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The role of innate lymphoid cells in the response to microbes at mucosal surfaces

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Abstract

Innate lymphoid cells (ILCs) are a lymphocyte population that is mostly resident at mucosal surfaces. They help to induce an appropriate immune response to the microbiome at homeostasis. In healthy people, the mucosal immune system works symbiotically with organisms that make up the microbiota. ILCs play a critical role in orchestrating this balance, as they can both influence and in turn be influenced by the microbiome. ILCs also are important regulators of the early response to infections by diverse types of pathogenic microbes at mucosal barriers. Their rapid responses initiate inflammatory programs, production of antimicrobial products and repair processes. This review will focus on the role of ILCs in response to the microbiota and to microbial infections of the lung and intestine.

Keywords

Innate lymphoid cells; mucosal tissues; homeostasis; infection; microbiome; pathogen

Introduction

Diverse microorganisms, including bacteria, viruses, and fungi, are associated with the mucosal barriers of the body[1]. These barrier surfaces include the gastrointestinal and respiratory tracts, along with others, such as the skin and reproductive tract. They are sites of continual interactions between microbes, tissue cells and the immune system. The bacterial contents of these sites are among the best-defined microbial constituents at these surfaces, and they can have both beneficial and deleterious effects on the immune response and inflammatory disease[2]. In the case of steady-state interactions with the microbiota, innate lymphoid cells (ILCs) have been reported to play important roles in regulating the immune response at mucosal barriers through the rapid production of cytokines and other mediators[3].

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AUTHOR CONTRIBUTIONS

G-Y.S., D.A.G., and M.K. planned the manuscript. G-Y.S. D.A.G. wrote the initial manuscript draft and reviewed the manuscript. M.K. wrote and reviewed the manuscript.

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Likewise, during infections, ILCs participate in the orchestration of the early response to clear pathogens at mucosal sites, thereby preventing systemic infection.

ILCs are cells that share a common progenitor with B and T lymphocytes, but they lack antigen receptors encoded by genes generated by RAG-dependent DNA rearrangements. This lack of receptor clonal diversity, coupled with their rapid responses, serves to categorize ILCs as part of the innate immune system. Studies suggest that ILCs arose approximately 500 million years ago in conjunction with adaptive immune B and T cells. They perhaps evolved to participate in the requirement for longer-lived and larger organisms to live in harmony with a more complex microbiota while providing defense against pathogens[4]. ILCs have been reported to participate in the course of several diseases of mucosal tissues, including inflammatory bowel disease, asthma and colorectal cancer, these topics have been reviewed elsewhere[5–8]. There also have been a number of recent, excellent reviews on ILC biology and function[9–13], including the role of these cells in general tissue homeostasis. Here we will focus specifically on the role of ILCs in influencing the response to the microbiome during homeostasis and during infection at two mucosal barriers, the lung and the intestine.

1-1. Subsets of ILCs

ILCs populate mucosal barriers, respond to cues from other cells and produce cytokines and other substances that mediate appropriate immune responses. While evidence for TLR function in ILCs in vitro has been reported[14, 15], in vivo evidence for direct detection of microbes by ILCs, either by TLR signaling, or by other means, is sparse. Therefore, ILCs generally are not the first responders. Like other lymphocytes, ILCs rely on cytokine signaling through the common cytokine receptor γ chain (γ_c or CD132) for their development. Thus, ILCs were not decreased in *Rag* deficient mice, but *Il2rg* deficient mice displayed a more than 90% reduction[9, 16]. Similar to $CD4^+$ T cells, functional subsets of ILCs have been identified, including, ILC1, ILC2 and ILC3, with ILC1s similar to Th1 cells, ILC2s similar to Th2 cells and ILC3s similar to Th17 cells. For example, ILC1s were reported to be similar to Th1 cells in their dependence on the transcription factor T-bet[17] and they exhibited the ability to secrete IFNγ. Likewise, ILC2s were similar to Th2 cells in their requirement for the transcription factor GATA-3 and they produced type 2 cytokines, prominently IL-5 and IL-13, but also IL-4 and IL-9[18, 19]. Finally, ILC3s showed similarities to Th17 cells and they depended on the transcription factor RORγt for their differentiation and they produced IL-22 as well as IL-17[19]. Together, these three subsets may be classified as helper ILCs.

There is heterogeneity within the three principal ILC subsets. For example, ILC2s could be divided further into two subsets, natural ILC2s (nILC2) and inflammatory ILC2 (iILC2)[20, 21]. nILC2s, which are Lin^- $ST2^+$ $KLRG1^{int}$ cells, were found in the lung during homeostatic conditions and responded to IL-33 stimulation. However, iILC2, which are Lin^- $ST2^-$ $KLRG1^{hi}$ cells, are generally not found in the lungs, nor in most other peripheral tissues in naïve mice. iILC2s were only present after helminth infection or IL-25 exposure following recruitment from the intestine to the lung[20, 21]. Interestingly, some iILC2s exhibited the ability to produce IL17 and expressed intermediate amounts of the

transcription factor that drives IL-17 expression, RORγt[20]. Additionally, ILC3s can be separated based on their expression of CCR6 and natural cytotoxicity receptors (NCR) such as NKp46 in mouse and NKp44 in human. $CCR6^+$ ILC3s are also known as lymphoid tissue inducer (LTi) cells and they have been demonstrated to aid in the development of lymph nodes and tertiary lymphoid follicles in peripheral tissues, including mucosal barriers[22]. Maternally-derived retinoic acid intake and fetal RA signaling control LTi cell differentiation before birth[23]. RA has multiple basal functions in the intestine that influence interactions with the microbiome and the response to infections, including homing of lymphocytes to the mucosae, IgA synthesis, regulatory T cell accumulation, and ILC subset skewing[24–28]. There is a degree of plasticity between the three main ILC subsets. For example, RA stimulation in the presence of IL-1β and IL-23 has been reported to drive ILC1 plasticity and conversion to ILC3s[29] but also, in other contexts, some ILC3 converted to ILC1[30, 31].

Natural killer (NK) cells may be classified as killer ILCs. They resemble cytotoxic $CD8^+$ T cells in their ability to produce perforin and granzyme B[32], although NK cells are sometimes placed in a separate lymphocyte category from ILCs. With regard to cytokine production, many NK cells produce IFNγ, similar to ILC1s, $CD8^+$ and Th1 $CD4^+$ cells[33, 34]. Additionally, both NK cells and ILC1 express characteristic surface receptors, such as NK1.1 and NKp46. NK cell development is distinct from helper ILCs, however, because precursors of NK cells did not require IL-7 or the transcription factor GATA3[35]. Instead, NK cell differentiation is distinguished by dependence on the transcription factor EOMES[36].

ILCs were shown to be generated in both the fetal liver and bone marrow from the common lymphoid progenitor[37, 38]. Studies of parabiotic mice have demonstrated that ILCs were mostly tissue resident cells[39], but the ILC subsets were differentially present in different sites. For example, the mouse lung contained a significant number of ILC2s[40], with lesser amounts of ILC1s and ILC3s at steady state[40]. In the intestine, ILC1s were the major subset within the small intestine epithelium[41, 42] and ILC3s were the predominant ILC subset in the lamina propria of both the small and large intestine[42, 43]. In the intestine, ILC2s were more frequent in the colon lamina propria compared to the small intestine[42, 43]. Of note, these findings are specific to the steady state and alterations in the proportions of the ILC subsets occur following some infections. NK cells are the only ILC type found to a significant extent in the circulation, but they also are the most numerous ILC type in the lung and several other tissues[42].

