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Airway innate lymphoid cells in the induction and regulation of allergy

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Abstract

The recent discovery of innate lymphoid cells has revolutionized our understanding of the pathogenesis of immune diseases including allergy and asthma. Innate lymphoid cells (ILCs) are a heterogeneous collection of lymphocytes that lack antigen-specificity (non-T, non-B cells) and potentially produce characteristic cytokines of T cell subsets (Th1, Th2, Th17). ILCs are divided into group 1 (ILC1s), group 2 (ILC2s), or group 3 (ILC3s). Similar to Th2 cells, ILC2s produce IL-4, IL-5, and IL-13, among others, and are present in increased numbers in samples from patients with many allergic disorders including asthma and chronic rhinosinusitis (CRS). Animal models have identified that ILC2s contribute to eosinophilic tissue infiltration, airway hyperresponsiveness, mucus production, as well as coordinate adaptive immune responses. Finally, recent studies support regulation of ILC2s by neuro-immune mechanisms as well as demonstrate a significant degree of plasticity between ILC subsets that may impact the immune responses in asthma and allergic airway diseases. Here, we review the current literature on ILC2s in human asthma and allergic airway diseases, as well as highlight some recent mechanistic insights into ILC2 function from *in vitro* studies and *in vivo* animal models.

Keywords

ILC2; Innate lymphoid cells; Asthma; AERD; Chronic rhinosinusitis

Introduction

Human allergic airway diseases are characterized by eosinophilic inflammation, mucus and IgE production, tissue remodeling, and the presence of a distinct cytokine profile that includes IL-4, IL-5, IL-9, and IL-13.¹ For decades, conventional CD4⁺ Th2 cells were considered the primary orchestrators of the allergic response through production of these cytokines. IL-4 mediates Th2 cell differentiation and IgE class switching, IL-5 induces eosinophilic tissue infiltration, IL-9 promotes mucus production and mast cell accumulation, and IL-13 has pleiotropic functions in airway hyperresponsiveness, remodeling, and

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Conflict of interest

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inflammation.² Although conventional CD4⁺ cells clearly contribute to the type 2 cytokine burden present in tissues of patients with allergic inflammation, emerging evidence supports a significant, and at times dominant, role for group 2 innate lymphoid cells (ILC2s) in promoting allergic type 2 inflammatory responses.³⁻⁵

ILC2s are a member of the broader group of innate lymphoid cells (ILCs) that include ILC1s, ILC2s, and ILC3s and have cytokine profiles similar to conventional CD4⁺ Th1, Th2, and Th17 cells.⁶⁻⁸ All ILCs develop from common lymphoid progenitors (CLP) and depend on inhibitor of DNA binding 2 (Id2), thymocyte selection-associated high-mobility group box protein (TOX), nuclear factor interleukin-3 regulated (NFIL3), as well as γ chain (γ c) and notch signaling.^{9,10} ILC1s promote immune responses to viruses, intra-cellular microbes as well as tumors and produce IFN γ and TNF- α .^{6,8,11} ILC2s produce Th2 cytokines and the growth factor amphiregulin and are involved in responses to helminths, allergens and some viruses.^{12,13} ILC3s produce IL-17 and IL-22 and promote neutrophilic responses to extracellular bacteria and fungi.^{6,8,11}

The transcription factor expression in ILCs also parallels their T cell counterparts and includes T-bet (ILC1s), GATA-3 (ILC2s), and ROR γ t (ILC3s).^{7,8,11} ILCs are predominately lineage-negative cells (except for NK cells as a member of ILC1s) that do not express distinct markers for T cells, B cells, or other known hematopoietic lineage-positive cells. Further, ILCs do not express antigen-specific receptors and are directly regulated (activation or inhibition) by cytokines, lipid mediators, and some cell-cell contact mechanisms.^{11,12,14} Interestingly, an additional novel population of IL-10 producing ILCs termed ILCregs were recently discovered in IL-10 reporter mice and provide suppressive activities in certain conditions.¹⁵ Given the lack of specific identifying markers and relatively low numbers of ILCs in tissues, ILCs were largely elusive to scientific study until discovery in the past decade after sophisticated approaches were applied to detect their presence.

ILC2s are of great interest to the field of allergic diseases as they rapidly produce large amounts of Th2 cytokines in tissues after activation.¹² Since ILC2s do not require antigen recognition, any stimulus (virus, irritant, allergen) that induces cytokines (IL-33, TSLP, IL-25) or lipid mediators (PGD₂, CysLTs) can activate ILC2 expansion and cytokine production.^{12,14,16} This paradigm can then help to explain exacerbations of type 2 inflammation that occur after viral or irritant triggers in patients with allergic airway diseases including allergic rhinitis, CRS, and asthma. Here, we review the current literature regarding ILC2s in human allergic airway disease as well as highlight novel mechanisms of ILC2 function.

