Innate lymphoid cells in tissue homeostasis and diseases

Aline Ignacio, Cristiane Naffah Souza Breda, Niels Olsen Saraiva Camara

Innate lymphoid cells (ILCs) are the most recently discovered family of innate immune cells. They are a part of the innate immune system, but develop from the lymphoid lineage. They lack pattern-recognition receptors and rearranged receptors, and therefore cannot directly mediate antigen specific responses. The progenitors specifically associated with the ILCs lineage have been uncovered, enabling the distinction between ILCs and natural killer cells. Based on the requirement of specific transcription factors and their patterns of cytokine production, ILCs are categorized into three subsets (ILC1, ILC2 and ILC3). First observed in mucosal surfaces, these cell populations interact with hematopoietic and non-hematopoietic cells throughout the body during homeostasis and diseases, promoting immunity, co-mmensal microbiota tolerance, tissue repair and inflammation. Over the last 8 years, ILCs came into the spotlight as an essential cell type able to integrate diverse host immune responses. Recently, it became known that ILC subsets play a key role in immune responses at barrier surfaces, interacting with the microbiota, nutrients and metabolites. Since the liver receives the venous blood directly from the intestinal vein, the intestine and liver are essential to maintain tolerance and can rapidly respond to infections or tissue damage. Therefore, in this review, we discuss recent findings regarding ILC functions in homeostasis and disease, with a focus on the intestine and liver.

Key words: Innate lymphoid cells; Intestine; Liver; Homeostasis; Inflammatory diseases

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Core tip: Receiving approximately 70% of blood through the portal vein, the liver represents one of the most important sites of defense against invading pathogens. In addition, the liver and the intestine are important immune organs, as they are often in contact with antigens and endotoxins produced by the gut microbiota. These organs are densely populated by innate immune cells such as natural killer cells, dendritic cells, macrophages, natural killer T cells and innate lymphoid cells (ILCs), which are rapidly activated by commensal and pathogenic antigens,
growth factors, cytokines and host metabolites. Recent studies have been focused on discovering the role of ILCs and how these cell populations can regulate the immune response. Our goal is to discuss innovative literature highlighting the importance of ILCs in the context of infectious disease, tissue repair, tolerance of gut microbiota and inflammatory diseases that affect the liver and intestine homeostasis.

INTRODUCTION

Innate lymphoid cells (ILCs) are the most recent family of innate immune cells discovered among the myriad of factors that make up the immune system. They belong to innate immune system but develop from the lymphoid lineage. However, contrary to T and B lymphocytes, ILCs do not have RAG-mediated recombined antigen receptors\(^1,2\). Their distribution is ubiquitous, being found throughout the body and enriched in mucosal surfaces.\(^3,4\) These cells are able to communicate with different cell types to orchestrate the immune system during homeostasis and inflammation\(^5,6\).

The non-cytotoxic ILCs consist of three different groups: ILC1, ILC2 and ILC3\(^5,7-10\). The ILC3s also include the lymphoid tissue inducer (LTi) cells. These cells were discovered in 1997 and are involved in the formation of secondary lymphoid tissues\(^11\).

Mirroring the Th subsets, the non-cytotoxic ILCs are separated based on cytokine expression, transcription factors during development, surface markers and distinct effector functions\(^5,6\). Although parallels between ILCs and Th subsets have been observed, ILCs lack pattern-recognition receptors and therefore cannot directly mediate antigen specific responses\(^3,11\). In fact, given that these cells are not directly activated by pathogen-associated molecular patterns it was unclear how ILCs discern infection, tissue injury or disruption of homeostasis. It is now known that ILCs present within adult tissues constitutively express cytokines, alarmins and growth factor receptors making them more sensitive to these mediators in their environment, enabling immediate ILC activation\(^3,12\). Despite being present in very low numbers, the wide distribution of ILCs in lymphoid and non-lymphoid tissues across species was seen as an indicator of the fundamental role of these innate cells in regulating multiple physiological processes throughout the body\(^7\).

Several studies have shown that ILCs are easily recovered in areas susceptible to microbial colonization or invasion by pathogens, such as barrier surfaces. Recently, it became known that ILC subsets play a key role in host immune responses to bacteria, fungi, viruses and extracellular parasites at these sites\(^6,13,14\). In addition, their interaction with the microbiota, nutrients and metabolites\(^6,13\) highlighted important functions for ILCs in triggering tissue repair and inflammation which, if unregulated, can result in exacerbated immune responses.

