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Chemokine regulation of innate lymphoid cell tissue distribution and function

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ABSTRACT

Three groups of innate lymphoid cells (ILCs) can be defined based on transcription factor requirements, cytokine production profiles, and roles in immunity. Given their strategic anatomical location into barrier tissues and the ability to rapidly produce cytokines and to cross-talk with other immune and non-immune cells, ILCs play fundamental functions in tissue homeostasis and regulation of immune responses. Several members of the chemokine family influence ILC tissue localization in the correct microenvironment by regulating their release from the bone marrow as well as their homing and retention in the tissues. In this review, we discuss the recent advances on how chemokine regulation of ILC tissue-positioning and functional interaction with other cells play essential roles in tissue-specific regulation of innate and adaptive immune responses.

1. Introduction

Innate lymphoid cells (ILCs) are a growing family of immune cells that play important roles in tissue development and remodeling in homeostasis and inflammation [1]. Differently from B- and T- lymphocytes, they do not express somatically rearranged antigen receptors on their membrane surface [2]. Mucosal and barrier surfaces are especially enriched by ILCs where they can directly communicate with hematopoietic and non-hematopoietic cells and can be activated by cytokines or by the triggering of a number of activating receptors.

Three major sub-family of ILCs (ILC1, ILC2 and ILC3) have been identified based on the different transcription factor (TF) requirement for their development and on the type of cytokines produced [3].

Conventional Natural Killer (cNK) cells are the first innate lymphoid cell identified, able to produce high levels of IFN-γ and endowed with a potent cytotoxic ability toward tumor and viral infected cells [4,5]. Natural Killer cells represent 10% of circulating lymphocytes in humans but are also present in several lymphoid and non-lymphoid organs [5]. Natural Killer cells are categorized into Group 1 ILCs (ILC1s), however in humans and mice several other ILC1 subset have been identified. All ILC1s share the ability to produce IFN-γ and TNF-α in response to pro-inflammatory cytokines (such as IL-12, IL-18) stimulation but only NK cells express the TFs Eomesodermin (EOMES) and TBX21 (T-BET) required for their development, while ILC1 are T-BET$^+$ EOMES$^-$ cells [6–8]. Moreover, according to the surface marker expression, different ILC1 subsets have been described; a T-BET$^+$ ILC1 subset expressing high levels of CD127 and CD161 was identified by Bernink et al., in tonsils and inflamed intestine, while a CD127$^-$, NKp44$^+$ and CD103$^+$ ILC1 subset was described in mucosal sites [9,10]. Besides TFs, the surface phenotype of ILC1s may help to distinguish them from NK cells. Markers characteristic of tissue resident cells (CD69, CD49a) are prevalently expressed by ILC1s while they lack the expression of L-selectin (CD62L) which guides lymphocytes homing to lymphoid organs and which is expressed by NK cells [11,12]. ILC1s are enriched in liver, uterus and are the predominant subset in the gut intraepithelial compartment, while bone marrow and spleen represent the main storage compartments for effector NK cells. Finally, recent study on salivary gland has allowed to identify a new ILC1 subset with an intermediate phenotype between cNK cells and tissue ILC1s, which expresses both T-BET and EOMES but endowed with lower IFN-γ producing ability [13].

Group 2 innate lymphoid cells (ILC2s) require IL-7 signaling and TFs RORα and GATA3 for their development and functional maturation

Abbreviations: ILC, innate lymphoid cell; TF, transcription factor; cNK, conventional natural killer; EOMES, Eomesodermin; TBX21, T-BET; ROR, retinoic acid receptor related orphan receptor; LTi, lymphoid tissue inducing; CCL, CC motif chemokine ligand; CXCL, CXC motif chemokine ligand; MLN, mesenteric lymph node; sLN, skin draining lymph nodes; NCR, Natural Cytotoxicity Receptor; ILF, isolated lymphoid follicles; EAE, experimental autoimmune encephalomyelitis

