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Review article

Characteristics of innate lymphoid cells (ILCs) and their role in immunological disorders (an update)

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ABSTRACT

Innate lymphoid cells (ILCs) are a novel family of hematopoietic effectors and regulators of innate immunity. Although these cells are morphologically similar to B cells and T cells, however they do not express antigen receptors. ILCs seems to have emerging roles in innate immune responses against infectious or non-infectious microorganisms, protection of the epithelial barrier, lymphoid organogenesis and inflammation, tissue remodeling and regulating homeostasis of tissue stromal cells. In addition, it has recently been reported that ILCs have a crucial role in several disorders such as allergy and autoimmunity. Based on their phenotype and functions, ILCs are classified into three major groups called ILCs1, ILCs2, and ILCs3. Here we reviewed the most recent data concerning diverse ILC phenotypes, subclasses, functions in immune responses as well as in immune mediated disorders.

Contents

1. Introduction

The immune system is divided into two main categories including innate and adaptive immunity. Innate immune

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responses provide initial defense against infections prior to adaptive immune system activation. Afterwards, adaptive immunity uses the mechanisms of innate immunity in order to eradicate antigens. Regulation of adaptive immune response is crucial in immunity against intracellular infections by T cells [1]. T helper1 (Th1) cells secrete several mediators such as lymphotoxin-α (LTα), interferon-γ (IFNγ) and interleukin-2 (IL-2) which are responsible for the type 1 cellular immune responses and they tend to be engaged in development of autoimmune diseases such as type I diabetes, rheumatoid arthritis (RA) and Crohn's disease. In contrast, Th2 cells express IL-4, IL-5, IL-9 and IL-13 cytokines and promote type 2 immunity which lead to development of asthma and allergic diseases and contribute in immune responses against parasites [2]. Th17 cells are another subset of T helper cells which are found in mucosal tissues especially in gastrointestinal tract. These cells play a vital role in host defense against extracellular pathogens including bacterial and fungal agents via recruitment of neutrophils and macrophages by secreting IL-17A, IL-17F, and IL22. Th17 cells are known to be involved in the pathogenesis of various autoimmune diseases including multiple sclerosis (MS), psoriasis and Job's syndrome [3–5].

Innate lymphoid cells (ILCs) are newly identified as a family of hematopoietic cell types which cooperate with T cells in cytokine secretion, as one of the main cytokine sources in immune system. However, they neither express lymphoid differentiation lineage markers (LIN−) nor antigen receptors which making them distinct cells from T cells and B cells [6]. ILCs are developed from hematopoietic lymphoid precursors and are identified by the absence of recombination activating genes (RAG1 or RAG2) expression [1]. Recent studies have indicated that the transcription factor Id2 (inhibitor DNA 2) is necessary for differentiation of all innate lymphocytes [6,7], suggesting that all innate lymphocytes might be derived from a common precursor.

Recently, several distinct ILC subsets have been recognized that each of those show distinct markers and cytokine as well as different functions in human and mouse. The earliest recognized member of innate lymphoid cells were killer (NK) cells and lymphoid tissue-inducer (LTi) cells that was described in 1975 [6] and 1997 [8], respectively. A major complication in the ILC field is the bewildering number of different names that have been used to characterize these cells. Here, we classified ILC populations into three major groups based on their phenotypical and functional characteristics, including: group 1 ILCs (ILC1 and NK cells); group 2 ILCs (ILC2) and group 3 ILCs (RORγt dependent ILCs including LTi, ILC17 and ILC22). These classified cells play broad roles in lymphoid organogenesis, lymphoid tissue development, protective immunity in mucosal surfaces, tissue remodeling and homeostasis in tissue stromal cells. In addition, they are newly known to be involved in several disorders such as allergy and autoimmunity [9,10]. In this review, recent studies regarding different ILC phenotypes and their functions in immune responses as well as in immune mediated pathogenesis of allergy, asthma, autoimmune diseases, cancer and immunodeficiency are explained.

2. Classification of ILC subsets

2.1. ILC1

Recently, a new ILC population have been identified that secrete type 1 cytokines especially IFNγ but not other signature cytokines including IL-17, IL-22, or IL-5 [2,11]. The first described subset of this group entitled natural killer (NK) cells. It seems that not only NK cells have cytotoxicity function against tumors, but also involve in the elimination of viruses and intracellular pathogens, so describing them as effector innate lymphocytes [12–14]. In mice, NK cells express the NKp46, and in certain mouse strains these cells also express NK1.1. In humans, NK cell populations are described by the markers CD16, CD56 and CD94 [15–17]. Most of human NK cells (approximately 90%) express $CD56^{dim}/CD16^{hi}$, whereas the remaining (10%) have $CD56^{hi}/CD16^{dim}$ phenotype [18]. The major cytokines of NK cells are IFNγ and TNFα. The count of human NK cells is considerably low in patients carrying mutations of the gene encoding γc [18–20]. They are distributed in secondary lymphoid organs, blood, and peripheral organs. Conventional NK cells are developed in bone marrow but a group of NK cell population, termed thymic NK cells, can also arise from thymus. Thymic NK cells in mice might be similar to human CD56 hi CD16 dim/− NK cells, but these cells in mice express CD127 and higher levels of Gata-3 compared with human CD56+ CD16+ NK cells [19].

Unlike NK cells, there are another population of ILCs with low cytotoxicity and ability of producing IFNγ that are suggested to be classified as ILC1 that have been involved in immunity to intracellular bacteria and parasites [21–23]. Although it has been proposed that ILC-1 might originate from NKp44+ group 3 ILC under the influence of IL-12 and IL-15 [22,24], but the exact origin of ILC1 cells is yet unknown [2]. Although there are various classifications regarding identification of ILC1 cells based on different CD marker phenotypes, these cells are distinct from other populations due to IFNγ production and absence of any of the TH2 cell-or TH17 cell-associated cytokines. Humans ILC1 populations are CD117- and express high levels of T-bet and low levels of RORγt [22]. Taken together, other surface markers and signature cytokines from NK and ILC1 cells indicated separately in mice and human in Table 1 and Fig. 1.

