Review

Molecular mechanisms of lymphatic vascular development

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Abstract. Lymphatic vasculature has recently emerged as a prominent area in biomedical research because of its essential role in the maintenance of normal fluid homeostasis and the involvement in pathogenesis of several human diseases, such as solid tumor metastasis, inflammation and lymphedema. Identification of lymphatic endothelial specific markers and regulators, such as VEGFR-3, VEGF-C/D, PROX1, podoplanin, LYVE-1, ephrinB2 and FOXC2, and the development of mouse models have laid a foundation for our understanding of the major steps controlling growth and remodeling of lymphatic vessels. In this review we summarize recent advances in the field and discuss how this knowledge as well as use of model organisms, such as zebrafish and Xenopus, should allow further in depth analysis of the lymphatic vascular system.

Keywords. Lymphangiogenesis, vascular remodeling, PROX1, VEGFR-3, FOXC2, Ephs/ephrins.

The lymphatic vasculature

The adult lymphatic system is composed of blind-ended capillaries, collecting vessels and lymphoid organs, such as lymph nodes, tonsils and Peyer’s patches. Lymph capillaries are characterized by the presence of loose intercellular junctions, little or absent basement membrane and the absence of surrounding smooth muscle cells or pericytes (Fig. 1a, b). Thin fibrillar structures, called anchoring filaments, connect the abluminal surface of lymphatic endothelial cells to the extracellular matrix, providing a way to sense the expansion of the interstitium during edema and preventing the collapse of lymphatic capillaries under high pressure conditions. Collecting lymph vessels, which transport lymph to the lymph nodes, are surrounded by a basement membrane and smooth muscle cells, which form a thinner and more disorganized layer than in blood vessels of a similar caliber. A distinguishing feature of collecting lymphatic vessels is intraluminal valves, which prevent lymph back flow (Fig. 1a, c). Lymphatic vessels are present in nearly all tissues, with the exceptions of the central nervous system, bone marrow, cartilage, cornea and epidermis. Virchow-Robin spaces, formed by prolongation of meninges, surround blood vessels as they enter the brain, and collect the interstitial fluid, thus playing a lymphatic vessel-like role.

One of the main functions of lymphatic vasculature is the maintenance of fluid homeostasis. Unlike the cardiovascular system, the lymphatic vasculature has no central pump and is not closed: interstitial proteins and water, extravasated from blood capillaries, are absorbed by lymphatic capillaries and transported to the blood circulation by the peristalsis of collecting lymphatic vessels and contractions of surrounding skeletal muscles. Another important function of the
The lymphatic system is immune surveillance: lymphocytes and antigen-presenting dendritic cells are transported by lymphatic vessels from the interstitium to the lymph nodes, where specific immune responses may be initiated. Lymphatic vessels also play a major role in the absorption of dietary fat, which is secreted by enterocytes in the form of lipid particles or chylomicrons. This task is carried out by lacteals, lymphatic capillaries located inside the villi of the small intestine. Chylomicrons may constitute up to 5–15% of lymph volume after ingestion of a fat containing meal, and up to 90% of dietary fat is absorbed from the gut in this manner.

In addition to their role in homeostasis, lymphatic vessels are involved in several human diseases, such as tumor metastasis, lymphedema and inflammation. In many solid tumors, peritumoral lymphatic vessels provide a route for the escape of tumor cells to the regional lymph nodes, whereas blocked or absent lymphatic vessels cause lymphedema. Secondary lymphedema, following lymph node removal, is an important cause of chronic disability in cancer patients. The role of lymphatic vasculature in human diseases has been recently reviewed [1–3], and we refer the reader to these sources for more detailed information. In the present review we will focus on the molecular mechanisms involved in the formation, growth and remodeling of the lymph vasculature during embryonic and early postnatal development.