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Review Article

Regulation of lymphangiogenesis—From cell fate determination to vessel remodeling

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Abstract

Lymphatic vessels are important for the maintenance of normal tissue fluid balance, immune surveillance and adsorption of digested fats. During the past decade, the identification of lymphatic-specific markers and growth factors has enabled detailed studies of the lymphatic system, and gain- and loss-of-function experiments have greatly increased our understanding of the mechanisms of normal lymphatic development. Understanding the basic biology has provided novel insights into the pathologic conditions of the lymphatic system that contribute to lymphedema, inflammation or lymphatic metastasis, and opened possibilities for the development of better therapeutic strategies. Here we review the current knowledge about the molecular mechanisms regulating the development of the lymphatic vasculature; of the differentiation of lymphatic endothelial cells, of the regulation of the growth of lymphatic vessels, and of remodeling of the vasculature into a network consisting of lymphatic capillaries and collecting lymphatic vessels. Furthermore, we will discuss the molecular mechanisms involved in the pathological conditions of the lymphatic vessels.

Keywords: Angiopoietin; Collecting lymphatic vessel; Ephrin; FOXC2; Lymphatic remodeling; Lymphedema; LYVE-1; Prox-1; VEGF

Contents

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Lymphatic vascular system

The main function of the lymphatic vasculature is to maintain normal tissue fluid balance by restoring interstitial fluid to the cardiovascular system. In addition, the lymphatic system is an important part of immune surveillance and involved in absorption and transportation of digested fats from the intestine [1]. Lymphatic vessels usually extend through a tissue accompanying larger blood vessels, sometimes ensheathing the veins as a plexiform net. They arise in the peripheral connective tissue as blind-ended capillaries that collect excess of extravasated tissue fluid, originating as capillary infiltration from the blood serum, and drain into larger lymphatic vessels. These vessels converge and unite, pass to the lymph nodes, and return the fluid to the venous circulation via the final collecting trunk, the thoracic duct. Different types of lymphatic vessels can be distinguished morphologically; the lymphatic capillaries are valveless endothelial tubes which have discontinuous basement membrane, overlapping endothelial cell junctions and lack pericytes and smooth muscle cells (SMCs), making them highly permeable to large macromolecules. In contrast, collecting lymphatic vessels have sparse SMC coverage, which helps in propelling lymph forward, and numerous, irregularly located valves, which prevent backflow. The luminal valves are, however, rare in the thoracic duct. Its two most prominent valves are situated at its termination in the subclavian vein where the free borders of the valves are directed towards the venous lumen in order to oppose influx of venous blood.

Establishment of lymphatic endothelial cell identity

During embryogenesis, the development of lymphatic vessels starts after the establishment of the blood vasculature when a subset of venous endothelial cells becomes committed to lymphatic endothelial lineage and sprouts from the major veins in jugular and perimesonephric area to form primitive lymphatic sacs (Fig. 1). The homeodomain transcription factor Prox-1 has been identified as a critical regulator of lymphatic endothelial cell (LEC) differentiation [2]. Targeted disruption of Prox-1 in mouse leads to arrest in the budding of the presumptive LECs and failure in lymphatic vessel development, while the development of blood vasculature is not affected [3]. Induction of polarized expression of Prox-1 in cardinal vein leads to upregulation of lymphatic-specific genes, such as vascular endothelial growth factor receptor 3 (VEGFR-3) and LYVE-1 [4]. In Prox-1-deficient embryos the lymphatic-specific gene expression was not induced but the mutant cells continued expressing blood vascular markers, suggesting that the cells were not committed to the lymphatic lineage [4]. In contrast, ectopic expression of Prox-1 in blood vascular endothelial cells (BECs) induced expression of lymphatic-specific

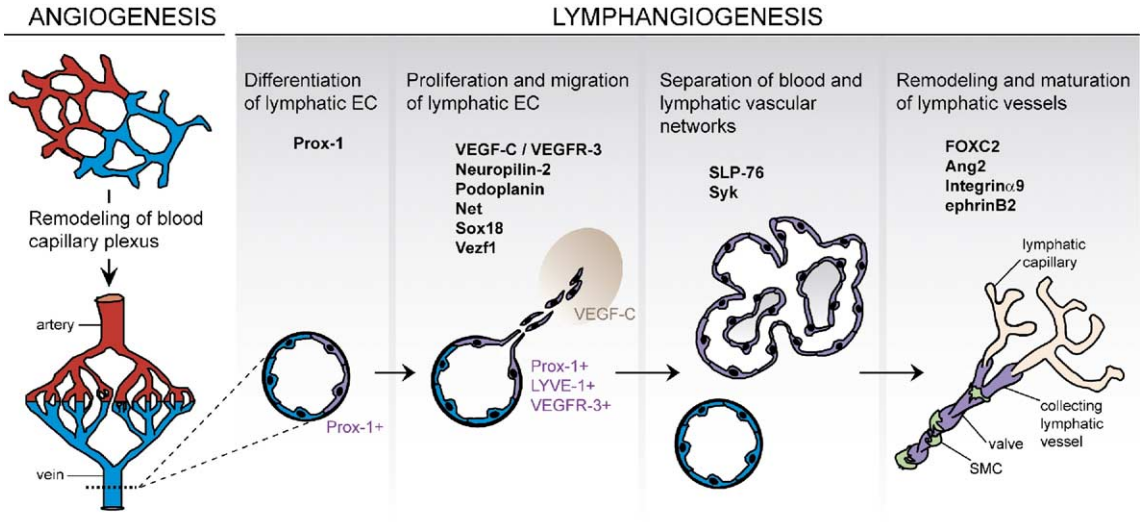

Fig. 1. Development of lymphatic vasculature during embryogenesis. After the remodeling of the blood vasculature, lymphatic endothelial cells differentiate and sprout from the major veins to form lymphatic capillary plexus. Further maturation involves establishment of collecting lymphatic vessel versus lymphatic capillary identities and acquisition of SMC coverage as well as formation of luminal valves in the collecting vessels. Proteins involved in different processes in lymphatic development are shown below each section.