2.2. ILC2

Another group of ILCs secretes type 2 cytokines and needs to IL-7 for their development. Nowadays, based on their common characteristics, these type 2 cytokine producing cells entitled ILC2 [2,11]. These cells also called natural helper cells (NHCs), nuocyte and innate helper 2 (IH2) cells that are found in the mesenteric fat-associated lymphoid cluster, liver, spleen, Peyer's patches and airway mesenteric lymph nodes [2,25]. For the first time, ILC2s were discovered in the fetal gut tissue in human. These cells were also found in blood, lungs and especially in nasal polyps of patients with chronic rinosinusitis [26,27]. In humans, ILC2s express several markers including ST2 (also known as IL-1RL1), IL-17RB [26,28], CRTH2 (chemoattractant receptor-homologous molecule expressed on TH2 cells) and CD161 [28]. On the other hand, mouse ILC2s are characterized by a lack of T, B, and myeloid cell markers, but express ICOS, SCA1, CD127, ST2, THY1+, IL-17RB and CD25 (Table 1) [29]. All identified type 2 ILCs could produce T helper type 2 (TH2) cytokines, predominantly IL-5 and IL-13, and also amphiregulin [26] in response to IL-25, IL-33 [30–32] and thymic stromal lymphopoietin (TSLP) [33,34] which might involved in the pathogenesis of asthma, allergy and host resistance against nematodes [35,36].

2.3. ILC3

This group of ILCs continuously expresses RORγt and need to IL-7Rα for their development and function [24,37]. ILC3 comprise the various subsets of ILC that are divided into three subsets based on the expression of various markers and cytokines.

The prototypical groups 3 ILCs are LTi cells, that were first identified as CD4+ CD3− cells scattered among fetal and neonatal lymph nodes [8,38]. In mice, LTi cells express integrin α4 β7, CD4, CD45, lymphotoxin (α, β), c-Kit, IL-7Rα, IL-1R, IL-23R and CCR6 (Table 1) [8,39]. Human LTi cells are identical to mouse LTi cells except that CD4 express on most mouse LTi cells but not on

Table 1
Characteristics of CD markers, localization and signature cytokine of ILC subsets.

ILC groups	ILC lineage	Marker		Localization	Signature cytokine	Refs.
		Human	Mice			
Group 1	ILC1	LIN−, NKp46+ NKp30+ NKp44+ CD127− CD117− T-bet+ RORγt^{low}	LIN− RORγt−, RORγt^{int} CD90+ SCA1+	Skin?	IFN γ	[2,22,47,105,145]
	NK cells	LIN−, CD56+, CD16+, CD94+, CD25+/−, IL-7Rα−, CD161+/−, NKp44+/−, NKp46+, IL-12Rβ2+, CRTH2−, CD122+, NKG2D+, CD161+, and KIR+	LIN−, NKp46+ NK1.1+ (strain dependent) CD122+ NKG2D+ CD161+ CD16+ CD11b+	Lymphoid tissues (thymic NK cells in thymus)	IFNγ−, TNFα, perforin, granzymes	[2,15,46,145,146]
Group 2	ILC2s	LIN−, ST2+, CRTH2 CD161+, CD127+, CD90+, CD45+, CD25+, IL-33R+, ICOS+,	LIN−, CD127+, CD45+, CD25+, IL-33R+, CRTH2+, CD161, ICOS+, SCA1+, ST2+, CD90+, and IL-17Rβ	(NH cells in FALC), skin	IL-5, IL-9, IL-13, low IL-4, amphiregulin	[28,29,145]
Group 3	LTi	LIN−, CD4−, CD45+, lymphotoxin (α, β)+, c-Kit+, IL-7Rα+, IL-1R+, IL-23R+ and CCR6+	LIN−, CD4+, CD45+, lymphotoxin (α, β)+, c-Kit+, IL-7Rα+, IL-1R+, IL-23R+ and CCR6+	Lymphoid tissues	Lymphotoxin α and β, IL-17A, IL-22	[2,8,39,42,46,145]
	ILC17	LIN−, CD25+, CD117+, IL-7Rα+, CD161+, NKp44−, NKp46+, CRTH−, IL-1R+, IL-23R+	LIN−, CD25+, CD117−, CD90+, IL-7Rα+, NKp46−, IL-1R+, IL-23R+	Intestine, skin	IL-17, IFN γ−	[11,46,47,53,105,145]
	ILC22	LIN−, NKp44+, NKp46+, NKp30+, CD117+, CD127+, CD161+, CCR6+, IL-1R+, IL-23R+	LIN−, CD90+, CD117+, CD127+, NKp46+, IL-1R+, IL-23R+	Intestine, skin	IL-22	[11,46,53,105,133,145]

LIN−: lineage marker-negative; FALC: fat associated lymphoid cluster; NH: nuocyte; Refs.: references LTi: lymphoid tissue-inducer; NK: natural killer cell; IFN: interferon; ILC: innate lymphoid cell; RORγt: retinoic acid receptor-related orphan receptor-γt; TNF: tumor necrosis factor; CRTH2: chemoattractant receptor-homologous molecule expressed on TH2 cells; ICOS: inducible T cell co-stimulator; CCR: CC-chemokine receptor; KIR: killer cell immunoglobulin-like receptor; SCA-1: stem cells antigen-1.

human LTi cells [17]. Human fetal LTi cells express CD56 and other NK cell markers such as NKp44 after treatment by IL-2 [17]. Adult LTi cells differ from their fetal counterpart due to expression of the T cell costimulatory molecule ligand (OX40-L) and CD30L [6]. LTi cells are developed independently of IL-15 [40] and need to RORγt for their development and activity [41]. LTi cells play a vital role in the development of lymphoid tissues [42]. In both human and mice, LTi cells are mainly found in fetal mesenteric lymph nodes [15] which are associated with the maintenance of T cell memory and immunity to enteric infections [43].