ILC2s in human allergic airway disease

Animal models have revealed important roles for ILC2s in allergen- and virus-driven lung inflammation and AHR suggesting that they may contribute to human allergic airway diseases (reviewed in Refs. 12 and 17).^{12,17} Following the early animal studies, ILC2s were subsequently detected at elevated levels in samples from patients with allergic rhinitis, chronic rhinosinusitis with nasal polyposis (CRScNP) and asthma.^{3,16,18,19} A proposed model for ILC2 responses in airway remodeling in asthma is depicted in Figure 1.

Allergic rhinitis

Allergic rhinitis (AR) is considered an IgE-mediated response to inhaled allergens that causes rhinorrhea, sneezing, itching, and congestion.²⁰ The pathogenesis of AR involves activation and accumulation of many cells including mast cells, T and B cells, basophils, eosinophils, and dendritic cells. In the effector phase of AR, allergen binding IgE on mast cells leads to cross-linking followed by release of many mediators including histamine, CysLTs, and prostaglandins. CysLTs and prostaglandin D₂ can specifically activate ILC2s and thus link ILC2s with mediators that are rapidly formed during active allergic rhinitis symptoms.^{21–23}

Recent human studies have investigated ILC2s in human allergic rhinitis.^{24–28} We initially reported that peripheral blood ILC2s are increased 4 h after nasal cat allergen challenge in cat-allergic individuals compared with diluent challenges administered at a separate visit.²⁵ Another report showed that ILC2s levels were increased in seasonal allergic rhinitis (SAR) patients during grass pollen season which was not found in non-atopic subjects.²⁴ Interestingly, SAR patients treated with SCIT showed reduced ILC2 levels during pollen seasons suggesting that immunotherapy modulated circulating ILC2s. A subsequent study found increased cytokine-producing ILC2s in peripheral blood of house dust mite (HDM) allergic individuals that correlated with symptom severity.²⁷ Interestingly, an additional study demonstrated that HDM and mugwort triggered AR had differences in ILC2 responses as peripheral blood ILC2s were increased in levels and activation from patients with HDM-AR compared to mugwort-AR.²⁸ Another group utilized a nasal allergen challenge (NAC) model and detected increased nasal mucosal ILC2s 6 h after challenge along with increased nasal fluid IL-5, IL-13, as well as chemokines CCL26/ Eotaxin-3, and CCL17/TARC.²⁶ These reports suggest that ILC2s are recruited early in the allergic nasal response to allergens in allergic rhinitis.

Early mediators that may be contributing to ILC2 recruitment and activation at this phase of reactions include CysLTs and PGD₂. However, it could also be that IL-33, an epithelial cytokine that activates ILC2s, is also contributing to ILC2 activation in allergic rhinitis. One study showed that IgE-activation of human mast cells leads to IL-33 secretion that was further processed into more biologically active forms (shorter and more potent forms of IL-33)²⁹ and could rapidly and potently activate ILC2s.³⁰ Thymic stromal lymphopoietin (TSLP) is another epithelial cytokine that activates ILC2s.³¹ TSLP has been found increased in nasal samples from patients with AR suggesting that it may also have a role in ILC2 responses in AR.^{32,33} Notably, there is evidence that IL-33 combined with TSLP can synergistically activate human ILC2s.³⁴ Since both mediators may be present in sinonasal disease, such combined activity of TSLP and IL-33 has important pathogenic implications.

Although ILC2s are recruited to the nasal mucosa in AR, the precise functions of ILC2s once present in the tissue are unclear. Mouse models of AR have significant limitations to test *in vivo* mechanisms present in humans, though one report utilized a ragweed sensitization protocol over 3 weeks to evaluate nasal type 2 responses.³⁵ Mice receiving ragweed developed nasal mucosal eosinophilia, Th2 cytokine and total IgE increases, as well as sneezing. RAG2 knockout mice that have ILC2s but lack T or B cells had significantly reduced eosinophilia and sneezing compared with wild type mice suggesting that adaptive

immune responses are required to initiate or propagate the eosinophilia. The authors suggested that ILC2s are dispensable in this model of AR. However, RAG2 KO mice also lack IgE production that may be necessary to initiate ILC2 activation through mast cell mediator secretion. Thus, the role of ILC2s *in vivo* in AR needs further investigation, and in addition to AR, ILC2s are also good candidates to promote eosinophilia in non-allergic rhinitis with eosinophilia (so-called NARES). NARES is characterized by nasal eosinophilia without evidence of systemic allergic sensitization. As ILC2s can directly promote eosinophilia through IL-5 secretion without effects on allergen-specific IgE production, this suggests that ILCs could contribute to NARES.

