European Journal of Microbiology and Immunology 3 (2013) 3, pp. 143–151
DOI: 10.1556/EuJMI.3.2013.3.1

INNATE LYMPHOID CELLS IN THE DEFENSE AGAINST INFECTIONS

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Received: July 2, 2013; Accepted: July 12, 2013

Barrier surfaces are under constant attack by potentially dangerous microbes. Interestingly, mucosal tissues contain a large number of innate lymphocytes now collectively referred to as innate lymphoid cells (ILCs). Different groups of ILCs are being distinguished, each of which produce an array of cytokines strikingly resembling the profile of the various T helper cell effector subsets. Over the last couple of years, evidence has been emerging that the various ILC subsets play important roles in immune defense against mucosal infections. In this review, I will introduce the various groups of ILCs and then focus on their roles for immunity to mucosal infections.

Keywords: natural killer (NK) cells, innate lymphoid cells (ILCs), *Helicobacter, Salmonella, Candida*

Introduction

The immune system is a network of migratory and tissue-resident cells that has developed to protect multicellular organisms against infections. As sensors of "infectious non-self," the cellular components of the immune system are equipped with immunoreceptors which, upon triggering, initiate a coordinated response against the pathogen. In vertebrates, the immune system consists of an adaptive and an innate arm. Lymphocytes (B and T cells) of the adaptive immune system are highly specific for "non-self" antigens because they express recombining receptors creating an almost infinite repertoire of specificities. While a highly antigen-specific response allows to specifically target pathogens, it comes at the cost of requiring clonal expansion of the few T or B cells specific for the respective antigen in order to be protective. Thus, the first weeks of infection are dominated by the action of the evolutionary older innate immune system that can rapidly react to pathogens. Its immune recognition receptors have broader specificities and, for example, can directly recognize entire groups of bacteria such as all gram-negative bacteria (i.e., pattern recognition receptors) or can sense aberrant (i.e., transformed or infected) cells, as is the case for some of the immunoreceptors expressed by innate lymphocytes such as natural killer (NK) cells. The two arms of the immune system are highly integrated and crosstalk on multiple levels. Powerful adaptive immunity requires signals from innate immune system components and, therefore, impaired innate immunity leads to crippled B and T cell responses [1]. Sometimes, innate immune cells are sufficient by themselves to deal with a pathogen, but the adaptive arm is required for memory responses upon re-encounter of a pathogen.

The cellular arm of the innate immune system consists of myeloid cells and a lymphoid compartment, innate lymphocytes. During the last couple of years, our understanding of innate lymphocytes has been profoundly transformed by the discovery of new innate lymphocyte lineages that are substantially represented at mucosal surfaces. These are now collectively referred to as innate lymphoid cells (ILCs) [2]. To categorize the various subsets as members of a family of ILCs may be justified, because all ILCs share a developmental program characterized by the requirement of the transcriptional regulator inhibitor of DNA binding 2 (Id2) [3–5] and of IL-7 receptor signaling for development and/or maintenance of all ILCs [4–8]. In this review, I will first introduce the various ILC lineages and then focus on their roles in the protection against infections.

Groups of innate lymphoid cells

In the last 5 years, it has become apparent that NK cells are not the solitary representative of innate lymphocytes. At least two more lineages have been identified, and they are now referred to as distinct groups of ILCs. Interest-

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ISSN 2062-509X / $ 20.00

ingly, the effector profiles of the currently recognized three groups of ILCs and the underlying transcriptional circuitry closely resemble that of the various T helper cell effector subsets. For an in-depth description of the transcriptional programs of ILCs, I can recommend reading some recent excellent reviews on this topic [9–13].

Group 1 ILCs

Group 1 ILCs (ILC1s) produce "type 1 cytokines" such as interferon-γ (IFN-γ) and tumor necrosis factor (TNF) and express the T-box transcription factor T-bet. According to the consensus proposal [2], conventional NK cells may be one ILC1 subset. Certainly, NK cells fulfill the ILC1 criteria in that they express T-bet [14–16] and are potent innate producers of IFN-γ and TNF [17]. However, most NK cell subsets do not developmentally depend on T-bet because conventional splenic NK cells are normally represented in mice lacking *Tbx21*, the gene encoding T-bet [14, 15]. This is in contrast to ILC2s and ILC3s that cannot develop in mice that are genetically deficient for their lineage-defining transcription factors (i.e., Gata3 or RORγt, respectively) [5, 18, 19]. Future studies will need to address if a subset of ILC1s exists that developmentally requires T-bet [20].

In humans, an NKp44$^+$ CD103$^+$ intraepithelial lymphocyte (IEL) subset has been identified that may be a T-bet-dependent ILC1 subset distinct from the NK cell lineage [21]. This IEL subset expresses markers of TGF-β imprinting (e.g., CD103, CD9, NEDD9) and adhesion molecules (e.g., CD49a, $\alpha_E\beta_7$ integrin) that allow for intraepithelial location similar to the activated phenotype observed for tissue-resident, memory CD8 T cells [22]. In mice, CD3-negative IELs did not express CD103 but displayed the cell surface receptor CD160, which is also found on all human NKp44$^+$ CD103$^+$ IELs. Mouse CD160$^+$ IELs could not be stimulated by IL-23 plus IL-1β for IFN-γ production (which can induce its expression in ILC3 subsets) but reacted promptly to the combination of IL-12 and IL-15. CD160$^+$ IELs resemble NK cells in that they express the NK cell receptors NKp46 and NK1.1 and developmentally depend on the transcription factor NFIL3 (also called E4BP4) which is strictly required for the development of NK cells [21, 23, 24]. In contrast to NK cells, CD3$^-$ CD160$^+$ IELs were independent of IL-15 receptor α for their development or maintenance. In line with the predicted ILC1 developmental requirements, CD3$^-$ CD160$^+$ IELs were reduced in T-bet-deficient mice but were independent of AhR or RORγt [21], both of which are required for the differentiation or maintenance of ILC3s [18, 19, 25–27]. CD3$^-$ CD160$^+$ IELs may thus represent a *bona fide* subset of ILC1s.

Recently, a series of reports have identified additional ILC subsets expressing T-bet [16, 28–30]. However, these papers are dealing with RORγt-expressing ILC3 populations that can initiate the expression of an intensifying T-bet gradient which may control functional plasticity of the ILC3 lineage [7, 16]. Therefore, these T-bet-expressing ILC3s will be discussed in detail below in the context of group 3 ILCs.

