Inflammatory group 2 innate lymphoid cells

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Received 29 April 2015, accepted 22 July 2015

Abstract

Group 2 innate lymphoid cells (ILC2 cells) are able to produce type 2 cytokines and to mediate type 2 immune protection and tissue homeostasis. ILC2 cells have often been considered to be a single set of cells that respond to IL-33 and/or IL-25. Recent evidence now indicates that ILC2 cells can be grouped into two distinct subsets: homeostatic or natural ILC2s (nILC2 cells); and inflammatory ILC2 cells (iILC2 cells). nILC2 cells reside in barrier tissues and primarily respond to IL-33. They play critical roles not only in immune protection but also in tissue repair and beige fat biogenesis. iILC2 cells are not present in peripheral tissues in the steady state but can be elicited at many sites by helminth infection or IL-25 treatment. IL-25-elicited iILC2 cells act as transient ILC progenitors with multipotency. They can be mobilized by distinct types of infections to develop into nILC2-like or ILC3-like cells, functioning in corresponding immune responses. The demonstration of the existence of iILC2 cells adds to our understanding of the complexity of ILC2 biology and makes necessary an analysis of the relationship between nILC2 cells and iILC2 cells.

Keywords: IL-25, IL-33, iILC2, ILC plasticity, nILC2

Introduction

Innate lymphoid cells (ILCs) are a population of lymphocyte-like cells with a series of both protective and homeostatic functions. Our understanding of these lineage-negative (Lin^- , i.e. lacking surface markers for T, B, NK and monocytes/macrophage lineages) is developing very rapidly. ILCs sense 'alarming' cytokines and offer critical first-line immune responses against pathogens. They lack TCRs and BCRs but can produce effector cytokines comparable to those produced by CD4^+ helper T (T_H) cell subsets (1).

The complexity of ILC function has now become apparent. ILCs provide early immune protection against infectious agents, mediate lymphoid organogenesis and tissue repair, participate in the transition from innate to adaptive immunity, contribute to inflammation and autoimmunity, repair tissue damage and regulate metabolic homeostasis (2). ILCs are often divided into two main lineages: killer ILCs; and helper-like ILCs. Killer ILCs are $\text{IL-7R}\alpha^-$ and represented by conventional natural killer (cNK) cells, which resemble cytotoxic CD8^+ T cells in some aspects. Helper-like ILCs express $\text{IL-7R}\alpha$ and are composed of various effector cytokine-producing subsets, including IFN- γ -producing ILC1 cells, IL-13- and IL-5-producing ILC2 cells and IL-17- and/or IL-22-producing ILC3 cells (3). Helper-like ILCs share many properties with CD4^+ T_H cells, such as cytokine production, utilization of common transcription factors, and mediation of physiological functions (4). Here, we focus on recent advances in the characterization of ILC2 properties,

regulation and function, with particular emphasis on inflammatory ILC2 cells (5).

Identification of ILC2 populations

The existence of lymphoid-like cells producing IL-13 and IL-5 was first reported in IL-25-treated $\text{Rag2}^{-/-}$ mice (which cannot produce mature T or B cells). Those non-B/non-T (NBNT) cells were MHC class II^{high}, $\text{CD11}^{\text{null}}$ and Lin^- cells that were able to amplify type 2 immune responses upon treatment with IL-25 (6). Later, similar type 2 cytokine-producing NBNT cell populations were identified in the early stage of *Nippostrongylus brasiliensis* infection; these cells contributed to worm expulsion (7–9). IL-33 is known to induce $\text{T}_\text{H}2$ responses, so the type 2 immunity-associated functions of IL-33 that were independent of T cells also hinted at the existence of an innate-like cell population capable of producing type 2 cytokines (10). In 2010, the publication of three important studies led to a clear notion of this set of innate effector leukocytes: natural helper (NH) cells were identified in mesenteric fat-associated lymphoid clusters (FALC) in naive mice (11); nuocytes were identified in mesenteric lymph nodes (MLN) of mice in response to IL-25 or IL-33 (12); and innate type 2 helper (Ih2) cells were identified systemically in response to IL-25 or IL-33 and after *N. brasiliensis* infection (13). Although whether those populations were a single cell type was unclear, they were designated as ILC2 cells (14), a nomenclature accepted by a group of pioneering authors (15, 16). Multipotent progenitor type 2 (MPP^{type2}) cells were also identified almost at the

