Minireview

Innate Lymphoid Cells in Tissue Homeostasis and Disease Pathogenesis

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Innate lymphoid cells (ILCs) are the most recently discovered family of innate immune cells. ILCs can be categorized into three groups on the basis of the transcription factors that direct their functions and the cytokines they produce. Notably, these functions parallel the effector functions of T lymphocytes. ILCs play a frontline role in host defense and tissue homeostasis by responding rapidly to environmental factors, conducting effector responses in a tissue-specific manner, and interacting with hematopoietic and non-hematopoietic cells throughout the body. Moreover, recent studies reveal that ILCs are involved in development of various inflammatory diseases, such as respiratory diseases, autoimmune diseases, or cancer. In this review, we discuss the recent findings regarding the biology of ILCs in health and inflammatory diseases.

Keywords: development, homeostasis, inflammation, innate lymphoid cells, plasticity, tropism

INTRODUCTION

Innate lymphoid cells (ILCs) are recently identified lymphocytes that lack antigen-specific receptors but have similar functions as T cells and thus serve as the innate counterparts to T cells (Diefenbach et al., 2014; Spits and Cupedo, 2012). They respond quickly to signals from the tissue environment and are in general enriched in barrier tissues (i.e., skin, lung, and intestine) rather than in lymphoid tissues. There are three ILC subsets, each of which displays a distinct predilection for particular tissues. Within these tissues, the ILCs play specific roles in homeostasis and disease (Mjösberg and Eidsmo, 2014; Patman, 2015) that will be discussed in this review.

INNATE LYMPHOID CELLS

ILC subsets

Unlike lineage cells such as T cells, B cells, and myeloid cells, ILCs do not express lineage markers (Vivier et al., 2018). Instead, they can be divided into three groups (group 1 ILCs, group 2 ILCs, and group 3 ILCs) on the basis of the cytokines they produce and the master regulatory transcription factors that drive their development and functions.

Group 1 ILCs include ILC1s and natural killer cells (NK cells). They express CD161 and interleukin (IL)-12 receptor beta (IL-12Rβ) on their surface, and their master transcription factor is T-bet (Cortez and Colonna, 2016; O'Sullivan, 2019). ILC1s are the innate counterpart to Th1 cells since they secrete interferon γ (IFNγ) and tumor necrosis factor α (TNFα), while NK cells are considered to be the innate counterpart to type 1 cytotoxic T (Tc1) cells since they produce TNFα, IFNγ, perforin, and granzyme.

Group 2 ILCs (ILC2s) express the IL-33 receptor (IL-33R) and the transcription factors GATA binding protein 3

(GATA3) and RAR-related orphan receptor alpha (RORα) (En-twistle et al., 2020). ILC2s are the counterparts to Th2 cells because they produce large amounts of type 2 cytokines such as IL-5 and IL-13. ILC2s also express other cytokines, including amphiregulin, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-9 (Morita et al., 2016).

Group 3 ILCs are subdivided into three populations according to their expression of C-C motif chemokine receptor 6 (CCR6) and natural cytotoxicity receptors (NCR) (i.e., NKp46 in mice and NKp44 in humans). Thus, the CCR6$^+$ cells are designated LTi; these cells produce lymphotoxins (LT). The CCR6$^-$ cells are divided further into NCR$^+$ ILC3s and NCR$^-$ ILC3s (Montaldo et al., 2015). ILC3s typically express IL-1 and IL-23 receptors and the RORγt and aryl-hydrocarbon receptor (AhR) transcription factors (Meininger et al., 2020).

Recently, several groups identified a new subset of ILCs, namely, IL-10-producing regulatory ILCs (ILCregs) (Golebski et al., 2021; Morita et al., 2019; Wang et al., 2017). Wang et al. showed that they express a distinct transcription factor, namely, ID3 (inhibitor of DNA binding 3), and that autocrine transforming growth factor beta (TGF-β) signaling is important for their development (Wang et al., 2017). However, other groups have also reported that ILCregs can be derived from ILC2s by retinoic acid (RA) (Golebski et al., 2021; Morita

et al., 2019). Further studies on the origin and functions of ILCregs are required.

