Innate Lymphoid Cells: An Emerging Population in Type 2 Inflammation

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Abbreviations

AAM	Alternatively activated macrophage
ACT 1	NF-κB activator 1
AD	Atopic dermatitis
APC	Antigen-presenting cell
Areg	Amphiregulin
BAL	Bronchoalveolar lavage fluid
CRS	Chronic rhinosinusitis
CRTH2	Chemoattractant receptor-homologous molecule expressed on T helper type 2 cells
CysLT2	Cysteinyl leukotriene receptor 2
DC	Dendritic cell
DR3	Death receptor 3
EGFR	Epidermal growth factor receptor
FPR2/ALX	Formyl peptide receptor 2/lipoxin A_4 receptor
γc	γ-Chain
GATA3	GATA binding protein 3
GFI1	Growth factor-independent 1 transcription repressor
ID2	Inhibitor of DNA binding 2
IFN-γ	Interferon-γ

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Ig	Immunoglobulin
IL	Interleukin
ILC	Innate lymphoid cell
ILC1	Group 1 innate lymphoid cell
ILC2	Group 2 innate lymphoid cell
ILC3	Group 3 innate lymphoid cell
LTD_4	Leukotriene D_4
LTi	Lymphoid tissue inducer
LXA_4	Lipoxin A_4
MHC II	Major histocompatibility class II
MPP^{type2}	Multipotent progenitor type 2
NFIL3	Nuclear factor interleukin 3 regulated
NK	Natural killer
PGD_2	Prostaglandin D_2
PLZF	Promyelocytic leukemia zinc finger protein
R	Receptor
RORα	Retinoic acid receptor-related orphan receptor α
RORγt	Retinoic acid receptor-related orphan receptor γ
SCF	Stem cell factor
STAT3	Signal transducer and activator of transcription 3
T-bet	T-box expressed in T cells
TCF1	Transcription factor 1
T_H2	T helper type 2
TL1A	Tumor necrosis factor-like ligand 1A
TNF	Tumor necrosis factor
TOX	Thymocyte selection-associated high mobility group box
TSLP	Thymic stromal lymphopoietin
VIP	Vasoactive intestinal peptide

Introduction

Type 2 immune responses play a key role in the initiation, maintenance, resolution, or prevention of numerous human disease states, including infection with parasitic helminths, allergic diseases, fibrosis, and metabolic disorders [1–5]. Type 2 cytokine responses drive protective immunity to parasitic helminths as well as pathologic allergic inflammation associated with diseases such as asthma, atopic dermatitis (AD), and food allergy [1–5]. In addition, these responses are also associated with tissue remodeling and repair and metabolic homeostasis [1–5]. Thus, type 2 immune responses are linked to a wide array of diseases that together are responsible for a significant public health and economic burden worldwide, and a better understanding of the regulation of type 2 inflammation has the potential to inform treatment and management of many of these diseases [1–5].

Type 2 immune responses begin with the production of epithelial cell-derived cytokines including interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP) and antigen presentation by antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages [1–3, 6, 7]. These early responses in turn promote production of the cytokines IL-4, IL-5, IL-9, and IL-13, development and activation of $CD4^+$ T helper type 2 (T_H2) cells, antigen-specific immunoglobulin (Ig)E production, and recruitment of innate effector cell populations such as eosinophils, mast cells, and basophils to the epithelial barrier [1–3, 6]. Together, these responses act back upon the epithelial barrier to regulate effector mechanisms such as mucus production, smooth muscle contractility, and barrier permeability that mediate helminth expulsion, result in signs and symptoms of type 2 inflammation, or contribute to reparative or homeostatic processes [1–5].

While a significant body of literature describes how responses by adaptive T and B cells promote type 2 cytokine responses, less is known regarding the regulation of innate immune responses that drive the initiation, maintenance, and resolution of these responses [1, 7]. Importantly, studies in the last 5 years have identified a novel subset of innate immune cells, the group 2 innate lymphoid cells (ILC2s), that is found in humans and mice in multiple tissues and is critical in the development of type 2 cytokine responses [3, 7–11]. This chapter describes recent advances in our understanding of the development and activation of ILC2s and how these cells contribute to type 2 inflammation in the context of helminth infection and allergy. Additionally, emerging work is discussed that describes alternative roles of ILC2s in promoting tissue remodeling and metabolic homeostasis. In particular, recent studies are highlighted that reveal how ILC2 responses could be targeted therapeutically to treat diseases in which ILC2-associated type 2 inflammation plays a role.

