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REVIEW

Pathological and therapeutic roles of innate lymphoid cells in diverse diseases

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Abstract Innate lymphoid cells (ILCs) are a recently defined type of innate-immunity cells that belong to the lymphoid lineage and have lymphoid morphology but do not express an antigen-specific B cell or T-cell receptor. ILCs regulate immune functions prior to the formation of adaptive immunity and exert effector functions through a cytokine release. ILCs have been classified into three groups according to the transcription factors that regulate their development and function and the effector cytokines they produce. Of note, ILCs resemble T helper (Th) cells, such as Th1, Th2, and Th17 cells, and show a similar dependence on transcription factors and distinct cytokine production. Despite their short history in immunology, ILCs have received much attention, and numerous studies have revealed biological functions of ILCs including host defense against pathogens, inflammation, tissue repair, and metabolic homeostasis. Here, we describe recent findings about the roles of ILCs in the pathogenesis of various diseases and potential therapeutic targets.

Keywords Innate lymphoid cell · Allergy · Inflammation · Asthma · Colitis

Introduction

The immune system has long been dichotomized into innate immunity, which consists of myeloid cells and other nonlymphoid cells, and acquired (adaptive) immunity, which is composed of the B cells and T cells that mediate humoral and cellular immunity. Nonetheless, recent studies have discovered a previously unrecognized group of innate immune cells that lack antigen specificity but belong to the lymphoid lineage, so-called innate lymphoid cells (ILCs) (Spits and Cupedo 2012). Unlike T and B cells, ILCs do not express antigen-specific T- or B-cell receptors, and do not possess markers of myeloid or dendritic cells (Walker et al. 2013). ILCs are mainly enriched at mucosal and nonmucosal barriers acting as first-line defenders, but they are also found in lymphoid and nonlymphoid tissues (Diefenbach et al. 2014). ILCs originate from common lymphoid progenitors (CLPs) and depend on a transcriptional repressor, inhibitor of DNA binding 2 (ID2) and cytokines that signal through the common γ-chain of IL-2 (Lim et al. 2017). The lack of common lineage markers and IL-7Rα are also shared features of this family of cells.

ILCs have been classified into three distinct groups according to the transcription factors that regulate their development, function, and cytokine production (Spits et al. 2013; Diefenbach et al. 2014; McKenzie et al. 2014) (Fig. 1). Furthermore, ILCs closely resemble T helper (Th) cells, such as Th1, Th2, and Th17 lineages, and show a similar dependence on transcription factors and produce distinct cytokines (Spits and Di Santo 2011). Group 1 ILCs (ILC1s) express T-box transcription factor (T-bet) and produce IFN-γ, as Th1 cells do (Bernink et al. 2013). ILC2s depend on GATA-binding protein 3 (GATA3) and retinoic acid receptor–related orphan receptor α (ROR-α) and produce Th2 cytokines, such as IL-4, IL-5, IL-9, and IL-13 (Turner et al. 2013; Walker et al. 2013). ILC3s, like Th17 cells, express RORγt and secrete IL-17A and IL-22 (Sanos and Diefenbach 2013).

Of note, studies indicate that ILC2s and ILC3s have the ability to transdifferentiate into T–bet$^+$ IFN-γ–secreting

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ILC1s in the presence of IL-12, at the cost of GATA3 and RORγt expression, respectively (Bernink et al. 2013; Klose et al. 2013, 2014). Conversely, IL-1β and IL-4 drive the transdifferentiation of ILC1s into ILC2s, whereas IL-23, IL-1β, and retinoic acid promote the transdifferentiation of ILC1s into ILC3s (Bernink et al. 2015; Bal et al. 2016; Ohne et al. 2016; Silver et al. 2016). Nevertheless, transdifferentiation between ILC2s and ILC3s has not been reported.

Since the discovery of ILCs, various functions of these cells in host defense against pathogens and in the regulation of inflammation, carcinogenesis, tissue repair, and metabolic homeostasis have been extensively studied (Spits and Di Santo 2011; Spits and Cupedo 2012; McKenzie et al. 2014). In this review, we summarize the latest research on ILCs and their various pathogenic roles and discuss their potential as therapeutic targets.

General features of ILC1s

ILC1s expressing T-bet and secreting IFN-γ can be subdivided into three subpopulations (Vonarbourg et al. 2010; Bernink et al. 2013; Fuchs et al. 2013; Klose et al. 2014). One expresses CD56 and CD103 and is found in tonsils and in the intestinal intraepithelial space. CD103 binds to integrin β7, a ligand of e-cadherin, and enhances epithelial-cell interactions. $CD103^+$ ILC1s or intraepithelial ILC1s (ieILC1s) produce IFN-γ when stimulated with IL-12, IL-15, and IL-18 (Vosshenrich et al. 2006; Chiossone et al. 2009; Klose et al. 2014) and have granules containing perforin and granzyme B that can lyse target cells. Another cell population expresses CD127 and CD161 but is deficient in CD56, CD94, granzyme B, and perforin (Bernink et al. 2013). These $CD127^+$ ILC1s express T-bet but lack Eomes and reside in the lamina propria (Gordon et al. 2012). $CD127^+$ ILC1s produce IFN-γ in response to IL-12 and IL-18 and are significantly involved in host protection from intracellular pathogens.

From the viewpoint of IFN-γ production, which is the unifying feature of ILC1s, conventional natural killer (cNK) cells can also be classified as ILC1s (McKenzie et al. 2014). Both cNK cells and ieILC1s produce IFN-γ in response to IL-12, IL-15, and IL-18 and exert cytotoxic action through the production of perforin and granzyme B, whereas $CD127^+$ ILC1s are devoid of perforin and granzyme B and are noncytotoxic. cNK cells and other ILC1 populations in mice share cell surface markers such as NKG2D, NK1.1, and NKp46 and transcription factors T-bet and Eomes (Cortez et al. 2014; Daussy et al. 2014; Sojka et al. 2014). In humans, cNK cells and other ILC1s also express transcription factors T-bet and Eomes (Nielsen et al. 2012; Bernink et al. 2015; Bjorklund et al. 2016; Michel et al. 2016; Roan et al. 2016). In this regard, precise discrimination of cNK cells from other ILC1 populations by means of the current criteria is complicated and hard despite ongoing identification of cell surface markers for discrimination (Table 1).

The role of ILC1s in infections

ILC1s participate in the innate immune response to intracellular bacteria, viruses, and parasites. In mice, $CD127^+$ ILC1s prevent infection by the protozoan parasite *Toxoplasma gondii* by recruiting myeloid cells (Klose et al. 2014; McKenzie et al. 2014). Defense against acute *Clostridium difficile* infection also appears to be mediated by ILC1s and IFN-γ because mice lacking ILC1s or deficient in IFN-γ are more susceptible to lethal *C. difficile* infection (Abt et al. 2015). Yang et al. (2015) reported that in humans, the number of ILC1s and their IFN-γ production increase during hepatitis B virus infection, and this upregulation of ILC1 is significantly associated with liver damage in patients with chronic hepatitis B, indicating proinflammatory effects of ILC1s on the pathogenesis of chronic hepatitis B (Table 2).