Development and differentiation of ILCs
ILCs develop from common lymphoid progenitors (CLPs) in the fetal liver and the adult bone marrow (Zook and Kee, 2016). In the mouse, the differentiation of CLPs into mature ILC subsets is regulated by the coordinated expression of a variety of transcription factors that activate or repress critical target genes. These transcription factors include ID2, NFIL3, promyelocytic leukemia zinc finger (PLZF) (encoded by *Zbtb16*), TCF1 (encoded by *Tcf7*), and GATA3 (Eberl et al., 2015; Vivier et al., 2018) (Fig. 1). NFIL3 plays a particularly important role since it controls ID2, GATA3, EOMES, and T-bet and thereby orchestrates ILC differentiation (Gascoyne et al., 2009; Male et al., 2014; Xu et al., 2015). The transcriptional ILC differentiation program starts with CLPs expressing NFIL3 and TCF1; this causes them to differentiate into early innate lymphoid progenitors (EILPs), which are the lineage-committed cells for ILCs and NK cells (Geiger et al., 2014; Tanriver and Diefenbach, 2014). The EILPs then differentiate into common helper ILC precursors (CHILPs) due to ID2 and GATA3 expression (Serafini et al., 2014; Tanriver and Diefenbach, 2014; Yagi et al., 2014).
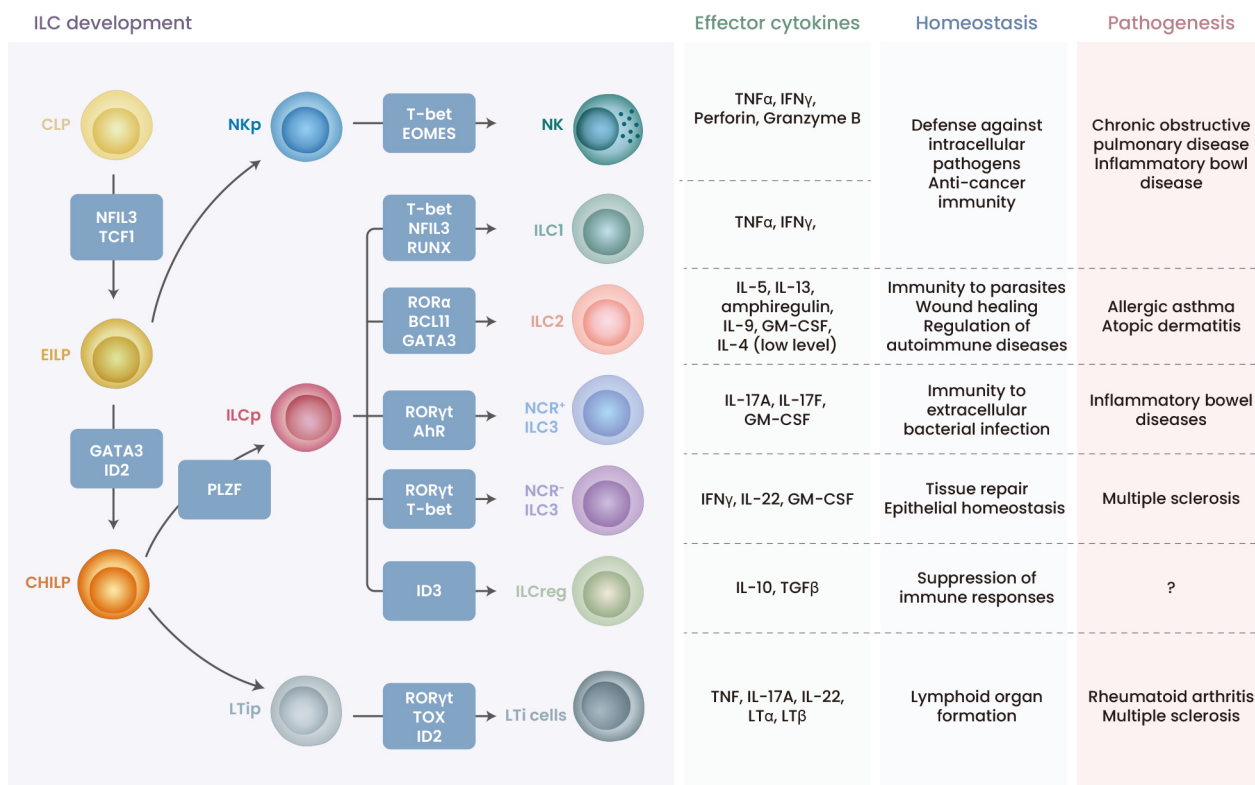

