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Colonization and effector functions of innate lymphoid cells in mucosal tissues

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Abstract

Innate lymphoid cells (ILCs) protect mucosal barrier tissues to fight infection and maintain tissue integrity. ILCs and their progenitors are developmentally programmed to migrate, differentiate and populate various mucosal tissues and associated lymphoid tissues. Functionally mature ILC subsets respond to diverse pathogens such as bacteria, viruses, fungi and parasites in subset-specific manners. In this review, we will discuss how ILCs populate mucosal tissues and regulate immune responses to distinct pathogens to protect the host and maintain tissue integrity.

Keywords

Innate lymphoid cells; migration; infection; mucosal tissues; intestine

1. Introduction

It is now firmly established that innate lymphoid cells (ILCs) are an essential component of the innate immune system. ILCs and NK cells emerge from common progenitors and form the ILC group. ILCs induce lymphoid organogenesis, mount innate immune responses, and regulate various biological processes to maintain tissue homeostasis [1]. ILCs are subdivided largely into three sub-groups, group 1 innate lymphoid cells (ILC1), group 2 innate lymphoid cells (ILC2), and group 3 innate lymphoid cells (ILC3), depending on their transcription factor requirement and effector functions. ILC subsets populate various organs and tissue sites in the body, and their composition and numbers differ significantly from tissue to tissue [2]. It has become clear that ILCs and their progenitors actively migrate from hematopoietic sites such as fetal liver or bone marrow (BM) to peripheral tissues. ILC subsets are specialized in responding to different pathogens. For example, ILC1 produce

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interferon (IFN)- γ and tumor necrosis factor (TNF)- α to control intracellular pathogens. ILC2 produce IL-4, IL-5, IL-9, and IL-13 in response to helminth infection. ILC3 produce IL-17, IL-22 and GM-CSF during infection by extracellular bacterial and fungal pathogens (Fig. 1). The expansion and contraction of ILC populations are regulated by a variety of factors produced in tissues in a subset-specific manner during infection. By producing key effector molecules such as cytokines, ILCs activate and regulate immune responses in a manner somewhat similar to T helper cells. In addition, ILCs maintain the integrity of barrier tissues [3, 4]. A mounting body of evidence indicates that ILCs regulate the activity of various cell types including T cells, B cells, macrophages, neutrophils, dendritic cells (DCs), eosinophils, and epithelial cells [5, 6]. In this review, we discuss our current understanding of the tissue distribution and effector functions of ILC subsets and outline important questions for future research. Please note that most of the information on ILCs discussed in this review has been obtained from studies on mice. We indicated species information only when the information was obtained from studies on species other than mice.

2. Development and effector functions of ILC subsets

ILCs originate from hematopoietic progenitors in the fetal liver during embryonic development or in the BM after birth [7]. Several common ILC progenitors with unique developmental potentials have been identified in the BM. These are the ILC/NK progenitors (α LP), the common 'helper-like' ILC precursors (CHILP), and the common ILC progenitors (ILCP) [8]. For development, ILC progenitors requires many transcription factors including nuclear factor interleukin 3 regulated (NFIL3), the transcription factor inhibitor of DNA binding-2 (Id2), thymocyte selection-associated high mobility group box protein (TOX), GATA binding protein 3 (GATA-3), and promyelocytic leukaemia zinc finger (PLZF). For detailed functions of these transcription factors, please see other reviews [5, 8, 9]. It is thought that ILC progenitors make precursors committed to each ILC subset either in the BM or periphery [2, 7]. In a manner similar to T helper cells, the so-called three master T helper cell transcription factors, T-bet, GATA-3 and ROR γ t, are generally required to generate or maintain ILC1, ILC2 and ILC3 respectively [8]. Moreover, GATA-3 is required for the development of all non-NK ILC subsets [10]. T-bet is also important for a subset of ILC3 that co-expresses IL-17 and IFN- γ [11].

Group 1 ILCs contain classical NK cells and non-NK ILC1 (referred to as ILC1 hereafter). Both cell types require the transcription factor T-bet (*Tbx21*) for their development. In a manner similar to Th1 cells, ILC1 produce IFN- γ and TNF- α , which activate various cell types including macrophages and NK cells [1, 12]. NK cells release perforin and granzymes to kill cells infected with intracellular pathogens such as viruses and, therefore, are similar to CD8⁺ cytotoxic T cells in effector function [13]. ILC1 are related to, but different from, NK cells in their transcription factor requirement for lineage development [14]. ILC1 require Id2 whereas NK cells require Eomes to develop in the BM. T-bet, NFIL3, and GATA-3 are also required for ILC1 development [8, 14].

