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Invited Review Article

Trained innate lymphoid cells in allergic diseases

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ABSTRACT

Group 2 innate lymphoid cells (ILC2s) reside in peripheral tissues such as the lungs, skin, nasal cavity, and gut and provoke innate type 2 immunity against allergen exposure, parasitic worm infection, and respiratory virus infection by producing T_H2 cytokines. Recent advances in understanding ILC2 biology revealed that ILC2s can be trained by IL-33 or allergic inflammation, are long-lived, and mount memory-like type 2 immune responses to any other allergens afterwards. In contrast, IL-33, together with retinoic acid, induces IL-10-producing immunosuppressive ILC2s. In this review, we discuss how the allergic cytokine milieu and other immune cells direct the generation of trained ILC2s with immunostimulatory or immunosuppressive recall capability in allergic diseases and infections associated with type 2 immunity. The molecular mechanisms of trained immunity by ILCs and the physiological relevance of trained ILC2s are also discussed.

Introduction

Innate lymphoid cells (ILCs) serve innate helper and cytotoxic functions to cope with infections by pathogens such as bacteria, parasitic worms, and fungi; allergen exposure; and tumor development.[1–8] ILCs lack rearranged antigen receptors, which require RAG1/RAG2. Cytotoxic ILCs are the most well-characterized ILCs, known as natural killer (NK) cells. Other ILCs are helper ILCs and lymphoid tissue inducer (LTi) cells. Helper ILCs are classified into ILC1s, ILC2s, and ILC3s based on their transcriptional requirements and effector cytokine production: T-bet-dependent IFN-γ and TNF-α production by ILC1s, GATA-3-dependent IL-5 and IL-13 production by ILC2s, and RORγt/AHR-dependent IL-17 and IL-22 production by ILC3s.[1,2,9–12] While NK cells express T-bet and produce IFN-γ similar to ILC1s, Eomesodermin expression furnishes NK cells with high cytotoxicity.[1,2,13] LTi cells are ILC3-related populations that are indispensable for lymphoid tissue organogenesis.[14] While high levels of RORγt/AHR expression in the LTi cells drive IL-17 and IL-22 production similar to ILC3s, LTi cells also express LTA and LTB, which activate stromal cells to develop secondary lymphoid organs during embryogenesis. Helper ILCs generally reside in peripheral tissues, while NK cells move around to locate aberrant cells, such as infected or transformed cells.[15,16] The cytokine receptor common subunit gamma (γc) family of cytokines is critical for the differentiation of helper ILCs and LTi cells, all of which express γc and its binding partner, IL-7 receptor α (IL-7Rα) chain.[1,2,17] Although the differentiation of ILC1s and NK cells requires IL-15 signaling through IL2Rβ/γc, other ILCs rely on IL-7 signaling through IL-7Rα/γc.[3,5,17]

ILC2s are associated with diverse biological processes, such as allergies, tissue repair, fibrosis, anti-parasitic worm immunity, and metabolic diseases.[1,3,4,18–20] In particular, the role of ILC2s in allergy pathogenesis has been intensively studied. Cumulative evidence indicates that ILC2s are major players in initiating allergic reactions by producing type 2 cytokines, including IL-5 and IL-13, especially in the lung, skin, nasal cavity, and intestines (Fig. 1).[4,19,21–24] IL-5 produced from activated ILC2s attracts eosinophils to the site of allergic inflammation in mice.[25] Other mouse data revealed that mucus production by epithelial cells is induced by ILC2-derived IL-13, which also elicits $CCL17^+$ dendritic cells (DCs) and subsequent T_H2 differentiation.[26] In addition, the absence of ILC2s alleviates murine allergic diseases, especially in the acute or subacute phase.[19,27] The relevance of ILC2s to human allergies has been described by many groups. Increased numbers of dysregulated ILC2s are observed in skin with atopic dermatitis,[19,21] the nasal polyps of chronic rhinosinusitis,[24] and sputum from asthma patients.[22] The physiological significance of dysregulated ILC2s in allergic patients remains obscure because ILC2-selective blockade

