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

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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 influence the induction, regulation and resolution of inflammation. ILCs have an important role in these processes in mouse models of infection, inflammation 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 used to selectively modulate ILC responses and limit chronic inflammatory diseases.

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Inflammation is defined as heat, redness, pain, swelling and loss of function. Whereas 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]. Although 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 innate lymphocytes that are relatively rare in comparison to adaptive lymphocytes in lymphoid tissues, but they are enriched at barrier surfaces of the mammalian body, such as the skin, lung and intestine, as well as in 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 immunoregulatory cytokines, and recent research has also identified a crucial 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 they share expression of the common gamma chain (γc, CD132), IL-7Rα (CD127), IL-2Rα (CD25), and Thy1 (CD90) markers, with some exceptions noted below[3–6].

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Received 3 April; accepted 27 May; published online 29 June 2015; doi:10.1038/nm.3892

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]—has contributed to our emerging knowledge of ILCs. Prototypical members of the ILC family were discovered many years ago, including the natural killer (NK) cells in 1975 (refs. 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 characterizations included simultaneous reports of innate lymphocytes that are predominant cellular sources of the cytokines IL-17 and IL-22 (refs. 21–28) or IL-5 and IL-13 (refs. 29–33) in the steady state or early after infection. These rapid and fundamental advances also generated redundant nomenclature based on the 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, on the basis of common expression of surface markers, transcription factors and cytokines[3].

Recent studies of ILCs have provoked a paradigm shift in our understanding of innate and adaptive immunity, and they have fueled additional extensive investigation into these cells because of the potential influence of ILCs in human health and disease. Mouse models indicate that ILCs have a fundamental role in the immune system by initiating, regulating and resolving inflammation. Further, studies in humans have revealed that ILC responses are substantially 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 used to modulate ILC responses and benefit human health.

Development and heterogeneity of the ILC family

ILCs initially develop in the fetal liver and later in the adult bone marrow from common lymphoid progenitors (CLPs)[34–36]. CLPs

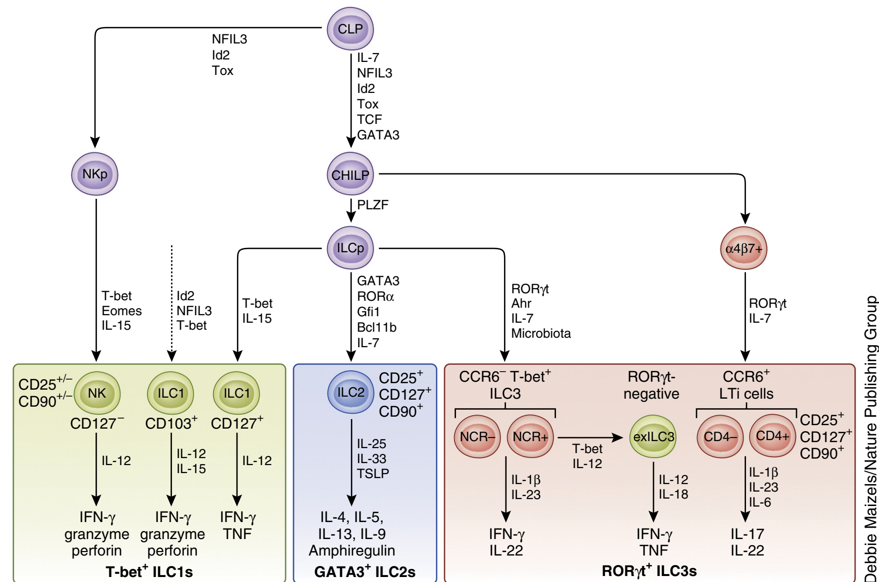

Figure 1 Development and heterogeneity of the ILC family. ILCs develop from distinct progenitors in the fetal liver or bone marrow. All ILCs develop from CLPs, which can differentiate into NKps or CHILPs. CHILPs can further differentiate into LTi cells through α4β7 integrin-expressing intermediate populations, or into other ILC populations through differentiation to a PLZF-dependent ILCp. Further sequential engagement of transcription factors, cytokines and microbial signals is critical for the development of three distinct groups of mature ILCs. ILC1s express T-bet, are responsive to IL-12, and produce IFN-γ. ILC2s highly express GATA3; are responsive to IL-25, IL-33 and TSLP; and produce IL-4, IL-5, IL-9, IL-13 and amphiregulin. ILC3s express RORγt, are responsive to IL-1β and IL-23, and produce IL-17 and/or IL-22.

also differentiate into cells of the adaptive immune system, such as T cells and B cells, but development of ILCs from CLPs occurs independently of somatic recombination, a defining feature of the adaptive immune system that permits the generation of antigen-specific receptors or secreted proteins such as the T cell receptor, B cell receptor and immunoglobulin. ILC development is regulated at the transcriptional level, with several precursor populations and transcription factors regulating each group (**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 it involves additional precursor cell populations (**Fig. 1**). These include NK cell precursors (NKps) that give rise to NK cells, as well as 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], whereas promyelocytic leukemia zinc finger (PLZF)-dependent ILC progenitors (ILCps) can give rise to other defined ILC subsets[35]. Although the specific interactions and functions of transcription factors in ILC development are not well defined, IL-7 signaling can induce NFIL3 and subsequently Id2 to support the generation of ILCps[39]. However, additional studies are required to further define these functional interactions, as NFIL3-deficient mice do not completely replicate the phenotype of Id2-deficient mice, which lack all ILCs. Further, although most of these developmental studies have necessarily used mice, CD34+ hematopoietic progenitor cells (HSCs) in the bone marrow or peripheral blood of humans can give rise to α4β7 integrin–expressing CD34+ progenitors in the lymphoid tissues and intestinal lamina propria, which have the potential to differentiate into either NK cells or LTi-like cells in a process that is influenced by the presence of aryl hydrocarbon receptor (Ahr) ligands, stem cell factor (SCF) and IL-15 (ref. 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 on the basis of shared expression of surface markers, transcription factors and effector cytokines (**Fig. 1**)[3–6].

Group 1 ILCs (ILC1s) respond to IL-12, constitutively express T-bet, and produce effector cytokines including interferon (IFN)-γ and tumor necrosis factor (TNF)[36,51,52]. ILC1s are considerably heterogeneous and can be distinguished into at least three subsets according to their differential expression and requirements for eomesodermin (eomes), T-bet, IL-15 and IL-7. Conventional NK cells are a subset of ILC1s requiring eomes and IL-15 for development from NKps, but not T-bet or IL-7 (ref. 36). ILC1s also include CD103+ intraepithelial ILC1s, which develop independently of IL-15 from an unknown precursor, express eomes, and require T-bet for differentiation[52]. Further, CD127+ ILC1s were also identified in humans and mice; they do not express eomes and develop independently of IL-7 from a CHILP and ILCp, but they require T-bet and IL-15 (refs. 36,51).

Group 2 ILCs (ILC2s) respond to the 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]. Although GATA3 is required for the development of most ILC subsets[48,49], it is also required for the maintenance and function of mature ILC2s in humans and mice[53–56]. RAR-related orphan receptor (ROR)-α 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]. The transcription factors Gfi1 and Bcl11b also contribute to the differentiation or lineage stability of mouse ILC2s[60–62]. Although mature ILC2s can be found in most anatomical locations, they seem to be enriched in the healthy lung, skin and adipose tissue of mice and humans[29,31,32,63–66].

Group 3 ILCs (ILC3s) respond to IL-1β, IL-6 and IL-23; constitutively express RORγt; and produce the effector cytokines IL-17 and/or IL-22 (refs. 21–28). Although all ILC3 share a developmental requirement for RORγt (refs. 24,67), substantial heterogeneity exists within this group. Fetal and adult LTi cells are members of the ILC3 group, and they develop independently of PLZF-dependent ILCps, are CCR6+, heterogeneous in expression of CD4, express IL-22 and IL-17, and are a source of lymphotoxin (LT). A subset of adult ILC3s can develop from PLZF-dependent ILCps after birth, are CCR6−, co-express T-bet, are heterogeneous in expression of natural cytotoxicity receptors (NCRs, such as NKp46 and NKp44), and can co-express IL-22 and IFN-γ. This T-bet+ ILC3 population requires T-bet, the presence of commensal bacteria and the Ahr for development[68–72]. T-bet+ ILC3s are almost exclusively found in the skin and intestinal lamina propria, whereas LTi-like ILC3s are enriched in the

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intestine and lymphoid tissues[28,68,73–75]. Further, as discussed below, ILC3s with a unique phenotype can develop in some inflammatory contexts in the intestine and liver[24,76].

