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Review Series

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The balance of power: innate lymphoid cells in tissue inflammation and repair

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Over the last ten years, immunologists have recognized the central importance of an emerging group of innate lymphoid cells (ILCs) in health and disease. Characterization of these cells has provided a molecular definition of ILCs and their tissue-specific functions. Although the lineage-defining transcription factors, cytokine production, and nomenclature parallel those of T helper cells, ILCs do not require adaptive immune programming. Both environmental and host-derived signals shape the function of these evolutionarily ancient cells, which provide pathogen protection and promote tissue restoration. As such, ILCs function as a double-edged sword, balancing the inflammatory and reparative responses that arise during injury and disease. This Review highlights our recent understanding of tissue-resident ILCs and the signals that regulate their contribution to inflammation and tissue repair in health and disease.

Introduction

Recent advances in cellular and molecular immunology have revealed the existence of a broad class of innate lymphoid cells (ILCs). ILCs are evolutionarily ancient cells, present in common ancestors of both jawless and jawed vertebrates, which endow the primordial immune system with the capacity for rapid defense against pathogens (1, 2). An array of ILC effectors have emerged to balance the collateral damage from sustained inflammation and to promote tissue restoration for overall organismal protection. Similarly to conventional T helper cells, ILCs can be classified by their lineage-defining transcription factors and effector cytokines; however, in contrast to T helper cells, ILCs do not require conventional adaptive programming. Instead, as primarily tissue-resident cells, environmental and organ-specific cues shape their effector functions and spatial location, enabling rapid modulation of host pathophysiology. This Review highlights the regulatory factors that drive tissue homeostasis of ILCs as they balance pathogen defense, tissue repair, and chronic inflammation. A better understanding of this complex biology will help address the diagnostic and therapeutic potential of ILCs in health and disease.

ILC development and subset function

All ILC development requires signaling through the common γ chain of the IL-2 receptor as well as inhibitor of DNA 2-dependent (ID2-dependent) differentiation from a common lymphoid progenitor (3, 4). Functionally, ILCs can be divided into cytolytic and noncytolytic ILCs. Cytolytic ILCs, also referred to as conventional NK (cNK) cells, release cytolytic effector molecules including perforin and granzyme B, which can kill tumor or virus-infected

tissue. In contrast to cNKs, noncytolytic or “helper” ILCs arise from a GATA-3-dependent common helper innate lymphoid precursor (CHILP) (5, 6). Helper ILCs are generally classified into subgroups according to their cytokine and transcription factor expression, which parallels T helper cell subsets: group 1 (ILC1), group 2 (ILC2), and group 3 (ILC3) (7, 8).

ILC1s. ILC1s are a phenotypically heterogeneous group of tissue-resident cells located in the intestine, liver, uterus, and salivary gland (9–11). These cells are characterized by the production of type 1 cytokines, including IFN- γ , and require T-BET expression. In contrast to cytotoxic cNKs, ILC1s are tissue-resident cells that do not require the T-box transcription factor eomesodermin (EOMES) for development and lack the MHC I-specific inhibitory receptors that guide cNK cytolytic function (11). Additional tissue- and organ-specific features of ILC1s also exist; for example, intraepithelial ILC1s reside in mucosal tissue and develop independently of IL-15, but require both EOMES and T-BET (12). Moreover, tissue-specific cues, including TGF- β , may regulate plasticity between cNKs and TNF- α -producing ILC1s, illustrating the diversity and heterogeneity of ILC1s (13, 14).

ILC2s. ILC2s are systemically dispersed in lymphoid and non-lymphoid tissues, including the brain, heart, lung, kidney, skin, intestine, and adipose tissue, where they play a central role in protection from parasitic infection, allergic inflammation, and local tissue repair (15–17). ILCs are characterized by the production of the type 2 cytokines IL-5 and IL-13, and the transcription factor GATA-3 is critical for ILC2 development in both mice and humans (5, 18). ILC2s express receptors that respond to secreted factors in the epithelium, including IL-25, IL-33, TSLP, and prostaglandin D₂ (CRT_h2). ILC2s play a key role in controlling both eosinophil homeostasis and allergic response through constitutive and inducible production of IL-13 in the intestine and lung, respectively (16). In adipose tissue, IL-25 and IL-33 trigger infiltration of ILC2s and subsequent regulation of IL-13-dependent inflammation (19), as well as “beiging” of adipose tissue (20) to increase energy consumption and limit obesity.

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ILC3s. ILC3s are most abundant at mucosal barrier surfaces. They are characterized by their expression and dependence on the transcription factor ROR γ t (7, 21). Lymphoid tissue inducer (LTi) cells, the prototypical ILC3 subtype, are critical for lymph node and Peyer's patch organogenesis (22). In addition to mucosal lymphoid structure development, LTi cells reorganize lymphoid tissue following infection (23) and promote adaptive barrier immunity in adult organisms (24, 25). Although LTi cells were discovered decades ago, more recent studies have revealed the presence of mucosal tissue ILCs that produce the Th17-related cytokines IL-22 and IL-17 in response to IL-1 β and IL-23 stimulation (26, 27). The commensal microbiota plays a key role in shaping the function of these cells during homeostasis and during intestinal inflammation (28, 29). These tissue-resident ILC3s can be further subdivided into CCR6 $^{+}$ LTi-like ILC3s and NCR $^{+}$ T-BET $^{+}$ ILC3s (30, 31).