Fig. 1. Development and function of ILCs. ILC differentiation proceeds in a stepwise fashion from hematopoietic stem cells (HSCs) to lymphoid lineage restricted precursors. The development of ILCs from CLPs requires ID2-mediated suppression of alternative lymphoid cell fates that generate B and T cells. CLPs further commit to the ILC/NK lineage *via* multi-potent ILCp. Individual subsets depend on the expression of specific transcription factors that determine their terminal differentiation and function. CLP, common lymphoid progenitor; EILP, early innate lymphoid progenitor; CHILP, common helper ILC precursor; NKp, NK cell precursor; ILCp, ILC precursor; LTip, LTi cell precursor.
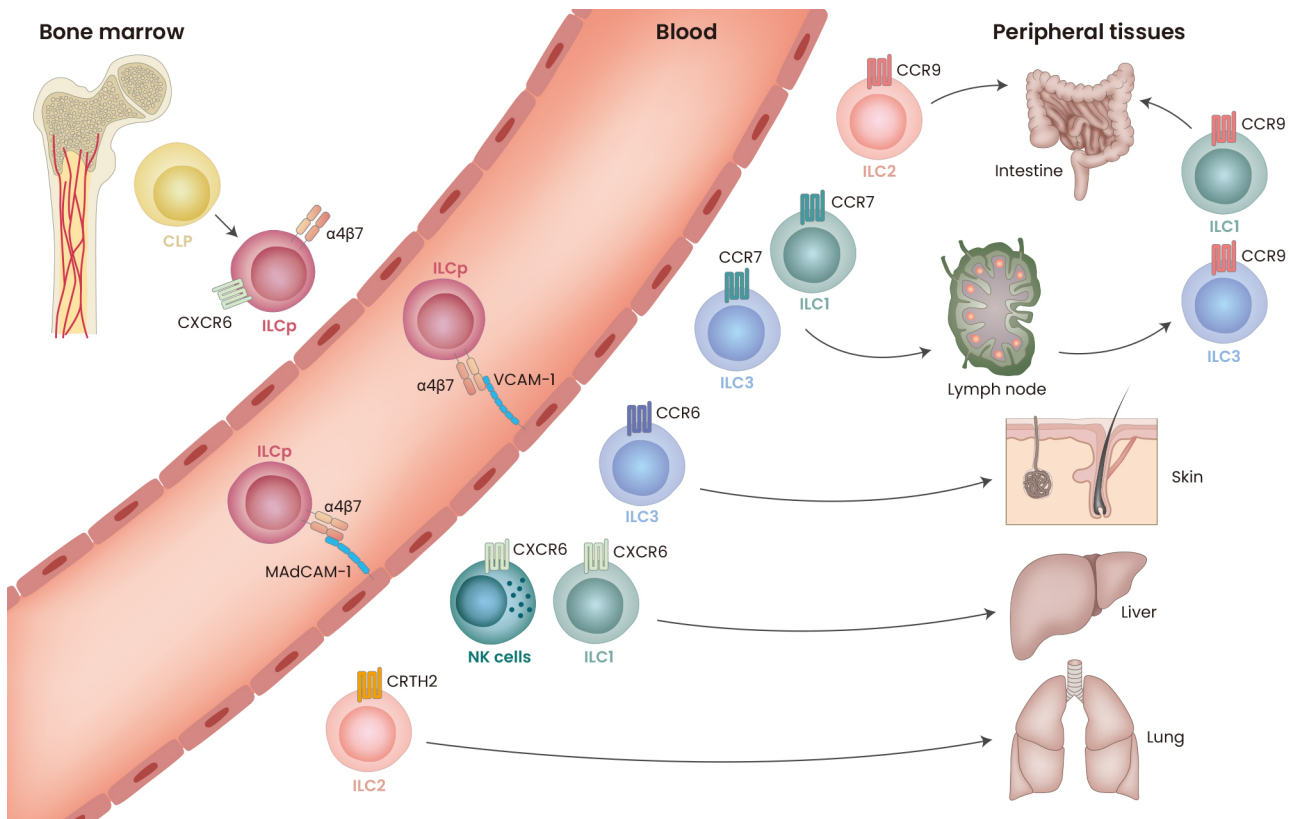
Fig. 2. Tissue tropism of ILCs. ILCp derived from bone marrow hematopoiesis enters the blood to home to lymphoid and non-lymphoid organs. This process requires the expression of various chemokine receptors and $\alpha4\beta7$ integrin. Their strategic position within tissues allows ILCs to act as a monitor of healthy tissue and to enable a rapid response to inflammatory signals. CLP, common lymphoid progenitor; ILCp, ILC precursor.

