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Innate lymphoid cells in the initiation, regulation and resolution of inflammation

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Abstract

A previously unappreciated cell type of the innate immune system, termed innate lymphoid cells (ILCs), has been characterized in mice and humans, and found to profoundly influence the induction, regulation and resolution of inflammation. ILCs play an important role in these processes in murine models of infection, inflammatory disease and tissue repair. Further, disease association studies in defined patient populations have identified significant alterations in ILC responses, suggesting a potential role for these cell populations in human health and disease. In this review, we discuss the emerging family of ILCs, the role of ILCs in inflammation, and how current or novel therapeutic strategies could be employed to selectively modulate ILC responses and limit chronic inflammatory diseases in patients.

Inflammation is defined as heat, redness, pain, swelling and loss of function. While acute inflammation is a necessary process to protect against infection and promote tissue repair, chronic inflammation directly contributes to the pathogenesis and progression of multiple infectious, inflammatory and metabolic disorders, including HIV/AIDS, inflammatory bowel disease, arthritis, psoriasis, allergy, asthma, diabetes, obesity and cancer[1,2]. While there are many well characterized cellular and molecular components of the innate and adaptive immune system that influence inflammatory processes, recent characterization of an emerging family of innate immune cells, termed ILCs, has revealed an essential role for these populations in the initiation, regulation and resolution of inflammation. ILCs are a population of innate lymphocytes that are relatively rare in comparison to adaptive lymphocytes in lymphoid tissues, but are enriched at barrier surfaces of the mammalian body, such as the skin, lung and intestine, as well as adipose and some mucosal-associated lymphoid tissues[3–6]. ILCs rapidly respond to cytokine and microbial signals and are potent innate cellular sources of multiple pro-inflammatory and immuno-regulatory cytokines, and recent research has also identified a critical role for ILCs in modulating adaptive immunity. Mature ILC subsets can be identified by a lack of known lineage markers associated with T cells, B cells, myeloid cells, or granulocytes, but share expression of the common gamma chain (γc, CD132), IL-7Rα (CD127), IL-2Rα (CD25), and Thy1 (CD90), with some exceptions noted below[3–6].

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A combination of advances in multi-parameter flow cytometry and the identification of novel cytokine pathways regulating immunity and inflammation, including the interleukin (IL-)23-IL-22 pathway[7–12] and epithelial-derived cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP)[13–17], contributed to our emerging knowledge of ILCs. Prototypical members of the ILC family were discovered many years prior, including the natural killer (NK) cells in 1975[18,19], and subsequently lymphoid tissue-inducer (LTi) cells[20]. However, it was not until more recently that other members of the ILC family were characterized. These included simultaneous reports of innate lymphocytes that are predominant cellular sources of the cytokines IL-17 and IL-22[21–28], or IL-5 and IL-13[29–33], in the steady state or early following infection. These rapid and fundamental advances also generated redundant nomenclature based upon functional potential of the identified cells, including NK-22 cells, LTi-like cells, natural helper cells, nuocytes and innate helper cells. To limit confusion, leaders in the field later unified a common terminology to classify these emerging cell populations as a new family of ILCs which encompasses three subsets, termed group 1,2 or 3 ILCs, based on common expression or dependence of surface markers, transcription factors and cytokines[3].

Recent investigations of ILCs has caused a shift in our understanding of innate and adaptive immunity, and has fuelled additional extensive investigation into these cells due to the potential influence of ILCs in human health and disease. Mouse models indicate that ILCs play a fundamental role in the immune system by initiating, regulating and resolving inflammation. Further, studies in humans have revealed that ILC responses are significantly altered in several disease states. Below we discuss the development and heterogeneity of ILCs, the role of human and mouse ILCs in inflammatory processes, and how current or novel therapeutic strategies could be employed to modulate ILC responses and benefit human health.

Development and heterogeneity of the innate lymphoid cell family

ILCs initially develop in the fetal liver and later in the adult bone marrow from common lymphoid progenitors (CLPs)[34–36]. CLPs also differentiate into cells of the adaptive immune system, such as T cells and B cells, but development of ILCs from CLPs occurs independent of somatic recombination, a defining feature of the adaptive immune system that permits the generation antigen-specific receptors or secreted proteins such as the T cell receptor, B cell receptor and immunoglobulin. ILC develop is regulated at the transcriptional level, with several precursor populations and transcription factors regulating each lineage (Fig. 1)[4,37,38]. Differentiation of all ILCs from a CLP requires the transcription factors inhibitor of DNA binding 2 (Id2), nuclear factor interleukin-3 regulated (NFIL3)[3,4,36,39–43], and thymocyte selection-associated high mobility group box (Tox)[44,45] and involves additional precursor populations (Fig. 1). These include NK cell precursors (NKp) that give rise to NK cells, and a common helper innate lymphoid precursor (CHILP) that gives rise to all other defined ILCs in a process that requires T cell factor 1 (TCF1)[46,47] and GATA binding protein 3 (GATA3)[48,49]. From CHILPs, several distinct progenitors expressing α4β7 integrin give rise to LTi cells[34], while a PLZF-dependent ILC progenitor (ILCp) can give rise to other defined ILC populations[35]. While the specific interactions and functions of transcription factors in ILC development are not well defined, one recent study elegantly demonstrated that IL-7

signaling can induce NFIL3 and subsequently Id2 to support the generation of ILC progenitors[39]. However additional studies are required to further define these functional interactions as NFIL3-deficient mice do not completely replicate the phenotype of Id2-deficeint mice, which lack nearly all ILCs. Further, while most of these developmental studies have necessarily employed mice, recent research by Romagnani and colleagues defined that $CD34^+$ hematopoietic progenitor cells (HSCs) in the bone marrow or peripheral blood can give rise to $\alpha4\beta7$ integrin expressing $CD34^+$ progenitors in the lymphoid tissues and intestinal lamina propria with the potential to differentiate into either NK cells or LTi-like cells in a process that influenced by the presence of aryl hydrocarbon receptor (Ahr) ligands, stem cell factor (SCF) and IL-15[50].

Mature ILCs provide a potent and early source of cytokines in response to various stimuli, including direct cytokine stimulation, or as a consequence of colonization with commensal microbes or pathogen infection. There is considerable phenotypic and functional heterogeneity in the mature ILC family, and broadly three groups of ILCs have been defined based upon shared expression of surface markers, transcription factors and effector cytokines (Fig. 1)[3–6].

Group 1 ILCs (ILC1) respond to IL-12, constitutively express T-bet, and produce the effector cytokines including IFNγ and TNF[36,51,52]. ILC1 are considerably heterogeneous and can be distinguished into at least three subsets based up differential expression and requirements for eomesodermin (eomes), T-bet, IL-15 and IL-7. Conventional NK cells are a subset of ILC1 requiring eomes and IL-15 for development from NKp, but not T-bet or IL-7[36]. ILC1 also include $CD103^+$ intraepithelial ILC1 that develop independent of IL-15 from an unknown precursor, express eomes, and require T-bet for differentiation[52]. Further, a $CD127^+$ ILC1 was also identified in humans and mice, which does not express eomes, develops independently of IL-7 from a CHILP and ILCp, but requires T-bet and IL-15[36,51].