Plasticity between ILC subsets provides another level of immune regulation and can be shaped by tissue-dependent cues (32). Fate-mapping studies have revealed that T-BET $^{+}$ ILC3s maintain functional plasticity with ILC1s, as T-BET expression downregulates ROR γ t, leading to an inflammatory phenotype associated with IFN- γ production (30, 33). Evidence of trans-differentiation from ILC3 to ILC1 as well as ILC2 to ILC1 has also been reported in Crohn's disease and chronic obstructive pulmonary disease (10, 34, 35). In addition, a potentially separate subset of regulatory ILCs producing IL-10 have been reported in both mouse and human (36, 37). Many of these ILC subsets and precursors also exist in circulating blood and secondary lymphoid tissue of humans (38, 39). Given the role for sustained cytokine exposure in driving this plasticity in vitro (40), it is likely that tissue-specific factors in both autoimmune and infectious disease shape ILC function locally.

Tissue-specific regulation of ILCs

Tissue-specific cues shape the function of adult ILCs in situ. ILC precursors seed the fetal intestine and possess the capacity to develop into all ILC lineages (41, 42). Genetic and parabiosis experiments have revealed evidence for the local proliferation of tissue-resident ILCs (43, 44). In particular, factors in the local microenvironment (including interferon and IL-27) and availability of IL-2 shape the development and function of ILC2s during helminth challenge. This tissue maturation of ILCs imprints subsets with distinct patterns of activating receptors, which enable them to respond to tissue-specific perturbations, including injury and tumor (45, 46). While these studies provide support for a tissue-resident ILC, the migratory capacity of ILCs remains a matter of debate (47), as the imprinted tissue homing of ILCs has been reported in both the skin and the gut (48, 49). Mechanistically, retinoic acid (RA) drives $\alpha_4\beta_7$ - and CCR9-dependent homing of ILC1s and ILC3s, whereas ILC2s acquire these receptors in the bone marrow (49). Tissue-resident macrophages in the gut express CXCL16, which actively retains and enables spatial colocalization with CXCR6 $^{+}$ NKp46 $^{+}$ ILC3s in the mucosal tissue (50). Transcriptional analysis of tissue-resident lymphocytes revealed a role for the transcription factors HOBIT and BLIMP1 in enforcing tissue residence by repressing *Klf2*, *S1pr1*, and *Ccr7* (51), but the molecular mechanisms accounting for tissue residency in ILC subsets remain unknown. Recent studies have revealed emerging roles for

the microbial and neural-derived factors in tissue-specific regulation of ILCs.

Microbial and metabolic regulation of tissue ILC function. The commensal microbiota and their metabolites play an important role in regulating ILC numbers and function. Although LTi cells develop in the absence of microbiota, the reduced number (29) and production of IL-22 (28) by ILC3s in germ-free mice lead to an increased susceptibility to inflammation. Mucosal association and/or lymphoid tissue residence are particular features of the microbial taxa that shape intestinal ILC3 responses (52–55). ILC2s can also develop in the absence of microbiota (56). Given the overall reduction in lymphocytic cellularity in germ-free mice, the higher proportion of ILC2s can skew the overall mucosal immune response (57). In addition to changes in cellularity, microbiota can induce transcriptional and epigenetic modifications underlying plasticity. High-resolution analysis of murine ILC subsets revealed that the removal of microbial signals diminished lineage-specific methylation marks (58). Following antibiotic treatment, both mucosal ILC1s and ILC2s gain transcriptional elements associated with ILC3s. Moreover, *Il17a* was reduced across all subsets and particularly in *Tbx21*-expressing clusters of ILC3s. This emerging molecular characterization is consistent with functional reports showing the potential role for the microbiome in ILC plasticity (30, 59) and may provide insight into therapeutic targets for regulating ILC function.

Specific microbial and dietary metabolites have also emerged as critical regulators of ILC development and function. All intestinal ILCs express the aryl hydrocarbon receptor (Ahr), which binds tryptophan-derived ligands from either dietary, bacterial, or endogenous sources (60, 61). Ahr ligands are critical for the post-natal expansion of intestinal ILC3s and the subsequent formation of intestinal lymphoid follicles (60, 62, 63). Ahr ligands enable ILC3 regulation of the commensal microbiota and homeostatic immunity (64). In contrast, cell-intrinsic Ahr inhibits key ILC2 effectors (65). This Ahr dependency establishes a link between dietary nutrients and the balance between ILC2 and ILC3 immunity in the gut. Host catabolism of dietary tryptophan can tune this response by modulating the availability of these Ahr ligands and enhancing IL-22-dependent colonization resistance (66). The timing of Ahr ligand stimulation can be critical. Transient colonization of pregnant dams is sufficient to induce macrophage and ILC3 recruitment to the intestine of progeny in utero, which subsequently limits inflammation induced by infectious challenge (67). Signaling from dietary-derived Ahr ligands is, therefore, a critical factor limiting inflammation.

In a similar fashion, dietary retinoids regulate both transcription and development of tissue ILCs. RA binding to intracellular receptors induces receptor-ligand complexes that transfer to the nucleus and bind to RA response elements (68). These response elements directly regulate both *Rorc* and *Il22* in type 3 immune responses. The availability of retinoids in utero also plays a key role in regulating population size of LTi and ILC3s. The progeny of mice that lack exposure to retinoids during this crucial period show increased susceptibility to viral infection (69).

In adult mice, nutritional status also regulates ILC-mediated immunity. Overall caloric intake can directly regulate ILC2 function through the release of vasoactive intestinal peptide (VIP) (16).