ILC1s as a disease factor

IFN-γ-secreting ILC1s are likely to be involved in inflammation because an increase in the numbers of ILC1s has been observed in many inflammatory diseases. ILC1 numbers are increased in inflamed intestinal samples from patients with Crohn's disease (CD) and in bronchial samples from patients with chronic obstructive pulmonary disease (COPD), whereas the ILC3 and ILC2 populations are smaller in CD and COPD patients, respectively. Similarly, Braudeau et al. (2016) reported an increase in ILC1 numbers, at the cost of ILC2s and ILC3s, in acute-phase anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

$CD56^{bright}$ ILC1–like cells have been detected in the synovial fluid and synovial tissue of patients with inflammatory arthritis, most of whom had rheumatoid arthritis (RA). These ILC1-like cells produce IFN-γ when they are exposed to IL-2, IL-12, and IL-15 (Dalbeth and Callan 2002). Upon stimulation by IL-12, IL-15, and IL-18, activated ILC1-like cells cause $CD14^+$ monocytes to produce TNF-α through direct cell-to-cell contact. Conversely, $CD14^+$ monocytes synergize with cytokines to promote IFN-γ production by ILC1-like cells (Dalbeth et al. 2004). In addition, increased proportions of ILC1-like cells in the peripheral blood of patients with systemic lupus erythematosus (SLE) have been reported (Schepis et al. 2009). Nonetheless, it has not been determined whether the observed $CD56^{bright}$ cells are cNK cells or noncytotoxic ILC1s. Given the results of a recent study showing the

Table 1 General biology of ILCs

ILC group	ILC lineage	Mice	Humans	Signature cytokines	References
Group 1 ILCs	CD127$^+$ ILC1s	Lin$^-$ CD11b$^-$ CD27$^+$ CD49a$^+$ CD49b$^-$ CD69$^+$ CD127$^+$ CD160$^+$ NKG2D$^+$ NK1.1$^+$ NKp46$^+$ T-bet$^+$ RORγt$^-$ THY1$^+$ SCA1$^+$	Lin$^-$ CD16$^-$ CD27$^+$ CD56$^-$ CD69$^-$ CD94$^-$ CD103$^-$ CD127$^+$ T-bet$^+$ IL-7Rα$^-$	IFN-γ, TRAIL	Daussy et al. (2014); Klose et al. (2014); Sojka et al. (2014); Bjorklund et al. (2016) and Roan et al. (2016)
	ieILC1s	CD11b$^-$ CD27$^-$ CD49b$^-$ CD69$^+$ CD127$^-$ CD160$^+$ NKG2D$^+$ NKp46$^+$ NK1.1$^+$ T-bet$^+$ Eomes$^+$	CD4$^-$ CD27$^-$ CD49a$^+$ CD49b$^-$ CD56$^+$ CD69$^+$ CD94$^+$ CD103$^+$ CD127$^-$ CD161$^-$ NKG2D$^+$ NKp44$^+$ NKp46$^+$ T-bet$^+$ Eomes$^+$	IFN-γ, Perforin, Granzyme	Fuchs et al. (2013) and Bernink et al. (2015)
	cNK cells	CD3$^-$ CD16$^+$ CD49a$^-$ CD49b$^+$ CD69$^-$ CD103$^-$ CD122$^+$ CD127$^-$ CD160$^-$ CD161$^+$ NKG2D$^+$ NK1.1$^+$ NKp46$^+$ T-bet$^+$ Eomes$^+$	CD3$^-$ CD4$^-$ CD7$^+$ CD49a$^-$ CD49b$^+$ CD56$^+$ CD69$^-$ CD103$^-$ CD122$^+$ CD127$^-$ CD161$^+$ NKG2D$^+$ NKp30$^+$ NKp44$^-$ NKp46$^+$ KIR$^+$ T-bet$^+$ Eomes$^+$	IFN-γ, TNF, Perforin, Granzyme	Nielsen et al. (2012); Cortez et al. (2014); Klose et al. (2014); Sojka et al. (2014) and Michel et al. (2016)
Group 2 ILCs	ILC2s	Lin$^-$ CD45^{hi} ICOS$^+$ SCA1$^+$ KLRG1$^+$ IL-7Rα$^+$ IL-17RB$^+$ CD25$^+$ ST2^{var} THY1$^+$	Lin$^-$ IL-7Rα$^+$ CD45^{hi} CD161$^+$ CRTH2$^+$ ST2$^+$ CD25$^+$ CysLT1R$^+$	IL-5, IL-9, IL-13, IL-4	Mjösberg et al. (2011), Licona-Limón et al. (2013), Walker et al. (2013), Diefenbach et al. (2014), McKenzie et al. (2014), Artis and Spits (2015), Doherty and Broide (2015), Halim (2016) and Konya and Mjosberg (2016)
Group 3 ILCs	NCR$^+$ ILC3s	Lin$^-$ RORγt$^+$ NKp46$^+$ THY1$^+$ IL-7Rα^{int} KIT^{int} CXCR5$^-$ CCR6$^-$	Lin$^-$ CD56$^+$ NKp30$^+$ NKp44$^+$ NKp46$^+$ IL-7Rα$^+$	IL-22	Luci et al. (2009) and Vonarbourg et al. (2010)
	LTi cells	Lin$^-$ RORγt$^+$ NKp46$^-$ THY1$^+$ IL-7Rα^{hi} KIT^{hi} CXCR5$^+$ CCR6$^+$; a proportion of Lti cells are CD4$^+$	Lin$^-$ IL-7Rα^{hi} CD45^{int} RORγt$^+$ CD7$^+$ CD161$^+$ CD4$^-$ CD94$^-$	LTα, LTβ, IL-17A, IL-22	Uhlig et al. (2006) and Elson et al. (2007)
	Double negative ILC3s	CD3$^-$ RORγt$^+$ CCR6$^-$ NKp46$^-$ CD127^{low}; heterogeneous mix of progenitor and effector cells	CD3$^-$ RORγt$^+$ CCR6$^-$ NKp46$^-$ NKp44$^-$ CD127^{low}; heterogeneous mix of progenitor and effector cells	IL-17A, IL-22, IFN-γ,	Buonocore et al. (2010), Sawa et al. (2010), (2011), Klose et al. (2013), Cording et al. (2014) and Melo-Gonzalez and Hepworth (2017)

enrichment of ILC1s in the synovial fluid of RA patients as compared to the levels in patients with psoriatic arthritis (Leijten et al. 2015), future studies are needed to determine whether these CD56^{bright} cells are ILC1s.

An increase in ILC1 numbers has also been found in the joints of patients with spondyloarthritis and in peripheral blood of patients with systemic sclerosis (SSc) along with NKp44$^-$ ILC3s and NKp44$^+$ ILC3s, respectively (Yeremenko et al. 2015; Roan et al. 2016). In SSc, the frequency of ILC1s increases due to significant changes in CD4$^+$ ILC1s, and these CD4$^+$ ILC1s, unlike CD4$^-$ ILC1s, produce TNF-α and GM-CSF, which are potent cytokines that promote SSc.