Identification and Definition of ILC2s

ILC2s are a newly described subset of innate cells within the ILC family, which includes classical natural killer (NK) cells and lymphoid tissue-inducer (LTi) cells [3, 7–17]. All ILCs lack expression of cell lineage markers associated with T cells, B cells, DCs, macrophages, and granulocytes, but do express CD90 (Thy1), the stem cell factor (SCF) receptor c-Kit, CD25 (IL-2 receptor (R)α), and CD127 (IL-7Rα) [3, 7–17]. As NK cells appear to have distinct developmental and functional characteristics when compared to other ILC subsets described below [3, 7–17], here the term "ILC" will be used to refer to only non-NK cell members of the ILC family.

The ILC family is currently categorized into three major subsets. These subsets are comparable to the three major $CD4^+$ T helper lineages and are distinguished by their differential requirements for transcription factors during development and expression of distinct transcription factors and effector cytokines by mature cells [8]. The group 1 ILCs (ILC1s) include newly described innate cells that are T-box expressed in T cells (T-bet)-dependent, produce interferon-γ (IFN-γ), and promote

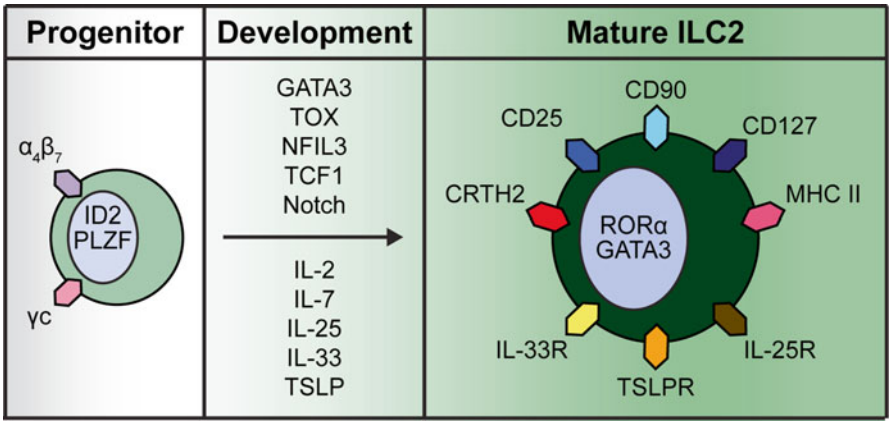

Fig. 1 A network of transcription factors and cytokines directs ILC2 development. ILC2s arise from a CLP that expresses the integrin $\alpha_4\beta_7$, the common γc receptor, and the transcription factors ID2 and PLZF. Signals from the cytokines IL-2, IL-7, IL-25, IL-33, and TSLP and the transcription factors GATA3, TOX, NFIL3, and TCF1, along with Notch signaling, guide the differentiation, maturation, and activation of ILC2s. These mature ILC2s are negative for lineage markers of T and B cells, monocytes, macrophages, and innate granulocytes, but they do express CD90 (Thy1), CD25, CD127, IL-25R, IL-33R, TSLPR, and CRTH2

immunity to intracellular pathogens and intestinal inflammation (classical NK cells are also categorized into this group). The group 3 ILCs (ILC3s) include retinoic acid receptor-related orphan receptor γ (RORγt)-dependent LTis and other RORγt-dependent cells that respond to IL-23, produce IL-17A and/or IL-22, and support lymphogenesis in the fetus and in adults, immunity to extracellular bacteria, and inflammation at multiple mucosal and barrier surfaces [8, 10, 12, 13, 15–19].

In contrast, ILC2s are dependent upon and express the transcription factors retinoic acid receptor-related orphan receptor α (RORα) [20, 21] and GATA binding protein 3 (GATA3) [22–27] (Fig. 1). These cells respond specifically to the epithelial cell-derived cytokines IL-25, IL-33, and TSLP and the tumor necrosis factor (TNF) family member TNF-like ligand 1A (TL1A) to produce IL-4, IL-5, IL-9, IL-13, and/or the epidermal growth factor receptor (EGFR) ligand amphiregulin (Areg) [3, 7–11]. These effector functions then support the development of type 2 inflammation in the context of immunity and allergic disease, and also contribute to the ability of ILC2s to maintain tissue homeostasis by promoting wound healing, tissue remodeling, and metabolic homeostasis [3, 7–11, 28–48].