VIP signaling through VIP receptor type 2 on ILC2s can induce IL-5- and IL-13-dependent eosinophil recruitment. The link between caloric intake and basal eosinophil response to allergic challenge opens a window for helminthic parasites to exploit during periods of reduced caloric intake or malnutrition. The co-occurrence of vitamin A deficiency with chronic malnutrition activates a mechanism that attempts to limit this ILC2 defect. Specifically, vitamin A deficiency promotes the accumulation of mucosal ILC2s and increased production of IL-13 (70). This response allows the host to sustain barrier immunity to helminth infection despite malnutrition. Expression of the RA receptor RXR γ and PPAR γ by ILC2s may mediate the direct sensing of vitamin A metabolites (61). ILC2 expression of additional genes involved in lipid sensing and fatty acid metabolism may similarly help to reduce barrier inflammation when dietary nutrients are limited (71).

Collectively, these pathways provide the circuitry linking nutrient availability to immune status, and this link is further imprinted by metabolic inflammatory checkpoints in ILCs (72). Next-generation sequencing platforms have revealed more extensive mechanisms for ILC subset metabolic regulation during inflammation, including mTOR and Notch signaling in ILC1s, sphingolipid and amino acid metabolism in ILC2s, and carbohydrate metabolism in ILC3s (58). Further studies are needed to functionally validate these findings.

Neuronal control of ILC immunity. The nervous system also provides critical signaling for guiding ILC functions in tissue. Neural-derived ligands for RET direct the fetal induction of lymphoid tissue organization in the intestine (73), and neuronal release of VIP links caloric intake with ILC2 immunity. These findings reflect close interaction of neural and immune pathways, which enable neuronal regulation of mucosal ILC immunity. ILC2s colocalize with cholinergic neurons in the lung and gut tissue (74–76). ILC2-specific expression of the receptor for neuromedin U (NMU) promotes ILC2 proliferation and type 2 cytokine production in synergy with IL-25. This cholinergic signal is required for eosinophil recruitment and helminth expulsion in mouse models. In addition, ILC2s colocalize with pulmonary neuroendocrine cells (PNECs) near airway branch points (77). PNEC production of calcitonin gene-related peptide (CGRP) triggers ILC2s and amplifies allergic asthma responses. This stimulatory input is balanced by adrenergic input through the β_2 -adrenergic receptor (β_2 AR), which is also highly expressed on ILC2s in intestinal tissue (78). β_2 AR signals repress ILC2 proliferation, cytokine production, and response to helminth infection. Together, these findings illustrate a critical role for neuronal signals in balancing ILC2 responses in the tissue.

In addition, neuronal signals converge on tissue ILC3s to limit inflammation. Enteric glial cells maintain spatial colocalization with ILC3s in the adult mouse intestine. Glial cells release GDNF family ligands in response to MYD88-dependent microbial signals, which subsequently trigger ILC3-autonomous RET-dependent production of IL-22 (79). This glial-ILC3 circuit limits inflammation and promotes IL-22-dependent tissue repair in mouse models of chemical and infectious colitis. Neural signals also promote ILC3-dependent tissue resolution independent of IL-22. Vagal nerve-derived acetylcholine upregulates production of the protective immunoresolvent molecule PCTRI by ILC3s (80). The same

study revealed that delayed tissue resolution following *E. coli* infection could be restored following either PCTRI or ILC3 administration. Collectively, these findings reveal neuroimmune regulation of ILC3 function in balancing tissue inflammation and restoration. The functional role for these pathways in ILCs and their ability to serve as pharmacologic targets in humans need to be assessed.

Tissue ILCs limit infection-triggered mucosal inflammation

The close proximity of tissue ILCs to barrier surfaces — in the skin, gut, and lung — not only facilitates rapid responses against invading pathogens but also limits rampant inflammation (Figure 1). Distinct mechanisms and functions are associated with each group of ILCs at the mucosal barrier.

As primary producers of mucosal IL-22, intestinal ILC3s play a critical role in protecting against gut bacterial infections (28, 81, 82). In response to IL-22, epithelial cells secrete antimicrobial peptides (REG3G, REG3B), lipocalin, and mucus to promote barrier protection against microbial damage. IL-22 can be triggered in the steady state by epithelial-adherent commensal microbiota, including segmented filamentous bacteria and adherent-invasive *E. coli* (54, 55). This homeostatic IL-22 induction, even in the absence of overt disease, helps to limit inflammatory colitis and has been correlated with mucosal healing in inflammatory bowel disease (IBD) (83, 84). Production of IBD-associated TNF-like ligand 1A (TL1A) by intestinal mononuclear phagocytes is a central regulator of ILC3 production of IL-22 and mediates protection during acute colitis (85). Similarly, ILC3-dependent protection occurs at other mucosal sites, including the lung, where commensal-dependent ILC3s protect against *Streptococcus pneumoniae* (86) and promote oropharyngeal barrier defense through IL-17 and IL-22 (87).

In addition to these direct effects, ILC3 production of IL-22 can also indirectly limit bacterial dysbiosis and inflammation at the gut barrier. The IBD-linked gene *FUT2* is strongly induced in the intestinal epithelium by IL-22. The fucosyltransferase encoded by *FUT2* is responsible for fucosylation of oligosaccharides on epithelial cells and provides a key nutrient for establishing a healthy and diverse microbiome (88–90). Mice lacking fucosyltransferase 2 have abnormal barrier function that renders the host more susceptible to enteric bacterial infections. Thus, by providing a nutrient substrate, ILC3-derived IL-22 promotes a healthy microbiota and colonization resistance to inflammation by potential pathobionts.