ILC1s as therapeutic targets

ILC1s have been shown to cause inflammation in several cases; therefore, block-ing IFN-γ is a possible way to weaken an ILC1-associated inflammatory disease. Thus, administration of an anti–IFN-γ antibody (Ab) may relieve the disease, and this approach is considered a promising therapeutic strategy against various inflammatory diseases, such as CD, RA, SLE, and SSc. Fontolizumab (marketed under the trade name HuZAF^{TM}), a humanized monoclonal Ab against IFN-γ, is an immunosuppressive therapeutic used for the treatment of autoimmune diseases such as CD and RA. Studies have shown that fontolizumab has excellent tolerability and clinical activity in patients with moderate to severe CD and is currently in a phase II clinical trial (Hommes et al. 2006). Nevertheless, its use against

Table 2 ILCs as possible therapeutic targets

Type	Associated disease	Target	Drug	References
ILC1	CD	IFN-γ	Fontolizumab (HuZAF™)	Hommes et al. (2006), Bernink et al. (2013) and Fuchs et al. (2013)
		IL-12	Ustekinumab (Stelara®), Briakinumab	Sandborn et al. (2012) and Niederreiter et al. (2013)
	COPD	IFN-γ	–	Bal et al. (2016)
	AAV	–	–	Braudeau et al. (2016)
	RA	IFN-γ	Fontolizumab (HuZAF™, Failure)	Dalbeth and Callan (2002), Dalbeth et al. (2004) and Leijten et al. (2015)
	SLE	IFN-γ	AMG-811	Schepis et al. (2009), Chen et al. (2015) and Werth et al. (2017)
	Spondyloarthritis	–	–	Yeremenko et al. (2015)
	SSc	TNF-α, GM-CSF	–	Roan et al. (2016)
ILC2	Allergic asthma	AXL/FPR2	Lipoxin A4	Halim (2016) and Konya and Mjosberg (2016)
		PGI_2	Cicaprost	Karta et al. (2016) and Konya and Mjosberg (2016)
		CRTH2	Fevipiprant, Timapiprant	Martinez-Gonzalez et al. (2015) and Wojno et al. (2015)
		Leukotriene receptor	Montelukast, Zafirlukast	Doherty et al. (2013)
		IL-5	Mepolizumab	Bel and Ten Brinke (2017)
		IL-4Rα	Dupilumab	Bel and Ten Brinke (2017)
	Rhinosinusitis	CRTH2	–	Doherty and Broide (2015)
	AD	IL-33, TSLP	–	Divekar and Kita (2015)
	Helminth infection	EGFR	Amphiregulin	Zaiss et al. (2006) and (2015)
	COPD	TSLP	Tezepelumab	Lau et al. (2017)
ILC3	CD	AHR	–	Qiu et al. (2012) and Zhao et al. (2016)
		Vitamin D receptor	Vitamin D	Konya et al. (2017)
		IL-23	–	Elson et al. (2007)
	Psoriasis	IL-17	Secukinumab (Cosentyx®)	Baeten et al. (2013) and Langley et al. (2014)
		IL-23	Ustekinumab (Stelara®)	Leonardi et al. (2008)
	RA		–	McInnes and Schett (2007) and Ren et al. (2011)
	AS	IL-17	Secukinumab (Cosentyx®)	Baeten et al. (2013), (2015)
	MS	CD25	Daclizumab	Lock et al. (2002) and Perry et al. (2012)
	Asthma	IL-17	–	Barnie et al. (2015) and Nagakumar et al. (2017)
	CRC	IL-22	–	Jiang et al. (2013) and Kirchberger et al. (2013)
	NSCLC	–	–	Carrega et al. (2015)

The drugs targeting cytokines are not necessarily based on ILCs, but could affect T cells

RA in a phase II clinical trial (NCT00281294) was terminated due to failure to meet the endpoint of the first phase. AMG-811 is a human monoclonal Ab against IFN-γ developed by Amgen, and its pharmacokinetic and pharmacodynamic profile in patients with SLE has been determined (Chen et al. 2015). AMG-811 has no significant therapeutic effects in patients with discoid lupus erythematosus despite its tolerability and the changes induced in biomarkers associated with IFN-γ (Werth et al. 2017).

In addition to IFN-γ, another ILC1-targeting stimulatory molecule, IL-12, is an alternative target for the treatment of CD. Ustekinumab (Stelara®) and briakinumab are monoclonal Abs targeting IL-12p40 and are potential therapeutic agents for CD (Sandborn et al. 2012; Niederreiter et al. 2013).

