Seminars in Immunology 26 (2014) 107–113

Contents lists available at ScienceDirect

Seminars in Immunology

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

Review

Development of human natural killer cells and other innate lymphoid cells

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ARTICLE INFO

Keywords:
NK cells
ILC2
ILC3
ILC development
NCR

ABSTRACT

Innate lymphoid cells (ILC) have recently gained much attention in immunology. They represent a novel developmentally related family. Three distinct subsets have been identified on the basis of phenotypic and functional criteria and termed ILC1, ILC2, and ILC3. The available data suggest that ILC play an important role in innate defenses against different pathogens, in lymphoid organogenesis, and in tissue remodeling. All these aspects are relevant in hematopoietic stem cell transplantation (HSCT), particularly in the haplo-HSCT setting, in which donor NK cells are known to play a major therapeutic role, while the involvement of other ILC is still undefined. In this context, it has been postulated that all ILC share a common precursor expressing the ID2 transcription factor. While the differentiation of human NK cells (belonging to ILC1) is now well characterized both in vitro and in vivo, limited information is available on the development of human ILC2 and ILC3 and of their relationships with NK cells. In this review, we will summarize the present knowledge on the developmental relationship among different ILC, with particular focus on early stages of NK cell differentiation, and their features shared with ILC2 and ILC3.

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1. Introduction

Natural killer (NK) cells are an important component of the innate immunity and provide a first-line of defense against tumors and viral infections [1]. They belong to the family of innate lymphoid cells (ILC). While NK cells have been known for almost 4 decades and have been extensively studied, other ILC have been better characterized in recent years. ILC play a relevant role in innate defenses against pathogens in different sites and in lymphoid tissue organization, primarily during fetal life [2]. ILC substantially differ from T and B cells because they do not undergo somatic rearrangements of genes coding for T or B cell receptors. ILC have been classified in three main groups (ILC1, ILC2, and ILC3) according to their cytokine profile and to the transcription factors (TFs) required for their differentiation [3]. ILC1 (including NK cells) are characterized by the ability to release IFNγ and require the expression of NFIL3, Tbet, and Eomes TFs. ILC2 produce the type 2 cytokines IL-13 and IL-5 and express the GATA3 TF. The third group of ILC is characterized by the production of IL-17 and IL-22 and depends on RORγt TF for its development and/or survival [3]. Altogether, ILC provide innate host defenses against different pathogens [3,4]. For example, NK cells play a key role in host defenses against viruses [1,5,6]. On the other hand, ILC2 contribute to immune responses against helminths [7], while ILC3 provide host defenses against extracellular pathogens. In addition, ILC3 are involved in lymphoid organogenesis during fetal life and in remodeling/maintenance of intestinal epithelial integrity during adult life (Table 1) [3]. Similarly to ILC3, also ILC1, in particular decidual NK cells (dNK), are involved in tissue building/remodeling [8]. The ILC populations are thought to be developmentally related because they derive from a common precursor expressing the ID2 TF. However, it has not been clearly established at which stage of development they start to differentiate into distinct cell lineages and whether they maintain a certain degree of plasticity [2,4,9]. Because of their role in innate defenses against different pathogens and their ability to promote secondary lymphoid organs (SLO) organization/remodeling, a better knowledge of their development and function appears particularly important in hematopoietic stem cell transplantation (HSCT). In this review, we will analyze the current knowledge on ILC differentiation and their lineage relationships.

2. ILC1

Group 1 ILC are characterized by the production of type 1 cytokines [3,4]. They include NK cells and recently described

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http://dx.doi.org/10.1016/j.smim.2014.01.006

Table 1
Main features of different ILC populations.

ILC group	Cells	Main transcription factors	Main effector cytokines	Functions
ILC1	NK cells iILC1	NFIL3 Tbet Eomes	IFNγ TNF	Cytotoxicity Viral defenses Anti-tumor activity
ILC2	Nuocytes Natural helper cells Innate helper cells	GATA3 RORα	IL-13 IL-5 IL-9	Helminth defenses Airway inflammation
ILC3	LTi LTi-like NCR$^+$ILC3	RORγt AHR	IL-17 Il-22 IL-8	Lymphoid organogenesis Tissue remodeling Extracellular pathogen defenses

subsets of IFNγ-secreting cells distinct from NK cells. In one report, a novel ILC1 subset has been described as intraepithelial cells in gut (named iILC1), while another group described the presence of a different ILC1 subset in inflamed mucosal tissues. Whether they indeed represent different ILC1 or rather specialized NK cells that have been conditioned by a peculiar tissue microenvironment remains to be defined [10,11].