Based on the emerging roles of ILCs in controlling tissue homeostasis, this review will highlight the advances in understanding how ILCs can participate in host defense in the context of immunity, microbiota, autoimmunity and tissue remodeling, focusing on the intestinal and liver pathophysiology.

ILCs DEVELOPMENT: AN OVERVIEW

Until the discovery of ILCs, conventional natural killer cells (cNKs) were the only innate cells able to respond to cytokines released by antigen presenting cells (APCs). Therefore, NK cells represent the prototypical member of the ILC family\(^1,15-18\). However, NKs have additional roles that set them apart from other ILCs, such as cytotoxicity and the ability to initiate immune responses against virus and tumor cells\(^18\). Besides, recent analysis of the progenitor cells and surface markers of the ILC family members indicate that NK cells and non-cytotoxic ILCs group do not come from the same lineage\(^7-10\).

The identification of the ILC precursors and the key factors required for development of the different ILC subsets is quite recent. It was found that the ILCs arise from a common lymphoid progenitor (CLP). Downstream, the precursors can develop into different ILC subsets and NK cells expressing the integrin \(\alpha 4\beta 7\) and the transcription factors NFI3 (nuclear factor- interleukin 3 regulated) and TOX\(^7,9,19,20\). First, the common helper-like ILC progenitor (CHILP), that expresses the transcriptional regulator inhibitor of DNA binding 2 (Id2), gives rise only to ILC1, ILC2, ILC3 and LTi cells\(^9,10,19\). Downstream to CHILP, another ILC precursor is able to give rise all ILCs subsets, but not LTi or cNK cells\(^10\). This precursor can express the transcription factor promyelocytic leukemia zinc finger (PLZF)\(^21,22\).

ILC SUBSETS

As mentioned before, ILC populations differ based on their transcription factors and production of signature cytokines, similar to Th cells. However, while ILC2s and ILC3s are well characterized, ILC1s are more complex to identify due to many shared characteristics with NK cells\(^23\). Both are responsive to inflammatory cytokines, such as interleukin (IL)-15 and IL-12, and produce interferon (IFN)\(\gamma\) and tumor necrosis factor (TNF) after activation\(^24,25\). ILC1s are enriched in the liver, skin, salivary glands, uterus, thymus and the gut\(^23,26\). Regarding transcription factors, T-bet is the most important and regulates the ILC phenotype and functions, such as the production of IFN-\(\gamma\). NK cells can

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ILCs induce protective immunity in response to infections

Following pathogen invasion and tissue damage, epithelial cells and innate immune cells produce cytokines and alarmins which cooperatively mobilize and activate ILCs subsets\(^{31}\). Studies have shown that ILC-derived cytokines have an important protective function against S. Typhimurium\(^ {37,46}\), C. rodentium\(^ {54,58}\), \(N.\) brasiliensis\(^ {32,48}\), and C. albicans\(^ {59}\) infections.

IFN\(\gamma\)-producing ILC1s contribute to protection against \(S.\) enterica \(\text{subsp. enterica}\) serovar Typhimurium infection in the colon. In addition, ILC3-derived IL-22 is required for the fucosylation of the intestinal epithelium which helps to protect against S. Typhimurium infection. Once bound to the receptor, IL-22 triggers a signaling cascade which induces fucosylation of epithelial cells, activation of the transcription factor STAT3 and consequently secretion of antimicrobial peptides alpha and beta defensins. Murine ILC3s are important to immune function in response to \(T.\) gondii\(^ {59}\). An increase of human ILC1s was shown in patients with chronic hepatitis B infection\(^ {60}\), indicating that this population can contribute to immunity in response to specific pathogens in both mice and humans.