Some 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 IFN-γ (refs. 51,68,72). However, it is currently unclear whether to classify these populations as ILC1s or ILC3s, 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-ILC3s (refs. 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], although additional research is required to fully characterize the extent of ILC plasticity, as well as to 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 on the basis of 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**).

ILC1s and intracellular pathogens. ILC1 populations have a crucial role in promoting immunity to intracellular pathogens (**Fig. 2a**). Rapid NK cell responses have been well characterized after 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 ILC1s are the dominant innate source of IFN-γ and TNF in mice after infection with the oral pathogen *Toxoplasma gondii*, and that they have role in recruiting inflammatory myeloid cells that control infection[36]. Consistent with this, genomic T-bet deficiency rendered mice highly susceptible to *T. gondii* infection, and adoptive transfer of ILC1s to lymphocyte-deficient mice (*Rag2*$^{-/-}$ *Il2rg*$^{-/-}$) was sufficient to boost immunity[36].

ILC2s and extracellular parasites. ILC2s rapidly respond after exposure to multicellular parasites that are typically extracellular (**Fig. 2b**). For example, ILC2s are an important innate cellular source of IL-13 in the intestine after 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 after parasite infection of mice[29,30,33]. ILC2s 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 ILC2s 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.

ILC3s and extracellular bacteria and fungi. ILC3s rapidly respond to infection of mice with either extracellular bacteria or fungi (**Fig. 2c**). NCR$^+$ ILC3s rapidly respond to infection of mice with the Gram-negative enteric pathogen *Citrobacter rodentium* by producing IL-22 (ref. 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 (ref. 22), and in mice ILC3 are a dominant and essential source of IL-22 for innate immunity to *C. rodentium* in the intestine[21,23]. IL-22 acts almost exclusively on non-hematopoietic cells, such as intestinal epithelial cells (IECs), and it stimulates production of anti-microbial 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, ILC3s 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 it induces the expression

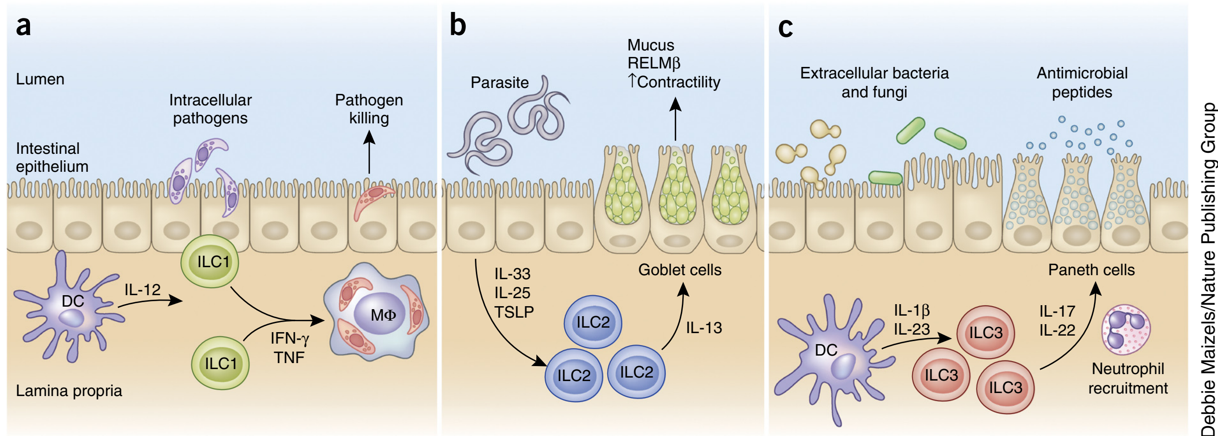

Figure 2 ILCs promote acute inflammation and innate immunity to pathogens. ILCs promote innate immune responses to a number of pathogens in the intestine. (**a**) ILC1s promote innate immunity to intracellular pathogens, such as *T. gondii*, by producing TNF and IFN-γ in response to DC-derived IL-12, and they subsequently promote recruitment of inflammatory myeloid cells. (**b**) After infection with the helminth parasites *N. brasiliensis* or *T. muris*, ILC2s produce IL-13 in response to epithelial cell–derived IL-25, IL-33 and TSLP, which increases smooth muscle contractility and mucus production from goblet cells. (**c**) ILC3s 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 *C. rodentium* and *C. albicans*. IL-17 and IL-22 promote neutrophil recruitment to the intestine and the production of antimicrobial peptides from IECs.

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of chemokines (Cxcl1 and Cxcl9) to recruit neutrophils to the site of infection[7–9,87]. ILC3-derived IL-17 also regulates neutrophils in neonatal mice, which is important for resistance to sepsis with Gram-negative opportunistic bacteria and is dependent upon the presence of commensal bacteria[88]. Collectively, this suggests that the ILC family has a key 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 the gastrointestinal tract (**Fig. 3**). These repair processes are essential to limiting sustained inflammation, preventing re-infection and restoring tissues to a state of homeostasis.

ILC2s and resolution of inflammation in the lung. In the lung of mice, ILC2s are activated in response to IL-33 after influenza virus infection and subsequent immune-mediated tissue damage[31] (**Fig. 3a**). Experimental depletion of ILC2s 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 the responses of ILC2 cytokines, 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 ILC2s[31]. Further, after infection and subsequent tissue damage induced by the migration of *N. brasiliensis* in the lungs of mice, autocrine production of IL-9 contributes to the survival of ILC2s and was associated with amphiregulin production and repair of the lung tissues[89]. ILC2s therefore represent a major ILC population in the lung that promotes tissue repair after infection. Mouse ILC2s also promote cutaneous wound healing in an excisional wound model (D.A., unpublished data). Although it has been demonstrated that human ILC2s express amphiregulin at the transcript level[90], additional work is needed to define whether human ILC2s are potent sources of amphiregulin and mediate tissue repair. Also, it currently remains unclear whether ILC2s can promote tissue repair at different anatomical locations.

ILC3s and resolution of inflammation in lymphoid tissues and the intestine. ILC3s promote tissue repair through several distinct mechanisms (**Fig. 3b**,**c**). Systemic viral infections can impair the architecture of secondary lymphoid organs after 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 $LT\alpha_1\beta_2$ and act on LTβR-expressing stromal cells to enhance their proliferation and survival[91] (**Fig. 3b**). Further, ILC3s can also promote tissue repair in the thymus of mice after total body irradiation[92]. In this context, CCR6⁺ ILC3s 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 in the lung after influenza infection or bleomycin-induced damage[87,93,94], which are two other organs in which the tissue-resident non-hematopoietic cells highly express the IL-22 receptor[8].