Group 2 ILCs (ILC2) respond to cytokines IL-25, IL-33 and TSLP, constitutively express high levels of GATA3, and produce the effector cytokines IL-4, IL-5, IL-9, IL-13 and amphiregulin[29–33]. While GATA3 is required for the development of most ILC subsets[48,49], it is also required for the maintenance and function of mature ILC2 in humans and mice[53–56]. RORα is also required for ILC2 development in mice[57,58], but is also highly expressed by other ILC subsets and its function is poorly defined[59]. Gfi1 and Bcl11b also contributes to the differentiation or lineage stability of mouse ILC2[60–62]. Although mature ILC2 can be found in most anatomical locations, they appear to be enriched in the healthy lung, skin and adipose tissue of mice and humans[29,31,32,63–66].

Group 3 ILCs (ILC3) respond to IL-1β, IL-6 and IL-23, constitutively express RORγt, and produce the effector cytokines IL-17 and/or IL-22[21–28]. Although all ILC3 share a developmental requirement for RORγt[24,67], significant heterogeneity exists within this group. Fetal and adult LTi cells are members of ILC3, which develop independently of PLZF-dependent ILCp, are $CCR6^+$, heterogeneous in expression of CD4, express IL-22 and IL-17, and are a source of lymphotoxin (LT). A subset of adult ILC3 can develop from PLZF-dependent ILCp after birth are $CCR6^-$, co-express T-bet, are heterogeneous in expression of natural cytoxicity receptors (NCR, such as NKp46 and NKp44), and can co-

express IL-22 and IFNγ. This T-bet$^+$ ILC3 population requires T-bet, the presence of commensal bacteria and the aryl hydrocarbon receptor (AhR) for development[68–72]. T-bet$^+$ ILC3 are almost exclusively found in the skin and intestinal lamina propria, while LTi-like ILC3 are enriched in the intestine and lymphoid tissues[28,68,73–75]. Further, as discussed below, ILC3 with a unique phenotype can develop in some inflammatory contexts in the intestine and liver[24,76].

Although still an emerging field, plasticity between ILC groups has been observed. ILC3 subsets can downregulate RORγt expression in mice and humans, resulting in a dominant expression of T-bet and sustained expression of IFNγ[51,68,72]. However, it is currently unclear whether to classify these populations as ILC1 or ILC3, and it is difficult to distinguish them from a stable ILC1 lineage without fate mapping approaches that genetically mark cells that express or previously expressed RORγt. Therefore many groups have termed these cells ex-ILC3[36,51,68,72]. Additional evidence suggests that a transient IL-25-responsive ILC2 population can differentiate into an IL-17-producing ILC3-like cell[77], however additional research is required to fully characterize the extent of ILC plasticity, as well as define the potential causes and consequences of this plasticity.

ILCs orchestrate acute inflammation to promote immunity to infection

Acute inflammation is necessary to mount an effective immune response to various infectious organisms. ILCs were first identified based on their ability to promote rapid and essential innate immune responses to different classes of pathogens in part by modulating local epithelial cell, myeloid cell or granulocyte responses (Fig. 2).

ILC1 and intracellular pathogens

ILC1 populations play a critical role in promoting immunity to intracellular pathogens (Fig. 2a). Rapid NK cell responses have been well characterized following exposure to multiple intracellular pathogens in both humans and mice[78]. However, the role of other ILC1 populations has been less clear. Recent evidence suggests that ILC1 are the dominant innate source of IFNγ and TNF in mice following infection with the oral pathogen *Toxoplasma gondii*, and play a role in recruiting inflammatory myeloid cells that control infection[36]. Consistent with this, genomic T-bet-deficiency rendered mice highly susceptible to *Toxoplasma gondii* infection, and adoptive transfer of ILC1 to lymphocyte-deficient mice (*Rag2*$^{-/-}$*Il2rg*$^{-/-}$) was sufficient to boost immunity[36].

ILC2 and extracellular parasites

ILC2 rapidly respond following exposure to multicellular parasites that are typically extracellular (Fig. 2b). For example, ILC2 are an important innate cellular source of IL-13 in the intestine following infection of mice with the parasite *Nippostrongylus brasiliensis*[29,30,33]. IL-13 can act on goblet cells to induce mucus production and on smooth muscle to enhance contractility, both of which are thought to contribute to expulsion of the parasites from the gastrointestinal tract[79]. IL-4 and IL-13 can also induce goblet cell expression of Relmβ, which limits parasitic infection[80]. Epithelial cell-derived IL-25 and IL-33 primarily promote the population expansion and cytokine production of ILC2s

following parasite infection of mice[29,30,33]. ILC2 can similarly promote IL-13-mediated immunity to other parasites in mice, including *Trichuris muris*[81]. Notably, this response could be enhanced by Vitamin A-deficiency[81], suggesting that ILC2 can respond to dietary stress and that the type 2 immune response may have adapted to support anti-parasite immunity in human populations with malnutrition.

ILC3 and extracellular bacteria and fungi

ILC3 rapidly respond to infections of mice with either extracellular bacteria or fungi (Fig. 2c). NCR^+ ILC3 rapidly respond to infection of mice with the gram-negative enteric pathogen *Citrobacter* rodentium by producing IL-22[22], which is essential for host protection[7]. These ILC3 responses in humans and mice can be promoted by dendritic cell (DC)-derived IL-23[22], and in mice ILC3 are a dominant and essential source of IL-22 for innate immunity to *Citrobacter rodentium* in the intestine[21,23]. IL-22 acts almost exclusively on non-hematopoietic cells, such as intestinal epithelial cells (IECs), and stimulates production of antimicrobial peptides (RegIIIγ and RegIIIβ), element-sequestering proteins (lipocalin-2, S100A8 and S100A9), mucus production (Muc1, 3, 10 and 13) and epithelial fucosylation (Fut2)[7–9,82–85]. These responses collectively limit the replication, dissemination and tissue damage induced by pathogenic and opportunistic bacteria. Similarly, ILC3 located in the oral mucosa promote IL-17-dependent innate immunity to infection with the fungal pathogen *Candida albicans* in mice[86]. IL-17 can act alone or synergistically with IL-22 to also promote antimicrobial peptide production and induces the expression of chemokines (Cxcl1 and Cxcl9) to recruit neutrophils to the site of infection[7–9,87]. ILC3-derived IL-17 also critically regulates neutrophils in neonatal mice, which is important for resistance to sepsis with gram negative opportunistic bacteria, and is critically dependent upon the presence of a commensal bacteria and microbial sensing pathways[88]. Collectively, this suggests that the ILC family plays a significant role in mediating acute inflammation in response to infection, which is important for the control and clearance of various classes of pathogens.

