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G. Eberl, M. Colonna, J. P. Di Santo, A. N. J. Mckenzie. Innate lymphoid cells: A new paradigm in immunology. Science, 2015, 348 (6237), pp.aaa6566. 10.1126/science.aaa6566 . pasteur-01402704

HAL Id: pasteur-01402704

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REVIEW SUMMARY

INNATE LYMPHOID CELLS

Innate lymphoid cells: A new paradigm in immunology

Gérard Eberl,*† Marco Colonna, James P. Di Santo, Andrew N. J. McKenzie

BACKGROUND: Innate lymphoid cells (ILCs) are a growing family of immune cells that mirror the phenotypes and functions of T cells. Natural killer (NK) cells can be considered the innate counterparts of cytotoxic $CD8^+$ T cells, whereas ILC1s, ILC2s, and ILC3s may represent the innate counterparts of $CD4^+$ T helper 1 (T_H1), T_H2, and T_H17 cells. However, in contrast to T cells, ILCs do not express antigen receptors or undergo clonal selection and expansion when stimulated. Instead, ILCs react promptly to signals from infected or injured tissues and produce an array of secreted proteins, termed cytokines, that direct the developing immune response into one that is adapted to the original insult. Thus, the power of ILCs may be controlled or unleashed to regulate or enhance immune responses in disease prevention and therapy.

ADVANCES: As with B cells and T cells, ILCs develop from the common lymphoid progenitor, but dedicated transcription factors supress the B and T cell fates and direct the generation of the different types of ILCs. ILC precursors may migrate from their primary site of production into infected and injured tissues, where they complete their maturation, similar to the differentiation of naïve T cells into T_H effectors. Cytokines produced by local cells as well as stress ligands and bacterial and dietary compounds regulate the maturation and activation of ILCs into effectors that play a major role in early immune responses to pathogens and symbionts, helminths, and allergen. The cytokines they produce induce innate responses in stromal, epithelial, and myeloid cells and regulate the activity of dendritic cells (DCs), which play a central role in the cross-talk between ILCs and T cells. In particular, ILCs activate tissue-resident DCs to migrate to lymph nodes, where they elicit specific T cell responses, which in turn regulate ILCs. ILCs also directly regulate T cells through the presentation of peptide antigens on major histocompatibility complex II. However, ILCs are also involved in immunopathology, during which their production of cytokines exacerbates the inflammatory process.

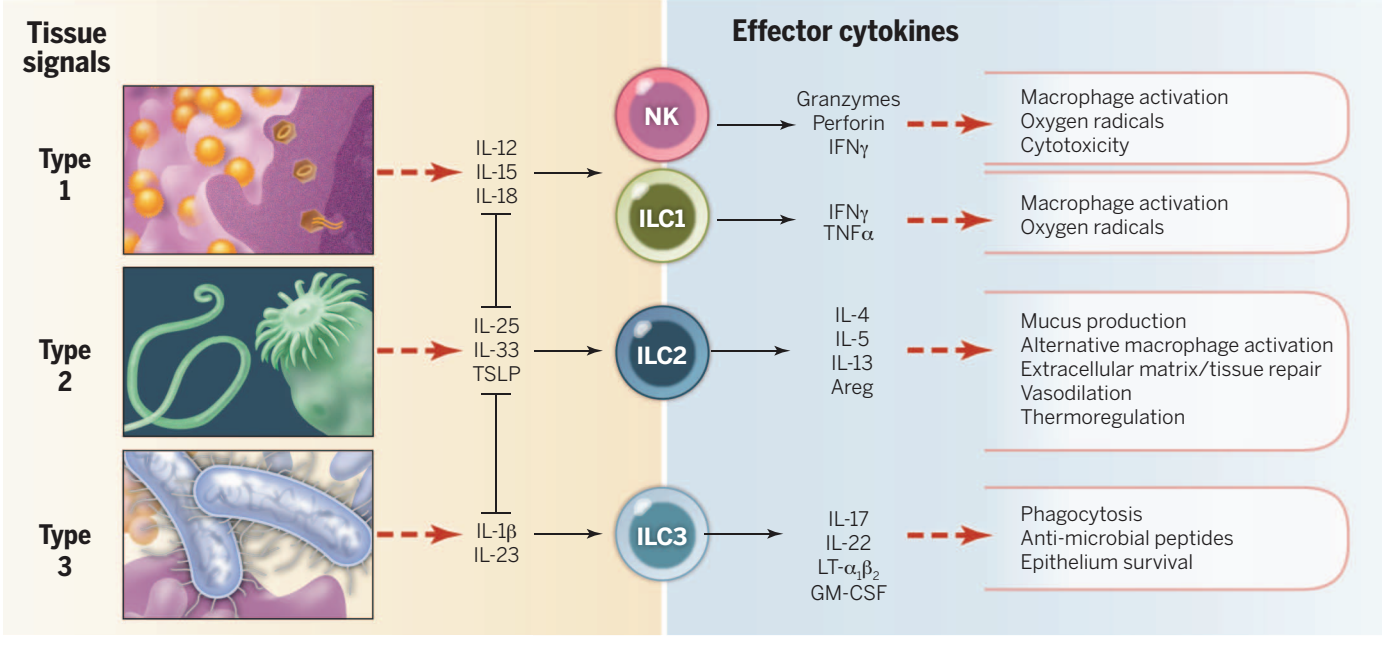
ILCs also play an intriguing role beyond immunity. In adipose tissues, they regulate thermogenesis and prevent local inflammation that may lead to metabolic syndrome, insulin resistance, and obesity-associated asthma. The functions of ILCs in host metabolism are a new area of research that will lead to insights into how the immune system is implicated in host functions not directly related to defense. Furthermore, ILCs are involved in repair responses upon infection and injury of epithelial cells, stromal cells, and stem cells.

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OUTLOOK: A logical next step will be the identification of molecules that allow manipulation of ILCs and the orchestration of the optimal immune response after vaccination and immunotherapy—or in contrast, to block detrimental responses. The combination of a prompt activation of ILCs with both effector and regulatory functions, with the expansion of antigen-specific B and T cells, should lead to new and powerful avenues in clinical immunology.

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Cite this article as G. Eberl *et al.*, *Science* **348**, aaa6566 (2015). DOI:10.1126/science.aaa6566



Signals from injured or infected tissues expand and activate NK cells, ILC1s, ILC2s, and ILC3s. The effector functions of ILCs mirror the functions of $CD8^+$ and $CD4^+$ T cells, with the major difference being the prompt activation of ILCs and their lack of (relatively slow) antigen-dependent clonal selection and expansion.