Group 2 ILCs

Innate sources of type 2 cytokines (IL-5 and IL-13) that are responsive to IL-25 stimulation have been identified some years ago [31–33]. However, a precise and in-depth characterization of these enigmatic cells has only been performed more recently. Koyasu and colleagues first identified a population of innate lymphocytes that populate fat-associated lymphoid clusters (FALCs) located alongside the blood vessels within the mesenteries of mice [4]. Within these lymphoid clusters, a population of Lin-negative lymphocytes that expresses high levels of Sca1 as well as Thy1, Kit, and IL-7Rα (CD127) consistent with an ILC phenotype was observed. Similar to the other ILC subsets, ILC2s also require IL-7R signaling for their maintenance and require Id2 expression for lineage specification [4]. This population is well represented in adipose tissues [4] but also in small intestine and colon; however, ILC2s are rather rare in lungs, spleen, and lymph nodes of uninfected mice [4, 5]. In addition, these cells were distinct from other ILC lineages as they developed independently of RORγt and IL-15 required for the development of ILC3s and NK cells, respectively [4, 5]. ILC2s expressed the cytokine receptors for IL-33 and IL-25, which are not found on the other ILC populations [4, 5, 34, 35]. ILC2s develop normally in mice lacking *Rag* (recombination activating genes) *1* and *2* gene expression. However, they are of the lymphoid lineage as they are absent in *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice that lack all lymphoid cells but have a largely normal myeloid compartment. ILC2s were producers of IL-5 and IL-13, in particular in response to IL-25 and IL-33, whereas they did not produce IL-17, IL-22, or IFN-γ [4, 34, 35].

ILC2s have also been identified in humans [36]. In the fetal gut, a population of CD45^{high} CD127$^+$ ILCs that co-expressed various ILC markers such as Kit (CD117) and CD161 but was negative for markers of other ILC lineages such as RORγt and NKp44 (ILC3) or for markers of mast cells and basophils (i.e., IL-3R, FcεR1) was identified. In addition, CD45^{high} CD127$^+$ ILCs expressed high levels of CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes), a receptor also found on Th2 cells. Stimulation of CRTH2$^+$ ILCs with IL-25 and IL-33 led to the production of IL-5 and IL-13 whereas they did not produce IL-22, IL-17A, or IFN-γ. Interestingly, nasal polyps from patients suffering from chronic rhinosinusitis, an allergic disorder, contained a large population of CRTH2$^+$ CD127$^+$ CD161$^+$ ILCs, whereas these cells were poorly represented in uninflamed nose tissue from healthy individuals [36]. Thus, human ILC2s are CRTH2$^+$ CD127$^+$ CD161$^+$ ILCs.

Recently, the transcriptional programs driving lineage specification of ILC2s became apparent. Similar to Th2 cells, ILC2 lineage specification required GATA-3 [5, 37]. Mice with a tissue-specific deletion of the *Gata*3

gene in all ILCs selectively lacked ILC2s and their lineage-specified progenitors, whereas ILC3s could develop in the absence of GATA-3 [5]. In addition, acute ablation of *Gata*3 revealed that this transcription factor is required for the maintenance of differentiated ILC2s [5]. The transcriptional network controlled by GATA-3 in ILC2s has not been explored yet, but *Rora* (the gene encoding retinoic acid-related orphan receptor α) may be a direct target of GATA-3 [38], and mice with a natural mutation of the *Rora* gene were found to lack ILC2s [39, 40]. Thus, ILC2s are GATA-3^{high} IL-25R^{+} IL-33R^{+} ILCs.

Group 3 ILCs

Two distinct subsets of ILC3s that may constitute separate lineages have now been recognized [16, 41]. CCR6^{+} Kit^{high} ILC3s emerge during prenatal development (E14.5) [42] and are most likely related to the previously described lymphoid tissue inducer (LTi) cells [19, 43, 44]. Indeed, ILC3s are strictly required for the prenatal development of lymph nodes and Peyer's patches as well as the postnatal formation of multiple intestinal lymphoid clusters (i.e., cryptopatches and isolated lymphoid follicles), all of which are lacking in *Rorc*$^{-/-}$ mice devoid of all ILC3 subsets [18, 19, 45]. Similar to LTi cells, a subset of CCR6^{+} ILC3s expresses CD4, whereas only few CCR6^{+} ILC3s are NKp46-positive [16, 41]. CCR6^{+} ILC3s produce large amounts of IL-22 and can be triggered for the production of IL-17A and IL-17F [16, 41].

In contrast, CCR6$^{-/low}$ Kit^{low} ILC3s are few in newborn mice but vigorously expand during the first 2–4 weeks after birth [16, 41]. Postnatal expansion of CCR6$^{-/low}$ ILC3s is controlled by signals of the aryl hydrocarbon receptor (AhR), a transcription factor activated by a large group of environmental and endogenous ligands (see below). CCR6$^{-/low}$ ILC3s also produce IL-22 but do not release IL-17A or IL-17F [16]. CCR6$^{-/low}$ ILC3s can up-regulate expression of the T-box transcription factor T-bet, which is required for their differentiation into NKp46^{+} CCR6^{-} ILC3s [16, 30]. T-bet^{+} CCR6$^{-/low}$ ILC3s are producers of IFN-γ and TNF [16, 28, 30]. Despite these differences, CCR6$^{-/low}$ and CCR6^{+} ILC3s are related because they continuously express the transcription factor RORγt and mice genetically lacking the *Rorc* gene do not have either ILC3 subset [16]. Interestingly RORγt fate-mapping of CCR6$^{-/low}$ subset of ILC3s revealed that these cells downregulate RORγt expression [7]. Such "ex-RORγt^{+}" ILC3s are phentotypically hard to discriminate from T-bet^{+} ILC1s [7, 16]. Available data indicate that plasticity of CCR6$^{-/low}$ ILC3s is under complex control of various cytokines [7, 46]. IL-23 and the intestinal microbiota promote T-bet expression of CCR6$^{-/low}$ ILC3s [16], whereas IL-7 seems to stabilize RORγt expression [7]. Interestingly, IL-23 has been reported to induce a plastic program in RORγt-expressing Th17 cells that can convert into a Th1-like cell when downregulating RORγt while up-regulating T-bet [47]. The up-regulation of T-bet in RORγt^{+} ILC3s and the engagement of a plasticity program have also been observed for human ILC3s [29, 46]. Collectively, the available data indicate that ILC3s are RORγt-expressing ILCs that can, based on the expression of CCR6, be subdivided into two functionally distinct subsets.