Chronic rhinosinusitis

Chronic rhinosinusitis with (CRSwNP) or without (CRSsNP) nasal polyps is a major cause of morbidity for patients and is associated with worsened asthma. Several reports have shown that ILC2s are enriched in nasal polyps and ILC2 numbers correlate positively with polyp and blood eosinophils as well as symptoms.^{19,36–39} As ILC2s are potent producers of IL-5, the finding that ILC2s are enriched in eosinophilic nasal polyps suggests that they may be involved in eosinophil recruitment and persistence in nasal polyps. Further, elevated levels of PGD₂, CysLTs, TSLP, and IL-33 (that all activate ILC2s) have been detected in CRS tissue.^{40,42–44} IL-33- and TSLP-stimulated nasal polyp ILC2s produce Th2 cytokines including IL-5 that is dependent on the Th2 transcription factor GATA-3, highly expressed by ILC2s.³⁴ Interestingly, a recent report additionally showed that solitary chemosensory cells (SCCs) that express taste receptors are a dominant source of IL-25, an epithelial cytokine that was one of the first shown to activate ILC2s.^{45,46} SCCs were found to be increased in number along with ILC2s in nasal polyps compared with turbinate tissue.⁴⁶ Overall, ILC2s appear to be likely contributors to the pathogenesis of CRS and nasal polyps, especially those with eosinophilic disease.

Aspirin Exacerbated Respiratory Disease (AERD)

Aspirin Exacerbated Respiratory Disease (AERD) is characterized by eosinophilic chronic rhinosinusitis with nasal polyps, asthma, and respiratory reactions to COX-1 inhibitors such as aspirin and NSAIDs.⁴⁷ Our group recently assessed ILC2 levels from nasal mucosa and blood at baseline, during NSAID reactions, and post desensitization in AERD patients.⁴⁸ During reactions, ILC2s were recruited to the nasal mucosa and reduced in the blood in AERD patients. Urinary LTE₄ and PGD₂ metabolites were increased during reactions and ILC2 levels correlated with symptom severity scores. Previous work has demonstrated that AERD tissue samples contain high levels of eosinophils along with increased PGD₂, CysLTs, IL-33, IL-25 and TSLP.^{47,49–51} These mediators can all activate ILC2s, either additively or synergistically.^{44,52} Of the chemotactic mediators, PGD₂ and CysLTs have been shown to induce chemotaxis of ILC2s and may play a role in ILC2 recruitment in AERD.^{21,23,52}

Asthma

Asthma is a heterogeneous disease although a majority of patients are thought to have type 2 cytokines in their airways and are thus considered “type-2 high” asthmatics.⁵³ The first report assessing levels of peripheral blood ILC2s in human asthma found no difference

between mild and severe asthmatics, as well as healthy controls.⁵⁴ However, reports since have demonstrated increased activation status and numbers of ILC2s in samples from pediatric and adult asthmatics compared with controls.^{3,18,55–57} One report found increased peripheral blood ILC2s and Th2 cytokine levels in allergic asthmatics compared with healthy controls and patients with allergic rhinitis.¹⁸ The first study to assess airway ILC2s showed that cytokine producing ILC2s are increased in the sputum of severe asthmatics compared with mild asthmatics and healthy controls.³ Interestingly, several patients with elevated airway ILC2s had been administered systemic corticosteroids suggesting ILC2 resistance to corticosteroids in these patients. A very recent report showed that TSLP imparts ILC2 corticosteroid resistance through STAT5 signaling and increased airway TSLP could be responsible for the presence of elevated ILC2s in severe asthma patients.⁵⁸ Treatments targeting upstream mediators such as TSLP⁵⁹ that activate ILC2s remain fruitful areas of therapeutic development for patients with asthma not responsive to current therapy including corticosteroids.

Similar to findings of allergen challenge studies in allergic rhinitis, one report demonstrated that airway ILC2s are increased after allergen challenge in atopic asthmatics.⁶⁰ The authors found that cytokine-producing ILC2s were increased in sputum and decreased in blood 24 h after allergen challenge. Another report, and in parallel with nasal polyp ILC2 studies, found that numbers of ILC2s in asthmatics correlated with numbers of eosinophils.⁵⁷ Interestingly, a recent human and mouse ILC2 transcriptomic and epigenomic study showed that ILC2 programs are specifically linked with known asthma susceptibility genes (including *rora*, *smad3*, *gata3*, *il13*, *il18r1*, and *il1r1l*) suggesting ILC2s may be key effectors in part regulated by genetic susceptibility in asthma.⁶¹ Overall, most studies suggest an increase of activated ILC2s in samples from asthma subjects and detailed animal studies (reviewed elsewhere¹²) support a role for ILC2s in airway hyperresponsiveness, lung eosinophilia, and mucus production.