ILC2 produce IL-4, IL-5, IL-13, enkephalin and amphiregulin as effector molecules, and require RAR-related orphan receptor (ROR) α , GATA-3, T cell factor 1 (Tcf1) and Bcl11b

for development [15–19]. The effector molecules of ILC2 induce eosinophil responses, mucus production and airway hyper-reactivity [16, 20, 21]. ILC2 also regulate metabolic homeostasis such as thermogenesis (i.e. heat generation) in adipose tissues through producing enkephalin and uncoupling protein 1 (UCP1) [15]. This regulation may be also regulated through activating eosinophils by ILC2 cytokines. IL-25 and IL-33, which are expressed by tissue cells such as epithelial cells and fat cells, activate ILC2 through their respective cell surface receptors (IL-17RB/IL-25R and ST2/IL-33R) [22, 23].

ROR γ t is required for ILC3 development and production of cytokines such as IL-17A and IL-22, which strengthen epithelial innate immunity and mount immune responses to clear extracellular pathogens [5]. Some ILC3 also produce IFN- γ and GM-CSF [11, 24]. IL-1 β and IL-23, secreted by tissue cells and antigen presenting cells such as CX₃CR1⁺ mononuclear phagocytes, activate ILC3 to produce IL-17A and IL-22 [25]. Some ILC3 express lymphotoxin $\alpha_1\beta_2$ and are specifically called lymphoid tissue-inducer (LTi) cells [26]. ILC3-derived IL-22 activates epithelial cells to produce anti-microbial peptides (AMPs), element-sequestering proteins and mucins to strengthen barrier immunity [27, 28]. In general, ILC3 are important to clear extracellular bacterial infection [28, 29].

ILCs affect adaptive immune responses. It has been reported that ILCs actively regulate T cell activity. ILC2 and ILC3 express major histocompatibility complex class II (MHC II) molecules [6, 30, 31]. ILC3 can present antigens to CD4⁺ T cells but the antigen presentation typically leads to T cell tolerance because ILC3 lack co-stimulatory signals such as B7-1 and B7-2 [30]. This function may be important in the steady state to suppress unnecessary activation of T cells. On the other hand, ILCs have the potential to influence T helper cell polarization because they produce cytokines that promote T cell polarization. This can be important during infection when ILCs are activated to produce cytokines to regulate T cell polarization in the presence of other antigen presenting cells. In this regard, ILC2 and the MHC II molecules that are expressed by ILC2 promote Th2 cell responses during helminth infection [31].

3. Regulation of ILC populations in various tissues

ILCs are widely distributed in the body from hematopoietic organs such as the BM to secondary lymphoid tissues and non-lymphoid tissues. The intestine, skin, lungs, and adipose tissues are relatively more enriched with ILCs, which account for ~2.5% of hematopoietic (i.e. CD45⁺) cells in the intestinal lamina propria, ~3.5% in the skin and lungs, and ~12% in adipose tissues [2]. Interestingly, ILC subsets are quite different from each other in their tissue distribution [2]. For example, ILC1 are enriched in the intraepithelial compartment of the intestine; ILC2 are enriched in the skin and adipose tissues; ILC3 are enriched in the intestinal lamina propria. This differential distribution of ILC subsets is indicative of potentially diverse and distinct functions of ILCs throughout the body.

NK cells outnumber all non-NK ILCs, making up greater than 80% of all ILCs in the BM, blood circulation, and secondary lymphoid tissues such as the spleen and lymph nodes [2]. IL-7 and IL-15 are key cytokines for NK cell development and effector function. These

cytokines promote the development of NK cells from common ILC progenitors such as α LP [14]. IL-12 and IL-15 induce proliferation, differentiation and activation of NK cells and ILC1 for IFN- γ production, which have been observed for both human and mouse ILCs [32–34].

ILC2 are the most abundant ILCs in the lungs, skin and white adipose tissues (WAT) [2, 15]. A specific group of cytokines, that includes IL-2, IL-25, IL-33, thymic stromal lymphopoietin (TSLP) and TNF-like ligand 1A (TL1A), activate ILC2 [5, 16]. Recent findings identified that a specialized type of intestinal epithelial cells, called tuft cells, induce ILC2 responses [35–37]. Tuft cells undergo expansion and produce IL-25 during helminth infection or in response to symbiotic protozoa. This response is induced by the cytokine IL-4. Another ILC cytokine, IL-9, promotes ILC2 survival [38]. Interestingly, physiological and metabolic cues, such as circadian rhythm and caloric intake, activate ILC2 for production of their effector cytokines such as IL-5 and IL-13 [39]. The number of ILC2 in WAT was decreased in high-fat diet-induced obesity [15]. Moreover, infection and nutrition status affect ILC2 activity. Helminth infection greatly increases ILC2 numbers in the gut [40, 41]. IL-33 activates ILC2, however this process is suppressed by IFN- γ induced during *Listeria monocytogenes* infection [40]. Interestingly, vitamin A deficiency increases the ILC2 population and enhances host resistance to helminth infection [41].