1-2. Essential Functions of ILCs

To assess the phenotype in mice lacking only ILCs, investigators have relied on several techniques, most often comparison of *Rag*$^{-/-}$ mice lacking B and T cells to analyses of *Rag*$^{-/-}$*gc*$^{-/-}$ deficient mice also lacking ILCs in addition to the absence of B and T cells. Some studies have analyzed the effect of ILC depletion by treatment of *Rag*$^{-/-}$mice with anti-Thy1 antibodies. These methods for deletion of all ILCs have limitations. For example, the microbiome is highly altered in *Rag*$^{-/-}$ mice and ILC populations in the intestinal epithelium of these mice were greatly expanded in number. Furthermore, anti-Thy1 antibodies could have effects even in T cell deficient *Rag*$^{-/-}$ mice on $Thy1^+$ cell types besides ILCs, such as

neuronal cells or fibroblasts. Therefore, while these methods have been used to provide much important information, and have supported suggestions that ILCs are critical for a variety of immune responses, studies in mice have been hampered by the absence of a means to specifically eliminate all ILCs, without effects on other cell types. Some methods have been developed, however, to analyze the function of particular ILC subsets. For example, *Staggerer/Rora*^{Flox}-*Cd127*^{Cre} mice, a strain with deletion of the gene encoding the transcription factor RORα mediated by *IL7ra*-driven Cre recombinase, were reported to be selectively deficient for ILC2s[44]. *Rora* is highly transcribed in a few other IL-7 receptor-dependent lymphocyte types, however, such as iNKT cells. Similarly, deletion of the gene encoding the aryl hydrocarbon receptor by Cre recombinase controlled by the gene encoding RORγt (*Rorc-Cre* x *Ahr*$^{f/f}$) specifically depleted ILC3s, although this also affected IL-22 secretion by CD4$^+$ T cells[45].

In humans, evidence for the essentiality of ILCs is still lacking. In fact, in severe combined immunodeficiency patients that received hematopoietic stem cell transplants, T lymphocytes were reconstituted but ILC reconstitution was absent or these cells were very limited in number. These patients showed no signs of disease after many years[46]. It remains to be determined if a more thorough categorization of similar individuals is required to rule out illnesses dependent on the absence of ILCs, or if this represents a species difference in the relative importance of ILCs comparing laboratory mice to humans. We note that the immune system of mammals contains additional populations of innate-like lymphocytes, including γδ T cells, iNKT cells and mucosal associated invariant T (MAIT) cells, and these lymphocytes all share aspects of their transcriptome and in some cases, show similar functions[47]. Furthermore, one innate-like population may expand in the absence of another[48]. Therefore, there could be a degree of redundancy between these cell populations, but this does not provide a cogent argument that ILCs are not important in any circumstance.

2. ILC interactions with the microbiome

Homeostasis between the immune system and the microbiome is essential for both the lung and the intestine. A diverse and appropriate population of commensals aids in promoting the optimal immune response to pathogens, while also preventing a destructive inflammatory response to nonpathogenic microbes. In this section, as summarized in Figure 1, we will describe how the different ILC subsets function to promote a barrier immune system in harmony with the microbiome.

2-1. ILC1s and NK cells

While NK cells and ILC1s play roles in the immune response to pathogens, by quickly producing IFNγ[34, 41], less is known about their relationship with the microbiome. In mice and humans, these cells produce IFNγ in response to IL-12, IL-15 and/or IL-18[33, 34]. ILC1s may also be important, however, for preventing infection with opportunistic intestinal pathogens, such as *Clostridium difficile*. *Rag1*$^{-/-}$ mice were largely protected from *Clostridium difficile* infection, while *Rag*$^{-/-}$*gc*$^{-/-}$ mice were susceptible[49]. Furthermore, mice deficient for both Rag2 and the transcription factor T-bet developed a spontaneous severe colitis dependent on the commensal organism *Helicobacter typhlonius*[50]. These data

suggest that colonic, T-bet-dependent ILCs may play an active role in modulating the response to elements of the microbiome.

2-2. ILC2s

ILC2s drive a type 2 immune response in both the lung and the colon that is reported to maintain an appropriate inflammatory balance in both organs[51]. ILC2s have been shown to be a major source of IL-13 in the lung at steady state[52], which is required for alternatively activated macrophage (M2) differentiation[53, 54]. M2 macrophages promoted tissue homeostasis, as opposed to the inflammation associated with excess M1 macrophages[55]. In the intestine, IL-13, produced in part by ILC2s, contributed to goblet cell differentiation and mucus production[56, 57], which are important for interactions with the microbiome and infectious agents. Consistent with this observation, mice deficient for IL-13R exhibited impaired mucus production[58]. ILC2s were not only capable of producing cytokines typical of type 2 or Th2 immune responses, but they also produced amphiregulin (AREG) which binds to epithelial growth factor receptor (EGFR). These data indicate that ILC2s can induce tissue healing responses that are important for limiting infection to barrier tissues[59].

ILC2s are maintained in the tissues by IL-2 and IL-7[60, 61], and they have the ability to respond to cytokines produced by other innate immune cells, such as IL-18, IL-25, IL-33 and TSLP[51, 62]. At steady state in mucosal barriers, epithelial cells produced amounts of IL-25 and IL-33 sufficient to drive basal levels of IL-5 and IL-13 production[51, 63, 64]. In the lung, reports indicated that epithelial IL-33 induced the IL-13 production by ILC2s that led to M2 macrophage accumulation[53, 54]. IL-33 secreted by lung epithelial cells acted as an alarmin indicating epithelial damage. Subsequent AREG production by ILC2s in response to IL-33 promoted resolution of tissue damage and maintenance of the barrier[59, 65]. At homeostasis, IL-25 is produced by tuft cells in the intestine and lung. Tuft cells are an epithelial type that likely can sense different small molecules, including microbiome-derived succinate, through expression and activation of the succinate receptor[66, 67]. In the intestine, tuft cell-derived IL-25 activated ILC2s to secrete IL-13[63] that contributed to a feedforward loop that further activated tuft cell IL-25 production. This loop allowed for an appropriate strength of the type 2 response[63]. IL-18 derived from several cell types also has been shown to stimulate IL-13 production by ILC2s, especially in the lung and skin[62]. Therefore, several cytokines can promote ILC2 activation under steady-state conditions, with the activation pathway somewhat tissue dependent.

There is also one report, however, suggesting that ILC2s directly sensed the microbiome. Human ILC2s expressed TLRs 1, 4 and 6. In culture, ILC2s were able to produce IL-5 and IL-13 in response to TLR stimulation[14]. The *in vivo* relevance of this observation remains to be determined.

There is controversy regarding the question of dependence of intestinal ILC2s by the microbiome. Transcriptional programs of ILC2 residing in the small intestine lamina propria have been shown to be affected by colonization by commensal bacteria[19]. One laboratory observed an increased number of ILC2s in the small intestine of germ-free mice[68], while a second report suggested there was no difference[62]. Furthermore, in this latter study, germ-free mice had the same number of resident ILC2s in lung and other tissues as specific

pathogen free mice, suggesting that the number of ILC2s was independent of the microbiota outside of the intestine[62].

2-3. ILC3s

The interaction of ILC3s with the microbiome has been explored most extensively in the intestine, where these cells are most numerous. The microbiome drives increased myeloid cell IL-23 and IL-1β at steady-state, which played a prominent role in ILC3 activation[69, 70]. Epithelial cells were also shown to be capable of producing IL-1β[71]. In response to IL-23 and IL-1β, ILC3s produced a variety of cytokines including IL-17, IL-22, IFNγ, and GM-CSF[72]. Notably, there was a clear role for the microbiome in the induction of ILC3 cytokine production, with reduced cytokines by ILC3s from germ-free mice[24, 73, 74].