Some ILC3s have been identified to be different from LTi cells due to expression of natural cytotoxicity receptors (NCRs), as they are divided into NCR+ ILC3 and NCR− ILC3 [11,44]. Moreover, NCR+ ILC3 and NCR− ILC3 are entitled as ILC22 and ILC17, respectively. Regarding NCR expression, human ILC22 expresses NKp44 and low NKp46 in addition to expressing NKp46, but mouse ILC22 only expresses NKp46 [15]. ILC22 which is found in mucosal tissues especially in intestinal tract [2], plays an important role by the IL-22-mediated innate immune response against certain bacteria (such as *Citrobacter rodentium*) in the gut [45]. Mouse ILC17 are almost similar to human ILC17 regarding CD markers except that CD117 express on human ILC17 but not in mouse ILC17 [11,46]. ILC-17 is proficient in producing IL-17 and involves in defense against extracellular bacteria and pathogenesis of inflammatory autoimmune diseases [6]. Other characteristics of ILC3 described in Table 1 and Fig. 1.

3. ILC development

Different transcription factors regulate the differentiation and development of various ILC subsets. It has been demonstrated that the cytokine receptors containing common γ chain (γc), including receptors of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, are essential for differentiation and development of ILCs. Distinct ILC subsets require different members of this family from cytokines [47–49]. All of the ILCs are developed from IL-7Ra bearing common lymphoid progenitors (CLP) [39,50–52] and need to express helix–loop–helix (HLH) transcriptional regulator inhibitor of DNA-binding 2 (Id2) [48,49]. One of the most important characteristics of these cells is high expression of Id2, whereas peripheral naive T cells express low level of Id2 and B cells lack this marker [48,53]. The development of T cells, B cells and dendritic cells (DCs) critically is depend on the E2A transcription factor family, including E12, E47, E2-2 and HEB [54]. However, the transcriptional activity of E2A proteins inhibits the development of several ILC subsets. On the other hand, the activation of Id (inhibitor of DNA binding) proteins inactivates the E2A function [53,54].

All NK1.1+ cells require IL-15 for their development, but thymus-derived CD127+ IFN-γ-producing NK cells also require IL-7 for their development; a characteristic which make them more similar to the other ILC subsets (ILC2, ILC22 and LTi) [7,40]. Investigations have demonstrated that NK cells are not derived from progenitors expressing RORγt. Thus, development of conventional NK cells and ILC2 cells seems to be RORc independent [17,45,55,56]. However, probably there is a subset of NK cells which expresses RORγt. NFIL3 (E4bp4) from a bZIP family transcription factor is vital for the development of NK cells [57,58] via playing a role in regulation of Id2 expression in NK precursor cells and immature NK cells [47]. Although Id2 is essential for optimal development of NK cells, this molecule plays an important role at a later developmental stage in the transition of pre-NK to immature NK cells [7,21,59]. Of note, the development of mouse thymic NK cells is dependent on IL-15, IL-7, and Gata-3 [60]. In mice, there is a population of thymic NK cells which are identical to human CD56 hi CD16 dim/− NK cells and express CD127, high levels of