same time; they were IL-25-elicited cells producing type 2 cytokines (17), but were demonstrated later as a mixture of myeloid cells and ILC2 cells (presumably IL-25-responsive iILC2 cells) (18). ILC2 cells then were shown to be present at many sites including spleen, liver, lung, intestinal lamina propria, skin, bone marrow and adipose tissue (19–28).

Although all the identified cell populations were referred to ILC2 cells, the heterogeneous phenotype of those cells suggested that different subsets might have existed among cells with this designation (12, 13). Our recent study has helped to clarify this issue through the identification of a novel set of ILC2 cells— inflammatory ILC2 cells (iILC2 cells) (5). Distinct from homeostatic or natural ILC2 cells (nILC2 cells) that naturally reside in the lung and mainly respond to IL-33, iILC2 cells are not found in most lymphoid or parenchymal tissues in naive mice but rapidly appear at several sites in response to intra-peritoneal administration of IL-25 or *N. brasiliensis* infection, but not IL-33 administration. IL-25 elicits large numbers of iILC2 cells in the lung, MLN, spleen and liver; these cells can be detected in bone marrow and peripheral blood; by contrast, IL-33 treatment only induces moderate expansion of nILC2 cells. Thus, two distinct ILC2 sets exist: tissue-resident, IL-33- or IL-33/IL-25-responsive nILC2 cells present at steady state; and IL-25-responsive iILC2 cells that are induced in inflammatory circumstances.

Human ILC2 populations have been identified in many sites, including lung (29, 30), intestine (29), nasal polyps (31, 32), skin (25, 33), peripheral blood (34, 35) and adipose tissue (28), and they have been shown to play important roles in various human diseases, such as chronic rhinosinusitis, asthma, atopic dermatitis and obesity. But the existence of iILC2 in human is unknown. Human ROR γ ⁺ ILC3 cells show the plasticity to produce both IL-17/IL-22 and IL-5/IL-13 (36); there is a possibility that those ILC3 cells may represent the human version of mouse iILC2 cells.

Comparison of various ILC2 populations

To clarify the relationship among the various ILC2 populations, we compare the surface markers, cytokine responsiveness and localization of the originally described NH cells, nuocytes and Ih2 cells in terms of our recent proposal that these cells consist of two cell populations, nILC2 cells and iILC2 cells (5, 11–13) (Table 1). NH cells are IL-7R α ⁺ c-Kit⁺ Thy1⁺ ST2⁺, phenotypically identical to nILC2 cells. Although the expression of IL-17RB (which is the receptor for IL-25 and also for IL-17B) was not tested on NH cells, those cells failed to respond to IL-25 alone, suggesting that they lack IL-17RB. Nuocytes are composed of ST2[−] and ST2⁺ cells (ST2 is the receptor for IL-33); the expression of IL-17RB on nuocytes is also heterogeneous. Similar to nuocytes, Ih2 cells can respond to both IL-33 and IL-25, suggesting they express both ST2 and IL-17RB. By contrast, iILC2 cells uniformly express large amounts of IL-17RB and they are all ST2[−]; nILC2 cells uniformly express ST2 and they are IL-17RB[−] or IL-17RB^{low}. Those comparisons lead us to conclude that nuocytes and Ih2 cells are a mixture of ST2-expressing nILC2s and IL-17RB-expressing iILC2 cells, and that NH cells are largely nILC2 cells.

