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Type 1 innate lymphoid cells: Soldiers at the front line of immunity

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ABSTRACT

Innate lymphoid cells (ILCs) are tissue-resident innate lymphocytes that have functions to protect the hosts against pathogens and that regulate tissue inflammation and homeostasis. ILC subsets rapidly produce particular cytokines in response to infection, inflammation, and tissue injury at the local environment. Type 1 ILCs (ILC1s) promptly and abundantly produce interferon (IFN)-γ but lack appreciable cytotoxic activity. ILC1s share many phenotypic, developmental, and functional characteristics with natural killer (NK) cells, which are circulating innate lymphocytes with potent natural cytotoxicity. However, recent studies have established ILC1s as distinct from NK cells. ILC1s predominantly reside in the liver—they initially were discovered as a liver-resident ILC subset—as well as in other lymphoid and non-lymphoid tissues. Accumulating evidence has demonstrated that ILC1s play an important and unique role in host protection and in immunomodulation in their resident organs. However, the pathophysiological role of tissue-resident ILC1s remains largely unclear. In this review, we summarize emerging evidence showing that ILC1s not only contribute to inflammation to protect against pathogens but also promote tissue protection and metabolism. We highlight a unique function of ILC1s in their resident tissues.

Overview and classification of ILCs

Innate lymphoid cells (ILCs) are the most recently established group of immune cell subsets. ILCs comprise innate lymphocyte subsets that lack expression of RAG-dependent rearranged antigen-specific receptors (i.e., the B cell receptor and the T cell receptor), which are expressed on adaptive immune cells [1,2]. Accumulating evidence has demonstrated ILCs retain the capacity to elicit immediate inflammation at their resident lymphoid and non-lymphoid tissues [1–5]. As tissue-resident innate immune cells, ILCs sense proinflammatory driver cytokines in the context of pathogenic signals and danger-associated molecular

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patterns (DAMPs) at the local sites of pathogen invasion and tissue damage; ILCs then swiftly mount local immune responses by producing particular types of effector cytokines [1–4,6]. Thus, ILC subsets establish the first line of host defense by invoking innate immune responses in their resident tissues. Recent studies support the concept that tissue-resident ILCs not only regulate local inflammation for host protection against pathogens but also modulate tissue injury, remodeling, homeostasis, and metabolism in their resident tissues [1,3–5,7–9].

ILCs are classified into 3 groups according to the particular types of effector cytokines that they can produce. Group 1, group 2, and group 3 ILCs functionally mirror $CD4^+$ T helper (Th) type 1 (Th1) cells, Th type 2 (Th2) cells, and Th type 17 (Th17) cells, respectively. Each of these pairs of cell types shows marked similarities in the effector cytokines that they produce, the cytokine receptors that they express and that drive effector functions, and the transcriptional programs that are required for their development; these programs are primarily regulated by the transcription factors T-bet (T-box transcription factor Tbx21; group 1 ILCs), GATA3 (GATA binding protein 3; group 2 ILCs), and RORγt (RAR-related orphan receptor γ; group 3 ILCs).

$T\text{-}bet^+$ group 1 ILCs mainly respond to tissue inflammation and intracellular pathogens, including viruses, intracellular bacteria, and certain parasites, in their resident tissues; after exposure to the driver cytokine interleukin (IL)-12, group 1 ILCs are activated and produce interferon (IFN)-γ. $GATA3^+$ group 2 ILCs are activated by acute and chronic tissue damage and extracellular bacteria, parasites, and allergens. Consequently, ILC2s proliferate in response to IL-25, IL-33, and thymic stromal lymphopoietin, and preferentially release IL-5 and IL-13 (and possibly IL-4) as well as amphiregulin as a tissue-protective factor. $ROR\gamma t^+$ group 3 ILCs are activated in response to local inflammation and extracellular microbes, including commensal microbiota, pathogenic microbes, and fungi, and secrete IL-17, IL-22, or both upon stimulation with IL-23 and IL-1β, and also IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the case of intestinal ILC3 [1,3,5,10–16]. In line with their tissue residency and ability to invoke prompt inflammation, ILCs orchestrate appropriate immune responses in the local environment to eradicate threats to hosts during early phases of pathogen invasion and tissue damage.