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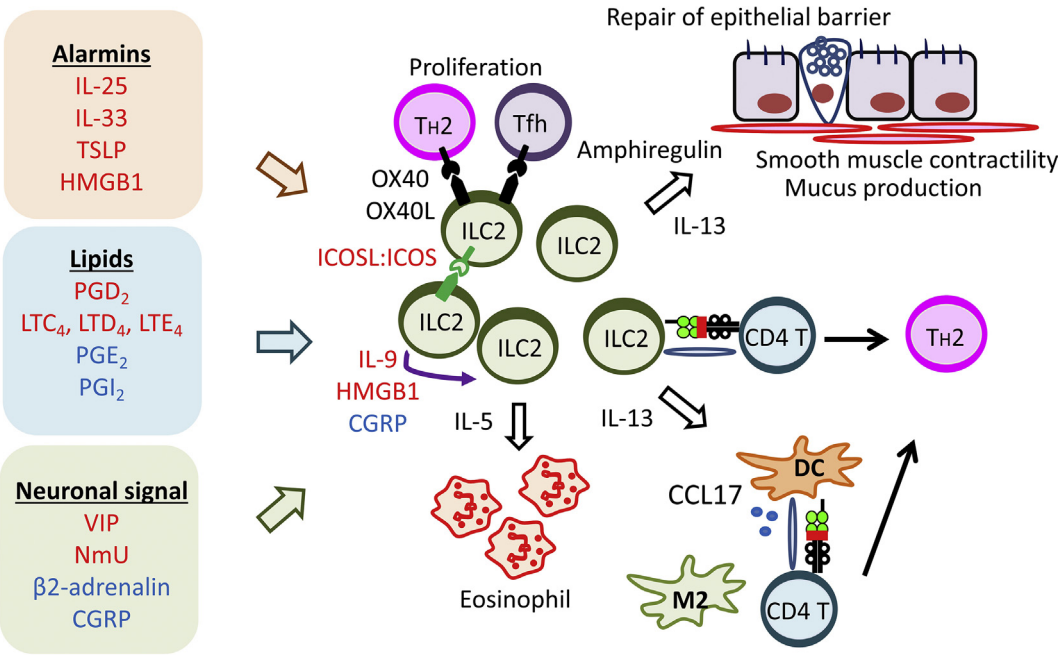

Fig. 1. ILC2s mediate innate type 2 immunity in allergic diseases. ILC2 activity is regulated by alarmins, lipids, and neuronal signals. Positive regulators (shown in red) are alarmins, PDG2, LTD4, VIP, NmU, and IL-9. Negative regulators (shown in blue) are PGE2, PGI2, β2-adrenalin, and CGRP. The ICOS:ICOSL interaction between ILC2s is required to sustain ILC2 activity. ILC2-derived IL-5 recruits eosinophils to the site of allergic inflammation. ILC2s also produce IL-13, which induces recruitment of CCL17+ DCs for Th2 differentiation, M2 acrophages, mucus production by goblet cells, and smooth muscle contractility. Amphiregulin from ILC2s contributes to epithelial barrier repair. ILC2s directly present antigens to CD4+ T cells for Th2 differentiation. OX40L on ILC2s ligates OX40 on Th2 and Tfh cells to enhance proliferation.

therapy has not yet been exploited. Nevertheless, ILC2s can be pharmacologic targets in patients with allergies.

Emerging data suggest that ILCs can be trained by inflammatory stimuli and persist to strongly respond to a second challenge by stimuli.[28–31] These ILCs have been referred to as “trained” or “memory-like” ILCs. Such recall responses were first found in human and mouse NK cells after cytokine stimulation. NK cells activated by IL-12 and IL-18 exhibit increased IFN-γ response against re-stimulation with cytokines or ligation of activation receptors after returning to the resting stage.[30,32] Meanwhile, mouse NK cells memorize virus-specific inflammation during murine cytomegalovirus (MCMV) infection.[29] In the MCMV-infected host, NK cells are mainly activated by viral protein m157, which directly ligates an NK cell activation receptor, Ly49H.[33,34] After MCMV infection, some activated Ly49H$^+$ NK cells persist for at least 50 days post-infection and mount recall responses against a second challenge of MCMV infection.[29] IL-12, IL-18, and activating signals through Ly49H and DNAM1 are required for the emergence of memory NK cells.[35,36] Virus-specific memory NK cells are also found in human NK cell populations expressing the NK cell-activating receptor NKG2C. Human NKG2C$^+$ NK cells are responsive to the human cytomegalovirus (HCMV) UL40 on non-MHC class I molecules, HLA-E, and they retain high memory reactivity against HCMV in patients who received hematopoietic stem cell transplantation.[31]