A further potentially confusing property of iILC2 cells is that although they are induced only in response to IL-25 and lack

Table 1. Comparison of various ILC2 populations

	IL-7R α	c-Kit	Thy1	KLRG1	ST2	IL-17RB	Responsiveness to IL-33	Responsiveness to IL-25	Tissue localization
Originally described ILC2 populations									
NH cells	+	+	+	NT	+	NT	Yes	No	FALC
Nuocytes	+	+/-	+	NT	+/-	+/-	Yes	Yes	MLN, small intestine
Ih2 cells	+	+/-	+	NT	NT	NT	Yes	Yes	MLN, spleen, liver, bone marrow
Recently proposed ILC2 populations									
nILC2	+	+	High	Int	+	-/low	Yes	Marginal	Lung
iILC2	+	+/-/low	Low	High	-	+	No	Yes	Lung, MLN, spleen, liver

NT, not tested.

ST2, they become ST2⁺ nILC2-like cells subsequent to IL-25 administration or *N. brasiliensis* infection, thus acting as progenitors of nILC2s or nILC2-like cells. It is possible that the early described nuocytes and Ih2 cells contain cells in transition from iILC2 cells to nILC2 cells.

It becomes apparent that the distinct ILC2 cells localize in different sites and have different phenotypes and cytokine responsiveness. nILC2 cells that reside in adipose tissues (originally NH cells) express ST2 but not IL-17RB and respond to IL-33 only. nILC2 cells in the lung express ST2 and are IL-17RB^{dull} or IL-17RB^{low}; they respond predominately to IL-33 and marginally to IL-25. Skin nILC2s can respond to thymic stromal lymphopoietin (TSLP, which binds IL-7R α in complex with CRLF2; IL-7 binds IL-7R α in complex with γ_c , the 'common' γ chain that is a component of many cytokine receptors) in addition to IL-33 and IL-25 (24, 33).

Cytokine production and regulation of ILC2 cells

ILC2 cells produce effector cytokines in response to stimulation by alarmin cytokines. IL-25, IL-33 and TSLP are the master stimulants of ILC2 activation and cytokine production. Basophil-derived IL-4 has also been suggested to play a role in ILC2 activation during acute papain challenge (37, 38). By sensing and responding to these cytokines, ILC2 cells provide a critical source of type 2 cytokines, particularly very early in infections or in T-cell-deficient mice. The expression of the effector type 2 cytokines IL-13, IL-5 and IL-9 and of granulocyte macrophage colony-stimulating factor potentially triggers eosinophil infiltration, mucus production by goblet cells, macrophage activation, mastocytosis, muscle contraction, tissue repair and metabolic homeostasis (29, 30, 39–46).

Neither IL-25 nor IL-33 stimulation induces IL-4 production by ILC2 cells, although ILC2 cells are capable of making large amounts of IL-4 upon treatment with phorbol 12-myristate 13-acetate (PMA) and ionomycin *in vitro* (8, 11). It has been reported that leukotriene D4 induces IL-4 expression by ILC2 cells (47). Furthermore, nILC2 cell production of amphiregulin plays an essential role in maintaining the integrity of the epithelial barrier during inflammation (48). It has also been reported that nILC2 cells produce methionine-enkephalin (MetEnk) peptides to promote 'beiging' of white adipose tissue and to limit obesity (28) (adipocytes are either 'brown' or 'white'; beiging is the appearance of cells resembling brown adipocytes within white adipose tissue).

iILC2 cells make large amounts of IL-13 and little IL-4 *in vivo*, and are capable of producing large amounts of IL-5 and IL-4 after PMA/ionomycin stimulation *in vitro* (49). It is to be determined that whether iILC2 cells can produce amphiregulin to mediate tissue repair and whether they express MetEnk to contribute to beige fat biogenesis.

Ogg *et al.* proposed that E-cadherin ligation to KLRG1 on human ILC2 cells inhibited IL-5 and IL-13 production by ILC2 cells, thus limiting atopic dermatitis (25). Notably, McKenzie *et al.* have reported that ILC2 cells could directly regulate T cell activation and proposed a cytokine-independent function for ILC2 cells (50). Through their expression of MHC class II, ILC2 cells could present antigen to T cells, triggering T cell-derived IL-2 production. Consequently, such IL-2 would

promote ILC2 proliferation and IL-13 production, amplifying type 2 immune responses. ILC2-derived IL-4 and OX40 ligand on ILC2s have also been reported to contribute to the crosstalk between ILC2 and T cells (51). In addition, during allergic lung inflammation, ILC2-derived IL-13 can promote migration of activated lung dendritic cells into draining lymph nodes where they prime naive T cells to differentiate into T_H2 cells (39). The complex regulation of ILC2 action, both cytokine-dependent and -independent, will be a subject of continuing study over the next several years.