ILC2s play a critical role in coordinating the inflammatory response to helminth infection in the lung and gut. ILC2s secrete the type 2 cytokines IL-5 and IL-13, which promote mucus and antimicrobial peptide (RELM β) production by intestinal goblet cells, limiting parasitic infections (15, 17, 91, 92). Recently, tuft cells were identified as the primary source of intestinal IL-25, which promotes ILC2 production of IL-13 (93–95). Tuft cells expand at weaning, when the increased abundance of polysaccharides in the intestine renders the host susceptible to gut infections (96, 97). In the case of *Tritrichomonas* infection, microbe-derived succinate actively triggers chemosensory receptors on tuft cells to induce IL-25 production. This microbe/IL-25/ILC2 circuit also enables ILC2 production of IL-13, which then drives stem cell proliferation,

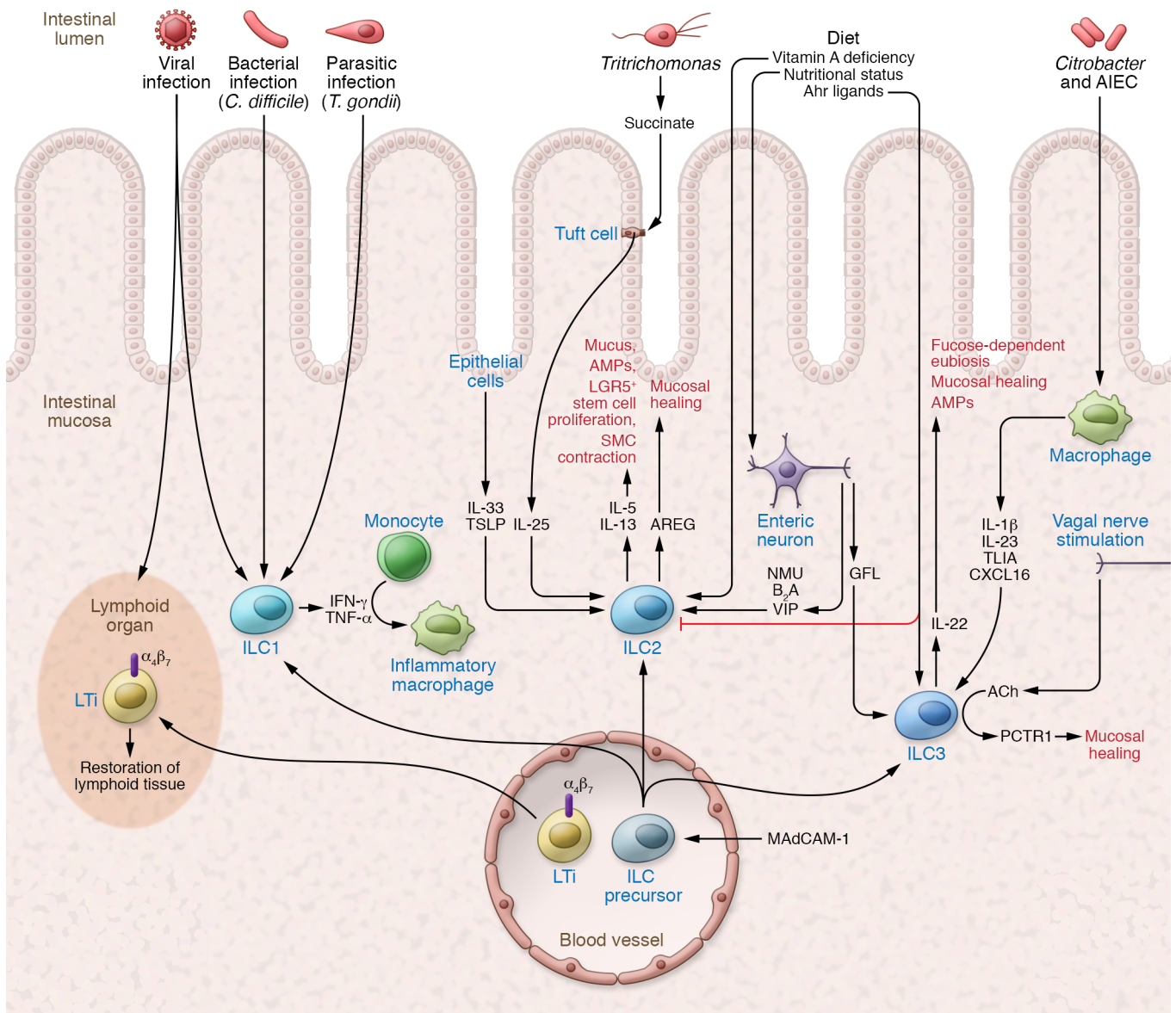


Figure 1. Tissue ILCs limit inflammation and promote restoration. ILCs serve as central mediators limiting inflammation from infectious and environmental triggers. Dietary as well as neuronal factors coordinate the response of ILC2s and ILC3s in the lamina propria. LTi cells play a critical role in restoring lymphoid tissue following viral infection. AREG, IL-22, and PCTR1 promote tissue repair and limit the impact of inflammation in the tissue. AIEC, adherent-invasive *E. coli*; GFL, GDNF family ligands; SMC, smooth muscle cell.

villous lengthening, and smooth muscle contraction to physically remove helminth infection. This “weep and sweep” response and remodeling of the intestine enforces compartmentalization and limits inflammation.

Finally, mucosal ILC1s also play a role in barrier defense, mounting a prototypical Th1-like response against pathogenic infections. During *Toxoplasma gondii* infection, ILC1s are the main producers of IFN- γ and TNF- α (11), and during intestinal *Clostridium difficile* infections, ILC1s mediate protection via T-BET and IFN- γ production (98). Tissue-resident ILC1s similarly serve an essential role in viral infection, enabling rapid production of IFN- γ to limit early viral burden (99). Furthermore, the transfer of ILC precursors into alymphoid mice promotes the recruitment of monocytes and helps limit extensive inflammation (11). Collec-

tively, these data reveal an essential role for ILCs in limiting tissue inflammation and promoting barrier defense.