Memory-like or trained ILC2s have been identified by Dr. Takei's group.[28] Once ILC2s are activated by certain allergic stimuli or IL-33, some activated ILC2s can survive while retaining recall capacity against any allergic stimuli until 3–4 months after the initial allergen exposure (Fig. 2). This recall response by trained ILC2s is nonspecific to allergen types and induces T_H2 differentiation.[28] Therefore, ILC2 memory is a reasonable explanation for how individuals can be sensitized by a broad range of antigens. Here, we will review how ILC2s sense environmental inflammatory cues and change their phenotypes to trained ILC2s or other heterogenic ILC2 populations in allergic diseases and infections that elicit type 2 immunity.

ILC2 activation via alarmins

ILC2s have been found in the skin, adipose tissue, gut, lungs, lymph nodes, meninges, joint fluid, islets, and fibrotic liver.[4,18,21,28,37–42] Peripheral ILC2s in these tissues are mainly activated by soluble molecules. Alarmin cytokines IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) play a major role in ILC2-mediated allergic inflammation. In general, allergens exhibit proteinase activity, which can disrupt epithelial cells and stromal cells resulting in extracellular release of IL-33 for ILC2 activation. After exposure to allergens, IL-25 and TSLP are also secreted from the epithelial cells, stromal cells and immune cells to induce ILC2 activation through their cognate receptors (Fig. 1).[1,19,21,41,43,44] Reporter knock-in mice with the IL-25 locus revealed that IL-25 is mainly expressed by rare epithelial cells known as tuft cells in the intestines and lungs.[44] Another study using IL-33 reporter mice showed that type II alveolar epithelial cells are major cells expressing IL-33 in ovalbumin-sensitized mice.[45] TSLP is expressed by epithelial cells as well as hematopoietic cells, such as DCs, basophils, and mast cells.[46] Recently, epithelial and mesenchymal high-mobility group box 1 (HMGB1) was reported as another alarmin that can promote ILC2 proliferation and cytokine production in humans and mice.[47–50] Mouse data showed that HMGB1 can be produced by airway smooth muscle and lung ILC2s, which also express RAGE, a receptor for HMGB1.[47] HMGB1 from IL-33-stimulated ILC2s acts on ILC2s themselves to enhance production of IL-5, IL-9, and IL-13. Collectively, these data indicate that alarmin-expressing cells differ in various tissues and constitute tissue-specific environments. Such tissue-imprinting signals contribute to the diverse heterogeneity of ILC2s. For example, gut

