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Another Brick in the Wall: Innate Lymphoid Cells of the Intestine

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Abstract: Since the recent identification of the expanding innate lymphoid cell (ILC) family, there has been an explosion of interest and research in the ontogeny, phenotype and function of these cells. In the intestine, ILCs are a significant component of the immune cell repertoire in the steady state and several recent studies have identified critical roles for ILCs in homeostasis and disease. In this review, ILC biology will be addressed in the context of intestinal homeostasis, inflammation and immunity to intestinal infections.

Keywords: Innate lymphocytes, helminth, protozoan, infection, intestine.

INNATE LYMPHOCYTE SUBSETS

Described almost 40 years ago, natural killer (NK) cells are the founding members of the innate lymphoid cell (ILC) family [1, 2]. These cells were described as a lymphoid cell population that did not express antigen receptors and could kill tumour cells without prior sensitization, an ability later ascribed to the "altered-" or "missing-self" hypothesis [3]. NK cell biology is well described [4] and will not be covered in detail here. Another population of innate lymphocytes, lymphoid tissue inducer cells (LTi cells), was identified as critical components in the development of lymphoid tissues over 20 years ago [5, 6]. It was later shown that LTi cells could produce IL-17 [7, 8], suggesting an immune function for these cells. Thus, the ILCs are technically not a novel population of cells but are an expanding family that are likely to play a critical role in homeostatic conditions as well as during immune responses.

The identification of distinct $CD4^+$ T helper (T_H) cell subsets that differ in their phenotype and function revolutionized the field of T cell immunology [9, 10]. T_H1 cells express T-bet and IFN-γ, T_H2 cells express Gata3 and IL-4, IL-5 and IL-13 and T_H17 cells express RORγt and IL-17 and IL-22. These phenotypic differences are directly associated with the physiological function of each cell type such as macrophage activation (T_H1 cells), goblet cell hyperplasia (T_H2 cells) and neutrophil recruitment (T_H17 cells). It is perhaps not surprising that recent data has shown that ILCs can also be grouped into similar subsets based on these conserved transcription factor and cytokine patterns. In addition to NK cells, T-bet-dependent ILC1s have been described recently [11], along with distinct GATA-3- and RORα-dependent ILC2s, and RORγt-dependent ILC3s [12]. It appears that the primary difference in these subsets, similar to T_H cells, is the differential production of cytokines that influences their function. ILC1s produce IFN-γ, ILC2s produce IL-5 and IL-13 (but not IL-4) and ILC3s produce IL-17 and IL-22. Although it is likely that the molecular mechanisms that control gene expression in ILC subsets will be similar to their $CD4^+$ counterparts, this remains to be shown. In fact, it has been shown that the molecular mechanisms regulating type 2 cytokine gene expression (IL-4, IL-5 and IL-13) in T_H2 cells and mast cells is distinct [13]. Additional aspects of T_H cell biology that may transfer to ILC subsets, including tissue tropism, expression of adhesion molecules, and immunological memory have yet to be examined in detail.

DEVELOPMENT OF INTESTINAL ILCS

Development of lymphoid cells including T cells, B cells and dendritic cells (DCs) is controlled by the E2A family of transcription factors (E12, E47, E2-2, HEB and HEBalt) [14]. E2A proteins function as transcriptional activators to promote T, B and dendritic cell development while simultaneously inhibiting differentiation of other lymphoid lineage cells including ILCs [15]. Inhibition of E2A family members is mediated by the Id family of proteins, of which Id2 has been identified to be critical for ILC development [16, 17]. Furthermore, responsiveness to the homeostatic cytokine IL-7 is also required for development of all ILC subsets [16, 18]. Thus, ILC development proceeds *via* an IL-7-dependent, Id2+ lymphoid precursor cell.

All ILC1 subsets, including NK cells, require the transcription factors T-bet and Nfil3 for their development [19]. However, although NK cells require IL-15 signaling for their development [20], ILC1s develop independently of IL-15Rα [11], suggesting these cells comprise a distinct lineage within the ILC1 family. However, all ILC1s including NK cells are responsive to IL-12 and IL-15, leading to production of IFN-γ. Thus, ILC1s are similar to T_H1 cells in both the cytokines they produce as well as the cytokines to which they respond, and may play a role in proinflammatory responses.