ILC3 are the dominant ILC subset in the intestinal lamina propria of the small intestine in the steady state [2]. IL-1b and IL-23 are important for ILC3 effector function because they activate ILC3 [24, 42]. Aryl hydrocarbon receptor (AHR) is a cytoplasmic receptor for plant phytochemicals and tryptophan derivatives, and these AHR ligands support the population of ILC3 in the intestine. AHR activation promotes ILC3 development and effector function in the intestine [43, 44]. In line with this, AHR-deficient mice are partially defective in IL-22 production by ILC3. Another factor that affects ILCs in the intestine is the microbiota [45, 46]. *Lactobacilli* species produce metabolites such as indole-3-aldehyde, which is an AHR ligand and activates ILC3 [47]. Nutritional status also affects the generation and function of ILC3 in peripheral tissues. The vitamin A metabolite retinoic acid (RA) increases the number of ILC3 in the gut [41, 48]. Vitamin A deficient (VAD) mice are partially deficient in ILC3 activity and are susceptible to *Citrobacter rodentium* infection [41]. RA supplementation promotes ILC3 responses during *C. rodentium* infection, whereas RA receptor inhibitors suppress ILC3 responses [48]. Also, vitamin A deficiency in pregnant females leads to defective development of LT α i cells in the fetal intestine [49].

Recent findings indicate that there is a high degree plasticity in ILC differentiation. For example, ILC3 and ILC1 can convert into each other [50]. This conversion accounts for the expansion and contraction of ILC subsets during active immune responses and is induced, in part, by the cytokines expressed by DCs. In this regard, IL-12 and IL-18 induce the conversion of ILC3 into ILC1 or ex-ILC3, whereas IL-23, IL-1 β , and RA induce the conversion of ILC1 into ILC3. Both human and mouse ILC2 can convert to ILC1 in response to IL-12, which is promoted by IL-1 β [51–54]. Thus, ILC populations are tightly regulated by various factors produced in tissues in the steady state or during infection.

4. Migration of ILCs to mucosal and non-mucosal tissues

A key question is how ILCs and their progenitors migrate into various mucosal tissues including the intestines. ILC progenitors, such as α LP, CHILP, ILCP and committed ILC precursors (NKP, ILC1P, ILC2P, and ILC3P), express homing receptors (HRs) and have the potential to migrate from the BM to peripheral tissues [2]. These progenitors combinatorially express CCR6, CCR7, CCR9, α 4b7, CXCR4, CXCR6, and/or S1P receptors [7, 55–60]. CCR7 is an HR for immune cell migration to lymphoid tissues [61]. CCR9 is an HR for migration to the small intestine [62]. α 4b7 is required for homeostatic migration of lymphocytes to both the small and large intestines. CXCR4 guides the migration of various cell types in both the BM and peripheral tissues. Sphingosine-1-phosphate receptors (S1P₁-S1P₅) regulate lymphocyte exit from lymphoid and non-lymphoid tissues for recirculation [60].

Some ILCs migrate preferentially to lymphoid tissues, while others migrate to non-lymphoid tissues such as the intestines [56, 63]. ILC1 and ILC3 can migrate from the lymphoid tissue to the intestines after functional maturation and an HR switch in gut-associated lymphoid tissues [55] (Fig. 2). Migration of ILCs from non-lymphoid to lymphoid tissues has been observed [64]. For example, NKp46⁺ ILC3 can migrate from the intestinal mucosa to mesenteric lymph nodes in a CCR7-dependent manner. ILC progenitors can also migrate from the BM to peripheral tissues [55]. For example, ILC2P can directly migrate from the BM to various peripheral tissues to establish peripheral ILC2 populations [55]. It appears that peripheral ILCs are divided into mature naïve (precursor) and effector types based on their maturation stages. For example, ILCs that express NKp46 also express CXCR6 and highly produce IL-22, but functionally less mature NKp46[−] ILC3 largely lack CXCR6 expression and the capacity to produce IL-22 [65]. This indicates the possibility that ILC subsets have heterogeneous migration programs tied to their maturation stages and effector functions. More studies should be performed in this regard.