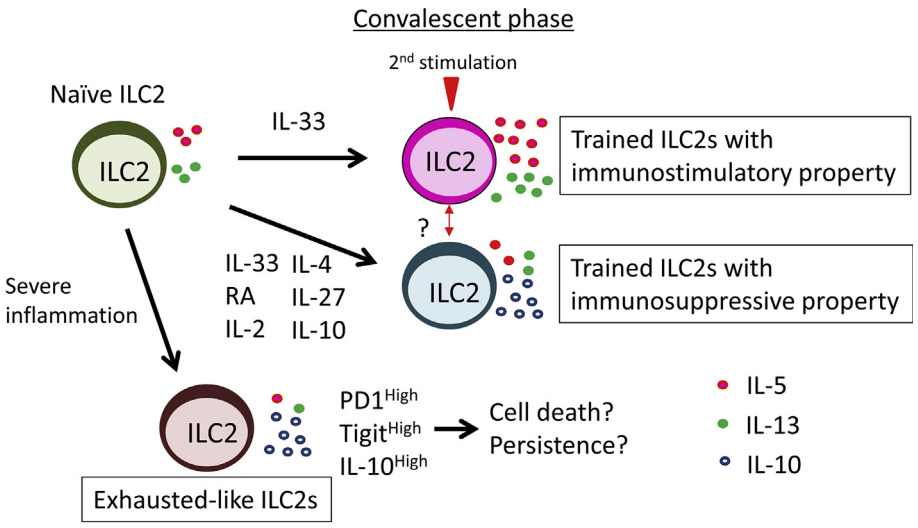

Fig. 2. The fate of ILC2s that experience allergic inflammation. ILC2s activated by IL-33 or allergic inflammation expand in the acute phase and then contract and persist in the convalescent phase. Such persistent ILC2s include an immunostimulatory population with a high capability for IL-5 and IL-13 production and an immunosuppressive population with a high capability for IL-10 production. The boundary between these populations remain unclear in vivo. IL-10 production by ILC2s is elicited by IL-33, retinoic acid, IL-2, IL-4, IL-27, and IL-10 in vitro. Severe allergic inflammation induces exhausted-like ILC2s with high expression of PD-1, Tigit, and IL-10 and low expression of IL-5 and IL-13. The fate of the exhausted-like ILC2s remains elusive.

ILC2s express more IL-25R but less ST2, a receptor for IL-33, than do fat and lung ILC2s, indicating that gut ILC2s depend on IL-25 for their homeostasis and activation.[51] Thus, tissue-specific alarmins are quite important for ILC2 activation.

Lipid mediators and ILC2s

ILC2s also receive regulatory signals from lipid mediators (Fig. 1).[52,53] Prostaglandin D_2 (PGD_2) and leukotrienes are produced by mast cells, eosinophils, and T_H2 cells during allergy development.[54] Of note, CRTH2, a receptor for PGD_2, is commonly used to identify human ILC2s among the lineage-negative population of peripheral blood.[55] Human ILC2s produce PGD_2, which contributes to the maintenance of ILC2 activity in an autocrine manner.[56,57] Murine peripheral blood ILC2s also express CRTH2 and migrate toward PGD_2, resulting in the accumulation of ILC2s in helminth-infected lungs.[58] Cysteinyl leukotrienes (cysLTs), leukotriene (LT) C4, LTD4, and LTE4 are released from eosinophils, basophils, and mast cells during allergies. Among these cysLTs, LTE4 augments cytokine production by human ILC2s when co-cultured with PGD_2, IL-25, IL-33, and TSLP.[56] Murine lung ILC2s can be activated by LTD4 in mice challenged with *Alternaria* species and produce IL-4, which is not induced by IL-33.[59] Meanwhile, PGE_2 and PGI_2 are inhibitory lipids that suppress IL-5 and IL-13 production by ILC2s in humans and mice.[60–62] Administration of a PGI_2 analog decreases ILC2 cytokine production and ILC2 numbers in lungs challenged with *Alternaria* extract, resulting in reduced airway inflammation.[62] Thus, lipid mediators play critical roles in regulating ILC2 activity in addition to alarmins.

Neuron-ILC2 axis

The nervous system provides critical signaling for ILC2 activity (Fig. 1). ILC2s are localized near peripheral neural endings in the lungs and intestines.[63–65] ILC2s express NMUR1, a receptor for neuropeptide neuromedin U (NmU), and perceives activation signals from neurons.[63–65] Caloric intake induces neuronal release of vasointestinal peptide (VIP), which promotes IL-5 and IL-13 production by ILC2s through its receptor VIP receptor 2.[66] In contrast to these stimulatory inputs, adrenergic signaling through the β2-adrenergic receptor (β2AR) on ILC2s inhibits IL-5 and IL-13 production.[67] Neuropeptide calcitonin gene-related peptide (CGRP) has ambivalent roles in controlling ILC2 activity.[68,69] Deletion of pulmonary neuroendocrine cells, which are lung epithelial cells that produce CGRP, leads to a reduction in allergic inflammation.[69] However, activated ILC2s also secrete CGRP, which supports IL-5 production with IL-33 and NmU but inhibits IL-13 production. When ILC2s lacking CGRP receptor signaling are adoptively transferred to $RAG2^{-/-}\gamma c^{-/-}$ mice, the mice show high resistance to helminth infection, suggesting that CGRP negatively affects ILC2 activity during the development of type 2 immunity.[68] Thus, the neuron-ILC2 axis is important for understanding the regulatory mechanisms of ILC2s.