ILC2 development

ILC cells share the common lymphoid progenitor (CLP) with T and B lineage cells. It is believed that a common ILC-specific progenitor (CILP) exists downstream of the CLP, giving rise to Id2⁺ precursors of the cNK killer-ILC lineage and to Id2⁺ precursors of the helper-like ILC lineage. A Lin⁺ Id2⁺ IL-7R α ⁺ α 4 β 7⁺ Flt3⁺ CD25⁺ progenitor, dubbed common helper-like ILC progenitor (CHILP), has been identified that can differentiate into non-NK ILC1 cells, ILC2 cells, and either CCR6⁺ or CCR6⁺ ILC3 cells (52). Through study of a *Zbt16* fate-mapping mouse line, a PLZF⁺ Lin⁺ c-Kit⁺ IL-7R α ⁺ α 4 β 7⁺ common ILC progenitor, designated ILC progenitor (ILCP), has been proposed that is capable of differentiating into non-NK ILC1 cells, ILC2 cells and CCR6⁺ ILC3 cells, but not CCR6⁺ ILC3 cells, which are lymphoid tissue inducer (LTi) cells (53). In addition, an extrahepatic arginase-1⁺ Id2⁺ fetal ILC precursor, termed fILCP, has been identified in the intestine, appearing by embryonic day 13.5. These fILCP cells have the capacity to develop into all the helper-like ILC subsets (54).

Both the cNK lineage and the helper-like ILC lineage rely on the γ_c chain for their development (11, 55). GATA-3 and IL-7R α are required for the development of helper-like ILCs, but not for the development of cNK cells (19, 21, 56–58).

For ILC2 development, GATA-3, ROR α and TCF-1 are critical transcriptional factors. Deletion of GATA-3 in all hematopoietic lineages at a very early developmental stage abolished all helper-like ILCs; deletion of GATA-3 later in development resulted in impaired differentiation of ILC2 cells but not ILC3 cells, suggesting that GATA-3 is essential for both development and maintenance of ILC2 cells (19, 21, 58). ROR α is highly expressed in ILC2 cells, and the development of ILC2 cells, but not other ILC subsets, is significantly impaired in *Rora*-deficient mice (59, 60). TCF-1 and Notch signaling also play a role in ILC2 development (61–63). IL-33 and IL-25 signaling might also play a role in ILC2 development. A normal number of nILC2 cells in the lung are present in ST2 or IL-17RB single knockout mice (5), but combined deletion of ST2 and IL-17RB caused severe reduction in the nILC2 population (9, 12), suggesting that nILC2 cells use IL-33 or IL-25 signaling alternatively for their development.

iILC2 cells represent an induced inflammatory cell population appearing in response to IL-25 or infections. But the source, or the progenitor, of iILC2 cells waits to be identified. The development of iILC2 cells relies on signaling through γ_c - and IL-7R α -containing receptors. While nILC2 cells were completely abolished in *Il7ra*^{−/−} mice, a small number of iILC2 cells was still detectable in such mice (5), indicating that IL-7 plays different roles in the development

of iILC2 cells and nILC2 cells. iILC2 cells are absent in *ROR α* -deficient mice (Y. Huang *et al.*, unpublished data), suggesting that iILC2 and nILC2 cells might share the same ILC2 progenitor (ILC2P) (Fig. 1). The dependence of GATA-3 for iILC2 generation has not been determined. Whether the Id2⁺ CHILP or PLZF⁺ ILCP is the progenitor of iILC2 cells is not yet known.