Although three independent groups identified ILC2 cells, it is probable that they characterized the same cell population based on function and phenotype. Originally termed natural helper cells, nuocytes and innate helper type 2 (Ih2 cells), ILC2s are induced in response to the epithelial cell-derived

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cytokines IL-25 and IL-33 [12], consistent with their expression of the IL-25 and IL-33 receptors. A separate IL-25-dependent ILC2 subset, termed multi-potent progenitor type 2 ($MPP^{type\ 2}$) has also been described [21]. This subset is distinct from the canonical ILC2 cells in that it is multi-potent, giving rise to macrophages, mast cells and ILC2s [22]. Furthermore, $MPP^{type\ 2}$ cells develop independently of Id2 and IL-33.

The transcription factor requirements for ILC2 development are an area of significant research. Similar to early T cell development, ILC2 development requires T cell factor-1 (Tcf1) [23], Notch [24], Rorα [24, 25] and Gata3 [26]. Expression of Notch is required to upregulate Tcf1 expression that directly leads to increased expression of the IL-7Rα chain and, in conjunction with Gata3, mediates CD25 and IL-25R expression. The zinc finger protein Growth Factor Independent-1 (Gfi1) has recently been shown to be critically required for ILC2 development [27]. Gfi-1 expression is required for expression of Gata3 in ILCs, similar to its role in TH2 cells [28]. In the absence of Gfi1, ILC2s acquire a dysregulated effector state and produce both IL-13 and IL-17. Thus, in addition to parallels with peripheral differentiation of T_H cells, ILC2s (and possibly other ILC family members) share conserved pathways withT cell development.

ILC3s display significant diversity, with distinct IL-17-producing and IL-22-producing subsets being identified [8, 29-33]. However, all ILC3s are dependent upon expression of the nuclear hormone receptor RORγt [29, 32-34], which was first identified as a critical factor in LTi cell development [34]. Interestingly, it is clear that some RORγt-dependent ILC3 subsets also depend upon T-bet for their development [35-37]. Whether these T-bet-dependent ILC3s are distinct from T-bet-independent ILC3s is not known and whether they fall into the ILC1 family remains unclear.

HUMAN ILC POPULATIONS

Although less well characterized than mouse ILCs, human equivalents of all three ILC groups have been identified. Much like in the mouse, NK cells in humans are the most well studied member of the ILC family. The importance of NK cells in human health has been illustrated by mutations in patients that impacts NK cells function and numbers. Recently, however, other ILC1s have been identified and characterized in various human tissues. In the tonsil, c-kit$^-$NKp44$^-$ILC1s were described and found to express transcripts for IFNγ and high levels of *TBX21* [38]. In addition, these ILC1s expressed high levels of the chemokine receptor *CXCR3*, which is important for migration to sites of inflammation. Accordingly, analysis of inflamed intestinal lamina propria of Crohn's disease patients showed a significant accumulation of c-kit$^-$NKp44$^-$ ILC1s that expressed *IFNG* and *CXCR3* [38]. Another population of intraepithelial NKp44$^+$CD103$^+$ILC1s that express *TBX21* and produced IFN-γ in response to IL-12 and IL-15 has recently been described [11]. These cells are also enriched at sites of intestinal inflammation such as in Crohn's disease. Interestingly, NKp44$^+$CD103$^+$ILC1s have a phenotype that is similar to tissue-resident memory CD8$^+$ T cells [39], and it is possible that conserved mechanisms control the phenotype, localization and function of tissue-resident innate and adaptive lymphoid cells.

Human ILC2s have also recently been characterized. Present in both fetal and adult gut, they were found to be lineage negative, CD127$^+$CD161$^+$ cells and are characterized by the expression of the T_H2 marker chemoattractant receptor homologous molecule expressed on T_H2 lymphocytes (CRTH2) [40]. Much like mouse ILC2s, human ILC2s respond to IL-25 and IL-33 by producing IL-13. Other aspects of human ILC2 biology in the intestine are unknown.