An important finding in asthma is airway remodeling that likely contributes to declines in lung function over time. The cardinal features of remodeling include mucus metaplasia and secretion, airway smooth muscle hypertrophy and hyperplasia, as well as subepithelial fibrosis. ILC2s can contribute to airway remodeling through multiple mechanisms (Fig. 1) including through IL-13 production and recruitment of TGF- β -producing eosinophils via IL-5 secretion.^{2,62} In the normal airway, there is repair of tissue integrity after viral infections and other insults. Work in mice has shown that ILC2s promote airway repair after influenza infection through production of the growth factor amphiregulin.⁶³ Thus, ILC2s may simultaneously promote aspects of pathologic tissue remodeling present in asthma as well as normal tissue repair.

Regulation of ILC2 function

The very recent discovery of a multitude of mediators that regulate ILC2 function suggests that ILC2s are finely tuned for activation and inhibition during inflammatory responses.¹⁴ Here, we review major categories of ILC2-modulating mediators including epithelial cytokines, lipid mediators, neuro-immune molecules, and cell-cell contact proteins.

Airway epithelial cytokines

ILC2s were discovered in mice after characterization of lymphoid cells that produced high levels of IL-5 and IL-13 in response to IL-25 and IL-33.¹² IL-25 (IL-17E) is an IL-17 family member and is secreted by epithelial cells, Th2 cells, and eosinophils, and binds to the IL-25R which is a heterodimer of IL-17RA and IL-17RB.⁶⁴ IL-33 is present as a biologically active pro-form bound to chromatin in epithelial cells, endothelial cells, and macrophages and binds to a heterodimer of ST2 and the IL-1 receptor accessory protein.^{29,65} Notably, though IL-25 and IL-33 potently activate ILC2s, these cytokines act on other immune cells including T cells, NKT cells, DCs, eosinophils, macrophages, basophils, and mast cells.^{66,67} Therefore, *in vivo* responses to IL-25 and IL-33 cannot be solely attributed to ILC2s.

ILC2s are a relatively rare population of cells which, along with being lineage-negative, likely led to their elusiveness to scientific community for decades. Despite being rare, ILC2s *in vitro* produce large amounts of IL-5 and IL-13 per cell (mg range for 50,000 cells) after stimulation with IL-33.⁶⁸ As ILC2s are not antigen specific, the potential exists for all or most ILC2s in a tissue to be activated by available IL-33 or other mediator. This is in contrast to T cells that largely require antigen peptide presentation for full activation. Though ILC2s demonstrated impressive capacity for IL-5 and IL-13 production, IL-4 was not secreted by ILC2s stimulated with IL-33.⁶⁸ Since the initial claims that ILC2s do not produce IL-4, an ample amount of data has now shown that ILC2s do make significant amounts of IL-4 when stimulated with other mediators such as cysteinyl leukotrienes (CysLTs).^{22,69} Importantly, IL-4 production by ILC2s may be a critical link to promoting adaptive Th2 cell responses.

After the initial mouse ILC2 studies with activation by IL-25 and IL-33, another group demonstrated that human ILC2s were activated by TSLP which potentiated ILC2 responses to IL-33.³⁴ Prior to the discovery of ILC2s, TSLP was found elevated in samples from asthma and atopic dermatitis patients.³¹ Further, TSLP was known to control adaptive CD4+ Th2 cell responses through OX40/OX40L interactions with dendritic cells, but effects on innate cells were unclear.⁷⁰ Therefore, the link between TSLP and ILC2 activation provided critical insight into mechanisms of type 2 inflammation.

Lipid mediators

Eicosanoids including CysLTs and PGD2 are generated during type 2 inflammation and have putative roles in promoting bronchoconstriction and inflammatory cell recruitment and activation.⁷¹ PGD2 was the first lipid shown to promote human ILC2 IL-13 production when combined with IL-2, IL-25 and IL-33.⁵⁴ The same report additionally showed that Lipoxin A4 (LXA4) abrogated the PGD2-driven increase in IL-13. Our laboratory then showed that ILC2s from mouse lung and bone marrow highly express CysLT₁ (high affinity receptor for leukotriene D4).²² ILC2s stimulated with leukotriene D4 (LTD4) rapidly produced high levels of IL-4, IL-5 and IL-13 *in vitro* and *in vivo*. Further work has shown that PGD2 and CysLTs promote human ILC2 cytokine production and chemotaxis.^{21,23,52} In addition to the inhibitory effects of LXA4 on ILC2 function, prostaglandin I2 (PGI2) and prostaglandin E2 (PGE2) reduce the activation of both mouse and human ILC2s.⁷²⁻⁷⁴ Thus, depending on the

milieu of activating and inhibitory cytokines and lipid mediators present, there is likely a fine-tuning of ILC2 responses resulting in a dynamic regulation of these cells. Overall, lipid mediators that are important in allergic airway diseases are clearly important modulators of ILC2 function, even independent of epithelial cytokines.⁷⁵