In the intestine, ILC3s have 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 ILC3s in intestinal tissues from disease patients relative to non-IBD controls[51,95,96]. In mouse models, production of IL-22 by ILC3s mediates tissue repair after experimental tissue damage induced by hematopoietic stem cell transplantation (HSCT) and subsequent graft-versus-host disease (GVHD), or after administration of dextran sodium sulfate (DSS)[97–99]. Following whole-body irradiation and HSCT, radio-resistant ILC3s respond to DC-derived IL-23 and produce IL-22. IL-22 acts on the intestinal

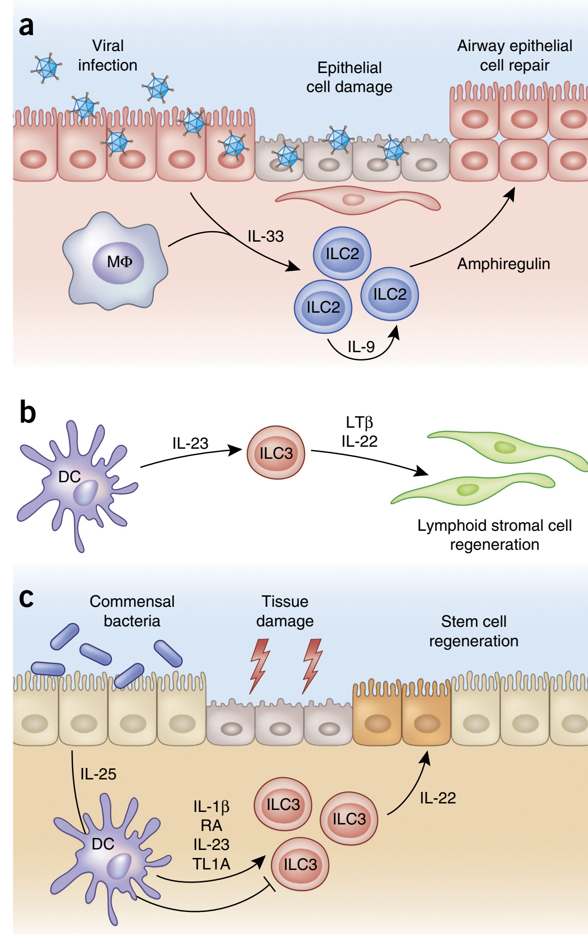

Figure 3 ILC2s and ILC3s promote the resolution of inflammation and tissue repair. (**a**) After viral infection in the lung, airway epithelial cells are damaged and, in conjunction with resident myeloid cell populations, produce IL-33. ILC2s respond to IL-33 and produce amphiregulin, which promotes 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 ILC3s and increased cytokine production, in response to DC-derived IL-23. ILC3s directly promote restoration of stromal cell compartments through production of $LT\alpha_1\beta_2$ 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, ILC3s are activated by DC-derived IL-1β, IL-23, TL1A and RA. Activation of ILC3s induces IL-22 production that directly promotes mucus production and epithelial cell repair, in part by acting directly on intestinal stem cells or progenitors.

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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 after irradiation, this causes GVHD and is associated with a decrease in intestinal ILC3s and enhanced intestinal tissue damage owing to a loss of IL-22 (ref. 98). In humans, ILC3s are not normally observed in the circulation, but they are found after 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 ILC3s 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 after 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 relative to naive mice, increasing IL-22 production and tissue repair[97]. ILC3 responses and IL-22–dependent tissue repair can also be enhanced in mice and humans after recognition of pathogenic or commensal microbes by CX3CR1$^+$ myeloid cells and subsequent production of IL-1β, IL-23 and TL1A (refs. 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 ILC3s, and regulating ILC3 proliferation[81,99,108]. In addition to promoting maintenance of the intestinal epithelium, during fetal development vitamin A and the metabolite RA control the size of secondary lymphoid tissues via LTi cells in mice, which could influence the efficiency of protection from viral infections later in life[108]. Thus, ILC3s have a major 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**).

ILC2s and chronic inflammation in the lung and skin. Increased ILC2 responses have been observed in multiple allergic diseases, including in 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 fluid 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 after exposure to allergens, chemicals or helminth parasites, or after 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 ILC2s in the human lung and could directly promote ILC2 responses *in vitro* through production of prostaglandin D2 (PGD2)[118]. The population expansion of ILC2s is thought to contribute to chronic inflammation through multiple mechanisms. Production of ILC2-derived 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 mouse lung function by enhancing airway smooth muscle cell contractility, increasing epithelial cell mucus production, polarizing macrophages to an alternatively activated macrophage (AAMac) phenotype and increasing collagen deposition[110,111]. ILC2s in mice can also promote chronic inflammation by enhancing T helper 2 cell (T_H2) responses either indirectly by IL-13–elicited migration of activated DCs to the lung draining lymph node and subsequent T_H2 cell priming[119], or directly by major histocompatibility complex class II (MHCII)-dependent interactions with CD4 T cells[120,121].

ILC3s, 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 bronchoalveolar lavage fluid of patients with asthma[124]. In a mouse model of psoriasis, ILC3s are the dominant source of IL-17 and IL-22 in the skin and are reduced by a p40-specific monoclonal antibody[125], which probably blocks the IL-23–mediated population expansion or activation of ILC3s. ILC3s are necessary and sufficient to induce psoriatic plaque formation in mice via production of IL-17 and IL-22 (ref. 125) (**Fig. 4b**). Further, although they are normally absent in the lungs of healthy mice[31], in a mouse model of obesity-induced asthma, ILC3s expand in response to NLRP3-dependent production of IL-1β by macrophages[124]. ILC3s were sufficient to promote IL-17–dependent airway hyper-responsiveness in this mouse model[124] (**Fig. 4b**).

The role of ILC3s in promoting intestinal inflammation is more complex, given the substantial heterogeneity observed in this cell lineage, the potential lineage plasticity, and the differential gating strategies used by different groups conducting human studies. Two reports observed an increased frequency in pro-inflammatory ILC3s in intestinal tissues from individuals with IBD[126,127], whereas another identified increased ILC3 production of IL-22 (ref. 102). However, as described in the next section, there have been many reports of tissue-protective functions of ILC3s in mouse models of intestinal inflammation, and additional reports of decreased ILC3 frequencies in people with IBD. The different reports may be explained by the selected mouse models and the heterogeneity and potential plasticity of ILC3s, as well as by the clinical phenotypes and tissue sources of the patient populations studied. Notwithstanding this, a unique ILC3 population has a role in two innate mouse models of intestinal inflammation (**Fig. 4c**). Administration of a CD40-specific monoclonal antibody or colonization with *Helicobacter hepaticus* in *Rag1*$^{-/-}$ mice induces colitis that is dependent on ILCs, RORγt, IL-17A and IFN-γ (ref. 24). The pro-inflammatory ILC3s observed in these models are largely absent in the steady state and lack expression of c-kit, and a portion of these cells co-expressed T-bet, IFN-γ and IL-17A (ref. 24). ILCs with a similar phenotype are also observed in mice that lack the genes encoding both T-bet and Rag2 (TRUC mice); these mice are a spontaneous model of innate cell-driven intestinal inflammation[76,128]. TRUC mice have increased IL-17A–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-17A production from human and mouse

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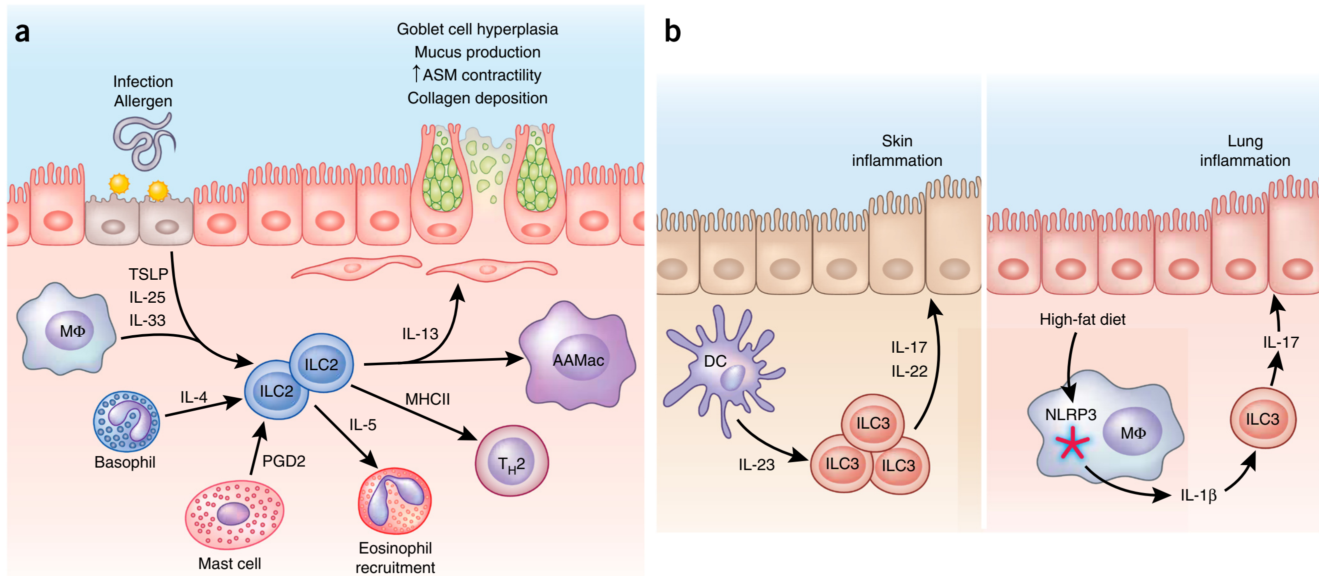

