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Natural killers or ILC1s? That is the question

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Abstract

Group 1 innate lymphoid cells (ILCs) comprise the natural killer (NK) cells and ILC1s. Both cells co-exist in peripheral tissues and despite effort to characterise the molecular identity and developmental pathways of ILC1s however their relationship with NK cells remains elusive. ILC1s and NK cells share many common features and analysis of ILC1s in tissues revealed a great heterogeneity and distinct transcriptional requirement of each ILC1 subsets complexifying the organisation of this group. Here, we discuss whether ILC1 and NK cells can be considered as distinct lineages based on their origin, location, phenotype or transcriptional regulation. Discrimination of NK cells and ILC1s represent an important challenge to unravel the individual functions of these cells during infection and tumour immunosurveillance.

Keywords

innate lymphoid cells; ILC1; NK cells; phenotype; transcriptional regulation; development; function; lineage

1. Introduction

Innate lymphoid cells (ILCs) provide the first line of defense against invading pathogens and are also involved in tissue repair [1]. Unlike T and B lymphocytes, ILCs develop

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DECLARATION OF INTERESTS

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independently of the recombinant activating gene (RAG), and their activity is not, therefore, regulated by antigen-specific receptors. Instead, their activity is dependent on cytokines, the engagement of activating and inhibitory receptors, and physiological signals from their microenvironment. They were initially classified into three subsets on the basis of the cytokines and transcription factors they express: group 1 ILCs (ILC1s), group 2 ILCs (ILC2s) and group 3 ILCs (ILC3s), which mirror the functions of T helper (h) 1, Th2 and Th17 cells, respectively. The classification of ILCs has recently been expanded to five groups, with the addition of NK cells and lymphoid tissue-inducer cells (LTi), previously classified as ILC1s and ILC3s, respectively, as distinct subsets [2]. This new classification is based on the evidence for distinctive developmental pathways for each of these subsets [3–8].

However, within group 1 ILCs, the definition of ILC1s and NK cells has been challenged by comparisons of these populations in different tissues, at steady state or in inflammatory conditions. Analyses of these populations at single-cell level have revealed considerable heterogeneity in the ILC1 subsets residing within tissues. It therefore remains unclear whether ILC1s and NK cells correspond to different developmental stages, activation states, functional plasticity or the imprinting of particular tissue microenvironments on the same lineage.

2. Do ILC1s and NK cells have different origins?

Not really

The developmental relationship between ILC1s and NK cells remains a matter of debate. All ILCs develop from common lymphoid progenitors (CLPs) in the fetal liver and adult bone marrow. The induction of the transcription factors Nfil3 and ID2 leads to the emergence of the innate lineage, which is characterized by the induction of $\alpha_4\beta_7$ on a subset of CLPs [8,9]. The resulting common innate lymphoid progenitors (CILPs) do not generate B and T cells, but can generate all ILC subsets *in vivo*. The identification a common helper-ILC progenitor (CHILP) suggested the existence of a branch between the ILC and NK cell lineages, as no NK cells were generated following the adoptive transfer of CHILPs. However, the distinction between CILPs and CHILPs is not clear, as these two types of progenitor seem to have very similar patterns of surface marker and transcription factor expression. The expression of PLZF in the ILC precursor (ILCp) marks the bifurcation of LTi and NK cells from the other ILC1, 2 and 3 subsets [4]. However, a fate mapping experiment showed that 25% of NK cells had expressed PLZF, suggesting NK cells and ILC1 share a progenitor expressing PLZF or that ILC1s might acquire an NK cell phenotype. Indeed, a recent analysis of the progenitor in triple reporter (ID2, PZLF and Bcl11b) mice revealed that $Id2^+Zbtb16^+$ CILPs retained the potential to generate NK cells [10**]. These data suggest that ILC progenitors retain the potential to generate ILC1s and NK cells, as currently defined, and that the type of cell actually generated depends on the microenvironment and the signals received by progenitor.