While the categorization of ILCs into the distinct subsets described above has been useful in providing a rubric for understanding the developmental requirements and effector functions of these cells, it remains possible that additional innate cell subsets exist, or that there may be functional plasticity among different subsets of ILCs [8, 10]. For example, cells termed multipotent progenitor type 2 (MPP^{type2})

cells were originally thought to be an ILC-like population that promoted type 2 immunity to helminth infection [49]. However, subsequent studies showed that these cells were distinct from ILC2s, as MPP^{type2} cells responded preferentially to IL-25 and exhibited a progenitor-like phenotype and function, while ILC2s responded preferentially to IL-33 and were terminally differentiated [50]. Regarding plasticity of ILC subsets, recent studies have shown that murine and human ILC3s could respond to IL-12 and IL-18, which mediates dynamic expression of RORγt and T-bet [51], loss of IL-17 and IL-22 expression, and acquisition of the ability to produce IFN-γ [51–54]. However, it remains unclear whether ILC2s demonstrate similar functional plasticity, and further studies will be required to fully dissect how ILC2s respond to changing environmental cues to modulate their characteristic effector functions.

Requirements for the Development of ILC2s

Following the identification of ILC2s and other ILC subsets, there has been tremendous interest in understanding the pathways that lead to the development and differentiation of ILC2s. All ILCs are derived from a bone marrow-resident common lymphoid progenitor that expresses the integrin $\alpha_4\beta_7$ [55–58]. Downstream of this precursor, the development of the three ILC subsets has been shown to be dependent on the transcription factors inhibitor of DNA binding 2 (ID2) [55, 58–60] and promyelocytic leukemia zinc finger protein (PLZF) [59]. In addition, ILC development was dependent upon the common γ-chain (γc or CD132), IL-7, the Notch pathway, and the transcription factors thymocyte selection-associated high mobility group box protein (TOX), nuclear factor, interleukin 3 regulated (NFIL3), GATA3, and transcription factor 1 (TCF1) [8, 10, 19, 27, 28, 31, 35, 55, 59–68] (Fig. 1).

The transcription factor GATA3 is particularly key for the development and maintenance of ILC2s [22–27]. While deletion of this factor at the earliest stages of ILC development in hematopoietic stem cells prevented the development of all ILCs [27, 68], deletion of GATA3 in downstream precursors only prevented the development of ILC2s, suggesting that sustained GATA3 expression is uniquely required for ILC2 differentiation [22–27, 68]. Other transcription factors coordinate the effects of GATA3 on ILC2 development, including growth factor-independent 1 transcription repressor (GFI1), a transcription factor that targets the *Gata3* gene and helps to maintain GATA3 expression [69]. In addition to GATA3, other transcriptional regulators contribute to the development of ILC2s [20, 21]. Together, these findings suggest a model in which multiple transcription factors converge in a regulatory network that controls the development of ILC2s (Fig. 1).

Regulation of ILC2 Effector Functions

Studies in multiple models and in humans suggest that ILC2s promote type 2 inflammation that contributes to protective immunity to helminth parasites and allergic disease, while supporting the maintenance of tissue remodeling mechanisms and metabolic homeostasis through production of IL-4, IL-5, IL-9, IL-13, and Areg and interactions with other innate and adaptive immune cells [3, 7–11]. The factors that drive the acquisition of ILC2 effector functions include a diverse array of cytokines and lipids derived from epithelial cells and other immune cells that are produced in response to helminth parasites, viruses, and fungi as well as allergens [3, 7–11]. In particular, the epithelial cell-derived cytokines IL-25, IL-33, and TSLP are critically important for ILC2 development, activation, and acquisition of effector function [25, 28–30, 32, 34, 39, 42–44, 48, 50, 70–77]. Other cytokines, including the γc cytokines IL-2, IL-4, and IL-7, also support the development of ILC2s and promote their activation [3, 7–11, 77–80]. Two recent studies have shown that the TNF family member TL1A acted on ILC2s that express death receptor 3 (DR3) to drive allergic inflammation in the lung and protective immunity to helminth parasites [40, 41]. Finally, autocrine signaling by IL-9 produced by ILC2s was demonstrated to be important in promoting ILC2 survival [45] (Fig. 2).