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Figure 4 ILCs can promote chronic inflammation. (**a**) In response to infection or allergen exposure, ILC2 responses are elicited in the lung (and skin) by epithelial cell– and myeloid cell–derived IL-25, IL-33 and TSLP. Further, ILC2 responses can be enhanced by basophil-derived IL-4 or mast cell-derived PGD2. Activated ILC2s can subsequently promote chronic inflammation via IL-5–dependent eosinophil recruitment, IL-13–mediated contraction of smooth muscle cells, collagen deposition, and AAMac differentiation, or by MHCII-mediated enhancement of T_H2 cell responses, resulting in allergy and fibrosis. (**b**) In patients with psoriasis and in mouse models of skin inflammation, ILC3 responses are increased, which can occur in response to DC-derived IL-23. ILC3s largely promote skin inflammation through production of IL-22 and IL-17. Further, ILC3s are increased in the bronchoalveolar lavage fluid of patients with asthma and in mouse models of obesity-induced asthma. In mice this occurs through activation of the NLRP3 inflammasome and macrophage (Mϕ) production of IL-1β. IL-1β activates ILC3s to produce IL-17, which directly promotes airway inflammation and hyper-responsiveness. (**c**) In the intestine ILC3s can promote IL-22–dependent tumor growth, which is in part dependent upon DC-derived IL-23. Further, ILC3s 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 ILC3s, production of IFN-γ following loss of RORγt in ILC3s and differentiation to ex-ILC3s, or direct activation of tissue-resident ILC1s.

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pro-inflammatory ILC3s[127]. ILC3s can also promote intestinal inflammation indirectly. After *T. gondii* infection, ILC3-derived IL-22 acts on IECs to promote expression of the T_H1 cell–promoting cytokine IL-18, which leads to subsequent tissue inflammation[129]. Further, IEC production of IL-18 was also shown to be 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 ILC3s and an upregulation of T-bet[68,72]. In fate-mapping mouse models, infection with *Salmonella enterica* or CD40-specific monoclonal antibody administration to *Rag2*$^{-/-}$ mice resulted in the development of ILCs that lost expression of RORγt; these ILCs resemble ILC1s in expression of T-bet and IFN-γ, and they promote intestinal inflammation[76,128]. In human samples and humanized mice this transition of RORγt$^+$ ILC3s to RORγt$^-$ ex-ILC3s is promoted by IL-12 or can be induced after experimental induction of intestinal tissue damage with DSS[51]. Consistent with these findings, one study revealed reduced frequencies of ILC3s and increased frequencies of ILC1s in intestinal tissue from individuals with IBD relative to non-IBD controls[51]. Further, unique intraepithelial ILC1s that develop independently of ILC3s were also enriched in intestinal tissues of individuals with IBD relative to non-IBD controls, and these may contribute to the development of intestinal inflammation through production of IFN-γ following administration of a CD40-specific monoclonal antibody to *Rag2*-deficient mice[52].

In the colon, ILC3s also promote colitis-associated tumor progression via production of IL-22 (ref. 123). In a novel model of colitis-associated cancer, *Rag1*$^{-/-}$ mice, which exhibit chronic intestinal inflammation when colonized with *H. 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 IL-22 production during the peak of intestinal inflammation is protective against tumor formation, whereas 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], although this occurred in the context of a genetically modified tumor that overexpressed IL-12. Further, given that the characterized ILCs were previously described as expressing RORγt, the possibility remains that these anti-tumor ILC responses were mediated by ex-ILC3s that lost RORγt expression and produced IFN-γ 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 promoting intestinal inflammation in the presence of adaptive immunity is lacking. Collectively, these studies defined a complex role for ILC1s, ILC2s and pro-inflammatory ILC3s or ex-ILC3s in promoting chronic inflammation in mice and humans.

ILCs limit chronic inflammation

ILCs can also have a 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**).

ILC2s and metabolic homeostasis. ILC2s have been characterized in the intestine, lung and adipose tissues of healthy humans and mice[29–33]. In the intestine of mice, ILC2s control the homeostasis of circulating eosinophils through constitutive production of IL-5, and they regulate 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 VIP 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, ILC2s can regulate eosinophil homeostasis and AAMac polarization[64,65]. In obese mice fed a high-fat diet, or in obese humans, frequencies of ILC2s are reduced in the adipose tissues as compared to non-obese controls, and this reduction in ILC2s is associated with a reciprocal increase in chronic low-grade systemic inflammation[64–66], suggesting a critical role for ILC2s in regulating metabolic homeostasis. Consistent with this, experimental depletion of ILCs exacerbates weight gain in mice and causes insulin resistance, whereas treatment

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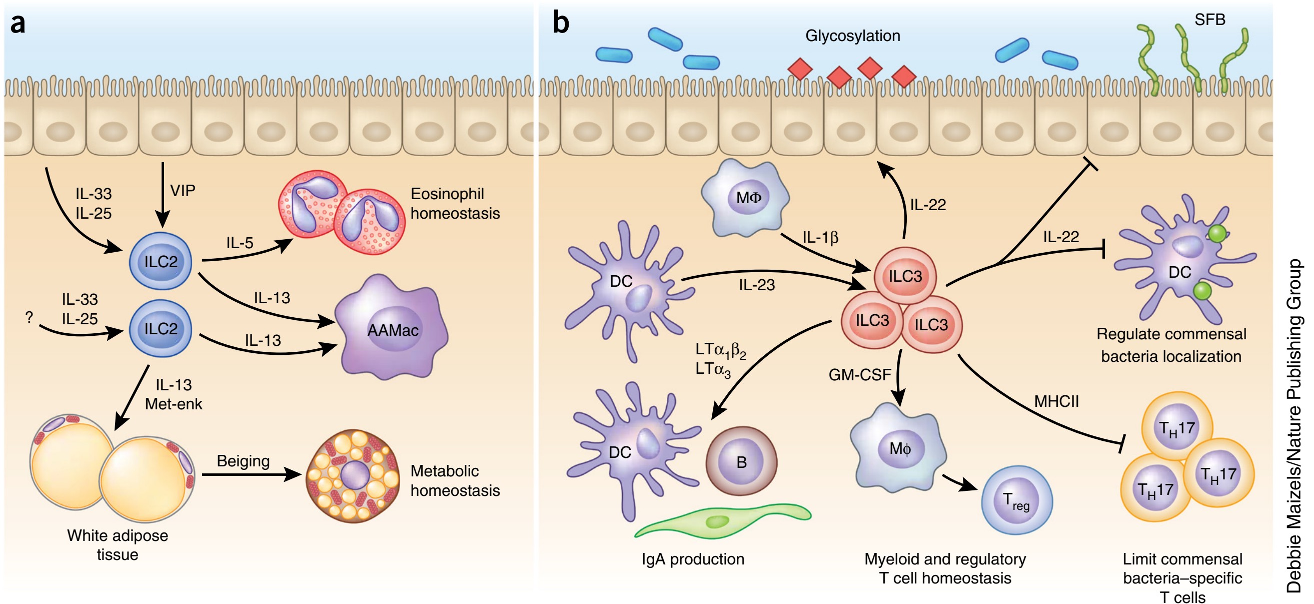

Figure 5 ILCs can prevent or limit chronic inflammation. (**a**) In the intestine, ILC2s respond to epithelial cell-derived IL-33, IL-25 and vasoactive intestinal peptide (VIP) to promote IL-5– and IL-13–dependent recruitment of eosinophils and differentiation of AAMacs. This process also occurs in adipose tissue, although 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**) ILC3s 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 after recognition of pathogenic or commensal microbes. Production of ILC3-derived $LT\alpha_1\beta_2$ or $LT\alpha_3$ 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 T_{reg} cell responses and tolerance to food antigens. ILC3-intrinsic MHCII can directly kill commensal bacteria-specific CD4$^+$ T cells with the potential to cause intestinal inflammation. Production of IL-22 by ILC3s can promote antimicrobial peptide production by IECs to limit colonization with commensal bacteria, such as segmented filamentous bacteria (SFB), or it can 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.