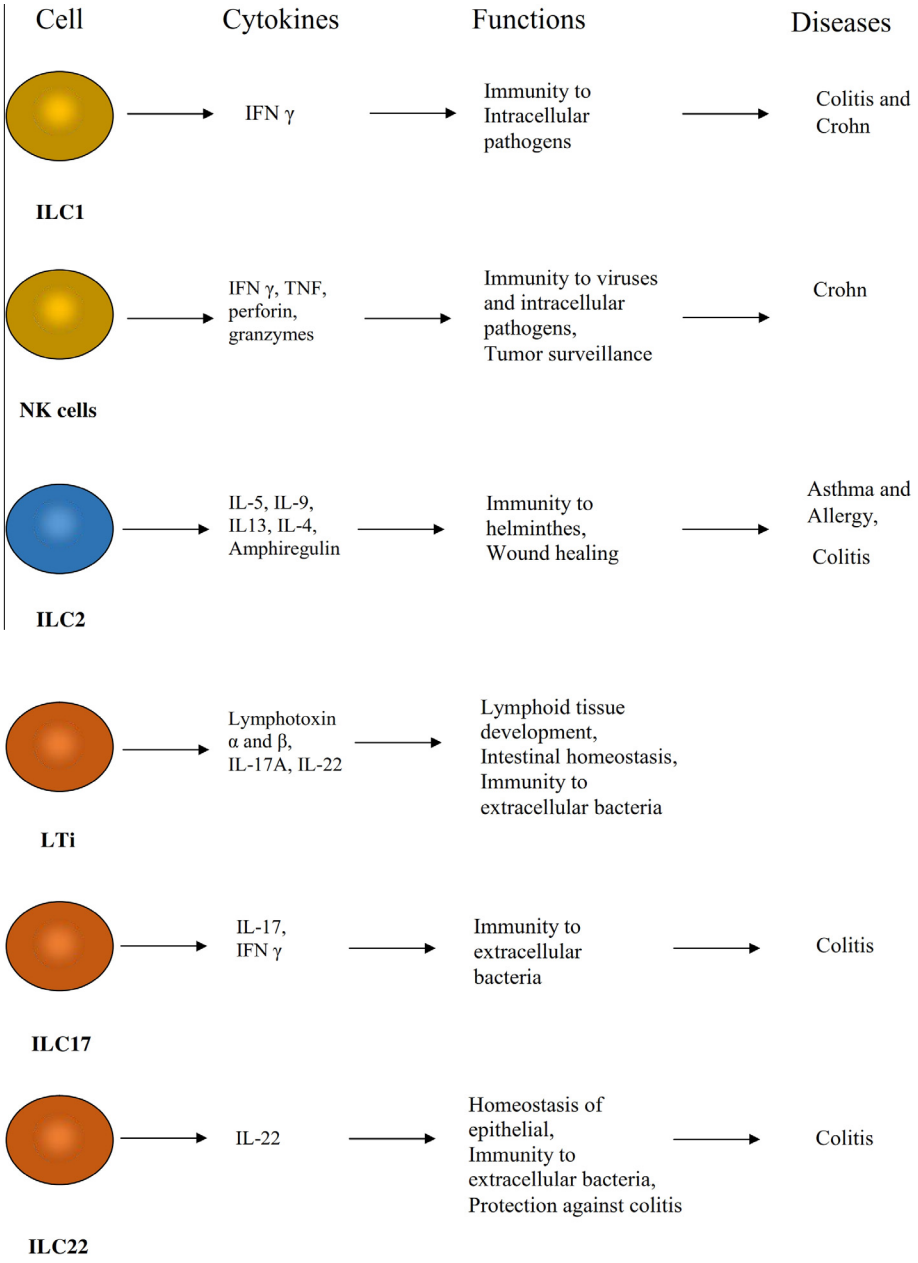

Fig. 1. ILC1 are defined by their capability to produce IFNγ, whereas NK cells could produce TNFα, perforin and granzymes in addition to IFNγ. Group 2 ILCs are able to produce T helper 2 (TH2) cell-associated cytokines, including IL-5, IL-4, IL-9, IL-13 and amphiregulin. Of note, human ILC2s produce IL-4 but mouse ILC2s might not produce this cytokine *in vivo*. LTi cells characterized by production of lymphotoxin α and β, IL-17A, IL-22; ILC17 secret high level of IL-17 and IFN γ; ILC22 identified by high production of IL-22. The cytokines produced by ILCs induce important physiological responses, such as wound healing, tumor surveillance and protection against infections. However, ILC-derived cytokines can also provoke immunopathology in diseases such as asthma and inflammatory bowel diseases (IBDs).

Gata-3 [19]. Human ILC1 express highly Tbet that might be involved in their development. Newly, a population of Tbet-dependent ILC1 in the mouse liver has been identified which similar to NK cell has cytotoxic activity [61] but is not able to express transcription factor Eomes and develops from a precursor which had no appreciable potential to differentiate into NK cells [21]. The human equivalent of these cells has yet to be recognized.

ILC2 subsets are γc receptor dependent and are responsive to IL-25 and IL-33 [30]. ILC2s are described by production of Th2 cytokines (IL-5 and IL-13). Thus, it might be expected that ILC2 development is depend on transcription factors including GATA-3, c Maf and NFAT2 which influence differentiation of Th2, however some data have indicated that RORα is critical for nuocyte differentiation [62]. Human ILC2s need to GATA3 for development and function, while Notch signaling induces development of human ILC2s [63]. In mice, GATA3 and Notch as well as TCF-1 and RORa drive the development and function of human ILC2s [34,48,64]. In addition, it has been recently demonstrated the transcription factors Gfi1 and Bcl11b also involve in the differentiation and development of mouse ILC2s [65–67].

In fetal liver ILC3 can originate from hematopoietic precursor. ILC3s are matured during migrating to the embryonic lymphoid tissues [53]. Recent studies have described the role of transcription factor Notch for the differentiation of ILC3 [50]. It has been demonstrated that Notch signaling helps to maximize the efficiency of LTi cell differentiation [41]. Likewise, LTi cell differentiation needs to

Table 2
ILC subsets, functions and disease associations.

ILC group	ILC lineage	Function	Disease associations
Group 1	ILC1	Immunity to intracellular pathogens (viruses, bacteria and parasites)	Colitis, murine crohn, human
	NK cell	Immunity to viruses and intracellular pathogens tumor surveillance	Crohn, human
Group 2	ILC2	Immunity to helminthes wound healing	Asthma and allergy, human and murine colitis, murine
Group 3	LTi	Lymphoid tissue development intestinal homeostasis immunity to extracellular bacteria	–
	ILC17	Immunity to extracellular bacterial and fungal pathogens, autoimmunity	Colitis, murine
	ILC22	Homeostasis of epithelial immunity to extracellular bacteria protection against colitis	Colitis, murine

some transcriptions factors such as Runx1 and Tox [68,69]. Furthermore, aryl hydrocarbon receptor (AhR) signals are required for the maintenance and expansion of postnatal emerging of ILC3 subset [47].

Mouse ILC3 require to some transcription factors including Notch, TCF-1, and RORγt for their development and function, however it is unclear yet whether these factors are essential for human ILC3 development. In mice, ILC22 needs to Tbet for their development, but the requirement of this factor for human ILC22 is unknown yet [43,70,71]. Furthermore, human and mouse ILC22 cells also express AhR and AhR-deficient mice have fewer ILC22 that have impaired IL-22 production [15].

3.1. Plasticity in ILCs

Recent reports suggest that there is plasticity among ILC subsets; however this has to be confirmed yet. It is supposed that a population of ILC3s were fate-mapped for prior expression of RORγt which could have functional and transcriptional plasticity as they may down regulate RORγt and obtain the ability to produce IFNγ following IL-12 and IL-23 induction [24]. In one study, after treatment with IL-7 and IL-2, it has been shown that human CD56+ NKp44+ IL-7Rα+ ILC3 population produce high levels of IFNγ in response to IL-23 stimulation, despite of preservation of RORγt expression [72,73]. Furthermore, it has been demonstrated in another study that mouse ILC22 differentiated into INF-g-producing ILC1s, as these cells downregulate RORγt and upregulate Tbet during this process [43]. Until now, no evidence of ILC2s plasticity to any other ILC subsets has been reported.