Subsequently, PLZF expression drives the development of ILC precursors (ILCp) from CHILPs (Constantinides et al., 2014; 2015). The ILCp exits the fetal liver or adult bone marrow and then circulate in the blood (Eberl et al., 2015). There is also evidence that some ILCp matures in the bone marrow before entering the bloodstream (Eberl et al., 2015; Walker et al., 2019).

Tissue tropism of ILCs

A growing body of evidence suggests that ILC subsets are strategically localized in specific tissues in a way that relates to their roles in immune responses (Bando et al., 2015; Kim et al., 2016a). Thus, ILC1s are largely located in the intraepithelium of the intestine (Fuchs et al., 2013); ILC2s predominate in the lung, skin, and white adipose tissue; and ILC3s are a major population in the lamina propria, cryptopatches, and Peyer's patches of the intestinal tract (Klose et al., 2013; Luci et al., 2009). This tissue tropism is determined in part by the tissues, which present a signature array of adhesion molecules and emit chemokines, and in part by the ILCp and mature ILCs, which express characteristic homing receptors, including integrins and chemoattractant receptors, that cause them to migrate from the circulation into the peripheral tissues (Lapidot et al., 2005). For example, ILCp expresses integrin $\alpha4\beta7$ (Constantinides et al., 2014; Possot et al.,

2011) while endothelial cells express the binding partners of $\alpha4\beta7$, namely, mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and vascular cell adhesion protein 1 (VCAM-1) at high levels (Deem and Cook-Mills, 2004; Erle et al., 1994). The encounter between ILCp and MAdCAM-1- and VCAM-1-positive endothelium causes the ILCp to stick and then extravasate into the tissue. Thus, $\alpha4\beta7$ guides ILCp to mucosal and non-mucosal tissues. Similarly, the ILCp expresses chemokine receptors that guide their migration towards the corresponding chemokines emitted by the tissues. These chemokine receptors include C-X-C motif chemokine receptor 6 (CXCR6), which seems to play an important role in the emigration of ILCp from the bone marrow and their peripheral seeding, and CCR7 and CCR9, which are key gut-homing receptors on ILCs (Chea et al., 2015; Kim et al., 2015; Patman, 2015; Possot et al., 2011; Zlotoff et al., 2010). Thus, by expressing specific homing receptors, ILCp and mature ILCs migrate to specific peripheral tissues (Fig. 2).

