



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.

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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 ROR γ t/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 ROR γ t/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 (γ c) family of cytokines is critical for the differentiation of helper ILCs and LTi cells, all of which express γ c and its binding partner, IL-7 receptor α (IL-7R α) chain.^{1,2,17} Although the differentiation of ILC1s and NK cells requires IL-15 signaling through IL2R β / γ c, other ILCs rely on IL-7 signaling through IL-7R α / γ c.^{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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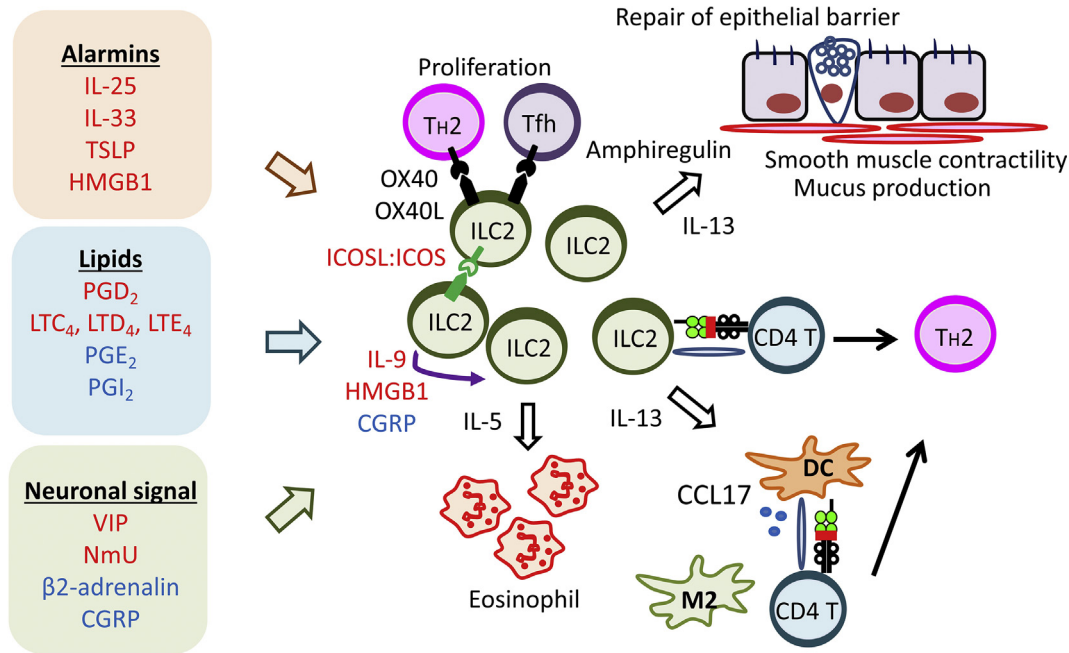


Fig. 1. ILC2s mediate innate type 2 immunity in allergic diseases. ILC2 activity is regulated by alarmins, lipids, and neuronal signals. Positive regulators (shown in red) are alarmins, PDG₂, LTD₄, VIP, NmU, and IL-9. Negative regulators (shown in blue) are PGE₂, PGI₂, β -adrenalin, and CGRP. The ICOSL:ICOS 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 macrophages, 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 Th₂ 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 heterogeneous 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

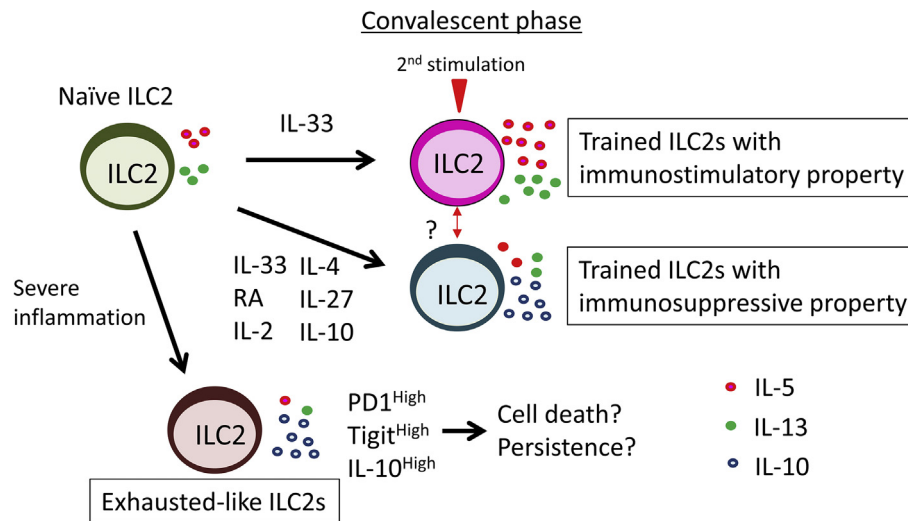


Fig. 2. The fate of ILC2s that experience allergic inflammation. ILC2s activated by IL-33 or allergic inflammation expand in the acute phase and then contract and persist in the convalescent phase. Such persistent ILC2s include an immunostimulatory population with a high capability for IL-5 and IL-13 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 D₂ (PGD₂) and leukotrienes are produced by mast cells, eosinophils, and T_H2 cells during allergy development.⁵⁴ Of note, CRTH2, a receptor for PGD₂, is commonly used to identify human ILC2s among the lineage-negative population of peripheral blood.⁵⁵ Human ILC2s produce PGD₂, which contributes to the maintenance of ILC2 activity in an autocrine manner.^{56,57} Murine peripheral blood ILC2s also express CRTH2 and migrate toward PGD₂, 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 PGD₂, 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, PGE₂ and PGI₂ are inhibitory lipids that suppress IL-5 and IL-13 production by ILC2s in humans and mice.^{60–62} Administration of a PGI₂ 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 β 2-adrenergic receptor (β 2AR) 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^{-/-} γ 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, Cbfb, 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 allergen-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.

