Innate lymphoid cells–a proposal for uniform nomenclature

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Innate lymphoid cells — a proposal for uniform nomenclature

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Abstract | Innate lymphoid cells (ILCs) are a family of developmentally related cells that are involved in immunity and in tissue development and remodelling. Recent research has identified several distinct members of this family. Confusingly, many different names have been used to characterize these newly identified ILC subsets. Here, we propose that ILCs should be categorized into three groups based on the cytokines that they can produce and the transcription factors that regulate their development and function.

Innate lymphoid cells (ILCs) are emerging as important effectors of innate immunity and have a central role in tissue remodelling. ILCs are defined by three main features: the absence of recombination activating gene (RAG)-dependent rearranged antigen receptors; a lack of myeloid cell and dendritic cell phenotypical markers; and their lymphoid morphology[1]. The prototypical ILC populations are natural killer (NK) cells and lymphoid tissue-inducer (LTi) cells. NK cells mediate early immune responses against viruses and are involved in immune responses against cancer cells. LTi cells are essential for the formation of lymph nodes during embryogenesis. These cell types were discovered in 1975 (REF. 2) and 1997 (REF. 3), respectively, and have been extensively studied since. Although NK cells and LTi cells have different functions, they are developmentally related, as both cell types require the common cytokine receptor γ-chain (γ_c; also known as IL-2Rγ) and the transcriptional repressor inhibitor of DNA binding 2 (ID2) for their development[4].

Recently, several distinct ILC populations have been identified that, similarly to NK cells and LTi cells, depend on γ_c and ID2 (REF. 5) for their development (FIG. 1). These ILC populations also rely on signalling through interleukin-7 receptor subunit-α (IL-7Rα) for their development and maintenance. Strikingly, these different ILC populations have distinct patterns of cytokine production that mirror the cytokine-secreting profiles of T helper (T_H) cell subsets[6]. For example, some ILC populations secrete the T_H17 cell-associated cytokines IL-17 and IL-22 following stimulation, whereas other ILC subsets were found to secrete the T_H2 cell-associated cytokines IL-5 and IL-13 in response to several stimuli[6].

Recent research suggests that ILC populations have important effector functions during the early stages of immune responses against microorganisms[7,8], and that they also contribute to tissue repair[9,10], the anatomical containment of commensal microorganisms[11] and the maintenance of epithelial integrity at barrier surfaces[12,13]. Moreover, some ILC subsets were also found to be involved in inflammatory diseases. For example, IL-17- and interferon-γ (IFNγ)-producing ILCs have been shown to mediate colitis in a mouse model of inflammatory bowel disease[14], whereas ILCs that produce T_H2 cell-associated cytokines cause lung inflammation in certain models of allergic asthma[15,16].

In this article, we provide a brief overview of the different ILC populations, discuss the current controversies regarding their relationships and propose a uniform nomenclature to denote these cells.

ILC nomenclature

A major complication in the ILC field is the bewildering number of different names that have been used to characterize these cells. For instance, IL-22-producing ILCs that were identified in mucosal tissues have been called NK22 cells[7], NKR-LTi cells, NCR22 cells[17] and ILC22s[6]. Similarly, ILCs that produce T_H2 cell-associated cytokines have been denoted natural helper cells[8], nuocytes[18] and innate helper 2 (I_H2) cells[19]. TABLE 1 and TABLE 2 provide overviews of the ILC populations that have been reported so far in mice and humans, respectively, and the cellular markers that have been used to define them.