Before the onset of adaptive immune responses, the innate immune response to the enteric pathogen \(C.\) rodentium is critically dependent on ILC3-derived IL-22. C. rodentium is a gram-negative bacterium which causes acute colitis in mice. As mentioned above, the expression of antimicrobial peptides, dependent on the STAT-3 pathway, is induced by IL-22 and contributes to maintenance of the epithelial barrier surface. In addition, mice deficient in IL-22 rapidly succumb to infection due to exacerbated intestinal inflammation, bacterial invasion and proliferation throughout the tissues\(^ {60}\). IL-23 production by DCs or CX3CR1- mononuclear phagocytes is necessary for ILC3 activation and it has been shown that ILC3s are the predominant source of IL-22 in the first week of C. rodentium infection\(^ {60}\). Satpathy et al\(^ {62}\) showed that \(il23a^{-}\) mice are more susceptible to infection with high
As IL-23 was found to be crucial for IL-22 production by ILC3s, but not by Th17 cells, this model suggests that ILC3s are essential for resistance to *C. rodentium* infection. To clarify this phenomenon, experiments with *Rag*−/− and *il2rg*−/− mice, which lack T cells and ILCs, showed that ILC-deficient mice are more susceptible to infection compared to wild type mice.[54,58] However, at a later infection stage, it was observed that T cell-derived IL-22 contributes substantially to *C. rodentium* clearance and tissue repair.[93]. Therefore, whether ILC3s and T cells can perform redundant functions cannot be ruled out. In addition to IL-22 and IL-33, IL-17 was also described to act as the first-line of defense during candidiasis by controlling fungal overgrowth and epithelial integrity. In the second stage, the Th1 response is crucial to prevent fungal dissemination.[63]

Table 1: Innate lymphoid cell functions across the intestine during homeostasis and inflammatory diseases

| ILC subtype | Function | Model | Evidence |
|-------------|----------|-------|----------|
| ILC1 | *T. gondii* infection | Oral infection C57BL/6 mice | Immunity to *T. gondii* infection is IFNγ-dependent; mice lacking T-bet expression had virtually no IFN-γ production in response to *T. gondii* infection and failed to control parasite replication [9] |
| ILC2 | *N. brasiliensis* infection | Balb/c subcutaneous infection | Combined absence of IL-25 and IL-33 signaling led to a defect in worm expulsion, that was rescued by ILC2-adoptive transfer [34] |
| ILC3 | *S. Typhimurium* infection | Fuc2-deficient C57BL/6 mice | Fucosylation of intestinal epithelial cells is catalyzed by Fuc2; IL-22-derived ILC3s induce the expression of Fuc2. Disruption of intestinal fucosylation led to increased susceptibility to infection by *S. Typhimurium* [57] |
| ILC3 | *C. albicans* infection | Oral infection C57BL/6 mice | Mice lacking IL-22-producing ILC3 cells showed heightened susceptibility to the pathogen [54,62] |
| ILC3 | *C. rodentium* infection | Fuc2-deficient C57BL/6 mice | IL-22 mediates protection in IL-17RA-deficient mice; an early IL-22-dominated response is then followed by Th1/Treg reactivity [65] |
| ILC2 | Epithelial repair after intestinal inflammation | Number of AREG-expressing ILC2s increases following intestinal inflammation. [74] |
| ILC2 | Repair of lymphoid tissue | LCMV infection induces the destruction of secondary lymphoid organs RORγT-deficient WT chimeras had impaired rebuilding of stromal cell compartment after LCMV infection [70] |
| ILC3 | Regeneration of intestinal epithelium | Intestinal microbiota represses the ILC3-producing IL-22 through the induction of IL-25 by IECs. RAG-2-deficient mice treated with IL-25 showed significant weight loss in response to DSS treatment [80] |
| ILC3 | Containment of the gut microbiota | Depletion of IL-22-producing ILC3s resulted in peripheral dissemination of commensal bacteria and systemic inflammation, which was prevented by administration of IL-22 [81] |
| ILC1 | Crohn’s disease | Human ILC1 population is increased in the inflamed intestine of people with Crohn’s disease [29,30] |
| ILC1 | Ulcerative colitis | Anti-CD40 colitis model | IELs from the small intestine of mice treated with anti-CD40 revealed a robust production if IFN-γ by ILC1s. Anti-Nk1.1 treatment reduced inflammatory infiltration and epithelial damage, suggesting that ILC1 can contribute to colitis through IFN-γ secretion [85] |
| ILC3 | Ulcerative colitis | Anti-CD40 colitis model | IL-25 by IECs. RAG-2-deficient mice treated with IL-25 showed significant weight loss in response to DSS treatment [80] |
| ILC3 | Crohn’s disease | Human | Ablation of LTα in RORγt + cells abrogated 1gA production in the gut and altered microbiota composition [81] |
| ILC3 | Colorectal cancer | C57BL/6 mice | Absence of IL-23 promotes tumor development accompanied by increased innate immune cell infiltration; tumorigenesis induced by IL-23 could not be initiated in RAG2−/−IL-23−/− double knockout mice; IL-23R expression was identified in gut associated lymphoid tissue [49] |

