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Taming the Beast within: Regulation of Innate Lymphoid Cell Homeostasis and Function

Wei Xu and James P. Di Santo

Although substantial parallels have been made between transcription factor regulation of cytokine production by innate lymphoid cell (ILC) and Th cell subsets, we are still learning how ILC subsets are regulated during immune responses. Critical factors that promote ILC development and stimulate their effector functions have been identified, but mechanisms that control their homeostasis and downregulate their cytokine secretion remain poorly understood. In this review, we consider some of the potential positive and negative regulators of ILC homeostasis and function in physiological and pathological conditions. The Journal of Immunology, 2013, 191: 4489–4496.

The recent discovery of a novel family of innate lymphoid cells (ILCs) has drawn new attention to the early events in innate immune responses and their effects on the generation of adaptive immunity. ILCs are important sources of cytokines, which promote immune responses to infections, orchestrate lymphoid organogenesis, and facilitate epithelial tissue remodeling. Based on their phenotype and functional characteristics, ILCs are classified into three groups (1, 2). Group 1 ILCs (ILC1s) include conventional NK cells and a newly identified innate cell population that lacks most NK cell functional characteristics, ILCs are classified into three groups (1, 2). Group 1 ILCs (ILC1s) include conventional NK cells and a newly identified innate cell population that lacks most of the receptors found on NK cells (see below); both are potent producers of IFN-γ. Group 2 ILCs (ILC2s) secrete IL-5 and IL-13 following stimulation by IL-25 or IL-33 ("alarmin") released by damaged epithelial cells or activated myeloid cells. Group 3 ILCs (ILC3s) include lymphoid tissue inducer (LTi) cells, natural cytotoxicity receptor (NCR)γ and NCRα–retinoic acid–related orphan receptor (ROR)γt subsets that produce cytokines IL-17A and/or IL-22. Functionally, the ILC family can be considered as "innate" equivalents of T effector cells (cytotoxic CD8 T cells and differentiated CD4 Th subsets), as they secrete a similar array of cytokines and activate an analogous set of target cells. Regulation of ILC effector functions can be considered as resulting from a "balance" of activating and inhibitory signals (Fig. 1).

ILC1s. NK cells were discovered some 30 years ago owing to their ability to spontaneously eliminate tumor cell targets ("natural cytotoxicity") (3). NK cells also eliminate cells infected by viruses, intracellular pathogens, or that are "stressed" by cancer or inflammation through perforin/granzymes or the FasL/Fas pathway or by releasing cytokines such as IFN-γ that prime pathogen-infected macrophages (4). Remarkably, these same effector mechanisms are also used by CD8+ CTLs (and by a subset of CD4+ Th1 cells) of the adaptive immune system, thus identifying NK cells and CTLs as the "professional killers" of the innate and adaptive immune systems, respectively. Functional differentiation of NK cells and CD8 CTLs is regulated by the transcription factors T-bet (Tbx21) and Eomes (5, 6), resulting in the capacity to produce potent proinflammatory cytokines, including IFN-γ, TNF-α, and a variety of myeloid cell–attracting chemokines. IFN-γ secretion by CD4+ Th1 cells, CD8+ CTLs, and NK cells is potentially activated by cytokines (e.g., IL-12, IL-18), suggesting a parallel mode of functional regulation (7). Based on their similarities to CD4+ Th1 and CD8+ T cells that predominantly produce IFN-γ, NK cells have been included within the ILC1 subset (1).