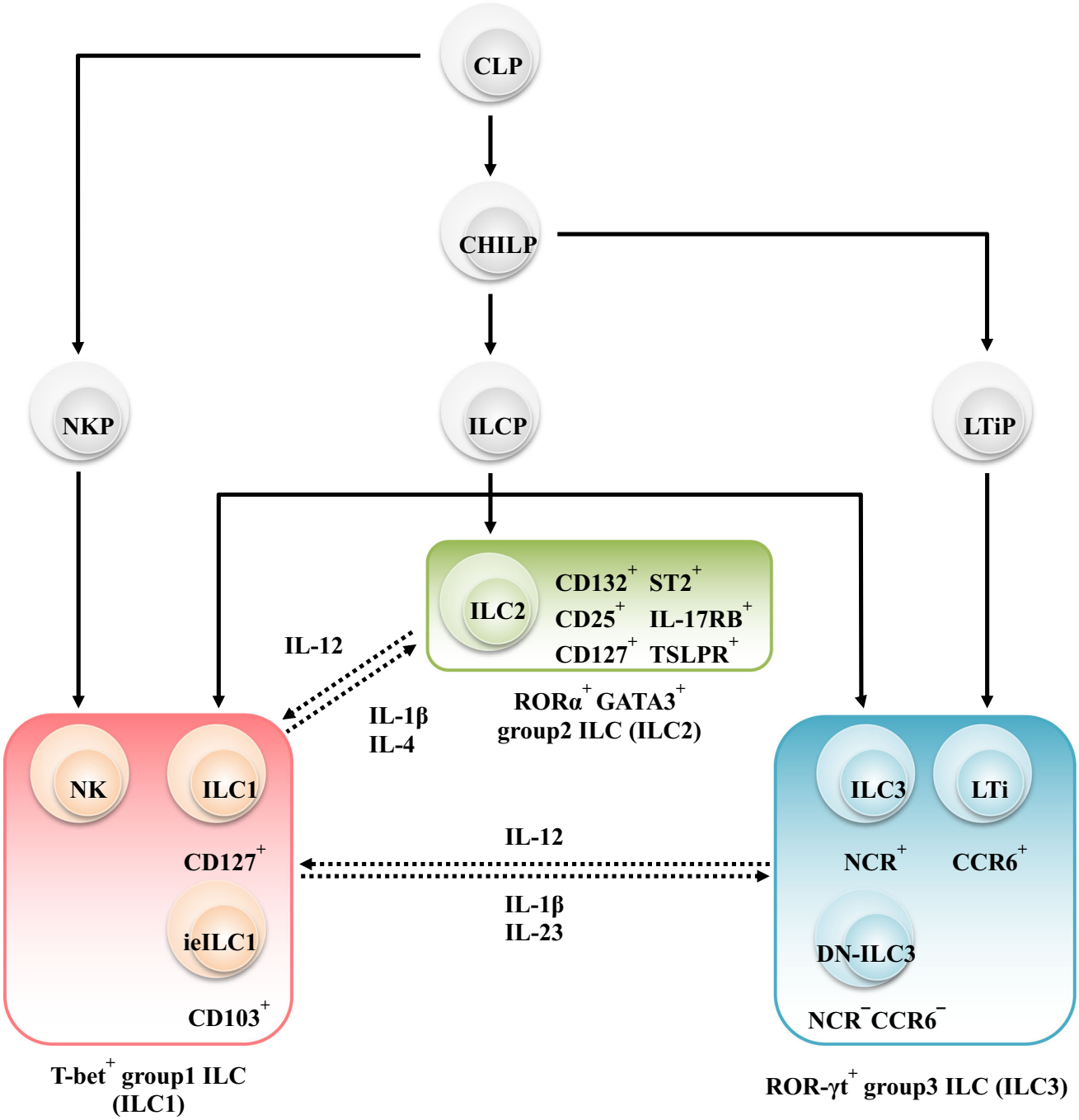

Fig. 1 Development and transdifferentiation of the ILC family. All ILC groups are derived from common lymphoid progenitors (CLPs). CLPs develop into NK cell precursors (NKPs) or common helper innate lymphoid precursors (CHILPs). CHILPs next differentiate into ILC progenitors (ILCPs) or LTi precursors (LTiPs). T-bet$^+$ ILC1s consist of NK cells derived from NKPs and ILC1s from ILCPs. ILC1s are further categorized into two subgroups: CD127$^+$ ILC1s and CD103$^+$ intraepithelial ILC1s (ieILC1s). All RORα^+GATA3$^+$ ILC2s are derived from ILCPs. ILC2s express various cytokine receptors, such as CD25, CD127, CD132, ST2, IL-17RB, and TSLPR. RORγt^+ ILC3s consist of NCR$^+$ ILC3s from ILCPs, CCR6$^+$ LTi cells from LTiPs, and heterogeneous NCR$^-$CCR6$^-$ double-negative (DN)-ILC3s. IL-1β and IL-4 drive the transdifferentiation of ILC1s into ILC2s, whereas IL-23, IL-1β, and retinoic acid promote the transdifferentiation of ILC1s into ILC3s. Transdifferentiation can also be reversed from ILC2s and ILC3s to ILC1s in response to IL-12

General features of ILC2s

$CD4^+$ Th2 cells have long been considered the major regulators of allergic inflammation because of their production of Th2 cytokines, such as IL-4, IL-5, and IL-13 (Doherty and Broide 2015; Halim 2016). On the other hand, ILC2s recently emerged as crucial players promoting Th2 immunity, which provides protection from helminth infections but causes allergic inflammatory diseases (van Rijt et al. 2016). Mouse and human ILC2s are phenotypically similar because they are $CD45^+$ but lack lineage markers (Walker et al. 2013). Instead, ILC2s express various cytokine receptors (R), such as common γ-chain (CD132 or IL-2Rγ), IL-2Rα (CD25), IL-7Rα (CD127), ST2 (IL-33R or IL-1R-like 1), IL-17RB, and thymic stromal lymphopoietin receptor (TSLPR), and are activated in response to IL-25, IL-33, and TSLP derived from epithelial cells (Licona-Limón et al. 2013). Furthermore, mouse ILC2s express Sca1, ICOS, and KLRG1 (McKenzie et al. 2014), whereas human ILC2s express cysteinyl leukotriene receptor 1 (CysLT1R), CD161 (C-type lectin receptor), and chemoattractant-receptor–homologous molecule expressed on Th2 cells (CRTH2) (Mjösberg et al. 2011; Konya and Mjosberg 2016). Once activated, ILC2s rapidly release large amounts of IL-5 and IL-13, which act on different types of cells and lead to Th2 inflammatory diseases in the airway, skin, and intestine (Diefenbach et al. 2014; McKenzie et al. 2014; Artis and Spits 2015). In addition, ILC2s mediate tissue repair and regulate metabolic homeostasis of glucose and lipids (Hams et al. 2013; Kim et al. 2013; Molofsky et al. 2013; Artis and Spits 2015).

ILC2s in allergic inflammatory diseases

Allergic asthma

Allergic asthma is a common airway disease caused by inappropriate immune responses to allergens. Asthma is characterized by airway hyperresponsiveness (AHR) and inflammation, leading to bronchoconstriction, excessive mucus production, and airway narrowing (Bousquet et al. 2000). Allergic asthma has long been considered a disease of the Th2 immune response; however, emerging studies have revealed that asthma is a more complex disease involving Th17 cells, ILC2s, and ILC3s as well as Th2 cells (Kim et al. 2016).

In addition to Th2 cells, ILC2s are another major source of IL-5 and IL-13, which perform critical functions in the pathogenesis of allergen-induced asthma by stimulating the growth and differentiation of eosinophils and by inducing airway epithelial cells and smooth muscle cells to contract. Halim (2016) demonstrated that in $Rag2^{-/-}Il2rg^{-/-}$ mice, which lack all types of ILCs [or lung natural helper cells as described by (Halim et al. 2014)], intranasal administration of a protease allergen (papain) does not induce eosinophil infiltration and mucus hyperproduction, whereas adoptive transfer of ILC2s induces airway inflammation after papain treatment. The protease activity of papain may cause epithelial cell damage and secretion of TSLP, IL-25, and IL-33, leading to activation of ILC2s. Additionally, a fungal allergen, *Alternaria alternata*, promotes IL-33 secretion in lungs and activates ILC2 proliferation in mice (Doherty et al. 2012). In a mouse model of ovalbumin (OVA)-induced asthma, OVA sensitization and exposure induces ILC2s to release IL-5 and IL-13 (Klein Wolterink et al. 2012). Nevertheless, OVA-driven ILC2 activation is a controversial topic because an OVA challenge has not always led to ILC2 activation and cytokine production in other studies (Li et al. 2016a).