ILCs promote the resolution of inflammation and tissue repair

In addition to their role in initiating acute inflammatory responses and immunity to pathogens, ILCs directly contribute to the resolution of inflammation by repairing damaged tissues including the lung, various lymphoid tissues, and gastrointestinal tract (Fig. 3). These repair processes are essential to limit sustained inflammation, prevent against re-infection, and restore tissues to a state of homeostasis.

ILC2 and resolution of inflammation in the lung

In the lung of mice, ILC2 expand in response to IL-33 following influenza virus infection and subsequent immune-mediated tissue damage (Fig. 3a)[31]. Experimental depletion of ILC2 in mice did not impair innate immunity to influenza, but rather limited repair of the airway epithelium and reduced lung function. This repair function was not mediated by ILC2 cytokine responses, such as IL-13, but rather was promoted by production of amphiregulin, a member of the epidermal growth factor family that was highly expressed by ILC2[31]. Further, following infection and subsequent tissue damage induced by the migration

of *Nippostrongylus brasiliensis* in the lungs of mice, autocrine production of IL-9 contributes to the survival of ILC2 and sustained amphiregulin production that mediates repair of the lung tissues[89]. ILC2 therefore represent a major ILC population in the lung that promotes tissue repair following infection. Murine ILC2s also promote cutaneous wound healing in an excisional wound model (Artis and Volk, pers. comm.). Although it has been demonstrated that human ILC2 express amphiregulin at the transcript level[90], additional work is needed to define whether human ILC2 are potent sources of amphiregulin and mediate tissue repair. Also, it currently remains unclear whether ILC2 can promote tissue repair at different anatomical locations.

ILC3 and resolution of inflammation in lymphoid tissues and the intestine

ILC3 promote tissue repair through several distinct mechanisms (Fig. 3b, c). Systemic viral infections can impair the architecture of secondary lymphoid organs following $CD8^+$ T cell-mediated killing of infected stromal cells[91]. If restoration of tissue homeostasis does not occur it can render a host susceptible to secondary infections. Disruption of lymphoid tissue architecture in mice promotes a local accumulation of LTi-like ILC3s that express $LT\alpha1\beta2$ and act on LTβR-expressing stromal cells to enhance their proliferation and survival (Fig. 3b)[91]. Further, ILC3 can also promote tissue repair in the thymus of mice following total body irradiation[92]. In this context, $CCR6^+$ ILC3 are partially radio-resistant and respond to irradiation-induced IL-23, promoting IL-22-dependent restoration of tissue integrity in the thymus[92]. IL-22 acts on thymic epithelial cells to promote cell survival and proliferation[92]. Further, IL-22-dependent tissue repair in mice has also been reported in the liver following chemical-induced hepatitis[79] and lung following influenza infection or bleomycin-induced damage[87,93,94], which are two other organs where the tissue resident non-hematopoietic cells highly express the IL-22 receptor[8].

In the intestine, ILC3 play an important role in regulating tissue repair (Fig. 3c). This may be particularly important in the context of human inflammatory bowel disease (IBD) because several reports have identified reduced numbers of ILC3 in intestinal tissues from disease patients relative to non-IBD controls[51,95,96]. In mouse models, ILC3 production of IL-22 mediates tissue repair following experimental tissue damage induced by hematopoietic stem cell transplantation (HSCT) and subsequent graft versus host disease (GVHD), or administration of dextran sodium sulfate (DSS)[97–99]. Following whole body irradiation and HSCT, radio-resistant ILC3 respond to DC-derived IL-23 and produce IL-22. IL-22 acts on the intestinal stem cell or progenitor compartments to limit apoptosis and preserve intestinal barrier function[98]. If alloreactive T cells with the capacity to attack donor tissues are co-transferred into mice following irradiation, this causes GVHD and is associated with a decrease in intestinal ILC3 and enhanced intestinal tissue damage due to a loss of IL-22[98]. Critically, in humans, ILC3 are not normally observed in the circulation, but are observed following chemotherapy for HSCT[100]. Furthermore, the levels of circulating ILC3s positively correlate with a reduced incidence of developing GVHD[100], suggesting a critical role for human ILC3 in limiting GVHD.

In the DSS model of intestinal damage and inflammation, ILC3 responses and production of IL-22 also promote tissue repair and maintain intestinal barrier function[82,97]. This process is

regulated by commensal bacteria, which induce expression of IL-25 by IECs following colonization in the postnatal period[97,101]. IL-25 acts on IL-25R$^+$ DCs to subsequently limit ILC3 responses in a contact-dependent manner[97]. However, upon induction of experimental tissue damage with DSS, IL-25 expression was reduced and ILC3 responses were enhanced to mediated IL-22-dependent tissue repair[97]. ILC3 responses and IL-22-dependent tissue repair can also be enhanced in mice and humans following recognition of pathogenic or commensal microbes by CX3CR1$^+$ myeloid cells and subsequent production of IL-1β, IL-23 and TL1A[102–105]. One potential reason for the differential roles of commensal bacteria in promoting or suppressing ILC3 responses could be explained by the differential regulation of IL-1β secretion by pathogenic bacteria and selective subsets of commensal bacteria[106,107]. The vitamin A metabolite retinoic acid (RA) can also enhance ILC3 responses in mice through multiple mechanisms including direct binding to the *Rorc* or *Il22* loci, promoting maturation of LTi-like ILC3, and regulating ILC3 proliferation[81,99,108]. In addition to promoting maintenance of the intestinal epithelium, during fetal development RA and Vitamin A promotes maturation of and larger secondary lymphoid tissues via LTi cells in mice, which could enhance protection from viral infections later in life[108]. Thus, ILC3 play a significant role in repairing damaged lymphoid tissues, airway epithelia, liver, and intestinal epithelia, thus preserving organ function.

ILCs promote chronic inflammation

ILCs can also promote chronic inflammation in several mouse models, and dysregulated ILC responses have been characterized in patient populations with chronic inflammatory disease of the lung, skin and intestine (Fig. 4).

ILC2 and chronic inflammation in the lung and skin

Increased ILC2 responses have been observed in multiple allergic diseases, including the skin of individuals with atopic dermatitis[63,90], in the nasal polyps of individuals with chronic rhinosinusitis[32], circulating in the blood of individuals with asthma[109], and in the bronchalveolar lavage of individuals with idiopathic pulmonary fibrosis[110]. In mouse models, dysregulated ILC2 responses contribute to chronic inflammation in the lung and skin (Fig. 4a). For example, ILC2 responses are elicited by epithelial cell- or myeloid cell-derived TSLP, IL-25 and IL-33 following exposure to allergens, chemicals, helminth parasites, or following influenza virus infection[29–32,63,90,111–115]. Basophils can also promote pro-inflammatory ILC2 responses in the skin and lung through production of IL-4 in mouse models of chemical-induced atopic dermatitis and protease allergen-induced airway inflammation[116,117]. Further, human mast cells co-localize near ILC2 in the human lung and could directly promote ILC2 responses *in vitro* through production of prostaglandin D2 (PGD2)[118]. The population expansion of ILC2 is thought to contribute to chronic inflammation through multiple mechanisms. Production of ILC2-dervied IL-5 can promote the recruitment of eosinophils into the lung and skin of mice, which contributes to tissue inflammation[114]. Further, ILC2-derived IL-13 can impair lung function of mice by enhancing airway smooth muscle cell contractility, increasing epithelial cell mucus production, polarizing macrophages to an alternatively activated phenotype (AAMacs) and increasing collagen deposition[110,111]. ILC2 in mice can also promote chronic inflammation

by enhancing Th2 cell responses either indirectly by IL-13-elicited migration of activated DCs to the lung draining lymph node and subsequent Th2 cell priming[119], or through direct MHCII-dependent interactions with CD4 T cells[120,121].

