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Review Article

Complexity of cytokine network regulation of innate lymphoid cells in protective immunity

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ABSTRACT

The body's surface provides a critical barrier shielding us from various mechanical and pathogenic insults by virtue of the physical protection it provides and the presence of specialized populations of innate lymphoid cells (ILCs) that sense inflammatory signals induced by pathogens. This response plays a central role in the development and activation of early immune responses. While ILCs depend on common γ-chain cytokine signaling for their development, an essential component of the armory of these cells is their capacity to produce defensive cytokines when activated by viruses, microbes and other parasites. In this review, we describe the multiple intrinsic and extrinsic pathways that comprise the cytokine circuitry regulating the development and function of ILC necessary for protective immunity.

1. Introduction

Innate lymphoid cells (ILC) belong to an expanding family of innate immune cells composed of three distinct subsets that are involved in homeostasis and protection of mucosal tissues and body surfaces. They depend on cytokine signaling for their development and are a critical source of cytokines at steady-state and during infection. Thus, they provide front-line protection at the onset of an immune response, limiting pathogen spread and ensuring tissue integrity. Individual populations of ILCs appear to display distinct cytokine signatures in a manner analogous to the specialized T helper (Th) cell subsets and as such have been classified using a similar nomenclature to Th cells (Fig. 1).

Group 1 ILC (ILC1) comprise interferon (IFN)-γ producing ILCs which include the prototypical ILC, the natural killer (NK) cell, and additional ILC1 subsets enriched in the intestinal mucosa and liver. These ILC1 subsets can be distinguished from conventional NK (cNK) by expression of CD49a and Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (Trail) [1,2]. Although recent reports suggest that cNK cells represent a distinct lineage [3,4], all ILC1 express the transcription factor T-box 21 (*Tbx21*, which encodes the T-bet) and require interleukin (IL)-15 to develop.

Group 2 ILC (ILC2) are present in multiple tissues including the intestine and lung. They play important roles in promoting immunity to helminth parasites and viruses and can drive allergic responses. They are a critical early source of IL-5 and IL-13. A common characteristic of ILC2 is their dependence on Gata-3 for their development and maintenance [5]. ILC2 are heterogeneous and include conventional ILC2 and the multipotent progenitor type 2 (MPP^{type2}) cells that retain the potential to generate macrophages, mast cells, and basophils [6]. Recent evidence suggests this latter population may form a distinct lineage from ILC2 but this requires further clarification [7].

Group 3 ILC (ILC3) comprise the classical lymphoid tissue inducer (LTi) cells that are responsible for the generation of secondary lymphoid tissues such as lymph nodes and Peyer's patch during embryogenesis, and a subset of NK cell receptor (NCR)-expressing ILC3 mainly found in intestinal mucosa. ILC3 express and depend on the transcription factor retinoic-related orphan receptor (Ror)γt for their development and produce the Th17 type cytokines, IL-17A and IL-22 [8–10].

Abbreviations: CILP, common innate lymphoid progenitor; CLP, common lymphoid progenitors; DC, dendritic cells; IBD, inflammatory bowel disease; ILC, innate lymphoid cells; IL, interleukin; LTi cells, lymphoid tissue inducer cells; MPP^{type2}, multipotent progenitor type 2; NCR, NK cell receptor; NK cells, natural killer cells; cNK cells, conventional natural killer cells; JAK, Janus Kinase; STAT, Signal transducer and activator of transcription.

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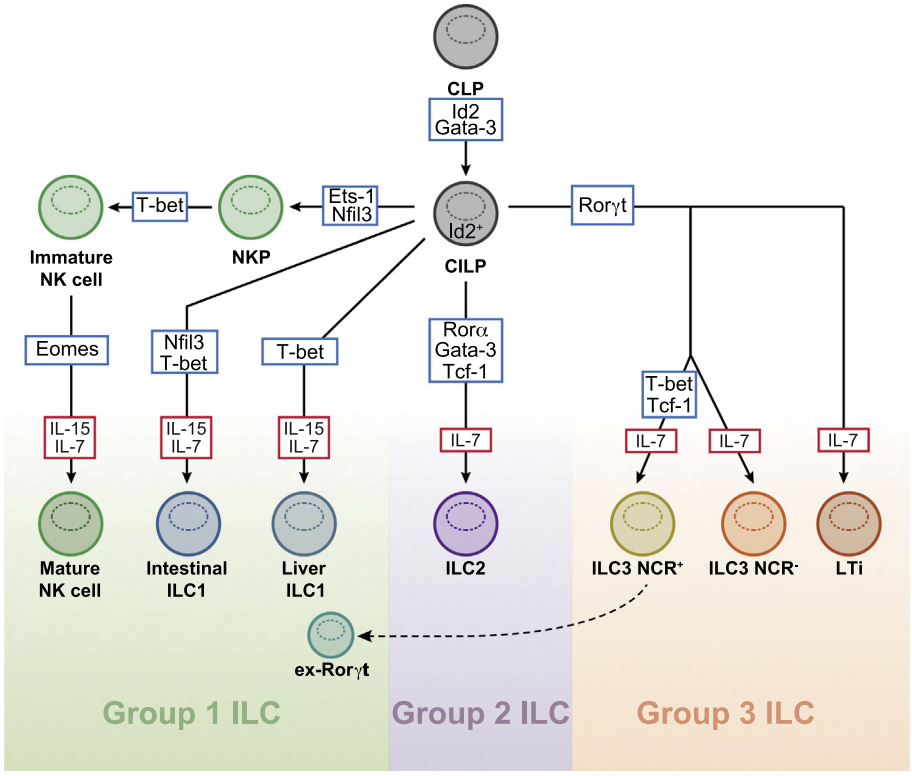