Much more comprehensively described are the human counterparts of murine group 3 ILCs. In addition to human LTi cells, ILC3s have also been identified, both of which are dependent on the transcription factor RORγt. In humans, several mucosal ILC subsets that produce IL-22 have been identified, including CD56$^+$RORγt$^+$ ILCs in the tonsil [7] and NKp44$^+$RORγt$^+$ cells found in the tonsil, Peyer's patch and small intestine [30], although they are most likely the same population of ILC [41]. ILC3s also accumulate in the inflamed intestine of Crohn's disease patients and are a source of IL-17 [42], while IL-22 producing RORγt$^+$ ILCs have also been identified in healthy intestinal tissues [12]. Overall, human and murine ILCs have many phenotypic and functional similarities and should prove to be important components of immune responses.

ROLE OF ILCS IN INTESTINAL HOMEOSTASIS

In the intestine, all three ILC lineages have been observed in the steady state. RORγt-expressing ILC3s form the majority of intestinal ILCs, with much fewer ILC1s and ILC2s present. Further, there appears to be anatomical separation of the subsets, with ILC1s found predominantly in the intraepithelial space [11] while ILC2s and ILC3s are found in the lamina propria. Despite the enrichment of ILCs in the intestine, the exact function of each ILC subset remains unclear.

The function of intraepithelial ILC1s in intestinal homeostasis is unknown. However, they have been found in higher numbers in inflamed intestinal tissues associated with Crohn's disease and are pathological in a mouse model of innate immune cell-mediated intestinal inflammation [11]. These results suggest a pathogenic role in disease states. These newly discovered ILC1s will most likely attract significant attention as potential targets to treat inflammatory diseases such as Crohn's disease.

The role of ILC2s in the steady state is not clear. In the absence of a specific method to delete ILC2s without affecting other cell lineages, it remains unknown whether loss of ILC2s affects intestinal homeostasis. Of the ILC populations, there are significantly fewer ILC2s in the intestine in the steady state, comprising less than 0.01% of total intestinal immune cells [24], suggesting a minor role in homeostatic mechanisms. A recent report has shown that a subset of ILC2s in the naïve intestine constitutively produce IL-5 but not IL-13 [43]. However, as T_H2 cells play an important role in immunity at barrier sites, it is likely that ILC2s that produce IL-5 and IL-13 will be important during infectious immune responses (see below).

In contrast to ILC1s and ILC2s, it is clear that ILC3s play a critical role in intestinal homeostasis. Mice lacking the *Rorc* gene that encodes RORγt display dysregulated intestinal development, due primarily to a lack of lymphoid tissues from the absence of LTi cells [44]. The function of non-LTi ILC3s in the intestine has been examined in both the steady state, as well as in models of intestinal inflammation [29, 45]. Depletion of IL-22-producing ILC3s led to peripheral accumulation of intestinal bacteria and innate and adaptive immune cell activation [45]. IL-22-producing ILC3s were critical for limiting the dissemination of *Alcaligenes* bacteria that are normally resident in Peyer's patches and mesenteric lymph nodes [45, 46]. Thus, in addition to promoting lymphoid tissue development in the intestine, ILC3s are critical for the anatomical containment of commensal bacteria.

A recent study has also shown a role for ILCs in regulation of adaptive immune responses. *Rorc*-deficient mice display increased frequencies of activated proliferating effector $CD4^+$ T cells, splenomegaly and heightened levels of commensal bacteria-specific serum IgG [47]. Importantly, oral administration with broad-spectrum antibiotics reversed these phenotypes, suggesting that lack of ILC3 cells was important for controlling intestinal responses to commensal bacteria. Surprisingly, a subset of ILC3 cells, the T-bet^- $NKp46^-$ $ROR\gamma t^+$ ILC3s, express high levels of MHC class II and are required to limit commensal bacteria-specific $CD4^+$ T cell responses [47]. In contrast to canonical MHC II-dependent activation by DCs, macrophages or B cells, which leads to T_H cell activation and proliferation, ILC3-mediated stimulation of T_H cells inhibits activation and proliferation, through yet to be determined mechanisms. Together, these studies illustrate an important role for specific ILC subsets in intestinal homeostasis.