Shared and unique properties of natural killer cells and type 1 ILCs

Group 1 ILCs consist of natural killer (NK) cells and type 1 ILCs (ILC1s) and are functionally defined as innate lymphocyte subsets with the potent ability to produce IFN-γ [1,3,5,17,18]. Acting as a driver cytokine, IL-12 strongly induces IFN-γ production by NK cells and tissue-resident ILC1s in several organs [19–24]. NK cells recognize virus-infected and transformed cells and exert the cytotoxicity against these target cells by using a variety of activating and inhibitory NK cell receptors that positively and negatively regulate the activation, cytotoxicity, and, production of IFN-γ and chemokines [25,26]. Historically, ILC1s were first found in the livers of mice as an atypical liver-specific subset of NK cells that does not express the traditional NK cell marker DX5 and that reciprocally expresses large amounts of the tumor necrosis factor (TNF) superfamily member TNF-related apoptosis-inducing ligand (TRAIL) [27]. As group 1 ILCs, ILC1s and NK cells share many features: the ability to produce large amounts of IFN-γ; dependence on T-bet for functional maturation; the requirement for IL-15 for development and homeostasis; overlapping transcriptomic signatures; and expression patterns of surface molecules, including cytokine receptors [1,5,7,11,12,17,18,28]. ILC1s also express several NK cell receptors on their cell surfaces [5,17,18,24,28]. Although a few studies have addressed the roles of activating NK cell receptors on ILC1s [24,29], whether activating and inhibitory signals though these NK cell receptors regulate the activation and function of ILC1s is largely unknown.

Despite these common features of ILC1s and NK cells, these two group 1 ILC members are developmentally, phenotypically, and functionally distinct immune cell subsets. ILC1s are believed to develop from a common ILC precursor with the potential to differentiate into all ILC subsets except NK cells, whereas NK cells develop from NK precursors with restricted potential to generate NK cells but none of the other ILC subsets, including ILC1s [10,21,30,31]. However, this bifurcation of developmental lineages between NK cells and the other ILC subsets is still under discussion, especially in humans [32–35]. Furthermore, recent studies have redefined ILC1s as a cell subset that is developmentally distinct from NK cells in light of their different requirements for transcription factors Nfil3 (Nuclear factor, interleukin 3 regulated, also known as E4BP4) and Eomes (Eomesodermin) during development [36–39]. Functionally, NK cells exert potent cytotoxic activity and circulate across lymphoid organs via the bloodstream and lymphatic system, whereas ILC1s are fundamentally tissue-resident lymphocytes with little to no cytotoxic activity [3–6,18].

Throughout the literature, ILC1s are described phenotypically as non-T, non-B lymphocytes that express IL-7Rα—which is expressed by the vast majority of ILC subsets except for NK cells—but not GATA3 or RORγt (or alternative markers of group 2 and group 3 ILC subsets) or traditional NK cell markers (i.e., DX5 on mouse NK cells and CD16 and CD56 on human NK cells); however, ILC1s in organs traditionally have been understood as tissue-resident NK cell subsets [5,11,19,21,36,39–47]. However, the precise phenotypic definition of ILC1s remains under debate, because a unique and reliable ILC1 marker that clearly distinguishes ILC1s from NK cells and that is stably expressed in an inflammatory environment has not yet been identified [3,5,17,18].