In humans, $CD117^+$ cells in the bloodstream or tissues can give rise to all ILC subsets, including NK cells, *in vitro* and *in vivo* [11]. Unbiased hierarchical stochastic neighbor-embedding (HSNE) analyses of blood $CD117^+$ ILCs revealed that the

$CD117^{+}CRTH2^{-}NKp44^{-}$ ILC population could be split into different subsets on the basis of KLRG1 and NKp46 expression. KLRG1-expressing ILCs correspond to a transitional stage of ILC2s, but they retain the potential to give rise to other ILC subsets if stimulated with appropriate signals. By contrast, NKp46-expressing ILCs give rise exclusively to ILC3s and ILC1s [12*]. CD200r, which can be used to distinguish between ILC1s and NK cells in mice [13], is also expressed on all human ILCs, but not on NK cells [12*]. This receptor can, therefore, be used to distinguish between NK cells and ILC1s in both humans and mice.

3. Can we define ILC1s and NK cells on the basis of their location and phenotype?

Yes, but essentially only at steady state.

One key characteristic distinguishing ILC1s from NK cells is their location: ILC1s reside in tissues, whereas NK cells recirculate in the bloodstream [14]. A careful analysis of $NKp46^{+}$ cells in diverse tissues revealed that several ILC1 subsets co-exist with NK cells (Figure 1).

Intrahepatic ILC1s were the first ILC1 subset distinctly different from NK cells to be discovered [15]. This unique subset was initially thought to correspond to immature NK cells, as the cells lack expression of most of the Ly49 molecules, CD49b and the transcription factor Eomesodermin (Eomes), which control the maturation of the NK cells, but express the death-inducing ligand TRAIL [15,16]. Transcriptional analyses of hepatic $TRAIL^{+}$ ILC1s and $CD49b^{+}$ NK cells showed that liver ILC1s displayed a unique expression patterns for chemokine receptors and adhesion molecules, including CXCR6, CXCR3, CD103, CD49a, CD69, and CD39; cytokine receptors, such as IL-7Rα, IL-17RD, IL-21R, and TGF-βR; and regulatory molecules, such as CD200R, PD1-L, ICOSL, and Lag3 [6,17,18]. Single-cell multiplex transcriptional analyses of liver $NK1.1^{+}$ $NKp46^{+}$ cells identified four clusters and revealed the presence of more than two subsets in the liver [19]. Eomes was detected in one of the hepatic ILC1 subgroups and was differentially expressed between NK subsets. These findings suggest that the use of Eomes expression to distinguish between ILC1 and NK cells may not be appropriate.

Thymic NK cells or ILC1s?

There is also some debate about the identity of $NKp46^{+}$ cells in the thymus. These cells were first described as NK cells, but their particular phenotype, including low levels of Ly49 and high levels of IL-7Rαand CD69 expression, and their requirement for the transcription factor GATA-3 for development, as reported for ILC1s [20], suggested that they might actually correspond to an ILC1 subset [21]. However, they also express Eomes and CD49b, which are generally associated with the NK cell lineage. Recent studies have shown that the NK1.1-expressing cells in the thymus are heterogeneous, with the majority of these cells having an ILC1-like phenotype ($CD122^{+}NK1.1^{+}CD127^{+}CD49b^{-}$), and a minority presenting an NK-cell phenotype ($CD122^{+}NK1.1^{+}CD127^{+}CD49b^{+}CD11b^{low}$). The cells of the $CD49b^{-}$ population express CD49a and CD103, but not Eomes, consistent with currently used definitions of ILC1s. However, the authors found that this population of $CD49b^{-}$ cells was absent from $Rag1^{-/-}$ mice and tested positive for CD1d tetramers, suggesting that they may belonged to the NKT lineage rather than the ILC1 lineage [22*] (Figure 1).

Salivary gland ILC1s or TGF-β-imprinted NK cells?