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REVIEW

INNATE LYMPHOID CELLS

Innate lymphoid cells: A new paradigm in immunology

Gérard Eberl,[1]* Marco Colonna,[2] James P. Di Santo,[3] Andrew N. J. McKenzie[4]

Innate lymphoid cells (ILCs) are a growing family of immune cells that mirror the phenotypes and functions of T cells. However, in contrast to T cells, ILCs do not express acquired antigen receptors or undergo clonal selection and expansion when stimulated. Instead, ILCs react promptly to signals from infected or injured tissues and produce an array of secreted proteins termed cytokines that direct the developing immune response into one that is adapted to the original insult. The complex cross-talk between microenvironment, ILCs, and adaptive immunity remains to be fully deciphered. Only by understanding these complex regulatory networks can the power of ILCs be controlled or unleashed in order to regulate or enhance immune responses in disease prevention and therapy.

During hematopoiesis, the common lymphoid progenitor (CLP) gives rise to antigen receptor–bearing T and B lymphocytes. Until quite recently, only two types of lymphoid cells had been recognized as deriving from CLPs but devoid of any antigen receptors. The first of these cells were the natural killer (NK) cells, which complement the cytotoxic $CD8^+$ T cells in killing infected, stressed, or transformed cells (*1*). The second were lymphoid tissue inducer (LTi) cells, which induce the development of lymph nodes and Peyer's patches (*2*, *3*). However, since 2008 the world of lymphoid cells has expanded dramatically. LTi-like cells were found that also express markers associated with NK cells and were termed NK22 cells, or natural cytotoxicity receptor 22 (NCR22) cells, for their concomitant expression of the cytokine interleukin-22 (IL-22) (*4*–*7*). Natural helper cells and nuocytes were described that expand in response to helminth infection and promote anti-worm and pro-allergic type 2 immune responses (*8*, *9*). Last, noncytotoxic NK-like cells were isolated from the intestinal epithelium (*10*, *11*). To avoid chaos in diversity, it was decided to reunite all these cells into one family of "innate lymphoid cells," or ILCs, and to create three categories—ILC1s, ILC2s, and ILC3s—that reflect the cytokine expression profiles of the classical $CD4^+$ T helper (T_H) cell subsets T_H1, T_H2, and T_H17 cells (Box 1) (*12*).

ILCs share the developmental origin and many of the phenotypes and functions of T cells. However, ILCs are activated by stress signals, microbial compounds, and the cytokine milieu of the surrounding tissue, rather than by antigen, in ways similar to the activation of memory or "innate" T cells, such as invariant NKT cells and subsets of γδ T cells. This mode of activation makes ILCs highly reactive and early effectors during the immune response. Furthermore, ILCs express the effector cytokines normally associated with T helper cells, and therefore, ILCs are expected to play a central role in the regulation of type 1, type 2, and type 3 (or T_H17 cell) responses, which control intracellular pathogens, large parasites, and extracellular microbes, respectively. The activity of ILCs may thus be harnessed to enhance responses against pathogens and tumors, during vaccination and immunotherapy, or inhibited to prevent autoimmune or allergic inflammation. Recent data also show that the role of ILCs extends beyond immunity into physiology through the regulation of fat metabolism and body temperature (*13*–*15*). In this Review, we discuss these intriguing issues in the light of the most recent developments.

Development and evolution of ILCs

Developing away from adaptive lymphocyte fate

ILCs develop from CLPs that give rise to B cell and T cell precursors, NK cell precursors (NKPs), and the recently described common helper ILC precursors (ChILPs) that express Id2 and variable levels of promyelocytic leukemia zinc finger (PLZF) (Fig. 1) (*16*–*18*). ChILPs generate all ILC groups but not NK cells, whereas $PLZF^+$ ILC precursors generate all ILC groups but not NK

Box 1. Warning: the limits of nomenclature.

The classification of ILCs into ILC1s, ILC2s, and ILC3s reflects both the phenotypical and the functional characteristics of T_H cells and serves to structure research into their phylogeny and functions. However, this classification also generates some debates because ILCs and T_H cells can coexpress cytokines of more than one type. For example, ILC3s and T_H17 cells are found to coexpress IFN-γ and IL-17—which are characteristic of type 1 and type 3 responses, respectively—during pathological inflammation (*56*, *103*, *128*). How should these cells be referred to, ILC3/1 cells or IFN-γ–expressing ILC3s? Furthermore, ILC3s can evolve into ILC1s by down-regulating the transcription factor RORγt and up-regulating the transcription factor T-bet (*103*, *129*). Therefore, it is possible that IFN-γ–expressing ILC3s are in fact cells that transit from an ILC3 phenotype to an ILC1 phenotype—"so-called ex-ILC3s." To further complicate an already opaque ILC world, a potential ILC2 precursor that is induced by IL-25 has been reported to have the capability to give rise to ILC3-like IL-17 producers, although in naïve mice or upon helminth infection, they appear to default to a more conventional and less plastic ILC2 phenotype (*43*). Last, fate mapping of $PLZF^+$ ILC precursors shows that LTi cells develop along a pathway distinct from that of the other types of ILCs (*17*). In addition, LTi cells and $NKp46^+$ ILC3s can be distinguished on the basis of their gene expression (*106*). This difference may have an evolutionary basis: because the programmed development of lymph nodes and Peyer's patches is induced by LTi cells only in mammals (*130*), LTi cells may be a recent acquisition, whereas ILCs may have appeared with the advent of vertebrates or even before (*49*).

NK cells present another difficulty for classification. NK cells express T-bet and produce IFN-γ and thus are type 1 cells such as T_H1 cells. However, they also express Eomesodermin-dependent perforin and granzymes, as do cytotoxic $CD8^+$ T cells. It is therefore suggested that NK cells mirror $CD8^+$ T cells, whereas ILC1s mirror $CD4^+$ T_H1 cells (*16*, *131*). Thus, NK cells may be termed "cytotoxic ILCs." Distinguishing NK cells from ILC1s can be achieved by fate-mapping of $Id2^+$ or $PLZF^+$ precursor cells (*16*, *17*) or by using Eomesodermin reporter mice. However, it is more difficult to discriminate these two ILC subsets by using surface markers because they vary from tissue to tissue. For example, discriminating the two cell types is relatively straightforward in the liver but more difficult in the spleen and small intestine (*106*). In the liver, ILC1s selectively express TRAIL and VLA1. In the spleen and small intestine, there are no distinctive surface markers identified, although the expression of CXCR6 on ILC1s and of the MHC class I receptors Ly49 and KIRs on NK cells can be partially informative. Last, surface markers used to discriminate these cell types may vary depending on cellular activation.