Interestingly, recent reports have shown that male and female steroid sex hormones regulate ILC2 function.^{76–79} Male mice were initially shown to have reduced HDM-induced lung inflammation compared with female mice and this difference was abolished with orchietomy.⁷⁷ Bone marrow from male mice lacking the androgen receptor transplanted into irradiated female wild type mice had similarly elevated lung ILC2 numbers and airway inflammation compared with female mice. Another report showed that circulating ILC2s are increased in women with severe asthma compared with men with severe asthma and testosterone suppressed ILC2-induced lung inflammation.⁷⁹ In support of these reports, uterine ILC2s were demonstrated to be increased by estrogen treatment in WT mice and were nearly absent in mice deficient in estrogen receptors.⁷⁸ Taken together, an array of lipid molecules including eicosanoids as well as sex steroids appear to be critical in the regulation of ILCs and ILC2 driven responses.

Neuro-immune control of ILC2s

The neuropeptide receptor NMUR1 is present on mouse and human ILC2s and stimulation with the neuropeptide neuromedin U (NMU) promotes Th2 cytokine production and type 2 inflammatory tissue responses.^{80–82} Notably, the NMU/NMUR1/ILC2 axis represents a critical link between peripheral neurons and ILC2s that could contribute to neuroinflammation. More recent work has shown that ILC2s also express b-2 adrenergic receptors that respond to catecholamines secreted by sympathetic nerves and the adrenal medulla.⁸³ Binding of the b-2 adrenergic receptor on ILC2s led to reduced activity and proliferation suggesting that b-2 is a negative regulator of ILC2s.

Very recently, mice deficient in pulmonary neuroendocrine cells (PNECs) demonstrated impairment in developing allergic lung inflammation.⁸⁴ Interestingly, PNECs that produce several neuro-endocrine products were shown to localize with ILC2s at airway branch points and stimulate ILC2 cytokine production through calcitonin gene-related peptide (CGRP). Further, mucus cell hyperplasia was mediated through PNEC production of the neurotransmitter g-aminobutyric acid (GABA). Overall, tissue resident ILC2s appear to be highly regulated by neuro-immune and neuro-endocrine mechanisms.

Additional modulators of ILC2 function

Additional regulators of ILC2 function include TLA1/DR3 and ICOS/ICOSL.^{85–88} ICOS and ICOS ligand as well as DR3 and TL1A are classically considered “co-stimulatory” molecules that provide signals between antigen presenting cells (APCs) and T cells. However, these molecules are also expressed on a wide array of cell types and regulate both innate adaptive responses. DR3 and ICOS are present on mouse and human ILC2s and promote activation.^{85–88} Interestingly, ICOS-ICOSL also regulates Treg/ILC2 interactions that can also promote suppression of ILC2s.^{89,90} Suppressive cytokines including IL-10 and TGF- β were further found to reduce ILC2 function, a property similar to suppression of

other immune cells by these cytokines.⁹¹ Type 1 interferons produced during viral infections as well as IFN γ and IL-27 also reduce ILC2 responses.⁹⁰ In an allergic response, the balance between such molecules that promote (DR3, ICOS) or dampen (IL-10, TGF- β , Tregs) ILC2 activation in type 2 inflammation may determine the subsequent severity of disease. Further, the availability of ligands or suppressive mediators in tissues may account for skewing towards or away from pathogenic allergic inflammation. Ongoing intensive investigations continue to uncover novel regulatory mechanisms of ILC2s at a rapid pace.

ILC2 regulation of adaptive Th2 responses

Initial allergen challenge mouse model studies of ILC2s largely utilized RAG-deficient mice (lack B and T cells but have ILC2s) in order to isolate the role of ILC2s separate from adaptive Th2 response.^{92,93} The downside of such models is that the contribution of ILC2s to lung inflammation in the presence of adaptive immunity could not be assessed. Recently, studies have utilized retinoid-related orphan receptor alpha (RORa) bone marrow transplant (BMT) models to attempt to overcome this obstacle.^{94,95} RORa is critical for ILC2 development, but has limited if any role in CD4+ Th2 cell development or responses.^{94,96,97} As RORa complete knockout mice have early neurologic demise, investigators have transferred RORa-deficient bone marrow into irradiated wild type hosts. This procedure also isolates the role of RORa to CD45 + hematopoietic cells. Notably, HDM and papain challenged RORa BMT mice that lack ILC2s did not generate an adaptive Th2 cell response, though these same mice undergoing a conventional OVA/alum models did have intact Th2 responses.⁹⁴ Potential mechanisms of ILC2-initiated Th2 cell activation include DC licensing and lymph node trafficking initiated by ILC2 IL-13 production as well as ILC2 production of IL-4 induced by leukotriene D4.^{69,98} Despite the very low numbers of ILC2s in tissues, cell-cell contact between ILC2s and other cell types including CD4+ T cells through MHCII and/or OX40 ligand has also been implicated in generating Th2 cell responses.^{99,100} Overall, ILC2s appear to have multiple roles in type 2 inflammation including early Th2 cytokine production as well as providing a critical link to adaptive Th2 immunity.