Recently, novel subsets of ILC1s were identified in human mucosal sites (8, 9). A human ILC1 subset that lacks expression of conventional NK cell surface markers (such as CD56, as well as the NCRs Nkp44 and Nkp46) and cytolytic effector molecules has been identified that strongly produced IFN-γ in response to IL-12 and IL-18 and showed high-level expression of Tbx21, Cxcr3, and Ccl3, demonstrating a close resemblance to CD4+ Th1 cells. These IFN-γ–producing ILC1s were found to be present in the intestine of patients with Crohn’s disease, an illness characterized by increased levels of Th1 cytokines. Another report identified a subset of NK receptor–expressing ILC1s in mucosal epithelium (9). These Nkp44+CD103+ ILCs also express transcription factor T-bet and Eomes and can secrete large amounts of IFN-γ, CCL4, and TNF-α in response to IL-12 and IL-15. Owing to their selective expression of integrins and CD103, these ILC1s were proposed to be the innate counterparts of tissue-
resistant memory CD8⁺ T cells. Whether these ILC1 subsets exist in other species or at other nonmucosal sites is not known.

ILC2s. Recently, several groups have described innate cells that rapidly produced “Th2-like” cytokines, including IL-5 and IL-13 (10–12). These cell subsets were initially referred to as “natural helper cells,” “nuocytes,” or “innate helper 2 cells” but have recently been renamed ILC2s (1). ILC2s are found systemically where they initiate Th2 responses during helminth and viral infections or in the context of inflammatory diseases, such as allergic asthma. ILC2s express receptors for IL-25 (IL-17RB), for IL-33 (T1/ST2), and for thymic stromal lymphopoietin (TSLP). Stimulation of ILC2s with IL-25, IL-33, or TSLP triggers production of IL-5 and IL-13 (the feature cytokines of type 2 immunity) as well as IL-6, IL-10, and GM-CSF (1, 2). Because ILC2s coexpress receptors for IL-25, IL-33, and TSLP, ILC2s may exert their function through different signaling pathways depending on microenvironment and the relative levels of these cytokines in tissues.

Development and type 2 cytokine secretion by ILC2s are regulated by Gata3 (13–15). NPATCH, Tcf7, and Rora are essential transcriptional regulators of ILC2 development via Gata3-dependent and -independent mechanisms (16, 17). ILC2s provide essential innate sources of IL-5 and IL-13 during helminth infections (such as Nippostrongylus brasiliensis) and are sufficient to mediate eosinophilia and worm clearance upon activation by exogenous cytokines IL-25 and IL-33 (12, 18). In the context of pulmonary viral infections, ILC2s produce amphiregulin (19) that promotes tissue repair. In contrast to these protective functions of ILC2s, overproduction of IL-5 and IL-13 by ILC2s may play a role in increased airway hyperreactivity that characterizes allergic asthma (20). Thus, ILC2s have both beneficial and disease-provoking characteristics (a recurrent theme in ILC biology). The mechanisms that determine the protective versus pathological properties of ILC2s remain to be determined but could provide a means to boost immune responses and avoid collateral tissue damage.

ILC3s. LTi cells represent the founding member of the ILC3s. LTi cells initiate organogenesis of lymph nodes and Peyer’s patches during fetal life by interacting with the local mesenchymal cells (21, 22). Small numbers of LTi-like cells have the capacity to produce IL-22 and/or IL-17A (24, 25) and thus resemble innate versions of RORγt-dependent Th17 cells. Recently, several groups have identified RORγt⁺ innate cells that express NCRs, produce IL-22, and are highly enriched in the intestinal mucosa (25–29). Similar to LTi cells, these NCR⁺ ILC3s require the transcription factor Rorc for their development. Additionally, the aryl hydrocarbon receptor was shown to be necessary for the optimal expression of IL-22 by distinct ILC3 subsets (30–32). IL-17A and IL-22 have major effects on epithelial cells of many tissues and are crucial in defense against extracellular pathogens such as Salmonella, Citrobacter, and Klebsiella (26, 33–35). It has also been suggested that expression of IL-17A promotes the inflammatory phenotype in some autoimmune diseases (36). Although IL-22 is generally considered as tissue-protective or reparative, overexpression of IL-22 in some cases maybe associated with disease progression, including tumor transformation (37–39).