In humans, ILC2s are present in lungs and bronchoalveolar lavage (BAL) fluid (Drake and Kita 2014). Prior to the identification of ILC2s, Allakhverdi et al. (2009) reported the presence of non-B, non-T lymphocytes that produce IL-5 and IL-13 in the sputum of asthmatic patients after an airway allergen challenge; however, it is not known whether these cells are ILC2s. In addition, both the number of ILC2 and IL-33 levels increase in BAL fluid while upstream cytokines and mediators, such as IL-25, IL-33, TSLP, leukotrienes, and prostaglandins, are upregulated in human asthma. Furthermore, genomewide association studies indicate that genetic polymorphisms near the *TSLP*, *IL-33*, *IL1RL1* (*IL-33R*), and *RORA* loci are strongly linked to asthma, thus pointing to the critical participation of lung ILC2s in human asthma (Kabata et al. 2015). Nonetheless, studies on the contribution of ILC2s to allergic asthma in humans are relatively limited, and this area needs to be further investigated.

In addition to environmental allergens, respiratory viral infections can trigger asthma or aggravate pre-existing asthma in humans (Jackson and Johnston 2010). Research shows that influenza infection activates ILC2s in an IL-33–dependent manner, and rhinovirus infection induces IL-33 and IL-25 and upregulates Th2 cytokines in asthmatic patients (Chang et al. 2011; Jackson et al. 2014). Hong et al. (2014) investigated the effect of rhinovirus infection on ILC2 responses in neonatal mice and found that neonatal infection with rhinovirus increases mucous metaplasia and AHR via IL-25 and IL-2. In contrast, these IL-25-driven Th2 responses to rhinovirus are not observed in adult mice, suggesting that the contribution of rhinovirus infection to asthma development is age-dependent.

In mice, ILC2s present in lungs were shown to contribute to AHR upon influenza virus infection (Chang et al. 2011). ILC2-depleted RAG2 knockout mice manifest reduced AHR after influenza infection. Nonetheless, transfer of wild-type ILC2s, but not IL-13 knockout ILC2s,

into IL-13 knockout mice restores AHR, indicating that IL-13 secreted by ILC2s is required for influenza-induced AHR. In addition to AHR induction, ILC2s have been demonstrated to stimulate tissue repair responses after influenza infection in mice (Monticelli et al. 2011). ILC2 microarray analysis has revealed that ILC2s produce large amounts of amphiregulin, a ligand for epithelial growth factor receptor (EGFR), which promotes epithelial cell growth and wound healing. Adoptive transfer of ILC2s or amphiregulin treatment of ILC2-depleted mice restores airway integrity and lung function after influenza infection, indicating that ILC2s participate in both the pathogenesis and repair responses after influenza infection.

Rhinosinusitis

Chronic rhinosinusitis (CRS) is a persistent inflammatory disease involving paranasal sinuses and the lining of nasal passages that lasts for 12 weeks or longer. CRS can be subdivided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) based on the results of endoscopic examination. Symptoms of CRSwNP are similar to those of CRSsNP and include nasal congestion, postnasal drip, facial pain, and headache; however, symptom severity varies with the size of the polyp masses within the nasal cavity (Hamilos 2011; Akdis et al. 2013). Mjösberg et al. (2011) and Mjösberg et al. (2012) demonstrated that ILC2s are enriched in the polyps of patients with CRS and that ILC2s present in polyps secrete Th2 cytokines in response to TSLP, IL-33, and cysteinyl leukotrienes (CysLT), which were also found to be upregulated in patients with CRS. In addition, ILC2s express CRTH2, and activation of CRTH2 through PGD_2 ligation stimulates ILC2 chemotaxis in CRS (Xue et al. 2014). CRS can also be categorized into eosinophilic CRS (eCRS) and non-eosinophilic CRS (non-eCRS), on the basis of the underlying inflammation (Sakuma et al. 2011). Studies suggest that eCRS is associated with severer symptoms, development of nasal polyps, and poorer treatment outcomes as compared to non-eCRS (Haruna et al. 2009; Soler et al. 2009). The number of ILC2s in polyps was found to increase as numbers of local and circulating eosinophils increased, pointing to the potential role of ILC2s in the activation and survival of eosinophils in CRS (Ho et al. 2015).

Allergic rhinitis (AR), or hay fever, is inflammation of nasal mucous membranes that is characterized by sneezing, itching, nasal congestion, postnasal drip, and rhinorrhea (Greiner et al. 2011). AR is commonly comorbid with CRS and is a predisposing factor for CRS development. Just as CRS, AR is associated with an increase in ILC2 numbers after an allergen challenge in sensitized patients. Doherty et al. (2014) demonstrated that a nasal cat allergen challenge increases the percentage of peripheral-blood $CRTH2^+$ ILC2s 4 h after the allergen challenge in humans. In addition, an increase in the number of peripheral-blood ILC2s is observed in patients with AR during pollen season, indicating the contribution of ILC2s to inflammatory responses in AR (Lao-Araya et al. 2014).

Atopic dermatitis (AD)

ILC2s have been detected in human and mouse skin and are known to be deeply involved in skin homeostasis. In mice, ILC2s residing in the skin are phenotypically distinct from the ILC2s found in other organs because skin ILC2s express CD103 but lack c-Kit; thus, skin ILC2s are designated as dermal ILC2s (dILC2s) (Roediger et al. 2013). In humans, skin ILC2s often express skin-homing chemokine receptors, such as CCR4, CCR10, and CLA, which distinguish these cells from circulating ILC2s. Once activated, dILC2s produce amphiregulin and stimulate the proliferation and migration of epithelial cells, leading to wound healing and skin repair (Salimi et al. 2013). In addition, IL-13 derived from dILC2s interacts with mast cells and represses the production of IL-6 and TNF-α after antigen exposure in mice (Roediger et al. 2013).

DILC2s are also involved in AD, a chronic inflammatory skin disease characterized by a defect in barrier function, infiltration of eosinophils, and elevated serum IgE levels (Roediger et al. 2014). In mice with established AD, dILC2 numbers are increased in the dermis, and these cells produce IL-4, IL-5, and IL-13 in response to TSLP and/or IL-33 (Salimi et al. 2013). Upregulation of TSLP and IL-33 has also been observed in human AD, and dILC2s are enriched in the skin lesions of patients with AD (Salimi et al. 2013). Moreover, prostaglandins can stimulate human dILC2s, whereas activating NK receptor (NKp30 or CD337)-positive human dILC2s can be activated by the tumor-associated surface molecule B7-H7, which is upregulated in the skin of patients with AD (Salimi et al. 2016).

ILC2s in helminth infections

Host protection from helminthic parasites is dependent on the production of Th2 cytokines. In mice infected with *Nippostrongylus brasiliensis*, this murine parasitic worm triggers the secretion of alarmins, such as IL-25, IL-33, and TSLP, which mediate activation of ILC2s (Moro et al. 2010; Neill et al. 2010; Price et al. 2010). In cooperation with Th2 cells, the activated ILC2s secrete a large amount of Th2 cytokines and induce Th2 immune responses, which are essential for successful clearance of parasitic infections (Williams et al. 2012). In response to parasitic infection, IL-4 activates human B cells and promotes isotype switching to IgE, generating immunity to parasites in vitro

(Gascan et al. 1991). IL-5 stimulates the growth and activation of eosinophils, which kill helminth larvae in the presence of Ab or complement and regulate the tissue homeostasis and metabolism that are crucial for the establishment and maintenance of parasites in the host (Hall et al. 1998; Behm and Ovington 2000; Klion and Nutman 2004; Huang and Appleton 2016). IL-13 induces mucus secretion by goblet cells and smooth-muscle contraction, leading to expulsion of the parasites, and increases the migration and turnover of epithelial cells in the mouse mucosa (Sun et al. 2016).