Peripheral ILCs express various HRs and have the potential to migrate between organs or specialized microenvironments within an organ. ILCs express many HRs, including those involved in leukocyte migration to lymphoid tissues (i.e. CCR6, CCR7, CXCR4, and CXCR5), intestines (CCR9, α 4 β 7), and skin (CLA, CCR5, CCR8, and CCR10) [55, 56, 64, 66–71]. Moreover, NK cells, ILC1, and ILC3 express CCR1, CXCR3, CXCR6 and CX₃CR1, which are involved in immune cell migration to non-lymphoid or inflamed tissues [32, 63, 65, 66, 72]. HR expression by ILCs is regulated by a number of factors including tissue-specific factors, such as RA and cytokines, which promote the maturation of ILC effector functions. As shown in Figure 2, RA induces the expression of CCR9 and α 4 β 7, but down-regulates CCR7 on ILC1 and ILC3 [55]. Interestingly, the gut HRs of ILC2 are not regulated by RA, indicating the presence of potentially distinct migration programs among ILC subsets. The HR expression by ILCs requires stimulation with cytokines such as IL-7. This is different from T cells, which require TCR stimulation as the underlying activation signal for HR switches [73]. Various cytokines, tissue factors and inflammatory mediators are likely to differentially regulate HR expression in ILCs.

5. ILC responses to microbes

ILCs regulate innate and adaptive immune responses to pathogens in various tissues [5]. ILCs profoundly affect the gut commensal flora, which in turn influences the homeostasis of ILCs [74]. ILC responses during infection are selective and determined by the type of pathogens. For example, ILC1 and some ILC3 respond to infection by intracellular bacteria. ILC3 also respond to extracellular bacterial and fungal infections. ILC2 respond to parasite infection and induce tissue repair following viral infection. ILCs amplify inflammatory responses by inducing the expression of chemokines and cytokines to recruit other leukocytes [67, 72, 75]. In this section, we will discuss how ILC subsets respond to commensal bacteria and various types of pathogens (Fig. 1).

5.1. ILC responses to commensal microbiota

The gastrointestinal tract, especially the colon, is colonized with ~trillions of bacterial cells per gram of fecal matter along with some yeasts cells. Dominant bacteria groups include *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria*. In normal symbiotic conditions, most of the gut bacteria, except certain tissue-associated bacteria such as segmented filamentous bacteria (SFB) and GALT-associated bacterial species, are present in the gut lumen, well separated from the epithelial surface by the mucous layer and tightly controlled by host antimicrobial factors [76]. In pathogenic or dysbiosis conditions, the mucous barrier between the epithelial surface and luminal bacteria becomes thinner, allowing the attachment of some bacteria to the epithelial surface [77]. This is due to a disrupted mucous layer and defective production of host anti-microbial factors, resulting from abnormal expansion of dysbiotics and decreased barrier functions.

Accumulating evidence indicates that commensal bacteria and ILCs regulate each other [74]. ILCs affect the microbiota composition and prevent tissue invasion by pathogenic microbes. ILC3 regulate gut microbiota, and this is mediated in part by IL-22. IL-22 induces the proliferation of intestinal epithelial stem cells for tissue regeneration and the production of AMPs such as RegIII β , RegIII γ , and β -defensins [78, 79]. IL-22 also induces the expression of element-sequestering proteins (i.e. S100A8 and S100A9, and lipocalin-2) and mucins, and promotes fucosylation of epithelial proteins [79–81]. These molecules keep commensal bacteria away from the epithelial surface. In this regard, an important function of ILC3 is to suppress the peripheral dissemination of commensal bacteria presumably through strengthening the barrier function [81]. A good example is the suppressive role of ILC3 on tissue invasion by *Alcaligenes species*. *Alcaligenes species* reside in the Peyer's patches of healthy humans and mice, but invade into systemic tissues when ILC3 activity is compromised by ILC depletion [82]. ILC3-induced AMPs such as calprotectin inhibit the overgrowth of *Alcaligenes* [81]. Additionally, ILC3 affect the microbiota through generating lymphoid tissues and activating other immune cells. For example, ROR γ ⁺ LT α cells induce the formation of fetal lymph nodes and gut-associated lymphoid tissues such as isolated lymphoid follicles and cryptic patches [83]. This can indirectly promote the production of IgA, which controls the gut microbiota [84].

As discussed in a previous section, AHR signaling is important for the IL-22 production by ILC3. Therefore, AHR ligands are important in regulating commensal bacteria. For example,

abnormal expansion of SFB was observed in *Ahr*^{-/-} mice and ILC-depleted mice [85]. ILC1 and ILC2 have the potential to indirectly affect gut bacteria by producing effector molecules such as IFN- γ , and Th2 cytokines. The abnormal expansion of *Helicobacter typhlonius* in *Rag2*^{-/-} *Tbx21*^{-/-} mice indicate that ILC1 are likely to be important [86]. More studies are required to identify specific roles of ILC1 and ILC2 in regulating gut commensal flora and dysbiotics.