4. Innate lymphoid cells and diseases

In recent years, several studies demonstrated various ILC functions during immune responses, suggesting that ILCs might have important role in the pathogenesis of immunological diseases (Table 2 and Fig. 1). We discussed role of ILCs in various immunological disorders in below.

4.1. Role of ILCs in infectious diseases

Different ILC populations with the ability of rapid secreting of immunoregulatory cytokines might be involved in immune responses against infections. Notably, the ILC subsets dominantly are located at mucosal surfaces and are highly exposed to infectious agents of the external environment. There is growing evidence that ILCs are involved in immune responses against infections and especially their anti-helminthes activities in the intestine is of interest [2].

The role of rapid NK cell responses in face with various intracellular pathogens has been identified in both humans and mice [74]. However, the role of ILC1 population has been less found. Klose et al. have indicated that ILC1s produced high amount of IFN-γ and TNF in mice during infection with the *Toxoplasma gondii*, leading to recruiting inflammatory myeloid cells that control infection [21]. Furthermore, it was found that mice lacking T-bet expression failed to control parasite replication and adoptive transfer of ILC1s to mice (*Rag2*−/−*Il2rg*−/−) increased immunity to *T. gondii* infection [21].

The first report about the role of ILCs in protective immunity has emerged from study on IL-25 deficient mice which it has been identified ILC2s were responding to *Nippostrongylus brasiliensis* infection through production of IL-13 [35]. It has been demonstrated that IL-13, as a major cytokine of Th2, has important role in protective immunity against helminthes in the intestine. For instance, for efficient elimination of *N. brasiliensis*, IL-13 promotes defensive responses, such as mucus secretion by goblet cells and contraction of intestinal smooth muscles [75,76]. This cytokine is not mainly secreted by T cells and this vital task is rather upon the ILCs. It has been shown that transferring wild-type ILC2s into IL-13 deficient mice could overcome the worm infection. Moreover, ILC2 produces IL-25 and IL-33 during *N. brasiliensis* infection and leads to induction of several the transcription factors including Act1, GATA3, TCF-1 and GFI1 which have vital role in IL-13 expression and worm expulsion. Thus, it is suggested that collaboration of several cytokines such as IL-13, IL-25 and IL-33 could be effected for worm expulsion [2,31]. Up to now, few studies have reported the role of ILC2 in other parasitic infections and it is not clear whether worm parasites could break away from ILCs defense line. Kang et al. has been reported that IL-25 (as a cytokine of ILC2) is produced from the epithelium and plays important role in elimination of the worm [77]. Furthermore, it has been demonstrated that murine gut ILC2s involve in removal of worms by producing IL-9 and IL-13 during infection with nematodes [31,78], but this activity regarding to human ILC2 remain to be confirmed. Of note, although ILC2s via production of type 2 cytokines are enough for removal of helminth infection, it is essential to exist Th2 cells for effective helminth expulsion [79], because ILC2s are maintained by Th2 cells during an infection [31]. This hypothesis confirmed by Neill et al. that demonstrated ILC2 could responded to IL-25 and IL-33 in Rag2 knockout mice, but the number of ILC2 reduced after activation, as these mice were not able to eliminate the worm burden impressively [31]. Altogether, these data indicate that ILCs could have vital role in protective immunity against infectious diseases particularly helminthes diseases.

In context of immunity to bacterial infections, there are vital roles for ILC1s and ILC3s in host defence. It has been demonstrated that depletion of IL-22-producing ILC3 (ILC22) in mice could lead to die due to *C. rodentium* infection within the first week [80]. Moreover, ILC22 along with lymphotoxin contribute to resistance to *Salmonella typhimurium* infection [81]. On the other hand, it has been seen that IFNγ-producing ILC1s involved in resistance to *Salmonella enterica*, as secretion of IFNγ through ILC1 is

necessary for the release of mucus-forming glycoproteins to protect the epithelial barrier during *S. enterica* infection [82].

Recently, Gladiator et al. has shown that ILC17 could be novel players of immunity against fungal pathogens. In mice, it has been described that ILC3s protective role begins in the early stages of infection with fungi such as *Candida albicans* through up-regulation of IL-17A and IL-17F (both are essential for opportunistic fungal clearance) in response to IL-23 [83]. Undeniable roles of IL-17 in defense against fungi have been demonstrated by various studies in animal models. It has been demonstrated that some skin disorders and mucosal infection diseases with *C. albicans* were seen in IL-17-deficient and IL-17R-deficient mice [84,85]. However, because in mice, ILC17 were found to be important in the immune response against *C. albicans*, it is speculated that human ILC17 also could play a role in the immune response against this fungal infection. This hypothesis needs to further investigations to confirm whether a defect in IL-17-secreting ILCs could be involved in fungal infections in humans.

Protective roles of IL-17 have also been shown in other fungal infectious agents like *Histoplasma capsulatum*, *Pneumocystis carinii*, and *Aspergillus fumigatus* [86–88]. Moreover, some genetic defects are detected that result in congenital chronic mucocutaneous candidiasis (CMC). The genes are associated with defects in adaptive IL-17 mediated immunity and may also affect innate IL-17 production [89]. Therefore, ILCs especially IL-17 producing ILCs, could have important roles in response to infectious agents, including fungal pathogens, as it is suggested that fungal control (especially *C. albicans*) is mediated by IL-17-secreting innate lymphoid cells (ILCs) and not by Th17 cells [83].