References

- Vivier E, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, et al. Innate lymphoid cells: 10 Years on. *Cell* 2018;**174**:1054–66.
- Ebihara T. Dichotomous regulation of acquired immunity by innate lymphoid cells. *Cells* 2020;**9**:1193.
- Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, et al. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature* 2010;**463**:540–4.
- Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* 2010;**464**:1367–70.
- Satoh-Takayama N, Vosshenrich CA, Lesjean-Pottier S, Sawa S, Lochner M, Rattis F, et al. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. *Immunity* 2008;**29**:958–70.
- Cella M, Fuchs A, Vermi W, Facchetti F, Otero K, Lennerz JK, et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* 2009;**457**:722–5.
- Ebihara T, Song C, Ryu SH, Plougastel-Douglas B, Yang L, Levanon D, et al. Runx3 specifies lineage commitment of innate lymphoid cells. *Nat Immunol* 2015;**16**:1124–33.
- Moral JA, Leung J, Rojas LA, Ruan J, Zhao J, Sethna Z, et al. ILC2s amplify PD-1 blockade by activating tissue-specific cancer immunity. *Nature* 2020;**579**:130–5.
- Yagi R, Zhong C, Northrup DL, Yu F, Bouladoux N, Spencer S, et al. The transcription factor GATA3 is critical for the development of all IL-7Ralpha-expressing innate lymphoid cells. *Immunity* 2014;**40**:378–88.
- Klose CS, Kiss EA, Schwierzeck V, Ebert K, Hoyler T, d’Hargues Y, et al. A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells. *Nature* 2013;**494**:261–5.
- Sawa S, Lochner M, Satoh-Takayama N, Dulauroy S, Berard M, Kleinschek M, et al. RORgammat+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota. *Nat Immunol* 2011;**12**:320–6.
- Qiu J, Guo X, Chen ZM, He L, Sonnenberg GF, Artis D, et al. Group 3 innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through aryl hydrocarbon receptor signaling and regulation of microflora. *Immunity* 2013;**39**:386–99.
- Dausy C, Faure F, Mayol K, Viel S, Gasteiger G, Charrier E, et al. T-bet and Eomes instruct the development of two distinct natural killer cell lineages in the liver and in the bone marrow. *J Exp Med* 2014;**211**:563–77.
- Sawa S, Cherrier M, Lochner M, Satoh-Takayama N, Fehling HJ, Langa F, et al. Lineage relationship analysis of RORgammat+ innate lymphoid cells. *Science* 2010;**330**:665–9.
- Sojka DK, Plougastel-Douglas B, Yang L, Pak-Wittel MA, Artyomov MN, Ivanova Y, et al. Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. *eLife* 2014;**3**:e01659.
- Gasteiger G, Fan X, Dikiy S, Lee SY, Rudensky AY. Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. *Science* 2015;**350**:981–5.