Mouse ILC1s are phenotypically defined as $NK1.1^+NKp46^+CD49a^+DX5^-Eomes^-$ lymphocytes (only in mouse strains that harbor the gene loci encoding the NK1.1 antigen) in the naïve state. The expression of these markers occasionally is modulated depending on the activation status, inflammatory conditions, and their resident tissues, and expression of NK1.1 and NKp46 is not specific to ILC1s but are shared by NK cells [21–23,36,39–42,44–47]. In mice, liver ILC1s—but not NK cells—stably express CD200R, as a reliable ILC1 marker used by a combination of DX5 or Eomes to

exclude inflammation-induced changes in the expression of cell surface molecules on ILC1s and NK cells [23,24].

Similar to the phenotypic definition of ILC1s in mice, human ILC1s are defined as a non-T, non-B lymphocyte subset that expresses IL-7Rα and the tissue-resident markers CD69 and CD103 in some tissues, including intestine. However, human ILC1s express little to no GATA3, RORγt, or the NK cell–associated molecules CD16, granzyme, perforin, Eomes, and occasionally express CD56 [19,20,43,48–52]. Mouse ILC1s have been found in the liver, intestines, thymus, spleen, lymph nodes, adipose tissues, salivary glands, skin, kidney, peritoneal cavity, and uterus [21–23,36,39–42,44–47]. Human ILC1s have been documented in the liver, intestines, tonsil, spleen, lymph nodes, adipose tissues, skin, blood, and lung [19,20,43,46,48–57]. Intriguingly, whereas mouse ILC1s reside predominantly in the liver, whereas human ILC1s instead are distributed throughout a broad spectrum of lymphoid and non-lymphoid organs [40,46,47,57]. The biological effects of ILC1s have been studied extensively in mouse models of tissue injury and of infectious, inflammatory, and metabolic disease.

ILC1s in the liver

ILC1s were identified initially as liver-resident ILCs in mice and are the most predominant ILC subset in that organ except for NK cells [17,27,36,37,40,47]. However, the pathophysiological role of liver ILC1s remains incompletely investigated. One previous study demonstrated that liver ILC1s have a non-redundant role as initial responders to viral infections in the liver [23]. In a mouse model of cytomegalovirus infection by hydrodynamics injection for direct delivery of mouse cytomegalovirus (MCMV) to the liver, liver ILC1s expressing CD200R represent the initial and primary producers of IFN-γ very early during the viral infection in this organ [23]. Importantly, liver ILC1s respond to IL-12, which is mainly released from liver conventional type 1 dendritic cells (cDC1), and rapidly produce IFN-γ prior to the initiation of NK cell-mediated anti-viral immune responses during MCMV infection [23]. Early during infection, liver ILC1s are essential for limiting the replication of MCMV in the liver in the early course of the infection in an IFN-γ-dependent manner, thus contributing to the host defense against MCMV infection [23]. These findings support a unique role of liver ILC1s in early host protection against the viral infection [Fig. 1].

Although it is increasingly evident that tissue-resident ILCs play important roles in tissue injury, homeostasis, and remodeling in several organs [1,3–5,7–9], little is known regarding the involvement of liver ILC1s in the pathogenesis of liver injury. We recently demonstrated that liver ILC1s—but not NK cells or other lymphocyte subsets—are activated and produce IFN-γ in the acute phase of drug-induced acute liver injury induced by the injection of carbon tetrachloride or low-dose acetaminophen in mice [24]. Intriguingly, activated liver ILC1s have a protective role in acute liver injury through their production of IFN-γ, which upregulates the survival factor Bcl-xL (B-cell lymphoma-extra large, also known as Bcl2-like 1 [Bcl2l1]) to promote the survival of damaged hepatocytes [24]. Signaling through the activating NK cell receptor DNAM-1, which promotes IFN-γ production by NK cells [58–60], is required for optimal activation of liver ILC1s and their production of IFN-γ during acute liver injury [24]. $CD11b^{-}$ dendritic cells (DCs), whose phenotype is consistent with liver cDC1 in the liver, produce IL-12 during acute liver injury [24]. Furthermore, extracellular adenosine triphosphate (ATP) is released as a DAMP molecule after acute liver damage and accelerates IL-12-driven IFN-γ production by liver ILC1s in a manner that depends on the purinergic ATP receptor P2RX7 [24]. These findings highlight an unexpected pathophysiological role of liver ILC1s in tissue protection during acute liver injury [Fig. 1]. During both MCMV infection and drug-induced acute liver injury, liver cDC1 are the major source of IL-12 and liver ILC1s display enhanced responsiveness to IL-12 and consequent augmented IFN-γ production as compared with other lymphocytes, including NK cells [23,24].