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cells or LTi cells. ILC development from CLP (via NKP or ChILP) therefore involves a stage of lineage restriction, in which B and T cell potentials are lost and ILC potential is reinforced. This is achieved through the coordinated expression of specific transcription factors that activate or repress target genes that are critical for subset-specific lymphocyte differentiation. For ILC development, several transcription factors have been shown to be critical at the ILC precursor stage, including Id2, Nfil3, and Gata3 (*19*–*24*). Our understanding of how these transcription factors promote ILC fate is incomplete, but one emerging concept involves obligate suppression of alternative lymphoid cell fates, on the basis of reciprocal repression as a means to control binary cell fate decisions. Id2 is a transcriptional repressor that acts to reduce the activity of E-box transcription factors (E2A, E2-2, and HEB), which are critical in early B and T cell development. Thus, increasing expression of Id2 in CLP promotes ILC development at the expense of the B and T cell fates (*20*, *25*). Accordingly, NKP and ChILP express variable levels of Id2, whereas CLPs do not express Id2 (*16*, *26*). In a similar fashion, Gata3 represses B cell fate by blocking EBF1 and thereby facilitates T and ILC differentiation from CLPs (*23*, *24*, *27*).

How Id2 or Gata3 expression is controlled as CLPs differentiate into NKP or ChILP is not fully understood. Signals produced by the microenvironment—for example, bone morphogenic proteins (BMP) and Notch ligands (*28*, *29*)—regulate Id2 expression, a mechanism that could apply to CLPs. Furthermore, the transcription factor Nfil3 links the peripheral circadian clocks involving the nuclear receptor Rev-ERBα to gene regulation (*30*), and its deletion affects multiple developmental processes within the hematopoietic system. In particular, Nfil3 controls differentiation of ILC via Id2 and the transcription factors RAR-related orphan receptor–γt (RORγt), Eomesodermin, and Tox (*21*, *22*, *31*). In addition, soluble factors, including cytokines, regulate Nfil3 expression (*32*), providing a link between signals from the tissue and fate decisions into the ILC lineages.

Do ILCs complete development in response to local cues?

Conventional wisdom suggests that the primary site of ILC development is the liver in the fetus, and the bone marrow after birth, because these primary lymphoid organs harbour CLP, NKP, and ChILP (*16*, *33*, *34*). Once generated, mature ILCs exit these sites, circulate in the blood, and enter tissues following codes based on adhesion molecules and chemokines, similar to the ones used by T cells. This model is supported by the dearth of tissue-resident ILCs under steady-state conditions, with the exception of mucosal sites, and the rapid recruitment of ILCs after infection or injury. However, ILC precursors—the NKP and the ChILP—may leave the fetal liver or the bone marrow and complete their maturation in response to local signals, much in the same way as naïve T cells differentiate into the different effector subsets during inflammation. In this view, ILC precursors would be the innate homologs of naïve T cells.

In support of this hypothesis, NKP and ILC3 precursors are found in human tonsils (*35*). In mouse, ILC3 precursors are found in the fetal gut (*19*), where their mature progeny induce the development of Peyer's patches, as well as after birth in the lamina propria of the small intestine (*36*). Fetal ILC precursors with the capacity to give rise to ILC1s, ILC2s, and ILC3s are present in the mouse intestine and accumulate in the developing Peyer's patches (*37*). The vitamin A metabolite retinoic acid (RA), produced by many types of cells outside lymphoid organs—including nerve cells (*38*), dendritic cells (DCs) (*39*), and stromal cells (*40*)—favors the maturation of ILC3s at the expense of ILC2s (*41*) and is required for the full maturation of ILC3s in the fetus and the adult (*42*). Furthermore, although IL-25 and IL-33 produced by epithelial cells both promote ILC2 differentiation, it has been proposed that IL-25 may act to expand precursors that retain ILC3 potential (*43*). Last, the aryl hydrocarbon receptor Ahr, which is triggered by ligands from diet, is also required for the maintenance and expansion of intestinal ILC3s after birth (*44*–*46*).

ILCs as evolutionary precursors to T cells

Even though the adaptive lymphocyte fate has to be blocked in CLPs to generate ILCs, striking similarities exist between ILC and T cell differentiation. Gata3, Nfil3, and Tcf1 (*21*–*24*, *47*, *48*) are shared by the precursor common to T cells and ILCs, and the signature transcription factors T-bet, Gata3, and RORγt, which determine the development of type 1, 2, or 3 cells, are highly conserved in both innate and adaptive lymphoid cells in mice and men. It is therefore tempting to propose that ILCs are the evolutionary precursors of T cells, even though definitive evidence has yet to be found that ILCs exist in invertebrates or early vertebrates that lack T or B lymphocytes (*49*). The emergence of ILCs, and thus of the lymphoid lineage, must also have provided a fitness advantage. As we now understand the function of ILCs and T_H cells, this advantage would build on the ability to rapidly direct immunity into type 1, 2, or 3 responses that are adapted to counter specific types of threats. Myeloid cells, as well as non-hematopoietic cells such as epithelial cells and stromal cells, produce cytokines in reaction to infection and injury, which activate a particular ILC subset and the production of effector cytokines. The reason why phagocytic myeloid cells, presumably the first type of immune cells to appear during evolution, would not perform this function is unclear, but may be related to the superior capacity of lymphoid cells to expand rapidly.