Several cell surface markers (CD4, c-Kit, CCR6, MHC class II) and transcription factors (T-bet) identify subsets of RORγt⁺ ILC3s with different tissue localizations and functional attributes (40–44). For example, CD4⁺CD3⁺IL-7Rα⁺ LTi cells lack NCR and T-bet expression but are CCR6⁺, collect in intestinal isolated lymphoid follicles, and coexpress IL-17A and IL-22 (40). Other ILC3 subsets include T-bet⁺...
Do ILCs demonstrate plasticity in their effector functions?

Many studies have demonstrated that phenotypic and functional properties of Th cells are not “fixed” and can “evolve,” giving rise to a T cells with cytokine profiles characteristic of a different Th subset under certain circumstances (46). Th cell plasticity relies on the environmental signals and the consequent activation and/or suppression of specific transcription factors. Functional plasticity has been observed in both human and mouse ILC3s (47, 48). IL-22–producing ILC3s can coexpress IFN-γ in response to cytokine stimulation (including IL-12 and IL-18 in the presence of IL-2 and IL-7). These IFN-γ–producing ILC3s retain RORγt transcripts, although at a lower level than are seen in IL-22–producing cells, and they express higher levels of T-bet. Interestingly, a study using a genetic lineage tracing (“fate mapping”) revealed that some NCR+ ILC3s can lose RORγt expression, possibly due to the deprivation of stabilizing signals from the environment (49). The reduction of RORγt expression generates a change in the cytokine production profile with an increase in IFN-γ and a decrease in IL-22. Note that these extrinsic factors that condition lymphocyte biology within a lineage-tracing model.

ILC functional plasticity may be instructed by the microenvironment to protect local tissues from pathologies. In a chronic colitis model (Tbx21−/− Rag2−/− ulcerative colitis mice), colonic ILC3s have a selective increase in IL-17A production that drives pathology (48). In contrast, Rag2−/− mice exhibit ILC3s that produce both IL-17A and IFN-γ. Because Tbx21 controls IFN-γ production in both Th17 cells and ILC3s, the inability of ILC3s to achieve a functional plasticity may explain the excessive IL-17A production. The plasticity of IFN-γ production in non–Th1 cells can be explained by the bivalent H3K4 and H3K27 modification of the Tbx21 gene in other Th cell subsets (50). Whether similar epigenetic modifications of lineage-specific transcription factors or cytokine genes also exist in the ILC subsets needs to be assessed by further studies.

Is there a dedicated regulatory ILC subset?

Uncontrolled immune responses with excessive production of proinflammatory cytokines can be deleterious to the hosts. Maintenance of immune homeostasis may be imposed by limiting resources (regulation of the availability of cytokines or other activating signals, thereby promoting competition) or through dominant suppressive mechanisms (production of soluble or cell-associated inhibitory soluble factors that can transduce negative signals). In adaptive immunity, dedicated subsets of regulatory T cells (Tregs), including “natural” or induced CD4+ Tregs, Tr1 cells, and subsets of CD8+ T cells, have been described that are essential for lymphocyte homeostasis and keep the adaptive immune system in check.

The transcription factor Foxp3 is a master regulator of CD4+ Treg fate and its expression correlates with the ability of Tregs to suppress T cell activation. Do ILC equivalents of Tregs exist? There have been no reports of a Foxp3–expressing ILC population, but regulatory Foxp3+ ILCs may use alternative (Foxp3-independent) pathways to generate immune suppression. Tregs modulate immune responses through release of inhibitory cytokines, including IL-10, TGF-β, and IL-35 (51, 52). Both IL-10 deficiency and TGF-β deficiency can lead to inflammatory disease in various organ systems (53, 54). ILCs expressing IL-10, TGF-β, and perhaps IL-35 could represent potential regulatory ILCs.