ILC3, chronic inflammation and cancer in the skin, lung and intestine

Increases in ILC3 frequencies, cell numbers and cytokine production have also been observed in individuals with chronic inflammatory diseases, including in the skin of patients with psoriasis[75,122], in tumors of patients with colitis-associated colon cancer[123], or in the BAL of patients with asthma[124]. In a mouse model of psoriasis, ILC3 are the dominant source of IL-17 and IL-22 in the skin and are reduced by an p40-specific monoclonal antibody[125], which likely blocks the IL-23-mediated population expansion or activation of ILC3. ILC3 are necessary and sufficient to induce psoriatic plaque formation in mice via production of IL-17 and IL-22 (Fig. 4b)[125]. Further, although normally absent in the lungs of healthy mice[31], Umestu and colleagues identified in a mouse model of obesity-induced asthma that ILC3 expand in response to NLRP3-dependent production of IL-1β by macrophages[124]. Further ILC3 were sufficient to promote IL-17-dependent airway hyper-responsiveness in this mouse model[124].

The role of ILC3 in promoting intestinal inflammation is more complex given the significant heterogeneity observed in this cell lineage, potential lineage plasticity, and differential gating strategies employed by different groups conducting human studies. Two reports observed an increased frequency in pro-inflammatory ILC3 in intestinal tissues from individuals with IBD[126,127], while another identified increased ILC3 production of IL-22[102]. However, as described in the next section, there have been many reports of tissue protective functions of ILC3 in mouse models of intestinal inflammation, and additional reports of decreased ILC3 frequencies in IBD patients. A potential explanation for the different reports may be due to the selected mouse models, heterogeneity and potential plasticity of ILC3, as well as the clinical phenotypes and tissue sources of the patient populations studied. Notwithstanding this, one study elegantly demonstrated a role for a unique ILC3 population in two innate mouse models of intestinal inflammation (Fig. 4c). In that study, administration of anti-CD40 monoclonal antibody or colonization with *Helicobacter hepaticus* in *Rag1*$^{-/-}$ mice induces colitis that is dependent upon ILCs, RORγt, IL-17 and IFNγ[24]. The pro-inflammatory ILC3 observed in these models are largely absent in the steady state, lack expression of c-kit, and a portion co-expressed T-bet, IFNγ and IL-17A[24]. ILCs with a similar phenotype are also observed in mice that lack both T-bet and Rag2 (TRUC mice), a spontaneous model of innate cell-driven intestinal inflammation[76,128]. TRUC mice have increased IL-17-producing ILCs relative to littermate controls, which act in synergy with DC-derived TNF to promote intestinal inflammation[76,128]. IL-6 was also found to be a critical cytokine that promotes IL-17 production from human and mouse pro-inflammatory ILC3[127]. ILC3 can also promote intestinal inflammation indirectly, as it has recently been demonstrated that following *Toxoplasma gondii* infection, ILC3-derived IL-22 acts on IECs to promote expression of the Th1 cell promoting cytokine IL-18, and subsequent tissue inflammation[129]. Further, IEC production of IL-18 was also important for ILC3 production of IL-22, indicating a previously unappreciated cross-regulatory circuit modulating inflammation and ILC3 responses[129].

Some of the pro-inflammatory ILCs may arise from a loss of RORγt expression in ILC3 and an upregulation of T-bet[68,72]. In fate-mapping mouse models, infection with *Salmonella enterica* or anti-CD40 monoclonal antibody administration to *Rag2*$^{-/-}$ mice resulted in the development of ILCs that lost expression of RORγt, resemble ILC1 in expression of T-bet and IFNγ, and contribute to driving intestinal inflammation[76,128]. In human samples and humanized mice this transition of RORγt^{+} ILC3 to RORγt^{-} ex-ILC3 is promoted by IL-12 or can be induced following experimental induction of intestinal tissue damage with DSS[51]. Consistent with these findings, a novel gating strategy from above revealed reduced frequencies of ILC3 and increased frequencies of ILC1, in intestinal tissue from individuals with IBD patients relative to non-IBD controls[51]. Further, a unique intraepithelial ILC1 that develops independently of ILC3 were also enriched in intestinal tissues of individuals with IBD relative to non-IBD controls, and may contribute to the development of intestinal inflammation through production of IFNγ following administration of anti-CD40 monoclonal antibody to *Rag2*-deficient mice[52].

In the colon, ILC3 also promote colitis-associated tumor progression via production of IL-22[123]. In a novel model of colitis-associated cancer, *Rag1*$^{-/-}$ mice, which exhibit chronic intestinal inflammation when colonized with *Helicobater hepaticus*, were administered the carcinogen azoxymethane (AOM) and found to develop colitis-associated colorectal cancer in an ILC- and IL-22-dependent manner[123]. The timing and regulation of IL-22 production is important to consider in the context of intestinal tumors, as Flavell and colleagues recently demonstrated that IL-22 production during the peak of intestinal inflammation is protective against tumor formation, while uncontrolled IL-22 production during the resolution of inflammation promotes intestinal tumorigenesis[130]. In contrast, in an implantable model of mouse melanoma, ILCs that were previously marked with RORγt expression could promote IL-12-mediated tumor rejection[131]. In this mouse model, ILCs induced expression of adhesion molecules in the tumor vasculature, which subsequently enhanced recruitment of immune cells and anti-tumor immunity[131], however this occurred in the context of a genetically modified tumor that overexpressed IL-12. Further, given that the characterized ILCs were described to previously express RORγt, the possibility remains that these anti-tumor ILC responses were mediated by ex-ILC3 that lost RORγt expression and now produced IFNγ and TNF. Further studies are required to define the role of ILCs in influencing pro- versus anti-tumor immune responses, and in particular a role for these cells in the presence of adaptive immunity is lacking. Collectively, these studies defined a complex role for ILC1, ILC2 and pro-inflammatory ILC3 or ex-ILC3 in promoting chronic inflammation in mice and humans.

ILCs limit chronic inflammation

ILCs can also play a significant role in limiting chronic inflammation either by influencing metabolic homeostasis, or by directly regulating innate and adaptive immune cell responses to non-harmful environmental stimuli in the intestine, such as commensal bacteria or dietary antigens (Fig. 5).