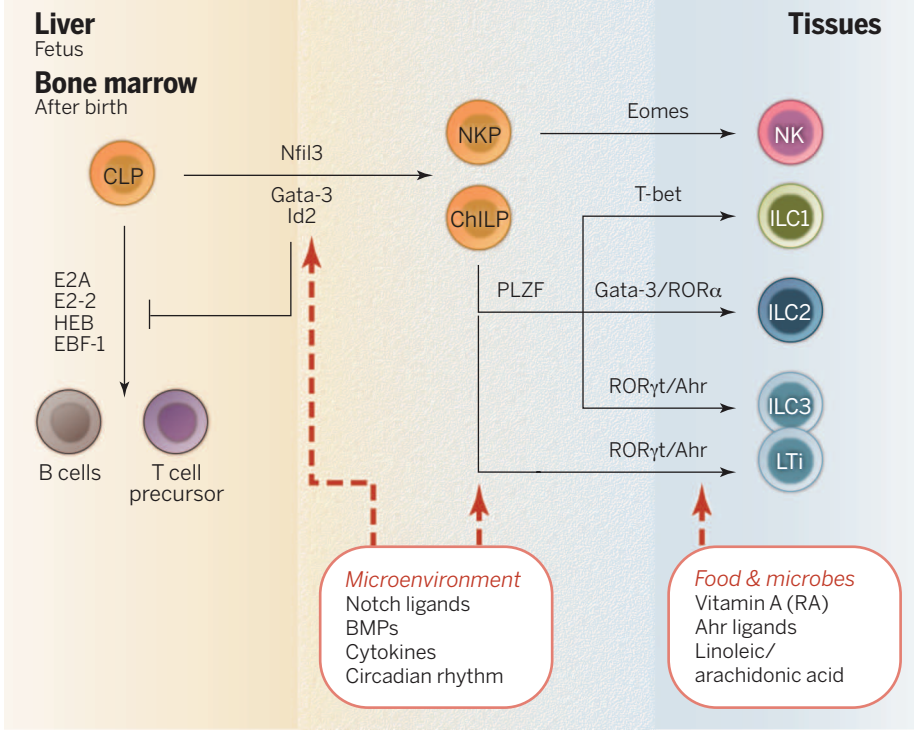


Fig. 1. The development of ILCs. The development of ILCs from common lymphoid progenitors (CLPs) requires Id2-mediated suppression of alternative lymphoid cell fates that generate B and T cells. Factors present in the microenvironment, such as Notch ligands, bone morphogenic proteins (BMPs), and cytokines, as well as the circadian rhythm, control expression of Nfil3, Gata3, and Id2, which determine the progression toward the ILC fate. Distinct precursors give rise to NK cells and ILCs (which, unlike NK cells, are noncytotoxic), while the transcription factor PLZF further divides the progeny of ChILPs into the PLZF-dependent ILC1s, ILC2s, and ILC3s and PLZF-independent LTi cells (although LTi cells tend to be grouped as ILC3s) required for the development of lymph nodes, Peyer's patches, and ILFs. The maturation of ILC precursors into mature ILCs may occur outside of primary lymphoid tissues, in ways similar to the maturation of naïve T_H cells into T_H1, T_H2, T_H17, and regulatory T cells (T_{reg} cells) and in response to a variety of signals produced by the tissue microenvironment.

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Once established as a diverse family of innate effector cells, the program of ILC development, differentiation, and function would serve as a "blueprint" for T cells. Emergence of the adaptive arm of the immune system, based on major histocompatibility complex (MHC) restriction and somatic rearrangements of antigen receptor genes, would be layered onto the ILC program, providing an exhaustive range of antigen specificity to the already existing effector cell diversity. Because clonal selection via the T cell receptor results in substantial cellular expansion, T cells may also be freed from the microenvironmental constraints that limit ILC expansion, providing more amplitude to immune effector and regulatory functions, as well as antigen-specific immunological memory.

Activation of ILCs

ILCs translate signal cytokines into effector cytokines

In the absence of adaptive antigen receptors, ILCs react to the microenvironment through cytokine receptors. NK cells and ILC1s expand and secrete interferon-γ (IFN-γ) in response to IL-12, IL-15, and IL-18 produced by myeloid cells as well as by nonhematopoietic cells in response typically to intracellular pathogens (Fig. 2) (*10*, *11*, *16*, *50*). ILC2s, on the other hand, respond to the epithelium-derived cytokines IL-25, IL-33, TSLP (thymic stroma lymphopoietin), basophil-derived IL-4, and products of the arachidonic acid pathway, in response to parasite infection, allergens, and epithelial injury (*8*, *9*, *51*–*53*). Activation of ILC2s leads to the production of high amounts of IL-4, IL-5, and IL-13. Last, ILC3s respond mainly to IL-1β and IL-23 produced by myeloid cells in response to bacterial and fungal infection (*54*–*56*). ILC3s produce lymphotoxins, GM-CSF (granulocyte-macrophage colony-stimulating factor), and IL-22, as well as IL-17 in the fetus, early after birth and during inflammation (*57*, *58*).

Thus, ILCs translate signal cytokines produced by myeloid and nonhematopoietic cells in tissues into effector cytokines that activate local innate and adaptive effector functions. For example, IFN-γ activates the production of microbicidal reactive oxygen species in myeloid cells, induces the production of antibodies for antibody-mediated cytotoxicity, and increases antigen presentation by MHC molecules (*59*). On the other hand, IL-5 induces the recruitment of eosinophils, and IL-13 stimulates the production of mucus by goblet cells [the secretion of which can also be induced by IFN-γ (*60*)] (*61*), whereas IL-17 and IL-22 induce the production of antimicrobial peptides by epithelial cells (*62*) and the recruitment of neutrophils through the expression of CXC chemokines by stromal cells (*63*).

NK cells also express an array of receptors that recognize MHC I, the constant domains of antibodies, and cell-surface molecules associated with cellular transformation, stress, and infection, the activation of which leads to cytotoxicity and the production of IFN-γ (*64*). These NK receptors are not antigen receptors but nevertheless confer some degree of specificity to the reactivity of NK cells. Because individual NK cells express different combinations and levels of NK receptors, triggering of one receptor may lead to the expansion of a subset of NK cells and thus to an increased response, or memory, upon reencounter of the trigger (*65*). Furthermore, a subset of ILC3s expresses the pan-NK marker NKp46 in mouse and NKp44 in human (*4*–*7*). NKp46 appears redundant for ILC3 responses against bacterial infection (*66*), but NKp44 can activate human ILC3s (*67*). Last, ILCs isolated from human tonsils were found to produce IL-5 and IL-13, as well as IL-22, in response to ligands that bind the pattern recognition receptor Toll-like receptor 2 (TLR2) (*68*), indicating that ILCs may also react to microbial compounds. Thus, it is possible that ILCs express different arrays of innate receptors that enable them to react to sets of molecules or proxies for type 1–, 2-, or 3-inducing cellular stresses, injuries or infections. However, although such receptors are well studied for NK cells, they remain to be described for the other types of ILCs.

How diet and the microbiota influence ILC development and activity

As mentioned earlier, the vitamin A metabolite RA is required for full maturation of ILC3s at the expense of ILC2s (*41*, *42*), and food-derived Ahr ligands are required for the maintenance of ILC3s after birth (*44*–*46*). Furthermore, TLR2 ligands can activate human ILC2s and ILC3s in vitro (*68*). That is, however, the state of our knowledge of the direct effects of diet and microbiota on ILCs. In contrast, much more is known on indirect effects of diet and microbes on the activation of ILCs.

In the absence of microbiota in germ-free mice, the activity of ILC3s in the intestine is substantially perturbed. Although the development of lymph nodes and Peyer's patches, induced by LTi cells, is programmed in the fetus, the formation of isolated lymphoid follicles (ILFs) in the intestinal lamina propria after birth is not (*69*). Bacteria are required to trigger the production of β-defensins and the chemokine CCL20 by epithelial cells, which induce the morphogenesis of ILFs through activation of $CCR6^+$ LTi cells