5.2. ILC responses to intracellular pathogens

Innate immunity is required to clear *Salmonella typhimurium* infection, which causes diarrhea and gastroenteritis [87]. For example, IFN- γ of innate origin is important to control *S. typhimurium* infection [88, 89]. IFN- γ activates a number of cell types including macrophages, NK cells, and T-cells, which fight intracellular pathogens [90, 91]. IFN- γ also stimulates goblet cells and enterocytes to produce mucus [89, 92]. An ROR γ t fate-mapping study revealed that NKp46⁺ ILC3, not NK cells, are the major source of IFN- γ during *S. typhimurium* infection [11, 93]. However, the role of ILC1 during *S. typhimurium* infection is currently unclear. IL-23 induces the expression of IL-17A and IL-22 by T-cells and ILC3 during *S. typhimurium* infection [11, 94, 95]. IFN- γ and IL-22 stimulate gut epithelial cells to produce RegIII and lipocalin 2 [96–98]. Lipocalin 2 inhibits bacterial growth by sequestering iron from bacteria [99]. ILC3-derived IL-22 and lymphotoxin induce fucosyltransferase 2 (Fut2), which adds L-fucose to the glycoproteins and glycolipids that are produced by epithelial cells [80]. The fucose group is metabolized by commensal bacteria into beneficial metabolites, such as short-chain fatty acids, to boost barrier immunity [100].

Another intracellular pathogen, *Listeria monocytogenes*, infects the intestinal tract by utilizing internalin A (InlA) and InlB, which respectively bind to E-cadherin and Met receptor tyrosine kinase expressed on intestinal epithelial cells [101]. Once within infected cells, *L. monocytogenes* escapes from hostile phagocytic vacuoles with listeriolysin O (LLO). IFN- γ and TNF- α play critical roles in fighting *L. monocytogenes* [102, 103]. Mice deficient in adaptive immune responses are still able to produce IFN- γ and TNF- α upon infection by *L. monocytogenes* [104–106], underlining potentially important roles of innate immune cells. Activation of macrophages by NK-derived IFN- γ is required for host survival during *L. monocytogenes* infection [107]. The NK-derived IFN- γ is required to block bacterial dissemination in the small intestine and mesenteric lymph nodes (MLN). Oral infection by *L. monocytogenes* induces ILC1 and ILC3 responses in the intestine [108].

Toxoplasma gondii is an obligate intracellular protozoan and causes toxoplasmosis. During *T. gondii* infection, IL-12 is produced by DCs, and IL-15 and IL-18 are produced by epithelial cells [109, 110]. IL-12 promotes the production of IFN- γ by T cells, NK cells and ILC1, and therefore it is important to fight *T. gondii* infection [111]. ILC1 produce IFN- γ and TNF- α during *T. gondii* infection [14]. While alymphoid *Rag2*^{-/-} *Il2rg*^{-/-} mice are highly susceptible to *T. gondii* infection, ILC1 infusion into *Rag2*^{-/-} *Il2rg*^{-/-} mice increased their resistance to *T. gondii* [14]. IL-15 supports the development of CD3⁺NKp46⁺NK1.1⁺CD127⁻ ILC-like cells, and IL-18 induces the expression of the

chemokine CCL3 to attract inflammatory monocytes that clear *T. gondii* infection [109]. Overall, NK cells, ILC1, and ILC3 play central roles in fighting intracellular pathogens.

5.3. ILC responses to extracellular bacteria

Citrobacter rodentium—*C. rodentium* is a widely used pathogen model for attaching and effacing *Escherichia coli* [112]. *C. rodentium* mainly colonizes the cecum and proximal colon of mice, and induces mucosal hyperplasia and the characteristic effacing of brush border microvilli [112, 113]. While T cells and B cells are required to clear *C. rodentium* infection, innate immunity is key to fighting *C. rodentium* infection [114]. Alymphoid *Rag2^{-/-}Il2rg^{-/-}* mice succumb to death following *C. rodentium* infection within ~10 days [115]. However, *Rag1^{-/-}* mice, which lack T and B cells, but have expanded ILCs, can survive for ~30 days [28, 116], underlining the importance of innate lymphoid cells in fighting *C. rodentium* infection. During *C. rodentium* infection, IL-22 was produced by CD4⁺ ILC3 cells and played a central role in fighting the pathogen [28, 29]. Depletion of ILCs in *Rag1^{-/-}* mice made them highly susceptible to *C. rodentium* infection. On the other hand, ILC3 transfer or IL-22 injection into *Rag2^{-/-}Il2rg^{-/-}* mice restored the host resistance to *C. rodentium* [29, 43]. Administration of AMPs into IL-22^{-/-} mice also enhanced the resistance to the pathogen [28]. Overall, ILC3, IL-22 and AMPs play key roles in mounting effective innate immunity against *C. rodentium*.