4.2. Role of ILCs in asthma and allergic inflammation

Several studies have indicated that the IL-25 and IL-33 expression are correlated with allergic airway diseases and have been identified as asthma-related genes [90–92]. In asthmatic lung tissue, an increased amount of IL-25 and IL-33 makes some physiological changes in the lungs including rapid type 2 responses, increased secretion of IL-5 and IL-13 as well as mucus production, eosinophilia, and hyper reactivity in airways. As mentioned, IL-25 and IL-33 could induce ILC2s to produce type 2 cytokines. One study on mice indicated that IL-33 more potently induce lung ILC2s compared with IL-25 correlating with airway contraction [93], whereas IL-25 induce other cells producing type 2 cytokines such as type 2 myeloid cells and MPP type 2 cells [94,95]. IL-33 and ILC2s have role in persistence of airway hyperreactivity, and IL-13 secreted by ILC2s induced IL-33 expression in epithelial cells [29]. Indeed, this feedback loop is supposed to be involved in developing chronic asthma. It has been described that adoptive transfer of nuocytes into IL-13 deficient mice which do not respond to IL-25 treatment results in eosinophilia. This note demonstrates that ILC2s are potent in expansion of asthma even in the absence of T cell derived IL-13 [36]. Mouse ILC2s are also responsible for airway hyper sensitivity induced by glycolipid antigens or papain [33]. Furthermore, IL-13 which is produced by ILC2s [28] could be involved in tissue remodeling and fibrosis and can also be correlated with fibrosis in type 2 immune response mediated diseases, while IL-5 promotes eosinophil infiltration into the lungs [96–98].

IL-9 is another Th2 cytokine which is highly expressed in the lungs of asthmatic patients and induces the asthma like phenotype including mucous production, airway remodeling and goblet cell hyperplasia. It has been demonstrated that blocking of IL-9 reduces airway hypersensitivity [36]. IL-9 could have an autocrine or paracrine effect on ILC2, leading to ILC2 survival as well as elevation of IL-5 and IL-13 production by these cells [99]. In one study, we have been found human Lin−/CD127+/CD161+ ILCs counts were significantly higher in the peripheral blood of the asthmatic patients compared with the healthy individuals. Moreover, we identified a significant elevation of the expression of IL-9, IL-17, IL-22 and IL-25 cytokines in serum and sputum samples of the asthmatic patients compared with normal individuals [100]. Indeed, it has been demonstrated that the elevation of IL-9, IL-17, IL-22 and IL-25 potentially related to severity of asthmatic symptoms. Furthermore, it was clarified that simultaneous increase in ILCs and eosinophils counts as well as inflammatory cytokines in asthmatic patients may describe the cooperation between ILCs, eosinophils and Th cells in initiation and remaining of allergic responses [100]. In addition, Mjösberg et al. have indicated TSLP induces human ILC2 to upregulate directly GATA3 via STAT5 which leading to the secretion of high amounts of type 2 cytokines such as IL-5 and IL-13 [28]. This data are highly relevant in the context of asthma especially in patients with severe asthma. These observations are approved by several studies in mouse models [33,36,101].

Mjösberg et al. have identified that human ILC2s were increased in the nasal polyps of patients with chronic rhinosinusitis. Chronic rhinosinusitis described by the presence of high level of IgE and elevated eosinophils that may be induced by the IL-5 and IL-13 [28]. Epithelial cells which are located in nasal polyps might be capable to produce high level of TSLP and IL-33, leading to increased IL-5 and IL-13 production via ILC2 in patients with this disease [28]. However, exact role of ILC2 in rhinosinusitis is unclear yet.

Moreover, it has been revealed that human ILC2s might be involved in the pathogenesis of atopic dermatitis, as high proportion of ILC2 populations has been found in the lesions of patients with atopic dermatitis [102,103]. Furthermore, one study have demonstrated that IL-5-producing ILC2 were also elevated in the lesional skin of mice with atopic dermatitis-like phenotype [104]. Thus, ILC2s and their cytokines or lipid mediators might be considered as new therapeutic targets for atopic dermatitis [102–105]. These data indicate that ILC2s might be involved in the pathogenesis of atopic dermatitis especially by IL-5 and IL-13 production. Identification of the interactions between ILCs and immune system cells as well as other cells, such as keratinocytes, epithelial cells and fibroblasts, may clarify the contribution of these cells to homeostatic conditions and pathogenesis of the disease.

The type 2 immune responses like respiratory allergic signs are also induced by some viral infectious agents such as influenza virus and rhinovirus. The details of this is not yet clear [106]. Chang et al. in a study indicated that influenza virus-induced asthma in mice is mediated by IL-33 dependent ILC2 and not by the adaptive immunity [107]. It has been observed that ILC2s are activated in the lungs after H1N1 influenza A virus infection. This type of infection induces IL-33 secretion in the lungs and creates airway hypersensitivity and increase in ILC2 number [107].

4.3. Role of ILCs in cancer

There is some evidence that demonstrate ILC cells could be involved in both protection against cancer and development of cancer in humans and experimental animals.

Studies on various models including transplantable melanoma tumor model have indicated the protective function of small numbers of adoptively transferred splenic IL-12 dependent NKp46+ cells against tumor development. *In vitro* examinations on antitumor activity of ILCs have shown that after treatment of IL-7 and IL-12, ILCs express transcripts of IL-22 and IFN-γ, but secrete only IFN-γ protein and inappreciable amount of IL-22 [108]. IFN-γ is a key cytokine in killing of cancerous cells due to its abilities in inhibit cellular proliferation, promote apoptosis and up-regulation of the expression of MHC class I and II molecules on tumor cells [109]. It has also been demonstrated that ILC1s could also secrete

high levels of IFN-γ in mucosal tissues [22,23]. Since ILC1 cells might have similar functions to those of the NK due to their similar phenotypes and cytokine production profiles, suggesting that ILCs (especially ILC1) could have anti-tumor effects on cancerous cells. However, this hypothesis need to further investigations to be clarified.