ILC plasticity

Once ILCp and mature ILCs enter the tissues, they seem to reside there and proliferate locally. A parabiosis mouse model showed that under homeostatic conditions, ILCs reside in the tissue whereas other lymphocytes circulate through the bloodstream (Gasteiger et al., 2015; Kim et al., 2016a; Moro
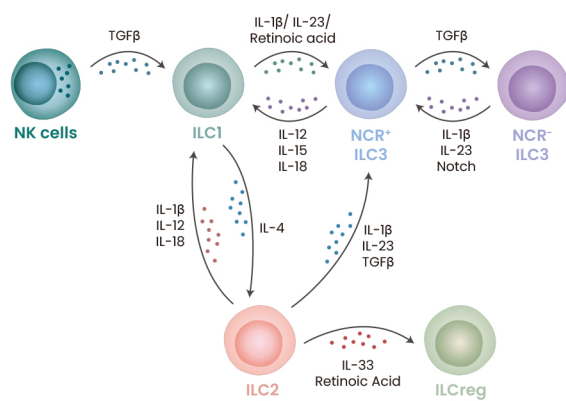
Fig. 3. Plasticity of ILCs. ILCs exhibit plasticity that can switch between fully polarized subsets to quickly adapt to changes occurring in the environment. The plasticity of ILC1, ILC2, and ILC3 depends on signals from the tissue microenvironment, mainly the cytokine milieu.

et al., 2016). In the tissue, ILCp matures into ILC subsets that appear to be shaped by microenvironmental cues (Lim and Di Santo, 2019).

While mature ILCs has less differentiation capacity than ILCp, it is clear that the ILC subtype phenotypes are plastic, meaning they can convert into other subtypes in response to environmental cytokines (Fig. 3). For example, a study that used the genetic fate mapping technique to mark cells showed that stimulating RORγt⁺ ILC3s with IL-12 and IL-15 increased their expression of T-bet and IFNγ, which is characteristic of ILC1s; this treatment also decreased their expression of RORγt (Bernink et al., 2015; Montaldo et al., 2015). The converse effect is also true: ILC1s can be changed both *in vivo* and *in vitro* into ILC3s by IL-2, IL-1β, and IL-23 (Bernink et al., 2015). There is a similar reversible axis of plasticity between ILC2s and ILC1s: ILC2s stimulated *in vitro* with IL-12 exhibit increased expression of T-bet and IFNγ, and this is reversed by IL-4 (Bal et al., 2016; Lim et al., 2016; Silver et al., 2016). This ILC plasticity highlights the consummate ability of ILCs to sense, communicate with, and adapt to the surrounding microenvironment. As we will see below, these activities of ILCs participate both in tissue homeostasis and inflammation.

ROLES OF ILCS IN TISSUE HOMEOSTASIS

ILCs help remodel injured tissue in a variety of ways, thereby maintaining tissue integrity. For example, by inducing stromal lymphoid tissue organizer cells to produce chemokines (i.e., C-X-C motif chemokine ligand 13 [CXCL13], CCL21, and CCL19) and adhesion molecules (VCAM-1, MAdCAM-1, and intercellular adhesion molecule 1 [ICAM-1]), the ILC3 subset LTi promotes the formation of secondary lymphoid organs such as Peyer's patches in the gut, which play an important role in gut homeostasis in the face of microbial colonization and food-derived antigens (van de Pavert et al., 2009). ILC3s also restore secondary lymphoid organs after they have been

destroyed by a viral infection (Scandella et al., 2008). Moreover, ILC3s help rehabilitate intestinal epithelium that has been damaged (for example by chemotherapy) by secreting IL-22 (Hazenberg et al., 2019): this induces IL-22 receptor-expressing intestinal stem cells to regenerate the epithelial cells (Wolk et al., 2004). In addition, the intestinal epithelial lesions in dextran sodium sulfate (DSS)-induced colitis can be repaired by ILC2s that have been stimulated with the epithelial cytokine IL-33: these cells produce amphiregulin, which binds to epidermal growth factor receptor (EGFR) on epithelial cells and thereby regulates their differentiation and proliferation (Monticelli et al., 2015). These effects of amphiregulin-expressing ILC2s are also critical for restoring airway epithelial integrity and tissue homeostasis after influenza virus infection (Monticelli et al., 2011). These observations suggest that therapeutically targeting homeostatic ILC responses in tissues could help manage tissue damage.