In addition to responding to cytokine stimuli, ILC2s also respond directly to bioactive lipids of the eicosanoid family that are produced in the context of allergic inflammation. Specifically, ILC2s express the prostaglandin D_2 (PGD_2) receptor chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2), and ligation of CRTH2 in vitro elicited chemotaxis of ILC2s and production of IL-5 and IL-13 [81–84]. ILC2s also responded to leukotriene D_4 (LTD_4) [85] and were inhibited by lipoxin A_4 (LXA_4) [81]. Together, these studies suggest that numerous proteins and lipids regulate ILC2 activation and effector function. However, additional studies will be required to more completely define the factors that regulate ILC2 activities in various tissues during the steady state or in the context of inflammation (Fig. 2).

ILC2s Contribute to Protective Immunity to Helminth Parasites

While the role of type 2 cytokines in mediating helminth expulsion has been appreciated for many years, the critical source of these cytokines in vivo was previously poorly defined [1, 2, 4, 6, 7, 86]. *Nippostrongylus brasiliensis* is a mouse-adapted intestinal nematode parasite used as a model of hookworm infection [87], and protective immunity in mice is dependent upon IL-13-mediated changes in the intestinal epithelium, including an increase in mucus production and changes in smooth muscle contractility, that lead to parasite expulsion [86]. Seminal work in 2006 showed that an innate cell population that expressed c-Kit and produced type 2 cytokines was required for resistance to *N. brasiliensis*, providing the first indication that innate cells, rather than adaptive $CD4^+$ T cells, were required as a source of type 2 cytokines during helminth infection [88].

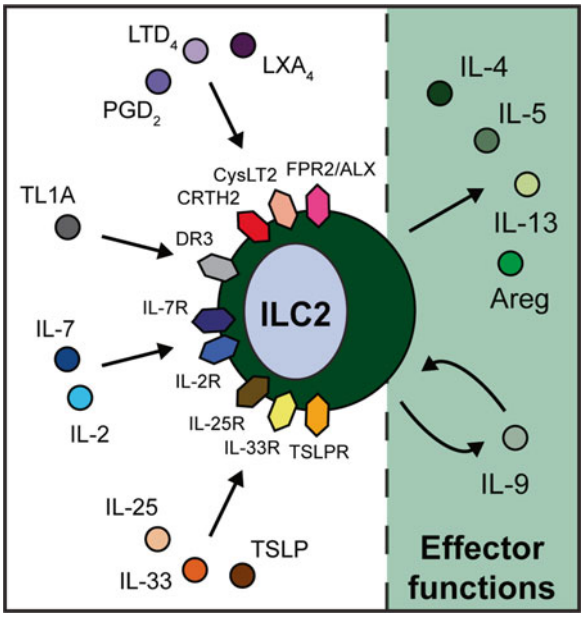

Fig. 2 Cytokines and bioactive lipids regulate ILC2 acquisition of effector function. The epithelial cell-derived cytokines IL-25, IL-33, and TSLP act on ILC2s, driving cell proliferation and production of the type 2 cytokines IL-4, IL-5, IL-9, and IL-13. IL-9 produced by ILC2s, in addition to other γc cytokines such as IL-2 and IL-7, promote ILC2 proliferation and survival. In addition, the TNF family member TL1A signals to its receptor, DR3, on the surface of ILC2s to elicit expression of effector cytokines. Finally, ILC2s also respond to the eicosanoids PGD_2, LTD_4, and LXA_4 through the receptors CRTH2, cysteinyl leukotriene receptor 2 (CysLT2), and formyl peptide receptor 2/lipoxin A_4 receptor (FPR2/ALX), respectively. PGD_2 and LTD_4 drive the activation of ILC2s, while LXA_4 limits ILC2 responses