ILC2 and metabolic homeostasis

ILC2 have been characterized in the intestine, lung and adipose tissues of healthy humans and mice[29–33]. In the intestine of mice, ILC2 controls the homeostasis of circulating eosinophils through constitutive production of IL-5, as well as tissue-resident eosinophils in the intestine through induced production of IL-13 and subsequent eotaxin expression[132]. Tissue recruitment of eosinophils in the intestine is regulated by nutrient intake and central circadian rhythms that induce vasoactive intestinal peptide (VIP) expression by IECs and stimulates ILC2 production of IL-13 through the VPAC2 receptor[132]. However, the functional significance of ILC2-mediated regulation of eosinophil homeostasis in the intestine is poorly understood. In adipose tissue of mice, ILC2 can regulate eosinophil homeostasis and alternatively activated macrophage polarization[64,65]. In obese mice fed a high-fat diet, or in obese humans, frequencies of ILC2 are reduced in the adipose tissues as compared to non-obese controls, and this reduction in ILC2 is further associated with a reciprocal increase in chronic low grade systemic inflammation[64–66], suggesting a critical role for ILC2 in regulating metabolic homeostasis. Consistent with this, experimental depletion of ILCs exacerbates weight gain in mice and causes insulin resistance, whereas treatment of mice on a high-fat diet with exogenous IL-25 or IL-33 increases ILC2 numbers and limits metabolic disease[64–66]. Mechanistically, this occurred either indirectly through recruitment of eosinophils and differentiation of alternatively activated macrophage in adipose tissues, or by directly acting on adipocytes via ILC2-derived IL-13 or methionine-enkephalin peptides[66,133]. Activation of adipocytes through these pathways induces expression of the transcription factor Ucp1 and beiging of white adipocytes[66,133], a process which induces thermogenesis, protects against insulin resistance and regulates metabolic homeostasis[134]. Additional research is required to further define how ILC2 orchestrate metabolic homeostasis, and whether this may also involve crosstalk with other IL-33R$^+$ cells, such as recently described subsets of Tregs[135–137].

ILC3s in chronic systemic and intestinal inflammation

ILC3 also limit chronic inflammation through several distinct mechanisms (Fig. 5b), which may particularly important in the intestine, as there are several reports of reduced frequencies of ILC3 in individuals with IBD or following human immunodeficiency virus (HIV) infection relative to controls[51,95,96,138–141]. In the intestine and associated lymphoid tissues of healthy humans, non-human primates and mice, ILC3 are a dominant source of IL-22 that is in part influenced by the colonization of the intestine with commensal bacteria[6,142]. Production of IL-22 restricts the anatomical localization or replication of specific species of commensal bacteria in mice. Impairment of this pathway promotes systemic dissemination of lymphoid tissue-resident commensal bacteria or increased colonization in the intestinal epithelium with segmented filamentous bacteria, resulting in low-grade systemic and intestinal inflammation[142,143]. This may be particularly important in the context of HIV infection and progression to acquired immune deficiency syndrome (AIDS), where there are defects in intestinal barrier function and systemic dissemination of commensal bacteria promote chronic immune activation and contribute to viral replication, loss of CD4 T cells and disease progression[144]. Strikingly, in humans and non-human primates, numbers of ILC3 and production of IL-22 are reduced in the intestine following pathogenic infection with HIV or SIV[138–141], and thus may be a novel therapeutic target to

limit disease progression. Production of IL-22 in mice can also promote colonization of the intestine with beneficial and diverse commensal bacteria that provide protection from intestinal inflammation and infection[83–85]. This occurs via ILC3- and IL-22-dependent fucosylation or glycosylation of IECs via *Fut2*, thus providing a sugar food source for beneficial microbiota, which in turn limit the growth of pathogens or opportunistic pathogens and protect from intestinal tissue damage[83–85]. IL-22 production by ILC3 also requires maintained expression of Id2 and subsequent regulation of the IL-23R and Ahr pathway, which is necessary to limit infection-induced damage in mice by regulating colonization resistance and the composition of intestinal commensal bacteria[145].

ILC3 can also limit chronic inflammation through indirect and direct regulation of the adaptive immune cell response (Fig. 5b)[146]. ILCs regulate homeostasis of myeloid cells in the intestine of mice through production of GM-CSF[147]. This process is regulated by macrophage sensing of intestinal commensal bacteria and production of IL-1β, which can act on ILC3 to promote GM-CSF expression[147]. Conversely, production of GM-CSF by ILC3 was essential to modulate myeloid cells and subsequently generate regulatory T cell responses to food antigens in the intestine and maintain oral tolerance[147]. Through production of LTα1β2 or a soluble LTα3, ILC3 can influence the production of T cell-independent and T cell-dependent IgA production in the intestine, respectively, which modulates the composition of the intestinal commensal bacteria[148,149]. Human and mouse ILC3 were found to also express MHCII, process and present antigens, and directly interact with CD4 T cells[150]. Genetic deletion of ILC3-intrisic MHCII in mice results in the development of spontaneous CD4 T cell-mediated intestinal inflammation, which was dependent upon commensal bacteria[150,151]. Mechanistically, $MHCII^+$ ILC3 induced cell death of activated commensal bacteria-specific CD4 T cells in the intestine of mice, revealing a previously unappreciated selection pathway in the intestine whereby T cells with the potential to cause local inflammation are deleted, akin to the process that occurs for self-reactive T cells during thymic selection[152]. While no differences were observed in the frequency of ILC3 in intestinal biopsies of pediatric IBD patients, a significant reduction of MHCII on ILC3 was observed relative to non-IBD controls, and this reduction inversely correlated with increased intestinal Th17 cells[152]. These studies identify an essential role for ILC3 in maintaining tissue homeostasis and limiting chronic inflammation in the intestine of humans and mice. Further studies are necessary to interrogate what causes dysregulated ILC3 numbers or responses in the context of chronic human diseases, such as HIV infection or IBD.

Potential therapeutic modulation of ILCs

Given the role of ILCs in the initiation, regulation and resolution of inflammation in mice, and characterized alterations of ILCs in defined patient populations, there is an urgent need to investigate whether therapeutic strategies can be employed to modulate ILC responses and provide clinical benefit. As a proof of principle, ILC responses were recently shown to be modulated in patients with multiple sclerosis (MS) following anti-CD25 monoclonal antibody (daclizumab) therapy[153]. Although the role of ILCs in MS is poorly defined, this study identified increased circulating numbers of ILC3-like cells in individuals with MS that were reduced following anti-CD25 monoclonal antibody treatment and associated with