ILCS IN INFLAMMATORY DISEASES

The local tissue microenvironment in inflamed tissues can be very different from that in healthy non-inflamed tissues. This can cause ILCs to change their phenotype and functions in both beneficial and pathogenic ways. We discuss below how ILCs act in several inflammatory diseases, namely, asthma, chronic obstructive pulmonary disease (COPD), multiple sclerosis (MS), and cancer (Fig. 1). It should be noted that despite the essential roles of ILCs in gut homeostasis and tissue repair (see above), these cells also contribute to inflammatory bowel diseases (IBD) and several infectious diseases. For detailed information on ILCs in IBD and infectious diseases, we recommend related excellent reviews (Panda and Colonna, 2019; Peters et al., 2016; Zeng et al., 2019).

Asthma
Asthma is a chronic inflammatory disease that affects about 300 million people worldwide (Beasley and Hancox, 2020). It is characterized by difficulty breathing, coughing, and wheezing that is caused by airway hyperresponseveness (AHR), mucus overproduction, and airway remodeling (Lambrecht and Hammad, 2015). Multiple studies show that ILCs may play key roles in asthma pathogenesis (Kim et al., 2016b; Scanlon and McKenzie, 2012). This was first discovered when allergic asthma models and patients were found to have pulmonary ILC2s that produce large amounts of type 2 cytokines; these cytokines have long been noted to play key pathogenic roles in this classical asthma endotype (Kim et al., 2016b). It is now thought that the pathogenic role of pulmonary ILC2s starts when these cells are activated by various factors that are promptly upregulated in the lungs by allergens: they include the epithelial cytokines IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) and the mast cell factors cysteinyl leukotrienes and prostaglandins (Doherty and Broide, 2019; Liu et al., 2018; Lund et al., 2017; Salimi et al., 2017). The activated ILC2s then recruit other immune cells, including eosinophils and alternatively activated (M2) macrophages; these cells induce AHR and airway inflammation (Halim et al., 2014; Wolterink et al., 2012).

Notably, ILC2s participate in influenza virus-induced asth-

ma in both a pathogenic and a beneficial way. Thus, the virus-damaged epithelial cells secrete IL-33, which stimulates ILC2s and thereby worsens airway inflammation (Chang et al., 2011). On the other hand, the influenza infection stimulates ILC2s to secrete amphiregulin, which causes the damaged epithelial cells to regenerate (Monticelli et al., 2011; Wills-Karp and Finkelman, 2011). ILC2s also play a well-recognized role in the pathology of eosinophilic asthma in humans: patients with severe asthma have increased numbers of ILC2s in their blood and sputum and the disease severity correlates with the amount of type 2 cytokines produced by ILC2s but not the Th2 cells (Liu et al., 2015; Smith et al., 2016). We also found that ILC2s induce the polarization of M2 macrophages in patients with eosinophilic asthma (Kim et al., 2019).

Interestingly, the latter study also showed that in non-eosinophilic asthma, ILC1s and ILC3s, but not ILC2s, activate classically activated (M1) macrophages (Kim et al., 2019). Thus, different types of ILCs may be responsible for the asthma phenotypes in humans. This is supported by studies showing that ILC3s may participate in the non-allergic asthma endotypes that appear to arise independently of Th2 cells (Everaere et al., 2016; Kim et al., 2014); these endotypes include those driven by obesity or environmental factors such as ozone, diesel particles, and cold air (Kim et al., 2010). For example, we observed that when mice were fed a high-fat diet, they spontaneously developed AHR and had significant lung numbers of CCR6$^+$ ILC3s that produced IL-17A, which is a potent neutrophil chemotactic agent. We then showed that these ILC3s were activated and induced to proliferate by IL-1β from M1 macrophages (Kim et al., 2014).