- Klose CS, Flach M, Mohle L, Rogell L, Hoyler T, Ebert K, et al. Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell* 2014;**157**:340–56.
- Lee MW, Odegaard JL, Mukundan L, Qiu Y, Molofsky AB, Nussbaum JC, et al. Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* 2015;**160**:74–87.
- Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, Wang X, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 2013;**210**:2939–50.
- Li D, Guabiraba R, Besnard AG, Komai-Koma M, Jabir MS, Zhang L, et al. IL-33 promotes ST2-dependent lung fibrosis by the induction of alternatively activated macrophages and innate lymphoid cells in mice. *J Allergy Clin Immunol* 2014;**134**:1422–32. e11.
- Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, Sonnenberg GF, et al. TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci Transl Med* 2013;**5**:170ra16.
- Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, O’Byrne PM, et al. Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. *J Allergy Clin Immunol* 2016;**137**:75–86. e8.
- Bruggen MC, Bauer WM, Reininger B, Clim E, Captarencu C, Steiner GE, et al. In situ mapping of innate lymphoid cells in human skin: evidence for remarkable differences between normal and inflamed skin. *J Invest Dermatol* 2016;**136**:2396–405.

24. Bal SM, Bernink JH, Nagasawa M, Groot J, Shikhaaga MM, Golebski K, et al. IL-1beta, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs. *Nat Immunol* 2016;**17**:636–45.
25. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 2013;**502**:245–8.
26. Halim TY, Hwang YY, Scanlon ST, Zaghoulani H, Garbi N, Fallon PG, et al. Group 2 innate lymphoid cells license dendritic cells to potentiate memory TH2 cell responses. *Nat Immunol* 2016;**17**:57–64.
27. Halim TY, MacLaren A, Romanish MT, Gold MJ, McNagny KM, Takei F. Retinoic-acid-receptor-related orphan nuclear receptor alpha is required for natural helper cell development and allergic inflammation. *Immunity* 2012;**37**:463–74.
28. Martinez-Gonzalez I, Matha L, Steer CA, Ghaedi M, Poon GF, Takei F. Allergen-experienced group 2 innate lymphoid cells acquire memory-like properties and enhance allergic lung inflammation. *Immunity* 2016;**45**:198–208.
29. Sun JC, Beilke JN, Lanier LL. Adaptive immune features of natural killer cells. *Nature* 2009;**457**:557–61.
30. Cooper MA, Elliott JM, Keyel PA, Yang L, Carrero JA, Yokoyama WM. Cytokine-induced memory-like natural killer cells. *Proc Natl Acad Sci U S A* 2009;**106**:1915–9.
31. Brillantes M, Beaulieu AM. Memory and memory-like NK cell responses to microbial pathogens. *Front Cell Infect Microbiol* 2020;**10**:102.
32. Romee R, Schneider SE, Leong JW, Chase JM, Keppel CR, Sullivan RP, et al. Cytokine activation induces human memory-like NK cells. *Blood* 2012;**120**:4751–60.
33. Arase H, Mocarski ES, Campbell AE, Hill AB, Lanier LL. Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. *Science* 2002;**296**:1323–6.
34. Smith HR, Heusel JW, Mehta IK, Kim S, Dorner BG, Naidenko OV, et al. Recognition of a virus-encoded ligand by a natural killer cell activation receptor. *Proc Natl Acad Sci U S A* 2002;**99**:8826–31.
35. Min-Oo G, Lanier LL. Cytomegalovirus generates long-lived antigen-specific NK cells with diminished bystander activation to heterologous infection. *J Exp Med* 2014;**211**:2669–80.
36. Nabekura T, Kanaya M, Shibuya A, Fu G, Gascoigne NR, Lanier LL. Costimulatory molecule DNAM-1 is essential for optimal differentiation of memory natural killer cells during mouse cytomegalovirus infection. *Immunity* 2014;**40**:225–34.
37. Hoyler T, Klose CS, Souabni A, Turqueti-Neves A, Pfeifer D, Rawlins EL, et al. The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. *Immunity* 2012;**37**:634–48.
38. Dutton EE, Gajdasik DW, Willis C, Fiancette R, Bishop EL, Camelo A, et al. Peripheral lymph nodes contain migratory and resident innate lymphoid cell populations. *Sci Immunol* 2019;**4**:eaau8082.