Here, we propose the classification of these ILC populations on the basis of their phenotypical and functional characteristics. Our proposed nomenclature is based on the T_H cell nomenclature and categorizes the ILC subsets into three groups (FIG. 1). Group 1 comprises ILCs that produce IFNγ. Group 2 comprises ILCs that produce type 2 cytokines (including IL-5 and IL-13) and are dependent on GATA-binding protein 3 (GATA3) and retinoic acid receptor-related orphan receptor-α (RORα) for their development and function. Group 3 includes all ILC subtypes that produce IL-17 and/or IL-22 and depend on the transcription factor RORγt for their development and function. The proposed ILC nomenclature differs from that of the T_H cell nomenclature in that the ILC group names are not connected to the so-called 'signature' cytokines. This might help to avoid confusion, for example in the case of group 3 ILCs, which can produce either IL-17 or IL-22 alone or both cytokines together and may also produce the T_H1 cell-associated cytokine IFNγ and the T_H2 cell-associated cytokine IL-13. Thus, rather than using the terms ILC17s and ILC22s to denote ILCs dedicated to the production of IL-17 and IL-22, respectively, we propose the term group 3 ILCs to describe all RORγt-dependent ILCs that can produce IL-17 and/or IL-22.

Group 1 ILCs

Group 1 ILCs are defined by the production of the signature cytokine IFNγ and the inability to produce T_H2 cell- and T_H17 cell-associated cytokines. The prototypical

member of this group is the NK cell. It has been firmly established that NK cells not only display cytotoxic activity, but are also able to produce large quantities of IFNγ following activation. The T_H1 cell-associated transcription factor T-bet (which is encoded by *Tbx21*) cooperates with eomesodermin, another T-box transcription factor, to regulate the development and function of NK cells[20] (FIG. 1). In mice, NK cells express the natural cytotoxicity triggering receptor (NCR) NKp46 (also known as NCR1), and in certain mouse strains these cells also express NK1.1 (also known as KLRB1C and NKRP1C). NKp46 is not an exclusive NK cell marker, as it is also expressed by mouse and human IL-22-producing ILCs. In humans, NK cell subsets are defined by the markers CD16, CD56 and CD94; however, CD56 is also found on human IL-22-producing ILCs[7,21,22], and therefore CD56 is not an exclusive marker for human NK cells.