ROLE OF ILCS IN INTESTINAL INFLAMMATION

Although intestinal inflammation that leads to inflammatory bowel diseases (IBDs) is becoming more and more common throughout the world, the factors that lead to IBD development remain unclear. A recent meta-analysis of genome-wide association studies in IBDs has shown a significant enrichment in genes associated with regulation of cytokine signaling and immune cell activation [48]. Although these results have been primarily associated with T cell function, it is possible that ILCs will contribute to disease etiology. Indeed, several studies have identified an association between ILCs and intestinal inflammation [11, 42]. However, it remains to be determined whether increased ILC numbers at inflamed sites in humans are the cause of the inflammation or an effect of the inflammatory processes initiated by ILC-independent mechanisms. Studies in mouse models of inflammation have begun to address the role of ILCs in the development of intestinal inflammation.

There are several models of innate intestinal inflammation in mice. First, injection of an agonistic anti-CD40 antibody into $Rag1^{-/-}$mice leads to an IL-23-dependent acute innate immune colitis and an IL-12-dependent systemic inflammatory response [49]. In this model, anti-CD40 induces robust production of IFN-γ from $CD160^+NKp46^+NK1.1^+$ ILC1s [11]. Critically, these cells were found to contribute to the pathogenesis of intestinal inflammation as depletion of these cells using anti-NK1.1 antibodies reduced epithelial damage and cellular infiltrates in the colon [11]. Another group found that IL-23-dependent $Thy1^+Sca\text{-}1^+Ror\gamma t^+$ $IL\text{-}23R^+$ILC3s produce IL-17 and IFN-γ following anti-CD40 treatment and depletion of these cells with anti-Thy1 antibodies resulted in a significant improvement in colitis [29]. In a related model of innate intestinal inflammation using infection with *Helicobacter hepaticus*, IL-23 promoted IL-17 production by a subset of ILC3s that was responsible for pathological sequelae [29]. Infection with *H. hepaticus* resulted in IFN γ and IL-17 production from colonic lamina propria cells. The production of these cytokines was required for pathology, as neutralizing either one resulted in decreased intestinal inflammation [29]. Thus, these studies are consistent with a proinflammatory role for ILCs in the pathogenesis of intestinal inflammation, independently of an adaptive immune response.

In contrast to these studies, a protective role for RORγt-expressing ILC3s in the development of chronic DSS-induced colitis has also been found. RORγt-deficient $Rag2^{-/-}$ mice develop more severe DSS-induced chronic colitis that control $Rag2^{-/-}$mice [50]. The authors of this study suggest that the loss of $Ror\gamma t^+IL\text{-}22^+$ ILCs in the colon is responsible for this effect. Indeed, IL-22 does appear to be a cytoprotective factor in the intestine [51], and defective expression of IL-22 may contribute to the onset or the inability to resolve inflammatory processes.

A role for ILC2s has also been suggested in a type 2 cytokine-dependent model of colitis. Intra-rectal administration of oxazolone results in IL-13-dependent intestinal inflammation [52]. Oxazolone treatment leads to the induction of IL-25 production that activates ILC2s to produce IL-13 [53]. Blocking IL-25 in this model leads to improved pathology and decreased ILC2s in the gut mucosa. As some forms of ulcerative colitis are associated with increased levels of IL-13 [54], it will be important to determine if IL-25-dependent ILC2s are associated with these forms of human IBDs.

ROLE OF ILCS IN INTESTINAL IMMUNITY

The intestine is a major barrier between the outside world and the internal tissues. As ILCs are present in the intestine in the steady state, it is likely that they will play a critical role in the early immune response to pathogenic organisms. However, there is very little data concerning the role of ILCs in immunity to intestinal pathogens. For example, although ILC1s produce IFN-γ in response to the cytokines IL-12 and IL-15, whether these cells are important sources of IFN-γ during infections with intracellular pathogens such as *Toxoplasma gondii* or *Cryptosporidium parvum* has yet to be determined. However, the role of ILCs in immunity to helminths is more well-defined, as intestinal helminth infections were instrumental in the discovery of ILCs.