The $CCR6^+$ subset of ILC3s were a significant pool of cells capable of secreting IL-17 and IL-22 in the intestine of mice[75], but they also exhibited additional functions that could affect the microbiome. $CCR6^+$ ILC3s highly expressed MHCII and exhibited antigen-presenting function[76]. As a result, they influenced commensal bacteria-specific $CD4^+$ T cell responses through direct presentation of microbiota-derived antigens. $CCR6^+$ ILC3s also expressed CD1d, allowing for antigen presentation to iNKT cells[77]. ILC3 expression of MHC class II, and likely their ability to carry out antigen presentation, negatively regulated the interaction of T follicular helper (T_{FH}) cells and B cells, which led to reduced mucosal IgA synthesis in the colon with corresponding effects on the microbiome[78]. In Peyer's patches and small intestine lamina propria, by contrast, both T cell-dependent and T cell-independent IgA at steady state were dependent on $ROR\gamma t^+$ ILCs, via ILC expression of the TNF super family member lymphotoxin[78–80]. In addition to IL-17 and IL-22, $CCR6^-$ ILC3s also could acquire expression of T-bet, which induced IFNγ and tumor necrosis factor (TNF) production[81]. This T-bet expression occurred in response to IL-12 and IL-15 production in response to the microbiome[29].

The function of ILC3s in the intestine was influenced by aryl hydrocarbon receptor signaling (AHR). AHR serves as a receptor for multiple ligands derived from endogenous, dietary or microbial sources. AHR stimulation in ILC3s improved cell survival and increased IL-22 production[82–84]. IL-22 acted on receptors expressed by intestinal epithelial cells (IECs) to promote intestinal stem cell regeneration, production of mucus and antimicrobial peptides, enhanced tight junction formation and fucosylation of proteins and lipids[85–89]. Notably, the anti-microbial peptides produced due to IL-22 stimulation prevented bacteria from associating with the mucus layer[90]. IL-22 receptor signals promoted the addition of terminal fucose sugars to proteins and glycolipids on the surface of epithelial cells. These terminal fucose sugars have been shown to influence the composition of the commensal microbiota[86, 91]. Therefore, while the microbiota induced homeostatic production of IL-22 by ILC3s, these lymphocytes in turn influenced the microbiota, in part by secreting IL-22. This cross-talk is exemplified by the increased colonization by a *Clostridiaceae* family microbe, segmented filamentous bacteria (SFB), in mice deficient for ILC3s[92]. SFB promoted homeostatic Th17 cell accumulation, which is non-inflammatory, in the lamina propria of the ileum[93, 94]. Of note, AHR-deficient mice displayed impaired IL-22 production and increased SFB colonization, suggesting that AHR stimulation may be an important

regulator of IL-22 function[95]. Prostaglandin E2 also promoted ILC3 production of IL-22 at steady state[96]. Blockade of prostaglandin E2 led to systemic infection and inflammation by commensal microbes, due to reduced ILC3 production of IL-22[96]. ILC3s also were shown to express the rearranged during transfection (RET) tyrosine kinase receptor, which allowed them to respond to glial-derived neurotrophic factor (GDNF) family ligands to drive IL-22 synthesis[97]. ILC3 production of GM-CSF and IL-2 also contributed to intestinal homeostasis[24, 98]. GM-CSF produced by ILC3s induced production of IL-10 and RA by intestinal macrophages and DCs, which promoted regulatory T cell (Treg) accumulation in the large intestine[24, 99, 100]. IL-2, also produced by ILC3s, was induced by production of IL-1β by intestinal macrophages. This IL-2 was important for maintaining Tregs in the small intestine[98]. Tregs have been found to prevent an aberrant immune response to the normal microbiome, in their absence, severe colitis resulted[101]. In conclusion, ILC3 can integrate several types of signals in order to influence the microbiome and the response of the immune system to commensal bacteria.

3. The effector functions of ILCs during infections

Once pathogens enter the body at mucosal sites, ILCs participate in the early defense response to clear pathogens in order to avoid systemic infections. ILC effector functions are primarily mediated through cytokine secretion during infection. NK cells have long been known to be potent first line effector cells in helping control pathogen infections[102, 103]. In this section, we will include NK cells but we will emphasize the roles of ILC1, ILC2 and ILC3 in reviewing knowledge about ILC effector functions against four types of pathogenic microbes, including various types of intracellular pathogens, extracellular bacteria, helminths and fungi. Of note, in a number of publications the essential function of ILCs has been demonstrated using immunocompromised mouse models of infection. Therefore, the susceptibility to these infections could be due to defects in the mucosal and/or systemic components of the immune system. Analyses of mucosal tissues, however, combined with studies of the early phases of the response, can help to identify an important ILC function in mucosal tissues, without necessarily excluding systemic effects. The overall findings on microbial infections discussed in this section have been summarized in Figure 2 and Table 1.

3-1. Intracellular pathogens

Obligate intracellular pathogens are entirely dependent on host cells to supply them with energy sources. Obligate intracellular pathogens include all viruses, certain protozoa, such as *Toxoplasma gondii*, and some bacteria. By contrast, facultative intracellular bacteria prefer the intracellular environment of host cells for growth but are capable of surviving outside of host cells. For protection against intracellular pathogens at acute infection, IFNγ is a most important cytokine (Figure 3a). IFNγ aids in clearing infected cells through the activation of macrophages and other cell types. Therefore, IFNγ-producing ILC subsets, such as NK cells, ILC1s, and some ILC3s, can be important for early host defense against this type of pathogens.

3-1-1. Viral infections—Enteric viruses that target IECs, such as rotavirus and norovirus, are a leading cause of gastroenteritis worldwide. Rotavirus has a preferential

tropism for the villous epithelium of the small intestine in humans and mice and is a leading cause of childhood gastroenteritis[104, 105]. IL22-producing ILC3s were shown to act as an amplifier of IFNλ production by IECs during rotavirus infection. IL-22R signals, acting together with signals to the IFNλ receptor, induced optimal STAT1 activation[106]. Murine norovirus (MNV) is typically asymptomatic, but it induced intestinal inflammation in genetically susceptible mice[107–109]. In fact, MNV promoted healthy intestinal function and reversed intestinal abnormalities in germ-free mice[68]. Interestingly, MNV improved the outcome following intestinal injury through induction of IL-22 by ILC3s in an IFNα R1- and CCR2-dependent manner[68, 110]. Human immunodeficiency virus (HIV), and its primate counterpart the simian immunodeficiency virus (SIV), target the gastrointestinal tract as a major site of viral transmission and replication[111–113]. These lentiviral infections break down the integrity of the gastrointestinal mucosa and lead to alteration of gut microbiome and associated disease progression[114–116]. HIV-1/SIV infection induced the rapid loss of ILC3s in the intestinal mucosa[117, 118]. Transcriptional profiling during acute infection revealed increased expression of genes linked with a strong IFN acute-phase response and evidence of gut barrier breakdown[119]. These studies suggest that IL-22 from ILC3s has a protective role against some enteric viral infections in the intestine, either through inhibition of viral replication in IECs or possibly by induction of epithelial cell proliferation and epithelial regeneration after damage.

Viruses that target the respiratory tract, such as influenza virus, respiratory syncytial virus (RSV), vaccinia virus (VACV), reovirus, and adenovirus, cause common colds, bronchiolitis and pneumonia. Influenza viruses typically infect the host through oral or nasal uptake of aerosolized virus particles leading to mild to severe pneumonia[120]. The role of NK cells during viral infection is usually protective[121]. After infection through interactions with DCs and macrophages, NK cells were recruited to the lung from the blood and became activated to secrete a variety of effector cytokines, including IFNγ,[122–124]. Influenza virus infection also enhanced ILC1 activation, similar to NK cells, and ILC1-derived IFNγ contributed to anti-viral immunity[125], likely through the activation of macrophages. Another report suggested, however, that the function of IFNγ in the lung during infection may be harmful by limiting protective ILC2 activity[126]. Influenza virus infection led to increased lung ILC2s[126] and ILC2-derived AREG in the lung helped limit immunopathology by restoring lung function and barrier integrity and by impairing remodeling of respiratory tissues after influenza virus-induced damage[65]. Interestingly, during influenza virus infection, ILC2s have also been reported to convert into ILC1s, providing another example of ILC subset plasticity[127]. Furthermore, ILC-derived IL22 has been suggested to contribute to host protection during influenza infection[128, 129]. Respiratory syncytial virus (RSV) causes infections of the lungs and respiratory tract and is the most common cause of bronchiolitis and pneumonia in infants.[130] A recent study demonstrated that an elevated ILC2 number in nasal aspirates correlated with infant RSV-induced disease severity[131]. $CD4^+$ T cells contributed to ILC2 activation during RSV infection, partly via IL-2 production in the lungs[132]. Lung ILC2s regulated RSV-induced $CD4^+$ T cell activation and expansion in turn, via OX40/OX40L interactions[133].