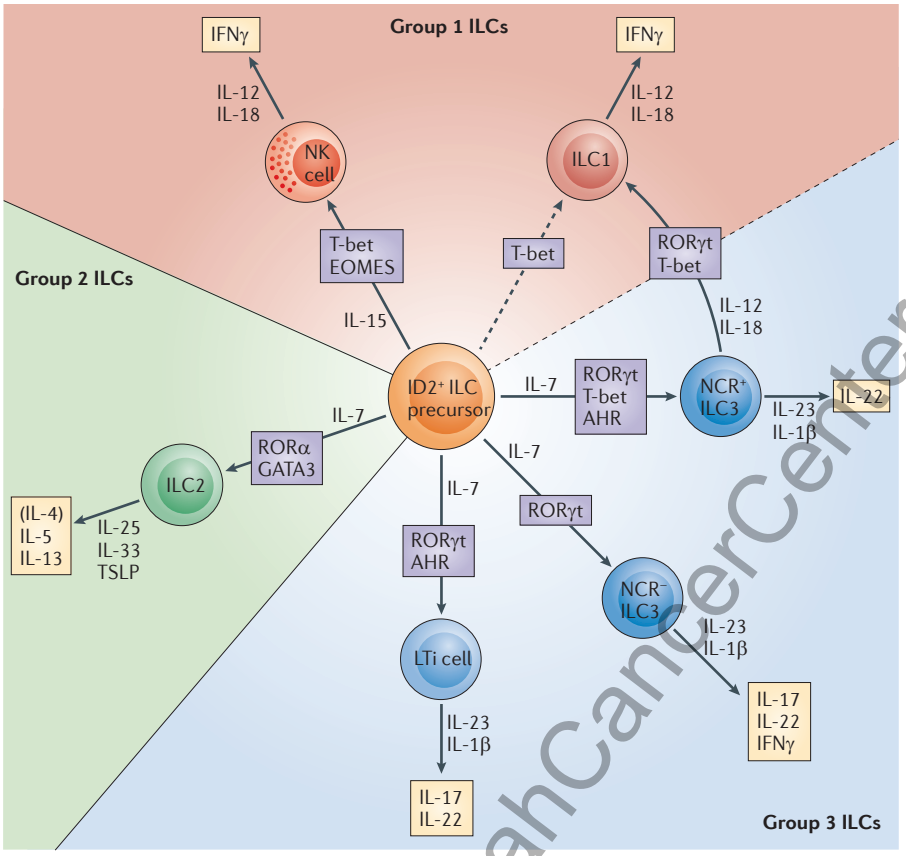

Figure 1 | **Classification of ILCs into three groups on the basis of their functional characteristics.** The proposed classification of innate lymphoid cells (ILCs) is based on functional criteria. Group 1 ILCs are defined by their capability to produce interferon-γ (IFNγ). Group 2 ILCs are able to produce T helper 2 (T_H2) cell-associated cytokines, including interleukin-5 (IL-5) and IL-13. Notably, human ILC2s produce IL-4 but mouse ILC2s might not produce this cytokine *in vivo*. Group 3 ILCs are capable of producing the T_H17 cell-associate cytokines IL-17 and IL-22. We hypothesize that all ILCs develop from a common precursor that may depend on expression of the transcriptional repressor inhibitor of DNA binding 2 (ID2). This common precursor has not yet been identified, and thus other developmental trajectories remain possible. All ILCs depend on the common cytokine receptor γ-chain (which is a component of the IL-2R, IL-7R, IL-9R, IL-15R and IL-21R complexes) for their development and maintenance (not shown). For example, natural killer (NK) cells require IL-15, whereas the other ILCs depend on IL-7. In addition to cytokine signalling, several transcription factors regulate the differentiation of ILCs into distinct subsets. Group 2 ILCs depend on the transcription factors GATA-binding protein 3 (GATA3) and retinoic acid receptor-related orphan receptor-α (RORα) for their development. By contrast, group 3 ILCs require the transcription factor RORγt for both their development and their function. In addition, a subset of group 3 ILCs, termed NCR^+ ILC3s, depend on the aryl hydrocarbon receptor (AHR) for optimal maintenance. The transcription factors needed for NK cell development are T-bet and eomesodermin (EOMES). By contrast, the developmental requirements of ILC1s (which are group 1 ILCs that are distinct from NK cells) are not yet fully elucidated. A significant proportion of ILC1s develop from NCR^+ ILC3s that downregulate RORγt and upregulate T-bet. It is currently unclear whether there are ILC1s that develop from the common precursor cells in a RORγt-independent manner. ILC1s and ILC3s produce their cytokines following stimulation by IL-12 and IL-23, respectively. Co-stimulation by the IL-1 family members IL-18 and IL-1β strongly increases cytokine production by these ILCs. The IL-17 family member IL-25, the IL-1 family member IL-33 and thymic stromal lymphopoietin (TSLP) are the strongest stimuli for inducing the activation of ILC2s.

Another subset of group 1 ILCs that produces IFNγ but not any of the T_H2 cell- or T_H17 cell-associated cytokines, and that is distinct from NK cells, has been identified in mice[23] and humans[24]. Here, we introduce the term ILC1s for these group 1 ILCs, to discriminate between them and NK cells. In humans, the ILC1 subset lacks expression of KIT (also known as CD117) and expresses high levels of T-bet and low levels of RORγt[24] (TABLE 2). The classification of ILC1s as group 1 ILCs on the basis of their IFNγ secretion is, however, not without debate, because there is evidence that IFNγ-producing ILCs develop under the influence of IL-12 from a subset of RORγt-expressing ILCs (which are classified as group 3 ILCs). The development of these IFNγ-producing ILCs was shown to be accompanied by the disappearance of RORγt expression[23] and a strong increase in T-bet expression[24]. More recently, it was observed that mice deficient for T-bet lack NKp46-expressing group 3 ILCs (which we term NCR^+ ILC3s (see below)) that produce IFNγ following activation with IL-12 (REF. 25). T-bet was found in another study to positively regulate IFNγ production and negatively regulate IL-17 production by ILCs[26]. Together, these studies indicate that there is plasticity in group 1 and group 3 ILCs, as suggested previously[23,27], and that T-bet and RORγt are important regulators of the plasticity of ILC subsets. This ILC plasticity is very similar to the plasticity between T_H1 and T_H17 cells[28,29]. It is also possible that some ILC1s develop in a RORγt-independent manner, but such a cell type has yet to be clearly defined. Further studies are needed to definitively categorize ILC1s.