ILC1s in the intestine

Intestinal ILC1s play a critical role in the first line of host defense against various intestinal bacteria and parasites. In previous studies, mice with dramatic decreases in group 1 ILCs (both ILC1s and NK cells) and those lacking all ILC subsets showed increased susceptibility to intestinal infection with *Citrobacter rodentium* and *Clostridium difficile* [37,61]. Host protection against intestinal infection by *C. difficile* is mediated through T-bet-dependent functional maturation of and IFN-γ production by intestinal ILC1s [61]. In response to infection with *Listeria monocytogenes* in mice, intestinal ILC1s produce IFN-γ, which is important for controlling the dissemination of *L. monocytogenes* to small intestine, mesenteric lymph nodes, and spleen [62]. Furthermore, IFN-γ production by intestinal ILC1s is both essential for the optimal release of mucus to protect the intestinal epithelial barrier during *Salmonella enterica* infection in mice and simultaneously involved in the development of severe enterocolitis after infection [63]. Moreover, intestinal ILC1s in mice contribute to innate host protection against infection with the intracellular parasite *Toxoplasma gondii* through the production of IFN-γ and TNF-α and the subsequent inflammation-induced migration of inflammatory monocytes that are required to control the intestinal infection [21]. These studies have clarified the importance of intestinal ILC1s as prompt producers of IFN-γ that contribute to the host defense against these intestinal pathogens [Fig. 1].

Contrary to the role in host protection against pathogenic microorganisms, the IFN-γ produced by intestinal ILC1s in mice amplifies mucosal inflammation during colitis induced by anti-CD40 agonistic antibodies [19] [Fig. 1]. These findings are reminiscent of observations that ILC1s accumulate in the inflamed intestinal tissues of mice with humanized immune systems in dextran sodium sulfate-induced colitis and in the inflammatory lesions of patients with Crohn's disease [19,20] [Fig. 1].

ILC1s in the adipose tissues

Adipose tissue ILC1s comprise a stable and tissue-resident cell population in the subcutaneous and visceral adipose tissues of mice and humans [22,29,64]. These ILC1s show homeostatic proliferation, and they accumulate in fat depots during the

