HHS Public Access

Author manuscript

Immunol Lett. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Immunol Lett. 2016 November ; 179: 19–24. doi:10.1016/j.imlet.2016.07.005.

Diversity and function of group 1 innate lymphoid cells

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Abstract

Innate lymphoid cells (ILCs) are a heterogeneous population of cells with diverse roles in immune responses. Three major groups of ILCs have been defined on the basis of similarity in their production of signature cytokines, developmental requirements, and phenotypic markers. Group 1 ILCs produce IFN-γ, express the T-box transcription factors (TF) Eomesodermin (Eomes) and/or T-bet. Group 2 ILCs secrete IL-5 and IL-13, express the TF GATA-3, and are identified by the expression of KLRG1, the receptor IL-7 (IL7R, also known as CD127), and the receptor for IL-33 (IL33R). Finally, group 3 ILCs produce IL-22 and IL-17 and express the TF RORγt along with the cell surface receptors CD127, NKp46, and CCR6. In this review, we will briefly overview each group in terms of phenotype, function and development and then focus more extensively on group 1 ILCs, expanding on their emerging diversity, their disparate functions and the differences between NK cells and ILC1.

Introduction

Innate lymphoid cells (ILCs) are a heterogeneous population of cells with diverse roles in immune responses (Cella et al., 2014; Cortez et al., 2015; Diefenbach et al., 2014; Eberl et al, 2015). ILCs are classified as innate cells because they do not require the RAG proteins developmentally; moreover, ILCs are considered lymphoid cells because they derive from the common lymphoid progenitor (CLP). Three major groups of ILCs have been defined on the basis of similarity in their production of signature cytokines, developmental requirements, and phenotypic markers (Fig. 1). Group 1 ILCs produce IFN-γ, express the T-box transcription factors (TF) Eomesodermin (Eomes) and/or T-bet, and, in mice, are distinguished by the expression of the cell surface receptors NK1.1 and NKp46. Group 2 ILCs secrete IL-5 and IL-13, express the TF GATA-3, and are identified by the expression of KLRG1, the receptor IL-7 (IL7R, also known as CD127), and the receptor for IL-33 (IL33R). Finally, group 3 ILCs produce IL-22 and IL-17 and express the TF RORγt along with the cell surface receptors CD127, NKp46, and CCR6. In this review, we will briefly overview each group in terms of phenotype, function and development and then focus more

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extensively on group 1 ILCs, expanding on their emerging diversity, their disparate functions and the differences between NK cells and ILC1.

Group 1 ILCs

Group 1 ILCs are defined based on their capacity to produce IFN-γ and are composed of at least two cell types, conventional NK cells and ILC1 (Cortez et al., 2015; Erick and Brossay, 2016; Sojka et al., 2014a) (Fig. 1). NK cells are present in numerous sites as they recirculate between the blood and tissues. ILC1 are tissue resident cells (and therefore also called tissue-resident NK cells) and have been identified in the liver, gut, spleen, skin, peritoneum, uterus, and salivary glands (Cortez et al., 2014; Crotta et al., 2014; Daussy et al., 2014; Fuchs et al., 2013; Gasteiger et al., 2015; Gonzaga et al., 2011; Klose et al., 2014; Seillet et al., 2014a; Sojka et al., 2014b). In mice, group 1 ILCs are phenotypically distinguished from other ILCs by their expression of the receptors NKp46 and NK1.1 (in mice expressing the *Nkrp1* epitope recognized by anti-NK1.1). IL-15 signaling is also needed for both NK and ILC1 development. A defining distinction between NK cells and ILC1 is the expression of the TFs Eomes and T-bet: NK cells are Eomes^{+}T-bet^{+} and require both TF to develop; ILC1 are Eomes^{-}T-bet^{+} and are dependent on T-bet but not Eomes for development. NK cells have been well studied in the context of viral and tumor immunity, however the contributions of ILC1 to various immune responses is currently under active investigation.