Subsequent studies formally defined this innate cell population as innate helper cells, nuocytes, or innate helper type 2 cells, again in the context of infection with *N. brasiliensis* [28–30], and these cells are now universally referred to as ILC2s [8]. During *N. brasiliensis* infection, ILC2s are the dominant producers of IL-13, and mice lacking ILC2s or IL-13 failed to efficiently expel parasites [28–30]. Adoptive transfer of IL-13-expressing ILC2s to mice deficient in ILC2s or IL-13 was able to promote parasite expulsion, thus identifying ILC2s as key players in mediating interactions between the immune system and the epithelial barrier that are required for protection against helminth parasites [28–30] (Fig. 3). While it remains unclear exactly how ILC2s contribute to protective immune responses during infection with helminths aside from *N. brasiliensis*, there are studies that suggest that ILC2s do contribute to immunity to diverse helminth species, such as *Strongyloides venezuelensis* [89, 90]. Similarly, Areg has been shown to be required for expulsion of the nematode parasites *Trichuris muris* [91], and ILC2s are a predominant source of Areg in some contexts [35], suggesting that ILC2s may contribute to immunity to *T. muris* as well.

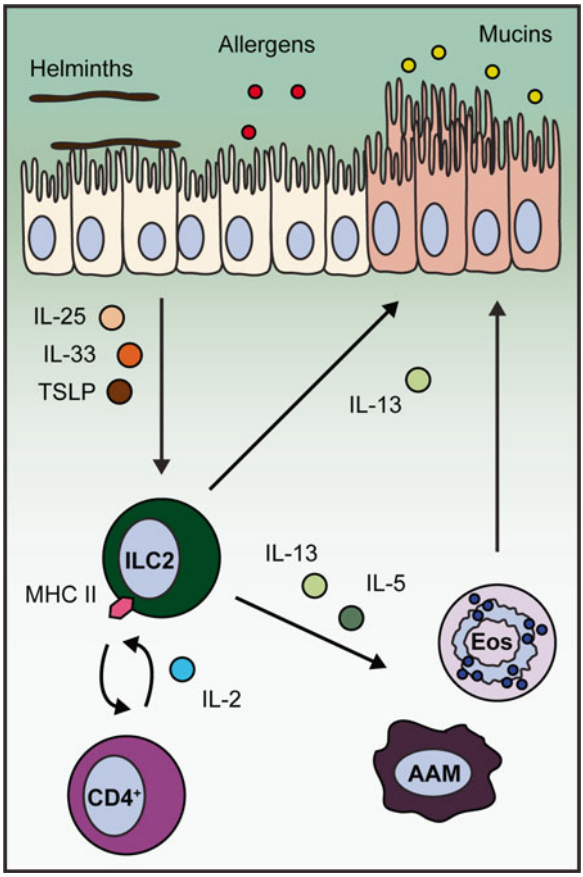

Fig. 3 ILC2s respond to cues from the epithelium and interact with innate and adaptive cells to promote type 2 inflammation. Following exposure to helminth antigens or allergens, epithelial cells produce the cytokines IL-25, IL-33, and TSLP. ILC2s respond to these cytokines and express IL-5 and IL-13. IL-5 and IL-13 act on other innate cell types such as eosinophils and macrophages to promote tissue eosinophilia and alternative activation of macrophages. These innate responses, coupled with the action of ILC2-derived IL-13 directly on the epithelium, serve to mediate changes in epithelial barrier physiology that contribute to increased mucin production and smooth muscle contractility. In addition, activated ILC2s interact with $CD4^+$ T cells via expression of MHC II, which drives T-cell production of IL-2 that acts back on ILC2s to support their continued proliferation, activation, and survival. Together, these ILC2-centric pathways contribute to type 2 inflammation that is protective during helminth infection and pathologic in the context of allergic disease

