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Review

Innate lymphoid cells and their stromal microenvironments

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ABSTRACT

In addition to the interaction between antigen presenting cells, T and B lymphocytes, recent studies have revealed important roles for a diverse set of auxiliary cells that profoundly influence the induction and regulation of immune responses against pathogens. Of these the stromal cells composed of various non-hematopoietic constituents are crucial for the creation and maintenance of specialized semi-static three-dimensional lymphoid tissue microenvironment, whereas the more recently described innate lymphoid cells are generated by the diversification of committed lymphoid precursor cells independently from clonally rearranged antigen receptor genes. Recent findings have revealed important contributions by innate lymphoid cells in inflammation and protection against pathogens in a tissue-specific manner. Importantly, lymphoid stromal cells also influence the onset of immune responses in tissue-specific fashion, raising the possibility of tissue-specific stromal – innate lymphoid cell collaboration. In this review we summarize the main features and interactions between these two cells types, with particular emphasis on ILC type 3 cells and their microenvironmental partners.

1. Introduction

The capacity to establish effective immune responses requires the presence of organized peripheral lymphoid organs. These sites are populated overwhelmingly with hematopoietic cells arranged into distinct anatomical territories following extravasation. The T and B cells together with various dendritic cells, macrophages and other myeloid cells are recruited to discrete territories created by sessile non-hematopoietic cells that form the three-dimensional tissue architecture as a stable physical platform, in addition to providing continuous instructions for the positioning, survival and expansion of hematopoietic cells [1]. Collectively these non-migratory constituents are referred to as stromal cells, and include several cell types with diverse developmental, structural and functional features that set them apart from the typically mobile hematopoietic cells. Compared to the hematopoietic cells, the precise analysis of these cells has been hampered by the lack of well-defined and specific markers, leading to cumbersome and difficult identification and isolation procedures. It is not surprising, therefore, that in a striking contrast with hematopoietic cells (that can be obtained from a variety of tissue sources in both rodents and humans with relative ease), the studies aimed at the stromal cells are lagging behind. Thus, despite their relatively early discovery, a clear discrepancy has remained between the available methodologies to study these cells and unraveling their apparent functional importance.

One crucial role of the lymphoid stromal cells prevails during the embryonic formation of lymphoid organs, when the undifferentiated precursors of these cells at predetermined locations are organized into highly specialized tissues for the immunological protection of the individual after birth. Studying these events has led to a seminal discovery of one peculiar lymphoid cell type, termed lymphoid tissue inducer (LTi) cells, that has opened the way to identifying a previously unknown set of leukocytes [2,3]. These innate lymphoid cells (ILCs) form a diverse family of developmentally related hematopoietic cells, and are present at low abundance. However, they exert profound influences on the host organism's immunity [4,5]. In this review we briefly overview the main characteristics of these cells, and present a comprehensive summary of their relationship with their stromal microenvironment, thus connecting two minor cell subsets which, in turn, may influence a broad spectrum of mobile lymphocytes engaging in adaptive immune responses (Fig. 1).

2. Main features of ILCs with focus on ILC3s

Innate lymphoid cells are generated from common lymphoid progenitors under the influence of several transcription factors promoting the differentiation along non-T/B lineage. These include the transcriptional repressor inhibitor of DNA binding 2 (Id2) [6,7], GAT-