Immunity to infection with intestinal helminth parasites requires the development of a type 2 immune response, characterized by production of the cytokines IL-4, IL-5 and IL-13 [55]. The cellular mechanisms that control the development of a protective type 2 response are becoming clearer. For example, infection with the intestinal helminth

parasites *Trichuris muris* [56] or *Nippostrongylus brasiliensis* [18, 57] leads to the activation of intestinal epithelial cell-dependent production of the cytokines associated with ILC2 development, IL-25 [58] and IL-33 [59]. In fact, some of the first hints of other non-T, non-B, non-dendritic cell lymphoid cells that had immune function came from studies examining the *in vivo* role of the cytokine IL-25 [57, 60, 61]. Injection of IL-25 into mice led to the increased production of IL-5 and IL-13 by a novel lymphoid cell type that was dependent upon γc signaling. In addition, loss of IL-25 led to impaired T_H2 cell responses and defective anti-helminth immunity [57, 58]. Due primarily to technological advances in flow cytometry and mouse molecular genetics, three independent groups identified ILC2s in the intestine that were induced following infection with the parasitic nematode *N. brasiliensis* [18, 62, 63]. These ILC2 cells produced high levels of the type 2 cytokines IL-5 and IL-13 and were critical for initiating protective type 2 immune responses to *N. brasiliensis*. Adoptive transfer of ILC2 cells can promote immunity to helminth infection. However, as it is not possible to specifically delete ILC2 cells in the intestine, it remains unclear whether ILC2 cells are absolutely necessary for immunity to helminth infection. It is interesting that ILC2s do not produce IL-4, the cytokine that is required to directly promote T_H2 cell responses. As naïve T_H cells do not respond to IL-13 [64], it remains unclear how early production of IL-5 and IL-13 can indirectly promote T_H2 cell responses. Possible mechanisms include direct effects on immune cells such as B cells, macrophages and DCs, and non-immune cells including epithelial cells and stromal cells.

Modulation of ILC2 responses has recently been shown to control chronicity of intestinal nematode infections. Infection with *Heligmosomoides polygyrus bakeri* results in the induction of IL-1β that can directly inhibit IL-25 and IL-33 expression by IL-1R1-expressing IECs [65]. The decreased levels of IL-25 and IL-33 results in an attenuation of ILC2s and subsequently decreased T_H2 cell responses. Thus, ILC2s play a central role in resistance and susceptibility to infection in the intestine.

As mentioned above, ILC3s play a critical role in the steady state. However, the role of ILC3 cells during infection is less clear. Depletion of CD4-expressing ILC3s (LTi cells) from Rag1-deficient mice resulted in significantly impaired immunity to the bacterial pathogen *Citrobacter rodentium* [66], highlighting a protective immune role for LTi cells in addition to their lymphoid tissue-promoting functions. The aryl hydrocarbon receptor (Ahr) has been shown to be important for the development and function of $ROR\gamma t^+$ ILC3s in the gut [67]. In the absence of Ahr, there was reduced expression IL-23R resulting in diminished IL-23-induced IL-22 production. Infection of Ahr-deficient mice with *C. rodentium* resulted in rapid weight loss and death, suggesting an important role for ILC3s and their production of IL-22 in controlling infection. Thus, ILC3s are required for protective immunity to bacterial challenge. In contrast, a recent study identified a detrimental role for ILC3s following infection with the prokaryotic parasite *Toxoplasma gondii* [68]. Infection led to an IL-15-dependent increase in $NKp46^+NK1.1^+$ ILC3s that produced high levels of the chemokine CCL3, which led to the CCR1-dependent recruitment of inflammatory monocytes, resulting in intestinal inflammation [68]. Taken together, these studies illustrate the complex role ILC3s play in intestinal immune homeostasis. Presently, it remains unclear whether manipulation of ILC3 function would be useful in promoting immunity to intestinal inflammation or if this would be at the expense of the role of ILC3s in intestinal homeostasis.

CONCLUDING REMARKS

In summary, it is clear that there are conserved developmental programs that are shared betweenT_H cells and ILC subsets. Functional similarities between T_H cells and ILCs is also likely, and manipulating and modulating ILC function during health and disease may prove to be a powerful novel therapeutic approach to treat many inflammatory diseases.

ABBREVIATIONS

DC	=	Dendritic cell
IL	=	Interleukin
ILC	=	Innate lymphoid cell
LTi	=	Lymphoid tissue inducer
NK	=	Natural killer

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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