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Review

Lymphatic system: An active pathway for immune protection

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ABSTRACT

Lymphatic vessels are well known to participate in the immune response by providing the structural and functional support for the delivery of antigens and antigen presenting cells to draining lymph nodes. Recent advances have improved our understanding of how the lymphatic system works and how it participates to the development of immune responses. New findings suggest that the lymphatic system may control the ultimate immune response through a number of ways which may include guiding antigen/dendritic cells (DC) entry into initial lymphatics at the periphery; promoting antigen/DC trafficking through afferent lymphatic vessels by actively facilitating lymph and cell movement; enabling antigen presentation in lymph nodes via a network of lymphatic endothelial cells and lymph node stroma cell and finally by direct lymphocytes exit from lymph nodes. The same mechanisms are likely also important to maintain peripheral tolerance. In this review we will discuss how the morphology and gene expression profile of the lymphatic endothelial cells in lymphatic vessels and lymph nodes provides a highly efficient pathway to initiate immune responses. The fundamental understanding of how lymphatic system participates in immune regulation will guide the research on lymphatic function in various diseases.

Contents

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1. Overview

Lymphatic vessels have three primary roles in normal human biology. The first is to maintain fluid balance. Fluid that leaks from blood vessels in peripheral tissues is transported through lymphatic vessels and returned to the blood circulation. This is important for regulating the amount and the composition of fluids in circulation and within peripheral tissues. The second role is to absorb dietary fats in the intestine and transport them back into the blood stream. The third function is to facilitate the host's immune defenses. Lymphatic vessels are well recognized as the channels through which antigens and immune cells are transported to their draining lymph nodes for immune protection. When infectious microorganisms invade peripheral tissues, lymphatic vessels transport the pathogens, or the antigen presenting cells that had engulfed the pathogens, to the lymph nodes. This initiates adaptive immunity that lead to production of cells and antibodies that will clear the pathogen and generate memory against it.

Antigens and dendritic cells (DCs) reach the draining lymph node through afferent lymphatic vessels; they must then enter the lymph node and migrate deep into it to activate T cells. Lymph nodes are enclosed in a collagen-rich capsule, which is underlined with lymphatic endothelial cells forming the subcapsular sinus. This structure is directly exposed to the incoming lymph. Lymphatic endothelial cells are also concentrated in the medullary area to form the medullary sinus (Fig. 1A). Macrophages are closely integrated between lymphatic endothelial cells in both the subcapsular sinus and the medullary sinus to sample antigens and pathogens present in the lymph [1–3]. Notably, the lymph and cells coming from the afferent lymphatics also maintain peripheral immune tolerance in the lymph node, which depends on the DC activation status and the lymph node stromal cell self-antigen expression [4–6]. Thus, lymphatic vessels participate in immune response either directly, by controlling the antigen/DC transport to the draining lymph node or indirectly, by shaping the lymph node microenvironment. Lymphatic system could support immunity through (i) antigen/DC entry into lymphatics, (ii) antigen/DC trafficking through afferent lymphatic vessels, (iii) antigen presentation in lymph nodes and (iv) lymphocytes exit from lymph nodes. We will discuss the potential roles of lymphatic endothelial cells in controlling the ultimate immune response. We will also discuss the involvement of these cells in shaping peripheral tolerance.

2. Lymphatic transport of antigen and cells to lymph node

2.1. Antigens entry into initial lymphatic vessels

The initial lymphatic vessels are composed of single layer of overlapping, oak leaf-shaped lymphatic endothelial cells expressing the lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), a typical initial lymphatic endothelial cell marker [7]. Intercellular junction molecules form "button" shaped junctions, with flaps constituting the primary lymphatic valve system (Fig. 1B) [8]. Opening of these valves creates a "hole" of approximately 2–3 μm in diameter, which allows fluid to flow through when extracellular fluid pressure is increased. This unique structure provides highly permeable portals that allows quick absorption of extracellular fluid and free access of the molecules and particles less than 1 μm in diameter into the lymphatic vessel lumen (Fig. 1C) [4]. Thus, infectious pathogens, such as bacteria and virus particles, could directly enter lymphatic vessels via these portals. The collected lymph is composed of interstitial fluid from the surrounding tissue and contains a pool of self-antigens resulting from homeostatic tissue metabolism and cell turn over [9]. The self-antigens from the lymph may partially activate DCs and these semi-activated DCs play important roles in maintaining peripheral tolerance [10].