ILCs promote lymphoid and mucosal tissue restoration

Tissue ILCs are also positioned to promote tissue and organ repair of both lymphoid and nonlymphoid structures (Figure 2). In addition to their role in fetal lymphoid tissue organogenesis, ILC3s are critical for restoring and maintaining tissue integrity following injury. After a viral infection, for example, LTi cells provide LT α β γ -dependent signaling in stromal cells to restore lymphoid tissue architecture (23). ILC-dependent restoration of immune tissue is also seen following radiation-induced thymic damage, wherein ILC3s promote thymic epithelial restoration via IL-22

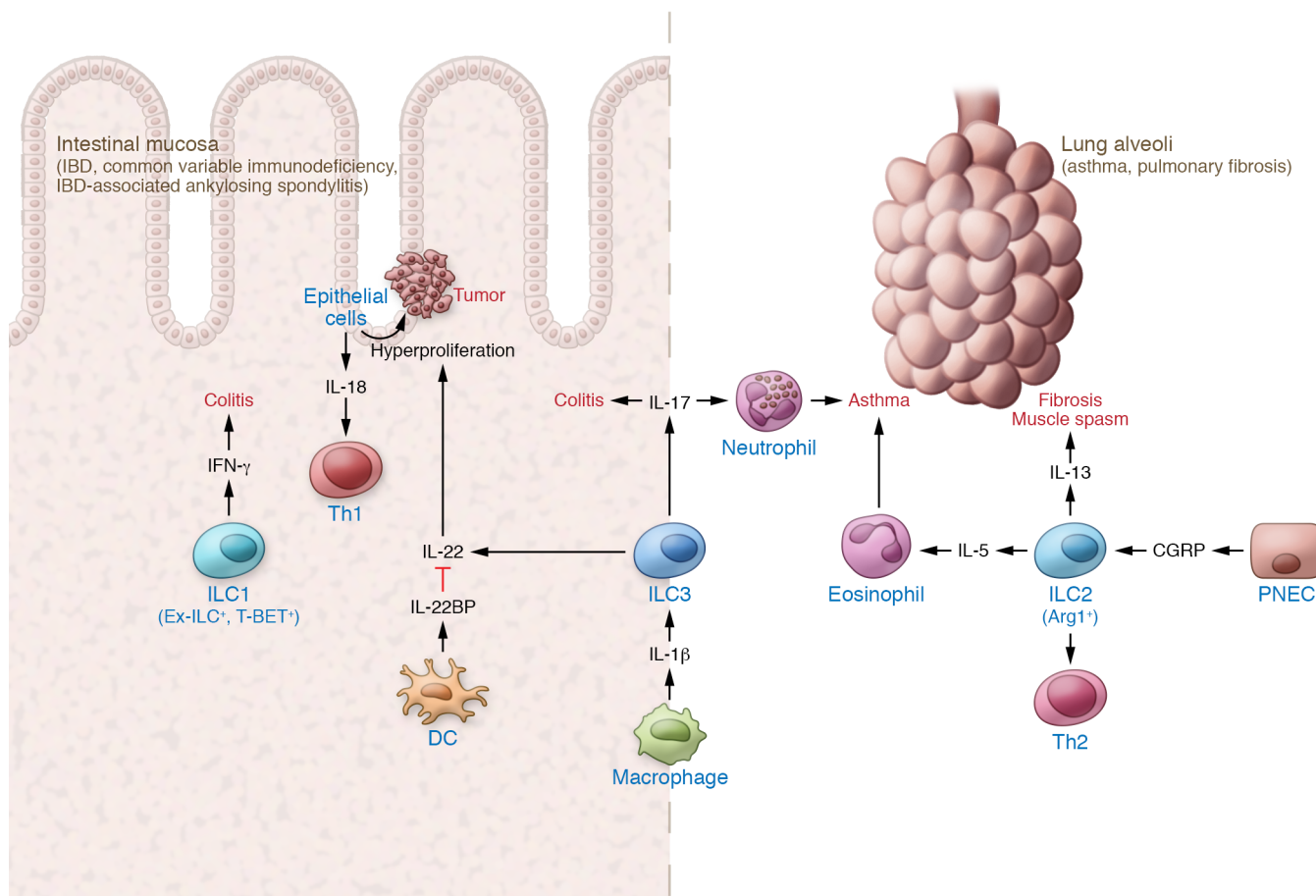


Figure 2. Tissue ILCs in chronic inflammation. Sustained activation of ILC effector functions promote inflammation. Restorative functions of IL-22 can lead to aberrant epithelial proliferation and IL-18 production to sustain an inflammatory Th1 response. ILC2 responses recruit eosinophil effectors, trigger smooth muscle contraction, and promote fibrosis.

(100). In addition, RANK-dependent signals from ILC3 support the maturation of AIRE⁺ medullary thymic epithelial cells (101). This support of lymphoid tissue repair underlies an essential role for ILC3 in restoring tissue integrity and could serve as an important therapeutic target following total-body irradiation.