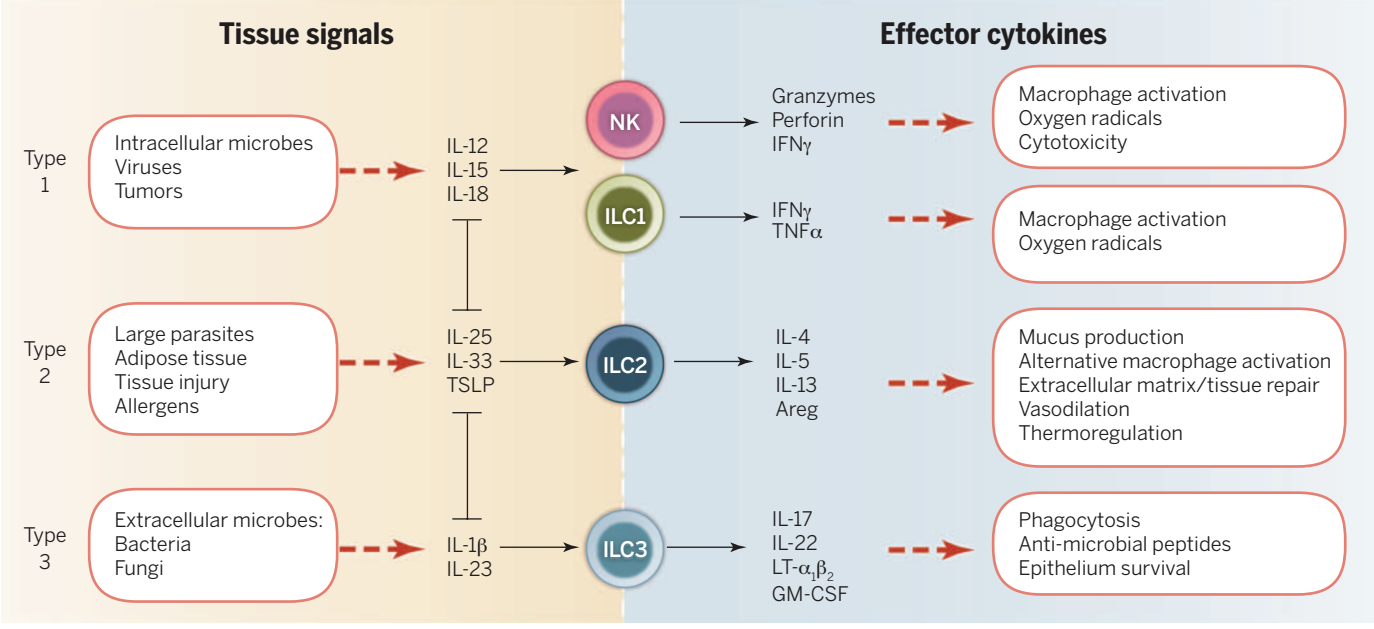


Fig. 2. Activation and functions of ILCs. The tissue signals that expand and activate ILC1s, ILC2s, and ILC3s, and the effector functions of ILCs, mirror the activation and functions of T cells. In this figure, NK cells, ILC1s, ILC2s, and ILC3s could be replaced by $CD8^+$ T cells, T_H1, T_H2, and T_H17 cells, respectively. However, whereas ILCs are activated promptly by tissue signals and therefore act upstream in the immune response, T cells are first selected and expanded on the basis of T cell receptor specificity, a process that typically requires several days.

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clustered in so-called cryptopatches (70) and the recruitment of CCR6$^+$ B cells to nascent ILFs (71). The B cell chemoattractant CXCL13, produced by dedicated stromal cells termed "lymphoid stromal cells" (LSCs), is also required for the development of lymphoid tissues through the recruitment of LTi cells from the bloodstream (72) and is induced by RA (38). Furthermore, microbiota induce the expression of CXCL16 by dendritic cells (DCs), which recruits ILC3s to the lamina propria and villi of the small intestine (73). Microbiota also negatively regulate the activity of ILC3s. The expression of IL-17 and IL-22 by ILC3s is highest in the fetus and gradually declines after birth as the intestinal tract is colonized. Microbiota induce the expression of the type 2 cytokine IL-25 by epithelial cells, which activates IL25R$^+$ DCs and the regulation of ILC3s through mechanisms that remain to be elucidated (57).

High-fat diet leads to the build-up of visceral adipose tissue (VAT). Intriguingly, ILC2s are associated with VAT (74) and were originally described as residents of "fat-associated lymphoid clusters" (FALC) on the mesentery (8). The production of IL-5 and IL-13 by ILC2s leads to the recruitment of eosinophils and the generation of alternatively activated macrophages (AAMs) that protect the organism from fat-induced ILC3-mediated inflammatory pathology (74, 75). It is unclear how fat tissue regulates the activation of ILC2s or ILC3s, but this possibly involves metabolites of arachidonic acid, such as prostaglandins and lipoxins, which are respectively activators and inhibitors of ILC2s (76).

Roles of ILCs in immunity

Do ILCs have specific effector functions?

Each cell type in an organism is expected to have a specific function that justifies its evolutionary conservation. However, NK cells, ILC1s, ILC2s, and ILC3s mirror the cytokine production and effector functions of CD8$^+$ T cells, T_H1, T_H2, and T_H17 cells (Fig. 2). Nevertheless, in contrast to T cells, ILCs do not undergo antigen-driven clonal selection and expansion, and therefore, ILCs act promptly like a population of memory T cells. As a consequence, within hours after infection or injury, the effector cytokines IFNγ, IL-5, and IL-13, or IL-17 and IL-22, which can be produced by both ILCs and T cells, are produced mostly by ILCs. In certain tissues, the prompt production of effector cytokines is shared with "innate" T cells, such as mucosa-associated invariant T (MAIT) cells that produce IFN-γ, IL-17, and IL-22 (77); invariant NKT (iNKT) cells that produce IFN-γ or IL-4 (78); and subsets of γδ T cells that produce IFN-γ and IL-17 within different epithelial and mucosal compartments (79–81). Nevertheless, each of these cell types reacts to distinct stimuli. For example, MAIT cells recognize microbial metabolites bound to the MHC-like molecule MR1, and iNKT cells respond to glycolipid moieties bound to the MHC-like molecule CD1d.

Regulation of adaptive immunity by ILCs

Because ILCs are activated early in the immune response to infection and injury, and produce type 1, type 2, and type 3 cytokines, it is expected that they regulate the developing adaptive immune response (82). ILCs have been found to do that in two ways: directly through the expression of MHC class II molecules (MHC II), and indirectly through the regulation of DCs (Fig. 3).

ILC3s were shown nearly two decades ago to express MHC II on their surface (2, 83), but the importance of this expression became clear only recently. ILC3s not only express MHC II but also transcripts for molecules associated with antigen processing and presentation, such as the invariant chain CD74 and the catalyzer of peptide exchange H2-DM, and can process exogenous antigen for presentation to CD4$^+$ T cells (84). In the intestine, ILC3s regulate the activity of T cells specific for microbiota-derived antigens, and as a consequence, the absence of MHC II on ILC3s leads to intestinal inflammation. In contrast, ILC3s activate CD4$^+$ T cells in the spleen upon antigen processing and presentation on MHC II (85). ILC2s also present antigen on MHC II and induce the production of IL-2 and IL-4 by CD4$^+$ T cells, which drive a positive feedback on growth and cytokine production by ILC2s expressing the receptors for IL-2 and IL-4 (86, 87). This dialogue is functionally important as MHC II–deficient ILC2s fail to cause efficient expulsion of parasitic helminths, even in the presence of MHC II$^+$ DCs (86).

