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Review

Shaping of the tumor microenvironment: Stromal cells and vessels

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ABSTRACT

Lymphomas develop and progress in a specialized tissue microenvironment such as bone marrow as well as secondary lymphoid organs such as lymph node and spleen. The lymphoma microenvironment is characterized by a heterogeneous population of stromal cells, including fibroblastic reticular cells, nurse-like cells, mesenchymal stem cells, follicular dendritic cells, and inflammatory cells such as macrophages, T- and B-cells. These cell populations interact with the lymphoma cells to promote lymphoma growth, survival and drug resistance through multiple mechanisms. Angiogenesis is also recognized as an important factor associated with lymphoma progression. In recent years, we have learned that the interaction between the malignant and non-malignant cells is bidirectional and resembles, at least in part, the pattern seen between non-neoplastic lymphoid cells and the normal microenvironment of lymphoid organs. A summary of the current knowledge of lymphoma microenvironment focusing on the cellular components will be reviewed here.

1. Introduction

Lymphomas are malignant neoplasms that typically arise in lymphoid tissues, however extranodal localizations are not uncommon. Recent studies provided compelling evidence that not only the genetic alterations harbored by lymphoma cells themselves but also interactions with the surrounding microenvironment are crucial for the growth and survival of malignant cells [1].

The lymphoma microenvironment is composed of a mixture of stromal cells, immune cells and extracellular matrix proteins as well as blood vessels. Cell subtypes that participate in the lymphoma microenvironment include nodal fibroblastic reticular cells (FRCs), follicular dendritic cells (FDCs), mesenchymal stem/stromal cells (MSCs), antigen-presenting cells (APCs) and immune cells (macrophages, mast cells, T- and B-cells). It has become increasingly evident that the crosstalk between lymphoma cells and their respective microenvironment is bidirectional and that multiple secreted factors and cell surface molecules contribute to the activation of major signaling pathways in both lymphoma and stromal cells. A better understanding of these complex interactions between lymphoma and microenvironment not only give us insights into the pathogenesis and progression of lymphomas, but also is essential for the development of novel effective treatment strategies. In this review, we will focus on the cellular component of the lymphoma microenvironment and its contribution to the provision of survival and proliferation signals to the lymphoma cells. Finally, we will briefly discuss nuclear factor κB (NF-κB) and Hedgehog (Hh) signaling pathways in the context of lymphoma microenvironment. These two pathways bridge external stimuli to internal cellular events that contribute to lymphomagenesis and lymphoma progression [2–9].

2. Stromal cells

2.1. Fibroblastic reticular cells

Fibroblastic reticular cells (FRCs), called adventitial/perisinusoidal reticular cells (ARC) in the bone marrow, are stromal cells that produce, ensheath and maintain the collagenous reticular fiber network of the paracortex in the lymph node (LN), splenic T-cell zone and hematopoietic bone marrow. Morphologically, FRCs resemble fibroblasts from other sites with long slender cytoplasmic processes, and have variable myofibroblastic features, as shown by electron microscopy and immunoreactivity with vimentin, keratin (8&18), smooth muscle actin, and desmin [10,11] (Fig. 1).

The LN reticular network has been conceptualized by Anderson and Shaw as a concentric arrangement of nested cylinders or “corridors” lined by a monolayer of FRCs that encircle high

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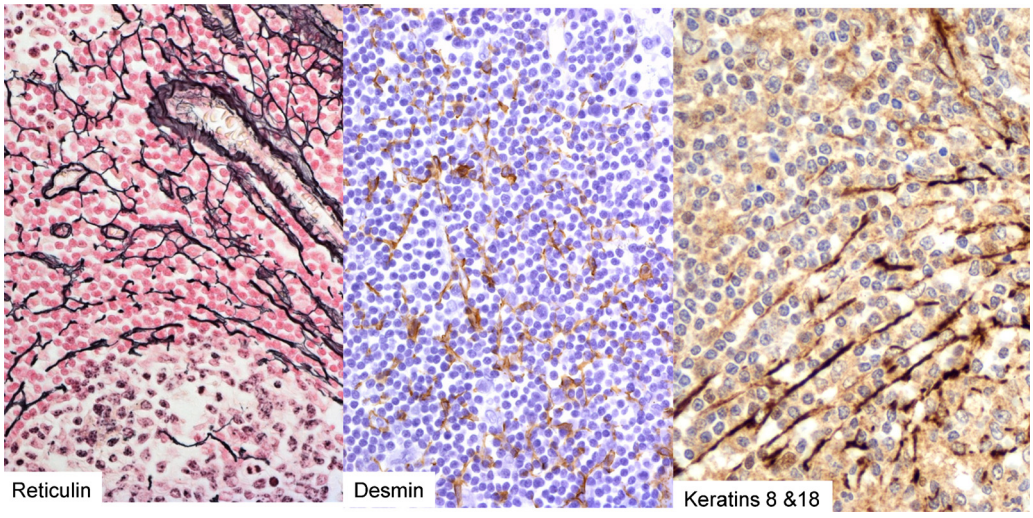

Fig. 1. T-cell paracortex. Left, reticulin stain highlights the reticular fiber network that delineates the "corridors" of the T-cell paracortex. The reticular network is produced by fibroblastic reticular cells (FRC). FRC are variable positive for desmin and cytokeratins 8&18 among other markers (center and right).