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[14]. They share several common features with Th2 cells being able to secrete the type 2 cytokines IL-5 and IL-13, as well as IL-4, IL-9 and the EGF receptor ligand, amphiregulin [15–17]. The surface receptor phenotype of ILC2s is characterized by the expression of IL-7R (CD127), IL-33R, IL-2R, and the PGD2 receptor (CRTH2). They can be activated by epithelial-cell derived cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) but also by cytokines of both stromal and hematopoietic source such as IL-2. Moreover ILC2s are sensitive to lipid mediators like prostaglandin D2 which exerts a chemo-attractive effect on these cells leading to their accumulation in inflammation sites [18]. ILC2s are tissue resident lymphocytes showing a preferential localization within barrier tissues like lung-intestinal mucosae and skin, where they exert protective roles against helminths and viral infection. Moreover, adipose tissue is enriched by ILC2s, which contribute to maintain metabolic homeostasis [19]. Due to the similarity with Th2 cells, ILC2s have been also associated with disorders characterized by an inappropriate Th2 response, such as allergies and asthma [20].

The group 3 ILCs (ILC3s) include several subsets of innate lymphocytes, mainly enriched in the mucosal tissues and mucosal associated lymphoid tissues (MALT) but they can be found also in spleen, lung, skin and liver [21]. They are characterized by the expression of the retinoic acid receptor related orphan receptor (ROR)γt and are guided by IL-7 in their differentiation [22]. Fetal lymphoid tissue inducer (LTi) cells and adult LTi-like cells are the first members of ILC3 family identified with a crucial role in lymphoid tissue development [23]. Mouse LTi cells include two main subsets $CD4^+$LTi and $CD4^-$LTi, while the human LTi subset lacks CD4 and express CD7 and CD161. These cells are IL-17 and IL-22 producers but express also proteins of TNF superfamily (LTα, LTβ, LIGHT) [24,25]. Mouse postnatal ILC3 can be divided into two subsets according to CCR6 receptor expression; $CCR6^-$ ILC3s can acquire the expression of T-bet that allows them to produce IFN-γ in addition to IL-22 [26]. Conversely the $CCR6^+$ ILC3s are $CD4^{-/+}$ and represent a source of IL-17 [27]. In humans ILC3 are mostly $CCR6^+$ but can be divided in two subsets according to NCR expression; in particular tonsil and intestine $NKp44^+$ILC3s represent an exclusive source of IL-22 and IFN-γ while $NKp44^-$ ILC3s are IL-17 producer [28]. In mice, NCR^+ cells express NKp46, are $CCR6^-$ and are scattered throughout the intestine, while NCR^- cells are mostly $CCR6^+$ and are mainly clustered in isolated follicles of the lamina propria (LP) and in cryptopatches [27,29].

ILC developmental program is not irreversible, since environmental signals can modulate transcription factor expression by one ILC group promoting conversion into cells with a phenotype characteristic of other ILC populations. These “plastic” properties have been documented for the first time when ILC3s conversion into ILC1s was observed upon exposure to IL-12 and IL-18 and may be promoted by cytokine-producing cells during environmental shaping that reflects pathological states [30–32].

2. Chemokine receptors and ILCs

Chemokines are small molecular weight (8–12 Kd) chemotactic cytokines able to impact cell tissue positioning during development and in homeostatic and inflammatory conditions [33–35]. The capacity to orchestrate immune cell migration into tissues is a major function of chemokines, influencing immune responses by regulating the type of innate and adaptive cells recruited into tissues. In addition, selected chemokines promote immune cell persistence into tissues and their co-localization with other immune cells, thus optimizing cell-cell interactions and the production of environmental factors critical for the development of immune response.