Group 2 ILCs

Group 2 ILCs (also known as nuocytes, natural helper cells, innate helper 2-I$_{H}$2) produce IL-5 and IL-13 in response to IL-25, IL-33 and TSLP (Cella et al., 2014; Cortez et al., 2015; Diefenbach et al., 2014; Artis and Spits) (Fig. 1). ILC2s are defined by expression of CD127, CD90, IL33R, KLRG1 and the TF GATA-3, whereas they lack other lineage markers, such as pan NK cell markers. Developmentally, ILC2s require IL-7 signaling and the TFs RORα and GATA-3. ILC2s are tissue resident cells and large populations have been found in the intestines and lungs (Gasteiger et al., 2015). Like TH2 cells, which produce similar cytokines, ILC2s contribute to immune responses directed against parasites and have been implicated in immune-mediated respiratory diseases.

Group 3 ILCs

Group 3 ILCs were initially described in human tissues as mucosal-associated lymphoid cells that expressed some NK cell markers, such as NKp44, and produced IL-22 (Cella et al., 2009). ILC3s now encompass several cell types: lymphoid tissue inducer (Lti) cells, which include both fetal Lti and adult Lti-like cells; NKp46^{-} ILC3; and NKp46^{+} ILC3 (Colonna, 2009; Cortez et al., 2015; Wojno and Artis, 2012) (Fig. 1). ILC3s require IL-7 signaling for their development and the TFs RORγt and aryl hydrocarbon receptor (AHR) (Lee et al., 2012b, 2012c). ILC3s express CD127, the receptors for IL-1 (IL1R) and IL-23 (IL23R). Some ILC3 express NKp46, while LTi cells can be CD4^{+}. They produce IL-22 and IL-17 upon stimulation with IL-23 and IL-1β. ILC3-derived IL-22 promotes protective immunity by maintaining epithelial integrity and is required to initiate antimicrobial programs of epithelial cells during bacterial infection (Lee et al., 2012b). LTi cells are also critical for the

development of secondary lymphoid tissues. Under certain conditions, ILC3s may also facilitate excessive intestinal inflammation and promote intestinal cancer (Kirchberger et al., 2013; Song et al., 2015).

Developmental pathways of ILCs

ILCs derive from the common lymphoid progenitor (CLP), which resides in the bone marrow (BM) and can give rise to B and T cells, as well as all ILC lineages (Yu et al., 2014) (Fig. 1). Downstream of the CLP, the CXCR6^{+} $\alpha_4\beta_7{}^{+}$ CLP (αLP), also known as the common innate lymphoid progenitor CILP (Yu et al., 2014), is a progenitor cell that gives rise to all ILCs but not T or B cells. This progenitor is capable of faithfully differentiating into all known ILC populations, including Eomes^{+} NK cells, Eomes^{-} ILC1s, ILC2s, NKp46^{+} ILC3s, NKp46^{-} ILC3s, and CD4^{+} LTi-like cells.

After the αLP, lineage divergence of ILC populations occurs via the CHILP (Common Helper-Like Innate Lymphoid Progenitor) (Klose et al., 2014). The CHILP was identified through the use of reporter mice for the transcriptional repressor Id2 and characterized as Id2^{+}Lin^{-}IL-7R$^{+}\alpha_4\beta_7{}^{+}$CD25^{-}. The CHILP can give rise to Eomes^{-} ILC1s, ILC2s, NKp46^{+} ILC3s and NKp46^{-} ILC3s including the CD4^{+} LTi-like subset, but not Eomes^{+} NK cells. Downstream of the CHILP is the ILCP (innate lymphoid cell precursor), which was identified through lineage tracing experiments for the TF PLZF (Constantinides et al., 2014). The ILCP was distinguished as PLZF^{high}Lin^{-}IL-7R^{+}cKit$^{+}\alpha_4\beta_7{}^{high}$CXCR6^{-} and found to differentiate to Eomes^{-} ILC1s, ILC2s, and some ILC3s, but not Eomes^{+} NK cells or LTi-like subsets.