As in the liver, NKp46$^+$ cells in the salivary gland were originally described as unconventional NK cells [23], however more recent analysis revealed that both NK cells and ILC1 co-exist [24]. ILC1 in the salivary gland are phenotypically close to those found in the liver, expressing CD49a, CD103, CXCR6, IL21R and CD69 [25]. However, salivary gland ILC1s also display some transcriptional features common to NK cells, such as the expression of *Eomes* and Ly49H, and a lack of CD127 (Figure 1). Salivary gland ILCs therefore provide another example of ILCs producing transcripts considered characteristic of both ILC1s and NK cells. The lack of TGF-β signaling triggers a loss of ILC1-associated markers, including CD49a, CD103 and CD69, on salivary gland NKp46$^+$ cells, but not on liver and intestinal ILC1s [25]. Moreover, recent studies have shown that tumor microenvironments enriched in TGF-β can modulate the features of NK cells, resulting in the acquisition of features characteristic of ILC1s and the downregulation of EOMES expression [26**]. These findings raise questions as to whether the microenvironment leaves an imprint on NK cells and induces the expression of ILC 1-associated markers. For a formal definition distinguishing between ILC 1 and NK cells, improvements are required in our understanding of the transcriptional requirements and expression profiles of these cells.

Intestinal ILC1s

In the small intestine, single-cell RNA-seq on the entire CD127$^+$ cell population highlighted the complexity and diversity of ILC states [27]. As only CD127$^+$ cells were analyzed, this analysis excluded a large proportion of NK cells and did not, therefore, fully capture all the diversity of group 1 ILCs [27]. However, it nevertheless revealed the existence of four clusters within the ILC1 group, with a gradient of *Tbx21* expression among ILC1s. The ILC1a cluster expressed *Gata3*, suggesting possible involvement in the plasticity between ILC1s and ILC2s reported in previous studies. Another subset expressed high levels of NKp46 and RORγt [5,28], potentially corresponding to a transient or plastic ILC state, as reported for ex-ILC3 cells acquiring an ILC1-like expression profile. In the presence of IL-12 produced by DCs, ILC3s lose RORγt and acquire Tbet expression, leading to the production of IFN-γ and the loss of IL-22 production [28]. Conversely, CD127$^+$ ILC1s can differentiate into Rorγt$^+$ ILC3s when exposed to IL-23 and IL-1β, whereas CD103$^+$ ILC1s and NK cells cannot [29].

In humans, two populations of ILC1s can be identified on the basis of CD127$^+$ and CD103$^+$ expression [29,30]. CD103$^+$ ILC1s also express NKp44, CD161 and, like NK cells, they express CD56, CD94 and Eomes. These cells are present in the tonsils and the ileal epithelium, but not in mesenteric lymph nodes [30], whereas CD127$^+$ ILC1s are present in the lamina propria [29].

So, can surface markers reliably distinguish ILC1s from NK cells?

Some markers, such as CD49a, CD103, CD69 and CXCR6, appear to be preferentially expressed on ILC1s, but a population of Lin$^-$NK1.1$^+$NKp46$^+$ cells also express these markers, together with EOMES or other NK cell markers, such as CD49b or Ly49H (Figure 1). This mixed phenotype in a particular tissue can be explained by imprinting effects of the microenvironment, such as the TGF-β in the salivary gland ILC1s, but it does not occur in

the liver [25]. Furthermore, these markers are not stable during activation, as the expression of CD49a and CD69 can be upregulated during MCMV infection or following exposure to cytokines, such as IL-2, IFN-γ, or IL-15 [25,31,32], suggesting that these key markers in $Lin^{-}NK1.1^{+}NKp46^{+}$ cells are not sufficient to distinguish ILC1s reliably from NK cells at different developmental or activation stages. Finally, enzymatic digestion used to isolate ILCs from tissues can disrupt the expression of some markers and potentially explain some phenotypical differences observed.

4. Do ILC1s and NK cells have different regulatory programs?

Yes, but this is not the case for all ILC1s.

No transcription factor controlling the development of ILC1 and NK cells differentially has yet been identified, at least if all ILCs are considered together. The transcriptional control of ILC1 development seems to depend on the tissue in which the cell resides. Both ILC1 and NK cells express Tbet, a defining characteristic of the ILC1 family, but EOMES controls the maturation of NK cells [16]. Tbet deficiency leads to the total loss of ILC1s, whereas NK cells persist but in smaller numbers [33] and with impaired functions [16,34,35].