ILC2s are regulated by cell/cell contact

Direct cell–cell interactions of ILC2s with themselves and other cell types can play a key role in shaping ILC2 functions (Fig. 1). Human and mouse ILC2s express inducible T cell costimulatory (ICOS) and ICOS ligand.[70] The ICOS:ICOS ligand pathway induces STAT5 activation in ILC2s, leading to IL-13 production and homeostatic survival of ILC2s. Adoptively transferred $ICOS^{-/-}$ ILC2s cannot elicit airway hyperreactivity in $Rag2^{-/-}Il2rg^{-/-}$ mice intranasally treated with IL-33. Glucocorticoid-induced tumor necrosis factor receptor (GITR) is expressed on resting and activated ILC2s in humans and mice.[71,72] Genetic deletion of GITR on ILC2s and blockade of GITR revealed that GITR is crucial for ILC2 effector functions, such as T_H2 cytokine production and proliferation. GITR signaling together with IL-33 strongly augments the production of IL-9, which supports ILC2 growth and cytokine production in an autocrine fashion.[72] However, GITR ligand-expressing cells that promote ILC2 activation in airway allergy remain unclear.

Expression of inhibitory receptors, KLRG1, Programmed cell death ligand 1 (PD-1), or T-cell immunoreceptor with immunoglobulin and ITIM domains (Tigit) on ILC2s can be induced by maturation or allergic inflammation.[37,73,74] $KLRG1^+$ cells are recognized as mature and/or activated ILC2s in mice.[37] Although ILC2 progenitor cells in the bone marrow are negative for KLRG1,

most gut ILC2s and approximately 50% of lung ILC2s express KLRG1. KLRG1 ligands include N- and R-cadherin expressed in the nervous system and E-cadherin expressed mainly on epithelial cells. Skin ILC2s of atopic dermatitis patients have a larger KLRG1$^+$ population than those in control healthy skin.[19] In humans and mice, the interaction of E-cadherin with KLRG1 inhibits ILC2 activity in vitro.[19] PD-1 and Tigit are checkpoint inhibitory receptors expressed on activated ILC2s[8,73,74] and are almost undetectable on steady-state ILC2s. PD-1 expression in murine ILC2s is upregulated by type 2 inflammation and negatively regulates the number of KLRG1$^+$ ILC2s by inhibiting STAT5 signaling during helminth infection.[73] Tigit can be expressed on severely activated ILC2s in the bronchoalveolar space of lungs instilled with high doses of papain.[74,75] Tigit$^+$ ILC2s secrete less IL-5 and IL-33 than Tigit$^-$ ILC2s. However, the functions of Tigit on ILC2s have yet to be described.

IL-33 is necessary for memory-like or trained ILC2s

Martinez-Gonzalez *et al.* first reported that some IL-33-stimulated mouse ILC2s can persist in the lungs and lymph nodes for up to 3–4 months and respond well to suboptimal doses of IL-33, TSLP, and IL-25.[28] Therefore, IL-33 is apparently required for the development of long-lasting trained ILC2s. However, the determining factors for trained ILC2 development are not well understood, especially when trained ILC2s are induced by allergens. Lung and lymph node ILC2s that have experienced inflammation due to *Aspergillus* protease can mount recall responses against different allergens, papain, or IL-33.[28] In this case, unknown co-stimulatory signals other than IL-33 may exist for the generation of trained ILC2s, but they have been poorly studied.

IL-25 is also a potent ILC2 stimulator in allergic diseases and helminth infections.[44] However, IL-25 may not be involved in trained ILC2s because it induces different subsets of ILC2s, inflammatory ILC2s (iILC2s).[76] The IL-25-responsive subsets are characterized by high levels of KLRG1 and IL17RB, a receptor for IL-25, and low levels of ST2, a receptor for IL-33, and these subsets appear in the lungs or intestines after *N. brasiliensis* infection or IL-25 administration.[76] Moreover, iILC2s have a migratory capacity that is not observed in major ILC2 populations. G protein-coupled sphingosine 1-phosphate (S1P) receptors are necessary for iILC2s to migrate from lymphoid tissues to lymphatic vessels.[77] iILC2s in intestines infected with *N. brasiliensis* can migrate to the lungs in an S1P-dependent manner and prevent severe epithelial destruction by *N. brasiliensis* larvae.[77] Since ILC2-trained immunity can be established by *Aspergillus* protease, cytokines other than IL-33 or activating ligands may contribute to ILC2-trained responses. TSLP may be involved in signaling required for trained ILC2s after allergen exposure because TSLP receptor expression is ubiquitously high on ILC2s in tissues.[51] Although many mechanisms underlying ILC2 activity have been reported, as mentioned earlier, most of them remain to be tested for ILC2-trained immunity.