Helicobacter—While immunocompetent mice are resistant to *H. hepaticus*, immunodeficient hosts such as *Rag2^{-/-}* mice are susceptible to the pathogen and develop immunodeficiency-associated intestinal inflammation [86, 117]. *H. hepaticus* induces chronic colitis in *Rag2^{-/-}* mice [118]. The cytokines IFN- γ and IL-17A, induced by IL-23 during infection, trigger intestinal inflammation [119]. Mice lacking T-bet in innate immune cells (*Tbx21^{-/-}Rag2^{-/-}*) develop spontaneous intestinal inflammation [86]. In these mice, the pathobiont bacteria *H. typhlonius* are expanded, inducing TNF- α expression and colitis [117]. TNF- α , produced by CD103⁻CD11b⁺ DCs, works together with IL-23 to induce the production of IL-17A by ILC3. In support of the inflammatory role of ILC3, T-bet-deficient alymphoid (*Tbx21^{-/-}Rag2^{-/-}Il2rg^{-/-}*) mice did not develop the colitis [117]. ILC depletion also ameliorated intestinal inflammation induced by *H. hepaticus* infection [120]. Collectively, these results depict the important roles of TNF- α , IL-23, T-bet⁺ ILCs, IFN- γ and IL-17A in mediating inflammatory responses during *Helicobacter* infection.

Clostridium difficile—*C. difficile*, a gram-positive spore-forming species, infects the intestine typically after prolonged use of antibiotics in hospitalized patients. *C. difficile* colonization in intestinal tissues releases toxins TcdA and TcdB, which glucosylate small GTPases and cause actin condensation and death of intestinal epithelial cells [121]. Innate immunity is important to clear the pathogen and induce infection-associated inflammatory responses. Mice deficient in MyD88 or IL-22 are highly susceptible to *C. difficile* infection [122, 123]. Also, mice deficient in NFIL3, which are defective in ILC and NK development, are highly susceptible to *C. difficile* infection [124]. ILC1, but not ILC3, play a major role in the anti-*C. difficile* immune response [125]. In line with this, both *Rag1^{-/-}Tbx21^{-/-}* and *Rag1^{-/-}Ifng^{-/-}* mice are highly susceptible to *C. difficile* [125].

Streptococcus pneumoniae—*S. pneumoniae*, a gram-positive alpha-hemolytic bacteria species, infects lungs through the nasopharynx. Innate immunity is required to effectively fight the pneumococci infection in humans [126]. ILC3 and their effector cytokines play key roles in fighting *S. pneumoniae* [127]. CCR6⁺ROR γ ⁺ ILC3 accumulate in lung tissues during *S. pneumoniae* infection and produce IL-17 and IL-22. Activated DCs stimulate the production of IL-22 by ILC3 during infection [127].

5.4 ILC responses to helminths

Infection by helminths typically activates T helper type 2 responses with the production of IL-4, IL-5, IL-9 and IL-13, which are required to kill and expel worms [128].

Nippostrongylus brasiliensis infect through the skin and colonize the lung at the third larval stage (L3) and, then, migrate to the proximal jejunum at L4 to become adult worms. While Th2 cells play central roles in the anti-*N. brasiliensis* response, *Rag2*^{-/-} mice, deficient in T cells and B cells, still can produce Th2 cytokines such as IL-5 and IL-13 to clear the pathogen [129]. However, *Rag2*^{-/-}*Il2rg*^{-/-} mice, which lack ILCs in addition to T and B cells, fail to produce Th2 cytokines and fight *N. brasiliensis* infection [129]. Moreover, mucin production and eosinophil recruitment were defective in *Rag2*^{-/-}*Il2rg*^{-/-} mice, but the transfer of ILC2 or ILC2P restored the deficiency [22, 56]. ILC2 are the major source of Th2 cytokines in T cell-deficient conditions [22, 130]. IL-5 expands and activates eosinophils, which are key granulocytes to kill helminthic parasites [131]. IL-13 induces the expression of CCL11 (an eosinophil chemoattractant), mucus production, smooth muscle contraction, and goblet cell expression of RELM β (an inhibitor of nematode chemotaxis), which work together to promote worm expulsion [1, 22, 130].