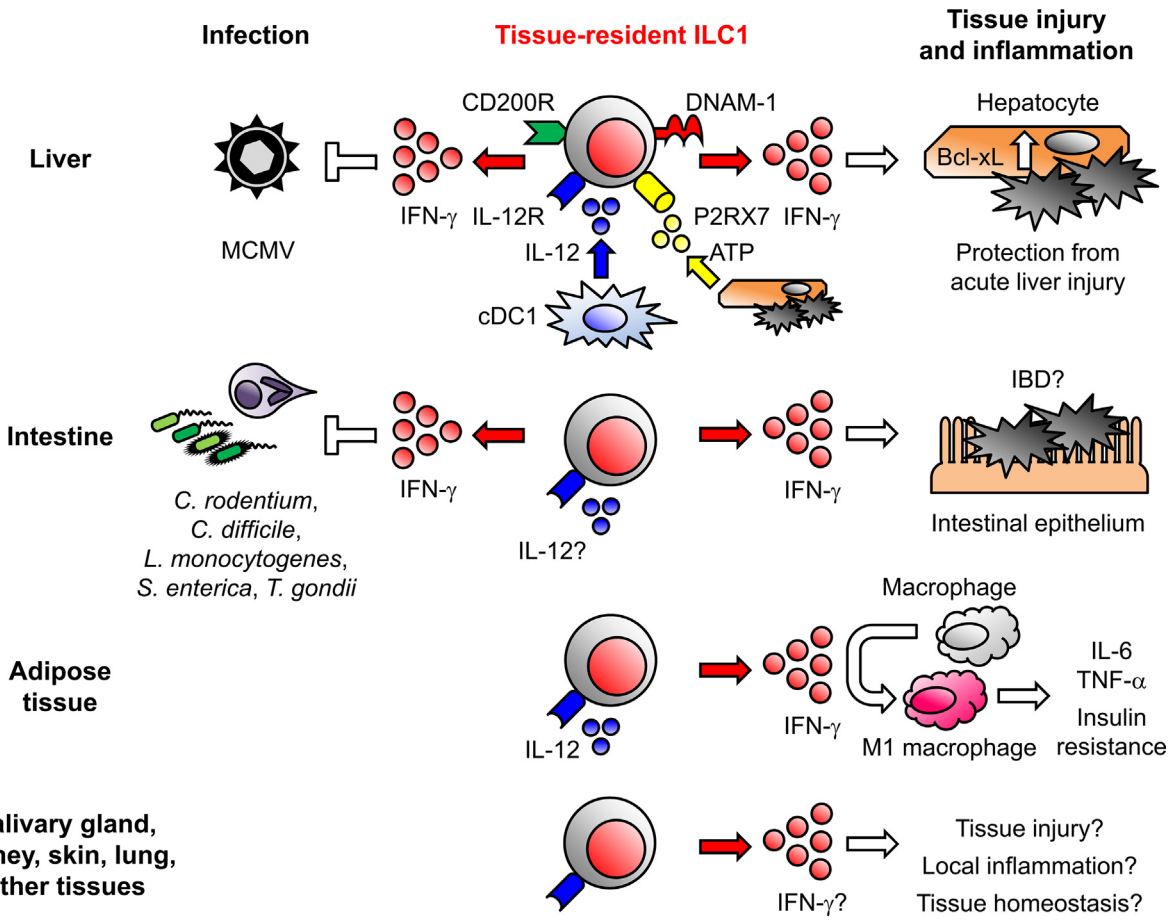

Fig. 1 **Functional roles of ILC1s as a producer of IFN-γ in the early phase during infection, tissue injury, and inflammation.** The IFN-γ produced by liver ILC1s limits the replication of MCMV. Liver ILC1 also protect hepatocytes from drug-induced acute injury via IFN-γ production for upregulating Bcl-xL in hepatocytes. In both cases, liver ILC1s produce IFN-γ predominantly in response to IL-12, which is primarily released from cDC1. In intestines, ILC1-derived IFN-γ protects against pathogens including bacteria and toxoplasma. In addition, ILC1s accumulate in the inflamed intestinal tissues of mice with colitis and patients with Crohn's disease. ILC1-derived IFN-γ may amplify mucosal inflammation. The IFN-γ produced by ILC1s in adipose tissues regulates the polarization and homeostasis of proinflammatory macrophages, implicating adipose-resident ILC1s in the promotion of local inflammation and obesity-associated insulin resistance. Although incompletely understood as yet, ILC1s in other organs—including salivary gland, kidney, skin, and lung—might influence tissue injury, local inflammation, and tissue homeostasis.

progression of diet-induced obesity. In addition, the frequency and number of ILC1s in adipose tissues dynamically respond to changes in diet and body weight [22,29,64]. Proinflammatory cytokines in adipose tissues are upregulated after diet-induced obesity, and the IL-12-IL-12R-STAT4 signaling axis in ILC1s plays critical roles in the proliferation, accumulation, and IFN-γ production of ILC1s during the development of obesity [22,64], however the type of immune cells that produce IL-12 remains to be determined.