reduced inflammatory markers in the cerebrospinal fluid[153]. Despite this advance, further high resolution profiling of ILC responses in defined patient populations, and during defined treatment strategies, is required to fully elucidate how we can modulate ILCs to limit human disease. There are many other therapeutics in the clinic or currently under development that could likely influence ILC differentiation, homeostasis or function. These include targeting the cytokine-cytokine receptor pathways that are critical for the differentiation, function and maintenance of ILCs such as IL-2-IL-2R, IL-12-IL-12R, IL-23-IL-23R, IL-1-IL-1R, TSLP-TSLPR and IL-6-IL-6R, targeting molecules critical for migration of ILCs such as α4β7 and MAdCAM-1, or targeting effector molecules of ILCs such as TNF-TNFR, IL-17-IL-17R, IFNγ and IL-13-IL-13R. It will be important to consider how these strategies may influence the pathologic versus protective functions of ILCs. For example, targeting the IL-23-IL-17 pathway has demonstrated efficacy in psoriasis and rheumatoid arthrisits[154–157]. However in IBD patients, blockade of IL-17 had limited efficacy and in some cases resulted in enhanced disease and susceptibility to fungal infections[158–161]. Given the role of ILC3 and IL-17 in promoting anti-fungal immunity[86], one possibility is that targeting IL-17 may have limited efficacy in certain conditions as it also targeted protective ILC3 responses. Therefore, the design of novel therapeutics may be necessary in order to find strategies that selectively modulate protective versus pathologic ILC responses. These could include novel small molecule inhibitors of transcription factors, other recently identified ILC modulators in mice and humans, such as the vitamin A metabolite retinoic acid, Lipoxin A4, or exogenous cytokines that may promote protective functions of ILCs or limit their pathologic potential[81,99,108,118].

Outstanding questions and future directions

Research on the biology of ILCs has already advanced our understanding of their development and the role they play in regulating acute and chronic inflammation as well as tissue repair. One future challenge is to better define this family of innate immune cells, and delineate how they specifically interact with other innate, adaptive and non-hematopoietic cells to promote, limit or resolve inflammation. A universal consensus of gating strategies on human and murine ILCs should be considered, as well as critical evaluation of translational studies, such as number of patients, current medication usage, longitudinal samples, source of healthy or non-diseased control tissues, tissue digestion protocols, and genetic and environmental factors like commensal bacteria. Further, additional mouse studies are needed to carefully define the potential plasticity of ILC populations, and identify novel functions and regulatory pathways influencing ILC responses. Defining these outstanding questions could prompt the development of novel therapeutic strategies, or promote new approaches that will permit selective regulation of protective versus pathologic ILC responses. These advances will be critical to advance our understanding of the cellular and molecular basis of inflammation and determine whether and how we can manipulate ILC responses to maintain healthy tissues and limit chronic inflammation.

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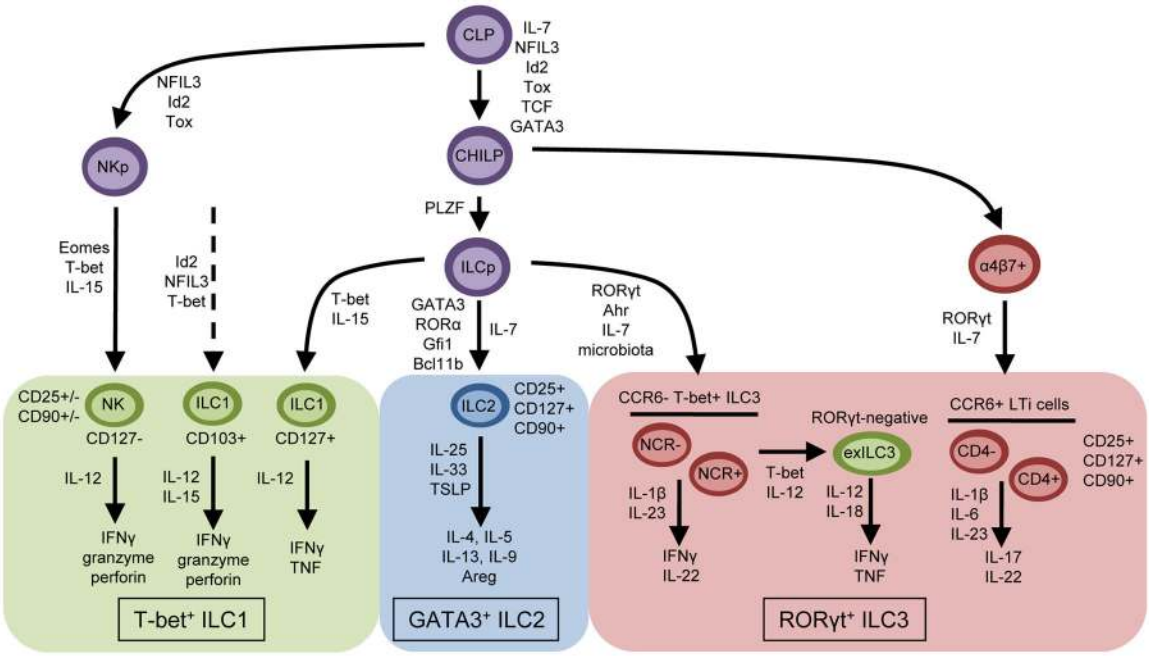

Figure 1. Development and heterogeneity of the ILC family

ILCs develop from distinct progenitors in the fetal liver or bone marrow. All ILCs develop from common lymphoid progenitors (CLPs), which can differentiate into NK cell progenitors (NKp) or common helper innate lymphoid precursors (CHILPs). CHIPs can further differentiation to lymphoid tissue inducer (LTi) cells through α4β7 integrin-expressing intermediate populations, or to other ILC populations through differentiation to a PLZF-dependent ILC progenitor (ILCp). Further sequential engagement of transcription factors, cytokines and microbial signals is critical for the development of three distinct groups of mature ILCs. ILC1 express T-bet, are responsive to IL-12, and produce IFNγ. ILC2 highly express GATA3, are responsive to IL-25, IL-33 and TSLP, and produce IL-4, IL-5, IL-9, IL-13 and Areg. ILC3 express RORγt, are responsive to IL-1β and IL-23, and produce IL-17 and/or IL-22.

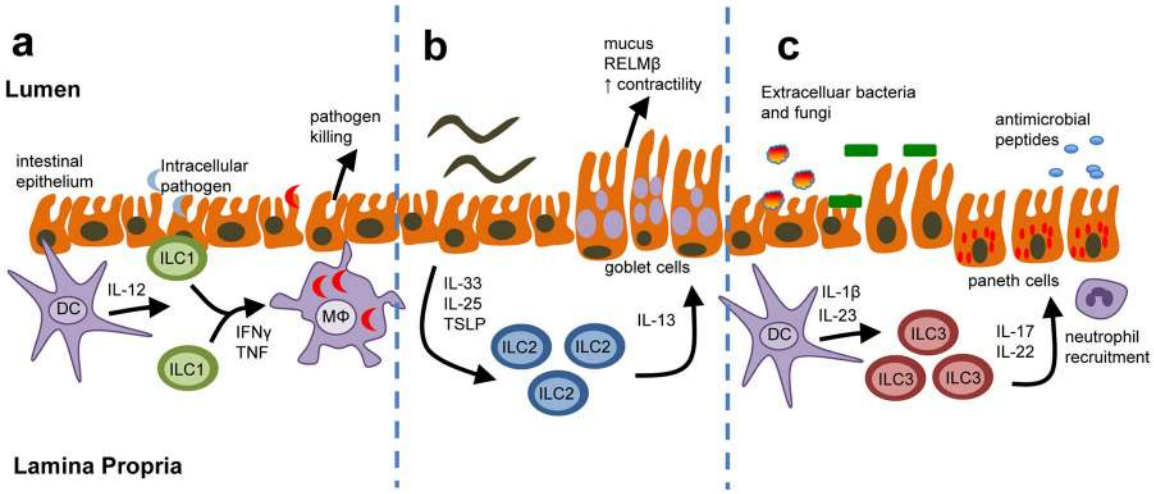

Figure 2. ILCs promote acute inflammation to mediate innate immunity to pathogens