ILC2 trafficking to the airway

During an inflammatory response, the degree of local proliferation of ILC2s versus ILC2 migration from blood is largely unclear. This is an important question as potential therapeutic targets aimed at trafficking versus local activation and proliferation may be beneficial in type 2 inflammatory diseases. As ILC2s are CD45 + bone marrow derived cells, they presumably traffic to tissues through the blood though their longevity in tissues has not been explored. Recently, a few groups have reported how ILC2 migrate to the lung and other sites. Our laboratory tested the role of b1 and b2 integrin blockade during allergen challenge in mice.¹⁰¹ Human and mouse lung ILC2s expressed receptors for b1 and b2 integrins which are used by cells to traffic into tissues. Blockade of b2 integrins, but not b1 integrins, reduced ILC2 numbers in mouse lung after allergen challenge. Importantly, proliferation and apoptosis were not affected suggesting that targeting trafficking was mainly responsible for the reduced ILC2 numbers.

Though IL-33 is known to regulate ILC2 activation and proliferation locally, a very recent report showed an additional role for IL-33 in bone marrow egress of ILC2s.¹⁰² IL-33 and ST2 deficient mice had increased ILC2 progenitors in the bone marrow and fewer in the mediastinal lymph nodes (MLN) and lungs at steady state. Administration of IL-33 reversed these changes and one mechanism highlighted was IL-33-induced reduction of CXCR4 to promote egress from the bone marrow. Similar to our studies, the authors also found that *Alternaria* exposure to the airways of mice leads ILC2 egress from bone marrow.¹⁰¹ IL-25 also appears to have a role in ILC2 trafficking as both IL-25 and helminth infection led to trafficking of ILC2s from the gut lamina propria to a diverse number of sites including the lung.¹⁰³ This migration of ILC2s occurred in lymphatics and was dependent on sphingosine 1-phosphate (S1P) for chemotaxis. Thus, though epithelial cytokines IL-25 and IL-33 are largely thought to regulate tissue resident ILC2 responses locally, these reports show a role for both cytokines in ILC2 trafficking responses that will require critical evaluation in humans as therapeutics targeting these cytokines are developed.

ILC2 plasticity in airway disease

Though ILC2s were initially considered fully differentiated cells that produce a distinct repertoire of cytokines, several reports quickly changed this paradigm and clearly showed that ILC2s, along with other ILCs, demonstrate plasticity depending on the cytokine milieu (Fig. 2). Initial studies showed that pro-inflammatory IL-1 cytokines IL-1a and IL-1b potently induce human ILC2 proliferation and Th2 cytokine production.^{41,104} However, in the presence of IL-12, IL-1b reduced ILC2 GATA3 expression and transformed ILC2s into an ILC1 phenotype (or “ex-ILC2”) that produce IFN γ . The IL-1 family cytokine IL-18 also appears to support ILC2 to ILC1 transformation.¹⁰⁵ Further studies have additionally demonstrated that notch signaling, sustained IL-33 presence and CysLTs induce IL-17 production from ILC2s.^{106,107} As subsets of severe asthma patients have airway neutrophilia and elevated levels of IL-17 or IFN γ ,¹⁰⁸ such ILC2 plasticity to become IFN γ or IL-17 producers may contribute to neutrophilia and associated cytokine responses.

Whether such plasticity contributes to human airway diseases *in vivo* remains unknown. In previous work, a mouse model of obesity-induced asthma showed that IL-1b produced after high fat diet intake led to ILC3 generation and AHR, thus supporting a role for ILC3 in an asthma model.¹⁰⁹ ILC3s produce IL-17 (a neutrophil chemotactic cytokine) that could contribute to neutrophilic inflammation found in some endotypes of asthma, especially non-allergic and severe asthma.¹¹⁰ IL-17 has been detected in elevated levels in some patients with severe asthma though whether the source is ILC3s is not known.¹¹¹

Finally, a distinct subset of ILC2s were recently demonstrated to produce IL-10 during papain or IL-33 challenge and represented a large portion of the IL-10 producing cells in the lung.¹¹² *In vitro*, the addition of IL-2 along with retinoic acid could induce IL-10 production from ILC2s.¹¹² *In vivo*, IL-2 enhanced expansion of IL-10 producing ILC2s and reduced lung eosinophilia in RAG deficient mice (have ILC2s but lack T or B cells) treated with IL-33.¹¹² Overall, the ILC community is at an early stage in the understanding of how ILC plasticity is regulated, especially in humans under conditions of disease.