Trained ILC2s and virus infection

Early-life viral infections, such as respiratory syncytial virus (RSV) and rhinovirus (RV) infection, are risk factors for asthma development.[78,79] Severe RSV infection in infants increases the risk for asthma at 13 years of age.[79] Infants who are admitted to the hospital for RV infection tend to acquire asthma by age 7.[78] A recent study suggests that severity of RSV infection in infants is associated with increased ILC2 numbers and activity in nasal aspirates.[80] Therefore, it is fascinating to assume that trained ILC2s could be induced by early-life viral infections and play a critical role in the development of school-age asthma.

Several mouse studies using BALB/c mice were conducted to elucidate how ILC2 contributes to type 2 inflammation caused by RSV or RV infection. Stier *et al.* clarified that infection with RSV clinical isolates induces IL-13-producing ILC2s through a TSLP-dependent mechanism in adult BALB/c mice.[81] Saravia *et al.* showed that neonatal RSV (A2 strain) infection promotes ILC2 activation and deteriorates asthma-like inflammation after reinfection with RSV at 4 weeks of age.[82] This asthma-like inflammation is dependent on IL-33 because a blockade of IL-33R by antibodies ameliorates the disease. Although absolute numbers of RSV-experienced ILC2s return to normal levels before reinfection, ILC2s proliferate well upon a second challenge of RSV infection. Therefore, frequent RSV infections may sustain the generation and reactivity of trained ILC2s.

Neonatal RV infection at day 6 leads to sustained asthma-like pathological changes, including IL-13-dependent mucous metaplasia and airway hyperresponsiveness.[83] This asthma-like disease relies on IL-25, IL-33, TSLP, and IL-13-producing ILC2s.[83,84] Interestingly, IL-17Rb expression on ILC2s is not altered by past RV infection in adult mice, unlike IL-33-activated trained ILC2s, which is described further in the next section.[83] The genetic background or inflammation types may affect IL-17R expression by activated ILC2s. Furthermore, infant mice infected with different strains of RV on days 6 and 13 showed exaggerated mucus metaplasia and airway hyperresponsiveness due to ILC2s, suggesting that early life re-infection with RV may train ILC2 recall responses.[85] Collectively, these data reveal a possible interaction of trained ILC2s with the development of virus-related asthma.

Machinery of ILC recall responses

Transcriptome analysis of trained ILC2s at 4 months after IL-33 stimulation and naïve ILC2s revealed that *Il17rb* mRNA expression is 2-fold higher in trained ILC2s than that in naïve ILC2s.[28] *Il17rb* encodes IL-17Rb, which combines with IL-17Ra to form IL-17R, an IL-25 receptor. Increased IL-17R expression on trained ILC2s permits increased cytokine production in response to IL-25. However, robust cytokine production by trained ILC2s is induced not only by IL-25 but also by IL-33 and TSLP.[28] Since expression levels of IL-33 and TSLP receptors are not differentially increased in trained ILC2s, there should be unknown pathways that confer the capability for memory-like responses in trained ILC2s.

Possible changes in chromatin accessibility or epigenetic markers may explain the trained immune responses by ILCs. The regulatory circuitries that control early responses by resting ILCs include active and poised enhancers.[86,87] Chromatin in proximity to effector genes is associated with early cytokine production by ILCs. An assay for transposase-accessible chromatin using sequencing (ATAC-seq) revealed that regulatory loci for ILC effector gene expression are accessible but poised before infection or cytokine stimulation in humans and mice. These chromatin proximities might contribute to enhanced recall responses by trained ILC2s as well as innate responses by naïve ILC2s. Epigenetic changes in memory NK cells after MCMV infection have been investigated.[88] Regulatory loci for effector gene expression are more accessible in memory NK cells induced by MCMV infection than those in naïve NK cells. For example, increased chromatin accessibility was found in the *Prf1* locus, which correlated with increased transcription. In addition, memory NK cells and memory CD8$^+$ T cells share common epigenetic signatures for cytotoxicity and marker expression, as exemplified by *Gzmb, Prf1, Klrg1,* and *Sell* loci.[88] Therefore, dynamic epigenetic modifications may support trained immunity by NK cells and ILC2s.