In addition to parasite expulsion, tissue repair and suppression of local inflammation are important for efficient coping with active parasitic infection because such infections cause tissue damage resulting from parasite invasion and infection-induced inflammatory responses (Allen and Sutherland 2014). Accordingly, ILC2-derived IL-9 is necessary for repairing damaged epithelial cells. Furthermore, ILC2s as well as Th2 cells and mast cells produce amphiregulin (AREG), which is a member of the epidermal growth factor (EGF) family of proteins (Zaiss et al. 2006, 2015). Amphiregulin interacts with EGF receptor to promote the proliferation of epithelial cells and mediates antihelminth immunity, inflammation suppression, and wound repair.

ILC2s as therapeutic targets

As robust stimulators of Th2 immunity, ILC2s have been suggested as potential therapeutic targets in allergic diseases, such as asthma, AD, and rhinosinusitis.

Lipoxin A4, an arachidonic-acid–derived negative regulator of ILC2s, is an endogenous lipid mediator with anti-inflammatory and proresolution properties (Konya and Mjosberg 2016) that binds to lipoxin A4 receptor or formyl peptide receptor 2 (AXL/FPR2) expressed on ILC2s and NK cells (Barnig et al. 2013). It inhibits IL-13 production by ILC2s and enhances the ability of NK cells to induce eosinophils in humans, thus pointing to new therapeutic strategies against asthma, such as AXL/FPR2 receptor agonists, which are possible drugs for allergic diseases (Christie et al. 1992; Wu et al. 2013).

Prostaglandin I_2 (PGI_2) or prostacyclin is also derived from arachidonic acid and also has inhibitory effects on ILC2 function (Karta et al. 2016; Konya and Mjosberg 2016). Zhou et al. (2016) reported that PGI_2 analog cicaprost inhibits IL-33–induced ILC2 proliferation in mice and decreases IL-5 and IL-13 secretion in response to IL-2 and IL-33 stimulation in humans. When cicaprost-treated mice are challenged with the allergy-causing fungus *Alternaria*, cicaprost reduces the number of ILC2s, and this action is accompanied by decreased IL-5 and IL-13 expression in lungs, suggesting that PGI_2 regulates airway inflammation by reducing ILC2 responses to aeroallergen (Zhou et al. 2016). Moreover, CRTH2, a receptor for prostaglandin D_2 (PGD_2) is highly expressed on ILC2s and Th2 cells, and PGD_2 ligation promotes $CRTH2^+$ ILC2 migration and IL-13 production in human experimental in vitro models (Martinez-Gonzalez et al. 2015; Wojno et al. 2015). In a murine model of helminth-induced Th2 inflammation, CRTH2-deficient mice show a decrease in the ILC2 response and in inflammation in lungs, suggesting that CRTH2 may be a promising therapeutic target in inflammatory diseases of lungs. Selective CRTH2 antagonists, such as fevipiprant and timapiprant, are currently being tested for the treatment of allergic diseases (Schuligoi et al. 2010; Townley and Agrawal 2012). In addition, leukotriene receptor antagonists, such as montelukast and zafirlukast, have been shown to prevent ILC2 activation in mice (Doherty et al. 2013).

In addition to lipid mediators and their receptors, upstream alarmins, including IL-25, IL-33, and TSLP, are attractive targets for treating allergic diseases (Divekar and Kita 2015). Antibodies blocking IL-25, IL-33, or TSLP, such as tezepelumab, have been reported to be beneficial for treating patients with COPD (Lau et al. 2017). On the other hand, blocking of alarmins may affect multiple cell types or have no effects owing to their redundant activities toward ILC2s (Cayrol and Girard 2014; Vannella et al. 2016). In addition, blocking of cytokines downstream of ILC2s, such as IL-4, IL-5, and IL-13, may be therapeutically effective (Bel and Ten Brinke 2017). Research has revealed that a humanized monoclonal Ab against IL-5 (mepolizumab) and a human Ab against IL-4Rα (dupilumab) have beneficial effects against allergic diseases in humans (Beck et al. 2014; Ortega et al. 2014).

General features of ILC3s

ILC3s comprise at least three subtypes: lymphoid tissue inducer (LTi) cells, natural cytotoxicity receptor $(NCR)^+$ ILC3s, and NCR^-CCR6^- double-negative ILC3s. All the subtypes have the common feature $Lin^-ROR\gamma t^+CD127^+$ $CD90^+$ (Sanos and Diefenbach 2013), and each subtype can be classified according to the expression of CCR6 and NCR (NKp46 in mice and NKp44 in humans). $NKp46^-$ $CCR6^+$ LTi cells were initially described as cells that are necessary for the development and formation of lymphoid tissue during the fetal period and after birth in mice (Melo-Gonzalez and Hepworth 2017). Recent studies, however, indicate that LTi cells can secrete cytokines such as IL-17 (Uhlig et al. 2006; Elson et al. 2007). NCR^+ ILC3s are the major populations of ILC3s in the murine small intestinal mucosal tissue, and these cells produce IL-22 (Luci et al. 2009; Vonarbourg et al. 2010). $NKp46^-CCR6^{-/lo}$ DN-ILC3s are a heterogeneous cell population that secretes IL-

17, IL-22, and IFN-γ (Melo-Gonzalez and Hepworth 2017). NCR^- ILC3s possess considerable plasticity and can be converted into NCR^+ ILC3s or IFN-γ–producing ILC1s (Vonarbourg et al. 2010; Melo-Gonzalez and Hepworth 2017). Just as in Th17 cells, the transcription factor RORγt plays an important role in the differentiation of all ILC3 subsets (Cording et al. 2014).

ILC3s secrete proinflammatory or anti-inflammatory cytokines, such as IL-17 and IL-22, in response to IL-1β, IL-6, and IL-23 (Sedda et al. 2014). IL-17 is a well-studied proinflammatory cytokine that recruits neutrophils and macrophages to induce inflammation. IL-22 is a double-edged cytokine that is known to have either proinflammatory or anti-inflammatory effects in inflammatory diseases (Neurath 2014). ILC3s can also take up and present antigens, indicating that ILC3s can regulate adaptive immunity (Hepworth et al. 2013). Through cytokine production and antigen presentation, ILC3 act as mediators of diverse inflammatory diseases, cancer, and even preeclampsia (Hepworth et al. 2013; Sonnenberg and Artis 2015). Accordingly, ILC3s are being studied as potential therapeutic targets in several diseases (Perry et al. 2012; Li et al. 2016b; Konya et al. 2017).