Summary

The discovery of group 2 innate lymphoid cells has completely altered classical paradigms of allergic airway disease. Despite a rapid increase in the number of ILC2 publications, we are still in our infancy when it comes to an understanding of their roles in human allergic airway diseases. Multiple studies have shown an association of asthma, CRS, AERD, and allergic rhinitis with increased ILC2 levels and activation of tissue ILC2s which supports their possible role in these diseases. Mouse models demonstrate important contributions by ILC2s in promotion of tissue eosinophilia, AHR, and mucus production in the airway. Recent discoveries demonstrating how ILC2s promote adaptive Th2 responses, are regulated by neuronal mediators, and that ILC2s undergo plasticity changes to produce ILC1 or ILC3 cytokines have expanded our understanding of these impressive cells. Importantly, targeting upstream or downstream ILC2 mediators may lead to promising potential therapeutic strategies for allergic airway diseases.

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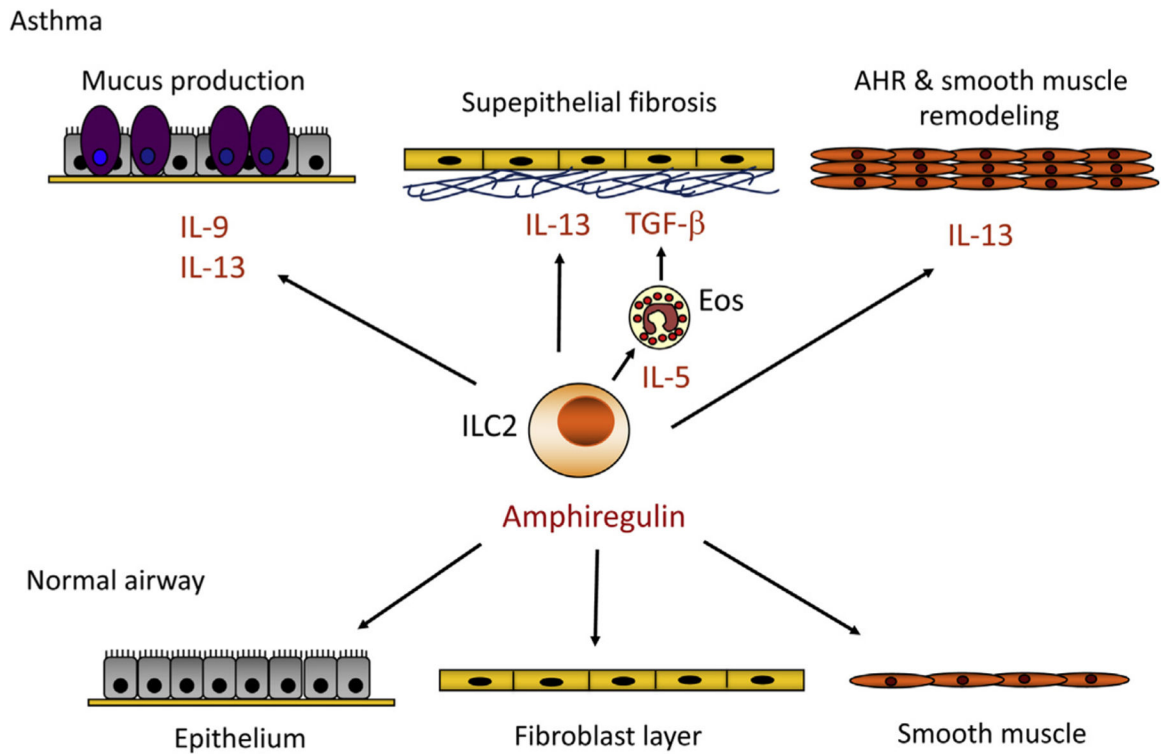
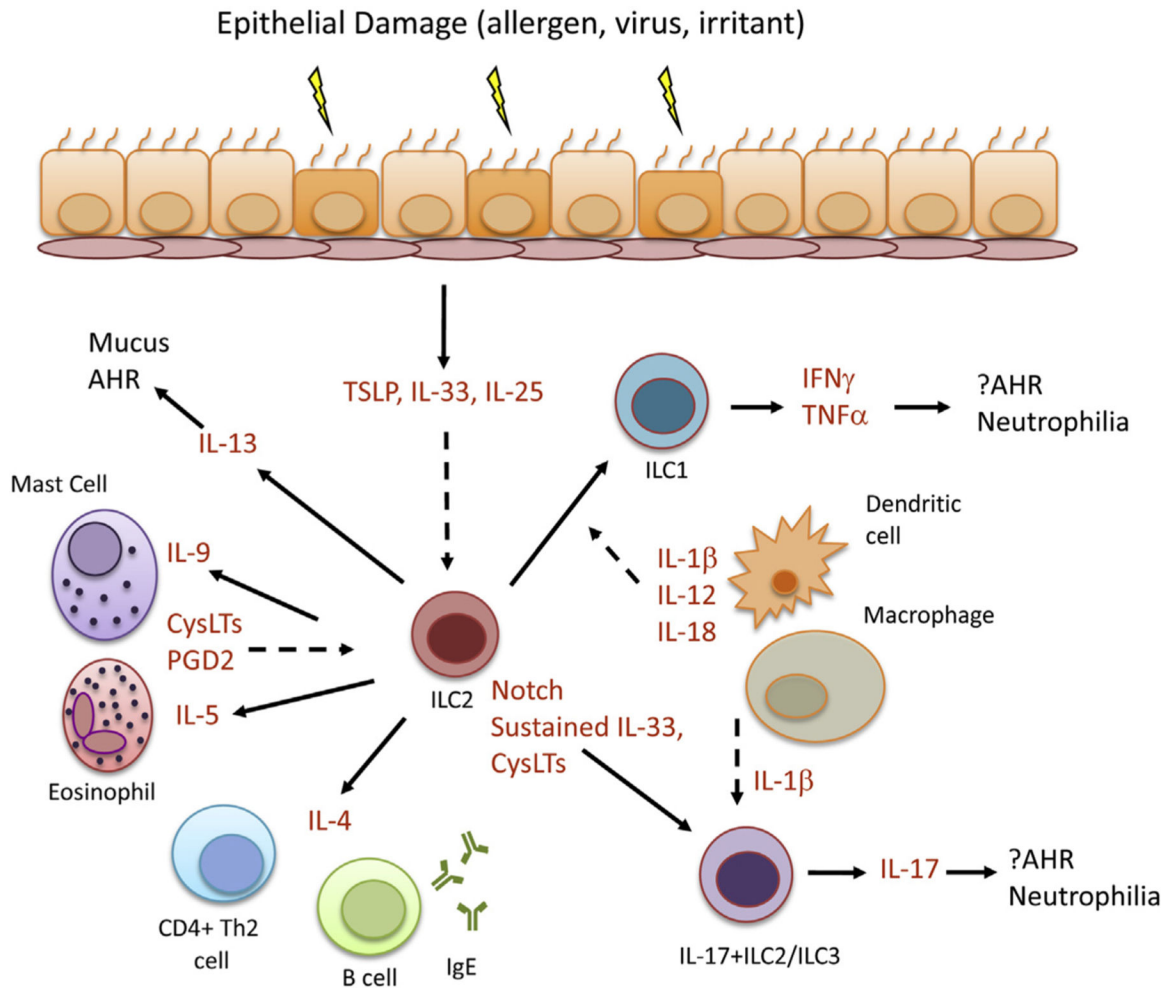