NFIL3 has also been identified as a master TF required for the development of multiple ILC lineages. NFIL3 was initially reported to be critical for the development of NK cells (Gascoyne et al., 2009; Kamizono et al., 2009). However, subsequent studies found a defect in ILC1s, ILC2s, and ILC3s in peripheral sites (Geiger et al., 2014; Seillet et al., 2014b). Moreover, *Nfil3*$^{-/-}$ mice have been reported to lack the αLP and CHILP; thus, it seems that NFIL3 acts to sustain the earliest ILC progenitors (Xu et al., 2015; Yu et al., 2014). However, we and others have found that ILC1 subsets in some tissues do not require NFIL3 for development (Boulenouar et al., 2016; Cortez et al., 2014; Seillet et al., 2014a; Sojka et al., 2014b). Moreover, NK cells were also found to develop independently of NFIL3 during viral infection (Firth et al., 2013). Thus, it is possible that unique factors present during infections or in certain tissues sustain ILC development in the absence of NFIL3, or that these cells derive from alternative progenitor populations.

NK cells and ILC1s: different cells or distinct developmental stages of the same cell?

Group 1 ILCs are composed of at least two subsets, conventional Eomes^{+} NK cells and Eomes^{-} ILC1s. There is some discrepancy in the literature regarding the relationship between NK cells and ILC1s. The original view is that Eomes^{-} ILC1s are immature NK cells (iNK) that have not fully developed their cytolytic potential, whereas Eomes^{+} NK cells in the tissues are mature NK cells (Gordon et al., 2012; Kim et al., 2002; Takeda et al.,

2005). A more recent viewpoint is that Eomes$^+$ NK cells are developmentally distinct from Eomes$^-$ ILC1s, which share a common developmental origin with ILC2s and ILC3s. Below we provide arguments to support the proposal that Eomes$^+$ NK cells and Eomes$^-$ ILC1s are the two extremes of a broad spectrum of cells with partially distinct origins and disparate functions that, together, constitute group 1 ILCs.

The original view: ILC1s as iNK cells

Conventional NK cell development occurs primarily in the BM and progresses through several stages that can be demarcated by the expression of specific cell surface markers and transcription factors (Geiger and Sun, 2016; Sun and Lanier, 2011; Yokoyama et al., 2004). The NK cell progenitor (NKP), which is a CD122$^+$Lin$^-$ cell, gives rise to iNK cells, which express NK1.1 and T-bet. As iNK cells progress to mature NK cells they begin to express NKp46, CD49b (also called VLA2 and DX5), and Eomes. Mature NK cells also variably express Ly49 inhibitory receptors that bind self-MHC class I molecules. Inhibitory signaling by these receptors is necessary for the acquisition of full effector capacity of mature cells, a process termed NK cell licensing (Elliott and Yokoyama, 2011; Yokoyama and Kim, 2006). Mature NK cells then exit the BM, circulate and reach peripheral tissues, where high expression of CD11b and CD43 can further delineate NK cells with more robust effector capacity.

The presence of a substantial population of NK1.1$^+$CD3$^-$ cells that resemble iNK cells due to their lack of maturation markers such as CD49b, CD11b, CD43, Ly49, and Eomes was originally observed within the liver of adult mice (Gordon et al., 2012; Kim et al., 2002; Takeda et al., 2005). These cells also preferentially expressed the death-inducing ligand TRAIL, which is not observed on adult BM or splenic NK cells. Fetal and neonatal NK cells from the liver, spleen, and BM were also found to express TRAIL and lack markers of mature NK cells such as CD49b. However, a time course examination revealed that, as mice aged, NK cells in the spleen and BM no longer expressed TRAIL but expressed CD49b, suggesting a link between aging and NK cell maturation. Importantly, purification of each population from the liver based on CD11b or TRAIL expression followed by transfer to host mice revealed that CD11b$^-$TRAIL$^+$ cells could give rise to the CD11b$^+$TRAIL$^-$ cells, but conversely CD11b$^+$TRAIL$^-$ cells did not give rise to CD11b$^-$TRAIL$^+$ cells. Altogether these results seem to indicate that CD49b-Eomes$^-$TRAIL$^+$ cells in the liver are iNK cells, which give rise to mature CD49b$^+$Eomes$^+$TRAIL$^-$ NK cells.