ILC3s in inflammatory diseases

Acute intestinal inflammation, i.e., inflammatory bowel disease (IBD)

IBD is a chronic relapsing inflammatory disease originating from acute colitis that has not been properly resolved. ILC3s are the most common ILC subtype present in the human intestine in the steady state, and these cells are a major source of GM-CSF upon IL-23 stimulation in mice and humans (Pearson et al. 2016). GM-CSF regulates acute intestinal inflammation by recruiting and maintaining inflammatory monocytes. In addition, ILC3s actively participate in chronic inflammatory diseases, such as CD and ulcerative colitis (UC). The frequency of inflammatory ILC3s is significantly elevated in the inflamed intestinal tissue of patients with IBD and in a mouse model of IBD (Geremia et al. 2011; Hepworth et al. 2013); besides, Longman et al. (2014) reported that ILC3s from the colon tissue of IBD patients produce more IL-22 than control tissue does. Moreover, Lo et al. (2016) demonstrated that ILC3s play a pivotal role in gut fibrosis in salmonella-induced gut fibrosis (which serves as a mouse model of CD) by secreting IL-22 and IL-17A. The pathogenic functions of IL-22, IL-17, and IFN-γ from ILC3s have been well studied in a mouse model of colitis. Eken et al. (2014) demonstrated that IL-22 produced by ILC3s promotes the development of colitis in a $Rag1^{-/-}$ mouse model of anti-CD40 Ab-induced colitis. Treatment with an anti-IL-22 Ab protects anti-CD40–injected mice from colitis, whereas addition of IL-22 via hydrodynamic gene delivery exacerbates colitis symptoms. In addition, IL-7Rα$^+$ ILCs producing IL-17A promote colitis in a Th1-specific T-box transcription factor $(Tbx21)^{-/-}Rag2^{-/-}$ model of UC (Powell et al. 2012). *H. hepaticus*–infected $Rag^{-/-}$ mice develop chronic colitis through induction of ILC3-derived IL-17A and IFN-γ (Hue et al. 2006; Buonocore et al. 2010), and depletion of all $Thy1^+$ ILCs with an anti-Thy1 Ab alleviates both acute and chronic colitis, while RORγt-deficient mice receiving an anti-CD40 Ab do not develop colitis; these data emphasize the pathological involvement of ILC3s in colitis (Buonocore et al. 2010). The above results show the importance of ILC3-mediated secretion of IL-22, IL-17, and IFN-γ in colitis.

Psoriasis

This is a common, chronic inflammatory autoimmune skin disease characterized by erythematous scaly plaques resulting from excess keratinocytes. Studies indicate that the number of $NKp44^+$ ILC3s is higher in the skin and peripheral blood of patients with psoriasis as compared to patients with AD or healthy volunteers (Teunissen et al. 2014; Villanova et al. 2014). In addition, the frequency of $NKp44^+$ ILC3s in the nonlesional skin of psoriasis patients is higher than that in healthy volunteers, indicating the possible role of $NKp44^+$ ILC3s in the pathogenesis (Villanova et al. 2014). Furthermore, the frequency of $NKp44^+$ ILC3s in the skin correlates with the severity of psoriasis. When patients with psoriasis receive anti-TNF therapy, decreases in inflammatory skin lesions and circulating $NKp44^+$ ILC3 are observed, indicating a correlation between the frequency of $NKp44^+$ ILC3s in blood and the clinical response to anti-TNF therapy. In Aldara-induced skin inflammation in a mouse model of psoriasis, ILC3s were also reported to be a major source of IL-17 and IL-22 in the skin and were shown to induce psoriatic plaque formation (Ward and Umetsu 2014).

RA and ankylosing spondylitis (AS)

RA is characterized by immune-cell infiltration and chronic inflammation caused by inflammatory cytokines such as IL-1, IL-6, IL-17, and TNF-α (McInnes and Schett 2007). Before the nomenclature for ILC was established, Ren et al. (2011) observed that numbers of $CD3^-CD56^{+-}$ $NKp44^+CCR6^+$ cells producing IL-22 are increased in the synovial fluid and peripheral blood of RA patients, and patients with large numbers of $CD3^-CD56^+NKp44^{+-}$ $CCR6^+$ cells show worse 28-joint disease activity scores. In addition, Koo et al. (2013) reported that increased lymphocyte infiltration of RA synovial fluid correlates with

upregulation of LTi-like cells and the expression of chemokines that recruit LTi or LTi-like cells expressing CXCR5 and CCR7.

AS is an autoimmune disease that induces chronic inflammation in the joints of the spine. The numbers of $lin^{-}RORc^{-}Tbet^{+}NKp44^{+}$ ILC3s are significantly increased in the gut, synovial fluid, and bone marrow of patients with AS in comparison with these numbers in healthy volunteers. $lin^{-}RORc^{-}Tbet^{+}NKp44^{+}$ ILC3s also express the inflammatory cytokines IL-17 and IL-22 as well as α4β7 integrin, pointing to recirculation of ILC3s between the gut and extraintestinal sites (Ciccia et al. 2015). Besides, a significant reduction in intestinal and circulating ILC3 numbers was observed in AS patients after anti-TNF treatment. These results are suggestive of a potential contribution of intestinal ILC3s to the development of AS in relation to their migration between the gut and inflamed sacroiliac joints and induction of inflammation.

Multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE)

MS is an inflammatory disease of the nervous system. The exact causes of MS are not known; however, a combination of genetic and environmental factors seems to contribute to the inflammatory process. Although the function of ILCs in MS is poorly understood, Perry et al. (2012) showed that LTi-like ILCs in cerebrospinal fluid initiate and sustain the formation of focal aggregates. Numbers of ILC3s, including LTi cells, are higher in the blood of patients with MS. In addition, stronger expression of IL-17 is observed in the brain lesions of MS patients according to gene microarray analysis, supporting the potential role of ILC3s in MS (Lock et al. 2002).

ILC3s reside in the meninges of naïve mice in the steady state. ILC3s produce IL-17 and GM-CSF and express CD30L and OX40L, which keep memory T cells alive. In EAE, a mouse model of MS, disease-induced T-cell trafficking in the meninges is impaired in ILC3-deficient $Rorc^{-/-}$ mice with transferred wild-type T cells. In addition, c-kit-mutant ($Kit^{W/Wv}$) mice that are EAE resistant have a lower number of LTi cells, indicating ILC3s' involvement in EAE (Hatfield and Brown 2015).

Asthma

Emerging studies have shown that asthma is also associated with ILC3s and Th2 immune responses. IL-17-expressing ILC3s are more frequently detected in human BAL fluid samples from patients with severe asthma than in BAL fluid samples from patients with mild asthma or healthy volunteers. Furthermore, in vitro culture of BAL fluid cells with IL-1β, IL-7, and IL-2 results in an increased number of IL-17-producing ILC3s, implying that IL-17-producing ILC3s can be found in lungs and play a role in the pathogenesis of asthma (Barnie et al. 2015). In addition, Nagakumar et al. (2017) found that the number of ILC3s expressing IL-17 is significantly higher in blood, sputum, and BAL fluid of patients with severe treatment-resistant asthma, whereas the number of Th17 cells is unchanged.

