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Guest editorial: Innate lymphocytes: Development, homeostasis, and disease

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1. Introduction

The Special Issue of Cytokine and Growth Factor Reviews entitled "Innate Lymphocytes: Development, Homeostasis, and Disease" contains a collection of articles authored by international leaders of the innate lymphoid cell (ILC) field and is aimed to provide an updated overview of the most relevant topics in this rapidly moving field of research. Herein, we will highlight the articles contained in this issue, along with the most recent discoveries in the ILC field.

2. ILCs: killers, helpers and regulators

The ILC system has enormously expanded in the last 10 years, and at present includes a wide range of cells with distinct phenotypes and functionalities [1]. This increased complexity has shed light on the similarities between innate and adaptive cells which extend from their ability to sustain polarized immune responses, to properties, such as plasticity and memory, conventionally considered as "adaptive" features [2]. Based on the expression of cytokines and transcription factors (TFs) previously associated with CD4+ T helper (Th) cells, ILCs are now divided in three major groups, namely ILC1, ILC2 and ILC3 [3], as illustrated in Fig. 1.

2.1. Type 1 ILCs

Natural Killer (NK) cells, the founding members of the ILC family, represent the prototype of cytotoxic ILCs and are seen as the innate counterpart of CD8+ cytotoxic T lymphocytes [4]. Because of their typical Th1 cytokine expression profile, NK cells fall into the group of type 1 ILCs. The role of NK cells in providing protection against viral infections and cancer has been largely dissected for over the past 40 years [5,6]. Nevertheless, recent findings have added novel mechanisms of action to the NK cell repertoire, including the ability to "sense" the presence of a growth factor in the tumor microenvironment. In this regard, expression of the natural cytotoxicity receptor (NCR) NKp44 (encoded by *NCR2*) enables human NK cells to directly recognize the platelet-derived growth factor (PDGF)-DD. When the human NKp44 is expressed in mice, murine NK cells show an enhanced ability to control dissemination of cancer cells expressing PDGF-DD [7]. Another aspect with a very promising impact in cancer therapy is the potential to block inhibitory checkpoint molecules expressed by NK cells. Notably, targeting both the Interleukin-1 receptor 8 (IL-1R8, also known as SIGIRR, or TIR8) or CIS, a member of the suppressor of cytokine signaling (SOCS) family, enhances the effector functions of NK cells, thus limiting cancer development and metastasis in mice [8,9]. Beyond protection against transformed and infected cells, NK cells are able to restrain immune responses by killing a wide range of immune cells. In this issue, **Zitti and Bryceson** discuss this aspect and provide a global overview of the mechanisms underlying NK cell functions in inflammation and autoimmunity, in the article entitled "*Natural Killer cells in inflammation and autoimmunity*".

Along with NK cells, the type 1 group also encompasses several subsets of tissue resident ILCs able to produce Interferon (IFN)-γ, and named ILC1. Unlike NK cells, ILC1 do not kill in a perforin/granzyme

Abbreviations: ILC, innate lymphoid cell; IFN, interferon; IL, interleukin; IL-1R8, interleukin-1 receptor 8; LDTF, lineage defining TF; LTi, lymphoid tissue inducer; NMU, neuromedin U; NCR, natural cytotoxicity receptor; NK, natural Killer; NGS, next generation sequencing; PDGF, platelet-derived growth factor; Th, T helper; TF, transcription factor; SDTF, signal dependent TF; STAT, signal transducer and activator of transcription; S1P, sphingosine 1-phosphate; SOCS, suppressor of cytokine signaling; TGF, transforming growth factor; TNF, tumor necrosis factor