Ablation therapy prior to stem cell transplantation has also helped to reveal a critical role for ILCs in nonlymphoid tissue repair and preservation of mucosal barrier function. In particular, radio-resistant ILC3s promote intestinal barrier function by supporting epithelial stem cells via production of IL-22 (102). IL-22 signaling at the intestinal crypt base triggers a STAT3-dependent antiapoptotic proliferative response in Lgr5⁺ stem cells, promoting barrier repair and function (103). Moreover, in addition to the proliferative response, IL-22 induces STAT3 transcription of genes involved in radiation-induced damage response (104). This tissue-restorative function of ILC3s is not limited to radiation-induced damage, as ILC3s also upregulate IL-22 production following chemical and infectious damage to the lung and gut (84, 105, 106). A similar effect is also seen in human IBD, where increased ILC3-derived IL-22 correlates with increased mucosal healing (84).

ILC2s also contribute to the tissue reparative response. ILC2 production of IL-13 promotes the accumulation of alternatively activated macrophages in both adipose and infected tissue wherein

they promote metabolic control and wound healing (107, 108). This process can mediate hepatic stellate cell activation in liver tissue remodeling and fibrosis (109, 110). Type 2 cytokines can also mediate tissue repair by acting directly on nonmyeloid parenchymal cells to facilitate muscle regeneration (111). Moreover, IL-13 production by ILC2s acts directly upon IL-13Rα1 on intestinal stem cells to promote β-catenin pathway-dependent renewal (112). In addition to classical type 2 cytokine production, ILC2s produce the EGF family member amphiregulin (AREG) in response to IL-33 to support tissue regeneration (56). Although ILC2s do not directly block influenza viral infection in the lung, IL-33 induction of AREG (but not IL-13) plays a crucial role in survival by restoring airway integrity (113). An analogous IL-33/ILC2/AREG pathway also plays a critical role in intestinal repair, linking mucosal ILCs with a central EGF pathway critical in supporting intestinal epithelial cell renewal (114). Autocrine production of IL-9 amplifies IL-5, IL-13, and AREG production following helminth infection in the lung and promotes tissue repair in the recovery phase of the infection (115). IL-9⁺ ILC2s are present in the joints of patients with quiescent rheumatoid arthritis, and treatment with IL-9 promotes ILC2-dependent Treg activation and resolution of inflammation in mouse models (116), but further studies are needed to explore the potential for ILC2-based therapeutic strategies.

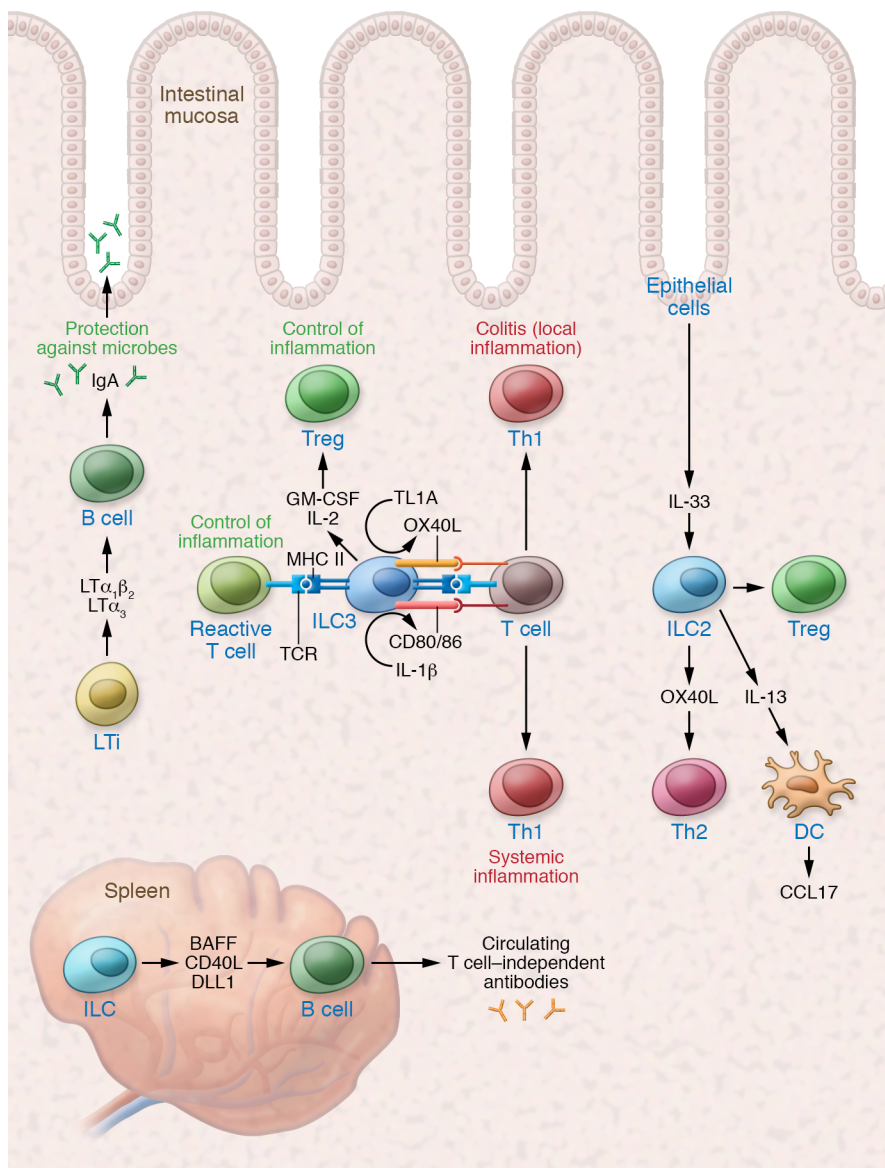


Figure 3. ILCs balance inflammatory and reparative adaptive immunity. LTI cells play a critical role in maintaining mucosal and systemic antibody production. MHC II⁺ ILC3s can limit the response of commensal-reactive T cells at steady state, but increases in TL1A or IL-1 β can promote the activation of local and systemic inflammatory T cells, respectively. IL-33 induction of OX40L by ILC2s can support tissue Th2 and Treg responses.