Tracing development of ILC1 and NK cells

The paradigm of liver iNK cells as precursors of mature NK cells was challenged through the use of reporter mice in which GFP was inserted into the 3′ end of the Eomes gene (Daussy et al., 2014). In these mice, the earlier phenotypic description of the two liver cell populations was fully recapitulated: GFP$^-$ (Eomes−) cells lacked expression of CD49b, had reduced expression of CD11b and Ly49, and expressed TRAIL, whereas the GFP$^+$ (Eomes$^+$) cells had the opposite phenotype. However, after transfer of purified GFP$^+$ or GFP$^-$ cells into host mice, GFP$^-$ (Eomes$^-$) cells did not give rise to GFP$^+$ (Eomes$^+$) cells in the liver or spleen. Even *in vitro* culture of GFP$^-$ cells with NK cell activating cytokines, such as IL-15

and IL-12, could not induce the upregulation of GFP, arguing that Eomes$^-$ cells are not iNK cells that give rise to mature Eomes$^+$ NK cells. While the discrepancies between the results of the different transfer experiments remain unexplained, it is possible that Eomes-driven GFP expression more faithfully distinguishes cell types than does TRAIL or CD11b expression, allowing for greater purity of cells before transfer.

Further evidence that Eomes$^-$CD49b$^-$ cells in the liver are not iNK cells has been found in studies examining ILC progenitor populations. One study used mice expressing GFP-Cre recombinase downstream of the TF PLZF, which were crossed with mice carrying a YFP gene downstream of a flox-stop-flox cassette in the ROSA26 locus (Constantinides et al., 2015). This experiment allowed for the identification of cells that actively expressed PLZF (YFP$^+$GFP$^+$), as well as cells that had expressed the TF at some point during their development (YFP$^+$GFP$^-$). While neither population of "NK" cells in the liver were GFP$^+$, CD49b$^-$ cells were strongly YFP$^+$ whereas the CD49b$^+$ cells were mostly YFP$^-$, as were CD49b$^+$ spleen NK cells. This result corroborated that CD49b$^-$Eomes-TRAIL$^+$ liver cells do not give rise to mature CD49b$^+$Eomes$^+$TRAIL$^-$ NK cells and in fact are a separate ILC subset designated ILC1.

Differential requirements of ILC1s and NK cells for Eomes and Tbet

Further support for a distinction between ILC1 and NK cells came from the analysis of their requirements for the TFs Eomes and T-bet. NK cells express Eomes and Tbet, whereas ILC1s only express T-bet. Moreover, mice that lack Eomes in hematopoietic cells do not have NK cells but maintain ILC1s (Gordon et al., 2012; Klose et al., 2014; Pikovskaya et al., 2016). In contrast, T-bet deficient mice lack ILC1s and have significantly fewer NK cells in the spleen, lung, and liver, although NK cells are present in the BM and small intestine (Sojka et al., 2014b). Together, studies of lineage tracing, differentiation of progenitor cells, and dependence on Eomes and T-bet provide considerable evidence that NK cells and ILC1s may be distinct cell types. Moreover, ILC1s can be classified along with ILC2s and ILC3s as helper-like cells that represent the innate counterparts of CD4$^+$ T helper cells, while NK cells can be viewed as a separate subset of cytotoxic ILCs that are the innate counterparts of CD8$^+$ T cells (Diefenbach et al., 2014; Klose et al., 2014; Serafini et al., 2014; Yagi et al., 2014; Zhong et al., 2016).

NK cells and ILC1s belong to the same ILC group

Despite developmental evidence, this helper versus cytolytic view of ILC1s and NK cells may be simplistic and conceal many developmental, functional, and phenotypical similarities between NK cells and ILC1s. A model in which NK cells and ILC1s are classified together as group 1 ILCs may be more appropriate (Fig. 1). First, it should be emphasized that by the broadest definition of the term, NK cells are ILCs because they do not require RAG proteins and derive from the CLP (Geiger and Sun, 2016; Yokoyama et al., 2004). The discovery of the αLP, which gives rise to all ILC populations and NK cells but not T or B cells, further substantiates this view (Yu et al., 2014). With regard to the gamma chain cytokine required for development, both NK cells and ILC1s mainly rely on IL-15 signaling for their development, whereas ILC2s and ILC3s are largely dependent upon IL-7

(Cortez et al., 2015). Although ILC1s express CD127, IL-7 is dispensable for their development (Daussy et al., 2014; Klose et al., 2014). Therefore, CD127 expression should be viewed as one of many phenotypic differences between ILC1s and NK cells, rather than a defining characteristic.