Numerous factors and pathways regulate ILC2 function during infection with helminth parasites. The cytokines IL-25 and IL-33 were required for the activation of these cells and subsequent parasite expulsion [28–30, 32], and expression of the signaling molecule NF-κB activator 1 (ACT1) in epithelial cells was critical for the efficient production of IL-25 and IL-33 following infection [92]. Another cytokine, TL1A, also elicited ILC2 responses in the context of helminth infection [40, 41]. Recent work has shown that eicosanoids can also regulate ILC2 responses following

helminth infection, as the PGD2 receptor CRTH2 mediated ILC2 accumulation and type 2 inflammation in the lung of mice that had been infected with *N. brasiliensis* [84]. A variety of transcription factors are required for optimal ILC2 responses. During *N. brasiliensis* infection, GATA3 was required for ILC2 development and function [22, 23], GFI1 regulated ILC2 responsiveness to IL-33 and supported maintained GATA3 expression [69], and TCF1 promoted ILC2 expansion [31]. Finally, very recent evidence suggests that interactions with T cells during infection are important in supporting ILC2 responses. Through expression of major histocompatibility class II (MHC II), ILC2s interacted with and activated naïve $CD4^+$ T cells, resulting in the production of Tcell-derived IL-2 that supported ILC2 expansion, effector function, and parasite expulsion [33]. Collectively, these data show that ILC2s are regulated by various cytokines and transcription factors in order to allow ILC2s to interact with other immune cells and the epithelium to mediate protective immunity to helminth infection (Fig. 3).

ILC2s Promote Allergic Inflammation

ILC2s are potent sources of type 2 cytokines and are subject to complex regulation by a variety of pathways and factors [3, 7–11]. Thus, it is not surprising that ILC2 responses are not solely protective during helminth infection, but can also drive pathologic type 2 cytokine-associated responses associated with allergy [3, 7–11]. A significant body of work now supports a key role for ILC2s in the initiation and maintenance of allergic inflammation at mucosal and barrier surfaces in the context of multiple allergic diseases, including allergic asthma, allergic airway inflammation, chronic rhinosinusitis (CRS), AD, and food allergy [3, 7–11].

Shortly after the discovery of murine ILC2s in the intestine and fat-associated lymphoid clusters [28–30], these cells were also identified in the murine lung [35, 93]. Numerous studies have now established that IL-25, IL-33, and/or TSLP can elicit ILC2-derived IL-5 and IL-13 production that contributes to airway hyperresponsiveness and allergic airway inflammation in various murine models [20, 24, 26, 31, 37–41, 69, 74–76, 78, 85, 94–98] (Fig. 3). Notably, bioactive lipids such as eicosanoids can also promote ILC2 responses that regulate type 2 inflammation in the lung. For example, murine lung ILC2s responded to LTD_4 by producing IL-4 and IL-5, which was associated with eosinophilia induced by exposure to *Alternaria* species [85]. Similarly, human ILC2s express the receptor for LXA_4, which regulated IL-13 production by ILC2s [81].

Importantly, new studies suggest that ILC2s contribute to allergic inflammation in the lung through a variety of mechanisms in addition to their ability to produce IL-5 and IL-13. For instance, in response to IL-2 signals, murine lung ILC2s produced IL-9 that was necessary for their survival and effector function in response to challenge with papain [99]. This dependence on IL-2 signaling suggests that ILC2 activities are closely tied with those of T cells, which are the primary source of IL-2 [100]. In support of this concept, recent work has revealed that ILC2s and T cells interact to coordinately drive allergic lung inflammation. In vitro co-culture of ILC2s

and CD4+ T cells led to Tcell proliferation and type 2 cytokine production, and co-transfer of these cells into mice that lacked both T cells and ILC2s drove allergic airway inflammation in response to ovalbumin or the cysteine protease bromelain [101] (Fig. 3). In addition, following exposure to papain, IL-13 from ILC2s promoted DC migration to the draining lymph node and priming of naïve T cells [102].

Notably, there is significant evidence to suggest that ILC2s play a role in asthma and upper and lower allergic airway inflammation in humans. Allergic rhinitis is characterized by type 2 cytokine responses in the upper airways and can be associated with the development of CRS [103]. Nasal polyps, a hallmark of CRS, had an enriched population of CRTH2-expressing ILC2s that responded to IL-25, IL-33, and TSLP [25, 34, 104, 105]. Additionally, ILC2s have been identified in the human adult and fetal lung that expressed IL-33R, CRTH2, and/or CD161 [34, 35, 81, 84], and levels of epithelial cell-derived cytokines and eicosanoids that activate ILC2s were elevated in the lung tissues of human asthmatics [81, 106–109]. Finally, ILC2s isolated from the peripheral blood of asthmatics were more numerous than ILC2s in the peripheral blood of healthy controls, and they also produced more IL-5 and IL-13 in response to stimulation [110]. Taken together, these studies indicate that eicosanoids and epithelial cell-derived cytokines activate ILC2s to produce cytokines and interact with innate and adaptive immune cells, leading to allergic airway inflammation in mice and humans (Fig. 3).