Vaccinia virus (VACV) initially replicates in airway epithelial cells before spreading to secondary sites of infection, mainly the draining lymph nodes, spleen, gastrointestinal tract,

and reproductive organs[134]. Recovery from a respiratory VACV infection required a controlled inflammatory response by both innate and adaptive immune cells. IFNγ production by $CD8^+$ T cells was demonstrated to control virus dissemination[134], and NK cells were the primary producers of early IFNγ production during VACV infection[135]. It is uncertain if IFNγ-producing helper ILC subsets contributed to early host defense against these viral infections.

3-1-2. Protozoan infections—Obligate intracellular protozoans that infect the small intestine epithelium are among the most common infections worldwide[136]. The innate immune system of immunocompetent hosts typically clears intestinal protozoans during acute infection. However, in immunocompromised individuals, these pathogens can cause chronic, potentially life-threatening, infections. The role of NK cells and NK cell-derived IFNγ for control of *T. gondii*, *Cryptosporidium* and other protozoan infections has been well-described[103, 137, 138]. Less is known, however, about the function of other ILC subsets during parasitic infections, and mechanistic studies have been mostly limited to *T. gondii*. *T. gondii* is a widespread protozoan that is capable of infecting all warm-blooded vertebrates[139]. Accordingly, *T. gondii* causes toxoplasmosis in humans, one of the most common infections worldwide[136]. *T. gondii* infection is caused by several means including ingestion of undercooked, contaminated meat or water, through contact with cat feces that contain *T. gondii*, by transfusion of infected blood, by infected organ transplantation or by transmission from mother-to-fetus through the placenta[140]. Following oral infection by *T. gondii*, the organism infects the gut mucosa by direct invasion of small intestine epithelial cells[141]. *T. gondii* crosses the intestinal barrier and expands locally in the small intestine, particularly in the ileum, within hours[142]. It can disseminate systemically to sites such as the mLN, liver and spleen within days and finally reaches the central nervous system (CNS)[143, 144]. IFNγ has been shown to have a critical function for survival during *T. gondii* infection through the elimination of the parasite[145]. During acute infection, TLR signaling in DCs led to interleukin-12 (IL-12) production that controlled the infection through initiating IFNγ production[146]. Following exposure to IL-12, IFNγ was mainly produced by T cells, NK cells and ILC1s. For production of IFNγ by NK cells, IL-12 and additional cytokines, such as IL-1β and IL-18, were required during *T. gondii* infection[147–149]. It has been shown, however, that parasite-infected NK cells were defective for host defense[150]. Furthermore, it is uncertain if NK cell IFNγ is actually beneficial during infection, as it was reported that antibody mediated NK cell depletion did not affect the survival of *T. gondii* infected mice[151]. Interestingly, ILC1s represent a primary IFNγ secreting population during acute infection with *T. gondii*[17]. ILCs may participate in immunopathology by other mechanisms besides excessive IFNγ production. For example, $NK1^+$ cells activated by IL-15 secreted CCL3 which enhanced intestinal recruitment of inflammatory monocytes during *T. gondii* infection[152]. $Ahr^{-/-}$ mice, which have a defect in ILC3s, were susceptible to *T. gondii*, but exhibited increased T cell activation following infection, suggesting that ILC3s contributed to host defense against *T. gondii* infection through limiting immunopathology mediated by T cell activation[153].

The protozoan *Giardia lamblia* is an extracellular pathogen found worldwide that causes giardiasis, a disease that is associated with gastrointestinal malfunction[154]. This infection

mostly occurs via oral uptake of *G. lamblia* cysts in contaminated drinking water. Following oral infection, *G. lamblia* colonizes the small intestine where the organism attaches to the intestinal epithelium, replicates vegetatively and disrupts intestinal barrier function. A recent study has shown that *G. lamblia* infection increased the number of ILC3s in the small intestinal lamina propria and augmented IL-17A production by them[155]. It is still not known, however, if this ILC3-derived IL-17A is important for host dense.

3-1-3. Facultative intracellular bacterial infections—Pathogenic facultative intracellular bacteria that target intestinal tissues, such as *Yersinia enterocolitica (Y. enterocolitica)* and *Salmonella typhimurium (S. typhimurium*) are common causes of food-borne infectious gastroenteritis. These bacterial infections can lead to severe systemic infections, especially in immunocompromised individuals. It is well known that IFNγ plays a critical role in intestinal immunity against them[156–158]. While $CD4^+$ T cells are important after the second week of bacterial infection, *Y. enterocolitica* is frequently cleared in 1–2 weeks[159, 160]. Furthermore, athymic (nude) mice, which lack T cells, are resistant to infection with *L. monocytogenes* and *S. typhimurium*[161, 162]. These studies suggest that innate immune cells are sufficient to mediate early host defense against these types of bacteria.

The role of ILCs in intestinal bacterial infection has been well demonstrated with several intracellular bacteria. *Y. enterocolitica* is a gram-negative, rod-shaped, pathogenic bacterium that infects the small intestine, especially the ileum. After oral uptake, *Y. enterocolitica* replicates in the small intestine, invades Peyer's patches of the distal ileum, and disseminates to the spleen and liver[163]. Recently, it has been shown that ILC populations, especially $CCR6^-$ ILC3s, including those that do or do not express NKp46, were a major source of IFNγ production for host protection against *Y. enterocolitica*[164, 165]. ILC1s and NK cells also released this cytokine after *Y. enterocolitica* infection, and likely contributed to host defense as well. The herpes virus entry mediator (HVEM), a member of the TNF receptor superfamily (also known as TNFRSF14), was expressed by all small intestine ILC subsets in mice and all ILCs in human peripheral blood[164, 166]. Interestingly, mice with an ILC3-specific deletion of the gene encoding HVEM exhibited reduced IFNγ production, higher bacterial burdens and increased mortality after *Y. enterocolitica* infection. LIGHT, a member of the TNF superfamily, was shown to serve as the ligand that signaled HVEM for the induction of protective IFNγ secretion from ILC3s. Thus, HVEM signaling mediated by LIGHT was shown to play a critical role in regulating ILC3-derived IFNγ production for protection following *Y. enterocolitica* infection[164]. HVEM signaling in cells other than lymphocytes also has a critical role for host defense against other bacterial infections, such as *Citrobacter rodentium*, *Streptococcus pneumoniae* and *Clostridium difficile*[167, 168].

S. typhimurium is a gram-negative, rod-shaped, pathogenic bacterium that can attach to IECs and attack them by producing toxins. Once *S. typhimurium* invades the gut mucosa, it can cause systemic infections. IFNγ plays a critical role in protection against *S. typhimurium*. IFNγ controlled mucin release by goblet cells restricted pathogen growth in intestinal tissue by formation of a mucin gel[169]. During salmonellosis, $NKp46^+$ ILC3s were the main source of protective IFNγ production[81, 170]. It has been shown that $Tbx21^{-/-}$ mice, which lack several IFNγ-producing cell types, including $NKp46^+$ ILC3s, had a significant

defect in the ability to secrete mucus[81]. IL-22 and lymphotoxin production by ILC3s contributed to host defense from *S. typhimurium* infection through induction by IECs of the fucosylation of their glycoproteins and glycolipids, which was mediated by the enzyme fucosyltransferase 2 (Fut2)[170]. The fucose group was metabolized by commensal bacteria into beneficial metabolites, such as short-chain fatty acids, that boosted barrier immunity. This process also led to reduced expression of the *S. typhimurium* virulence gene[86].