39. Russi AE, Walker-Caulfield ME, Ebel ME, Brown MA. Cutting edge: c-Kit signaling differentially regulates type 2 innate lymphoid cell accumulation and susceptibility to central nervous system demyelination in male and female SJL mice. *J Immunol* 2015;**194**:5609–13.
40. Rauber S, Luber M, Weber S, Maul L, Soare A, Wohlfahrt T, et al. Resolution of inflammation by interleukin-9-producing type 2 innate lymphoid cells. *Nat Med* 2017;**23**:938–44.
41. McHedlidze T, Waldner M, Zopf S, Walker J, Rankin AL, Schuchmann M, et al. Interleukin-33-dependent innate lymphoid cells mediate hepatic fibrosis. *Immunity* 2013;**39**:357–71.
42. Dalmas E, Lehmann FM, Dror E, Wuest S, Thienel C, Borsigova M, et al. Interleukin-33-activated islet-resident innate lymphoid cells promote insulin secretion through myeloid cell retinoic acid production. *Immunity* 2017;**47**:928–42. e7.
43. Halim TYF, Rana BMJ, Walker JA, Kerscher B, Knolle MD, Jolin HE, et al. Tissue-restricted adaptive type 2 immunity is orchestrated by expression of the costimulatory molecule OX40L on group 2 innate lymphoid cells. *Immunity* 2018;**48**:1195–1207. e6.
44. von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 2016;**529**:221–5.
45. Hardman CS, Panova V, McKenzie AN. IL-33 citrine reporter mice reveal the temporal and spatial expression of IL-33 during allergic lung inflammation. *Eur J Immunol* 2013;**43**:488–98.
46. Dewas C, Chen X, Honda T, Junttila I, Linton J, Udey MC, et al. TSLP expression: analysis with a ZsGreen TSLP reporter mouse. *J Immunol* 2015;**194**:1372–80.
47. Loh Z, Simpson J, Ullah A, Zhang V, Gan WJ, Lynch JP, et al. HMGB1 amplifies ILC2-induced type-2 inflammation and airway smooth muscle remodelling. *PLoS Pathog* 2020;**16**:e1008651.
48. Norlander AE, Peebles Jr RS. Innate type 2 responses to respiratory syncytial virus infection. *Viruses* 2020;**12**:521.
49. Wan J, Huang L, Ji X, Yao S, Hamed Abdelaziz M, Cai W, et al. HMGB1-induced ILC2s activate dendritic cells by producing IL-9 in asthmatic mouse model. *Cell Immunol* 2020;**352**:104085.
50. Zhang K, Jin Y, Lai D, Wang J, Wang Y, Wu X, et al. RAGE-induced ILC2 expansion in acute lung injury due to haemorrhagic shock. *Thorax* 2020;**75**:209–19.
51. Ricardo-Gonzalez RR, Van Dyken SJ, Schneider C, Lee J, Nussbaum JC, Liang HE, et al. Tissue signals imprint ILC2 identity with anticipatory function. *Nat Immunol* 2018;**19**:1093–9.
52. Doherty TA, Broide DH. Lipid regulation of group 2 innate lymphoid cell function: moving beyond epithelial cytokines. *J Allergy Clin Immunol* 2018;**141**:1587–9.
53. Konya V, Mjosberg J. Lipid mediators as regulators of human ILC2 function in allergic diseases. *Immunol Lett* 2016;**179**:36–42.
54. Kostenis E, Ulven T. Emerging roles of DP and CRTH2 in allergic inflammation. *Trends Mol Med* 2006;**12**:148–58.
55. Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. *Nat Immunol* 2011;**12**:1055–62.
56. Salimi M, Stoger L, Liu W, Go S, Pavord I, Klenerman P, et al. Cysteinyl leukotriene E4 activates human group 2 innate lymphoid cells and enhances the effect of prostaglandin D2 and epithelial cytokines. *J Allergy Clin Immunol* 2017;**140**:1090–100. e11.
57. Xue L, Salimi M, Panse I, Mjosberg JM, McKenzie AN, Spits H, et al. Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy Clin Immunol* 2014;**133**:1184–94.
58. Oyesola OO, Duque C, Huang LC, Larson EM, Fruh SP, Webb LM, et al. The prostaglandin D2 receptor CRTH2 promotes IL-33-induced ILC2 accumulation in the lung. *J Immunol* 2020;**204**:1001–11.
59. Doherty TA, Khorram N, Lund S, Mehta AK, Croft M, Broide DH. Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. *J Allergy Clin Immunol* 2013;**132**:205–13.