ILCs and immunity to infections

Group 2 ILCs and immunity to helminth infections

Infections with helminths lead to the induction of type 2 immunity, and type 2 immunity is required for worm expulsion [48]. It is believed that Th2 cells in concert with mast cells and eosinophils lead to efficient control of infection. Infection of mice with the nematode parasite *Nippostrongylus* (*N.*) *brasiliensis* has served as one of the best investigated models of Th2-mediated anti-parasite immunity. *N. brasiliensis* is a rat parasite that has been experimentally adapted to the mouse. Mice are infected subcutaneously with free-living third stage larvae (L3) which migrate to the lungs. From there, they are coughed up and swallowed reaching the intestine where they develop into lumen-dwelling adult worms. In the proximal jejunum, adult worms mate and produce eggs that develop outside of the host into infectious L3 larvae completing the replication cycle. After 10–12 days of infection, immunocompetent mice expell *N. brasiliensis*. Worm expulsion requires type 2 immunity involving the cytokines IL-5, IL-13, and IL-9, all of which can be produced by Th2 cells and ILC2s [49]. These cytokines induce the expression of genes in epithelial cells (e.g., *Muc2*, *Ang4*) which are required for worm expulsion [49].

Koyasu and colleagues observed that injections of the cytokine IL-33 into *Rag2*$^{-/-}$ mice resulted in the production of IL-5 and IL-13 and in goblet cell hyperplasia [4]. Similarly, McKenzie and colleagues reported that injections of IL-25 and IL-33 resulted in the production of IL-13 by innate (i.e., CD3^{-} CD19^{-}) lymphocytes [34]. In contrast, no such effect was seen, when IL-33 was injected into alymphoid *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice indicating that innate lymphocytes are the relevant sources of IL-5 and IL-13 in response to IL-33 [4]. Normal levels of IL-5 and IL-13 were detected in the serum of *N. brasiliensis*-infected *Rag2*$^{-/-}$ mice whereas *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice failed to produce IL-5 or IL-13 after *N. brasiliensis* injection. Injection of ILC2s into the peritoneal cavity of *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice restored IL-13 production and allowed for goblet cell activation, whereas injection of Th2 cells into *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice did not allow for immediate IL-13 production [4]. Using IL-13 reporter mice, it was shown that ILC2s are the major source of IL-13 during the first week of infection [4, 34]. Collectively, these data indicate that ILC2s may be the relevant source of IL-13 early during infection with nematodes.

Mice deficient for the IL-25 receptor (*Il17rb*$^{-/-}$ mice) cannot control *N. brasiliensis* infections and do not show eosinophil recruitment [34]. Transfer of *in vitro* expanded

ILC2s restored worm control and eosinophil infiltration [34]. Along the same lines, alymphoid *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice have high worm numbers in the intestine compared to *Rag2*$^{-/-}$ mice. Interestingly, *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice reconstituted with ILC2Ps, the lineage specified precursor of mature ILC2s, restored parasite control, and expression of IL-13-dependent genes by Paneth cells and goblet cells (e.g., *Muc2*, *Ang4*) required for worm expulsion [5]. In addition, alymphoid mice reconstituted with ILC2s show increased recruitment of eosinophils indicating that ILC2s are indispensable for the recruitment of eosinophils to the sites of helminth infection [5]. Eosinophil infiltration was dependent on the presence of IL-13-producing cells [50]. While IL-4 was selectively produced by CD4$^+$ T cells, both ILC2s and Th2 cells were involved in the production of IL-13 [50]. Future experiments will need to reveal the specific roles that ILC2s and Th2 cells play in resistance to *N. brasiliensis*. Such experiments will require the development of tools that allow for the specific manipulation of ILC2s while Th2 cells are left intact and *vice versa*.

Group 3 ILCs and immunity to infections

Citrobacter rodentium

Citrobacter (*C.*) *rodentium* infection in mice is a good model of human attaching-and-effacing (A/E) intestinal infections caused by enteropathogenic or enterohemorrhagic strains of *Escherichia* (*E.*) *coli* (EPEC, EHEC) [51–53]. Both *C. rodentium* and EPEC or EHEC strains carry a pathogenicity island referred to as locus of enterocyte effacement (LEE) [51, 54]. Like for EHEC or EPEC-encoded LEE in human infections, *C. rodentium* LEE encodes genes that allow attachment of LEE-carrying bacteria to mouse colonic epithelial cells resulting in effacement of brush border microvilli, termed an A/E lesion, and in colonic mucosal hyperplasia [55]. Although CD4$^+$ T cells and B cells are required for eradication and adaptive immunity to *C. rodentium*, innate immune system components are also important because T and B cell-deficient mice survive for the first 30 days of infection [56–58].

Recently, it became clear that IL-22 is required for early resistance to *C. rodentium* infection because *Il22*$^{-/-}$ mice rapidly succumb to the infection within the first 8–12 days [58]. This correlates well with the kinetics of IL-22 production following *C. rodentium* infection [58]. IL-22 production is dependent on the expression of IL-23 likely by mononuclear phagocyte subsets whereas IL-6 was not required [58]. IL-22 is a cytokine acting exclusively on non-hematopoietic cells (e.g., epithelial cells, mesenchymal stroma) because of the restricted expression of the IL-22 receptor [59]. Our understanding of the IL-22-controlled gene expression program within epithelial cells and how this relates to immunity to infection is far from complete. Genomewide transcriptional analyses of colon epithelial cells stimulated with IL-22 have shown that expression of a small family of lectin-like secreted antimicrobial proteins, Reg3 proteins [60], is controlled by IL-22 [58]. The exact mode of action is still a bit unclear. Nevertheless, reconstitution of Reg3γ expression in *Il22*$^{-/-}$ mice by application of recombinant Reg3γ-Fc fusion protein, conferred partial resistance to *C. rodentium* infection, indicating that Reg3 may be a major IL-22-controlled factor in epithelial cells required for the protection against *C. rodentium* infection [58].

The cellular source of IL-22 was initially identified as CD11c$^+$ cells, possibly dendritic cells (DCs) [58, 61]. However, consecutive studies revealed that CD4$^+$ ILC3 subsets are the main source of IL-22 during *C. rodentium* infection, and depletion of ILCs led to rapid death following infection [62]. Further evidence came from studies investigating the role of the AhR for development and function of ILC3s. AhR is a cytoplasmic sensor of polycyclic compounds including toxins (e.g., dioxin) and dietary phytochemicals (e.g., glucosinolates, flavonoids) [63]. Binding of such ligands to the cytoplasmic AhR leads to nuclear translocation where AhR acts as a transcription factor inducing the expression of a battery of AhR or xenobiotic response genes [63]. Interestingly, ILC3s from AhR-deficient mice produce reduced levels of IL-22 possibly because of synergy between AhR and RORγt-controlled transcription of the *Il22* gene [25–27]. In addition, *Ahr*$^{-/-}$ mice cannot maintain the pool of CCR6$^{-/low}$ ILC3s so that the overall number of IL-22-producing cells is dramatically decreased leading to high susceptibility to *C. rodentium* infection [16, 25, 26]. Collectively, the data promote the view that IL-22-producing ILC3s are absolutely required for resistance to A/E-types of intestinal infections.