Furthermore, ILC1-derived IFN-γ plays a critical role in the polarization and homeostasis of proinflammatory macrophages (also known as classically activated macrophages [M1 macrophages]) in adipose tissues [22,29]. Consequently, through the modulation of proinflammatory macrophages, ILC1s promote a shift toward an inflammatory environment in adipose tissues, thus leading to obesity-related glucose intolerance and insulin resistance [22,29] [Fig. 1]. In addition, ILC1s promote fibrogenesis of adipose tissues, hepatic steatosis, and diabetic changes during obesity [64]. Furthermore, during diet-induced obesity, IL-12-activated ILC1s in the adipose tissue induce the upregulation of fibrosis-related genes and extracellular matrix genes in visceral adipose tissues through IFN-γ-dependent activation of the TGF-β-Smad3 signaling pathway and macrophages [64].

ILC1s in other tissues

Although tissue-resident ILC1s presumably are involved in tissue homeostasis, tissue injury, and local inflammation in their resident environment, their function in tissues other than liver, intestines, and adipose tissues has been little studied [Fig. 1].

The salivary glands of mice contain a population of ILC1s [65,66]. Salivary gland ILC1s display a unique expression pattern of cell surface molecules, and their transcriptomic

profiles overlap those of ILC1s in the liver and intestine and of NK cells [65,66]. The development of ILC1s in salivary glands is regulated by the TGF-β-mediated suppression of a transcriptional program which is controlled by Eomes [65,66]. Although the physiological role of salivary ILC1s is currently unclear, TGF-β-mediated imprinting of their transcriptional signatures is linked to the development of salivary glands and the age [65], suggesting that these ILC1s might regulate the tissue microenvironment or maturation of salivary glands.

A study indicated that kidney ILC1s—but not NK cells—mediate acute kidney injury in a mouse model of ischemia-reperfusion [41]. In that study, depletion both of NK1.1-expressing NK cells and ILC1s protected mice from acute kidney injury after ischemia-reperfusion, whereas the preferential ablation of NK cells failed to ameliorate the severity of damage [41]. These findings implicate the involvement of kidney ILC1s in the exacerbation of ischemia-reperfusion-induced acute kidney injury, although the cellular and molecular mechanisms through which kidney ILC1s accomplish this effect are unknown. Previous studies have revealed the detrimental role of IFN-γ in acute tissue damage [67–75], suggesting the involvement of tissue-resident ILC1s in the pathogenesis of acute or chronic tissue injury in several organs.

In a mouse model of hapten-induced contact hypersensitivity, skin ILC1s increased in number and produced TNF-α and IFN-γ [76]. In that study, the genetic ablation of ILC2s exaggerated the contact hypersensitivity by enhancing type 1-skewed immune responses, whereas genetic ablation of group 1 ILCs (both ILC1s and NK cells) decreased clinical scores of contact hypersensitivity [76]. Although further studies are required to determine the effects of skin ILC1s and the molecular mechanisms underlying the exacerbation of contact hypersensitivity, these findings imply that skin ILC1s may be associated with pathogenic skin inflammation. The concept of "type 1-type 2 cytokine balance" has recently been expanded to include ILC subsets: that is, IFN-γ released from ILC1s and NK cells suppresses ILC2-associated innate type 2 immune responses in tissues [77–79]. Therefore, future studies need to address the potential beneficial roles of tissue-resident ILC1s during acute and chronic tissue remodeling in organs, such as fibrosis in the liver, lung, and kidney. This concept is consistent with the anti-fibrotic effect of IFN-γ, which is largely mediated by counterbalancing type 2 cytokines [64,77,80–88].

Adaptive immune features of ILC1s

NK cells acquire adaptive immune features including antigen-specific clonal expansion of effector NK cells and differentiation into long-lived memory NK cells with augmented cytotoxicity and enhanced production of IFN-γ [59,89–93]. Given the functional redundancy of NK cells and ILC1s, it is entirely possible that ILC1s have the potential for antigen-dependent proliferation and differentiation into a long-lived subset with enhanced IFN-γ production.