The role of ILCs in the infection of lung tissue with facultative intracellular bacteria also has been demonstrated. *Mycobacterium tuberculosis* (*Mtb*) mainly affects the lungs and is among the ten leading causes of mortality worldwide[171]. The importance of IFNγ-producing T cells for protection against *Mtb* has been demonstrated[172] and NK cell-derived IFNγ was protective in T cell-deficient mice[173]. During *Mtb* infection, ILCs, especially ILC3s, accumulated in the lungs of humans and mice, and mice with specific deletion of ILC3s exhibited increased susceptibility to *Mtb* infection. Increased susceptibility in this model was observed in $Il17^{-/-}Il22^{-/-}$ double knockout mice, implicating a role for these ILC3-derived cytokines. Furthermore, *Mtb* infection increased expression of the C-X-C motif chemokine receptor 5 (CXCR5) on circulating ILC3s and also increased plasma levels of its ligand, C-X-C motif chemokine ligand 13 (CXCL13). ILCs therefore located in lymphoid follicles and granuloma-like structures after *Mtb* infection[174]. These data suggest a protective role for ILC3s in regulating early *Mtb* infection through signaling by CXCR5 and ILC3 secretion of cytokines. The mechanism underlying the protective effects of IL-17 and IL-22 in this infection remains unknown. Previously, it has been proposed that IL17-producing $CD4^+$ T cells promoted chemokine expression in the lung and the recruitment of IFNγ-producing $CD4^+$ T cells, which ultimately impaired bacterial growth[175]. IL-17 and IL-22 derived from ILC3s could have a similar function.

In several other infections of mice with facultative intracellular bacteria, ILCs have been shown to be activated early to secrete cytokines such as IFNγ, including infections with *Campylobacter jejuni* and *Shigella flexneri*[176, 177]. While these data suggest that ILC responses could be essential for host defense against these microbes, this remains to be demonstrated.

3-2. Helminth infections

Helminths are invertebrates with elongated, flat or round bodies and are comprised of three taxonomic groups: roundworms (nematodes), tapeworms (cestodes), and flukes (trematodes). They can live as parasites in animals and plants, or as free-living organisms in aquatic and terrestrial environments. Infection by helminths is generally prevalent in developing countries and can cause morbidity and mortality in immunocompromised or malnourished individuals. To study helminth infections, *Nippostrongylus brasiliensis (N. brasiliensis)*, which is a gastrointestinal roundworm that infects rodents, is widely used. Third stage larvae (L3) of *N. brasiliensis* infect mice through the skin and migrate to the lungs, where they are coughed up, swallowed and reach the small intestine. Intestinal worms develop into mature adults that produce eggs. They are expelled in C57BL/6 mice by day 10–15 post-infection (p.i.)[178]. Production of the Th2 cytokines IL-13 and IL-5 was shown to be required for worm expulsion, through the induction of goblet cell hyperplasia, which is

important for mucin secretion, and activation and recruitment of eosinophils to the sites of infection (Figure 3b)[179]. Interestingly, *Rag1*$^{-/-}$ mice were protected from *N. brasiliensis* infection and had similar levels of IL-13 and IL-5 compared to C57BL/6 mice[180]. Furthermore, adoptive transfer of IL13^{+} ILC2s rescued impaired worm expulsion, suggesting that ILC2 function is sufficient for worm clearance[180, 181].

Infection with a different helminth, *Heligmosomoides polygyrus* (*H. polygyrus)* was controlled by IL-4-dependent immunity. *H. polygyrus* is a naturally occurring intestinal roundworm of rodents. Following *H. polygyrus* infection, ILC2s produced significant amounts of IL-4, and this contributed to subsequent ILC2 expansion and Th2 cell differentiation[182]. ILC2s also expanded *in vivo* in response to the type-2-inducing cytokines IL-25 and IL-33[61, 180, 181, 183]. IL-25 was constitutively produced by tuft cells, and tuft cell numbers were markedly increased in the small intestine following helminth infections with *N. brasiliensis* or *H. polygyrus*[63, 67, 184]. After infection, tuft cell-derived IL-25 stimulated ILC2s to secrete increased IL-13, which acted on epithelial stem cells to promote differentiation of tuft and goblet cells. In this way, a tuft cell-ILC2-epithelial response positive feedback circuit is generated that can drive small intestinal remodeling during parasite infection[67]. ILC2s activated by IL-25 also promoted antigen-specific Th2 and Th9 function that contributed to the control of infection with the roundworm *Trichinella spiralis*. This infection is caused by consuming undercooked or raw meat[185]. Lack of IL-22, in contrast, impaired worm expulsion upon *N. brasiliensis* infection and infection with a different helminth, the roundworm *Trichuris muris*, despite normal levels of type 2 cytokine production. This was due to reduced goblet cell hyperplasia, suggesting that ILC3-derived IL-22 also contributed to host defense against helminths[186].

ILC2 function is negatively and positively regulated during infections by several molecules, including transcription factors and cytokines known to regulate cytokine production by other immune cell types. For example, the transcription factor AHR, important for IL-22 production, is highly expressed by intestinal ILC2s. AHR expression by ILC2s, however, suppressed the normal cellular functions of these cells through inhibition of expression the IL-33 receptor ST2, IL-5, IL-13 and AREG, in a cell-intrinsic manner[187]. AHR deficiency therefore enhanced ILC2 function, and led to enhanced protective immunity against intestinal *H. polygyrus* infection[187]. Loss of the Th1 and ILC1 transcription factor T-bet also led to expansion and increased activity of ILC2s and enhanced protection from the roundworm *Trichinella spiralis*[188]. By contrast, loss of ILC-intrinsic Arginase 1 (Arg1) prevented ILC2 responses after *N. brasiliensis infection*[189]. It was shown that Arg1 is critical for regulating ILC2 responses through its effects on cellular metabolism, by controlling arginine catabolism, polyamine biosynthesis and aerobic glycolysis[189]. ILC2s preferentially use fatty acids (FAs) to maintain their function during helminth infection and it has been proposed that enhanced FA usage and FA-dependent IL-13 production by ILC2s could represent a host adaptation to maintain barrier immunity under dietary restriction[190].

In the lung, infection with the roundworm *Strongyloides venezuelensis* (*S. venezuelensis*) increased the number of alveolar epithelial type II cells (ATII) and the level of IL-33. ATII-derived IL-33 induced accumulation of ILC2s, which produced IL-5 and IL-13, leading to lung eosinophilic inflammation and worm expulsion[191]. Interestingly, *S. venezuelensis*-

exposed mice were significantly more resistant to infection by *N. brasiliensis* and this resistance also was dependent on ILC2s, suggesting that mice acquired a type of immune memory or trained immunity by ILC2s following *S. venezuelensis* infection[192]. Infection with the fluke *Schistosoma mansoni* (*S. mansoni)* elicited the expression of TSLP and IL-33, which may have activated ILC2s[193], although ILC2 activation was not tested. Using a mouse model of coinfection with *Mtb* and *S. mansoni*, however, IL-25 and ILC2s induced pulmonary fibrosis that occurred independently of T cell-mediated antigen-specific responses[194]. In summary, ILCs have been shown to provide protection from infection of mice with a variety of helminths, in most cases by eliciting and stimulating type 2 immunity.