ILCs also regulate DCs. The production of IFN-γ by NK cells increases the production of IL-12, IL-15, and IL-18 by DCs, driving a positive feedback loop between NK cells and DCs that promotes the differentiation of T_H1 cells (88). Likewise, the production of IL-13 by ILC2s leads to the activation of DCs, their migration into the draining lymph nodes and the differentiation of T_H2 cells (89). In the absence of ILC2s, the levels of IL-13 are insufficient to instigate the migration of DCs to the lymph nodes in response to lung injury, and T_H2 responses are impaired (89). Last, ILC3s activate DCs through membrane-bound lymphotoxin (LT) $\alpha_1\beta_2$, which in turn produce elevated levels of IL-23, which promotes the activity of ILC3s and the differentiation of T_H17 cells (90), as well as nitric oxide, which activates B cells (91).

Because ILCs promote T cell activation through DCs, it is likely that T cells promote ILC activation through similar mechanisms, establishing positive feedback loops between ILC, T cells, and DCs. However, this cross-talk also provides controls on the activity of ILCs because a decrease in the source of T cell antigen and of signals from the affected tissue should exhaust the positive feedback. In addition, competition between ILC and T cells for common activating cytokines from DCs and the affected tissue may also regulate ILC activity. In agreement with this hypothesis, the activity of ILC3s is increased in the absence of T

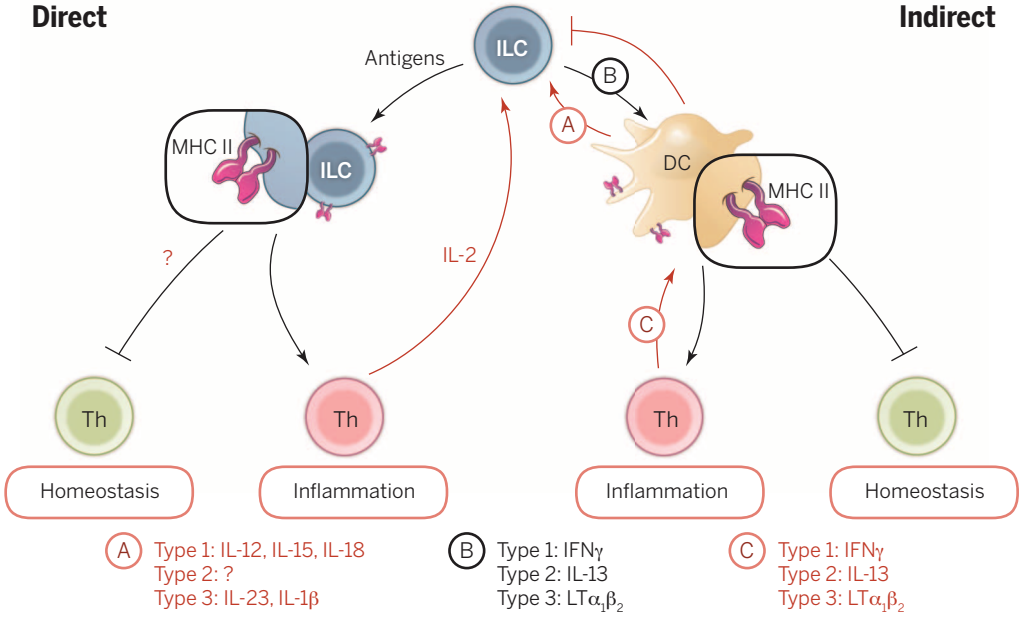


Fig. 3. Regulation of adaptive immunity by ILCs. ILCs regulate T cells both directly through antigen presentation on MHC II, and indirectly through the regulation of DCs. The cross-talk between ILCs, DCs, and T cells establishes a complex regulatory network involving positive and negative feedbacks, the dynamics of which remain to be elucidated. The mechanisms by which ILCs repress CD4$^+$ T_H cell activation remain unclear but may involve the lack of costimulatory molecules in the context of steady state (84). It also remains unclear how DCs negatively regulate the activity of ILCs (57). Red lines depict feedback loops, and "A," "B," and "C" list the type 1, type 2, or type 3 cytokines involved in a specific cross-talk. ILC3s also activate B cells in the intestine through lymphotoxin-mediated recruitment of T_H cells and activation of dendritic cells (91), as well as marginal-zone B cells in the spleen (132).

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cells (57). Furthermore, the dependence of ILC2s on IL-2 raises the possibility that both ILC2s and T cells are regulated by regulatory T cells through the removal of IL-2 from the microenvironment.

ILCs in tissue protective and repair responses

ILC2s are involved in tissue-repair responses through the production of amphiregulin (a ligand of the epidermal growth factor receptor) and IL-13. Upon infection of mouse lungs with the H1N1 influenza virus, ILC2s contribute to tissue repair through the expression of amphiregulin (92). Furthermore, injury to the bile duct, which can lead to severe liver disease, leads to the IL-33–mediated activation of ILC2s that promote cholangiocyte proliferation and epithelial restoration through the release of IL-13 (93). In VAT, IL-13 production by ILC2s protects from fat-induced inflammation promoted by ILC3s, which leads to metabolic syndrome, insulin resistance, and diabetes (74). More generally, IL-13 leads to the recruitment of eosinophils and the generation of AAMs (75) and promotes the production of extracellular matrix by stroma cells and mucus by epithelial cells, mechanisms involved both in repair responses and in defense against large parasites (94).

ILC3s promote tissue protective and repair responses through the production of $LT\alpha_1\beta_2$ and IL-22. Infection of lymph nodes with lymphocytic choriomeningitis virus leads to the destruction of lymphoid stromal cells (LSCs). ILC3s restore LSCs through $LT\alpha_1\beta_2$ and activation of LTβ receptor on LSCs (95). IL-22 has a general role in protecting epithelial cells, mostly through the activation of antiapoptotic pathways. In a model of graft-versus-host disease (GvHD), ILC3s protect intestinal epithelial stem cells from GvHD-induced cell death (96). In that context, a subset of ILC3s resists full-body irradiation and provides IL-22 to the stem cells. A similar ILC3-mediated mechanism was found to protect the thymus from the consequences of full-body irradiation (97). IL-22 also protects hepatocytes from acute liver inflammation, but the source of IL-22 was, at the time, attributed to T_H17 cells (98). The source of IL-22 was later recognized to include ILC3s in the $CD45RA^+$ cell transfer model of colitis (99).

ILCs and fat: Roles beyond immunity?