The plasticity of inflammatory ILC2 cells

In the CD4 lineage, naive cells appear uncommitted as to fate. Their effector phenotype depends on the cytokine environment and type of dendritic cells present during the TCR-based priming process (64). By contrast, ILCs are generally considered to be terminally differentiated cells. They appear to have already adopted a particular phenotype and their cytokine production is dependent on cytokine-based stimulation. For ILC1 cells, the key stimulatory or alarming cytokines are IL-18 and IL-12; for nILC2 cells, IL-33 and/or IL-25; and for ILC3 cells, the combination of IL-1 and IL-23 (1). Whether a single ILC population also had plasticity or flexibility in its cytokine-producing potential was unknown. It has been reported that deficiency of Gfi-1 (a transcriptional repressor that has diverse functions, for example, in hematopoiesis and oncogenesis) leads ILC2 cells to lose their restricted cytokine-production phenotype (49); these *Gfi1*^{-/-} ILC2 cells can produce both IL-13 and IL-17 upon stimulation with PMA plus ionomycin, suggesting that ILCs may have plasticity in their cytokine-producing potential.

This suspicion has been confirmed by the study of iILC2 cells (5). ‘T_h2’ culture conditions, consisting of IL-4, IL-33, anti-IFN- γ and anti-IL-12, cause iILC2 cells to enhance their IL-13/IL-4-producing capacity. ‘T_h17’ culture conditions, including IL-1 β , IL-23, IL-6, transforming growth factor- β , anti-IL-12, anti-IFN- γ and anti-IL-4, result in cells that are good IL-17 producers upon stimulation while still retaining an IL-13-producing capacity, due to co-expression of GATA-3 and ROR γ t. *In vivo*, transferred IL-25-elicited iILC2 cells develop into nILC2-like cells in the later phases of *N. brasiliensis* infection. By contrast, when transferred to mice infected with *Candida albicans*, for which IL-17-dominated responses can be effective, iILC2 cells lose IL-13-producing capacity and become IL-17 single producers. iILC2 cells fail to produce IFN- γ or to express T-bet even when cultured under ‘T_h1’ conditions (IL-12 and anti-IL-4). Thus, although iILC2 cells lack antigen-specific receptors, they read and distinguish types of microbial pathogens through epithelium-derived cytokines and display the plasticity to be converted into distinct cytokine producers, to react properly and to orchestrate immune responses.

Conclusion

According to our proposal, ILC2 cells can be grouped into two distinct types—nILC2 cells and iILC2 cells. nILC2 cells represent tissue-resident ST2⁺ ILC2 cells; they are present in steady state and primarily respond to IL-33. iILC2 cells represent IL25-induced ST2⁻ IL-17RB⁺ ILC2 cells; they are

Fig. 1. Lineage map of ILC2 development. Both nILC2 and iILC2 share the same progenitor (CHILP) with other helper-like ILC lineages, according to the dependence on IL-7 signaling. *ROR α* is critical for the development of both nILC2 and iILC2, suggesting the possible existence of an ILC2 progenitor. But it is also possible that iILC2 cells develop directly from CHILP or directly from the ILCP.

undetectable in steady state but can be rapidly elicited by IL-25 or infections. Several surface markers, including KLRG1, ST2, IL-17RB and Thy1, help to define and distinguish these two ILC2 groups. In addition, iILC2 cells can be the transient progenitors of nILC2 cells, and iILC2 cells also have the plasticity to become ILC3-like cells during 'ILC3-associated' infection.

Why the originally described ILC2 populations reported by separate research groups had different phenotypes was confusing. This enigma has been solved by our identification of iILC2; the heterogeneous phenotype of nuocytes or Ih2 cells can be explained by their being mixtures of nILC2 and iILC2. But new puzzles emerge. What and where are the progenitors to iILC2 cells? What is developmental relationship between nILC2 and iILC2? Is there any difference in physiological function between nILC2 and iILC2? These important questions wait to be answered.

Funding

Division of Intramural Research, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health.

Acknowledgements

All animal experimentation carried out by our group and described in this article was performed in accord with approved procedures of the NIAID Division of Intramural Research Animal Care and Use Committee.

Conflict of interest statement: The authors declared no conflict of interests.

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