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 AAMacs in adipose tissues, or directly by 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 ILC2s orchestrate metabolic homeostasis, and whether this may also involve crosstalk with other IL-33R$^+$ cells, such as recently described subsets of regulatory T (T_{reg}) cells[135–137].

ILC3s in chronic systemic and intestinal inflammation. ILC3s also limit chronic inflammation through several distinct mechanisms (**Fig. 5b**), which may be particularly important in the intestine, as there are several reports of reduced frequencies of ILC3s in individuals with IBD or with 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, ILC3s 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 AIDS, in which there are defects in intestinal barrier function such that systemic dissemination of commensal bacteria promotes chronic immune activation and contributes to viral replication, loss of CD4$^+$ T cells and disease progression[144]. In humans and non-human primates, numbers of ILC3s and production of IL-22 are reduced in the intestine after pathogenic infection with HIV or simian immunodeficiency virus (SIV)[138–141], and thus may be a novel therapeutic target for limiting disease progression. Production of IL-22 in mice can also promote colonization of the intestine by 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 limits the growth of pathogens or opportunistic pathogens and protects against intestinal tissue damage[83–85]. IL-22 production by ILC3s also requires maintained expression of Id2 and subsequent regulation of the IL-23R and Ahr pathways, which is necessary to limit infection-induced damage in mice by regulating colonization resistance and the composition of intestinal commensal bacteria[145].

ILC3s can also limit chronic inflammation through indirect and direct regulation of the adaptive immune cell response[146] (**Fig. 5b**). ILCs regulate homeostasis of myeloid cells in the intestine of mice through production of granulocyte macrophage colony-stimulating factor (GM-CSF)[147]. This process is regulated by macrophage sensing of intestinal commensal bacteria and production of IL-1β, which can act on ILC3s to promote GM-CSF expression[147]. Conversely, production of GM-CSF by ILC3s was essential to modulate myeloid cells and subsequently generate T_{reg} cell responses to food antigens in the intestine and maintain oral tolerance[147]. Through production of $LT\alpha_1\beta_2$ or a soluble $LT\alpha_3$, ILC3s 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 ILC3s were also found to 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 on commensal bacteria[150,151]. Mechanistically, MHCII$^+$ ILC3s 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]. Although no differences were observed in the frequency of ILC3s in intestinal biopsies of pediatric IBD patients, a substantial reduction of MHCII on ILC3s was observed relative to non-IBD controls, and this reduction inversely correlated with increased intestinal T_H17 cells[152]. These studies identify an essential role for ILC3s 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 in the reported alterations of ILCs in defined patient populations, there is an urgent need to investigate whether therapeutic strategies can be used 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) after CD25-specific 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 after CD25-specific 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 specific treatment regimens, 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 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 arthritis[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 ILC3s 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,

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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 have 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 to delineate how they specifically interact with other innate, adaptive and non-hematopoietic cells to promote, limit or resolve inflammation. A universal consensus on gating strategies on human and mouse ILCs should be considered. A critical evaluation of translational studies is needed, and it should be focused on examining patient numbers, current medication use, longitudinal samples, sources of healthy or non-diseased control tissues, tissue digestion protocols, and genetic and environmental factors such as commensal bacteria. Further, additional mouse studies are needed to carefully define the potential plasticity of ILC populations, and to 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 for our understanding of the cellular and molecular basis of inflammation and to determining whether and how we can manipulate ILC responses to maintain healthy tissues and limit chronic inflammation.

ACKNOWLEDGMENTS
Research in the Sonnenberg laboratory is supported by the US National Institutes of Health (NIH) (DP5OD012116), the National Institute of Allergy and Infectious Disease Mucosal Immunology Studies Team (MIST) Scholar Award in Mucosal Immunity and the Institute for Translational Medicine and Therapeutics Transdisciplinary Program in Translational Medicine and Therapeutics (UL1-RR024134 from the US National Center for Research Resources). Research in the Artis laboratory is supported by the NIH (AI061570, AI074878, AI095466, AI095608, AI102942, AI097333 and AI106697), the Burroughs Wellcome Fund Investigator in Pathogenesis of Infectious Disease Award and the Crohn's and Colitis Foundation of America.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper.