Alarmin cytokines, such as IL-25 and IL-33, activate ILC2 to produce IL-5 and IL-13 [22, 68]. In line with this, IL-25 receptor-deficient mice are highly susceptible to *N. brasiliensis* infection [22]. ILC2 and their effector cytokines are also important for immune responses to other parasites such as *Trichuris muris* and *Strongyloides venezuelensis* [41, 132]. For complete and effective elimination of parasites, Th2 responses are required. ILC2 appear to promote the development of Th2 cells through cytokine (e.g. IL-4) production and antigen presentation [31]. Thus, ILC2 and T cells work together to efficiently mount immune responses to helminth infection.

5.5 ILC responses to fungi

Neutrophils are key phagocytes required to clear fungal pathogens such as *Candida albicans* [133]. IL-17 plays a central role in fighting *C. albicans* infection [134]. IL-17 induces CXCL1 and CXCL2 to recruit neutrophils and activates their phagocytic ability [135]. IL-17 is mainly produced by ILCs and Th17 cells [136]. ROR γ ⁺ ILC3 produce IL-17 at early stages of *Candida* infection. ILC3-derived IL-17 is also required for protection against oropharyngeal candidiasis in mice [137]. ILC3-deficient mice, caused by pan-ILC depletion in *Rag1*^{-/-} mice or *ROR γ* deficiency, are highly susceptible to *Candida* infection [137]. In a manner similar to immune responses to extracellular bacteria, IL-23 stimulates ILC3 to produce IL-17 during *Candida* infection [137, 138]. In line with this, IL-23p19^{-/-} mice are highly susceptible to infection [137]. ILC3 also produce IL-22 during *Candida* infection [97]. In humans, genetic variations in the *IL-22* gene locus are linked to vulvovaginal

candidiasis [97]. IL-22 and IFN- γ play a key role in fighting *C. albicans* infection. [139]. However, the role of ILC1 in regulating anti-fungal responses remains uncertain.

5.6 ILC responses to viruses

Innate immunity provides the first line of defense against influenza virus infection in the respiratory tract [140]. The critical roles of NK cells in anti-viral immune responses are well established [141]. Because this subject has been extensively reviewed by others, we briefly highlight key features of NK cells in this review. NK cells detect virus-infected cells through various NK receptors such as killer immunoglobulin-like receptors (KIR), natural cytotoxicity receptors (e.g. NKp46, NKp44 and leukocyte immunoglobulin-like receptors), C-type lectin-like receptors (e.g. Ly49 receptors and CD94-NKG2A/C/E) and signaling lymphocyte activation molecule (SLAM) family receptors (e.g. 2B4) [142]. These NK receptors recognize various signals on target cells that signify infection or oncogenic transformation, and the combined signals from the receptors either activate or inhibit NK cell cytotoxicity [143]. For example, NKp46 (CD335) and DNAM-1 (CD226) on NK cells recognize virus-infected cells [143–145]. This triggers NK activation to kill the target cells. On the other hand, many MHC class I molecules act as inhibitory ligands for CD94-NKG2A and KIR2DL1/2/3 (CD158a/b) [146–148]. This recognition inhibits NK cells from killing uninfected normal cells [149]. NK cells also regulate immune responses through production of cytokines such as IFN- γ and TNF- α [150].

The roles of non-NK ILC1 and ILC3 in regulating anti-viral immune responses have not been established so far. It has been observed that infection by simian or human immunodeficiency virus depletes ILC3 in addition to CD4⁺ T cells [151–154]. While the mechanism is still unclear, the ILC3 depletion is mediated by plasmacytoid DCs, IFN-I, and the CD95/FasL pathway [155].

Lung ILC2 play largely two different roles during viral infections: 1) mediating inflammatory responses and 2) maintaining epithelial integrity and airway remodeling to restore lung function. Influenza infection induces inflammatory responses, leading to airway hyper-reactivity (i.e. exaggerated airway narrowing). Lung ILC2 (i.e. Lin⁻CD25⁺ST2⁺c-Kit⁺Sca-1⁺CD90.2⁺ cells) mediate the airway inflammatory responses in mice during infection by H3N1 influenza virus [21]. In this study, ILC2 depletion abolished the inflammatory response, whereas ILC2 transfer restored it. During infection by influenza virus, IL-13 and IL-33 activate ILC2, neutrophils and macrophages [21]. ILC2 help repair damaged lung tissues during influenza viral infection. This is mediated in part by ILC2-derived amphiregulin, which in turn induces the expression of heparin-binding EGF-like growth factor, TGF- α , epiregulin, epigen, betacellulin and neuregulin, all of which promote the repair of damaged tissues following infection [156]. However, it remains to be determined if ILC2 play an active role in eliminating viral pathogens.