Increased risk of cancer and tumorigenesis is associated with the production of inflammatory mediators during inflammation and injury by activated innate cells [1]. One study has shown that differential accumulation of IL-17$^+$IL-22$^+$ colonic innate lymphoid cells (cILCs) occurs in bacteria-induced colon cancer. These cells differ from LTi and ILC22 cells. In dysplastic inflammation mice reduction of ILC17 and ILC22 blocks the development of invasive colon cancer. Depletion in IL-17 amounts blocks some stages of intestinal inflammation, but blockage in dysplasia and colorectal cancer (CRC) needs neutralization of IL-22; it shows that IL-22 has a unique role in sustaining cancer in this model. Investigations indicate that the selective function of IL-22 is inducing STAT3 phosphorylation and proliferation of epithelial cells. Interestingly, IL-22$^+$CD3$^+$ and IL-22$^+$CD3$^-$ cells were detected in human CRC. The important role of IL-22 in CRC highlights the demands for more studies on this cytokine as a therapeutic target in patients suffering from colon cancer [110]. However, one study has demonstrated that IL-22 could be considered as an anti-tumor cytokine and has tumor growth restraining functions in mice. Huber et al. have described that IL-22 play a vital role in controlling tumorigenesis and epithelial cell proliferation in the colon, as *Il22*−/− mice demonstrated development of colon cancer [111]. Although IL-22 could active proangiogenic factors via inducing growth of established tumor, it seems unlikely that IL-22 be able to begin tumor formation alone [112,113]; as IL-22 might be involved in promote other factors and mechanisms related to cancer progression. Thus, IL-22 could have both pro-tumor and anti-tumor mechanisms that might be related to the status of tissue microenvironment and/or the tumor stage. In other cancers such as cutaneous T-cell lymphoma [114] and hepatic carcinoma [115], IL-22 has been demonstrated to has vital role in humans. In these diseases, IL-22 is produced not only by T cells but also by non-T cells, and it will be of interest to determine whether ILC22s are that cellular source.

Furthermore, it has been demonstrated that IL-17-producing ILC3s could also contributing to development of tumorigenesis in mice gut [116] via the IL-23/IL-17 signaling pathway during chronic gastrointestinal infection or acute stimulation with carcinogen agents. Moreover, IL-17 could induce tumor growth through angiogenesis that leading to tumor metastasis [117].

In a study conducted by Galli et al., it was found that mature innate immune cells show significant plasticity into various cellular functions and destiny in response to environmental signals [118]. While this is a main property in regulation of immune responses to injury or infection, it may also be a tool in the process of tumorigenesis. There are several studies that confirm ILC subsets can show functional plasticity in response to environmental cues [24,72,73]. It could be speculated this plasticity among ILC which results in production of various cytokines, might lead to development of cancer or protection against cancer. However, further investigations are essential to understand the plasticity and function of ILCs within the tumor microenvironment.

4.4. Role of ILCs in autoimmune diseases

The dysregulation of RORγt-dependent ILCs as well as production of IL-17 and IL-22 may contribute to some autoimmune diseases like psoriasis, rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) [3].

IBD, such as Crohn's disease and ulcerative colitis, are categorized in chronic inflammatory disorders of the gastrointestinal tract. Intra-epithelial ILC1s and IFNγ-producing ILC3s could provoke inflammation in mice, as depletion of IFNγ could improve colitis in some models of mice [23,119]. Human ILC1s are associated with Crohn's disease, whereas their murine counterpart has been demonstrated to contribute to the development of experimental colitis [22,23]. IFNγ-producing ILCs could contributing to development of human IBD due to elevation of ILC1 and reduction of ILC22 in inflamed intestinal tissues of patients with IBD [22,23], because ILC22 could be involved in protection against IBD in mouse models [45,55]. It could be speculated that reduction of ILC22 might be due to differentiation of ILC3s toward ILC1s in inflamed mucosal tissues. In context of protective role of ILC22, IL-22 actives antimicrobial molecules and antiapoptotic pathways that contribute to inhibition of tissue damage and tissue repair. These activities involve in elevation of intestinal barrier integrity and epithelial innate immunity [120]. In one study, it has been shown in a mouse model that IL-23 in colon can stimulate RORγt+ ILCs in order to secrete IL-17 and induce intestinal colitis [119]. Indeed, ILC17 could be involved in IBD in T-cell-independent mouse models [119,121] Thus, blockade of either IL-17 or IFN-γ was sufficient to significantly reduce colitis [119]. Buonocore et al. have described that depletion of Thy1+ ILCs in a mouse model of colitis which induced by the administration of anti-CD40 specific antibodies, resulted in reduction of IFN-γ, IL-22, TNF-α and abrogation of colitis [119]. This clears that RORγt-dependent ILC3s has important role in this disease [119]. Since there are various subpopulations of ILCs in the intestine and that multiple ILCs could be active during under inflammatory conditions such as IBD, It is suggested to categorize accurately the ILC populations in the inflamed human intestine. Of note, the vital role of IL-17A, IL-17F, IL-22 and IFNγ in IBD have been demonstrated, but it has been reported that ulcerative colitis has a type 2 immune phenotype as the amount of IL-4, IL-5 and IL-13 cytokines is depended on the severity of intestinal pathology in the patients [2]. Recently, IL-13 producing ILC2s have been described in an oxazolone-induced mouse model of colitis, which is characterized by a type-2 inflammatory response. However, further studies could be done to identify the role of ILC2s in human IBD [122].

It has been reported that NK cells also could be involve in the pathogenesis of IBD. Takayama et al. indicated that intestinal NKp44− NKp46+ NK cells could produce IFN-γ, while NKp44+ NKp46− NK cells secret IL-22 in the intestine [10]. They have found elevated IFN-γ-producing NKp46+ NK cells in inflamed mucosa of patients with Crohn's disease, whereas IL-22-producing NKp44+ NK cells have significantly reduced in these patients compared with healthy individuals. Indeed, disruption of balance between IFN-γ-producing NKp46+ and IL-22-producing NKp44+ NK cells in inflamed mucosa and also elevation of IFN-γ-producing NKp46 + cells may contribute to the development of patients with Crohn's disease.