Disruption of Foxp3 in mice results in impaired generation and function of Tregs, thus leading to deadly lymphoproliferative disorders that are characterized by hyperactivation of adaptive immunity. To what extent Treg deficiency also results in ILC dysregulation is not known. Generalized inflammation may indirectly promote ILC recruitment and activation. Alternatively, Tregs may directly suppress ILCs. Recent reports have demonstrated that Tregs regulate NK cell subset development through modulation of soluble factors (IL-2) that can stimulate early NK cell progenitors (55, 56). Treg production of TGF-β and IL-10 (and other factors) may directly influence ILC subset activation, thereby providing a direct control of ILC homeostasis and effector function (see below).

Factors regulating ILC homeostasis and function

The cytokine milieu comprises those soluble and cell-associated factors that are available within tissues or in the circulation, and it represents one of the most important extrinsic factors that condition lymphocyte biology within diverse microenvironments. The availability, composition, and levels of factors within the cytokine milieu have profound effects on ILC differentiation. ILCs are derived from common lymphoid progenitors in the bone marrow where stromal cells produce essential cytokines for their development and survival, an important one being IL-7. In the peripheral lymphoid organs or mucosal sites, ILCs may undergo further maturation and activation due to cytokines that promote ILC effector functions (IL-12, IL-23, IL-25, IL-33), whereas later phases of the response may be dominated by “suppressive” cytokines (TGF-β, IL-10) that downregulate ILC function (Fig. 2). Moreover, mucosal sites (skin, lung, intestine, and colon) harbor unique commensal microbial communities that likely interact with the epithelial barriers and trigger site-specific cytokines and chemokine profiles. As such, these different niches may influence the composition, magnitude, and quality of the ILC immune responses.

Common cytokine receptor γ-chain family of cytokines. Development of all ILC subsets is facilitated by cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) that share the common cytokine receptor γ-chain in their receptor complexes. These cytokines regulate the development and homeostasis of innate and adaptive lymphocytes as well as their functions during immune responses. Mice lacking the common γ-chain are severely deficient in all known ILC subsets, and it has been shown that IL-7 is necessary for generation of group 2 and 3 ILCs, whereas IL-15 dominantly promotes NK cell development (1). Because roles for IL-2, IL-7, and IL-15 in T, B, and
NK cell biology has been extensively reviewed (57), we will focus on the role for these cytokines in regulating ILC2 and ILC3 homeostasis and function.

**IL-2.** Murine ILC2s express IL-2Rα (CD25) and IL-2 can promote the expansion of ILC2s in in vitro combination with IL-25 or IL-33 (11). It was suggested that the maintenance of ILC2 numbers and cytokine production requires the presence of T cells, as *N. brasiliensis* infection in *Rag2−/−* mice failed to sustain the ILC2 population or the levels of IL-5 and IL-13 production (10). Delivery of exogenous IL-2 into *Rag2−/−* mice was sufficient to overcome this defect, suggesting that IL-2 provided by T cells or NKT cells may be critical for ILC2 homeostasis (58). Whereas subsets of splenic ILC3s express CD25, these cells were unaffected in mice deficient in IL-2 signaling, ruling out a critical role for IL-2 in ILC3 development (59). It remains possible that IL-2 might modify the functional capacity of certain ILC3 subsets.

**IL-7 family: IL-7 and TSLP.** IL-7 signals through IL-7R composed of IL-7Rα (CD127) and the common γ-chain. IL-7Rα is also used by TSLP, a paralog of IL-7 that signals in a common γ-chain–independent fashion. Early stages of lymphopoiesis require IL-7 for the maintenance of IL-7Rα+ multipotent progenitor cells, including common lymphoid progenitors that give rise to all ILC subsets in addition to T and B cells. ILC2 and ILC3 are IL-7Rα+ and these ILC subsets are strongly reduced in the absence of IL-7 (2). During both fetal and adult life, IL-7 signaling regulates the size of the LTi cell pool by promoting cell survival (60–62). In a similar fashion, IL-7 may sustain the homeostasis of ILC2 and NCR+ ILC3. In adults, IL-7 is proposed to stabilize RORγt expression in ILC3, although the underlying mechanism remains obscure (49). Further studies using conditional IL-7R ablation or tissue-specific deletion of IL-7 may provide better insights into the role for IL-7 signaling in mature ILC homeostasis and function.