Salmonella enterica

In humans, gastroenteritis caused by non-typhoidal *Salmonella* (*Salmonella typhimurium*, *S. enteritidis*) is a self-limiting disease characterized by nausea, vomiting, fever, diarrhea, and cramping. Non-typhoidal *Salmonella* infections are generally acquired by the ingestion of food from infected livestock and, therefore, Salmonellosis is considered to be a zoonosis. Unfortunately, a self-limiting *Salmonella* infection model is unavailable in mice. Oral infection of susceptible mouse strains with *S. typhimurium* leads to systemic disease with bacteremia and septic lesions in non-mucosal organs which is reminiscent of typhoidal salmonellosis in humans (i.e., mouse typhoid) [64]. Oral infection of mice with *S. typhimurium* does not lead to colonization of the intestine with *Salmonella* and does not cause intestinal inflammation or disease [65]. In mice, *Salmonella* induced enterocolitis can be studied when mice are pretreated with a single dose of streptomycin [65–67]. The ensuing acute enterocolitis is characterized by diffuse inflammation of cecum and colon, broad epithelial lesions, and inflammatory infiltrates dominated by neutrophil granulocytes [67]. Although systematic histopathological data for human *Salmonella* enterocolitis are not available (due to the self-limiting nature of the disease), the available data indicate that *Salmonella*-

induced pathology resembles that found in the mouse system. A remaining caveat is that *S. typhimurium*-infected mice develop enterocolitis and systemic typhoid at the same time.

It is well documented that the immune response following *S. typhimurium* infection contributes to both innate resistance and to the ensuing inflammation. One key cytokine controlling *Salmonella* infection is IFN-γ [68]. In line with its capabilities to activate antimicrobial programs in mononuclear phagocytes and to enhance T cell responses [69], IFN-γ controls the systemic spread of the pathogen and bacterial load in mucosal tissues [70]. However, excessive IFN-γ production also contributes to mucosal inflammation. In addition to its action on hematopoietic cells required for pathogen restriction, it was recently observed that expression of the IFN-γ receptor on stromal cells (e.g., enterocytes, goblet cells) was required for mucus excretion from goblet cells [70]. Thus, IFN-γ does not only contribute to innate protection by immune cells but also by controlling mucus release by goblet cells required to fortify the epithelial barrier [70].

The innate cellular sources of IFN-γ in the context of *S. typhimurium* infection were not well defined, and it was widely assumed that NK cells are the main IFN-γ source during early phases of the infection [71]. Considering that ILC3s also express NK cell receptors such as NKp46 and NK1.1 [72–76], the role of ILC3s during *Salmonella* enterocolitis has been recently addressed [16]. Interestingly, ca. 80% of the IFN-γ-producing cells early following infection were NKp46$^+$ T-bet$^+$ ILCs (i.e., CD127$^+$ NKp46$^+$ cells), whereas only 20% of the IFN-γ was contributed by conventional NK cells (i.e., CD127$^-$ NKp46$^+$ cells) [16]. Lymphoid cells are the major source of IFN-γ because *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice had only very few IFN-γ-producing cells [16]. Depletion of all ILCs by anti-Thy1 antibody injections into infected *Rag2*$^{-/-}$ mice, lacking B and T cells, virtually abolished IFN-γ production. Analysis of RORγt fate map mice revealed that a substantial ILC subset contributing to IFN-γ expression was NKp46$^+$ T-bet$^+$ ILC3s that had downregulated RORγt [7, 16]. The main driver of IFN-γ production by these ILC3 subsets was IL-12, whereas IL-23 had only a neglible effect [16], which is in line with previously published data [77]. Consistent with the robust production of IFN-γ by ILCs, mucus excretion was impaired in mice depleted of all ILCs or genetically lacking T-bet which have impaired IFN-γ production by ILC3s and possibly perturbed development of ILC1 subsets [16]. Furthermore, interference with IFN-γ production by ILC3s led to reduced intestinal inflammation. Thus, IFN-γ-producing ILC subsets contribute to innate barrier protection but also to the immunopathology observed after *Salmonella* infections [16].

While IL-23 production was not required for IFN-γ release by ILCs, it is required for the expression of IL-17 and IL-22 following *S. typhimurium* infection [77]. Mice lacking IL-23 expression showed reduced intestinal inflammation indicating that both IFN-γ and IL-23-controlled cytokines contribute to enterocolitis. It is well established that *Salmonella* exploits the inflammatory response to establish mucosal infections [78–80]. Interestingly, IL-17 and IL-22 control the expression of epithelial antimicrobial proteins such as those of the Reg3 lectin-like family and of lipocalin 2 [81]. Lipocalin 2 inhibits bacterial growth by interfering with the bacteria's acquisition of iron [82–84]. The *iroN* gene locus of *Salmonella typhymurium* encodes a protein required for iron acquisition and was responsible for lipocalin-2 resistance of the bacteria, because *iroN* mutants were recovered in lower numbers from the colon of wildtype but not of lipocalin-2-deficient mice [81]. Thus, the *iroBCDE iroN* locus of *S. typhimurium* conferred a competitive advantage to the bacterium when colonizing the inflamed intestine [81].

Helicobacter hepaticus and *Helicobacter typhlonius*

Helicobacter (*H.*) *hepaticus* can trigger chronic colitis in mice on the 129SvEv background lacking components of the adaptive immune system (i.e., 129SvEv *Rag2*$^{-/-}$ mice), a disease referred to as "innate colitis" [85]. Development of intestinal pathology in this model was dependent on IL-23 production and colitogenic mice injected with anti-IL-23p19 antibodies showed reduced production of various pro-inflammatory cytokines, including IFN-γ, IL-6, IL-1β, and IL-17A [85]. Both IL-17A and IFN-γ contributed to *H. hepaticus*-mediated colitis [86]. Analysis of the cells co-producing IL-17 and IFN-γ isolated from the colon of *H. hepaticus*-infected mice revealed that the main innate source of IL-17 is NKp46$^-$ CCR6$^+$ RORγt$^+$ ILCs [86]. Indeed, depletion of all ILCs (including ILC3s) led to reduced *H. hepaticus*-induced intestinal inflammation [86]. In addition to IL-23, IL-1β was found to be an important factor for augmenting the accumulation and activation of IL-17A-producing ILCs in the *H. hepaticus* model of innate colitis [87]. Intriguingly, IL-17A and IFN-γ-producing ILC subsets were also found to accumulate in the inflamed intestine of patients suffering from Crohn's disease [88]. The induction of colitis by *H. hepaticus* infection requires the genetic background of 129SvEv mice. Through a genetic approach employing congenic mice, an interval on mouse chromosome 3 was determined whose genes may be involved in driving colitis in this particular genetic background [89]. Thus, ILC3s, if inappropriately stimulated by pathobionts (such as *H. hepaticus*) in a genetically susceptible host, can drive intestinal inflammation.

