaces [92]. Overall, these studies provide a new approach for blocking allergic lung inflammation by controlling neuropeptide receptors, suggesting the development of a new treatment for asthma (see Figure 2).

3.2.2.2. Calcitonin gene-related peptide (CGRP)

Pulmonary neuroendocrine cells (PNECs) are rare endoderm-derived lung epithelial cells that constitute ~1% of the airway cell population [95]. PNECs reside in close proximity to ILC2s near airway branch points and act through calcitonin gene-related peptide (CGRP) to stimulate ILC2s and elicit downstream immune responses. In addition, PNECs act through the neurotransmitter gamma-aminobutyric acid (GABA) to induce goblet-cell hyperplasia, and lungs from human asthmatics show increased levels of PNECs (see Figure 2). These findings show that the PNEC–ILC2 neuro-immunological module functions at airway branch points to amplify allergic asthma responses [96].

3.2.2.3. Vasoactive intestinal peptide (VIP)

VIP is a member of the neuropeptide secretin family that is expressed in neurons of the intestine and pancreas and bronchial nucleus of the brain, which controls circadian rhythms. VIP receptors include the G protein-coupled receptors VPAC1 and VPAC2 [97]. During allergen exposure, activated nociceptors release VIP, which stimulates lung-resident ILC2s and newly differentiated T_H2 cells *via* the VPAC2 receptor. Type 2 cytokines, including IL-5 and IL-13, are released by ILC2s and T_H2 cells and initiate the chemotaxis and activation of eosinophils and macrophages, mucus production by goblet cells, and smooth muscle contraction, culminating in allergic inflammation and bronchial hyperresponsiveness (see Figure 2). Additionally, IL-5 activates nociceptors to trigger the release of VIP and other neuropeptides, leading to additional IL-5 production and creating an inflammatory signaling loop that promotes allergic inflammation [98].

3.2.2.4. Catecholamines

Catecholamines include adrenaline, norepinephrine and dopamine, and a recent study has shown that the sympathetic nervous system enhances the levels of IL-33 and ILC2s in adipose tissue. In addition, cold exposure induces IL-33 expression and increases eosinophil and ILC2 counts in adipose tissue, and sympathetic denervation induced by 6-hydroxydopamine (6-OHDA) eliminates this effect [99]. A new study has demonstrated that murine ILC2s express the b2-adrenergic receptor (b2AR) and colocalize with adrenergic neurons in the intestine. Although b2AR deficiency resulted in exaggerated ILC2 responses and type 2 inflammation both in intestinal and lung tissues, b2AR agonist treatment was associated with impaired ILC2 responses and reduced inflammation *in vivo*. These data provide the first evidence of a neuronal-derived regulatory circuit that limits ILC2-dependent type 2 inflammation [100] (see Figure 2).

3.2.2.5. Acetylcholine

Parasympathetic nerves produce acetylcholine, which can directly affect immune cells *via* muscarinic and nicotinic acetylcholine receptors. ILC2s express the α7-nicotinic acetylcholine receptor (α7nAChR), which is thought to have an anti-inflammatory role in several inflammatory diseases. A specific agonist for α7nAChR expressed on ILC2s reduces ILC2 effector function while decreasing expression of the key ILC2 transcription factor GATA-3 and critical inflammatory modulator NF-κB and reducing

phosphorylation of upstream kinase IKKα/β. Additionally, the specific α7nAChR agonist decreases cytokine production and AHR in a humanized ILC2 mouse model. Collectively, these data suggest that ILC2-expressed α7nAChR is a potential therapeutic target for the treatment of asthma mediated by ILC2 [101] (see Figure 2).

3.2.3. Regulation of ILC2 by epithelial cells

Brush cells, also termed tuft, caveolated, multivesicular, and fibrillovesicular cells, are components of the epithelial layer in the gastrointestinal and respiratory tracts [102]. Tuft cells, which are not only present in the mucosa of the respiratory tract but also in the small intestine, constitutively secrete IL-25, thereby regulating type 2 immune responses [103]. In helminth infection, tuft cell-derived IL-25 further stimulates ILC2s to secrete IL-13, which acts on epithelial crypt progenitors to promote differentiation of tuft and goblet cells, leading to increased frequencies of both. Tuft cells, ILC2s and epithelial progenitors therefore comprise a response circuit that mediates epithelial remodelling associated with type 2 immunity in the small intestine and perhaps at other mucosal barriers populated by these cells [104, 105]. A recent study demonstrated that dietary polysaccharides enable mice to accept *Tritrichomonas* colonization, resulting in the accumulation of acetate and succinic acid, metabolites of protoplasmic hydrogenates [106]. Tuft cells also express the succinic acid receptor (SUCNR1) and provide succinate in drinking water to activate ILC2 *via* a tufted-TRPM5- IL-25-dependent pathway [107] (see Figure 2).