TSLP signals via the TSLP receptor complexed with the IL-7Rα-chain. Overexpression of TSLP restored T and B cell differentiation as well as lymph node development in IL-7−/− mice (63). Whether TSLP can compensate for IL-7 in promoting generation of ILC2 and other ILC3 subsets from early lymphoid progenitors is not known. TSLP is constitutively expressed in intestinal epithelial cells (64). Deficiency in TSLP signaling results in a reduction of LTi-like cells but not IL-22–producing ILC3 in the intestine, whereas the numbers of both ILC3 subsets are decreased in IL-7−/− mice, which suggests that these two cytokines have both redundant and distinct roles in ILC3 biology (49).

Interestingly, transgenic overexpression of TSLP was associated with allergic inflammatory diseases such as atopic dermatitis and asthma (65), whereas disruption of TSLP signaling led to defective expression of pathogen-specific Th2 cytokine responses and a failure to control infection by *Trichuris* (64). One explanation for this is that TSLP can trigger rapid IL-13 secretion and promote significant ILC2 expansion. TSLP-mediated production of IL-13 is STAT5+ and GATA3-dependent and can be further enhanced by costimulation with IL-33 (66). It was recently shown that skin-associated ILC2s are dependent on TSLP but not IL-33 or IL-25 signaling for their secretion of Th2 cytokines (67). It is possible that TSLP signaling can promote Th2 responses in distinct ILC2 subsets in a tissue-specific fashion.

**IL-1 family: IL-1β, IL-18, and IL-33.** The IL-1 family of cytokines includes 11 members (IL-1α, IL-1β, IL-1Rα, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, and IL-38) that have potent effects on hematopoietic and nonhematopoietic cells (reviewed in Ref. 68). IL-1 family cytokines signal through specific receptors containing a Toll/IL-1R homology domain that leads to the activation of transcription factors such as NF-kB and AP-1 through a MyD88/TRAF6 pathway. Some IL-1 family cytokines...
IL-25 (IL-17E) belongs to the IL-17 cytokine family by inflammasome-induced caspase-1 to become biologically active. IL-33, in contrast, is translated as a fully biologically active protein and can be processed into a more active form by specific enzymes in neutrophils, but it is degraded and inactivated by caspases and other extracellular proteases (69). IL-1 was initially described as a cofactor for T cell activation that synergized with other signals to activate cytokine secretion (70). A similar biology may exist for the effects of some IL-1 family cytokines that stimulate ILCs. Concerning this family of soluble factors, the cytokines IL-1α, IL-1β, IL-18, and IL-33 have been shown to have effects on distinct ILC subsets.

IL-1β is a member of the IL-1 cytokines that also include IL-1α and the soluble IL-1Ra that antagonizes IL-1 responses. IL-1α and IL-1β have similar effects on multiple cell types and promote sterile inflammation via activation of macrophages, neutrophils, NK cells, T cells, and stromal fibroblasts through chemokines, proinflammatory cytokines, and enzymes involved in the production of prostaglandins or NO. Importantly, IL-1β plays an inductive role in Th17 responses and can potently stimulate differentiated Th17 cells (70). The IL-1R is expressed by RORγt+ ILC3s in mice and humans and can act in concert with IL-23 to stimulate RORγt+ ILC3s for production of IL-17A and IL-22 (47).

IL-18 was first discovered as an IFN-γ-inducing factor that promoted cytokine secretion from T cells (71). IL-18 acts alone in this respect, but it can also potently synergize with IL-12 to boost IFN-γ production from Th1 cells, NK cells, and human ILC1s (8). Moreover, IL-18 appears to be required for functional “priming” of NK cells (72). Whether IL-18 has a regulatory role in other ILC subsets is not known.