Another line of evidence for a role of ILC3s in colitis pathogenesis came from the TRUC model (*Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ ulcerative colitis, TRUC). Mice deficient for the transcription factor T-bet (*Tbx21*$^{-/-}$ mice) and *Rag2* develop spontaneous intestinal inflammation [90]. Aberrant outgrowth of disease-promoting bacterial communities is a prominent feature of the disease because mice treated with antibiotics resolved disease and *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ mice housed under germ-free conditions did not develop colitis [90, 91]. Early stages of disease are characterized by high TNF expression in colonic DC subsets [90]. In

TRUC mice, a prominent population of Thy1$^+$ IL-17A-producing cells could be found that co-expressed markers of NKp46$^-$ CCR6$^+$ ILC3s such as RORγt and IL-7Rα [92]. Indeed, alymphoid *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice did not develop colitis demonstrating that "innate colitis" requires innate lymphocyte subsets [92]. Depletion of all ILCs by application of anti-Thy1 antibodies virtually abolished colitis in *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ mice [92]. A role of specific bacterial communities for the pathogenesis of TRUC was further supported by the observation that rederivation of *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ mice by embryo transfer did no longer allow for the development of spontaneous colitis [92]. Analysis of differences in the representation of microbial species revealed the presence of a *Helicobacter* species (*H. typhlonius*) only in colitis-prone TRUC mice but not in the rederived (healthy) mice. Interestingly, inoculation of rederived *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ mice with *H. typhlonius* restored colitis causally linking *H. typhlonius* to colitis development in *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ mice [92]. Following gavage of *H. typhlonius* into T-bet-proficient *Rag2*$^{-/-}$ mice, intestinal ILCs produced high levels of IFN-γ. In contrast, ILCs of *Tbx21*$^{-/-}$ *Rag2*$^{-/-}$ mice did not produce IFN-γ but responded with high level IL-17A production [92]. Thus, TRUC may be caused by inappropriate production of IL-17A in response to a bacterial infection, when T-bet-controlled "type 1 immunity" cannot be engaged.

Candida albicans

C. albicans is a clinically relevant fungal pathogen which is normally effectively controlled by neutrophils [93]. Immunity to *Candida* infections has been linked to the IL-17 pathway, and allelic variants of genes involved in IL-17 signaling have been linked to fungal diseases and particularly to mucocutaneous candidiasis [94–96]. *Candida* infections lead to a strong induction of Th17 cell-mediated immunity which is relevant for vaccine responses [97, 98]. Indeed, mice lacking the IL-17RA are highly susceptible to *C. albicans* infections [99]. Based on these data, it was believed that Th17 cells are the relevant cellular source to protect against *Candida* infections. However, a recent report has demonstrated that IL-17 production by ILC3s is required for the protection against oropharyngeal candidiasis [100]. While IL-17 production was required for resistance to oropharyngeal candidiasis, components of the adaptive immune system (*Rag1*$^{-/-}$ mice) were not, excluding Th17 cells as the relevant source of IL-17A and/or F [100]. Indeed, IL-17 production was not reduced in T cell-deficient mice, and RORγt-dependent Lin$^-$ Thy1$^+$ CD127$^+$ Sca1$^+$ cells were found to be the major sources of IL-17A and IL-17F in response to *Candida*. Depletion of all ILCs with anti-Thy1 antibodies led to susceptibility to *Candida* infection, and *Rorc*$^{-/-}$ mice which lack all ILC3 subsets could also not contain the infection. Control of yeast infection was driven by IL-23 production, whereas IL-1 was dispensable [100]. Thus, IL-17-producing ILC3s but not Th17 cells are protective against mucosal *Candida* infections.

References

1. Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R: Toll-like receptors control activation of adaptive immune responses. Nat Immunol 2, 947–950 (2001)
2. Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE, Powrie F, Vivier E: Innate lymphoid cells – a proposal for uniform nomenclature. Nat Rev Immunol 13, 145–149 (2013)
3. Yokota Y, Mansouri A, Mori S, Sugawara S, Adachi S, Nishikawa S, Gruss P: Development of peripheral lymphoid organs and natural killer cells depends on the helix–loop–helix inhibitor Id2. Nature 397, 702–706 (1999)
4. Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, Furusawa J, Ohtani M, Fujii H, Koyasu S: Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. Nature 463, 540–544 (2010)
5. Hoyler T, Klose CS, Souabni A, Turqueti-Neves A, Pfeifer D, Rawlins EL, Voehringer D, Busslinger M, Diefenbach A: The Transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. Immunity 37, 634–648 (2012)
6. Satoh-Takayama N, Lesjean-Pottier S, Vieira P, Sawa S, Eberl G, Vosshenrich CA, Di Santo JP: IL-7 and IL-15 independently program the differentiation of intestinal CD3-NKp46+ cell subsets from Id2-dependent precursors. J Exp Med 207, 273–280 (2010)
7. Vonarbourg C, Mortha A, Bui VL, Hernandez PP, Kiss EA, Hoyler T, Flach M, Bengsch B, Thimme R, Holscher C, Honig M, Pannicke U, Schwarz K, Ware CF, Finke D, Diefenbach A: Regulated expression of nuclear receptor RORgammat confers distinct functional fates to NK cell receptor-expressing RORgammat(+) innate lymphocytes. Immunity 33, 736–751 (2010)
8. Vonarbourg C, Diefenbach A: Multifaceted roles of interleukin-7 signaling for the development and function of innate lymphoid cells. Semin Immunol 24, 165–174 (2012)
9. Vosshenrich CA, Di Santo JP: Developmental programming of natural killer and innate lymphoid cells. Curr Opin Immunol 25, 130–138 (2013)
10. Klose CS, Hoyler T, Kiss EA, Tanriver Y, Diefenbach A: Transcriptional control of innate lymphocyte fate decisions. Curr Opin Immunol 24, 290–296 (2012)
11. Cherrier M, Ohnmacht C, Cording S, Eberl G: Development and function of intestinal innate lymphoid cells. Curr Opin Immunol 24, 277–283 (2012)
12. Spits H, Cupedo T: Innate lymphoid cells: emerging insights in development, lineage relationships, and function. Annu Rev Immunol 30, 647–675 (2012)
13. Hoyler T, Connor CA, Kiss EA, Diefenbach A: T-bet and Gata3 in controlling type 1 and type 2 immunity mediated by innate lymphoid cells. Curr Opin Immunol 25, 139–147 (2013)
14. Townsend MJ, Weinmann AS, Matsuda JL, Salomon R, Farnham PJ, Biron CA, Gapin L, Glimcher LH: T-bet regulates the terminal maturation and homeostasis of NK and Valpha14i NKT cells. Immunity 20, 477–494 (2004)
15. Gordon SM, Chaix J, Rupp LJ, Wu J, Madera S, Sun JC, Lindsten T, Reiner SL: The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. Immunity 36, 55–67 (2012)