3-3. Extracellular bacterial infections

Extracellular bacterial pathogens may adhere to epithelial cell surfaces and some secrete potent toxins leading to infectious disease. One of the best studied examples of such a pathogen in the intestine is *Citrobacter rodentium (C. rodentium)*, a gram negative, enteric murine pathogen that shares an infection strategy and virulence factors with the human diarrheagenic pathogens enteropathogenic *E. coli* and enterohemorrhagic *E. coli* (EPEC and EHEC). *C. rodentium* mainly colonizes the cecum and proximal colon and causes acute, robust colitis, colonic crypt hyperplasia and dysbiosis[195]. *C. rodentium* were able to colonize the colon by day 7–14 p.i., but bacterial levels in the cecum and colon virtually were cleared by day 21–28 p.i. in wild type mice[196]. While T cells and B cells were required for clearance of *C. rodentium*, ILCs were essential for early host defense. Mice deficient for the bZip transcription factor Nfil3, which have a loss of NK cells, ILC1s, and ILC3s, were highly susceptible to *C. rodentium* infection[197]. The ILC3 subset of ILCs was essential in absence of T cells, but partially redundant when T cells were present[45]. Considering ILC3 subsets, $NKp46^+$ ILC3s were not required in fully immune competent mice, suggesting that LTi and/or $NKp46^-$ ILC3s provided protection[45].

IL-22 was shown to be important for protection from *C. rodentium*[198] and IL22-deficient mice therefore exhibited increased intestinal epithelial damage, systemic bacterial burden and mortality (Figure 3c)[53, 74, 198–200]. This cytokine played crucial roles in host defense against *C. rodentium* and other extracellular pathogens by maintaining the epithelial barrier through multiple functions, including induction of antimicrobial peptide expression, stimulation of epithelial cell proliferation, and modification of the microbiome. ILC3s, stimulated by IL-23, were the main source of IL-22 early, while $CD4^+$ T cells were the major source of IL-22 later in *C. rodentium* infection [201, 202]. IL-22 was indispensable for the induction of anti-microbial agents by colonic epithelial cells, such as RegIIIγ and RegIIIβ, following *C. rodentium* infection. Exogenous RegIIIγ improved the survival of IL-22 deficient mice, suggesting that IL-22 mediated production of anti-microbial proteins was essential[52].

Several factors have been shown to regulate the differentiation and localization of intestinal ILC3s with consequences for the host response to *C. rodentium*. IL-22-producing ILC3s were observed to be Ahr-dependent, as a consequence, Ahr was critical for the clearance of *C. rodentium*.[42, 82, 187]. Mice with epithelial-specific overexpression of *Cyp1a*, which depletes Ahr ligands, also displayed loss of $IL22^+$ ILC3s and increased susceptibility to *C.*

rodentium infection[203]. The transcription factor Ikaros is a binding partner of Ahr in ILC3s. Ikaros negatively regulated the number of ILC3s in a cell-intrinsic manner, through zinc finger-dependent inhibition of the transcriptional activity of Ahr. Therefore, in mice deficient for Ikaros expression, ILC3s exhibited an enhanced protective activity for *C. rodentium*[204]. Recently, GPR183, a G protein receptor that binds oxysterols, was shown to be required for ILC3-mediated protection against *C. rodentium* by influencing the localization of ILC3s in the lamina propria[205].

Clostridium difficile (*C. difficile)* is a spore-forming, gram-positive, toxin-producing anaerobic bacterium that overgrows in hospitalized patients after prolonged use of antibiotics. It causes infectious diarrhea and pseudomembranous colitis[206]. The pathogenicity of *C. difficile* is mediated by two clostridial toxins, toxin A (TcdA) and B (TcdB), which disrupt the cytoskeletal structure and the tight junctions of epithelial cells[207]. Antibiotic-treated IL-22-deficient mice were susceptible to *C. difficile* infection[208], providing a model system for studying pathogenesis by these bacteria. ILCs were the predominant source of IL-22 and IFNγ following *C. difficile* infection[49]. Loss of ILC1s in mice lacking T-bet (*Tbx21*$^{-/-}$ mice) that are also Rag protein deficient, or ILC1-derived IFNγ led to increased susceptibility to *C. difficile*[49]. In the absence of IL-22, enterobacterial pathobionts translocated from the intestinal lumen into peripheral organs following *C. difficile* infection[208]. Thus, these studies showed that ILC1-derived IFNγ and ILC3-derived IL-22 have a cooperative role for host defense against *C. difficile* in the intestine and peripheral organs.

Gram-positive *Streptococcus pneumoniae* (*S. pneumoniae*) and gram-negative *Klebsiella pneumoniae* (*K. pneumoniae*) are extracellular commensal bacteria in humans. However, they also can act as opportunistic pathogens that cause acute or chronic infections, especially in immunocompromised hosts. *S. pneumoniae* is the most common cause of community-acquired pneumonia. It is a commensal bacterium of the human upper respiratory tract, but under specific circumstances, it can migrate to the lower respiratory tract, causing pneumonia, otitis media, septicemia and meningitis[209, 210]. *S. pneumoniae* induced IL-17 and IL-22 production in the lung, especially by CCR6^{+} ILC3s[211]. IL-22 deficient mice were susceptible to *S. pneumoniae* infection, which could be rescued by systemic administration of recombinant IL-22[212]. Most lung ILC3s co-expressed RORγt and CCR6. The CCR6 ligand, CCL20, was strongly upregulated in the lung during infection, suggesting that recruitment of ILC3s to the lung might be due to increased CCL20[211]. Flagellin, the agonist for Toll-like receptor 5 (TLR5) enhanced the production of IL-17 and IL-22 by ILC3s via activation of DCs, thereby contributing to protection from *S. pneumoniae*[211, 213]. In contrast, ILC2-derived IL-13 was detrimental in *S. pneumoniae* infection due to the persistence of M2 type alveolar macrophages, which were less efficient in triggering inflammatory responses compared to M1 macrophages[53]. It has been shown that IL-22 production by NKp46^{+} ILCs was increased during *K. pneumoniae* infection and that Il-22 promoted host defense[214]. The importance of IL-22 in this infection is controversial, however, as another study reported that IL-17A produced by ILC3s contributed to *K. pneumoniae* through enhancement of the antimicrobial activity of inflammatory monocytes by IL-17A[215]. IFNγ production by NK cells also contributed to protection from *K. pneumoniae* by promoting macrophage activation[178].

3-4. Fungal infections

Many kinds of fungi colonize the human body, but they usually do not cause infection in healthy individuals. However, fungi can become opportunistic pathogens and cause various fungal diseases in immunocompromised individuals, ranging from mild mucosal infections to severe systemic infections. Examples include *Candida albicans* (*C. albicans*), which can be found in the oral cavity, intestine and skin. Similarly, *Cryptococcus neoformans* (*C. neoformans*) and *Aspergillus fumigatus* (*A. fumigatus*) can be found in the lung. These three fungi are often present without causing disease, but they cause many cases of opportunistic mycoses that are associated with a high rate of mortality[216].

The mucosal epithelium is the first line of defense against *Candida* species. Upon recognition of the invading *Candida* species, epithelial cells secreted antimicrobial peptides, such as β-defensins, to inhibit fungal growth[217, 218]. It is well known that IL-17 is required for protective antifungal immunity at mucosal surfaces[219]. IL-17 induced expression of antimicrobial peptides, which have direct antifungal activity toward *Candida*[220]. IL-22 can act with IL-17 to enhance expression of these antimicrobial peptides[221]. IL-17 also was shown to have a critical role in the prevention of invasive fungal infections by activating neutrophils to kill fungi[222]. Interestingly, athymic mice which lack T cells were resistant to *C. albicans*, indicating that innate immune cells have an essential function[161]. Indeed, ILCs were the primary source of IL-17 during oropharyngeal *C. albicans* infection[223] (Figure 3d). IL-17A and IL-17F were produced upon *C. albicans* infection in an IL23-dependent manner[223]. ILC2s, which express intermediate amounts of RORγt, contributed to protection against *C. albicans* infection through production of IL-17[20].