Transcriptome analysis of mouse ILC populations from multiple mouse tissues confirmed that NK cells and ILC1s are more similar to each other with regard to their gene expression, than they are to ILC2s and ILC3s (Robinette et al., 2015). Phenotypic analyses of mouse NK cells and ILC1s corroborated in addition to NKp46 and NK1.1 (in mice expressing the *Nkrp1* epitope recognized by anti-NK1.1) these cells also share expression of other pan-NK markers such as NKG2D, NKG2A/C/E, and possibly some Ly49 family members (Cortez et al., 2014; Daussy et al., 2014; Fuchs et al., 2013; Gordon et al., 2012; Klose et al., 2014; Seillet et al., 2014a; Sojka et al., 2014b).

Another compelling reason for classifying both ILC1s and NK cells as group 1 ILCs is based upon their functional capacities. Both cell types rapidly produce IFN-γ upon stimulation with activating cytokines such as IL-12 and IL-18 (Cortez et al., 2015). Additionally, although liver ILC1s and NK cells express different levels of granzymes and perforin (Daussy et al., 2014), both cell types are capable of cytolytic degranulation and can mediate the killing of target cells at comparable levels (Daussy et al., 2014; Kim et al., 2002; Sojka et al., 2014b; Takeda et al., 2005). ILC1s express high amount of granzyme C, which has been reported to induce apoptosis in a manner similar to other granzymes, highlighting the cytotoxic potential of ILC1s (Cai et al., 2009; Getachew et al., 2008; Johnson et al., 2003). Thus, NK cells and ILC1s share similar defining effector mechanisms: IFN-γ production and cytotoxicity. ILC1s also express TRAIL, which can induce killing of target cells expressing the TRAIL receptor, bestowing ILC1s with an additional capacity to induce cell death. While NK cells have been extensively studied for their roles in viral infection and tumor rejection, it is currently unclear to what extent ILC1s have distinct, complementary, or redundant functions in these contexts or whether they predominantly act in discrete types of immune responses.

ILC1s have unique tissue residency features

One noticeable feature that distinguishes ILC1s from NK cells is their expression of markers associated with tissue residency, such as CD49a and CD69. CD49a (also known as VLA-1) is an integrin which can bind collagens and is associated with homing to non-lymphoid tissues (Meharra et al., 2000). CD69 inhibits sphingosine-1-phosphate (S1P) receptor 1 (S1PR1), thereby blocking egress from tissues in response to S1P gradients (Shiow et al., 2006). In contrast, ILC1s lack CD62L, a selectin that mediates homing to lymphoid organs and is highly expressed by a population of NK cells (Rosen, 2004). This tissue resident phenotype is reminiscent of tissue resident memory T cells, which reach peripheral sites through the blood after priming and expansion in secondary lymphoid organs and blood and remain there indefinitely to prevent reinfections (Carbone et al., 2013; Mackay et al., 2013; Zhang and Bevan, 2013). Indeed, parabiosis experiments have revealed that ILC1s are *bona fide* tissue resident cells, in contrast to NK cells which recirculate between the blood and tissues (Gasteiger et al., 2015; Sojka et al., 2014b).

ILC1s from various tissues were also found to express significantly more CXCR6 mRNA than NK cells. While the analysis of CXCR6-deficient mice has led to conflicting results on the impact of CXCR6 on total ILC1 numbers in tissues (Chea et al., 2015; Robinette et al., 2015; Satoh-Takayama et al., 2014), it is possible that CXCR6 may be important for positioning ILC1s in specific locations crucial for immune responses.

Group ILC1s include more subsets: the example of salivary gland ILCs

Although NK cells and ILC1s are the two major types of group 1 ILCs, this group may encompass other cells. Certain ILC3 populations are capable of down-regulating RORγt and upregulating T-bet expression. These cells also upregulate NK1.1 and NKp46 and are capable of producing IFN-γ (Klose et al., 2013). Furthermore, these ex-RORγt ILC3s are dependent on T-bet, similar to other ILC1s (Fig. 1).