16. Klose CS, Kiss EA, Schwierzeck V, Ebert K, Hoyler T, d'Hargues Y, Goppert N, Croxford AL, Waisman A, Tanriver Y, Diefenbach A: A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells. Nature 494, 261–265 (2013)
17. Trinchieri G: Biology of natural killer cells. Adv. Immunol. 47, 187–376 (1989)
18. Sun Z, Unutmaz D, Zou YR, Sunshine MJ, Pierani A, Brenner-Morton S, Mebius RE, Littman DR: Requirement for RORgamma in thymocyte survival and lymphoid organ development. Science 288, 2369–2373 (2000)
19. Eberl G, Marmon S, Sunshine MJ, Rennert PD, Choi Y, Littman DR: An essential function for the nuclear receptor RORgamma(t) in the generation of fetal lymphoid tissue inducer cells. Nat Immunol *5*, 64–73 (2004)
20. Leavy O: Innate-like lymphocytes: Will the real ILC1 please stand up? Nat Rev Immunol 13, 67 (2013)
21. Fuchs A, Vermi W, Lee JS, Lonardi S, Gilfillan S, Newberry RD, Cella M, Colonna M: Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells. Immunity 38, 769–781 (2013)
22. Cauley LS, Lefrancois L: Guarding the perimeter: protection of the mucosa by tissue-resident memory T cells. Mucosal Immunol *6*, 14–23 (2013)
23. Gascoyne DM, Long E, Veiga-Fernandes H, de Boer J, Williams O, Seddon B, Coles M, Kioussis D, Brady HJ: The basic leucine zipper transcription factor E4BP4 is essential for natural killer cell development. Nat Immunol 10, 1118–1124 (2009)
24. Kamizono S, Duncan GS, Seidel MG, Morimoto A, Hamada K, Grosveld G, Akashi K, Lind EF, Haight JP, Ohashi PS, Look AT, Mak TW: Nfil3/E4bp4 is required for the development and maturation of NK cells in vivo. J Exp Med 206, 2977–2986 (2009)
25. Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C, Diefenbach A: Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science 334, 1561–1565 (2011)
26. Lee JS, Cella M, McDonald KG, Garlanda C, Kennedy GD, Nukaya M, Mantovani A, Kopan R, Bradfield CA, Newberry RD, Colonna M: AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. Nat Immunol 13, 144–151 (2012)
27. Qiu J, Heller JJ, Guo X, Chen ZM, Fish K, Fu YX, Zhou L: The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. Immunity 36, 92–104 (2011)
28. Sciume G, Hirahara K, Takahashi H, Laurence A, Villarino AV, Singleton KL, Spencer SP, Wilhelm C, Poholek AC, Vahedi G, Kanno Y, Belkaid Y, O'Shea JJ: Distinct requirements for T-bet in gut innate lymphoid cells. J Exp Med 209, 2331–2338 (2012)
29. Bernink JH, Peters CP, Munneke M, Te Velde AA, Meijer SL, Weijer K, Hreggvidsdottir HS, Heinsbroek SE, Legrand N, Buskens CJ, Bemelman WA, Mjosberg JM, Spits H: Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat Immunol (2013)
30. Rankin LC, Groom JR, Chopin M, Herold MJ, Walker JA, Mielke LA, McKenzie AN, Carotta S, Nutt SL, Belz GT: The transcription factor T-bet is essential for the development of NKp46(+) innate lymphocytes via the Notch pathway. Nat Immunol 14, 389–395 (2013)
31. Fort MM, Cheung J, Yen D, Li J, Zurawski SM, Lo S, Menon S, Clifford T, Hunte B, Lesley R, Muchamuel T, Hurst SD, Zurawski G, Leach MW, Gorman DM, Rennick DM: IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. Immunity 15, 985–995 (2001)
32. Hurst SD, Muchamuel T, Gorman DM, Gilbert JM, Clifford T, Kwan S, Menon S, Seymour B, Jackson C, Kung TT, Brieland JK, Zurawski SM, Chapman RW, Zurawski G, Coffman RL: New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. J Immunol 169, 443–453 (2002)
33. Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, McIlgorm A, Jolin HE, McKenzie AN: Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. J Exp Med 203, 1105–1116 (2006)
34. Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, Bucks C, Kane CM, Fallon PG, Pannell R, Jolin HE, McKenzie AN: Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature 464, 1367–1370 (2010)
35. Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisley CJ, Erle DJ, Locksley RM: Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci U S A 107, 11489–11494 (2010)
36. Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, Fokkens WJ, Cupedo T, Spits H: Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol 12, 1055–1062 (2011)
37. Mjosberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, Te Velde AA, Fokkens WJ, van Drunen CM, Spits H: The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. Immunity 37, 649–659 (2012)
38. Klein Wolterink RG, Serafini N, van Nimwegen M, Vosshenrich CA, de Bruijn MJ, Fonseca Pereira D, Veiga Fernandes H, Hendriks RW, Di Santo JP: Essential, dose-dependent role for the transcription factor Gata3 in the development of IL-5+ and IL-13+ type 2 innate lymphoid cells. Proc Natl Acad Sci U S A 110, 10240–10245 (2013)
39. Wong SH, Walker JA, Jolin HE, Drynan LF, Hams E, Camelo A, Barlow JL, Neill DR, Panova V, Koch U, Radtke F, Hardman CS, Hwang YY, Fallon PG, McKenzie AN: Transcription factor RORalpha is critical for nuocyte development. Nat Immunol 13, 229–236 (2012)
40. Halim TY, MacLaren A, Romanish MT, Gold MJ, McNagny KM, Takei F: Retinoic-acid-receptor-related orphan nuclear receptor alpha is required for natural helper cell development and allergic inflammation. Immunity 37, 463–474 (2012)
41. Sawa S, Cherrier M, Lochner M, Satoh-Takayama N, Fehling HJ, Langa F, Di Santo JP, Eberl G: Lineage relationship analysis of RORgammat+ innate lymphoid cells. Science 330, 665–669 (2010)
42. Cherrier M, Sawa S, Eberl G: Notch, Id2, and RORgammat sequentially orchestrate the fetal development of lymphoid tissue inducer cells. J Exp Med 209, 729–740 (2012)
43. Mebius RE, Rennert P, Weissman IL: Developing lymph nodes collect CD4+CD3- LTbeta+ cells that can differentiate to APC, NK cells, and follicular cells but not T or B cells. Immunity *7*, 493–504 (1997)
44. Yoshida H, Honda K, Shinkura R, Adachi S, Nishikawa S, Maki K, Ikuta K, Nishikawa SI: IL-7 receptor alpha+