The chemokine family comprises at least 50 known members, classified according to the number and relative positioning of N-terminal conserved cysteine residues into four family: CC, CXC, XC, CX3C chemokines. Activation of cell migration and of other cell functions are initiated by binding of chemokines to specific receptors belonging to the superfamily of seven-transmembrane spanning G-protein coupled receptors (GPCR)s. Chemokine receptors are classified into four groups, according to the type of chemokines they bind: CCR, CXCR, XCR and CX3CR, binding CC, CXC, XC, CX3C chemokines, respectively [36].

In lymphocytes, chemokines have been mainly characterized for the ability to control T-cell immunity by promoting recruitment into lymphoid tissues where optimal priming can occur due to co-localization with dendritic cells (DC) [37,38]. Priming in lymphoid tissues promotes a switch of chemokine receptor expression in T cells leading to expression of distinct combinations of tissue homing chemokine receptors by the different effector and memory cell subsets. These homing receptor switches limit their ability to interact with microvessels present in distinct anatomical compartments, thus allowing acquisition of tissue-specific tropism. Indeed, T cell subsets expressing CCR4 and CCR10 are more prone to home and persist into skin than to other tissues, since their cognate ligands are expressed by skin endothelial cells and keratinocytes, respectively [39,40]. On the other hand, the CCR9 ligand, CC motif chemokine ligand (CCL)25, is expressed on gut endothelial and epithelial cells contributing to the homing of effector T cells which prevalently express CCR9 along with the other gut homing receptor, the integrin α4β7 [41–43].

Several bodies of evidence demonstrate a role for chemokines in the organization of ILC tissue distribution very similar to that described for T cells. Distinct ILC populations differently express chemokine receptors and the expression correlate with the tissue distribution of ILC subsets. Yet, the mechanisms regulating ILC tissue specific localization are only now beginning to be elucidated. While cNK cells are widely distributed in the body anatomic compartments and use blood circulation to home into tissues, few mature ILCs are found in circulation and this led to hypothesize that ILC tissue distribution is mainly dependent upon differentiation of bone marrow-derived precursors that had previously migrated there. On the other hand, ILC2 cells are found in the blood circulation, mostly expressing CCR6, which might direct their migration into various epithelial tissues [44]. In addition, ILC2 precursors in BM and mature cells into intestine express CCR9, while in the skin ILC2s mainly express CCR10 and have variable expression of CCR4 [45,46]. ILC3s highly express CXCR6, especially the $NKp46^+$ subset, while CCR6 is expressed by the majority of $NKp46^-$ cells and expression of CCR7 and CCR9 have also been observed by all ILC3 subsets [26,27,29,47,48]. Expression of CCR7 in spleen and CCR9 in specific gut districts was also documented for ILC1s. In the liver, a population of ILC1s also named “tissue-resident NK cells” constitutively expresses CXCR6 and CXCR3 as opposite to the cNK cell counterpart. Among ILC1, chemokine receptor expression and function on cNK cells have been widely reviewed elsewhere [49–52] and an in-depth discussion of their trafficking mechanisms is beyond the scope of this review.

3. Chemokines in ILC migration and tissue distribution

It is becoming increasingly evident that the positioning of ILCs in specific areas of a tissue district has deep implications for ILC functions, allowing interaction with supporting cells (i.e. DC) or soluble factors (i.e. cytokines). ILCs are mainly distributed in barrier organs, including skin, lung and gut, where they play key roles in the maintenance of tissue homeostasis and regulation of immune responses (Fig. 1).

Conventional NK cells continuously traffic in the tissues using the blood circulation contributing to immunosurveillance, and are rapidly recruited to sites of infection or inflammation, while most ILCs are tissue-resident cells that have developed specifically *in situ* before perturbation of tissue homeostasis.

The expression pattern of chemokine receptors as well as tissue environmental stimuli able to modulate expression of their counter-ligands influence the tissue localization of ILCs by regulating their tissue tropism or retention as well as their microenvironmental distribution (Fig. 1). In addition, ILC populations are rapidly able to respond to perturbation of tissue homeostasis by changing their expression pattern