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Lymphatic collecting vessel maturation and valve morphogenesis

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ABSTRACT

The lymphatic vasculature plays an essential role in the maintenance of tissue interstitial fluid balance and in the immune response. After capture of fluids, proteins and antigens by lymphatic capillaries, lymphatic collecting vessels ensure lymph transport. An important component to avoid lymph backflow and to allow a unidirectional flow is the presence of intraluminal valves. Defects in the function of collecting vessels lead to lymphedema. Several important factors and signaling pathways involved in lymphatic collecting vessel maturation and valve morphogenesis have now been discovered. The present review summarizes the current knowledge about the key steps of lymphatic collecting vessel development and maturation and focuses on the regulatory mechanisms involved in lymphatic valve formation.

Organization and function of the lymphatic vascular system

The lymphatic vascular system is a one-way transport system responsible for the maintenance of fluid homeostasis. The lymphatic vasculature is organized into a network of lymphatic vessels that collect extravasated tissue fluid from the interstitial space and drain it back to the venous circulation. This allows the transport of interstitial proteins in excess and waste back to the blood circulation. It is also involved in fat absorption and represents the major route for immune cells and soluble antigens to reach the lymph nodes where immune responses are activated.

During development, after the establishment of a primary lymphatic vasculature, lymphatic vessels undergo further remodeling to form a functional lymphatic vessel network consisting in a hierarchical vascular tree composed of lymphatic capillaries, pre-collectors and collecting vessels (Fig. 1). Lymphatic capillaries are blind-ended thin walled vessels. They lack mural cell coverage, are devoid of a continuous basement membrane, and are connected to the extracellular matrix by anchoring filaments (reviewed in (Schulte-Merker et al., 2011)). Fluid uptake in lymphatic capillaries is governed by the increase in interstitial fluid pressure. The entry into the capillaries is facilitated by discontinuous VE-cadherin positive button junctions. The lymph contained in capillaries is then drained into pre-collector lymphatic vessels and further into larger lymphatic collecting vessels. Pre-collectors display similar properties as capillaries with the exception that they also contain bi-leaflet intraluminal valves like those seen in large collecting vessels. Collecting vessels are characterized by the presence of zipper-like junctions between endothelial cells, a continuous basement membrane, smooth muscle cell (SMC) coverage and the presence of valves (reviewed in (Schulte-Merker et al., 2011)). These valves, that are regularly distributed, prevent retrograde flow and ensure a unidirectional lymph flow back to the blood circulation. Collecting vessels are divided into distinct functional units, called lymphangions. A lymphangion corresponds to the part of the vessel located between two valves. They constitute contractile compartments, active lymph propulsion being achieved by the intrinsic contractions of the lymphangions. This is in contrast with what occurs at the level of capillaries where the main identified factors influencing lymph flow, such as the respiratory movements and the surrounding skeletal muscle contractions, are indirect. However, lymphatic contractile mechanisms remain poorly understood. The collecting lymphatic vessels drain into trunks and ducts that connect with the blood vascular system at both right and left subclavian veins and at the left jugular vein which are the major physiological connections between blood and lymph vessels (reviewed in (Margaris and Black, 2012)).

The lymphatic vasculature participates in the pathogenesis of several diseases (reviewed in (Tammela and Alitalo, 2010)). Indeed, the impairment of lymphatic drainage resulting from lymphatic vascular insufficiency can lead to lymphedema development. This may occur as a consequence of infection, trauma or surgery that has disrupted lymphatic vessels. It results in a marked swelling of the tissues in the injured region. Lymphedema may also have, in some cases, a congenital origin (reviewed in (Tammela and Alitalo, 2010) and (Schulte-Merker et al., 2011)). Since the collecting lymphatic vessels are connected with the chains of lymph nodes that are essential components of the immune response, the lymphatic vascular system affects the efficiency of the immune function. Finally, lymphatic vessels can also serve as a way for tumor cells to reach lymph nodes and eventually more distant sites and thus promote tumor cell dissemination.