Adipose tissue is associated with the immune system at several levels. Lymph nodes and lymphoid clusters on the mesentery are embedded in adipose tissue for reasons that remain unclear (8). Type 2 responses, including ILC2s, are required to avoid the induction of type 3 responses that lead to metabolic syndrome, insulin resistance, diabetes, as well as obesity-associated asthma (100). In contrast, high-fat diet increases gut permeability and leads to the accumulation of bacteria in VAT, the recruitment and activation of type 1 macrophages, and a shift of the immune response associated with VAT from a protective type 2 to a pathogenic type 3 response (101, 102). Furthermore, ILC2s have recently been shown to regulate thermogenesis from beige fat in a process that appears to involve immune cells beyond immunity (13–15). The sensing of cold by nerves triggers their release of catecholamines that activate the biogenesis and activation of brown adipose tissue (BAT) for thermogenesis. Subcutaneous white adipose tissue (scWAT) can also undergo browning under these circumstances, but its low innervation cannot provide the levels of catecholamines required for the conversion of scWAT into beige fat. Macrophages, however, are recruited to cold-stressed scWAT and produce catecholamines, amplifying the signals released by nerves. This activity of macrophages is dependent on IL-4 produced by eosinophils, as well as on IL-5 and IL-13 produced by ILC2s, replicating the recruitment and activation process induced by ILC2s in VAT. ILC2s also produce methionine-enkephalin peptides, which induce beiging of VAT (15). Last, IL-4 and IL-13 induce the differentiation of adipocyte precursors directly into beige fat (14).

ILCs in pathology

High frequencies of ILC1s are found in Crohn's disease patients and in mouse models of colitis, contributing to the pathology through the production of IFN-γ (10, 11). ILC3s are also associated with inflammatory pathology when producing both IL-17 and IFN-γ during colitis and infection with *Salmonella enterica* (56, 103), as well as with obesity-induced airway hyperreactivity through the production of IL-17 (Fig. 4) (100). The pathogenicity of ILC3s was demonstrated when comparing mice deficient in T and B cells only with those lacking T cells, B cells, and ILCs (56). These studies show that ILC3s can be pathogenic (or sufficient to induce pathology) but nevertheless fail to show that ILC3s are necessary for the development of pathology in the presence of adaptive immunity. The difficulty stems from the lack of mutant mice that lack ILC1s or ILC3s while developing a normal set of T_H1 or T_H17 cells. A chimera system has been established to partially alleviate this difficulty (104). In this system, mature T and B cells are adoptively transferred into Rag-deficient mice, which lack these cell types but develop ILCs. Antibody depletion against a congenic marker depletes ILCs but leaves the T cell compartment intact.

In contrast, the ILC2s field has benefited from RORα-deficient mice that lack ILC2s but not other types of lymphocytes—in particular, T_H2 cells (18, 105). RORα message is also expressed in ILC1s and ILC3s (106) but does not appear to be required for ILC3 development (105). RORα-deficient mice, termed staggerer mice, also develop an undersized cerebellum that translates into behavioral defects (107). Chimeric mice that lack RORα only in the hematopoietic compartment fail to develop acute lung pathology in response to papain, a protease allergen, demonstrating the role of ILC2s in priming the allergic response involving T_H2 cells (89, 105). RORα-deficient mice were further used to show that ILC2s are required to

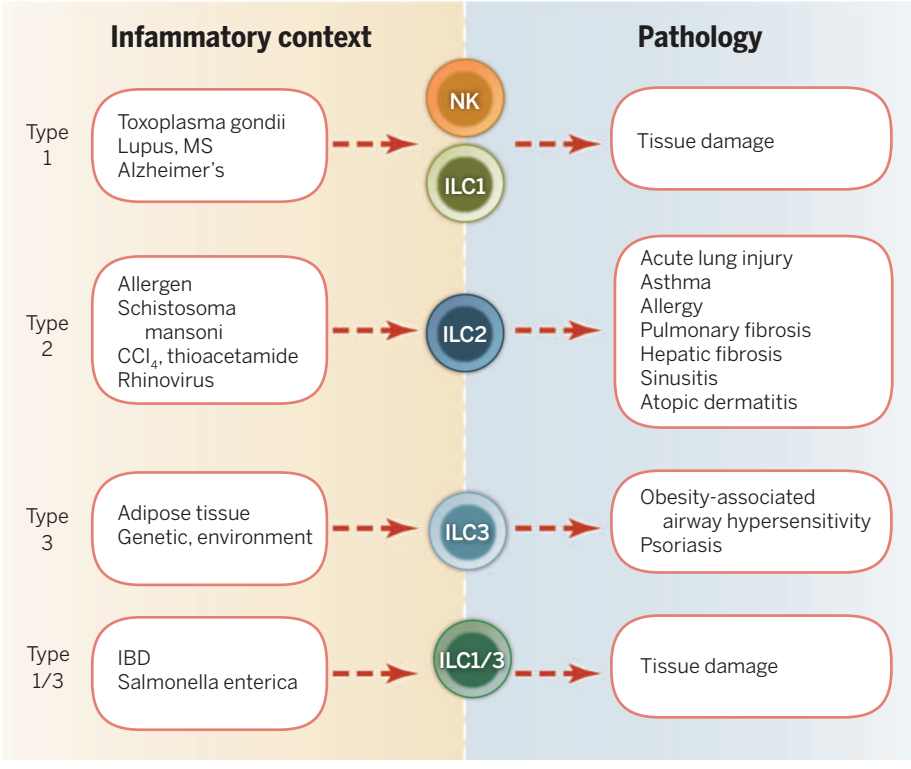


Fig. 4. ILCs in pathology. Pathogens, allergens, chemicals, diet, metabolic states, and genetic factors can induce type 1, type 2, or type 3 inflammatory conditions that lead to pathology involving ILCs. Listed are examples of pathologies shown to involve ILCs, even though in most cases the causative role of ILCs, or their requirement in the pathology, remains to be established. Strong intestinal inflammatory pathology induced during inflammatory bowel disease (IBD) or by *Salmonella enterica* generates ILCs that produce both type 1 (IFN-γ) and type 3 (IL-17) effector cytokines.

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expel the helminth *Nyppostrongylus brasiliensis* from the intestine (*18*) and to induce pulmonary fibrosis upon infection with *Schistosoma mansoni* through the production of IL-13 (*108*). The tools available to specifically ablate ILC2s recently expanded after the generation of mice that express the diphtheria toxin receptor (DTR) on ILC2s but not on T cells, allowing for time-controlled ablation of ILC2s (*86*).

ILC2s and IL-13 are also associated with hepatic fibrosis induced in mice by thioacetamide, carbontetrachloride, and *Schistosoma mansoni* (*109*), and with pulmonary fibrosis (*108*), chronic rhinosinusitis (*110*), and atopic dermatitis (*111*, *112*), as well as allergen- (*112*, *113*) and rhinovirus-induced asthma exacerbation in patients (*114*, *115*). Last, ILC2s are proposed to play a central role in asthma-induced obesity. ILC2s in VAT protect from obesity through the release of IL-5 and IL-13 and the recruitment of eosinophils (*74*). However, the accumulation of eosinophils into the asthmatic lungs may prevent their recruitment to VAT and thereby type 2 immunity from protecting the organism from high-fat diet–induced obesity (*116*).