In the lungs of neutropenic mice with *A. fumigatus* infection, NK cells were the major population of cells capable of generating IFNγ and NK cell-derived IFN-γ also was essential to host defense against *A. fumigatus*[224, 225]. During infection with *C. neoformans*, IL-33/ST2 signaling contributed to the expansion of ILC2s and their production of IL-13 that likely facilitated *C. neoformans* growth and dissemination, although type 2 immune responses from $CD4^+$ T cells also played a role in this example of infection-induced immunopathology. However, ILC2s were not able to induce type 2 inflammation in pulmonary cryptococcosis in the absence of adaptive lymphocytes[226, 227].

Conclusions

ILCs are the most recently discovered lymphocyte population, but already numerous studies have demonstrated that they can act as sentinels of the mucosal immune system which contribute to an appropriate immune response to the microbiome while providing active protection following acute infection. For example, at steady state, ILC2s and ILC3s respond to diverse cues and produce cytokines to maintain and integrity of the mucosal tissues. Infection-augmented IL-4, IL-5 and IL-13 production by ILC2s plays a critical role in the clearance of helminths. Also, ILC3 production of IL-17, IL-22, and other cytokines such as IFNγ, directly contribute to host defense against extracellular bacterial and fungal infections. Finally, during viral, bacterial and protozoal infections, NK cells and ILC1s become activated and serve as early producers of IFNγ to drive pathogen clearance. It is likely that the full range of signals inducing tissue-resident ILC activation, the types of

responses that can be elicited by ILCs, and the full extent of the plasticity between ILC subsets remain to be fully characterized. NK cells have been studied much longer, and it is known that primed NK cells could be recruited into a secondary immune response following viral infection[228]. This phenomenon, sometimes referred to as 'innate memory', suggests that ILCs might exhibit similar changes after stimulation. In fact, ILC2s stimulated with IL-33 during an allergy response acquired a memory-like phenotype because, compared to naïve ILC2s, they produced even higher levels of cytokines after a subsequent IL-33 stimulation[229]. Additional research will be required to characterize the long-term responses of ILCs to acute activation signals and to identify the mucosal infections in humans in which the responses by these cells are most significant for host protection.

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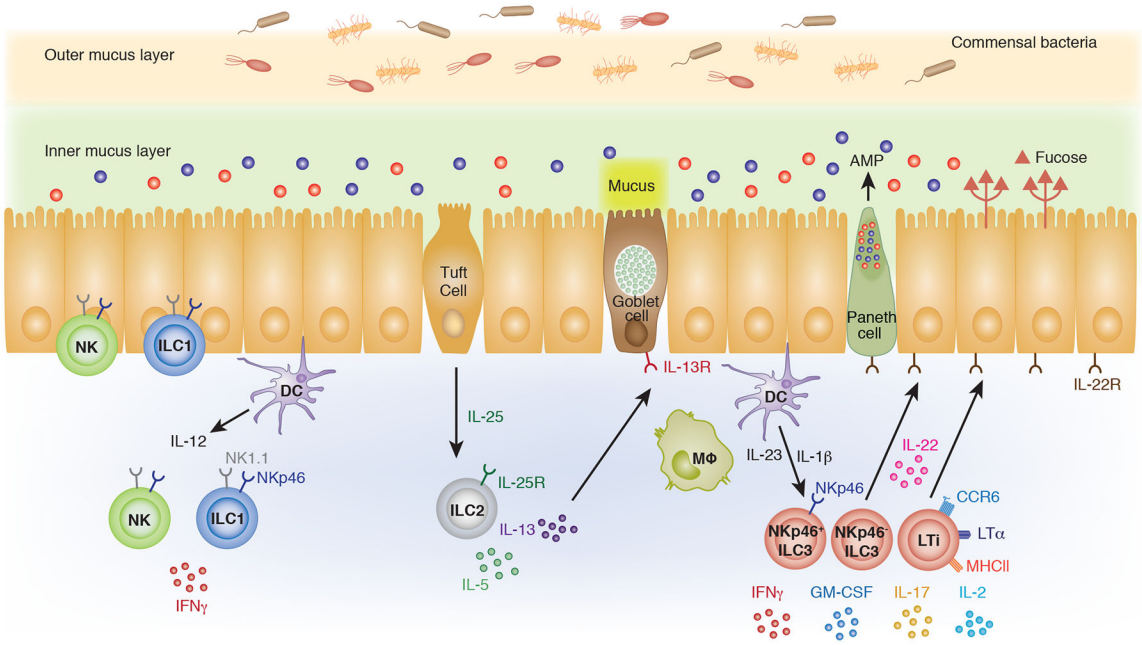


Figure 1. The role of ILCs in mucosal tissue at steady state.

ILC subsets in the intestine are illustrated and for simplicity the role of cytokines in activating ILCs is emphasized, as opposed to other influences of ILC behavior. NK cells and ILC1s can be found mostly in the epithelium. Expression of IL-25R by ILC2s in the lamina propria allows them to respond to IL-25 from tuft cells. Activation of ILC2s leads to IL-5 and IL-13 production, which promotes goblet cell mucus production. Lamina propria ILC3s respond to IL-23 and IL-1β production by myeloid cells. Steady state cytokine production by ILCs, especially IL-22, signals Paneth cells and epithelial cells to induce antimicrobial peptide (AMP) production and other responses, such as fucosylation of glycoproteins and glycolipids, both of which contribute to the composition of the microbiome.

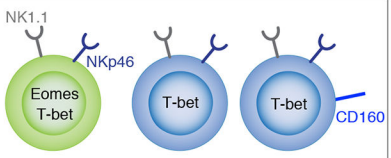
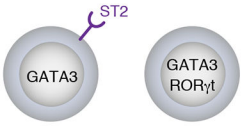
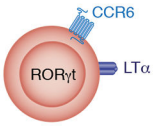
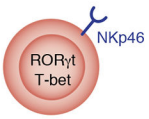
	NK	ILC1	ieILC1	nILC2	iILC2	LTi (CCR6$^+$ ILC3)	NKp46$^{+/-}$ILC3 (CCR6$^-$ ILC3)
Surface markers & Transcription factors							
Stimulator cytokines	IL-12 IL-15 IL-18	IL-12 IL-15 IL-18	IL-12 IL-15	IL-25 TSLP IL-18 IL-33	IL-25 TSLP IL-18	IL-23 IL-1β	IL-23 IL-1β
Effector cytokines	IFNγ Perforin Granzyme	IFNγ	IFNγ	IL-4 IL-5 IL-13 IL-9 AREG	IL-4 IL-5 IL-13 IL-17	IL-17 IL-22 GM-CSF LT IL-2	IL-17 IL-22 GM-CSF IFNγ IL-2
Viruses	Respiratory virus (*influenza*)					Enteric virus (*rotavirus, norovirus*)	
Protozoa	Intracellular protozoa (*T. gondii*)					Intracellular protozoa (*T. gondii*) Extracellular protozoa (*G. lamblia*)	
Facultative intracellular bacteria						Enteric bacteria (*Y. enterocolitica, S. typhimurium*) Respiratory bacteria (*Mtb*)	
Helminths				*N. brasiliensis, H. polygyrus, T. spiralis, S. venezuelensis, S. mansoni, T. muris*			
Extracellular bacteria	Enteric bacteria (*C. difficile*)					Enteric bacteria (*C. difficile, C. rodentium*) Respiratory bacteria (*S. pneumoniae, K. pneumoniae*)	
Fungi				Respiratory fungi (*C. neoformans*)		Oral/Intestinal fungi (*C. albicans*)	

Figure 2.

ILC subsets and functions during infection. ieILC1 = intraepithelial ILC1.