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1. Grivennikov, S.I., Greten, F.R. & Karin, M. Immunity, inflammation, and cancer. *Cell* **140**, 883–899 (2010).
2. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
3. Spits, H. *et al.* Innate lymphoid cells–a proposal for uniform nomenclature. *Nat. Rev. Immunol.* **13**, 145–149 (2013).
4. Walker, J.A., Barlow, J.L. & McKenzie, A.N. Innate lymphoid cells–how did we miss them? *Nat. Rev. Immunol.* **13**, 75–87 (2013).
5. Sonnenberg, G.F., Mjösberg, J., Spits, H. & Artis, D. SnapShot: innate lymphoid cells. *Immunity* **39**, 622 (2013).
6. Sonnenberg, G.F. & Artis, D. Innate lymphoid cell interactions with microbiota: implications for intestinal health and disease. *Immunity* **37**, 601–610 (2012).
7. Zheng, Y. *et al.* Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nat. Med.* **14**, 282–289 (2008).
8. Sonnenberg, G.F., Fouser, L.A. & Artis, D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. *Nat. Immunol.* **12**, 383–390 (2011).
9. Aujla, S.J. *et al.* IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat. Med.* **14**, 275–281 (2008).
10. Ouyang, W., Kolls, J.K. & Zheng, Y. The biological functions of T helper 17 cell effector cytokines in inflammation. *Immunity* **28**, 454–467 (2008).
11. Harrington, L.E., Mangan, P.R. & Weaver, C.T. Expanding the effector CD4 T-cell repertoire: the Th17 lineage. *Curr. Opin. Immunol.* **18**, 349–356 (2006).
12. Ahern, P.P., Izcue, A., Maloy, K.J. & Powrie, F. The interleukin-23 axis in intestinal inflammation. *Immunol. Rev.* **226**, 147–159 (2008).
13. Fallon, P.G. *et al.* Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. *J. Exp. Med.* **203**, 1105–1116 (2006).
14. Saenz, S.A., Taylor, B.C. & Artis, D. Welcome to the neighborhood: epithelial cell-derived cytokines license innate and adaptive immune responses at mucosal sites. *Immunol. Rev.* **226**, 172–190 (2008).
15. Liew, F.Y., Pitman, N.I. & McInnes, I.B. Disease-associated functions of IL-33: the new kid in the IL-1 family. *Nat. Rev. Immunol.* **10**, 103–110 (2010).
16. Liu, Y.J. *et al.* TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu. Rev. Immunol.* **25**, 193–219 (2007).
17. Fort, M.M. *et al.* IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. *Immunity* **15**, 985–995 (2001).
18. Kiessling, R., Klein, E., Pross, H. & Wigzell, H. "Natural" killer cells in the mouse. II. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Characteristics of the killer cell. *Eur. J. Immunol.* **5**, 117–121 (1975).
19. Pross, H.F. & Jondal, M. Cytotoxic lymphocytes from normal donors. A functional marker of human non-T lymphocytes. *Clin. Exp. Immunol.* **21**, 226–235 (1975).
20. Mebius, R.E., Rennert, P. & Weissman, I.L. Developing lymph nodes collect $CD4^+CD3^-$ $LT\beta^+$ cells that can differentiate to APC, NK cells, and follicular cells but not T or B cells. *Immunity* **7**, 493–504 (1997).
21. Sonnenberg, G.F., Monticelli, L.A., Elloso, M.M., Fouser, L.A. & Artis, D. $CD4^+$ lymphoid tissue-inducer cells promote innate immunity in the gut. *Immunity* **34**, 122–134 (2011).
22. Cella, M. *et al.* A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. *Nature* **457**, 722–725 (2009).
23. Satoh-Takayama, N. *et al.* Microbial flora drives interleukin 22 production in intestinal $NKp46^+$ cells that provide innate mucosal immune defense. *Immunity* **29**, 958–970 (2008).
24. Buonocore, S. *et al.* Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature* **464**, 1371–1375 (2010).
25. Sawa, S. *et al.* Lineage relationship analysis of $ROR\gamma t^+$ innate lymphoid cells. *Science* **330**, 665–669 (2010).
26. Cupedo, T. *et al.* Human fetal lymphoid tissue-inducer cells are interleukin 17-producing precursors to $RORC^+CD127^+$ natural killer-like cells. *Nat. Immunol.* **10**, 66–74 (2009).
27. Crellin, N.K. *et al.* Regulation of cytokine secretion in human $CD127^+$ LTi-like innate lymphoid cells by Toll-like receptor 2. *Immunity* **33**, 752–764 (2010).
28. Sanos, S.L. *et al.* RORγt and commensal microflora are required for the differentiation of mucosal interleukin 22–producing $NKp46^+$ cells. *Nat. Immunol.* **10**, 83–91 (2009).
29. Moro, K. *et al.* Innate production of T_H2 cytokines by adipose tissue-associated $c\text{-}Kit^+Sca\text{-}1^+$ lymphoid cells. *Nature* **463**, 540–544 (2010).
30. Price, A.E. *et al.* Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc. Natl. Acad. Sci. USA* **107**, 11489–11494 (2010).
31. Monticelli, L.A. *et al.* Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. *Nat. Immunol.* **12**, 1045–1054 (2011).
32. Mjösberg, J.M. *et al.* Human IL-25– and IL-33–responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. *Nat. Immunol.* **12**, 1055–1062 (2011).
33. Neill, D.R. *et al.* Nuocytes represent a new innate effector leukocyte that mediates type 2 immunity. *Nature* **464**, 1367–1370 (2010).
34. Cherrier, M., Sawa, S. & Eberl, G. Notch, Id2, and RORγt sequentially orchestrate the fetal development of lymphoid tissue inducer cells. *J. Exp. Med.* **209**, 729–740 (2012).
35. Constantinides, M.G., McDonald, B.D., Verhoef, P.A. & Bendelac, A. A committed precursor to innate lymphoid cells. *Nature* **508**, 397–401 (2014).
36. Klose, C.S. *et al.* Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell* **157**, 340–356 (2014).
37. Diefenbach, A., Colonna, M. & Koyasu, S. Development, differentiation, and diversity of innate lymphoid cells. *Immunity* **41**, 354–365 (2014).
38. Artis, D. & Spits, H. The biology of innate lymphoid cells. *Nature* **517**, 293–301 (2015).
39. Xu, W. *et al.* NFIL3 orchestrates the emergence of common helper innate lymphoid cell precursors. *Cell Rep.* **10**, 2043–2054 (2015).
40. Geiger, T.L. *et al.* Nfil3 is crucial for development of innate lymphoid cells and host protection against intestinal pathogens. *J. Exp. Med.* **211**, 1723–1731 (2014).
41. Yu, X. *et al.* The basic leucine zipper transcription factor NFIL3 directs the development of a common innate lymphoid cell precursor. *Elife* doi:10.7554/eLife.0440 (2014).
42. Seillet, C. *et al.* Nfil3 is required for the development of all innate lymphoid cell subsets. *J. Exp. Med.* **211**, 1733–1740 (2014).
43. Kobayashi, T. *et al.* NFIL3-deficient mice develop microbiota-dependent, IL-12/23-driven spontaneous colitis. *J. Immunol.* **192**, 1918–1927 (2014).
44. Seehus, C.R. *et al.* The development of innate lymphoid cells requires TOX-dependent generation of a common innate lymphoid cell progenitor. *Nat. Immunol.* **16**, 599–608 (2015).