These observations together demonstrate the crucial importance of ILCs in asthma. Further intensive exploration of ILCs is needed since targeting these immune axes could be of therapeutic value.

Chronic obstructive pulmonary disease

COPD includes pulmonary emphysema and chronic bronchitis and is a progressive respiratory disease characterized by long-term breathing problems and obstructed airflow (Rabe and Watz, 2017). The most common risk factor for COPD is smoking. The signature immune responses in this disease are activated neutrophils, macrophages, Th1 cells, Th17 cells, and CD8$^+$ T cells (Bhat et al., 2015; Ni and Dong, 2018).

Although there are fewer studies on COPD than on asthma, several reports suggest that ILCs are also involved in COPD pathogenesis. Kearley et al. showed that chronic exposure to cigarette smoke exacerbates virus-induced lung inflammation and that this associates with a shift away from ILC2 responses to proinflammatory macrophage and NK cell responses using a murine model of virus-induced COPD. Specifically, smoke exposure increases IL-33 secretion from epithelial cells while simultaneously decreasing and increasing IL-33R expression on ILC2s and macrophages/NK cells, respectively (Kearley et al., 2015). Notably, Silver et al. showed that (inflammatory triggers of COPD also provoke pathogenic ILC subset plasticity. They first showed that viral infection and long-term smoking convert ILC2s into ILC1-like populations that express IL-12Rβ2, IL-18 receptor alpha (IL-18Rα), T-bet,

and IFNγ. Subsequently, they showed that the severity of COPD correlates with increased ILC1s and decreased ILC2s in the peripheral blood (Silver et al., 2016). The role of ILC3s in COPD is less well studied than the ILC1s and ILC2s, but it has been shown that COPD patients have higher ILC3 frequencies in lung biopsies than control subjects (De Grove et al., 2016). Moreover, COPD lungs, but not unused donor lungs, abundantly express the gene set that relates to the ILC3 subset LTi (Suzuki et al., 2017). Therefore, further studies on the relevance of ILCs, including the ILC3s, in COPD pathogenesis are warranted.

Multiple sclerosis

MS is the most common inflammatory demyelinating disease of the central nervous system (CNS) (Reich et al., 2018). Clinical presentation of MS depends on the location of the demyelinating lesions, leading to its heterogeneous characteristics. It includes sensory or motor symptoms, fatigue, pain, and cognitive decline (Filippi et al., 2018). Since MS is regarded to be a Th17 cell-mediated disease, most of the research on ILCs in MS has focused on the ILC3 subsets. Accordingly, it has been shown that compared to control subjects, patients with MS have higher numbers of ILC3s, including LTi cells, in their cerebrospinal fluid and blood (Degn et al., 2016; Gross et al., 2017). However, when MS patients were treated with Daclizumab, which blocked IL-2 receptor alpha and previously used to treat relapsing MS, their circulating ILC3s (LTi cells) dropped, but NK cells rose. Notably, significant treatment effects were not observed on the frequencies of activated T cells (Perry et al., 2012). These findings suggest that ILC3s contribute to MS pathogenesis. This is supported by studies in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. Hatfield and Browns showed that ILC3s are normal resident cells in the meninges (which are where the immune cell infiltration to the CNS starts) and that in EAE, these cells overexpress IFNγ, IL-17, and GM-CSF. This suggests that ILC3s could contribute at an early stage to EAE pathogenesis (Hatfield and Brown, 2015). Moreover, Kwong et al. showed that when encephalitogenic T cells are transferred to T-bet depleted mice, the infiltration of T cells into the CNS is lower than in wildtype mice. It was then shown that the specific loss of T-bet expression in NKp46$^+$ T-bet$^+$ ILCs (i.e., ILC1s or the NKp46$^+$ subset of ILC3s) impairs the ability of the encephalitogenic T cells to invade the CNS (Kwong et al., 2017). These results suggest that despite the fact that ILCs are a minor population in the CNS, they can control the initiation of inflammation in EAE.