Recent studies on salivary gland (SG) ILCs also indicate that NK cells and ILC1s are not the only cells that meet the criteria for group 1 ILCs. The SGs are exocrine glands that produce copious amounts of saliva, about one liter a day, to maintain the integrity of the oral environment (Treuting and Dintzis, 2012). Saliva is a complex mixture of various proteins that have multiple functions in promoting digestion, homeostasis of the oral cavity, and immunity (Fábián et al., 2012; Feller et al., 2013; Treuting and Dintzis, 2012). SGs contain T cells, B cells, and antigen presenting cells, which are thought to promote a largely tolerogenic environment (Commins, 2015; Novak et al., 2008). SGs are also sites for production of sIgA (Brandtzaeg, 2007; Teeuw et al., 2004), which bind bacteria and inhibit their adhesion to epithelial surfaces. Interestingly, $CD3^{-}NK1.1^{+}$ cells are very numerous in this tissue and can represent up to 50% of total $CD45^{+}$ cells (Cortez et al., 2014; Tessmer et al., 2011). These $CD3^{-}NK1.1^{+}$cells had previously been characterized as iNK cells with reduced functional capacity (Tessmer et al., 2011). However, we found that these cells have an intermediate phenotype, with features of both NK cells and ILC1s (Cortez et al., 2014; Cortez et al., 2016). SG $CD3^{-}NK1.1^{+}$ cells express both CD49a and CD49b, in contrast to NK cells, which are $CD49a^{-}$ $CD49b^{+}$, and ILC1s that are $CD49a^{+}CD49b^{-}$. Like ILC1s, SG $CD3^{-}NK1.1^{+}$ cells express tissue residency markers, including CD49a, CD69, CD103, as well as the death-inducing molecule TRAIL, and very little or no CD62L. Like NK cells, SG $CD3^{-}NK1.1^{+}$ cells express NKp46, NKG2D, as well as activating and inhibitory Ly49 family members, such as Ly49H and Ly49G2. Gene expression analysis of SG $CD3^{-}NK1.1^{+}$ cells and comparison with transcriptional profiles of ILC1s, ILC2s, ILC3s, and NK cell populations confirmed that SG $CD3^{-}NK1.1^{+}$ cells form a separate ILC cluster within the group 1 ILCs that is distinct from spleen and liver NK cells as well as from liver, spleen, and intestinal intraepithelial ILC1s.

SG $CD3^{-}NK1.1^{+}$ ILCs also have unique features that distinguish them from both NK cells and ILC1s. Indeed, they are ineffective at production of IFN-γ and have reduced surface staining of CD107a, a marker of cytolytic degranulation. In fact, SG $CD3^{-}NK1.1^{+}$ ILCs are capable of alternative functions that neither NK cells nor ILC1s possess. SG $CD3^{-}NK1.1^{+}$ ILCs amply express CD39, a surface enzyme that breaks down ATP and ADP to AMP (Antonioli et al., 2013a) and CD73, a 5'ectonucleosidase that functions to convert AMP to adenosine (ADO). Together, CD39 and CD73 mediate the degradation of inflammatory ATP

and the production of anti-inflammatory ADO. In summary, SG $CD3^{-}NK1.1^{+}$ ILCs have features characteristic of both NK cells and ILC1s in addition to notable functional traits unique to themselves and hence are a novel population of group 1 ILCs that is distinct from NK cells and ILC1s (Fig. 2).

Concluding remarks

In conclusion, group 1 ILCs are a heterogeneous population of IFN-γ-producing cells, which also have cytolytic potential in different contexts. While functionally similar, NK cells and ILC1 derive from distinct progenitors and have differential expression and requirements for the TFs Eomes and T-bet. One striking difference between the two cell types is that ILC1 are tissue resident and express markers that promote this feature. The SG also maintains a population of tissue resident ILCs with a gene expression profile that is intermediate between ILC1 and NK cells. Unlike NK cells and currently defined ILC1, SG ILC1 are not dependent upon Tbet or Eomes, although both TF are expressed. SG ILC1 are also poor producers of IFN-γ but have additional functionalities including the capacity to generate immune suppressive adenosine from ATP. Thus, SG ILCs may represent a population that preferentially reduces inflammation and promotes immune suppression, a function that is in line with the immune privilege of the salivary gland. The unique function of this group 1 ILC within SG suggests other ILC1 may be functionally geared toward specific responses in their tissue of residency.