45. Aliahmad, P., de la Torre, B. & Kaye, J. Shared dependence on the DNA-binding factor TOX for the development of lymphoid tissue-inducer cell and NK cell lineages. *Nat. Immunol.* **11**, 945–952 (2010).
46. Yang, Q. *et al.* T cell factor 1 is required for group 2 innate lymphoid cell generation. *Immunity* **38**, 694–704 (2013).
47. Mielke, L.A. *et al.* TCF-1 controls ILC2 and NKp46⁺RORγt⁺ innate lymphocyte differentiation and protection in intestinal inflammation. *J. Immunol.* **191**, 4383–4391 (2013).
48. Yagi, R. *et al.* The transcription factor GATA3 is critical for the development of all IL-7Rα-expressing innate lymphoid cells. *Immunity* **40**, 378–388 (2014).
49. Serafini, N. *et al.* Gata3 drives development of RORγt⁺ group 3 innate lymphoid cells. *J. Exp. Med.* **211**, 199–208 (2014).
50. Montaldo, E. *et al.* Human RORγt⁺CD34⁺ cells are lineage-specified progenitors of group 3 RORγt⁺ innate lymphoid cells. *Immunity* **41**, 988–1000 (2014).
51. Bernink, J.H. *et al.* Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nat. Immunol.* **14**, 221–229 (2013).
52. Fuchs, A. *et al.* Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-γ-producing cells. *Immunity* **38**, 769–781 (2013).
53. Hoyler, T. *et al.* The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. *Immunity* **37**, 634–648 (2012).
54. Mjösberg, J. *et al.* The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. *Immunity* **37**, 649–659 (2012).
55. Klein Wolterink, R.G. *et al.* Essential, dose-dependent role for the transcription factor Gata3 in the development of IL-5⁺ and IL-13⁺ type 2 innate lymphoid cells. *Proc. Natl. Acad. Sci. USA* **110**, 10240–10245 (2013).
56. Furusawa, J. *et al.* Critical role of p38 and GATA3 in natural helper cell function. *J. Immunol.* **191**, 1818–1826 (2013).
57. Wong, S.H. *et al.* Transcription factor RORα is critical for nuocyte development. *Nat. Immunol.* **13**, 229–236 (2012).
58. Halim, T.Y. *et al.* Retinoic-acid-receptor-related orphan nuclear receptor alpha is required for natural helper cell development and allergic inflammation. *Immunity* **37**, 463–474 (2012).
59. Robinette, M.L. *et al.* Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets. *Nat. Immunol.* **16**, 306–317 (2015).
60. Spooner, C.J. *et al.* Specification of type 2 innate lymphocytes by the transcriptional determinant Gfi1. *Nat. Immunol.* **14**, 1229–1236 (2013).
61. Walker, J.A. *et al.* Bcl11b is essential for group 2 innate lymphoid cell development. *J. Exp. Med.* (in the press, 2015).
62. Yu, Y. *et al.* The transcription factor Bcl11b is specifically expressed in group 2 innate lymphoid cells and is essential for their development. *J. Exp. Med.* (in the press, 2015).
63. Kim, B.S. *et al.* TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci. Transl. Med.* **5**, 70ra116 (2013).
64. Molofsky, A.B. *et al.* Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J. Exp. Med.* **210**, 535–549 (2013).
65. Hams, E., Locksley, R.M., McKenzie, A.N. & Fallon, P.G. Cutting edge: IL-25 elicits innate lymphoid type 2 and type II NKT cells that regulate obesity in mice. *J. Immunol.* **191**, 5349–5353 (2013).
66. Brestoff, J.R. *et al.* Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature* **519**, 242–246 (2015).
67. Eberl, G. *et al.* An essential function for the nuclear receptor RORγ(t) in the generation of fetal lymphoid tissue inducer cells. *Nat. Immunol.* **5**, 64–73 (2004).
68. Klose, C.S. *et al.* A T-bet gradient controls the fate and function of CCR6-RORγt⁺ innate lymphoid cells. *Nature* **494**, 261–265 (2013).
69. Kiss, E.A. *et al.* Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. *Science* **334**, 1561–1565 (2011).
70. Lee, J.S. *et al.* AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. *Nat. Immunol.* **13**, 144–151 (2012).
71. Qiu, J. *et al.* The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. *Immunity* **36**, 92–104 (2012).
72. Vonarbourg, C. *et al.* Regulated expression of nuclear receptor RORγt confers distinct functional fates to NK cell receptor-expressing RORγt⁺ innate lymphocytes. *Immunity* **33**, 736–751 (2010).
73. Bouskra, D. *et al.* Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. *Nature* **456**, 507–510 (2008).
74. Mackley, E.C. *et al.* CCR7-dependent trafficking of RORγ⁺ ILCs creates a unique microenvironment within mucosal draining lymph nodes. *Nat. Commun.* **6**, 5862 (2015).
75. Teunissen, M.B. *et al.* Composition of innate lymphoid cell subsets in the human skin: enrichment of NCR⁺ ILC3 in lesional skin and blood of psoriasis patients. *J. Invest. Dermatol.* **134**, 2351–2360 (2014).
76. Powell, N. *et al.* The transcription factor T-bet regulates intestinal inflammation mediated by interleukin-7 receptor⁺ innate lymphoid cells. *Immunity* **37**, 674–684 (2012).
77. Huang, Y. *et al.* IL-25-responsive, lineage-negative KLRG1^{hi} cells are multipotential 'inflammatory' type 2 innate lymphoid cells. *Nat. Immunol.* **16**, 161–169 (2015).
78. Sun, J.C. & Lanier, L.L. NK cell development, homeostasis and function: parallels with CD8⁺ T cells. *Nat. Rev. Immunol.* **11**, 645–657 (2011).
79. Maizels, R.M., Hewitson, J.P. & Smith, K.A. Susceptibility and immunity to helminth parasites. *Curr. Opin. Immunol.* **24**, 459–466 (2012).
80. Artis, D. *et al.* RELMβ/FIZZ2 is a goblet cell-specific immune-effector molecule in the gastrointestinal tract. *Proc. Natl. Acad. Sci. USA* **101**, 13596–13600 (2004).
81. Spencer, S.P. *et al.* Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. *Science* **343**, 432–437 (2014).
82. Sugimoto, K. *et al.* IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. *J. Clin. Invest.* **118**, 534–544 (2008).
83. Pham, T.A. *et al.* Epithelial IL-22RA1-mediated fucosylation promotes intestinal colonization resistance to an opportunistic pathogen. *Cell Host Microbe* **16**, 504–516 (2014).
84. Goto, Y. *et al.* Innate lymphoid cells regulate intestinal epithelial cell glycosylation. *Science* **345**, 1254009 (2014).
85. Pickard, J.M. *et al.* Rapid fucosylation of intestinal epithelium sustains host-commensal symbiosis in sickness. *Nature* **514**, 638–641 (2014).
86. Gladiator, A., Wangler, N., Trautwein-Weidner, K. & LeibundGut-Landmann, S. Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection. *J. Immunol.* **190**, 521–525 (2013).
87. Sonnenberg, G.F. *et al.* Pathological versus protective functions of IL-22 in airway inflammation are regulated by IL-17A. *J. Exp. Med.* **207**, 1293–1305 (2010).
88. Deshmukh, H.S. *et al.* The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice. *Nat. Med.* **20**, 524–530 (2014).
89. Turner, J.E. *et al.* IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J. Exp. Med.* **210**, 2951–2965 (2013).
90. Salimi, M. *et al.* A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J. Exp. Med.* **210**, 2939–2950 (2013).
91. Scandella, E. *et al.* Restoration of lymphoid organ integrity through the interaction of lymphoid tissue-inducer cells with stroma of the T cell zone. *Nat. Immunol.* **9**, 667–675 (2008).
92. Dudakov, J.A. *et al.* Interleukin-22 drives endogenous thymic regeneration in mice. *Science* **336**, 91–95 (2012).
93. Matsumoto, A. *et al.* IL-22-producing RORgammat-dependent innate lymphoid cells play a novel protective role in murine acute hepatitis. *PLoS ONE* **8**, e62853 (2013).
94. Kumar, P., Thakar, M.S., Ouyang, W. & Malarkannan, S. IL-22 from conventional NK cells is epithelial regenerative and inflammation protective during influenza infection. *Mucosal Immunol.* **6**, 69–82 (2013).
95. Takayama, T. *et al.* Imbalance of NKp44⁺NKp46⁻ and NKp44⁻NKp46⁺ natural killer cells in the intestinal mucosa of patients with Crohn's disease. *Gastroenterology* **139**, 882–892 (2010).
96. Ciccia, F. *et al.* Interleukin-22 and interleukin-22-producing NKp44⁺ natural killer cells in subclinical gut inflammation in ankylosing spondylitis. *Arthritis Rheum.* **64**, 1869–1878 (2012).
97. Sawa, S. *et al.* RORγt⁺ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota. *Nat. Immunol.* **12**, 320–326 (2011).
98. Hanash, A.M. *et al.* Interleukin-22 protects intestinal stem cells from immune-mediated tissue damage and regulates sensitivity to graft versus host disease. *Immunity* **37**, 339–350 (2012).
99. Mielke, L.A. *et al.* Retinoic acid expression associates with enhanced IL-22 production by γδ T cells and innate lymphoid cells and attenuation of intestinal inflammation. *J. Exp. Med.* **210**, 1117–1124 (2013).
100. Munneke, J.M. *et al.* Activated innate lymphoid cells are associated with a reduced susceptibility to graft-versus-host disease. *Blood* **124**, 812–821 (2014).
101. Zaph, C. *et al.* Commensal-dependent expression of IL-25 regulates the IL-23-IL-17 axis in the intestine. *J. Exp. Med.* **205**, 2191–2198 (2008).
102. Longman, R.S. *et al.* CX(3)CR1⁺ mononuclear phagocytes support colitis-associated innate lymphoid cell production of IL-22. *J. Exp. Med.* **211**, 1571–1583 (2014).
103. Manta, C. *et al.* CX(3)CR1⁺ macrophages support IL-22 production by innate lymphoid cells during infection with *Citrobacter rodentium*. *Mucosal Immunol.* **6**, 177–188 (2013).
104. Aychek, T. *et al.* IL-23-mediated mononuclear phagocyte crosstalk protects mice from *Citrobacter rodentium*–induced colon immunopathology. *Nat. Commun.* **6**, 6525 (2015).
105. Satoh-Takayama, N. *et al.* The chemokine receptor CXCR6 controls the functional topography of interleukin-22 producing intestinal innate lymphoid cells. *Immunity* **41**, 776–788 (2014).
106. Franchi, L. *et al.* NLRC4-driven production of IL-1β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense. *Nat. Immunol.* **13**, 449–456 (2012).
107. Seo, S.U. *et al.* Distinct commensals induce interleukin-1β via NLRP3 inflammasome in inflammatory monocytes to promote intestinal inflammation in response to injury. *Immunity* **42**, 744–755 (2015).
108. van de Pavert, S.A. *et al.* Maternal retinoids control type 3 innate lymphoid cells and set the offspring immunity. *Nature* **508**, 123–127 (2014).