In summary, we propose here that NK cells and IFNγ-producing non-cytotoxic ILC1s should be classified as group 1 ILCs.

Group 2 ILCs

Group 2 ILCs require IL-7 for their development[8] and produce T_H2 cell-associated cytokines in response to stimulation with the cytokines IL-25 (also known as IL-17E)[30,31], IL-33 (REF. 8) and thymic stromal lymphopoietin (TSLP)[16] (FIG. 1).

Table 1 | **Phenotypical markers of mouse ILC subsets**

Marker	Group 1 ILCs		Group 2 ILCs			Group 3 ILCs		
	NK cells	ILC1s	ILC2s (natural helper cells)	ILC2s (nuocytes)	ILC2s (I_H2 cells)	LTi cells	NCR$^+$ ILC3s*	Colitogenic NCR$^-$ ILC3s
CD4	–	–	–	–	–	+	10%	–
CD25	+‡	low	+	+	+	+ (75%)	ND	+
CD90 (also known as THY1)	–/+§	ND	+	+	+	+	+	+
CD117 (also known as KIT)	–	–	+	+	+	+	+	–
CD127 (also known as IL-7Rα)	–/+§	+	+	+	+	+	+	+
SCA1 (also known as LY6A)	+‡	ND	+	+	+	–	ND	+
ICOS	low‖	ND	ND	+	+	ND	–‖	ND
NKp46 (also known as NCR1)	+	–	–	–	–	+	+	–
IL-1R	–	+	–‖	ND	ND	+	+	+
IL-23R	–	–	ND	ND	ND	+	+	+
IL-12Rβ2	+	+	–	–	–	–	–	–
ST2 (a subunit of IL-33R)	–	–	+	+	+	–	ND	ND
IL-17RB (a subunit of IL-25R)	–	–	+	+	+	–	–	–

ICOS, inducible T cell co-stimulator; I_H2, innate helper 2; IL, interleukin; ILC, innate lymphoid cell; LTi, lymphoid tissue-inducer; NCR, natural cytotoxicity triggering receptor; ND, not determined; NK, natural killer; SCA1, stem cell antigen 1. *Also referred to as NK22 cells, NCR22 cells, NKR-LTi cells and ILC22s. ‡Following activation. §On subset of cells. ‖As determined by microarray analysis; natural helper cells do not respond to IL-1β.

ILCs that produce IL-5 in response to IL-25 were discovered in 2002 (REFS 30,31). Subsequently, these IL-25-responsive ILCs were found to mediate resistance to the helminth *Nippostrongylus brasiliensis*[32]. A series of studies published in 2010 further characterized these cells and identified the IL-1 family member IL-33 as another stimulatory cytokine for group 2 ILCs. Koyasu and collaborators found IL-5- and IL-13-producing KIT$^+$SCA1$^+$ ILCs in fat-associated lymphoid clusters and named these cells natural helper cells[8]. In addition, ILCs that produce IL-13 in response to IL-25 and IL-33 were identified by two groups in distinct IL-13-reporter mice and were named nuocytes[18] and I_H2 cells[19], respectively (TABLE 1).