2.2. Cell entry into initial lymphatic vessels

DCs are known to be the most potent antigen presenting cells. The peripheral DCs are constantly migrating to the draining lymph node during tissue steady state, carrying self-antigen to maintain peripheral tolerance. They do so by causing self-reactive T cells anergy or clonal depletion [10]. It is estimated that approximately 5% of DCs in lymph nodes are derived from skin during steady state [11]. Upon activation, DCs quickly sample and process foreign antigens, increase expression of co-stimulatory molecules and CCR7 and strikingly accelerate their migration speed toward lymphatic vessels. DC migration through the interstitial area is integrin independent and relies on ameboid movement under chemotaxis of CCL21 [12]. CCL21, the CCR7 ligand, is expressed by lymphatic endothelial cells. CCL21 exhibits cluster pattern on lymphatic endothelial cell and attract DCs migration [13]. Once DCs reach a lymphatic vessel, they seek the endothelial cell portals (Fig. 1C), dock on lymphatic by interacting with CCL21 and squeeze through the portal into the lymphatic vessel lumen without any involvement of proteolysis or integrin interaction [12,14]. The initial lymphatic vessels are critically required for migration of tissue DCs to the draining lymph node, and their absence leads to a deficient induction of immune response or tolerance [15]. However, even a very low density of initial lymphatic vessels is sufficient for DCs to traffic to the draining lymph node [16].

In addition to DCs, a population of effector-memory T cells also circulates from peripheral tissue to the draining lymph node. While tissue resident memory T cells lack CCR7 expression, the migrating memory T cells express it and enter lymphatic vessels, likely using the same cues as DCs [17,18]. However, it is not clear how CCR7 expression is induced in the migrating memory T cells. Neutrophils can also enter lymphatic vessels, the mechanism of neutrophil trafficking in lymphatic vessel remains to be clarified [19–21]. Although CCR7 was shown to be involved in neutrophil entry to lymphatic vessels [19], another study claimed that neutrophils rely on macrophage-1 Ag, LFA-1, CXCR4 and sphingosine-1-phosphate receptor 4 for lymphatic trafficking but not on CCR7 [20]. This area of research has gained more attention in the past several years.

2.3. Antigen and cell trafficking through afferent lymphatic vessels

Initial lymphatic vessels merge into pre-collecting and collecting lymphatic vessels while extending to draining lymph node. In collecting lymphatic vessels, junction molecules transit to a continuous "Zipper" pattern, thus dramatically reducing permeability to peripheral fluid (Fig. 1B) [8]. Collecting lymphatic vessels gradually loose LYVE-1 expression, gain continuous basement membrane and acquire smooth muscle cell coverage. These morphological changes also contribute to the reduced permeability of collecting lymphatic vessels. It is obvious that this vessel morphology favors transport of lymph and cells rather than material collection from the surroundings. However, it is not clear if antigens or cells are able to directly enter collecting lymphatic vessels from peripheral tissue. Collecting lymphatic vessels possess luminal valves, which are strategically distributed to prevent back flow, favoring lymph and cell movement toward lymph nodes (Fig. 1B). The vessel sections spanning between two valves is called lymphangion. The lymphangions along the large collecting lymphatic vessels display phasic contractions (lymphatic pumping), which drive lymph transport [22].

Soluble molecules, solid particles and cells traveling through the lymphatic vessels are considered to be passively carried with the