Cancer

While cancer is a complex disease, studies in recent years have started to elucidate the roles of ILCs in tumor development. The study of Dadi et al. showed that ILC1s can have anti-tumor effects: when breast cancer arises spontaneously in mice, the mammary glands contain elevated frequencies of ILC1s that bear NK cell characteristics (IFNγ and granzyme B production) and are cytotoxic to tumor cells (Dadi et al., 2016). By contrast, a study with MCA1956 carcinogen-induced sarcoma shows that by expressing TGF-β, tumors can escape NK cell-mediated tumor control by converting cyto-

toxic NK cells into ILC1s, which are unable to control tumor growth and metastasis (Gao et al., 2017).

The roles of ILC2s in cancer immune response are also controversial. *Rag*^{-/-} mice challenged with IL-33-expressing B16-melanoma cells develop tumors less effectively than mice challenged with wildtype tumor cells: this is due to the IL-33-mediated expansion and activation of cytotoxic NK cells. However, this beneficial effect of IL-33 is tempered by its effect on ILC2s, which inhibit NK cell activation and cytotoxicity *via* immunosuppressive enzyme CD73 (Long et al., 2018). Similarly, ILC2s produce IL-13 in the acute promyelocytic leukemia animal model, which activates monocytic myeloid-derived suppressor cells (M-MDSCs) thereby enhances tumor progression (Trabanelli et al., 2017). However, several other studies observe that ILC2s can also have anti-tumor effects. Thus, genetic deletion of ILC2s in mice associates with increased tumor growth and metastasis (Saranchova et al., 2018). Moreover, in pancreatic ductal adenocarcinoma, intratumoral ILC2s activate CD103$^+$ dendritic cells and enhance the anti-tumor responses of CD8$^+$ T cells (Moral et al., 2020). In addition, in a lung metastatic melanoma model, ILC2s produce IL-5, thereby activating eosinophils and increasing their anti-tumor response (Ikutani et al., 2012). Moreover, ILC2s produce IL-9, which is important to suppress metastasis of cancer cells, in tumor microenvironment (Park et al., 2020; Wan et al., 2021).

Similarly, divergent roles were observed for ILC3s. For examples, in models of preclinical breast cancer and invasive colon cancer, ILC3s promote tumor growth and metastasis by producing IL-22 (Irshad et al., 2017; Kirchberger et al., 2013). By contrast, in the B16 melanoma model, NKp46$^+$ ILC3s increase leukocyte invasion and tumor suppression by producing IL-12 and upregulating ICAM-1 and VCAM-1 (Eisenring et al., 2010).

Although studies over the last few years have provided critical insights into the role of ILCs in anti-tumor immune responses, many aspects remain to be explored.

CONCLUSION

Since ILCs adapt remarkably quickly and fluidly to environmental cues and orchestrate downstream immunity, including adaptive immune responses, they are fundamental frontline defenders of the host. However, because of their sparsity relative to other immune cells, the importance of ILCs has long been underestimated. Since ILCs share many properties with T cells, specific treatment targeting ILCs is not available until now. However, the present review clearly shows that ILCs participate in both tissue homeostasis and disease pathogenesis, thus could be potential therapeutic targets for managing diseases. ILCs might play an important role in priming the immune response at the various stages of the disease by secreting large amounts of cytokines prior to T cells by rapidly responding to alarmins. Therefore, targeting alarmins could be one of the promising approaches to regulating ILCs for disease control, although further experiments are required.

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AUTHOR CONTRIBUTIONS

J.K., S.R., and H.Y.K. wrote and revised the manuscript.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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