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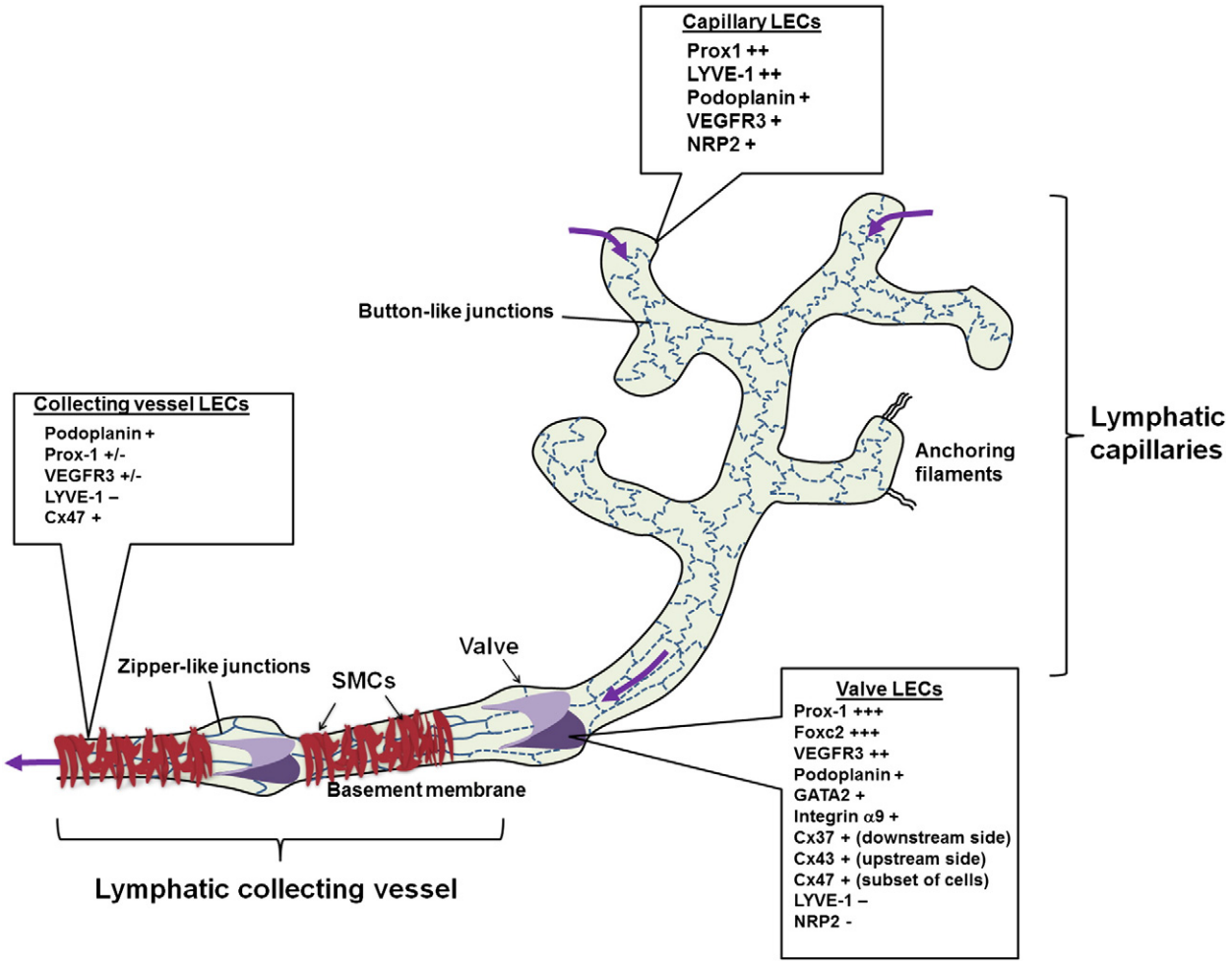

Fig. 1. Schematic representation of the organization and of the molecular identity of the lymphatic vasculature. The blind-ended lymphatic capillaries capture fluids, proteins and cells from the interstitial space. They are constituted of oak leaf-shaped cells that are connected to the extracellular matrix by anchoring filaments and that display button-like intercellular junctions. Lymphatic endothelial cells (LECs) of the collecting lymphatic vessels that transport the lymph have a basement membrane and exhibit zipper-like intercellular junctions. Collecting vessels are covered by smooth muscle cells (SMCs) that possess intrinsic contractile activity ensuring lymph propulsion. They contain intraluminal valves to prevent backflow. The LECs of capillaries, collecting vessels and valve-forming cells exhibit differences in their molecular identity. Their respective expression profiles are indicated in boxes.

Overview of lymphatic vascular development

In the mouse mammalian embryo, it has been demonstrated that the lymphatic vasculature originates from a subset of blood venous endothelial cells of the cardinal veins at E9-9.5 (reviewed in (Martinez-Corral and Makinen, 2013), (Koltowska et al., 2013) and (Yang and Oliver, 2014)). The intersomitic veins and the superficial venous plexus have been recently characterized as other locations where can arise lymphatic endothelial cell progenitors (Yang et al., 2012) (Hagerling et al., 2013). Lymphatic competence as defined by cellular expression of LYVE-1 (lymphatic vessel endothelial hyaluronan receptor 1) and VEGFR3 (vascular endothelial growth factor receptor 3) represents the first step towards differentiation into the lymphatic lineage. These lymphatic endothelial cell (LEC) progenitors then migrate out the cardinal veins to form the primary lymphatic sacs. The subsequent expansion of a primary lymphatic vascular plexus is achieved through proliferation and sprouting from these sacs. The specification of lymphatic fate is controlled by key transcription factors: COUP-TFII (Chicken ovalbumin upstream transcription factor II), SOX18 (SRY-related HMG-box 18) and Prox1 (Prospero-related homeobox domain 1), whereas lymphatic endothelial migration and sprouting leading to the primary lymphatic plexus has been shown to be mainly under the control of VEGFC (Vascular endothelial growth factor C) and of its receptor VEGFR3 (Francois et al., 2011; Karkkainen et al., 2004). This primary network further undergoes remodeling and maturation to give a functional lymphatic network composed of lymphatic capillaries, pre-collectors and collecting lymphatic vessels. This later process starts at E15.5 and continues early after birth. It involves the acquisition of specific characteristics that allow the specialized function of each type of lymphatic vessel (reviewed in (Martinez-Corral and Makinen, 2013)). As a consequence, lymphatic capillaries and collecting vessels display distinct molecular identities (Fig. 1).

On the other hand, it is important to note that the characterization of the morphological and functional differences between the lymphatic vasculature of different organs or tissues has been poorly investigated and remains very limited.

Lymphatic remodeling and collecting vessel identity specification

The specification of collecting vessels is characterized by the deposition of a thin continuous basement membrane, the recruitment of SMCs and the formation of luminal valves. Collecting vessel identity is also characterized by the down-regulated expression of several lymphatic endothelial markers highly expressed in LECs during development and in lymphatic capillaries (Fig. 1). After maturation, LYVE-1 is almost completely lost on endothelial cells of the collecting vessels (Norrmen et al., 2009). Gene targeting experiments in mice have revealed that LYVE-1 deficiency does not significantly affect lymphatic development and function (Gale et al., 2007). Thus, the significance of LYVE-1 down-regulation during collecting vessel maturation remains to be