IL-33 is a proinflammatory molecule that is released by necrotic cells after tissue injury (73). Administration of IL-33 in mice triggers eosinophil-associated inflammation in the lung and gut that requires IL-13 production but is independent of adaptive lymphocytes, mast cells, basophils, or NK cells (74). It was later shown that ILC2s are responsible for this IL-33–mediated eosinophilia via ILC2 expansion/accumulation and cytokine secretion. It has also been demonstrated that IL-33 synergizes with IL-7 for Notch-induced development of ILC2s from common lymphoid progenitors in vitro (17).

IL-25. IL-25 (IL-17E) belongs to the IL-17 cytokine family with six members in total, IL-17A–F. IL-25 was shown to play an important role in the development of Th2-mediated allergic inflammation by regulating CD4+ T cells and ILCs (75). IL-25 can trigger ILC2s for rapid clearance of N. brasiliensis acute infection but also is implicated in the induction of acute lung inflammation during allergy (75). It has been shown that both IL-25 and IL-33 treatments in Rag2−/− mice are sufficient to bypass the requirement for adaptive immunity during worm expulsion (12). However, IL-25 and IL-33 may stimulate ILC2s to different states of activation as defined by the expression of certain surface markers (CD25, Sca1) (75). IL-25–stimulated ILC2s produce other cytokines such as IL-9 that contribute to the development of immunity and inflammation in the airway.

Interestingly, IL-25 appears capable of regulating IL-22 responses from ILC3s. One model proposes that commensal microbiota stimulate IL-25 expression that can act via dendritic cells that subsequently reduce ILC3-derived IL-22 (29). In the absence of IL-25, basal IL-22 levels are increased. This effect is contact-dependent, although the cell–cell interactions are yet to be defined.

IL-12 and IL-23. IL-12 and IL-23 are proinflammatory cytokines that share structural and functional activities. IL-12 is a heterodimeric cytokine comprised of the p35 and p40 subunits, whereas IL-23 has a unique p19 subunit but uses the same p40 subunit. Both IL-12 and IL-23 are released by APCs, mainly the CD11c+ dendritic cells and macrophages in response to microbial stimuli or stress (76). IL-23 is constitutively expressed in part of the intestine (77) and stimulates secretion of Th17 cytokines (IL-17A, IL-17F, IL-22) from T cells and non–T cells, including ILC3. In contrast, IL-12 directs differentiation of Th1 T cells and promotes IFN-γ production from T cells, NK cells, and ILC1s through T-bet (5, 6, 8, 41, 47). IL-23 induces secretion of IL-17/IL-22/IFN-γ in both LTi/LTl-like cells and NCR+ ILC3s that are associated with IL-23–driven innate intestinal inflammation (24–27, 29, 42, 78). In Th17 cells, IL-23 functions to promote cell proliferation and maintain their phenotype (36). Whether IL-23 is responsible for ILC3 expansion/maintenance of ILC3s remains to be determined. TGF-β. More than 40 members of the TGFs have been identified and the TGF-β subfamily has 6 members, of which TGF-β1 is best characterized for its potent effects on the immune system. TGFs are produced as latent proteins that require maturation to achieve full activity. Active TGF-β binds broadly expressed heterodimeric receptors that signal through SMAD adaptors to regulate gene expression (79). TGF-β1–deficient mice manifest a multiorgan infiltrative disease that occurs early in life and results is death within 3–4 wk (80). The precise mechanisms responsible for the demise of TGF-β1–deficient mice are only partly understood. One clear effect is the absence of Tregs, as TGF-β1 can potently prime the differentiation of this subset from naive T cell precursors. As such, the widespread T cell activation that accompanies TGF-β1 deficiency in some ways resembles that of Treg deficiency following ablation of Foxp3. Moreover, much of the disease phenotype in TGF-β1 knockout mice can be recapitulated by overexpression of a dominant-negative TGF-βRII transgene in the T cell lineage (81). Thus, TGF-β production by Tregs (Tr1) has important consequences for immune homeostasis of adaptive lymphocytes.