6. Concluding remarks

ILCs and their progenitors actively migrate into mucosal tissues and associated secondary lymphoid tissues. Once within peripheral tissues, ILCs undergo expansion and functional maturation. The migration of functionally mature ILCs from lymphoid to non-lymphoid

tissues is important for tissue-specific immune responses. While the importance is yet to be determined, reverse migration of effector ILC3 back to lymphoid tissues has been observed. Thus, the migration program of ILCs appears to be dynamic and complex, mimicking that of both adaptive and innate immune cells. A number of tissue factors and cytokines regulate ILC numbers and composition in a manner specific for ILC subsets and tissue sites. ILCs regulate the inflammatory responses of epithelial cells and immune cells to control commensal microbiota and pathogens on mucosal surfaces. Another important function of ILCs is to maintain and restore epithelial integrity, which is important for host survival following infection by pathogens.

We still do not fully understand how ILCs coordinate their functions with adaptive immune cells to eliminate pathogens. More studies are required to understand the roles of ILCs in shaping adaptive immune responses. For example, it has not been established whether ILC1 and ILC3 play any roles in inducing Th1 and Th17 responses respectively. ILCs can induce T cell tolerance by presenting antigens without expressing co-stimulation signals, but they also produce cytokines that promote T cell polarization. It is important to study the relative roles of these functions and determine the exact time and location for the seemingly contradictory responses. More studies are required to fully understand the effector functions of ILCs during infection and inflammatory responses. In this regard, it is important to identify additional effector molecules of ILCs. It is known that ILCs regulate the microbiota but more studies are required to precisely understand the potentially selective functions of ILC subsets in regulating gut microbiota. Novel host factors that enhance, suppress or induce pathogen-specific ILC responses should be identified. Pathogens use various virulence factors to evade host immune responses. In this regard, it is important to find such virulence factors that might preferentially incapacitate ILCs.

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Figure 1. ILC responses to distinct types of pathogens

ILCs play central roles in host defense at mucosal surfaces. (A) Upon infection by intracellular pathogens, IL-12 and IL-15 are produced by DCs and macrophages and activate ILC1. ILC1 produce IFN- γ , which plays many roles including activation of phagocytes harboring intracellular pathogens and stimulating the mucin production by goblet cells. (B) During infection by helminths, epithelial cells produce alarmin cytokines such as IL-25, IL-33, and TSLP, which activate ILC2 for production of Th2 cytokines, such as IL-5, IL-9, and IL-13. These cytokines activate eosinophils, mast cells, B cells, T cells, goblet cells, and intestinal neuronal cells to eliminate parasites. AREG, an epidermal growth factor receptor (EGFR) ligand, is also produced by ILC2 for epithelial remodeling during viral infection. (C) In response to commensal microbiota and extracellular bacterial and fungal pathogens, antigen presenting cells and epithelial cells produce IL-1 β and IL-23, which stimulate ILC3 to produce GM-CSF, IL-17, IL-22 and/or LT. These cytokines induce myelopoiesis and induce immune responses mediated by neutrophils and other phagocytes. ILC3 and ILC2 can regulate T cells through antigen presentation. Induction of T cell tolerance was reported for ILC3, whereas enhanced Th2 responses were observed for ILC2. Abbreviations: AMP, antimicrobial peptide; AREG, amphiregulin; CBA, commensal bacteria antigen; LT, lymphotoxin; MHC II, major histocompatibility complex II; PAMP, pathogen-associated molecular pattern; TCR, T cell receptor; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin.

Figure 2. Migration of ILCs to the intestine

ILCs originate from the BM and fetal liver. The progenitors and precursors of ILCs at various developmental stages express homing receptors such as CCR7, CCR9, $\alpha 4\beta 7$, and CXCR6. These cells migrate to peripheral tissues including mesenteric lymph nodes and intestines. ILC precursors differentiate into mature ILCs in the periphery and at this time, ILCs switch their homing receptors from naïve to effector types. DCs in MLNs and gut-associated lymphoid tissues (GALTs) such as Peyer's patches produce cytokines and retinoic acid (RA), which activate ILC1 and ILC3 to change their homing receptors from CCR7 to CCR9 and $\alpha 4\beta 7$. After the homing receptor switch, ILCs can migrate to the small and large intestines. Only ILC1 and ILC3 can undergo the RA-dependent homing receptor switch. ILC2 do not undergo this type of homing receptor switch. Instead, ILC2P express CCR9 and $\alpha 4\beta 7$ in BM and can directly migrate to the intestines. Some effector ILC3 can migrate from the intestinal lamina propria back to mesenteric lymph nodes in a CCR7-dependent manner.