Immunology Letters 179 (2016) 19–24

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Diversity and function of group 1 innate lymphoid cells

Victor S. Cortez, Marco Colonna*

Department of Pathology and Immunology, Washington University School of Medicine, Saint Louis, MO, USA

ARTICLE INFO

Article history:
Received 30 June 2016
Accepted 5 July 2016
Available online 6 July 2016

Keywords:
Innate immunity
Interferon-gamma
NK cells
ILC

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) T-bet and/or Eomesodermin (Eomes), group 2 ILCs secrete IL-5 and IL-13 and express the TF GATA-3, while group 3 ILCs produce IL-22 and IL-17 and express the TF RORgt. 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.

Contents

1. Introduction

Innate lymphoid cells (ILCs) are a heterogeneous population of cells with diverse roles in immune responses [7,14,17]. 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 extensively on group 1 ILCs, expanding on their emerging diversity, their disparate functions and the differences between NK cells and ILC1.

* Corresponding author.
E-mail addresses: mcolonna@pathology.wustl.edu, mcolonna@wustl.edu (M. Colonna).

http://dx.doi.org/10.1016/j.imlet.2016.07.005
0165-2478/

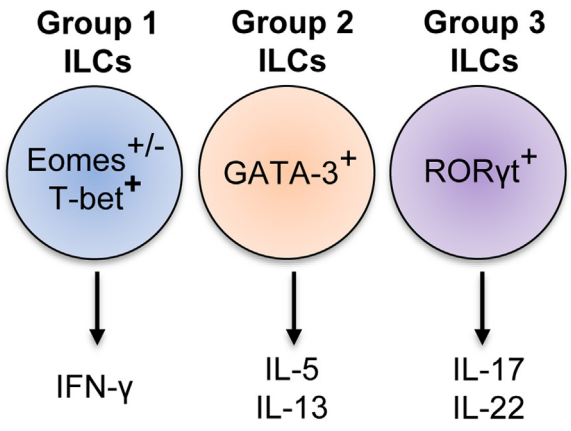

Fig. 1. Diversity of mouse ILCs. Three major groups of ILCs have been defined on the basis of signature cytokines they produce, the transcription factors they express, and the requirements for their developmental.

2. 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 [14,48] (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 [13,15,16,21,23,27,34,44,49]. 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.

3. Group 2 ILCs

Group 2 ILCs (also known as nuocytes, natural helper cells, innate helper 2-I_H2) produce IL-5 and IL-13 in response to IL-25, IL-33 and TSLP [7,14,17]; 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 [23]. Like TH2 cells, which produce similar cytokines, ILC2s contribute to immune responses directed against parasites and have been implicated in immune-mediated respiratory diseases.

4. 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 [6]. 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 [9,14]; [52] (Fig. 1). ILC3s require IL-7 signaling for their development and the TFs RORγt and aryl hydrocarbon receptor (AHR) [36]. 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 [35]. 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 [32,50].

5. 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 [60] (Fig. 1). Downstream of the CLP, the CXCR6$^+$ $\alpha_{4\beta7}{}^+$ CLP (αLP), also known as the common innate lymphoid progenitor CILP [60], 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) [34]. The CHILP was identified through the use of reporter mice for the transcriptional repressor Id2 and characterized as Id2$^+$Lin$^-$IL-7R$^{+\alpha}{}_{4\beta7}{}^+$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 [11]. The ILCP was distinguished as PLZF^{high}Lin$^-$IL-7R$^+$cKit$^{+\alpha}{}_{4\beta7}{}^{high}$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 [22,30]. However, subsequent studies found a defect in ILC1s, ILC2s, and ILC3s in peripheral sites [25,45]. Moreover, *Nfil3*$^{-/-}$ mice have been reported to lack the αLP and CHILP; thus, it seems that NFIL3 acts to sustain the earliest ILC progenitors [57,60]. However, we and others have found that ILC1 subsets in some tissues do not require NFIL3 for development [2,13,44,49]. Moreover, NK cells were also found to develop independently of NFIL3 during viral infection [20]. 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.

6. 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 [28,31,53]. 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.