In mice, ILCs are rarely detected in lungs, representing only 0.4–1% of all live cells in the steady state (Monticelli et al. 2011). By contrast, in a model of obesity-induced asthma, IL-17A–producing ILC3s are upregulated 3- to 4-fold by IL-1β produced by macrophages (Kim et al. 2014).

ILC3s in cancer

A recent study revealed that ILC3s are directly related to the development of colorectal cancer (CRC) through IL-22. In a mouse model of *H. hepaticus* azoxymethane (AOM)-induced CRC, colonic ILCs producing IL-17 and IL-22 accumulate in inflamed colon tissue. Kirchberger et al. (2013) reported that in a CRC model, IL-22 blockade with an anti-IL-22 Ab can significantly reduce tumor burden, whereas an anti-IL-17 Ab does not have an antitumorigenic effect but does decrease inflammation, suggesting that IL-22 is a novel therapeutic target in CRC. In addition, an increase in IL-22 production is observed in human CRC tissue (Jiang et al. 2013; Kirchberger et al. 2013). Jiang et al. (2013) demonstrated that IL-22 enhances tumor development and metastasis via activation of STAT3 in human UC and CRC, confirming the participation of IL-22 in CRC.

Carrega et al. (2015) reported that human non–small cell lung cancer (NSCLC) is related to NCR^{+} ILC3s. The latter cells are present in the lymphoid infiltrates of human NSCLC and produce proinflammatory and chemotactic or angiogenic cytokines. These NCR^{+} ILC3s can interact with tumor cells and tumor-associated fibroblasts and are more frequently detected in early-stage NSCLC than in advanced-stage NSCLC, implying a role for NCR^{+} ILC3s in the formation of tertiary lymphoid structures (TLSs). In fact, a positive correlation is observed between TLS density and the number of NCR^{+} ILC3s in tumor infiltrates. This result, along with the finding that TLSs correlate with better survival, suggests that NCR^{+} ILC3s may be an effective prognostic factor of NSCLC (Carrega et al. 2015).

ILC3s as therapeutic targets

Dysregulation of ILC3s has been implicated in many inflammatory diseases and cancers; consequently, ILC3s have been suggested as therapeutic targets.

Aryl hydrocarbon receptor, a ligand-dependent transcription factor, is involved in the regulation of differentiation and in the functioning of murine ILCs in the gut (Qiu et al. 2012). Maintaining the intestinal ILC composition is critical for homeostasis and immunity, and dysregulated ILC composition can lead to destruction of the intestinal barrier and excessive immune reactions, resulting in inflammation or cancer. In humans, NKp44$^+$ ILC3s, NKp44$^-$ ILC3s, and ILC1s differentially express aryl hydrocarbon receptor (its expression in NKp44$^+$ ILC3s is the highest, expression in NKp44$^-$ ILC3s is intermediate, and ILC1s do not express this receptor), and downregulation of aryl hydrocarbon receptor is required for conversion from ILC3s to ILC1s. NKp44$^+$ ILC3s play a protective role against the pathogenesis of CD, and aryl hydrocarbon receptor signaling is essential for the maintenance of NKp44$^+$ ILC3s in the intestine. Li et al. (2016b) observed that ILC1s accumulate at the expense of NKp44$^+$ ILC3s in the inflamed tissue of patients with CD, indicating impairment of the aryl hydrocarbon receptor signaling pathway followed by ILC3-to-ILC1 conversion. Furthermore, Zhao et al. (2016) reported that microRNA-124 induces intestinal inflammation by inhibiting aryl hydrocarbon receptor in CD patients. A knockdown of microRNA-124 and aryl hydrocarbon receptor activation repress inflammation in lipopolysaccharide-stimulated cells in vitro and in a mouse model of TNBS-induced colitis, supporting the notion that aryl hydrocarbon receptor on ILCs is a potential target for the treatment of CD.

Vitamin D deficiency is a risk factor of IBD (Ardesia et al. 2015). Konya et al. (2017) isolated ILC3s from human tonsils and the gut, and demonstrated that ILC3s-timulation under the influence of IL-23 and IL-1β induces expression of vitamin D receptor and downregulates the IL-23 receptor pathway in response to the active form of vitamin D, 1α,25-dihydroxy vitamin D_3 (1,25D) through a negative feedback loop in vitro. As a result, vitamin D decreases the secretion of such cytokines as IL-17F, IL-22, and GM-CSF from ILC3s, implying that vitamin D is an interesting therapeutic agent that modulates the IL-23 receptor pathway and ILC3s in intestinal inflammation.

Treatment with daclizumab (Zinbryta®), a humanized anti-CD25 monoclonal Ab, decreases the inflammation associated with MS without affecting activated T cells. Daclizumab reduces the number of circulating ILC3s and modifies the phenotype of LTi cells toward NK cells by modulating the differentiation of hematopoietic progenitors in patients with MS (Perry et al. 2012). In May 2016, the FDA approved daclizumab for the treatment of relapsing MS.

IL-23—expressing ILC3s perform essential functions in intestinal immunity, and therapeutic strategies targeting downstream cytokines, such as IL-23, are promising approaches to IBD therapy. Elson et al. (2007) reported that administration of an anti–IL-23 monoclonal Ab prevents and alleviates active colitis in a mouse model of T-cell–mediated colitis. Administration of an anti–IL-23 monoclonal Ab downregulates inflammatory cytokines and chemokines in the inflamed colon.

In addition, targeting the IL-23–IL-17 axis with the anti–IL-17A monoclonal Ab secukinumab (Cosentyx®) and an anti-p40 (subunit of IL-12 and IL-23) monoclonal Ab ustekinumab (Stelara®) has therapeutic effects in both AS and psoriasis (Leonardi et al. 2008; Baeten et al. 2013; Baeten et al. 2015). Although these antibodies, which target the IL-23–IL-17 axis, have initially been intended to target Th17 cells, ILC3s are also an important component of this axis. Despite the contribution of the IL-23–IL-17 axis control to host immunity, neutralizing these cytokines can also have adverse effects, such as tuberculosis, fungal infections, and upper respiratory tract effects (Griffiths et al. 2010; Langley et al. 2014; Baeten et al. 2015; Feagan et al. 2016).

Closing remarks

Numerous studies on ILCs have been conducted in the past 7 years since their discovery, resulting in the identification of three ILC subsets and their development and functions. Despite the beneficial roles of ILCs in immunity and homeostasis, they can also have detrimental effects and are involved in various diseases, from allergic rhinitis to autoimmune inflammatory diseases and cancer; therefore, ILCs are a critical factor in some diseases.

Despite intensive research, much remains to be learned about how each type of ILCs influences the onset, progression, and prognosis of ILC-associated diseases as well as the immune response. In addition, the potential therapeutic targets in ILC-associated diseases need to be determined.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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