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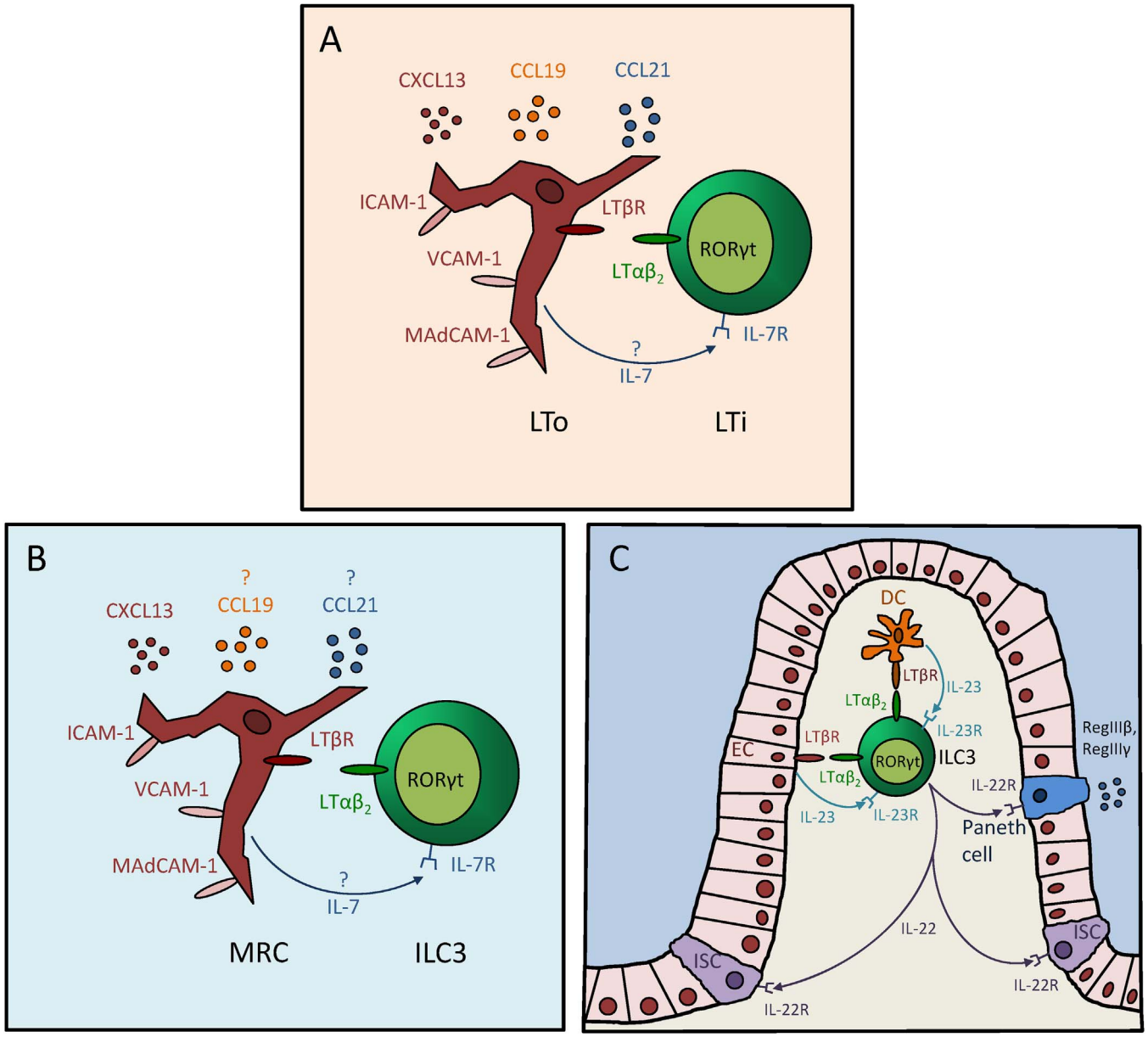

Fig. 1. ILC – stromal interactions. A, fetal lymph node anlagen; B, adult lymph node; C, adult lamina propria. Details are described in text.Abbreviations: LTo, lymphoid tissue organizer; LTi, lymphoid tissue inducer; MRC, marginal reticular cell; ILC3, innate lymphoid cell type 3; ISC, intestinal stem cell; EC, epithelial cell; DC, dendritic cell.

A-binding protein 3 (GATA3), promyelocytic leukemia zinc finger protein (PLZF), nuclear factor interleukin-3 (Nfil3), T cell factor-1 (TCF1) and thymocyte selection associated high-mobility group box (TOX). Their intercellular communication requires the signaling through IL-7Rγ chain and the binding of Flt3 ligand [8]. Although ILCs reside in lymphoid organs, they are most abundant at mucosal and barrier surfaces, where they form a complex defense system against extracellular bacteria, viruses and helminthes. Based primarily on their ability to produce Th1, Th2 and Th17/22 cell-associated cytokines respectively, ILCs can be divided into three groups—group 1 ILCs, group 2 ILCs and group 3 ILCs (ILC1-3) [9].

Discovered first, natural killer (NK) cells represent the prototypical cell of group 1 ILCs, which were reviewed in detail recently [10]. Briefly, type 1 ILCs in both humans and mice are a heterogeneous group of cells characterized by the expression of T-bet and the production of IFNγ. However, there exist subsets of ILC1 cells specific for various tissues, including the liver, intestine, thymus, and salivary glands [11]. NK cells were originally described to have important roles in the immune response against tumors, intracellular pathogens, and non-self structures, acting mainly in a direct cytotoxic manner [12–14]. Due to the limited availability of specific markers for various ILC1 subsets, the exact function of these cells is hard to distinguish from that of the NK cells, although both cytotoxic and non-cytotoxic ILC1s have been described [15,16].

The second group of ILCs was first identified as Th2 cytokine-producing innate cells in mesenteric fat-associated lymphoid clusters and mucosa-containing tissues, including the gut and the airways. The development of these cells is regulated by a complex network of transcription factors such as GATA-3 and RORα [6,17]. Upon stimulation by IL-25 and IL-33 ILC2s can induce allergy and asthma through the production of Th2 cytokines, and they also play an important role in intestinal parasitic worm clearance [18].

Group 3 ILCs comprise a phenotypically heterogeneous group of cells characterized by the expression of the RORγt transcription factor and the requirement of the aryl hydrocarbon receptor (AhR) [19–22]. ILC3s are involved in developmental and regenerative processes during embryogenesis and also in postnatal life. These RORγt-dependent cells are most abundant in the intestinal lamina propria during inflammatory