The importance of ILC2s in mediating type 2 inflammation in the upper and lower airways suggests that these cells contribute to other atopic diseases at different tissues sites. In support of this idea, levels of the epithelial cell-derived cytokines that activate ILC2s, including IL-25, IL-33, and TSLP, have been shown to be increased in the skin of patients with AD [111–114] and in the intestine of patients with food allergy [115–117]. Indeed, the ILC2 population was expanded in AD and AD-like lesions in humans and mice, respectively [43, 77], where these cells responded to IL-2, IL-25, IL-33, and TSLP, produced IL-5 and IL-13, and interacted with innate granulocyte populations to mediate allergic inflammation [44, 73, 77, 118]. While a role for ILC2s in food allergy has not yet been described, ILC2s in the intestine could drive inflammation in response to IL-25 in a murine model of oxazalone-induced colitis [119], suggesting that further research investigating the contribution of ILC2s to type 2 inflammation in the gastrointestinal tract is warranted. Collectively, studies in murine models of allergic disease and in human patients with allergic disease suggest that ILC2s play a key role in driving allergic inflammation at multiple mucosal and barrier surfaces, and that these cells and their effector functions could be targeted in the treatment of upper and lower allergic airway inflammation, AD, and potentially food allergy in humans.

ILC2s Support Tissue Remodeling and Wound Healing

While the role for ILC2s in promoting pathologic and protective type 2 inflammation is now well-established [3, 7–11], new data are emerging that highlight additional functions of ILC2s. In particular, ILC2s appear to contribute to tissue

remodeling, wound healing, and tissue homeostasis in a number of contexts [3, 7–11]. A role for ILC2s in tissue remodeling was initially described during influenza A virus infection in mice, in which ILC2 depletion led to a defect in the ability of the lung epithelium to repair itself following virus-induced tissue damage [35]. In this context, lung ILC2s produced the EGFR ligand Areg, which was critical in mediating efficient repair of the lung tissue [35]. A recent study supports the idea that ILC2s have tissue-protective roles in the lung during infection with other pathogens, as IL-9 promoted survival of ILC2s in the lung that produced Areg and contributed to tissue repair following migration of the helminth *N. brasiliensis* through the lung [45]. The tissue-protective effects of ILC2s do not appear to be limited to the lung. Recent evidence suggests that cholangiocytes, the epithelial cells of the bile duct, also derive protective benefits from ILC2s. In response to IL-33, expansion of an IL-13-producing ILC2 population supported cholangiocyte proliferation in a murine model of biliary atresia [120]. Interestingly, this cholangiocyte hyperplasia was also associated with an increase in cholangiocarcinoma in mice, suggesting that precise regulation of ILC2-dependent tissue repair mechanisms is required to avoid pathologic outcomes [120].

In keeping with this idea, emerging evidence suggests that ILC2s can also contribute to dysregulated tissue remodeling associated with fibrosis and pathology [42, 72]. Following challenge with *Schistosoma mansoni* eggs, the development of pulmonary fibrosis was dependent upon IL-25-elicited ILC2s that produced IL-13, and the same study showed that ILC2 frequency and number were increased in the bronchoalveolar lavage (BAL) fluid of human patients suffering from idiopathic pulmonary fibrosis [48]. Also, in a model of hepatic fibrosis, ILC2s that responded to IL-33 and produced IL-13 were important in driving fibrotic processes [72]. Thus, similar to the capacity of ILC2s to contribute to both protective immune responses against helminth parasites and detrimental type 2 responses during allergic inflammation, the ability of ILC2s to drive tissue remodeling processes can be either beneficial or pathological. While the regulation of these activities is likely tissue- and disease-specific, further work is required to dissect the pathways that influence ILC2-mediated tissue remodeling and to determine whether these cells and their activities could be targeted to regulate tissue remodeling and homeostasis in various disease states.

