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Innate lymphoid cells, precursors and plasticity

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ABSTRACT

Innate lymphoid cells (ILC) have only recently been recognized as a separate entity of the lymphoid lineage. Their subpopulations share common characteristics in terms of early development and major transcriptional circuitry with their related cousins of the T cell world. It is currently hypothesized that ILCs constitute an evolutionary older version of the lymphoid immune system. They are found at all primary entry points for pathogens such as mucosal surfaces of the lung and gastrointestinal system, the skin and the liver, which is the central contact point for pathogens that breach the intestinal barrier and enter the circulation. There, ILC contribute to the first line defense as well as to organ homeostasis. However, ILC are not only involved in classical defense tasks, but also contribute to the organogenesis of lymphoid organs as well as tissue remodeling and even stem cell regeneration. ILC may, therefore, implement different functions according to their emergence in ontogeny, their development and their final tissue location. We will review here their early development from precursors of the fetal liver and the adult bone marrow as well as their late plasticity in adaptation to their environment.

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1. Introduction

Innate lymphoid cells (ILC) are a recently identified group of tissue-resident lymphocytes. ILC are components of the innate immune system as they do not express immune recognition receptors that are assembled by recombination of receptor elements and do not depend on RAG (recombination activating gene) proteins for their development. In an analogy to T cell lineages, however, ILC can be subdivided into two major lineages, cytotoxic ILC (*i.e.*, conventional (c)NK cells), which possess the potential to directly kill target cells, and cytokine-producing, helper-like ILC, which contribute to the body defenses by the secretion of cytokines. Currently, three subgroups of helper-like ILC (ILC1, ILC2 and ILC3) can be distinguished based on the expression of the transcriptional regulators T-bet, GATA-3 and RORγt and the release of signature cytokines such as IFN-γ and TNF (for ILC1), IL-5 and IL-13 (for ILC2) or IL-22 and IL-17 (for ILC3) [1]. It has been frequently pointed out that the effector cytokines produced by helper-like ILC and their key transcriptional regulators bear resemblance with the various T helper (Th) cell effector populations (Fig. 1).

NK cells were defined to be NKp46$^+$ CD3ε^- lymphocytes that can, in a class I MHC-independent fashion, lyse tumor target cells. Recently, it became clear that the NKp46$^+$ CD3$^-$ population is more complex and contains, in addition to NK cells, subsets of ILC3 and helper-like ILC1 [2,3]. Cytotoxic ILC or *bona fide* cNK cells are now considered to be a refined population of NKp46 (also called NCR1)$^+$ innate lymphocytes that developmentally depend on the T-box transcription factor Eomesodermin (Eomes) but not on the related transcription factor T-bet [4]. NK cells recognize virus infected and tumor cells *via* germ-line encoded immune recognition receptors (*e.g.*, NKG2D, NKp46) and mediate their killing by releasing cytotoxic vesicles that contain granzymes and perforin [5]. NK cells but not helper-like ILC express class I MHC-specific inhibitory receptors (KIR in humans or Ly49 receptors in mice and CD94/NKG2A in both species) that safeguard tolerance of NK cells to healthy, class I MHC-expressing "self" cells.

NK cells were initially believed synonymous with ILC1, because, similar to Th1 cells, they express T-bet and produce IFN-γ. Only the recent discovery of an IFN-γ and TNF-producing NKp46$^+$ ILC subset that did not express Eomes, but was dependent on T-bet for its development allowed for the differentiation between cytotoxic NK

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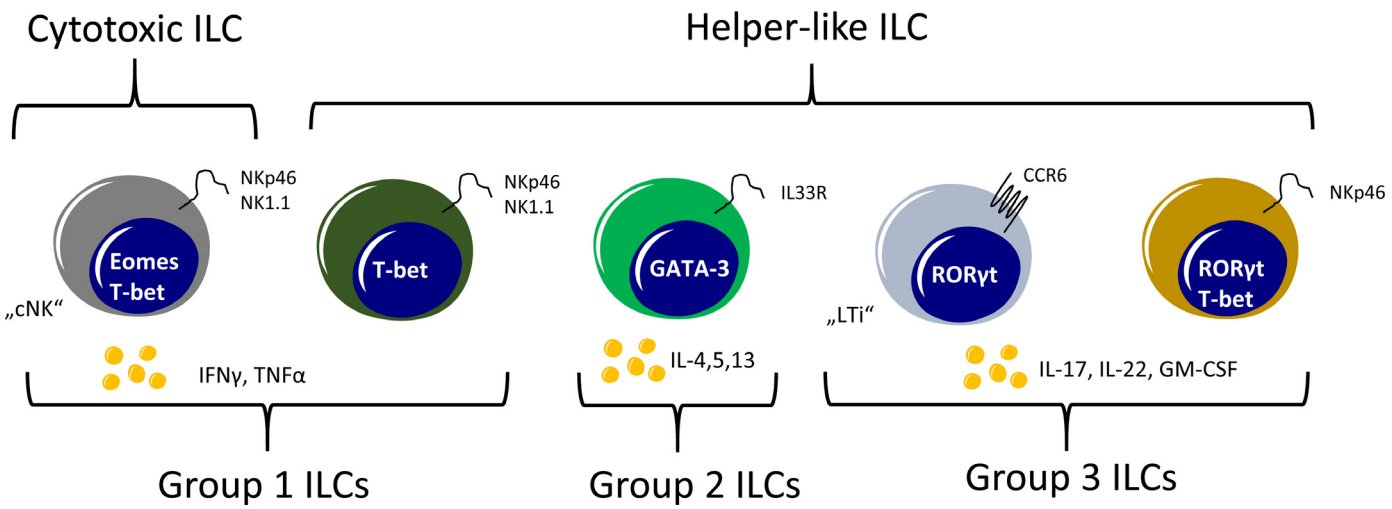