60. Maric J, Ravindran A, Mazzurana L, Bjorklund AK, Van Acker A, Rao A, et al. Prostaglandin E2 suppresses human group 2 innate lymphoid cell function. *J Allergy Clin Immunol* 2018;**141**:1761–73. e6.
61. Zhou Y, Wang W, Zhao C, Wang Y, Wu H, Sun X, et al. Prostaglandin E2 inhibits group 2 innate lymphoid cell activation and allergic airway inflammation through E-prostanoid 4-cyclic adenosine monophosphate signaling. *Front Immunol* 2018;**9**:501.
62. Zhou W, Toki S, Zhang J, Goleniewska K, Newcomb DC, Cephus JY, et al. Prostaglandin I2 signaling and inhibition of group 2 innate lymphoid cell responses. *Am J Respir Crit Care Med* 2016;**193**:31–42.
63. Cardoso V, Chesne J, Ribeiro H, Garcia-Cassani B, Carvalho T, Bouchery T, et al. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* 2017;**549**:277–81.
64. Klose CSN, Mahlakoiv T, Moeller JB, Rankin LC, Flamar AL, Kabata H, et al. The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* 2017;**549**:282–6.
65. Wallrapp A, Riesenfeld SJ, Burkett PR, Abdulnour RE, Nyman J, Dionne D, et al. The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* 2017;**549**:351–6.
66. Seillet C, Luong K, Tellier J, Jacquolot N, Shen RD, Hickey P, et al. The neuropeptide VIP confers anticipatory mucosal immunity by regulating ILC3 activity. *Nat Immunol* 2020;**21**:168–77.
67. Moriyama S, Brestoff JR, Flamar AL, Moeller JB, Klose CSN, Rankin LC, et al. beta2-adrenergic receptor-mediated negative regulation of group 2 innate lymphoid cell responses. *Science* 2018;**359**:1056–61.
68. Nagashima H, Mahlakoiv T, Shih HY, Davis FP, Meylan F, Huang Y, et al. Neuropeptide CGRP limits group 2 innate lymphoid cell responses and constrains type 2 inflammation. *Immunity* 2019;**51**:682–95. e6.
69. Sui P, Wiesner DL, Xu J, Zhang Y, Lee J, Van Dyken S, et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* 2018;**360**:eaan8546.
70. Maazi H, Patel N, Sankaranarayanan I, Suzuki Y, Rigas D, Soroosh P, et al. ICOS:ICOS-ligand interaction is required for type 2 innate lymphoid cell function, homeostasis, and induction of airway hyperreactivity. *Immunity* 2015;**42**:538–51.
71. Galle-Treger L, Sankaranarayanan I, Hurrell BP, Howard E, Lo R, Maazi H, et al. Costimulation of type-2 innate lymphoid cells by G1TR promotes effector function and ameliorates type 2 diabetes. *Nat Commun* 2019;**10**:713.
72. Nagashima H, Okuyama Y, Fujita T, Takeda T, Motomura Y, Moro K, et al. G1TR cosignaling in ILC2s controls allergic lung inflammation. *J Allergy Clin Immunol* 2018;**141**:1939–43. e8.
73. Taylor S, Huang Y, Mallett G, Stathopoulou C, Felizardo TC, Sun MA, et al. PD-1 regulates KLRG1(+) group 2 innate lymphoid cells. *J Exp Med* 2017;**214**:1663–78.
74. Miyamoto C, Kojo S, Yamashita M, Moro K, Lacaud G, Shiroguchi K, et al. Runx/Cbfbeta complexes protect group 2 innate lymphoid cells from exhausted-like hyporesponsiveness during allergic airway inflammation. *Nat Commun* 2019;**10**:447.
75. Ebihara T, Taniuchi I. Exhausted-like group 2 innate lymphoid cells in chronic allergic inflammation. *Trends Immunol* 2019;**40**:1095–104.
76. Huang Y, Guo L, Qiu J, Chen X, Hu-Li J, Siebenlist U, et al. IL-25-responsive, lineage-negative KLRG1(hi) cells are multipotential 'inflammatory' type 2 innate lymphoid cells. *Nat Immunol* 2015;**16**:161–9.
77. Huang Y, Mao K, Chen X, Sun MA, Kawabe T, Li W, et al. S1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense. *Science* 2018;**359**:114–9.
78. Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;**111**:66–71.
79. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;**354**:541–5.