CD3(−) cells in the embryonic intestine induces the organizing center of Peyer's patches. Int Immunol 11, 643–655 (1999)
45. Eberl G, Littman DR: Thymic origin of intestinal alphabeta T cells revealed by fate mapping of RORgammat+ cells. Science 305, 248–251 (2004)
46. Cella M, Otero K, Colonna M: Expansion of human NK-22 cells with IL-7, IL-2, and IL-1beta reveals intrinsic functional plasticity. Proc Natl Acad Sci U S A 107, 10961–10966 (2010)
47. Hirota K, Duarte JH, Veldhoen M, Hornsby E, Li Y, Cua DJ, Ahlfors H, Wilhelm C, Tolaini M, Menzel U, Garefalaki A, Potocnik AJ, Stockinger B: Fate mapping of IL-17-producing T cells in inflammatory responses. Nat Immunol 12, 255–263 (2011)
48. Finkelman FD, Shea-Donohue T, Morris SC, Gildea L, Strait R, Madden KB, Schopf L, Urban JF, Jr.: Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. Immunol Rev 201, 139–155 (2004)
49. Neill DR, McKenzie AN: Nuocytes and beyond: new insights into helminth expulsion. Trends Parasitol 27, 214–221 (2011)
50. Liang HE, Reinhardt RL, Bando JK, Sullivan BM, Ho IC, Locksley RM: Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. Nat Immunol 13, 58–66 (2012)
51. Schauer DB, Falkow S: Attaching and effacing locus of a *Citrobacter freundii* biotype that causes transmissible murine colonic hyperplasia. Infect Immun 61, 2486–2492 (1993)
52. Schauer DB, Falkow S: The eae gene of *Citrobacter freundii* biotype 4280 is necessary for colonization in transmissible murine colonic hyperplasia. Infect Immun 61, 4654–4661 (1993)
53. Eckmann L: Animal models of inflammatory bowel disease: lessons from enteric infections. Ann N Y Acad Sci 1072, 28–38 (2006)
54. Deng W, Li Y, Vallance BA, Finlay BB: Locus of enterocyte effacement from *Citrobacter rodentium*: sequence analysis and evidence for horizontal transfer among attaching and effacing pathogens. Infect Immun 69, 6323–6335 (2001)
55. Deng W, Puente JL, Gruenheid S, Li Y, Vallance BA, Vazquez A, Barba J, Ibarra JA, O'Donnell P, Metalnikov P, Ashman K, Lee S, Goode D, Pawson T, Finlay BB: Dissecting virulence: systematic and functional analyses of a pathogenicity island. Proc Natl Acad Sci U S A 101, 3597–3602 (2004)
56. Vallance BA, Deng W, Knodler LA, Finlay BB: Mice lacking T and B lymphocytes develop transient colitis and crypt hyperplasia yet suffer impaired bacterial clearance during *Citrobacter rodentium* infection. Infect Immun 70, 2070–2081 (2002)
57. Vallance BA, Deng W, Jacobson K, Finlay BB: Host susceptibility to the attaching and effacing bacterial pathogen *Citrobacter rodentium*. Infect Immun 71, 3443–3453 (2003)
58. Zheng Y, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, Ouyang W: Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat Med 14, 282–289 (2008)
59. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R: IL-22 increases the innate immunity of tissues. Immunity 21, 241–254 (2004)
60. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, Koren O, Ley R, Wakeland EK, Hooper LV: The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science 334, 255–258 (2011)
61. Pickert G, Neufert C, Leppkes M, Zheng Y, Wittkopf N, Warntjen M, Lehr HA, Hirth S, Weigmann B, Wirtz S, Ouyang W, Neurath MF, Becker C: STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J Exp Med 206, 1465–1472 (2009)
62. Sonnenberg GF, Monticelli LA, Elloso MM, Fouser LA, Artis D: CD4(+) lymphoid tissue-inducer cells promote innate immunity in the gut. Immunity 34, 122–134 (2011)
63. McIntosh BE, Hogenesch JB, Bradfield CA: Mammalian Per-Arnt-Sim proteins in environmental adaptation. Annu Rev Physiol 72, 625–645 (2010)
64. Carter PB, Collins FM: The route of enteric infection in normal mice. J Exp Med 139, 1189–1203 (1974)
65. Hapfelmeier S, Hardt WD: A mouse model for *S. typhimurium*-induced enterocolitis. Trends Microbiol 13, 497–503 (2005)
66. Bohnhoff M, Drake BL, Miller CP: Effect of streptomycin on susceptibility of intestinal tract to experimental *Salmonella* infection. Proc Soc Exp Biol Med 86, 132–137 (1954)
67. Barthel M, Hapfelmeier S, Quintanilla-Martinez L, Kremer M, Rohde M, Hogardt M, Pfeffer K, Russmann H, Hardt WD: Pretreatment of mice with streptomycin provides a *Salmonella enterica* serovar *Typhimurium colitis* model that allows analysis of both pathogen and host. Infect Immun 71, 2839–2858 (2003)
68. Rhee SJ, Walker WA, Cherayil BJ: Developmentally regulated intestinal expression of IFN-gamma and its target genes and the age-specific response to enteric *Salmonella* infection. J Immunol 175, 1127–1136 (2005)
69. Godinez I, Haneda T, Raffatellu M, George MD, Paixao TA, Rolan HG, Santos RL, Dandekar S, Tsolis RM, Baumler AJ: T cells help to amplify inflammatory responses induced by *Salmonella enterica* serotype *Typhimurium* in the intestinal mucosa. Infect Immun 76, 2008–2017 (2008)
70. Songhet P, Barthel M, Stecher B, Muller AJ, Kremer M, Hansson GC, Hardt WD: Stromal IFN-gammaR-signaling modulates goblet cell function during *Salmonella Typhimurium* infection. PLoS One 6, e22459 (2011)
71. Harrington L, Srikanth CV, Antony R, Shi HN, Cherayil BJ: A role for natural killer cells in intestinal inflammation caused by infection with *Salmonella enterica* serovar *Typhimurium*. FEMS Immunol Med Microbiol 51, 372–380 (2007)
72. Sanos SL, Bui VL, Mortha A, Oberle K, Heners C, Johner C, Diefenbach A: RORgammat and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46+ cells. Nat Immunol 10, 83–91 (2009)
73. Luci C, Reynders A, Ivanov, II, Cognet C, Chiche L, Chasson L, Hardwigsen J, Anguiano E, Banchereau J, Chaussabel D, Dalod M, Littman DR, Vivier E, Tomasello E: Influence of the transcription factor RORgammat on the development of NKp46+ cell populations in gut and skin. Nat Immunol 10, 75–82 (2009)
74. Cupedo T, Crellin NK, Papazian N, Rombouts EJ, Weijer K, Grogan JL, Fibbe WE, Cornelissen JJ, Spits H: Human fetal