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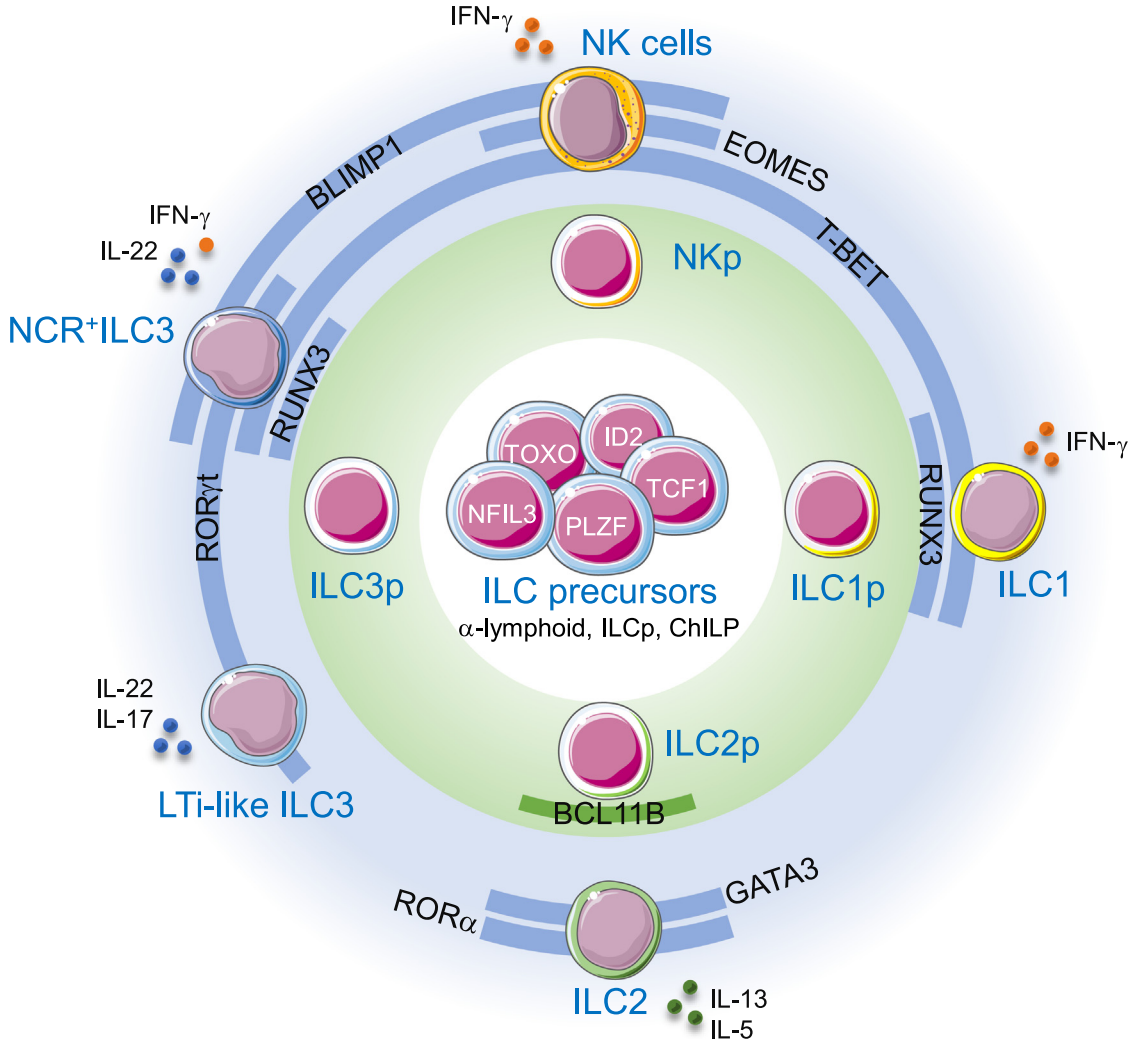

Fig. 1. Transcription factors underlying diversification of ILC phenotypes. ILCs are divided in three groups according to their functional similarity with T cells. NK cells represent the innate counterpart of CD8+ cytotoxic T lymphocytes and produce cytokines associated to the Th1 cytokine profile. The type 1 group also includes a heterogeneous population of ILCs producing IFN-g, namely ILC1. On the other hand, ILC2 provide protection of the mucosal tissues by producing IL-13 and IL-5, while LTi-like cells and NCR+ ILC3 produce IL-22 and differ for IL-17 and IFN-γ production. ILCs originate from the bone marrow, starting from pluripotent ILC progenitors. A dedicated set of TFs regulate further differentiation and generation of committed ILCp.

dependent manner, do not circulate, and their features vary according to the tissues in which they reside [10]. Despite these phenotypic and functional differences, the boundaries separating NK and ILC1 have become less distinct, and plasticity occurs both in physiological and pathological conditions [11]. The transforming growth factor (TGF)-β plays a fundamental role in driving conversion of NK cells towards the ILC1 phenotype [12–14]. Recent evidence has demonstrated that tumors can exploit the NK/ILC1 transition promoted by TGF-β to escape innate immune surveillance. Indeed, ILC1 are less efficient in controlling tumor spread as compared to NK cells, but also favor tumor growth by producing the tumor necrosis factor (TNF)-α, after conversion [13]. If this pro-tumor activity represents the dark side of the ILC1 functions, the bright side is their ability to maintain early protection against viruses by quickly producing high levels of IFN-γ during the early stages of infection [15].

2.2. Type 2 ILCs

ILC2 are characterized by a potent release of Interleukin(IL)-13 and IL-5 quickly after activation. Beyond protection against helminth infections, these cells have drawn increasing attention because of their important role regulating allergic diseases and obesity [16]. Moreover, a role for ILC2 in chronic pathologies, including gut and lung fibrosis, is beginning to emerge. This topic is discussed in this issue by **Mikami and colleagues** in the article entitiled "*Innate lymphoid cells in organ fibrosis*". During inflammation, the interactions of ILC2 with both the mucosal epithelium and the enteric nervous system are key to sustain an efficient type 2 response. In particular, the IL-13 produced by ILC2 directly acts on epithelial crypt progenitors, promoting the differentiation of goblet and tuft cells. In turn, tuft cells express IL-25, which is required both to maintain the homeostatic pool of ILC2, and to enhance their functions during infection [17–19]. On the other hand, the interaction between mucosal neurons and ILC2 relies on the neuropeptide neuromedin U (NMU), which directly triggers ILC2 functions and contributes to maintaining immunity against worm infections and lung inflammation [20–22]. In contrast to ILC1, which are generally considered resident cells, inflammatory ILC2 (iLC2) generated during infection can rapidly redistribute from the intestine to the lung and other tissues [23]. The lung-resident ILC2 maintain a different transcriptional profile from the lung iILC2 generated in the intestine. For