ILCs in chronic inflammation: a double-edged sword

The same characteristics and effector functions of tissue ILCs that limit inflammation and promote tissue repair can have pathogenic effects during chronic activation. Sustained production of IL-22 following *T. gondii* infection can trigger epithelial production of IL-18 and sustain a Th1 inflammatory loop (117), enabling collateral cross-reactive adaptive immunity against commensal microbial antigens and sustaining intestinal inflammation (118). Furthermore, chronic overproduction of IL-22 in RAG-deficient mice infected with *Helicobacter hepaticus* sustains epithelial hyperproliferation and, in the presence of the carcinogen azoxymethane, drives the development of colorectal cancer (119). The IL-22–

binding protein (IL-22BP) produced by dendritic cells provides a tissue-restricted brake for this hyperproliferative response and limits the potential for tumorigenesis in both colitis-associated cancer and mice carrying a dominant mutation in the adenomatous polyposis coli (*Apc*) gene (120). In the absence of IL-22BP, mice susceptible to epithelial proliferation have increased tumor formation. Thus, even tissue-restorative responses of ILCs need to be tightly regulated to prevent damage associated with chronic activation.

A similar dichotomy is noted for ILC2s, which are recognized as the primary producers of type 2 effector responses in asthma and pulmonary fibrosis (121). Through the production of IL-5, ILC2s play a central role in recruiting eosinophils, the main effectors of allergic inflammatory disease, to the lung. Furthermore, smooth muscle contraction and mucus production induced by IL-13 can trigger allergic asthma symptoms, including respiratory spasms and mucus plugging. Sustained production of IL-13 also contributes to increased collagen deposition, resulting in chronic fibrotic tissue damage (122, 123). Constitutive expression of TL1A mimicking chronic inflammation triggers ILC2- and IL-13-dependent small intestinal and lung tissue allergic pathology (124). Supporting the potential role for ILC2 in chronic pathology, dermal and circulating ILC2s are elevated in patients with systemic sclerosis, and cell counts correlate with dermal and pulmonary fibrosis (125). Profibrotic functions of ILC2 occur in multiple organs, including the skin (126) and the kidney (127), and increased circulating ILC2s have been reported in patients with rheumatoid arthritis (128). Thus, chronic activation of ILC2s can lead to a sustained cycle of type 2 allergic responses and fibrotic disease pathology.

Local microenvironment cues can reprogram ILCs in situ to promote inflammation. NLRP3-dependent IL-1 β production by macrophages during lung inflammation expands tissue ILC3s and increases IL-17 production, resulting in airway hyperresponsiveness (129). Similarly, in the intestine, chronic infection induces resident mononuclear phagocyte (MNP) production of IL-23, which can drive accumulation of proinflammatory ROR γ t-dependent ILCs that express both IL-17A and IFN- γ (59, 130). Transcriptional plasticity may underlie this transition in effector function. The induction of T-BET expression in ILC3s can antagonize ROR γ t expression and induce proinflammatory ex-ILC3 ILC1s that produce IFN- γ (30, 33). In human IBD, while an initial increase in ILC3 production of IL-22 correlates with mucosal healing (84), chronic colitis may reflect a transition from

tissue-repairing ILC3s to inflammatory ex-ROR γ t⁺ ILC1s (10, 131). The intestinal microenvironment and microbiota may enable the gut to serve as a portal for this transition. Intestinal biopsies from patients with IBD-associated ankylosing spondylitis showed an expansion of T-BET⁺ ILC3s (132), and the expansion of TL1A-producing CX3CR1⁺ MNPs promoted T-BET⁺ ILC3 activation in the synovial tissue (133). A parallel population of ex-ILC3s are also enriched in the synovial fluid of patients with psoriatic arthritis. Additional studies are needed in humans to define potential targetable tissue-specific cues that promote inflammatory ILCs in situ.

ILC regulation of adaptive immunity and T cell inflammation

ILCs have evolved to coordinate tissue-specific adaptive immunity (Figure 3). At barrier surfaces, they promote compartmentalization and limit tissue inflammation. For example, LT α i cells provide survival and stimulation factors for B cells (25, 134). In the intestine, ILC3 expression of several TNF superfamily members (including LT α β ₂, LT α ₃, BAFF, APRIL, and LIGHT) plays a critical role in supporting homeostatic production of intestinal IgA. ILC3-derived LT α β ₂ is required for T cell-independent IgA, while ILC3-derived LT α ₃ can compensate for the absence of T cells (25). Systemically, splenic ILCs provide BAFF, CD40L, and DLL1 to support innate-like B cell antibody production against circulating antigens (135). ILC support of humoral immunity, therefore, functions to promote compartmentalization and limit intestinal inflammation.

Tissue ILC3s can also regulate local T cell effectors. LT α i expression of OX40L and CD30L supports homeostatic persistence of tissue CD4⁺ memory T cells (136). In addition, induction of ILC3-derived IL-22 by adherent microbiota triggers epithelial cell regulation of IL-17 production by intestinal T cells (54). Under homeostatic conditions, commensal microbiota and IL-1 β also stimulate ILC3 production of GM-CSF as well as IL-2, which act via nonredundant pathways to promote intestinal Tregs (137, 138). Antigen processing and presentation by MHC II⁺ ILC3s provide a mechanism for antigen-specific regulation of commensal-specific T cells (139). While IL-1 β can trigger splenic ILC3 expression of CD80 and CD86 to support T cell activation (140), the absence of these costimulatory molecules on intestinal ILC3s limits homeostatic T cell activation (141). Under an inflammatory microenvironment such as IBD, these regulatory mechanisms are reduced (138, 141). Moreover, increased TL1A, which is highly expressed by MNPs in IBD, can induce robust expression of the costimulatory molecule OX40L on MHC II⁺ ILC3s and drive colonic T cell-dependent inflammation (85). Additional studies are needed to elucidate the contribution of ILC3s to mucosal T cell immunity and their potential role as therapeutic targets.