Fig. 1. Transcriptional regulation of ILC diversification. Schematic view of the transcriptional network of ILC development. The common lymphoid precursor (CLP) gives rise to a common innate lymphoid progenitor (CILP) that expresses Id2. At this stage, the CILP has lost its potential to give rise to B or T cells but can generate all ILC subsets. The requirement for the each transcription factor and cytokines during the different developmental stages are indicated respectively in blue and red boxes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. ILC development

ILC develop from common lymphoid progenitors (CLP) in the fetal liver that also give rise to B and T cells [11,12] (Fig. 1). Due to the dependence of all ILC on the transcription factor Inhibitor of DNA binding 2 (Id2), it has been speculated that a common innate lymphoid progenitor (CILP) may exist downstream of the CLP and give rise specifically to ILC. Recently, the use of a novel Id2-green fluorescent protein reporter (Id2-GFP) mouse, allowed the identification of the earliest precursor giving rise to NK cells, providing the first evidence of an ILC committed precursor [13]. This precursor, named the pre-pro NK cell (lineage$^-$Id2$^+$CD127$^+$Flt3$^-$), had lost its potential to give rise to B or T cells. It lacked most canonical NK cell-specific surface markers but did express Id2 and high levels of the IL-7 receptor [13]. More recently, it has been shown that the pre-pro NK cell population contains a precursor able to generate ILC2 and ILC3, in addition to ILC1 [4].

A hallmark of all ILC except NK cells is their expression of the IL-7 receptor alpha chain (IL-7Rα, CD127) [14]. IL-7R is composed of the common γ (γc) chain and the unique α chain. The α chain of the IL-7R is also utilized by thymic stromal lymphopoietin (TSLP), while the γ chain is a shared component of cytokine receptors for IL-2, IL-4, IL-9, IL-15 and IL-21. Similar to most other lymphocytes, IL-7 signaling plays an important role during the earliest stages of ILC development for the maintenance of the IL-7Rα$^+$ multipotent progenitor cells, including CLP [15] that give rise to all ILC subsets, in addition to T and B cells. All ILC subsets express IL-7Rα are strongly reduced in the absence of IL-7. NK cells are an exception as, although they can express IL-7Rα, they do not rely on IL-7 signaling for their development [4,16–20]. In the case of ILC3, IL-7 appears to support cell survival rather than proliferation of progenitors [21] and acts to stabilize Rorγt expression in mature cells [22]. Precisely how IL-7 directly affects ILC progenitors and other ILC subsets has not yet been elucidated. Further studies using conditional mice for expression of the IL-7R may provide greater insight into the mechanisms underpinning IL-7 signaling in ILC homeostasis and function.

3. Group 1 ILC (ILC1)

Group 1 ILC (ILC1) are potent producers of IFN-γ and include (i) cNK cells, (ii) liver-resident ILC1, (iii) intestinal ILC1, and possibly (iv) ex-Rorγt ILC3.

cNK cells are critical mediators of viral infection and anti-tumor responses, while other ILC1 appear to play an important role in fighting intestinal infection [4]. Whether they play additional roles in infection and anti-tumor responses has not yet been investigated in detail.

All ILC1 subsets can be defined by expression of Id2 and NKp46, however liver-resident and intestinal ILC1 are distinguished from cNK cells by their dependency on T-bet and lack of expression of eomesodermin [1,2]. Recent evidence suggests that these different subsets represent distinct lineages [4,23]. cNK cells express the integrin CD49b whereas liver-resident and intestinal ILC1 lack CD49b and express CD160, CD49a and Trail [3,24]. cNK cells and intestinal ILC1 depend on the transcription factor Nuclear factor, interleukin 3 regulated (Nfil3) for their development while liver-resident ILC1 do not suggesting that intestinal and liver-resident ILC1 may be distinct populations [3]. In addition to the three populations of ILC (cNK cells, liver ILC1 and intestinal ILC1), a fourth subset of ILC1 is proposed to exist. These are known as "ex-Rorγt ILC3" because they have been shown to arise from NCR$^+$ ILC3 that appear to down-regulate their normally high levels of Rorγt, and switch on the ability to produce IFN-γ. This transition is coupled