2.1. NK cells

NK cells were identified in the 1970s on a functional basis, i.e. according to their ability to kill tumor cells without previous activation [12–15]. NK cells display cytolytic activity not only against tumor cells, but also against virus-infected cells. In addition, they can rapidly release pro-inflammatory cytokines and chemokines involved in early inflammatory responses [6]. Notably, upon activation, they may also sense various bacterial products via their toll-like receptors, an event resulting in a remarkable and rapid increase in their cytolytic activity and cytokine production [16,17]. Human NK cell function is tightly regulated by an array of inhibitory and activating receptors. Among the various inhibitory NK cell receptors, an important role is played by Killer Ig-like Receptors (KIRs), that recognize allotypic determinants of HLA-A, -B, and -C molecules, and by the heterodimer CD94/NKG2A specific for the non-classical HLA-E molecule [18]. Regarding the activating NK cell receptors, the prototypes are represented by NKp46, NKp44, and NKp30, that have been collectively named Natural Cytotoxicity Receptors (NCRs) [19–24]. The NCRs ligands are only partially known and may include pathogen-derived molecules and cellular ligands. These ligands include the human leukocyte antigen-B-associated transcript 3 (BAT-3) and B7H6 for NKp30, a novel isoform of the mixed-lineage leukemia-5 protein (MLL5) for NKp44, while viral proteins are reported as NKp46 ligands [25–30]. In addition to NCR, other activating receptors and co-receptors are involved in NK cell function. These include NKG2D (recognizing MICA/B and ULBPs molecules), DNAM-1 (specific for CD155 and CD112), CD16 (FcγRIII), NKp80 (specific for AICL), CD244 (that binds CD48), and NTBA (mediating homophilic interaction) [31–39].

Peripheral blood (PB) NK cells are not a homogeneous population. Thus, two main subsets can be identified on the basis of the levels of expression of CD56 surface antigen, i.e. CD56^{dim} and CD56^{bright} NK cells [40]. CD56^{dim} NK cells are predominant in PB, display potent cytolytic activity and rapidly release IFNγ and other type I cytokines and chemokines upon cell triggering via activating NK receptors [41–44]. A large fraction of CD56^{dim} co-expresses CD16. CD56^{bright} NK cells represent a minority in PB while they are predominant in tissues and SLO. They are poorly cytotoxic and are thought to be responsible for the long-lasting production of chemokines and cytokines (mainly IFNγ and TNF), particularly upon stimulation with IL-2 or IL-15 [40]. PB CD56^{bright} and CD56^{dim} NK cell subsets also differ in the expression of KIRs and CD94/NKG2A. Thus, CD56^{bright} cells virtually lack KIRs while expressing high-levels of CD94/NKG2A. In contrast, variable fractions of CD56^{dim} cells are KIR$^+$ and may or may not co-express CD94/NKG2A. The two NK cell subsets also differ in the levels of activating NK receptors and express different sets of chemokine/cytokine receptors and adhesion molecules [40,45,46]. NK cells primarily exert their function in tissues and SLO where they migrate early during inflammation in response to chemotactic factors induced by invading pathogens [47,48]. Importantly, NK cell function is greatly influenced by the microenvironment (i.e. cell-to-cell contact and/or soluble factors) both in physiological and in pathological conditions [49,50]. Indeed, the interactions occurring between NK cells and other cell types can determine the final outcome of both innate and adaptive immune responses [51,52]. Interestingly, a particular physiological condition in which NK cells are influenced by the tissue microenvironment is pregnancy [8,49,53]. During the first trimester, dNK cells represent as much as 50–70% of lymphoid cells in the decidual tissue. dNK cells are poorly cytolytic and release peculiar cytokines, different from those typical of PB NK cells [54–56]. The functional properties of NK cells may be significantly impaired in certain pathological conditions. This phenomenon has been investigated particularly in tumors, in which NK cell interaction with tumor or tumor-associated cells and exposure to inhibitory cytokines or other soluble mediators may compromise NK cell-mediated tumor cell killing and cytokine release [57–60].

2.2. NK cell development

NK cells derive from CD34$^+$ hematopoietic precursor cells (HPCs) through the sequential acquisition of receptors and functional capabilities. Information on NK cell differentiation derives primarily from studies in mice. Human NK cell development can be analyzed in vitro by culturing HPC with appropriate media and in vivo by monitoring the NK cell reconstitution after HSCT [61,62].

The commitment of the NK cell lineage and its further differentiation into mature NK cells requires both the expression of specific TFs and the exposure to an appropriate cytokine milieu. As mentioned above, NK cells originate from HPC precursors that express the ID2 TF [63,64]. The NK cell lineage commitment requires specific TFs including PU.1, Ets-1, TOX, and NFIL3 (also known as E4BP4) [65–70]. The achievement of later stages of maturation requires Eomes and Tbet TFs, which promote, respectively, the expression of the cytolytic machinery and the IFNγ production

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