endothelial venules (HEV) and radiate outwards to the sinuses [12]. FRC provide physical routes or "corridors" for leukocyte trafficking and for the interactions between antigen presenting cells (APCs) and lymphocytes (Fig. 2). Also, FRCs actively participate in the LN expansion/contractility, access of T-cells into the paracortex and promoting chemokinesis of dendritic cells (DCs) within LN [13–17]. In addition, FRCs form specialized conduits that transport small molecules and chemokines along the reticular fiber from the nodal subcapsular sinuses to the abluminal surface of the HEV located deep in the LN paracortex [15,18,19]. FRCs are in intimate contact

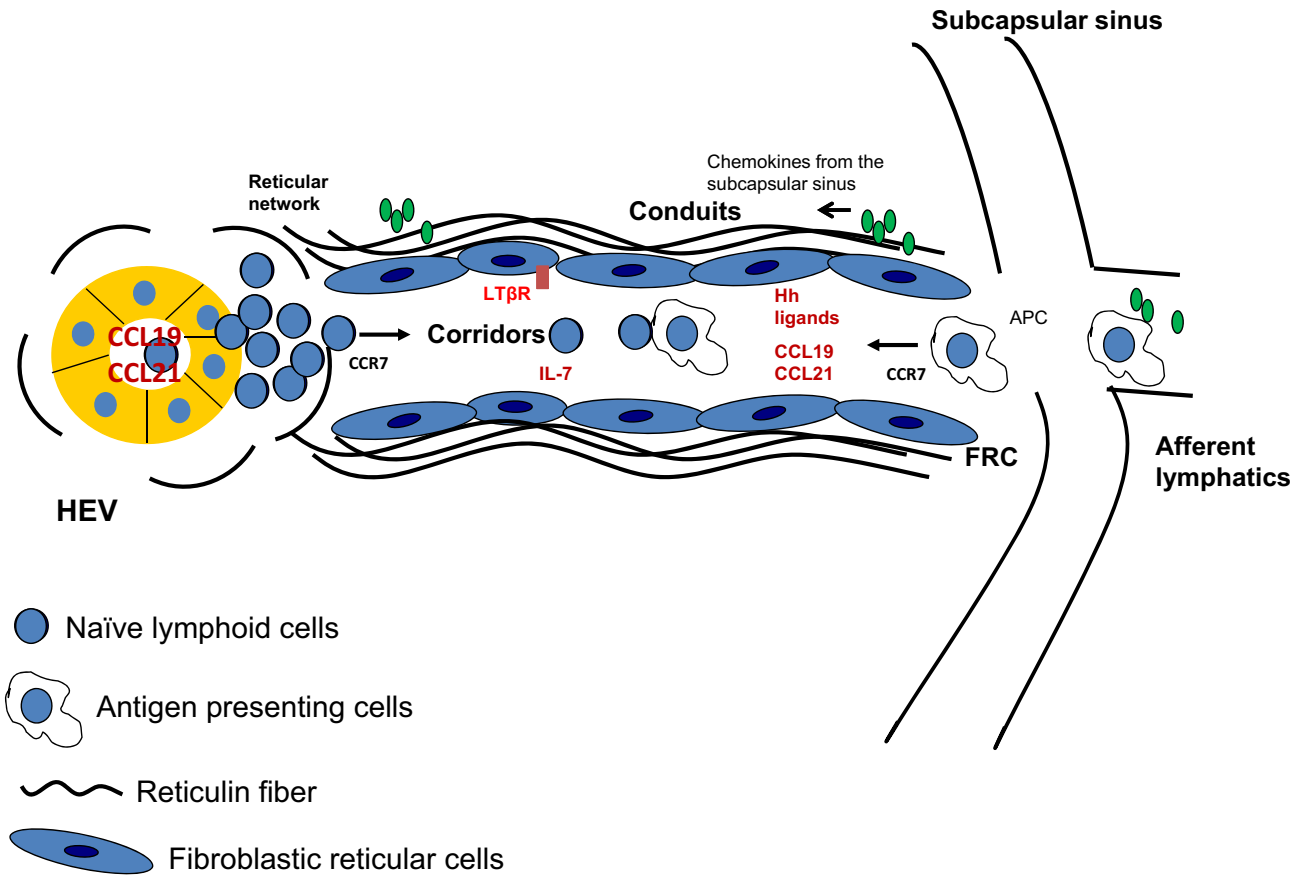

Fig. 2. Schematic representation of the "corridors and conduits" of the paracortex. The corridors are lined by an epithelium-like monolayer of FRCs and are filled with lymphocytes and antigen presenting cells (APC). The lymphocytes trafficking inside of the corridors enter to the lymph node through the high endothelial venules (HEV) and the APC enter through the afferent lymphatics. The conduits are postulated to be located between the FRC monolayer of cells and the basal membrane. The conduits transport cytokines and chemokines (represented in green) from the sinuses and afferent lymphatics to the HEV. The homing of naïve T cells and migratory dendritic cells to the nodal paracortex is mediated by the homeostatic chemokine receptor CCR7. The CCR7 ligands, CCL19 and CCL21, are produced by FRCs. IL-7 is another cytokine produced by FRCs and FRCs express LTβR that after stimulation contributes to enhance the secretion of CCL19 and CCL21 by FRCs. Hh ligands are also produced and secreted by FRC.

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