ILCs promote innate immune responses to a number of pathogens in the intestine. (**a**) ILC1 promote innate immunity to intracellular pathogens, such as *Toxoplasma gondii*, by producing TNF and IFNγ in response to DC-derived IL-12 and subsequently promoting recruitment of inflammatory myeloid cells. (**b**) Following infection with the helminth parasites *Nippostrongylus brasiliensis* or *Trichuris muris*, ILC2 produce IL-13 in response to epithelial-cell derived-IL-25 and IL-33, which increases smooth muscle contractility and mucus production from goblet cells. (**c**) ILC3 produce IL-17 and IL-22 in response to DC-derived IL-23 and IL-1β, which promotes innate immunity to fungi and extracellular bacteria, such as *Citrobacter rodentium* and *Candida albicans*. IL-17 and IL-22 promote neutrophil recruitment to the intestine and the production of antimicrobial peptides from IECs.

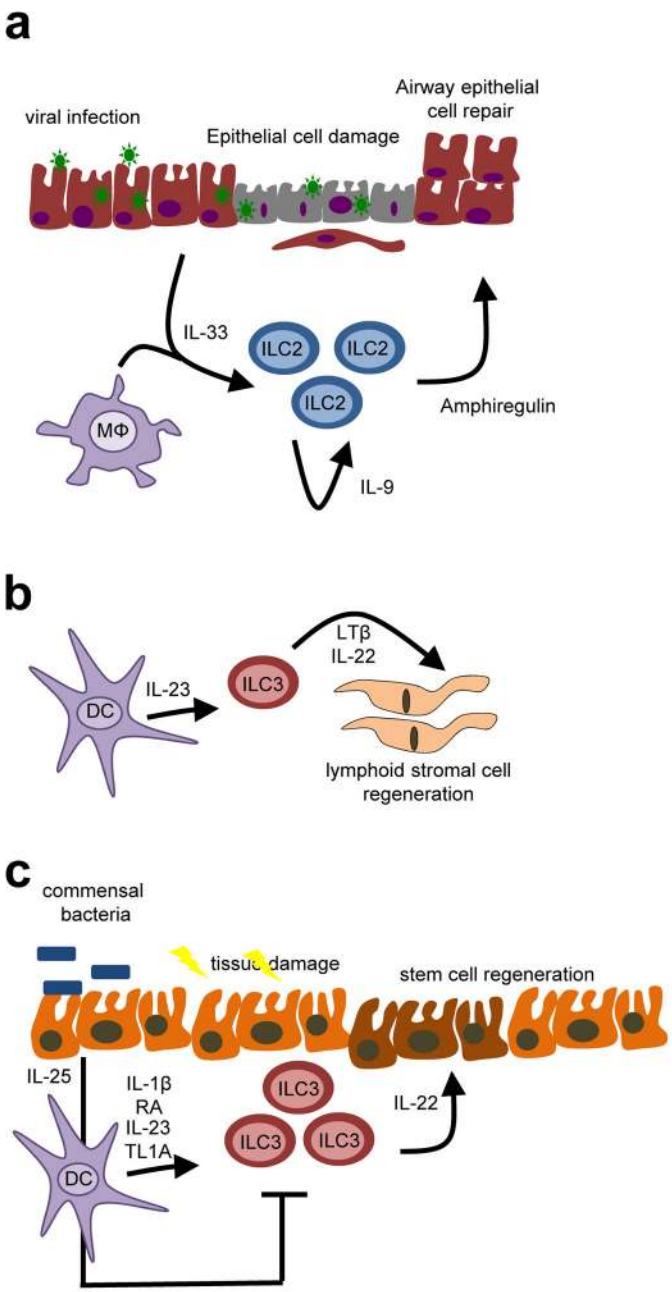

Figure 3. ILC2 and ILC3 promote the resolution of inflammation and tissue repair

(**a**) Following viral infection in the lung, airway epithelial cells are damaged and produce IL-33 in conjunction with resident myeloid cell populations. ILC2 respond to IL-33 and produce amphiregulin, which promotes repair of the airway epithelium. (**b**) In lymphoid tissues, such as the spleen and thymus, stromal cell damage induced by viral infection or irradiation results in increased numbers of ILC3 and cytokine production, in part through production of DC-derived IL-23. ILC3 directly promote restoration of stromal cell compartments through production of LTα1β2 and IL-22, which increase the proliferation and survival of tissue resident stromal cells. (**c**) In the intestine, ILC3 responses can be

limited by a regulatory loop whereby commensal bacteria induce IEC expression of IL-25, which acts on DCs to limit ILC3 cytokine responses in a contact-dependent manner. In contrast, upon chemical-, infection- or irradiation-induced damage of the intestine, ILC3 are activated by DC-derived IL-1β, IL-23, TL1A and retinoic acid (RA). Activation of ILC3 induces IL-22 production that directly promotes mucus production and epithelial cell repair, in part by acting directly on intestinal stem cells or progenitors.