lymphoid tissue-inducer cells are interleukin 17-producing precursors to RORC+ CD127+ natural killer-like cells. Nat Immunol 10, 66–74 (2009)
75. Cella M, Fuchs A, Vermi W, Facchetti F, Otero K, Lennerz JK, Doherty JM, Mills JC, Colonna M: A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. Nature 457, 722–725 (2009)
76. Satoh-Takayama N, Vosshenrich CA, Lesjean-Pottier S, Sawa S, Lochner M, Rattis F, Mention JJ, Thiam K, Cerf-Bensussan N, Mandelboim O, Eberl G, Di Santo JP: Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. Immunity 29, 958–970 (2008)
77. Godinez I, Raffatellu M, Chu H, Paixao TA, Haneda T, Santos RL, Bevins CL, Tsolis RM, Baumler AJ: Interleukin-23 orchestrates mucosal responses to *Salmonella enterica* serotype *Typhimurium* in the intestine. Infect Immun 77, 387–398 (2009)
78. Stecher B, Robbiani R, Walker AW, Westendorf AM, Barthel M, Kremer M, Chaffron S, Macpherson AJ, Buer J, Parkhill J, Dougan G, von Mering C, Hardt WD: *Salmonella enterica* serovar *typhimurium* exploits inflammation to compete with the intestinal microbiota. PLoS Biol 5, 2177–2189 (2007)
79. Stecher B, Denzler R, Maier L, Bernet F, Sanders MJ, Pickard DJ, Barthel M, Westendorf AM, Krogfelt KA, Walker AW, Ackermann M, Dobrindt U, Thomson NR, Hardt WD: Gut inflammation can boost horizontal gene transfer between pathogenic and commensal Enterobacteriaceae. Proc Natl Acad Sci U S A 109, 1269–1274 (2012)
80. Kaiser P, Diard M, Stecher B, Hardt WD: The streptomycin mouse model for *Salmonella* diarrhea: functional analysis of the microbiota, the pathogen's virulence factors, and the host's mucosal immune response. Immunol Rev 245, 56–83 (2012)
81. Raffatellu M, George MD, Akiyama Y, Hornsby MJ, Nuccio SP, Paixao TA, Butler BP, Chu H, Santos RL, Berger T, Mak TW, Tsolis RM, Bevins CL, Solnick JV, Dandekar S, Baumler AJ: Lipocalin-2 resistance confers an advantage to *Salmonella enterica* serotype *Typhimurium* for growth and survival in the inflamed intestine. Cell Host Microbe 5, 476–486 (2009)
82. Berger T, Togawa A, Duncan GS, Elia AJ, You-Ten A, Wakeham A, Fong HE, Cheung CC, Mak TW: Lipocalin 2-deficient mice exhibit increased sensitivity to *Escherichia coli* infection but not to ischemia-reperfusion injury. Proc Natl Acad Sci U S A 103, 1834–1839 (2006)
83. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, Akira S, Aderem A: Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 432, 917–921 (2004)
84. Goetz DH, Holmes MA, Borregaard N, Bluhm ME, Raymond KN, Strong RK: The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. Mol Cell 10, 1033–1043 (2002)
85. Hue S, Ahern P, Buonocore S, Kullberg MC, Cua DJ, McKenzie BS, Powrie F, Maloy KJ: Interleukin-23 drives innate and T cell-mediated intestinal inflammation. J Exp Med 203, 2473–2483 (2006)
86. Buonocore S, Ahern PP, Uhlig HH, Ivanov, II, Littman DR, Maloy KJ, Powrie F: Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. Nature 464, 1371–1375 (2010)
87. Coccia M, Harrison OJ, Schiering C, Asquith MJ, Becher B, Powrie F, Maloy KJ: IL-1beta mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4(+) Th17 cells. J Exp Med 209, 1595–1609 (2012)
88. Geremia A, Arancibia-Carcamo CV, Fleming MP, Rust N, Singh B, Mortensen NJ, Travis SP, Powrie F: IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. J Exp Med 208, 1127–1133 (2011)
89. Boulard O, Kirchberger S, Royston DJ, Maloy KJ, Powrie FM: Identification of a genetic locus controlling bacteria-driven colitis and associated cancer through effects on innate inflammation. J Exp Med 209, 1309–1324 (2012)
90. Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, Glickman JN, Glimcher LH: Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. Cell 131, 33–45 (2007)
91. Garrett WS, Gallini CA, Yatsunenko T, Michaud M, DuBois A, Delaney ML, Punit S, Karlsson M, Bry L, Glickman JN, Gordon JI, Onderdonk AB, Glimcher LH: Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. Cell Host Microbe 8, 292–300 (2010)
92. Powell N, Walker AW, Stolarczyk E, Canavan JB, Gokmen MR, Marks E, Jackson I, Hashim A, Curtis MA, Jenner RG, Howard JK, Parkhill J, Macdonald TT, Lord GM: The transcription factor T-bet regulates intestinal inflammation mediated by interleukin-7 receptor(+) innate lymphoid cells. Immunity 37, 674–684 (2012)
93. LeibundGut-Landmann S, Wuthrich M, Hohl TM: Immunity to fungi. Curr Opin Immunol 24, 449–458 (2012)
94. Hernandez-Santos N, Gaffen SL: Th17 cells in immunity to *Candida albicans*. Cell Host Microbe 11, 425–435 (2012)
95. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Chrabieh M, Audry M, Gumbleton M, Toulon A, Bodemer C, El-Baghdadi J, Whitters M, Paradis T, Brooks J, Collins M, Wolfman NM, Al-Muhsen S, Galicchio M, Abel L, Picard C, Casanova JL: Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 332, 65–68 (2011)
96. Cypowyj S, Picard C, Marodi L, Casanova JL, Puel A: Immunity to infection in IL-17-deficient mice and humans. Eur J Immunol 42, 2246–2254 (2012)
97. Bar E, Gladiator A, Bastidas S, Roschitzki B, Acha-Orbea H, Oxenius A, LeibundGut-Landmann S: A novel Th cell epitope of *Candida albicans* mediates protection from fungal infection. J Immunol 188, 5636–5643 (2012)
98. Wuthrich M, Gern B, Hung CY, Ersland K, Rocco N, Pick-Jacobs J, Galles K, Filutowicz H, Warner T, Evans M, Cole G, Klein B: Vaccine-induced protection against 3 systemic mycoses endemic to North America requires Th17 cells in mice. J Clin Invest 121, 554–568 (2011)
99. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, Ho AW, Hai JH, Yu JJ, Jung JW, Filler SG, Masso-Welch P, Edgerton M, Gaffen SL: Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med 206, 299–311 (2009)
100. Gladiator A, Wangler N, Trautwein-Weidner K, LeibundGut-Landmann S: Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection. J Immunol 190, 521–525 (2013)