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109. Bartemes, K.R., Kephart, G.M., Fox, S.J. & Kita, H. Enhanced innate type 2 immune response in peripheral blood from patients with asthma. *J. Allergy Clin. Immunol.* **134**, 671–678 (2014).
110. Hams, E. *et al.* IL-25 and type 2 innate lymphoid cells induce pulmonary fibrosis. *Proc. Natl. Acad. Sci. USA* **111**, 367–372 (2014).
111. Chang, Y.J. *et al.* Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. *Nat. Immunol.* **12**, 631–638 (2011).
112. Halim, T.Y., Krauss, R.H., Sun, A.C. & Takei, F. Lung natural helper cells are a critical source of T_H2 cell-type cytokines in protease allergen-induced airway inflammation. *Immunity* **36**, 451–463 (2012).
113. Bartemes, K.R. *et al.* IL-33-responsive lineage$^-$CD25$^+$CD44^{hi} lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs. *J. Immunol.* **188**, 1503–1513 (2012).
114. Imai, Y. *et al.* Skin-specific expression of IL-33 activates group 2 innate lymphoid cells and elicits atopic dermatitis-like inflammation in mice. *Proc. Natl. Acad. Sci. USA* **110**, 13921–13926 (2013).
115. Kabata, H. *et al.* Thymic stromal lymphopoietin induces corticosteroid resistance in natural helper cells during airway inflammation. *Nat. Commun.* **4**, 2675 (2013).
116. Kim, B.S. *et al.* Basophils promote innate lymphoid cell responses in inflamed skin. *J. Immunol.* **193**, 3717–3725 (2014).
117. Motomura, Y. *et al.* Basophil-derived interleukin-4 controls the function of natural helper cells, a member of ILC2s, in lung inflammation. *Immunity* **40**, 758–771 (2014).
118. Barnig, C. *et al.* Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. *Sci. Transl. Med.* **5**, 74ra126 (2013).
119. Halim, T.Y. *et al.* Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity* **40**, 425–435 (2014).
120. Oliphant, C.J. *et al.* MHCII-mediated dialog between group 2 innate lymphoid cells and CD4$^+$ T cells potentiates type 2 immunity and promotes parasitic helminth expulsion. *Immunity* **41**, 283–295 (2014).
121. Mirchandani, A.S. *et al.* Type 2 innate lymphoid cells drive CD4$^+$ Th2 cell responses. *J. Immunol.* **192**, 2442–2448 (2014).
122. Villanova, F. *et al.* Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44$^+$ ILC3 in psoriasis. *J. Invest. Dermatol.* **134**, 984–991 (2014).
123. Kirchberger, S. *et al.* Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J. Exp. Med.* **210**, 917–931 (2013).
124. Kim, H.Y. *et al.* Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat. Med.* **20**, 54–61 (2014).
125. Pantelyushin, S. *et al.* Rorγt$^+$ innate lymphocytes and $\gamma\delta$ T cells initiate psoriasiform plaque formation in mice. *J. Clin. Invest.* **122**, 2252–2256 (2012).
126. Geremia, A. *et al.* IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. *J. Exp. Med.* **208**, 1127–1133 (2011).
127. Powell, N. *et al.* Interleukin-6 increases production of cytokines by colonic innate lymphoid cells in mice and patients with chronic intestinal inflammation. *Gastroenterology* doi: 10.1053/j.gastro.2015.04.017. (2015).
128. Ermann, J., Staton, T., Glickman, J.N., de Waal Malefyt, R. & Glimcher, L.H. Nod/Ripk2 signaling in dendritic cells activates IL-17A-secreting innate lymphoid cells and drives colitis in T-bet$^{-/-}$Rag2$^{-/-}$ (TRUC) mice. *Proc. Natl. Acad. Sci. USA* **111**, E2559–E2566 (2014).
129. Muñoz, M. *et al.* Interleukin-22 induces interleukin-18 expression from epithelial cells during intestinal infection. *Immunity* **42**, 321–331 (2015).
130. Huber, S. *et al.* IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. *Nature* **491**, 259–263 (2012).
131. Eisenring, M., vom Berg, J., Kristiansen, G., Saller, E. & Becher, B. IL-12 initiates tumor rejection via lymphoid tissue-inducer cells bearing the natural cytotoxicity receptor NKp46. *Nat. Immunol.* **11**, 1030–1038 (2010).
132. Nussbaum, J.C. *et al.* Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* **502**, 245–248 (2013).
133. Lee, M.W. *et al.* Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* **160**, 74–87 (2015).
134. Brestoff, J.R. & Artis, D. Immune regulation of metabolic homeostasis in health and disease. *Cell* **161**, 146–160 (2015).
135. Vasanthakumar, A. *et al.* The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells. *Nat. Immunol.* **16**, 276–285 (2015).
136. Burzyn, D. *et al.* A special population of regulatory T cells potentiates muscle repair. *Cell* **155**, 1282–1295 (2013).
137. Schiering, C. *et al.* The alarmin IL-33 promotes regulatory T-cell function in the intestine. *Nature* **513**, 564–568 (2014).
138. Klatt, N.R. *et al.* Loss of mucosal CD103$^+$ DCs and IL-17$^+$ and IL-22$^+$ lymphocytes is associated with mucosal damage in SIV infection. *Mucosal Immunol.* **5**, 646–657 (2012).
139. Gray, E.E., Friend, S., Suzuki, K., Phan, T.G. & Cyster, J.G. Subcapsular sinus macrophage fragmentation and CD169$^+$ bleb acquisition by closely associated IL-17-committed innate-like lymphocytes. *PLoS ONE* **7**, e38258 (2012).
140. Kim, C.J. *et al.* A role for mucosal IL-22 production and Th22 cells in HIV-associated mucosal immunopathogenesis. *Mucosal Immunol.* **5**, 670–680 (2012).
141. Li, H. *et al.* Hypercytotoxicity and rapid loss of NKp44$^+$ innate lymphoid cells during acute SIV infection. *PLoS Pathog.* **10**, e1004551 (2014).
142. Sonnenberg, G.F. *et al.* Innate lymphoid cells promote anatomical containment of lymphoid-resident commensal bacteria. *Science* **336**, 1321–1325 (2012).
143. Qiu, J. *et al.* Group 3 innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through aryl hydrocarbon receptor signaling and regulation of microflora. *Immunity* **39**, 386–399 (2013).
144. Brenchley, J.M. *et al.* Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat. Med.* **12**, 1365–1371 (2006).
145. Guo, X. *et al.* Innate lymphoid cells control early colonization resistance against intestinal pathogens through ID2-dependent regulation of the microbiota. *Immunity* **42**, 731–743 (2015).
146. Hepworth, M.R. & Sonnenberg, G.F. Regulation of the adaptive immune system by innate lymphoid cells. *Curr. Opin. Immunol.* **27**, 75–82 (2014).
147. Mortha, A. *et al.* Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science* **343**, 1249288 (2014).
148. Kruglov, A.A. *et al.* Nonredundant function of soluble LTα_3 produced by innate lymphoid cells in intestinal homeostasis. *Science* **342**, 1243–1246 (2013).
149. Tsuji, M. *et al.* Requirement for lymphoid tissue-inducer cells in isolated follicle formation and T cell-independent immunoglobulin A generation in the gut. *Immunity* **29**, 261–271 (2008).
150. Hepworth, M.R. *et al.* Innate lymphoid cells regulate CD4$^+$ T-cell responses to intestinal commensal bacteria. *Nature* **498**, 113–117 (2013).
151. Goto, Y. *et al.* Segmented filamentous bacteria antigens presented by intestinal dendritic cells drive mucosal Th17 cell differentiation. *Immunity* **40**, 594–607 (2014).
152. Hepworth, M.R. *et al.* Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4$^+$ T cells. *Science* (in the press, 2015).
153. Perry, J.S. *et al.* Inhibition of LTi cell development by CD25 blockade is associated with decreased intrathecal inflammation in multiple sclerosis. *Sci. Transl. Med.* **4**, ra106 (2012).
154. Papp, K.A. *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N. Engl. J. Med.* **366**, 1181–1189 (2012).
155. Leonardi, C. *et al.* Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N. Engl. J. Med.* **366**, 1190–1199 (2012).
156. Genovese, M.C. *et al.* LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. *Arthritis Rheum.* **62**, 929–939 (2010).
157. Bowman, E.P., Chackerian, A.A. & Cua, D.J. Rationale and safety of anti-interleukin-23 and anti-interleukin-17A therapy. *Curr. Opin. Infect. Dis.* **19**, 245–252 (2006).
158. Hueber, W. *et al.* Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* **61**, 1693–1700 (2012).
159. Targan, S.R. *et al.* Mo2083 A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AMG 827 in subjects with moderate to severe Crohn's disease. *Gastroenterology* **143**, e26 (2014).
160. Kaser, A. Not all monoclonals are created equal: lessons from failed drug trials in Crohn's disease. *Best Pract. Res. Clin. Gastroenterol.* **28**, 437–449 (2014).
161. Colombel, J.F., Sendid, B., Jouault, T. & Poulain, D. Secukinumab failure in Crohn's disease: the yeast connection? *Gut* **62**, 800–801 (2013).

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