Human and mouse ILC2s process and present MHC-class II (MHCII) antigens for T_H2 differentiation in vitro.[89] MHCII-

deficient ILC2s are not able to expel *N. brasiliensis* when adaptively transferred to IL-13-deficient mice infected with the worms. If the antigen-presenting ability were enhanced in trained ILC2s, T_H2 responses against the same allergen could be augmented by trained ILC2s. However, this possibility remains to be tested.

Long-lived IL-10-producing ILC2s

IL-10 is a major immunosuppressive cytokine that can be produced by ILCs.[2,74,90–94] Murine NK cells mainly produce IL-10 during infections with MCMV, lymphocytic choriomeningitis virus (LCMV), *Toxoplasma gondii*, and *Listeria monocytogenes*.[2] ILC2s can also produce IL-10 at sites of severe allergic inflammation and persist in tissues for some time.[90] IL-10-producing lung ILC2s emerge after systemic injection of IL-33 and remain in the lung through day 30 (Fig. 2). The long-lived ILC2s quickly proliferate and produce IL-10 in response to the second challenge of IL-33. Frequent intranasal administration of papain at high doses is required to observe IL-10-producing ILC2s that are more likely to emerge in the bronchoalveolar space than in the lung parenchyma.[74]

Robust IL-10 secretion by murine lung ILC2s is induced when cultured with IL-2, IL-7, IL-33, and retinoic acid in vitro.[90] Another mouse study observed that intestinal ILC2s producing IL-10 can be elicited by IL-2, IL-4, IL-27, IL-10, and NmU.[91] Transcription factors Runx1 and Runx3 negatively regulate IL-10 production.[74] IL-33-activated ILC2s lacking both Runx1 and Runx3 or their binding partner, Cbfβ, exhibit a so-called “exhausted-like” phenotype featuring high IL-10 production, low IL5/IL-13 production, and high expression of exhaustion markers such as PD-1 and Tigit. Similar low-reactive ILC2s with high expression of PD-1 and Tigit can be found even in wild-type mice sensitized with high doses of papain. Future studies to investigate the longevity of the “exhausted-like” ILC2s are warranted (Fig. 2).

Human ILC2s also acquire the ability to produce IL-10 when stimulated with retinoic acid in vitro.[95] Activation of $CD4^+$ T cells and ILC2s is suppressed by IL-10-producing ILC2s. An increase in human IL-10-producing ILC2s is observed in nasal tissue from chronic rhinosinusitis patients with nasal polyps. Another report clarified that increased IL-10-producing ILC2s in peripheral blood are associated with improvement of allergic rhinitis during allergic-specific immunotherapy against house-dust-mite.[96] Therefore, IL-10 derived from ILC2s is relevant to human allergies and may have an inhibitory role in chronic allergies.

Conclusion

ILC2s can be trained by IL-33 and allergen stimuli and persist with memory-like properties in the peripheral tissues for a long time. Lung ILC2s have been mainly studied for ILC2 recall responses in asthma-related models, whereas other allergic models remain to be tested for memory-like responses. The pathological importance of trained ILC2s remains unclear because specific depletion of trained ILC2s or trained ILC2-specific deletion of genes is technically difficult. IL-33 potentiates the induction of immunostimulatory and immunosuppressive trained ILC2s during allergy (Fig. 2). If IL-10-producing trained ILC2s are specifically induced by retinoic acid or other possible reagents, the immunosuppressive trained ILC2s could be harnessed for antigen desensitization therapy. We are just starting to understand the molecular mechanism underlying ILC2 longevity and recall responses. Controlling the fate of ILC2s toward allergy development or suppression is crucial to utilize ILC2s as therapeutic approaches to prevent allergy deterioration.

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Conflict of interest

The authors have no conflict of interest to declare.

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