IFN: Interferon; Fut2: Fucosyltransferase 2; AREG: Amphiregulin; LTα: Lymphotixin α; C57BL/6: Balb/c; DSS: Dextran sodium sulfate; GM-CSF: Granulocyte-macrophage colony-stimulating factor; EGFR: Epidermal growth factor receptor; IL: Interleukin; ILC: Innate lymphoid cell. **WJH** | www.wjgnet.com 982 August 18, 2017 | Volume 9 | Issue 23 |
The fact that dying and damaged epithelial cells discharge alarmins which can be sensed by ILC2s suggests a close interaction between these two cell types. In fact, ILC2s expressing amphiregulin can regulate cell differentiation and proliferation by binding to the epidermal growth factor receptor (EGFR). IL-33-stimulated ILC2s can induce the repair of intestinal epithelial lesions after DSS-induced colitis by amphiregulin secretion[74]. This cytokine, IL-33, as well as ILC2s, have been in the spotlight due to their contributions to the improvement of obesity-induced insulin resistance. IL-33 can bind the ST2 receptor and induce the production of large amounts of anti-inflammatory cytokines by ILC2s in adipose tissue. These cytokines lead to polarization of the adipose tissue macrophages to an M2 phenotype[75,76]. In the liver, unlike in DSS-induced colitis and adipose tissue, IL-33 was identified as a key mediator of hepatic fibrosis. It is released in response to chronic hepatocellular stress and, after binding to ST2, culminates in ILC2s activation, as mentioned above. These cells produce anti-inflammatory and tissue remodeling cytokines, such as IL-13 and IL-4. In turn, IL-13 can activate HSCs in an IL-4Ra- and STAT6 transcription-factor-dependent fashion, a pro-fibrotic cascade. Accordingly, IL-33 plays a role in a profibrotic cascade as the apex of the signaling pathway[77]. Another study showed that HBV infected patients have higher concentrations of IL-33 in serum compared to healthy controls. In addition, that concentration decreases following 12 wk of treatment[78]. These findings indicate that, in certain conditions, ILC2s can be manipulated, avoiding excessive tissue remodeling, when IL-33-stimulated ILC2s secrete IL-13 and IL-4, inducing fibrosis mediated by liver stellate cells (Figure 2)[79].

Besides their tissue repair properties, ILC2s play a role in limiting exacerbation of inflammatory responses. This can occur through the production of type 2 cytokines, that can suppress type 1 and type 17 inflammation[79], showing the diverse roles that ILCs can play.

**ILCs and the crosstalk with the intestinal microbiota**

Complementary to their role in promoting immunity against pathogens, ILCs are also evolved with tolerance mechanisms regarding interactions between the host and the commensal microbiota. Recent studies have begun to disclose how ILC3s interact with gut bacteria, diet-derived factors and various cell types to maintain intestinal homeostasis.

Although the organization of ILC subsets in the gut-associated lymphoid tissues and murine intestinal tissues occur independently of microbiota colonization, the anatomical retention of lymphoid tissue resident bacteria seems to be related with ILC3s function[80]. For example, B cells can be activated by ILC3s through lymphotoxin α1β2 which induces the proliferation and the production of immunoglobulin A (IgA),
subsequently contributes to neutralization of commensal bacteria in the lumen and prevents an inappropriate immune response\(^8\). Furthermore, it was shown that ILC3s express MHC class II and although they do not express co-stimulatory molecules necessary to activate T-cells, depletion of ILC3s or selective deletion of MHC class II in these cells is associated with exacerbated bacteria-specific Th17 cell response and intestinal inflammation\(^8\). These data suggest that ILC3s can drive a host immune tolerogenic state in the intestine by controlling the functions of other immune cell types.