Unlike the intestine, there is little information about the number and activities of ILCs in human skin. Psoriasis is an inflammatory skin disease characterized by symptoms including thickening of epidermal layer of skin abnormal keratinocyte proliferation, dermal microvascular changes and local infiltration of leukocytes. The IL-23 and IL-17A are involved in the pathogenesis of psoriasis [123–126]. In patients with psoriasis high levels of IL-17A and IL-23 were found in lesional skin [123,124,127]. Efficient treatment of psoriatic patients with anti-IL-12/23p40 and anti-IL-17 antibodies indicates the importance of these cytokines in pathogenesis of psoriasis [128–130]. It has been found which three groups of ILC subsets exist in human skin [105,131].

The number of ILC22 is higher in both human nonlesional and lesional skin from patients with psoriasis compared with healthy skin that might be involved in the pathology of psoriasis [131–133]. One study has reported which the frequency of

NKp44+ ILC3 associated with disease severity using PASI score [132] while another study could not demonstrate an identical finding [133]. Another studies on a drug induced psoriasis model of mice showed that RORγt$^+$ ILCs and γδ T cells initially secrete IL-17A, IL-17F and IL-22, and are also required for the early development of psoriatic-like plaque [134,135] suggesting that IL-22 and IL-17 producing ILCs may have role in the pathogenesis of psoriasis. It has been reported that one psoriatic patient with treatment of the anti-TNF antibody (adalimumab) demonstrated a correlation between therapeutic response and a reduction of NKp44+ ILC3 in the peripheral blood [133]. This reduction indicates potential importance of NCR+ ILC3 in the pathogenesis of psoriasis and these data raise a question whether the population of NKp44+ ILC3 could be consider as a biomarker for psoriasis. Furthermore, ILC3s could regulate the function of CD4+ T cells to induce tissue homeostasis in the intestine [136], thus this note provokes the question whether interaction between CD4+ T cells and ILC3s could maintain tissue homeostasis in the skin of psoriatic patient. However, further investigations are essential to clarify these ambiguities.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that primarily affects multiple joints and ultimately leads to destruction of bones and cartilage. Several studies have shown that enhanced expression of IL-7 results in induction of lymphotoxin α-β in RA patients and this elevation contributes to the joint inflammation. Furthermore, elevation of IL-7R expression has been revealed in RA synovial tissue [137–139]. Bekiaris et al. have been reported a CD4+ CD3− innate-like lymphoid population in normal human subjects that characterized by constitutive expression of TNF and IL-7-dependent induction of surface LTαβ. Moreover, it has been shown that expression of CCR6 on the CD4+ CD3− population defined a CD127 (high) subset that is highly responsive to IL-7. They have been demonstrated that this subset of ILCs exist in the peripheral blood from rheumatoid arthritis patients [140]. Based on role of IL-7, IL-7R and lymphotoxin α-β in development of RA disorder, it seems ILC could involve in pathogenesis of this disease and probably other chronic inflammatory diseases. Thus, the blockage of IL-7R-mediated immune activation by soluble hIL-7R alpha could be considered as a therapeutic approach for immunotherapy of RA [137–139].

Pemphigus vulgaris (PV) is an autoimmune disease which characterized with blisters on the skin and mucous membranes. Acantholysis in the epidermal layer develops through the effect of anti-desmoglein 3 auto-antibodies [141,142]. In one study, a highlight increase in the number of peripheral blood NK cells in patients with PV was identified. They reported that NK cells of patients with PV show reduced mRNA levels of IL-12 receptor β2, IL-10, perforin and granzyme B, while IL-5 mRNA was present in NK cells of the patients with active disease [141]. Proliferation of T cells in culture of NK cells with autologous CD4+ T cells in the presence of desmoglein3 peptides, suggesting that NK cells can act as antigen-presenting cells in PV patients. NK cells probably enhance T cells to produce IL-6, IL-8 and IFN-γ. However, peripheral blood NK cells of PV patients seem to be activated and may link to the pathogenesis of the disease through enhancing Th2 responses or production of inflammatory cytokines. The role of NK cells as antigen-presenting cells in PV patients are unclear and needs more investigation [141–143].

4.5. Role of ILCs in immunodeficiency

The role of ILCs in immunodeficiencies is rarely surveyed and we encounter a paucity of such researches in this context. We have been identified that there was a significant reduction of IL-17-producing ILCs along with Th17 cells in patients with common variable immunodeficiency (CVID). This may indicate a new mechanism for their defect in humoral immune responses [144]. Thus, it is necessary to investigate the role of ILCs in immunodeficiency diseases in future studies.

5. Conclusion

In recent years, ILCs have emerged as a rudimental element of immune response against infectious agents. Latest studies have obviously showed that families of ILCs have different physiological roles such as immune protection and lymphoid tissue development during wound healing and homeostasis in host. These evidences have been confirmed by the characterization of the factors like transcription factors which are responsible for the differentiation and maintenance of involved ILC subsets in the immune responses. Environmental conditions also may result in ILCs plasticity from a subset to another one. The evidences about the development, function, and heterogeneity of the ILC family have made interesting advances in the immunology. In addition, it is supposed that main role of ILCs is to initiate and support the adaptive immune responses. Dysfunction of ILCs is related to different diseases, for example NK cells (as a ILC1 subset) has role in skin diseases, RORγt-dependent cells are associated with IBD and colitis whereas ILC2s are involved in allergic diseases of lung and gastrointestinal tract. More studies about the innate lymphoid cells may result in more therapeutic ways to overcome these pathologic conditions. Various researches in the field of innate lymphoid cells are in progress, but still lots of questions remain unclear about the main role of ILCs in health and disease.

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