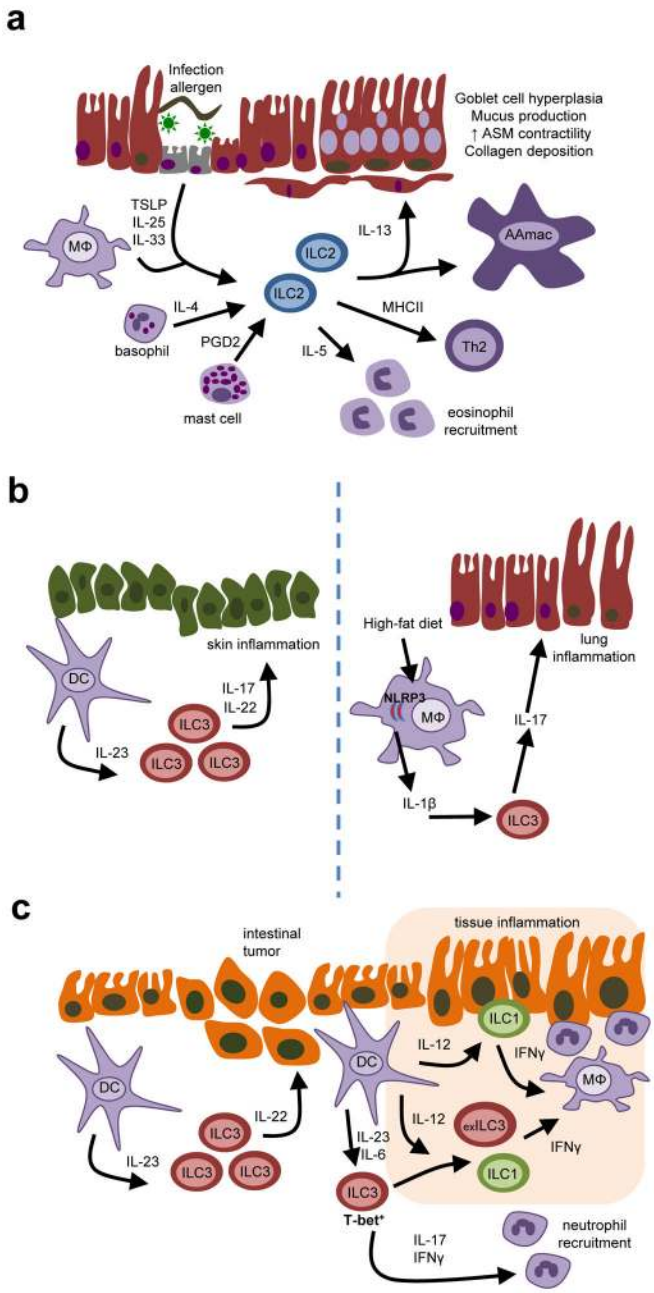

Figure 4. ILCs can promote chronic inflammation

(**a**) In response to infection or allergens ILC2 responses are elicited in the lung (and skin) by epithelial cell- and myeloid cell-derived IL-25, IL-33 and TSLP. Further, ILC2 responses can be enhanced by basophil-derived IL-4 or mast cell-derived prostoglandin D2 (PGD2). Activated ILC2 can subsequently promote chronic inflammation via IL-5-dependent eosinophil recruitment, IL-13-mediated contraction of smooth muscle cells, collagen deposition, and alternatively activated macrophage (AAMac) differentiation, or MHCII-mediated enhancement of Th2 cell responses, resulting in allergy and fibrosis. (**b**) In patients with psoriasis and mouse models of skin inflammation, ILC3 responses are increased, which can occur in response to DC-derived IL-23. ILC3 largely promote skin inflammation

through production of IL-22 and IL-17. Further, ILC3 are increased in the BAL of patients with asthma and in mouse models of obesity-induced asthma. In mice this occurs through activation of the NLRP3 inflammasome and macrophage production of IL-1β. IL-1β activates ILC3 to produce IL-17 and directly mediate airway inflammation. (**c**) In the intestine ILC3 can promote IL-22-dependent progression of tumors, which is in part dependent upon DC-derived IL-23. Further, ILC3 can mediate tissue inflammation in the intestine in response to DC-derived IL-23 and IL-12. This may occur through production of IL-17 by ILC3, production of IFNγ following loss of RORγt in ILC3 and differentiation to ex-ILC3, or direct activation of tissue resident ILC1.

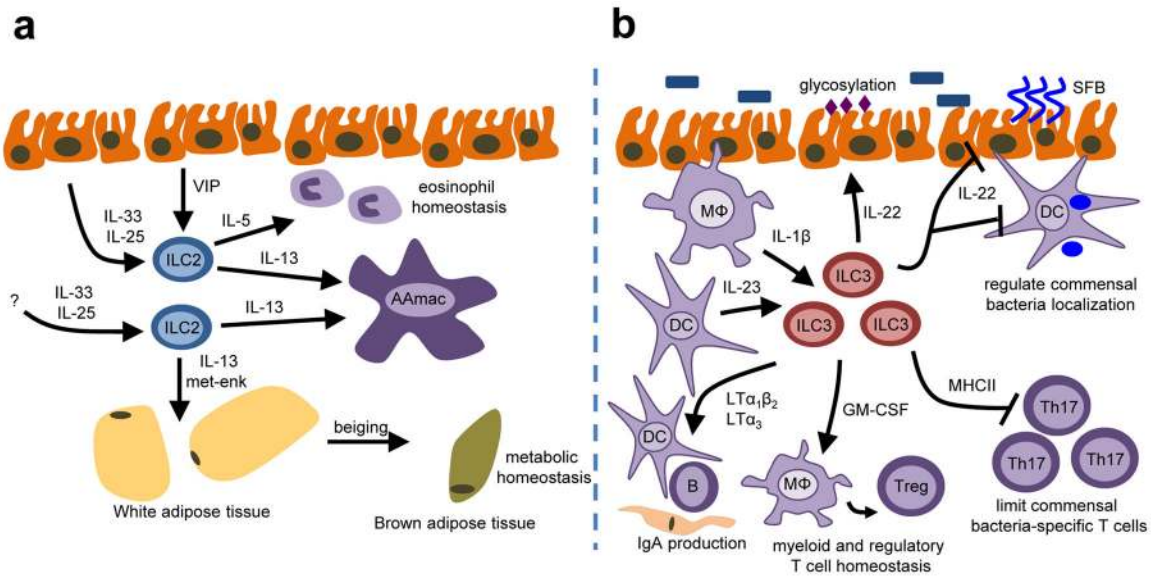

Figure 5. ILCs can prevent or limit chronic inflammation

(**a**) In the intestine, ILC2 respond to epithelial cell-derived IL-33, IL-25 and vasoactive intestinal peptide (VIP) to promote IL-5 and IL-13-dependent recruitment of eosinophils and differentiation of alternatively activated macrophages (AAMacs). This process also occurs in the adipose tissues, however the sources of IL-25 or IL-33 are less well defined. Differentiation of AAMacs or direct stimulation of adipocytes with IL-13 or methionine-enkephalin peptides (met-enk) can promote metabolic homeostasis through a process known as beiging in the adipocytes. (**b**) ILC3 can limit chronic inflammation by regulating innate and adaptive immune responses in the intestine. ILC3 responses are induced in response to myeloid cell- and DC-derived IL-1β and IL-23 following recognition of pathogenic or commensal microbes. Production of ILC3-derived LTα1β2 or LTα3 can promote IgA production by B cells indirectly by modulating stromal cell or DC responses. Production of ILC3-derived GM-CSF can influence myeloid cell homeostasis to subsequently promote regulatory T cell (Treg) responses to food antigens. ILC3-intrisic MHCII can directly kill commensal bacteria-specific CD4 T cells with the potential to cause intestinal inflammation. Production of IL-22 by ILC3 can promote antimicrobial peptides by IECs to limit colonization with commensal bacteria, such as segmented filamentus bacteria (SFB), or regulate the anatomical localization of lymphoid tissue resident commensal bacteria. Further, ILC3-derived IL-22 can induce fucosylation of IECs to promote colonization with beneficial bacteria.