The role for TGF-β in regulating innate lymphocytes has not been fully explored. Overexpression of dominant-negative TGF-βRII under the CD11c promoter unexpectedly resulted in the expansion of an activated NK cell population that strongly produced IFN-γ. This was shown to be due to low-level expression of CD11c in the NK lineage, generating a blockade of TGF-β signaling in mature NK cells. This result demonstrated that TGF-β plays a suppressive role in NK cell homeostasis (82). Whether other ILCs are under negative regulation by TGF-β remains to be shown, but if this is the case, one can also expect that some aspects of the disease phenotype in TGF-β–deficient mice may also be secondary to hyperactivation of various ILC subsets.

IL-10. IL-10 is a broadly immunosuppressive cytokine, inhibiting production and release of inflammatory cytokines by macrophages and monocytes, especially at mucosal sites. IL-10 is produced by most cells of the immune system.
(dendritic cells, macrophages, T and B cells) and triggers effects through a receptor comprised of IL-10Rα- and IL-10Rβ-chains (83). IL-10 plays an important regulatory role in Th cell differentiation, acting to inhibit IL-12 production and thereby reduce Th1 development and IFN-γ production. Additionally, IL-10 may induce “tolerogenic” dendritic cells that produce IL-1R antagonist, TGF-β, and, in humans, immunosuppressive HLA-G (84). Loss of IL-10 signaling leads to systemic inflammation and an intestinal wasting syndrome that appears triggered by commensal bacteria (53). During viral infections and chronic stimulation by parasites, IL-10 can be paradoxically induced in Th1 and in NK cells and appears to play an important role in limiting inflammation (85, 86). Tregs and Tr1 cells are known producers of IL-10 that have been implicated in the maintenance of peripheral T cell tolerance (83, 87).

IL-10R is broadly expressed in hematopoietic cells and thus may have a role in downregulating ILC responses in tissues (Fig. 2). This is achieved through suppression of proliferation (TH17 cells), cytokine production (TH1 cells), and, by promoting survival of Foxp3+ Tregs. Conditional deletion of IL-10R in ILC subsets should provide a means to assess the importance of this immunosuppressive pathway in ILC activation and homeostasis.

ILC regulation through inhibitory cell surface receptors. NK cells are well characterized for MHC class I–specific inhibitory receptors that can recruit protein tyrosine phosphatases (SHP1). These receptors act as negative regulators to intracellular signaling cascades and counterbalance tonic signals through activating receptors. Other inhibitory receptors that bind several ligands carry ITIM motifs in their cytoplasmic domains that function in a similar fashion (4). The KLRG-1 receptor is one example and is upregulated during NK cell activation in the context of viral infection. Interestingly, KLRG-1 is also detected on a subset of tissue-resident ILC2s (13), suggesting a similar mechanism during ILC2 activation. Whether ligand engagement of KLRG-1 is critical for ILC function is not clear, but the expression of ITIM-associated receptors within the different ILC subsets suggests that receptor-bound inhibitory phosphatases may also play a role in the regulation of ILC effector functions.

Conclusions

With the identification and characterization of new ILC subsets it becomes apparent that ILCs are a complex family of innate cells that have a diverse range of functions in innate immunity. Following infection or inflammation, ILCs rapidly provide critical early cytokine production prior to the development of adaptive Th cell subsets. ILCs and T cell subsets share many functional attributes that can be explained, at least partially, by their common signals for generation, differentiation, and activation. A similar analogy may extend to ILC regulation, whereby the mechanisms known to regulate Th responses may come into play. Owing to these functional parallels, ILCs can generate a required cytokine environment that is coherent with the one produced by Th cells, providing a continuous immune reaction. ILCs may persist in tissues to promote repair or remodeling that occurs under steady-state conditions. Beyond their protective roles, ILCs may also be involved in the autoimmune diseases where dysregulated cytokine production may provoke or exacerbate disease pathologies. A better understanding of the factors that positively and negatively regulate ILC homeostasis and function could have an impact on vaccine development and the treatment of autoimmune diseases.

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References