Nfil3 was one of the first transcription factors identified as exerting differential control over ILC1s and NK cells in the liver [6] and, subsequently, in the salivary gland [24,36,37] and uterus [33]. However, ILC1s in other tissues require Nfil3 for their development [9,38,39]. The transcription factor Hobit is required for hepatic ILC1s, but not for NK cells or ILC1s in the small intestine [40] (Figure 1).

Gata3 regulates the development of ILC progenitors [20] and thymic ILC1s [21], but does not affect the development of NK cells. The deletion of Gata3 in hematopoietic stem cells impairs ILC1 development in the small intestine, but it remains unknown whether this deletion affects liver or salivary gland ILC1s [20].

The long non-coding RNA Rroid, which controls Id2 transcription in ILC1s and NK cells but not in other ILCs, has different effects on ILC1s in different tissues [41]. Its deletion results in low levels of NK cells and ILC1s in the liver, lung, and spleen, but ILC1s from the small intestine and the salivary gland are not affected.

These particular transcriptional requirements for ILC1s increase the number of subsets and complexify the classification of the ILC1 family. They also make it more difficult to develop an ILC1-deficient model for studies of the role of these cells in immune responses.

5. Do ILC1s and NK cells have different roles in immunity?

Yes, at different times.

One crucial reason for identifying ILC1s and NK cells as different lineages relates to the possibility of these cells having different immunological functions. Early re-investigations of the role of NKp46-expressing cells in the control of infection were performed with specific markers found on liver ILC1s, such as CD49a. During infection with *Toxoplasma gondii or Clostridium difficile*, ILC1s are the major source of IFN-γ and TNF-α, producing much

more of these cytokines than NK cells or NKp46 ILC3s [5,42]. However, in the absence of an ILCl-deficient model, these studies used Tbet$^{-/-}$ mice, which have relatively normal numbers of cells [5,42], but impaired NK cell function [34,35,43]. It therefore remains difficult to draw any firm conclusions concerning the specific and non-redundant roles of ILC1s. Interestingly, Rroid$^{-/-}$ mice, which have no ILC1s or NK cells in any organ other than ILC1s in the small intestine and salivary glands, can clear *Salmonella enterica* infection, supporting the hypothesis that intestinal ILC1s rather than NK cells control bacterial infection [41].

A temporal analysis of ILC1s during viral infection showed that these cells were required for optimal viral control, as they served as an early source of IFNγ [13**]. The elimination of liver ILC1s in Hobit-deficient mice leads to an increase in viral load after mouse cytomegalovirus (MCMV) clearance [13**]. CD49a^{+}Eomes^{-}CD200rl^{+} ILC1s remained Eomes^{-} after adoptive transfer, confirming that endogenous ILC1s constitute a stable lineage during inflammation. By contrast, CD49b^{+}Eomes^{+} NK cells in MCMV-infected mice displayed an increase in the expression of markers associated with an ILCl phenotype, such as CD39a and CD69, and no upregulation of CD200r, suggesting that this marker may be more reliable for tracking ILC1s in an inflammatory context [13**]. However, CD200r can be upregulated on liver NK cells in obese individuals [44]. This conversion to an ILCl phenotype is also mediated by TGF-β in the salivary gland [25] and in the tumor microenvironment [26**].

The conversion of NK cells into ILC1s is accompanied by a loss of antitumor properties. CD49a acquisition is followed by the upregulation of CTLA-4, Lag3 and CD96, and the downregulation of IFN-γ, contributing to tumor growth [26**]. It is, therefore, important to unravel the roles of *bona fide* ILC1s and TGF-β-imprinted NK cells that have acquired an ILC1 phenotype.