Group 2 ILC populations produce not only IL-5 and IL-13 but also IL-6 and IL-9 (REF. 33) and are important in host resistance against nematodes. Moreover, group 2 ILCs are involved in the repair of damaged respiratory tissue following acute infection with influenza virus. This repair process is mediated by the epidermal growth factor family member amphiregulin, which is also produced by group 2 ILCs[10]. However, not all the functions of group 2 ILCs are protective, as these cells mediate pathology in a mouse model of virus-mediated exacerbation of allergic asthma[15]. Similarly to T_H2 cells, group 2 ILCs are dependent on the transcription factor GATA3 for their development and function[34,35]. In addition, group 2 ILCs require RORα[36,37] for their development (FIG. 1). The above-mentioned common features of natural helper cells, nuocytes and I_H2 cells suggest that these populations represent one cell type, and we propose the use of the term ILC2s to collectively describe them. However, at present it cannot be excluded that natural helper cells, nuocytes and I_H2 cells are instead distinct stable subsets of group 2 ILCs. Further analyses of the molecular signatures of the different group 2 ILC populations and the elucidation of their mechanisms of development will help to clarify this issue.

In humans, only one subset of group 2 ILCs has been characterized. Human ILC2s express ST2 (also known as IL-1RL1), which is a component of the IL-33 receptor, and IL-17RB, which is a subunit of the IL-25 receptor[10,38]. In addition, human ILC2s express CRTH2 (chemoattractant receptor-homologous molecule expressed on T_H2 cells; also known as prostaglandin D2 receptor 2) and CD161, which is expressed by most human ILCs[38] (TABLE 2). As in the case of mouse group 2 ILCs, GATA3 drives the development and function of human ILC2s[39].

In summary, we propose here that the name ILC2s should be used to denote the populations of ILCs that produce T_H2 cell-associated cytokines. Further characterization of natural helper cells, nuocytes and I_H2 cells may eventually justify subdivision of the group 2 ILC population in the future.

Group 3 ILCs

Group 3 ILCs are defined by their capacity to produce the cytokines IL-17A and/or IL-22. Like T_H17 cells, group 3 ILCs depend on the transcription factor RORγt for their development and function. In addition, the development of group 3 ILCs depends on IL-7Rα (similarly to that of group 2 ILCs) (FIG. 1). The prototypical group 3 ILCs are LTi cells, which are crucial for the formation of secondary lymphoid organs during embryogenesis. An effector role for LTi cells in innate immunity has also been suggested, as LTi cells are capable of producing IL-17A and IL-22 following stimulation[40].

Recently, another subset of group 3 ILCs was identified. These group 3 ILCs depend on RORγt for their development and function, similarly to LTi cells, but have phenotypes that are distinct from those of LTi cells[7,41–43] (TABLE 1). So, here we introduce the term ILC3s to describe group 3 ILCs that are distinct from LTi cells. Notably, some ILC3s have been reported to differ from LTi cells by expressing the NCR NKp46, and we propose to call these ILCs NCR$^+$ ILC3s. These NCR$^+$ ILC3s produce IL-22 but not IL-17A, and they are also known as NK22 cells[7], NCR22 cells[17], NKR-LTi cells[23] and ILC22s[6]. However, it should be noted that IL-22 is also produced by other ILC3 subsets (such as CD4$^+$ ILC3s), which lack NCR expression[12]. IL-22-producing ILC3s are crucial for the IL-22-mediated innate immune response against certain

bacteria (such as *Citrobacter rodentium*) in the gut[43]. Another ILC subset within the group 3 ILC population was found to mediate pathology in a mouse model of innate colitis[14]. The cells of this subset lack expression of NKp46 and secrete both IFNγ and IL-17A in addition to IL-22. Depletion of these NCR$^-$ ILC3s or the use of antibodies specific for IFNγ and IL-17A ameliorated colitis in RAG2-deficient mice infected with *Helicobacter hepaticus*, indicating the pathogenic potential of NCR$^-$ ILC3s[14].