ILC2s similarly play a critical role in mounting a robust Th2 response (142, 143). ILC2-derived IL-13 promotes migration of tissue dendritic cells to the draining lymph node to prime Th2 immunity and elicits tissue dendritic cell production of Th2 cell-attracting chemokine CCL17 to potentiate memory Th2 responses (144). Evolving work has illustrated a potential role for tissue-derived cytokines serving as a checkpoint for type 2 immunity (145). With respect to ILC2 regulation of Th2 immunity, tissue-specific release of IL-33 during intestinal or lung inflammation can also upregulate OX40L on ILC2s, which subsequently regulates pro-

TECTIVE Th2 immunity and Treg expansion in situ (146). Collectively, these pathways enable tissue ILC-mediated control of adaptive immunity in balancing inflammatory and restorative tissue responses.

Future directions: targeting ILCs in the treatment of human disease

It is important to consider the limitation that the majority of studies examining ILC function in vivo were performed in the absence of adaptive immunity, which may impede their translatability to human pathophysiology and the generation of novel therapeutics. Potential redundancy with effector T and B cells may exist and may reflect quantitative or kinetic differences in preventing infection and limiting inflammation. For example, selective targeting of NCR⁺ ILC3s during *Citrobacter* infection showed that this subset is dispensable in the presence of T cells (147, 148). Human data, however, are limited in addressing the selective function of ILCs. Surprisingly, T cell reconstitutions in patients with severe combined immunodeficiency following hematopoietic stem cell transplantation (HSCT) revealed no clear increase in clinical disease susceptibility despite persistently fewer ILCs (149). Despite these findings, the increased susceptibility to mucosal pathogens *Candida* and *Mycobacterium* in patients with biallelic disruption of the RORC gene may illustrate subtle, yet crucial, features of mucosal immunity for which ILCs are required (150). Additional studies are required to fully capture the critical tissue ILC role in preventing infection and limiting inflammation in human diseases.

Despite these limitations, there is convincing evidence for ILC function in tissue restoration. ILC3 production of IL-22 following HSCT is a critical factor in tissue healing. Illustrating a potential role for ILC3 as a biomarker of tissue healing following HSCT, clinical data revealed an inverse correlation between mucosal (102) and circulating ILC3s (151) with the severity of graft-versus-host disease. Similarly, in humans with acute IBD, increased ILC3-derived IL-22 correlates with mucosal healing — a critical clinical endpoint in IBD (84). In addition, AREG production following an acute asthma attack promotes tissue remodeling (152). As reviewed above, microbiota- and microbial-derived metabolic factors serve as potential therapeutic regulators of these tissue-restorative functions of ILCs. Additional studies in humans are needed to understand both diagnostic and therapeutic strategies to promote ILC3-based healing.

An important consideration with these approaches, however, is to limit inflammation associated with sustained ILC response. With the commercial availability of specific biologic therapies targeting effector cytokines as well as key trafficking molecules, diagnostic immunophenotyping may enable more precise utilization of therapies. Recent studies showing both mucosal and systemic Th17/ILC3 activation in IBD-associated spondyloarthritis (55, 153) highlight the need to investigate the efficacy of anti-IL-12/23 therapy in this clinical phenotype. Moreover, since the gut may serve as the portal for inflammatory TL1A-producing macrophages and α β ₇⁺, T-BET⁺ ILCs in the synovial fluid (132), additional studies are needed to know whether anti-TL1A therapy or blockade of gut-derived α β ₇⁺ lymphocytes will limit extraintestinal ILC inflammation (154, 155). In addition, sustained inflammation and pulmonary production of IL-25 in idiopathic pulmonary fibrosis

lead to the accumulation of ILC2s and IL-13-mediated fibrotic disease (122). Clinical evidence targeting IL-13 in adults supports this as a target in limiting inflammation and fibrosis associated with moderate to severe asthma (156, 157). Recent data showing a role for the microRNA miR-19 in regulating ILC2 gene expression networks highlight the potential for microRNA as a novel therapeutic target (158). Further studies are needed in humans to define diagnostic clinical and molecular signatures of ILC-mediated disease in guiding precision therapy.

One key to improving therapeutic approaches is a better understanding of ILC subsets in human disease. The expansion of inflammatory ILCs in chronic IBD (10, 131) may reflect plasticity between ILC3s and ILC1s. T-BET⁺ inflammatory ILCs are also expanded in patients with common variable immunodeficiency (159). The expansion of NKp44⁺ ILC3s in the dermal tissue from psoriatic lesions may similarly reflect this plasticity, and their reduction following successful treatment with TNF- α blockade therapy reveals the potential therapeutic relevance of understanding the interplay between ILC3 and ILC1 pathways (160). Pre-

liminary data show that the expansion of inflammatory ILC3s in multiple sclerosis is reduced following anti-CD25 therapy (161), but additional analysis of these populations from inflammatory tissue is needed to define novel molecular targets (162). Clinical studies coupled with emerging sequencing technologies that offer comprehensive genomic characterization of tissue-specific ILC subsets will be critical in identifying ILC targets that can be therapeutically manipulated to treat human disease.

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