Fig. 1. Cytotoxic and helper-like ILC lineages.
Innate lymphoid cells (ILC) can be separated based on key functions into cytotoxic and helper-like ILC. Cytotoxic ILCs, also known as conventional NK cells, mediate the direct killing of virus infected or tumor cells by the directed release of granzymes and perforin. Helper-like ILC support and amplify immune responses by the release of cytokines. ILC can therefore also be characterized according to their lineage defining transcription factors and their subsequent release of effector cytokines. Type 1 ILCs express T-bet and release IFN-γ, type 2 responses are mediated by high levels of GATA-3 and the production of IL-5 and IL-13. Type 3 ILC depend on RORγt for their development and will aid the immune response by the secretion of IL-22, IL-17 and GM-CSF.

cells and cytokine-producing helper-like ILC1 [2–4,6]. Earlier studies had already encountered this population as an unusual TRAIL (TNF-related apoptosis-inducing ligand)-expressing NK cell subset found in the liver, a site pathogens would need to pass when entering the bloodstream through the intestines [7,8]. However, since ILC1 and NK cells express T-bet as well as various activating NK receptors (*e.g.*, NKG2D, NKp46 and NK1.1), they were not recognized as a separate lineage but rather believed to be immature NK cells [4,8]. ILC1 produce IFN-γ and TNF similar to NK cells, but show no appreciable ability to directly kill their target cells. They are an important component for the efficient innate control of intracellular parasites such as *Toxoplasma gondii* [2]. By now, several lines of evidence suggest that cytotoxic ILC and helper-like ILC constitute distinct ILC lineages. (1) Helper-like ILC share a common progenitor (see below) that has no developmental potential for cNK cells; (2) All helper-like ILC are dependent on GATA-3 expression for their development whereas cNK cells are not [9]; (3) Conventional NK cells but not helper-like ILC express class I MHC-specific inhibitory receptors; (4) All helper-like ILC express IL-7Rα which is not found on NK cells. In conclusion, NK cells and ILC1 are constituents of group 1 ILC as they both express the transcription factor T-bet and are involved in the defense against intracellular pathogens. NK cells represent a branch of the ILC family as they are the only subset endowed with appreciable cytotoxic properties [10].

ILC2 are an important component of type 2 immune responses [11,12]. Previous studies discovering this cell type have also referred to these cells as nuocytes [13] or natural helper cells [14]. ILC2 express the highest levels of GATA-3 among all ILC [15,16] as well as RORα [17,18], allowing them to produce type 2 cytokines such as IL-5 and IL-13. While all helper-like ILC require GATA-3 during early lineage specification (*i.e.*, when deleting GATA-3 in all hematopoietic cells using Vav-Cre), deletion of GATA-3 after the up-regulation of Id2 (by using Id2-Cre^{ERt2}) only affects the maintenance of ILC2 [9,15]. ILC2 are activated by factors released upon damage to mucosal layers of the lung or the intestine such as IL-33, TSLP and IL-25 [13,14,19,20]. The released interleukins help to mount an efficient type 2 immune response against helminths and protozoa during which ILC2 act in concert with T cells but also with other innate effector cells like eosinophils or basophils [21–23]. An interesting and emerging common theme of ILC biology is that ILC produce effector molecules that control the function of non-hematopietic cells at border surfaces, thereby likely contributing to organ homeostasis [24]. In that vein, ILC2 produce the EGF-like growth factor amphiregulin that supports tissue repair [25] and influence adipocyte differentiation, in particular beige fat biogenesis [26–28]. Very recently, ILC2 were demonstrated to influence intestinal epithelial cell differentiation towards the secretory lineage in order to support a “weep-and-sweep” response to expel helminths [29–31].

ILC3 are a complex group of ILC that developmentally depends on the transcription factor RORγt. One constituent of ILC3 are the previously identified lymphoid tissue inducer (LTi) cells that orchestrate the development of lymph nodes and Peyer’s patches during fetal development and the organogenesis of cryptopatches and isolated lymphopid follicles of the small intestine during the first weeks after birth [32–35]. While LTi cells have been recognized for years, it became only recently apparent that ILC3 can be found in the intestine of adult mice where they produce effector cytokines reminiscent of Th17 cells such as IL-17A, IL–17 F and IL-22 [36–40]. ILC3 are likely the most relevant source of IL-22, a cytokine specifically acting on epithelial and stromal cells because of the expression of its receptor by these cell types but not by hematopoietic cells [41]. A number of reports have shown that IL-22 is involved in the protection against bacterial [42,43] and viral infections [44,45]. One other major cytokine produced by a subset of ILC3 is IL-17A and F, which is involved in the defense against bacterial [46] and fungal pathogens [47]. ILC3-derived GM-CSF controls the functionality of mononuclear phagocytes for priming of Treg [48]. IL-22 can also have pro-inflammatory functions [49,50] possibly dependent on the location of ILC3, the kinetics of IL-22 production and the general cytokine environment.

Interestingly, ILC3 display a high degree of variability and plasticity and certain subsets express, in addition to RORγt, T-bet and produce type 1 cytokines such as IFN-γ, allowing them to fight a wide range of different pathogens [51,52]. As all other ILC, ILC3 do not express any recombined antigen recognition receptors, but a subset of ILC3 expresses activating NK cell receptors (such as NKG2D, NKp46 in mice and humans or NKp44 in humans). The main activators for ILC3 seem to be cytokines such as IL-23, IL-1α [44] and IL-1β [53] but the role of immune recognition receptors will need to be more rigorously analyzed in the future [54]. Apart from their role in the protection of the mucosa from pathogens,

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