Several recent studies have addressed adaptive immune features of ILC1s [94,95]. In particular, one study has demonstrated that MCMV-experienced liver ILC1s proliferate and persist in that organ after MCMV infection; this is reminiscent of the adaptive immune features of MCMV-specific NK cells during the infection, specifically in the context of the activating NK cell receptor Ly49H on NK cells and the specific ligand MCMV m157 glycoprotein on infected cells during MCMV infection [59,89–93,95]. Liver ILC1s change their phenotypes, transcriptional profiles, and epigenetic landscapes after MCMV infection, and persistent IL-18R^{+} ILC1s show enhanced IFN-γ production in response to a secondary MCMV challenge [95]. These MCMV-primed ILC1s expand and differentiate into a long-lived subset of liver ILC1s, which is potentially mediated through the interaction of the activating NK cell receptors NKR-P1A and or NKR-P1C and their ligand MCMV m12 glycoprotein [95].

In addition, liver ILC1s in mice mediate hapten-specific contact hypersensitivity and the hapten-specific memory formation, consistent with hapten-specific immunological memory formation by liver-resident NK cells [94,96,97]. After hapten sensitization, liver ILC1s proliferate and migrate into skin-draining lymph nodes in a CXCR3-dependent manner. Due in part to a CXCR6-CXCL16 interaction, these sensitized ILC1s again migrate to and then reside in the liver, where they are responsible for hapten-specific memory responses and their maintenance via the lymph node-liver axis [94]. These studies have revealed the proliferation activity and long-term persistence of liver ILC1s in certain inflammatory conditions [94,95]. However, unlike adaptive immune features of NK cells in an activating NK cell receptor-ligand-dependent manner [90,92,93], the activating NK cell receptor–ligand interaction, that drives antigen-specific proliferation of ILC1s and their differentiation into a long-lived subset, and the antigen specificity of these long-lived ILC1s have not been fully elucidated.

ILC1s in humans

Several studies have reported functional annotations of tissue-resident ILC1s in humans. Unlike the strict compartmentalization of mouse ILC1s in the liver, human ILC1s are distributed more widely throughout both lymphoid and non-lymphoid organs, including liver, small and large intestines, tonsil, spleen, lymph nodes, adipose tissues, skin, blood, and lung. In addition, the frequencies of ILC1s in these tissues vary with aging and obesity [19,20,29,43,46,48–57]. Furthermore, in humans, the transcriptional signatures and heterogeneity of mucosal tissue-resident ILC1s differ markedly from those of lymphoid tissue-resident ILC1s. These findings imply that tissue-resident ILC1s have unique functions that are linked to the resident tissue environment [57].

Previous studies have shown increased proportions of ILC1s in the inflamed intestinal tissues of patients with Crohn's disease and in the lungs of patients with chronic obstructive pulmonary disease [19,20,48,52]; however the frequency of skin ILC1s in patients with psoriasis and atopic dermatitis is similar to that in normal skin of healthy individuals [54,55]. These findings strongly suggest that ILC1s are involved in the pathogenesis of various inflammatory diseases in mucosal tissues. However, the contribution of tissue-resident ILC1s to the development and progression of

these inflammatory diseases and the molecular mechanisms through which these ILC1 affect remain to be elucidated.

Concluding remarks

Accumulating evidence has demonstrated that ILC1s help to protect the host against pathogens by promptly mounting local inflammation. In addition, ILC1s play a regulatory function to promote tissue protection against tissue injury and maintain the homeostasis of their resident environment. By extension, tissue-resident ILC1s likely have a unique and tissue-specific function that is inextricably linked to both the tissue environment in which they exist and their ability to produce IFN-γ abundantly and promptly. However, experimental evidence that supports this concept is currently limited. Further studies are needed to elucidate the tissue-specific pathophysiological roles of ILC1s in their resident tissues and to provide key insights into the regulation of ILC1 functions to promote health and prevent organ-specific pathogenesis.

Conflicts of interest

The authors declare no competing interests.

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