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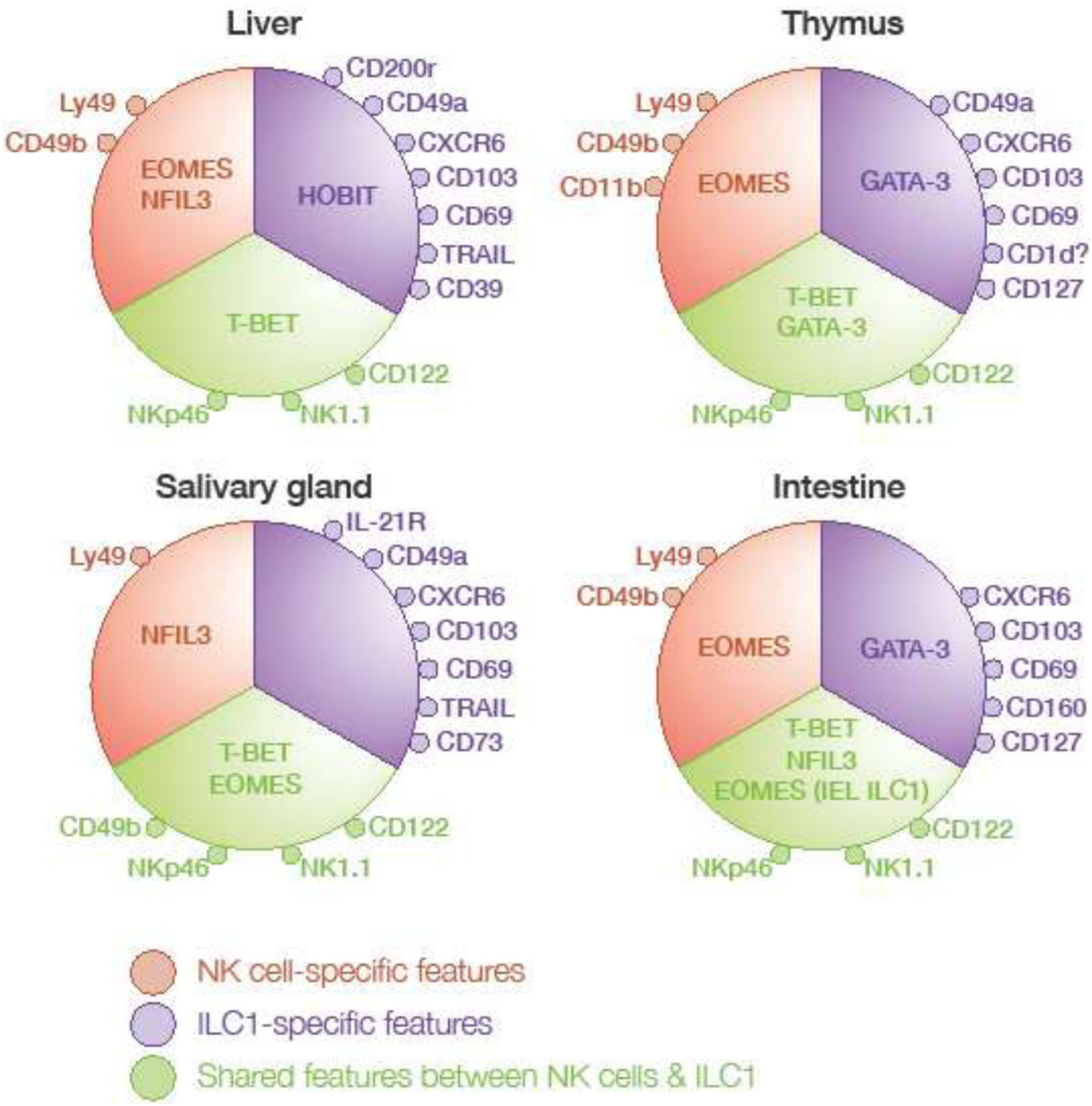

Figure 1: Tissue-specific markers and transcriptional requirements of the group 1 ILC in mouse.

Characteristic markers and transcription factors of ILC1 and NK cells in the liver, thymus, salivary gland and intestine are shown. Common features of ILC1 and NK cells are depicted in green, while ILC1 and NK cell-specific receptors and transcription factors are shown in purple and red respectively (IEL, intraepithelial lymphocytes).