Acknowledgments

This work was supported by NIH awards UO1 AI095542, RO1 DE021255 and RO1 DK103039. We thank Susan Gilfillan for critical comments.

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Highlights

- ILC1 and NK cells are IFN-γ-producing cells
- ILC1 are tissue resident, NK cell recirculate
- Salivary gland ILC1 are poor producers of IFN-γ
- Salivary gland ILC1 generate adenosine from ATP

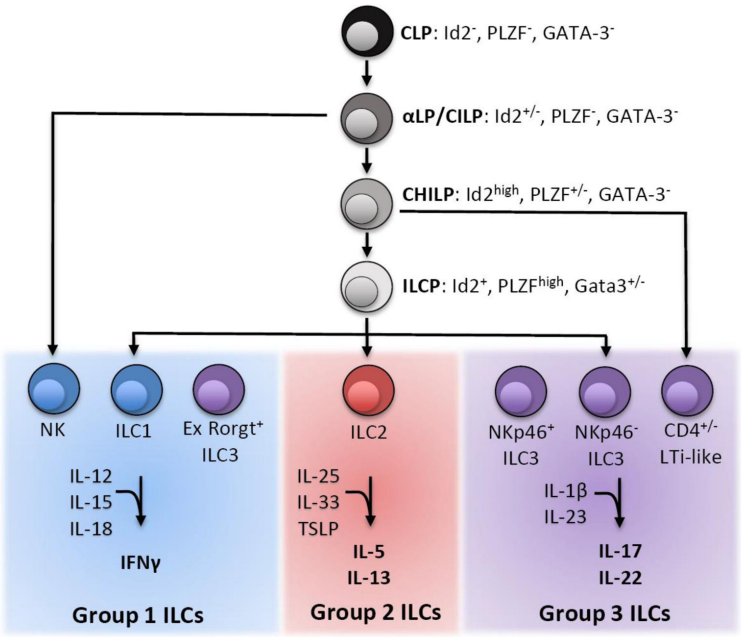

Figure 1. Development and diversity of mouse ILCs

Three major groups of ILCs have been defined on the basis of signature cytokines, developmental requirements, and marker expression ILCs. Top panel depicts the developmental pathway leading to ILC development. CLP, common lymphoid progenitor; aLP, $\alpha_4\beta_7$ expressing CLP; CILP, common innate lymphoid progenitor; CHILP, Common Helper-Like Innate Lymphoid Progenitor; ILCP, innate lymphoid cell precursor. Bottom panels indicate ILCs groups, their subsets and the stimuli that induce the secretion of signature cytokines IFNγ, IL5/IL13, IL17/IL22.

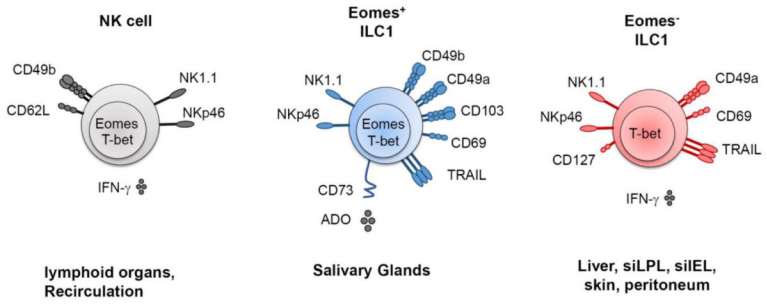

Figure 2. Diversity of group 1 ILCs

Group 1 ILCs consist of at least three major cells types: conventional NK cells, Eomes^{-} ILC1, and Eomes^{+} salivary glands ILC1. Major phenotypic cell surface markers, transcription factors and markers and secreted products are indicated. ADO, adenosine.