In humans, LTi cells were identified in fetal mesenteric lymph nodes. The surface markers of human LTi cells are identical to those of their mouse counterparts with the exception of CD4, which is expressed on most mouse LTi cells but not on human LTi cells[22] (TABLE 2). Moreover, in addition to expressing NKp46, the human equivalents of mouse NCR$^+$ ILC3s express other NCRs, namely NKp30 and NKp44, which are not expressed in mice[7]. Human NCR$^+$ ILC3s secrete IL-22 and not IL-17A, whereas human fetal NCR$^-$ LTi cells produce mostly IL-17A following stimulation[44].

It is clear that the group 3 ILC population is heterogeneous and comprises cell types that produce either IL-17A and/or IL-22, or IL-17A, IL-22 and IFNγ. Group 3 ILC subsets might represent distinct stable cell populations, or alternatively these subsets may be different forms of the same plastic cell type. These issues should be resolved by investigation of the developmental relationships between group 3 ILCs and the transcription factors that drive their development. Here, we propose that the name LTi cells should be maintained to denote group 3 ILCs involved in lymph node formation and the formation of cryptopatches and isolated lymphoid follicles in the intestine. In addition, we propose the introduction of the term ILC3s for other group 3 ILCs, with prefixes such as NCR$^+$, IL-22$^+$ or the tissue location used to specify particular subsets.

Concluding remarks

In this article, we propose a framework for ILC nomenclature that takes into account the classification of NK cells and LTi cells as ILCs. We have categorized all ILC subsets into three groups on the basis of their functional characteristics. FIGURE 1 summarizes the ILC subsets contained in each group and the functional attributes used to classify them. In addition, it reflects the current state of knowledge of the developmental relationships between these ILC subsets. It is assumed that all ILCs are derived from a common precursor, but this hypothesis requires confirmation through the identification and precise characterization of the putative precursor cell. Further details on the development and function of these ILC subsets can be found in several recent reviews[1,45–49]. The goal of this proposed nomenclature is to reduce the confusion that is caused by the introduction of different names during the initial identification of ILCs. However, it should be noted that the study of ILCs is currently a very active research field and it is possible that new findings may lead to changing insights. Additional ILC subsets may be identified in the future, and an improved understanding of the mechanisms underlying the development of the ILC subsets and their *in vivo* functions may lead to regrouping or even renaming. As such, this proposal represents a work in progress. Nonetheless, we encourage workers in the ILC field to adopt this nomenclature.

Table 2 | **Phenotypical markers of human ILC subsets**

Marker	Group 1 ILCs		Group 2 ILCs	Group 3 ILCs	
	NK cells	ILC1s	ILC2s	LTi cells	NCR$^+$ ILC3s*
CD4	–	–	–	–	–
CD25	–/+‡	low	low	ND	low
CD56	+	–	ND	–	50%
CD117 (also known as KIT)	–	–	+/–	+	+
CD127 (also known as IL-7Rα)	–/+§	+	+	+	+
CD161	–/+§	+/–	+	+/–	+
NKp44 (also known as NCR2)	–/+‖	–	–	–	+
ICOS	low	+	+	ND	+
NKp46 (also known as NCR1)	+	–	–	–	+
CRTH2	–	–	+	–	–
IL-1R	–	+	+	+	+
IL-23R	–	–	ND	+	+
IL-12Rβ2	+	+	–	–	–
ST2 (a subunit of IL-33R)	–	–	+	–	–
IL-17RB (a subunit of IL-25R)	–	–	+	–	–

CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; ICOS, inducible T cell co-stimulator; IL, interleukin; ILC, innate lymphoid cell; LTi, lymphoid tissue-inducer; NCR, natural cytotoxicity triggering receptor; ND, not determined; NK, natural killer. *Also referred to as NK22 cells. ‡CD56^{hi}CD16$^-$ cells express CD25. §Not on all cells. ‖NKp44 is expressed by activated but not resting NK cells.

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