Targeting ILCs for prevention and therapy

Because ILCs act promptly in response to infection and injury, and regulate type 1, type 2, and type 3 responses, they may be targeted to critically enhance or block immune responses early during vaccination, immunotherapy, and inflammatory pathology. Toward this goal, it is imperative that the fundamental molecular signals that regulate ILC diversity and commitment are defined comprehensively. Although ILC-specific targets have not yet been identified, the activation pathways and effector molecules they share with T cells can be targeted early in the immune response. For example, inhibitors of RORγt have been identified primarily to block T_H17-mediated inflammatory pathology, but these inhibitors obviously can be used to block ILC3s as well (*117*, *118*). Similarly, RORα, a nuclear hormone receptor similar to RORγt, may be targeted to modulate ILC2s. Agonists for RORγt and RORα may also be developed to enhance the generation and activity of ILC3s and ILC2s in order to enhance defense against mucosal pathogens or to modulate fat-induced metabolic diseases and allergy. A similar strategy may be followed to modulate the activity of NK cells and ILC1s by targeting T-bet.

The activity of ILC2s is promoted by the arachidonic acid metabolites leukotriene D_4 (LTD_4) and prostaglandin D2 (PGD_2) through the cysteinyl leukotriene receptor 1 (CysLT1R) and the "chemoattractant receptor-homologous molecule expressed on T_H2 cells" CRTH2 (*76*), respectively, but is impaired by the arachidonic metabolites lipoxin A_4 (LXA_4) and maresin-1 (*119*). Thus, an arsenal of lipid mediators, or inhibitors of these mediators (Montelukast, a leukotriene receptor antagonist), may be developed to control the activity of ILCs. The cytokines inducing the development and activity of specific subsets of ILCs—such as IL-12, IL-25 and IL-33, or IL-1β and IL-23 for ILC1s, ILC2s, or ILC3s, respectively, as well as IL-2—may also be targeted, although the precise involvement of ILCs in specific diseases have not been determined within the multifarious effects that arise from blocking these pathways. For example, treatment with Daclizumab, an antibody targeting the IL-2Rα (CD25), of multiple sclerosis patients resulted in a decrease in the frequency of RORγt$^+$ ILCs and an increase in the numbers of NK cells that correlated with drug efficacy (*120*). In addition, Ustekinumab, an antibody directed against the p40 subunit common to IL-12 and IL-23, shows high clinical efficacy against psoriasis (*121*). Furthermore, antibodies against IL-25 and IL-33 have shown efficacy in mouse models of allergic lung inflammation (*122*, *123*), and intravenous antibody to TSLP given before allergen challenge in mild asthmatic patients improves asthma symptoms (*124*). These cytokines can also be blocked by microbial compounds. For example, the excretory/secretory products of the helminth *Heligmosomoides polygyrus* impair the activity of ILC2s in response to airways challenges with extracts of the fungal allergen *Alternaria alternata*, presumably through suppression of the initial *A. alternata*–induced IL-33 production (*125*). Alternatively, microbial compounds may be used to boost one type of ILC in order to block the other types of ILCs. Last, the effector cytokines produced by ILCs may be targeted with antibodies against IFN-γ, IL-5, and IL13, or IL-17. For example, Mepolizumab (antibody to IL-5) and Lebrikizumab (antibody to IL-13) have shown encouraging results in clinical trials against asthma (*126*, *127*).

Concluding remarks

The multiple facets of ILC development, activation, and function need to be further explored before efficient manipulation of ILCs can be achieved in the clinic. The developmental pathways leading to the different types of ILCs appear to be relatively complex, and modulation of these pathways by the microenvironment remains poorly understood, with questions remaining about ILC subset plasticity and stability. It will also be insightful to explore the development of ILCs not only during ontogeny, but also during evolution, in order to assess whether "cytotoxic" ILCs (NK cells) and "helper" ILCs (ILC1s, ILC2s, and ILC3s) served as a blueprint for the appearance of CD8$^+$ cytotoxic and CD4$^+$ T_H cells.

Much remains to be uncovered on the activation and function of ILCs. We propose that ILCs promptly translate signals produced by infected or injured tissues into effector cytokines that activate and regulate local innate and adaptive effector functions. Signals produced by the tissues activating ILCs include cytokines, and possibly also stress ligands and microbial compounds. In terms of function, ILCs and T cells produce similar sets of effector cytokines; however, the hallmark of ILCs is prompt and antigen-independent activation, placing them upstream as probable orchestrators of adaptive responses. Therefore, the cross-regulation of ILCs and T cells, involving DCs as a central platform of information exchange, needs to be deciphered by using new mouse models that allow targeting each cell type individually. Furthermore, a role for ILCs beyond immunity, such as in the regulation of fat metabolism, needs to be unravelled in order to understand the integration of the immune system in host physiology.

Such accumulated knowledge should lead to a new type of immunotherapies based on the manipulation of ILCs. Because ILCs appear to play a major role in adjusting the developing immune response to the original insult, the manipulation of ILCs should allow the optimal shaping of immune responses in prevention and therapy. In the context of immunopathology, the manipulation of ILCs may allow blocking the development of detrimental types of immune responses.

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ACKNOWLEDGMENTS

G.E. is supported by grants from the Institut Pasteur, the Agence Nationale de la Recherche (ANR), and the Pasteur-Weizmann Council. M.C. is supported by grants from the U.S. National Institutes of Health (1U01AI095542, R01DE021255, and R21CA16719). J.P.D. is supported by grants from the Institut Pasteur, Inserm, La Ligue National Contre le Cancer, and the ANR. A.N.J.M. is supported by the UK Medical Research Council (MRC) and the Wellcome Trust.

10.1126/science.aaa6566

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Innate lymphoid cells: A new paradigm in immunology
Gérard Eberl, Marco Colonna, James P. Di Santo and Andrew N. J. McKenzie (May 21, 2015)
Science **348** (6237), . [doi: 10.1126/science.aaa6566]

Editor's Summary

Cells acting at the intersection of immunity

For years, scientists divided the immune system into two arms: innate and adaptive. The cell types involved in the two arms differ in specificity and in how quickly they respond to infections. More recently, immunologists discovered a family of immune cells termed "innate lymphoid cells," which straddle these two arms. Eberl *et al.* review current understanding of innate lymphoid cells. Like innate immune cells, they respond to infection quickly and do not express antigen receptors; however, they secrete a similar suite of inflammatory mediators as T lymphocytes. Better understanding of the processes regulating these cells may allow for their therapeutic manipulation.

Science, this issue 10.1126/science.aaa6566

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