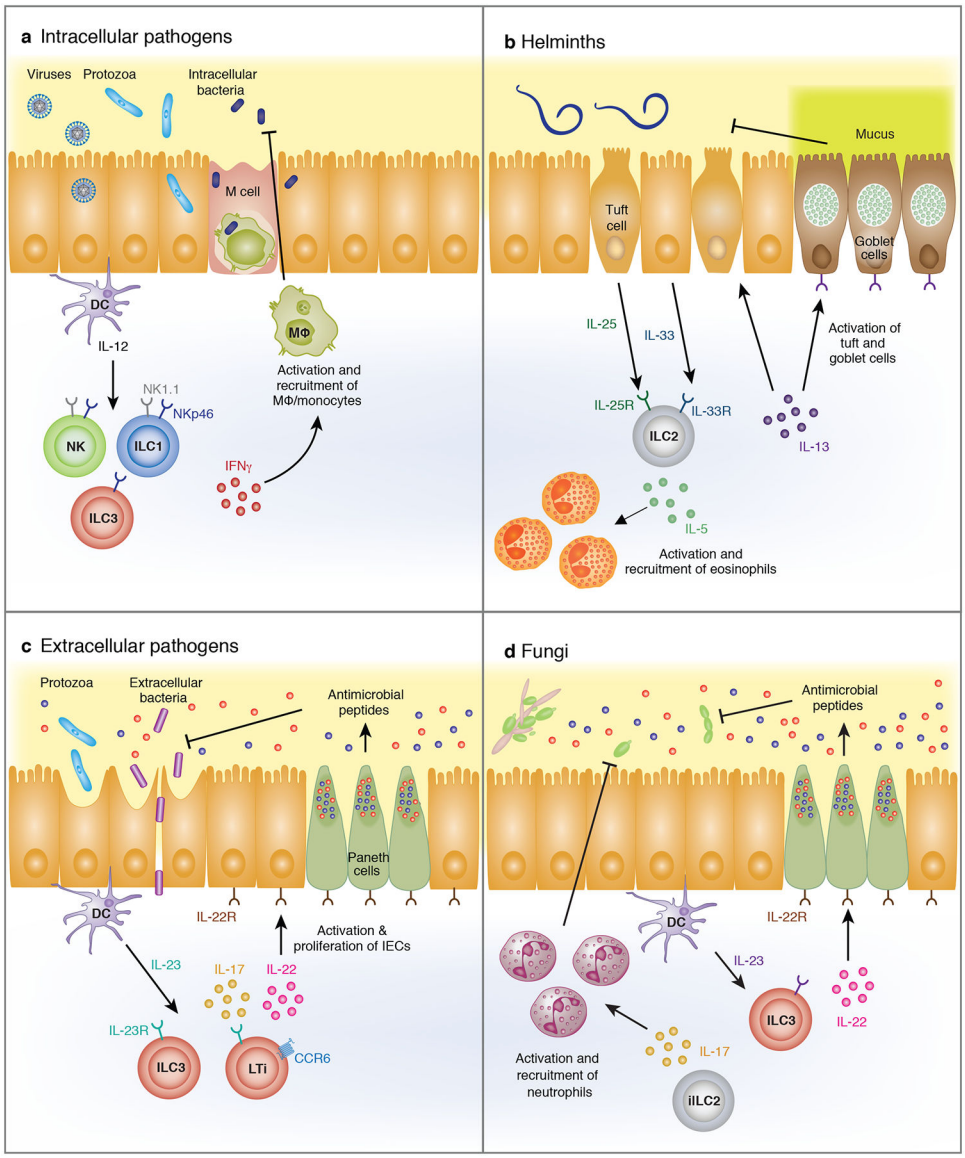


Figure 3. The effector functions of ILCs during intestinal mucosal infection.

For simplicity the role of cytokines in activating ILCs is emphasized. **a**. Following infection by intracellular pathogens, such as viruses, protozoa, and facultative intracellular bacteria, myeloid-derived IL-12 activates NK cells, ILC1 and CCR6^{-} ILC3 (NKp46^{+} ILC3 and NKp46^{-} ILC3) to stimulate the production of IFNγ. ILC-derived IFNγ recruits and activates phagocytes to clear pathogens. **b**. Following helminth infection, increases in tuft cell-derived IL-25 and IEC-derived IL-33 drive IL-5 and IL-13 production by ILC2s. ILC2-derived IL-5 recruits and activates eosinophils, and IL-13 induces the production of mucus by goblet cells for clearance of helminths. **c**. Upon infection by extracellular pathogens such as protozoa and bacteria, DC-derived IL-23 and IL-1β activate ILC3 to produce IL-22 and IL-17. ILC3-derived IL-22 and IL-17 induce the production of antimicrobial peptides for host defense. **d**. Upon infection by fungi, DC-derived IL-23 activates ILC3 to produce IL-22 and IL-17. ILC3-derived IL-22 and IL-17 induce the production of antimicrobial peptides.

iILC2, which express intermediate amounts of RORγt, also can produce IL-17 to protect against fungal infection.

Table 1.

Effector functions of ILCs against microbial mucosal pathogens

Pathogen			Mucosal tissue	Involved ILC subsets*	Main cytokine	Immune response	Ref
Viruses	***Rotavirus***	Non-enveloped DS RNA virus	SI	ILC3	IL-22	Protective	106
	Murine Norovirus (MNV)	Non-enveloped SS RNA virus	SI	ILC3	IL-22	Protective	68, 110
	Influenza virus	Enveloped virus SS RNA virus	respiratory tract	ILC1 ILC2 ILC	IFNγ AREG IL-22	Protective Protective Protective	125 65 128, 129
	Respiratory syncytial virus (RSV)	Enveloped virus SS RNA virus	Lung	ILC2	?	Protective	131–133
Protozoa	***Toxoplasma gondii***	Obligate intracellular parasite	SI	ILC1 ILC3	IFNγ	Protective	17 153
	Giardia lamblia	Extracellular parasite	SI	ILC3	IL-17	?	155
Facultative intracellular bacteria	***Yersinia enterocolitica***	Gram −	SI	NKp46^{+}ILC3 NKp46^{-}ILC3	IFNγ	Protective	164
	Salmonella typhimurium	Gram −	LI	NKp46^{+}ILC3	IFNγ	Protective	81, 170
	Mycobacterium tuberculosis	Gram −/+	Lung	ILC3	IL-17, IL-22	Protective	174
Helminths	***Nippostrongylus brasiliensis***	Roundworm	SI, Lung	ILC2 ILC3	IL-5, IL-13 IL-22	Protective Protective	180, 181 186
	Heligmosomoides polygyrus	Roundworm	SI, Lung	ILC2	IL-4	Protective	182
	Trichinella spiralis	Roundworm	SI	ILC2	IL-4, IL-5, IL13	Protective	185
	Strongyloides venezuelensis	Roundworm	SI, Lung	ILC2	IL-5, IL-13	Protective	191
	Schistosoma mansoni	Fluke	SI, Lung	ILC2	IL-13	Protective	194
	Trichuris muris	Roundworm	LI	ILC2 ILC3	IL-5, IL-13 IL-22	Protective Protective	190 186
Extracellular bacteria	***Clostridium difficile***	Gram +Opportunistic pathogen	SI, LI	ILC3 ILC1	IL22 IFNγ	Protective Protective	208 49
	Citrobacter rodentium	Gram–Pathogen	LI	ILC3	IL-22	Protective	53, 74, 198–200
	Streptococcus pneumoniae	Gram +Opportunistic pathogen	Lung	CCR6^{+}ILC3 ILC2	IL-22 IL-13	Protective Pathological	211, 212 53
	Klebsiella pneumoniae	Gram - Opportunistic pathogen	Lung	CCR6^{+} ILC3	IL22, IL-17	Protective	214, 215
Fungi	***Candida albicans***	Opportunistic invasive mycoses	Oral, intestine	ILC3	IL-17, IL-22	Protective	230, 231
	Cryptococcus neoformans	Opportunistic invasive mycoses	Lung	ILC2	IL-13	Protective	226, 227

*NK cells indicated only for those infections with no role demonstrated for helper ILCs