Fig. 1.

ILC2 contributions to airway remodeling in asthma and normal tissue repair responses. Activated ILC2s produce IL-13 that promotes subepithelial fibrosis, airway hyper-responsiveness (AHR), smooth muscle increases, and epithelial mucus production (along with IL-9). Further, ILC2s produce IL-5 which induces proliferation of eosinophils that express the pro-fibrotic growth factor TGF-β. In the normal airway, amphiregulin production by ILC2s may maintain normal tissue homeostasis and repair lung structures after viral infections.

**Fig. 2.**

Activated ILC2 responses and plasticity in allergic airway diseases. TSLP, IL-33, and IL-25 are induced by epithelial damage after exposure to allergens, specific viruses or irritants. These cytokines, as well as cysteinyl leukotrienes (CysLTs) and prostaglandin D2 (PGD2) induce Th2 cytokine production from ILC2s. IL-5 promotes tissue eosinophilia, IL-13 induces AHR, mucus production and immune cell recruitment, and IL-9 promotes mast cell accumulation and mucus production (not shown). CysLTs specifically induce ILC2 IL-4 production that can promote Th2 cell differentiation and IgE class switching from B cells. ILC2s can also be converted to ILC1-like cells by IL-1 β , IL-12 and IL-18 leading to production of IFN γ and TNF α . Sustained production of IL-33, notch ligands, and CysLTs also induce IL-17 from ILC2s. IL-1 β may also directly promote ILC3 generation in obesity. Th1/Th17 cytokines may promote neutrophilic airway disease as well as AHR in some circumstances. Inhibitory pathways not shown, and reviewed elsewhere.⁹¹