4. Crosstalk between ILC2 and T_H2

As potential key synergists in immune activation and intermediates between damaged epithelium and adaptive immune system, ILC2s are hot research topics. Although previous studies have begun to reveal the mechanisms by which ILC2s can affect T_H2 cells, the importance of ILC2s in adaptive type 2 immunity is unclear, especially because T_H2 and Treg cells may also be directly activated by IL-33. Although adaptive type 2 immune cells are rare in most tissues under steady-state conditions, ILC2s are tissue-resident cells and quickly respond to type 2 alarmins by generating cytokines common to T_H2 (IL-5 and IL-13) and Treg (Amphiregulin) cells. Therefore, the division of labour and interaction between ILC2s and adaptive type 2 immune cells remains a basic unsolved problem (see Figure 2).

MHC-II-expressing ILC2s interact with antigen-specific T cells to instigate a dialog in which IL-2 production from T cells promotes ILC2 proliferation and IL-13 production [85, 86]. Such studies demonstrate the importance of ILC2s for the efficient development of rapid T_H2 cell responses.

In addition to MHC-II-mediated activation of helper T cells, the cognate interaction between the co-stimulatory molecule ICOSL on ILC2s and ICOS on T cells promotes T cell accumulation following IL-33 administration [108]. Furthermore, ICOS-ICOSL autocrine signals can enhance ILC2 proliferation [77] and a novel PD-L1-controlled mechanism for type 2 polarization, with ILC2s mediating an innate checkpoint to control adaptive T helper responses [81]. OX40L expression by ILC2s is required for IL-33-driven T_H2 and Treg cell expansion [90].

ILC2s can also regulate the function of T cells, not by directly acting on immature CD4 T cells but by cooperating with DCs to induce T_H2 activation [9]. Contrary to models in which ILC2s help to initiate and maintain type 2 responses, ILC2 and CD4 T cell responses have been proposed to develop independently through the tissue-localized exposure of these cells to locally produced cytokines, which would constitute the checkpoint that activates the type 2 response, as opposed to the interaction of these cells in tissue [109]. Therefore, interaction between ILC2s and adaptive type 2 immune cells is highly complicated, varying according to anatomical location, activating signals and the time phase of the immune response. There is no doubt that the study of the interaction between ILC2s and T_H2 is challenging, but it has also become a hot topic in the study of the type 2 immune response.

5. Summary

As our understanding of T_H2 cells becomes more clearer, the role of these cells in the entire network of asthmatic cells becomes more apparent. However, there are still many questions regarding how to integrate various signals received by T cells to form transcriptional and epigenetic landscapes to support the T_H2 cell response [110]. For example, how do polarized T_H2 cells migrate back to the

pulmonary allergic inflammatory site? Why does IL-33 selectively control IL-5 and IL-13 expression but not that of IL-4? What role does IL-4 play in T_H2-mediated asthma [111]? Since ILC2s were described in detail in 2010, ILC2s have been well followed with a great deal of enthusiasm. As evidence grows in this new field, it is now recognized that ILC2s are associated with multiple disease conditions in addition to asthma. There are still many questions to be solved, including the following:

a. What is the heterogeneity of ILC2s in the body? Overall, the tissue distribution of these cells and their diversity complicate analysis. Further study of this heterogeneity is necessary.
b. Do ILC2s express specific surface molecular markers that may serve as targets for future targeted treatment of inflammatory diseases? Due to the lack of known cell-specific surface markers, current strategies for the specific consumption of ILCs are limited. A selective marker, or a specific marker that distinguishes subsets of ILC from different plastic stages, will be helpful in finding new ways to treat inflammatory diseases.
c. Although ILC2 cells can induce eosinophils, airway hyperresponsiveness, and mucus secretion, it is necessary to further examine interaction in the T_H2-IgE- mast cell pathway, which is most relevant to the clinical manifestations of asthma.

Research on ILC2s has become increasingly popular in recent years. How to further clarify the effect of ILC2s on asthma and how to treat these cells as a therapeutic goal remains a challenge, which requires our continued efforts in the future.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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