ILC2s Promote Metabolic Homeostasis

Cutting edge studies in ILC2 biology have begun to focus on how ILC2s contribute to the maintenance of metabolic homeostasis [42, 46, 47, 121, 122]. Previous work has demonstrated that a type 2-polarized cytokine environment in adipose tissue elicits alternatively activated macrophage (AAM) activities and the accumulation of eosinophils, which in turn are associated with metabolic homeostasis [5, 123–125]. In contrast, classical activation of macrophages and T_H1-polarized inflammation in the adipose is associated with obesity, insulin resistance, and metabolic disease

[126–130]. These previous findings, coupled with the observations that ILC2s are potent sources of type 2 cytokines in other tissues [3, 7–11], prompted an investigation of the role of ILC2s in maintaining type 2 cytokine responses that support metabolic homeostasis.

An initial study demonstrated that IL-13 played a role in limiting hyperglycemia, which is associated with insulin resistance. IL-13 limited glucose production by inhibiting genes involved in gluconeogenesis in the liver via signal transduction and activator of transcription 3 (STAT3) [121], suggesting that sources of IL-13, such as ILC2s, might contribute to glucose homeostasis. In addition, IL-5-responsive eosinophils in the adipose have been associated with the maintenance of healthy adipose tissue function in the lean state, and another study has shown that IL-33-elicited ILC2s that produced IL-5 maintained eosinophil and AAM populations in the fat [46]. Supporting a role for ILC2 effector functions in promoting metabolic homeostasis in the adipose, IL-25 treatment resulted in an increase in ILC2 populations in obese mice, associated with the expansion of eosinophil and AAM in the adipose, increased weight loss, and improved glucose tolerance. Similarly, ILC2 depletion in obese *Rag1*$^{-/-}$ mice resulted in increased weight gain and glucose intolerance, and transfer of ILC2s to obese mice led to weight loss and improved insulin sensitivity [42].

In addition to their role in regulating immune cells that contribute to metabolic homeostasis in the fat, ILC2s that reside in the intestine produced IL-5 following caloric intake in response to vasoactive intestinal peptide (VIP), a neuropeptide produced following feeding that is tied to circadian rhythms. These data thus establish a link between ILC2s, caloric intake, and eosinophil responses that have been associated with metabolic homeostasis [47]. A very recent publication has also shown that IL-33-responsive ILC2s in the fat regulate adiposity and the recruitment of beige adipocytes that control caloric expenditure [122]. Together, these studies suggest that ILC2s may be key regulators of metabolic processes in the steady state. Of note, a very recent study has shown that micronutrient deficiencies appear to influence ILC2 responses that mediate protective immunity against pathogens [131], suggesting that ILC2s are also key players in coordinating nutrition and metabolism during infection and inflammation. Further studies will be needed to better understand how ILC2s sense nutritional status to regulate metabolic homeostasis during the steady state and following encounters with pathogens.

Conclusions and Future Directions

A rapidly advancing body of work highlights the key role that ILC2s play in protective and pathologic type 2 immune responses in the context of helminth infection, allergic disease, tissue remodeling and repair, and metabolic homeostasis [3, 7–11]. Together, these studies provide new insight into how the innate immune system contributes to type 2 cytokine responses that participate in a variety of key biologic processes [1]. However, numerous outstanding questions remain regarding the development, effector function, and regulation of ILC2s. The precise developmental

paths that lead to ILC2 hematopoiesis remain unclear, and how ILC2 populations turn over in the steady state and change in the course of aging is unknown. Also, it seems likely that cytokines and factors in addition to the epithelial cell-derived cytokines and eicosanoids shape ILC2 responses. In particular, the pathways that negatively regulate ILC2 responses and the mechanisms that control ILC2 migration are poorly understood. Similarly, ILC2s likely produce cytokines or other factors in addition to type 2 cytokines and Areg. Further work will be required to more comprehensively profile the effector molecules produced by ILC2s and how these cells interact directly and indirectly with epithelial cells and innate and adaptive immune cells. Most importantly, our current understanding of ILC2 biology suggests that these cells and their effector functions could be targeted therapeutically in human diseases in which type 2 cytokine responses play a role, including helminth infection, allergic disease, fibrosis, and metabolic disease. Future studies that investigate ILC2 responses in humans and in murine models of human diseases could result in the development of innovative new therapies that target innate immune pathways involved in the pathogenesis of multiple inflammatory diseases.

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