Controversial results have been found regarding the influence of microbiota on ILC3 function. The production of protective levels of IL-17A, IL-17F and IL-22 and the responsiveness to IL-23 suggest that both human and mice ILC3s contribute to intestinal homeostasis\(^14\).
Despite some studies that have shown that murine ILC IL-22 production is not affected after alteration of bacterial communities\(^8\), other works show that microbial products influence the level of IL-22 secretion in mice and humans\(^7,14\), and that germ-free mice have decreased IL-22-expressing ILC3s\(^9\). In addition, epithelial cells stimulated by commensal microbiota release IL-25 which acts on CD11c\(^+\) cells to limit IL-22 secretion derived from ILC3s\(^8\). Future work will be needed to elucidate the mechanisms by which this interaction occurs and how this process is regulated. In attempt to explain how ILC3s communicate with environmental factors in the intestine, recent studies have focused on whether dietary substances can be sensed by ILC3s. Fucose can be used as a carbohydrate source by commensal bacteria. ILC3s facilitate the transfer of fucose to the surface of intestinal epithelial cells which is critical for resistance to infection with Salmonella Typhimurium and to maintain the appropriate number of bacteria in the lumen\(^8\). Another example is the relationship between the level of vitamin A and ILC3 functions, whereby vitamin A deficiency was related with impaired ILC3 responses\(^8\), suggesting that these cells sense signals from host-derived nutrients and directly from the microbiota.

**ILCs promote chronic inflammatory diseases**

Besides their function in promoting tissue homeostasis, the chronic activation of ILCs can also induce inflammation at mucosal surfaces. IL-23 is a powerful activator of ILC3s and this axis is intimately linked to inflammatory bowel disease (IBD). Infection-induced and sterile inflammation models of colitis such as S. typhimurium, Helicobacter hepaticus, Helicobacter typhlonius infectious models or anti-CD40 models have been used to better understand the ILC3 functions, which are thought to be related to stimulation by IL-23 or IL-12 and consequently release of IL-17, GM-CSF and IFN-\(\gamma\)\(^8\). IL-17-producing ILC3s have been shown to play a key role in T-cell independent mouse models and, in this context, CD127 blockade seems to reduce ILC3 numbers and ameliorates disease. It is believed that activation of dendritic cells leads to TNF and IL-23 release which in turn results in an expansion of IL-17 producing ILCs\(^8\). In contrast, ILC3-derived IL-22 protects mice from intestinal inflammation triggered by C. rodentium infections, DSS-induced colitis and the transfer of T cells\(^5,13,6,8\). In some murine colitis models, the blockade of intra-epithelial ILC1s and IFN-\(\gamma\)-producing ILC3 ameliorates the inflammation on the mucosal layer\(^1,2\). Conversely, although a consistent role for ILCs in human IBDs continues to be discussed, several studies have reported varying numbers of these cells in intestinal samples. Patients with Crohn’s disease presented an increase in ILC1 populations accompanied by decreased levels of IL-22-producing ILC3s in inflamed intestinal tissues\(^29,30\). In addition, in pediatric patients with Crohn’s disease, a lower expression of MHC class II on ILC3s was observed than in control subjects without IBD; a reduction of MHC class II was correlated with increased numbers of Th17 cells\(^9\). Together, these data suggest that ILC1s and ILC3s might participate in the establishment and the development of inflammation, and ILC3s might reduce pathogenic T cells trough MHC class II interactions.

Evidence regarding the function of ILCs in tumorigenesis are emerging from studies investigating the pro-carcinogenic role of cytokines and chronic inflammation. Human colorectal cancer (CRC) samples showed increased expression of IL-23 receptor, and the induced expression of IL-23 in mice led to the development of adenomatous tumors originating in the duodenum. Although the contribution of adaptive cells remains unclear, this model would indicate a potential role for ILC3s\(^92,93\). Moreover, IL-22-producing ILC3s might also be related in human CRC because uncontrolled IL-22 production facilitates tumor-infiltrating lymphocytes and IL-22 levels in the tumor were significantly higher than in non-tumor sections from the same patients\(^94\).

**Future perspectives**

The liver and intestine are complex organs that have multiple interactions with the microbiota, nutrients, metabolites and diverse types of cell to maintain the host homeostasis. The importance of the ILC family in the immunity panel is growing fast. Many studies have been done to elucidate the specific ILCs function in different sites triggering immunity, tissue repair and inflammation. However, the molecular mechanism by which ILC subsets play specific roles and their consequences for the host homeostasis remain unclear. Future studies focusing on how ILC responses are regulated and how they integrate the immune cells in different organs might provide therapeutic potential in the treatment of diverse diseases.

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