80. Vu LD, Siefker D, Jones TL, You D, Taylor R, DeVincenzo J, et al. Elevated levels of type 2 respiratory innate lymphoid cells in human infants with severe respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med* 2019;**200**:1414–23.

81. Stier MT, Bloodworth MH, Toki S, Newcomb DC, Goleniewska K, Boyd KL, et al. Respiratory syncytial virus infection activates IL-13-producing group 2 innate lymphoid cells through thymic stromal lymphopoietin. *J Allergy Clin Immunol* 2016;**138**:814–24. e11.
82. Saravia J, You D, Shrestha B, Jalgama S, Siefker D, Lee GI, et al. Respiratory syncytial virus disease is mediated by age-variable IL-33. *PLoS Pathog* 2015;**11**: e1005217.
83. Hong JY, Bentley JK, Chung Y, Lei J, Steenrod JM, Chen Q, et al. Neonatal rhinovirus induces mucous metaplasia and airways hyperresponsiveness through IL-25 and type 2 innate lymphoid cells. *J Allergy Clin Immunol* 2014;**134**:429–39.
84. Han M, Rajput C, Hong JY, Lei J, Hinde JL, Wu Q, et al. The innate cytokines IL-25, IL-33, and TSLP cooperate in the induction of type 2 innate lymphoid cell expansion and mucous metaplasia in rhinovirus-infected immature mice. *J Immunol* 2017;**199**:1308–18.
85. Rajput C, Han M, Ishikawa T, Lei J, Jazaeri S, Bentley JK, et al. Early-life heterologous rhinovirus infections induce an exaggerated asthma-like phenotype. *J Allergy Clin Immunol* 2020;**146**:571–82. e3.
86. Shih HY, Sciume G, Mikami Y, Guo L, Sun HW, Brooks SR, et al. Developmental acquisition of regulomes underlies innate lymphoid cell functionality. *Cell* 2016;**165**:1120–33.
87. Koues OI, Collins PL, Cella M, Robinette ML, Porter SI, Pyfrom SC, et al. Distinct gene regulatory pathways for human innate versus adaptive lymphoid cells. *Cell* 2016;**165**:1134–46.
88. Lau CM, Adams NM, Geary CD, Weizman OE, Rapp M, Pritykin Y, et al. Epigenetic control of innate and adaptive immune memory. *Nat Immunol* 2018;**19**:963–72.
89. Oliphant CJ, Hwang YY, Walker JA, Salimi M, Wong SH, Brewer JM, et al. MHCII-mediated dialog between group 2 innate lymphoid cells and CD4(+) T cells potentiates type 2 immunity and promotes parasitic helminth expulsion. *Immunity* 2014;**41**:283–95.
90. Seehus CR, Kadavallore A, Torre B, Yeckes AR, Wang Y, Tang J, et al. Alternative activation generates IL-10 producing type 2 innate lymphoid cells. *Nat Commun* 2017;**8**:1900.
91. Bando JK, Gilfillan S, Di Luccia B, Fachi JL, Secca C, Cella M, et al. ILC2s are the predominant source of intestinal ILC-derived IL-10. *J Exp Med* 2020;**217**: e20191520.
92. Ali AK, Komal AK, Almutairi SM, Lee SH. Natural killer cell-derived IL-10 prevents liver damage during sustained murine cytomegalovirus infection. *Front Immunol* 2019;**10**:2688.
93. Clark SE, Burrack KS, Jameson SC, Hamilton SE, Lenz LL. NK Cell IL-10 production requires IL-15 and IL-10 driven STAT3 activation. *Front Immunol* 2019;**10**:2087.
94. Mehrotra PT, Donnelly RP, Wong S, Kanegane H, Geremew A, Mostowski HS, et al. Production of IL-10 by human natural killer cells stimulated with IL-2 and/or IL-12. *J Immunol* 1998;**160**:2637–44.
95. Morita H, Kubo T, Ruckert B, Ravindran A, Soyka MB, Rinaldi AO, et al. Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid. *J Allergy Clin Immunol* 2019;**143**:2190–201. e9.
96. Boonpiyathad T, Tantilipikorn P, Ruxrungtham K, Pradubongsas P, Mitthamsiri W, Piedvache A, et al. IL-10-producing innate lymphoid cells increased in house-dust-mite allergic rhinitis patients following immunotherapy. *J Allergy Clin Immunol* 2020. <https://doi.org/10.1016/j.jaci.2020.10.029>.