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Lymphatic vascular specification and its modulation during embryonic development

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ABSTRACT

Despite its essential roles in development and disease, the lymphatic vascular system has been less studied than the blood vascular network. In recent years, significant advances have been made in understanding the mechanisms that regulate lymphatic vessel formation, both during development and in pathological conditions. Remarkably, lymphatic endothelial cells are specified as a subpopulation of pre-existing venous endothelial cells. Here, we summarize the current knowledge of the transcription factor pathways responsible for lymphatic specification and we also focus on the factors that promote or restrict this event.

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Introduction

The specification and sprouting of the earliest lymphatic vessels

The lymphatic vasculature and its origins

The lymphatic vasculature is crucial for interstitial fluid drainage, immune surveillance and lipid absorption. The lymphatic vessel network is composed of a hierarchy of blind-ended lymphatic capillaries, pre-collecting lymphatic vessels and collecting lymphatic vessels. Capillaries absorb fluid, proteins and extravasated macromolecules. The resulting intravascular lymph is then delivered, through the collecting vessels, to the lymph nodes (where 40% of fluid absorption occurs) or further via the subclavian veins and returned to the blood circulation (Földi, 2004). The disruption of the establishment or the maintenance of this homeostatic process leads to a variety of pathologies that prominently include lymphoedema and inflammatory disorders (Alitalo, 2011).

Although the lymphatic vasculature was identified centuries ago, its formation during embryonic development has only been characterized in depth from the beginning of the 20th century. Two main hypotheses have been proposed to explain the origin of the lymphatic vasculature in the embryo. Using dye-injection experiments in pig embryos, Florence Sabin proposed that endothelial cells bud from veins to form lymph sacs (LS), which in turn sprout in a centrifugal pattern to form the entire lymphatic vascular network (Sabin, 1902). In contrast, Huntington proposed that the lymphatic vessels arise from mesenchymal cells, independently of the vein (Huntington, 1908). Since these initial observations, experiments performed largely using the mouse model system but also more recently in zebrafish embryos, have demonstrated that most lymphatic endothelial cells (LECs) differentiate from the embryonic veins, and most prominently from the cardinal vein (CV) (Wigle and Oliver, 1999; Srinivasan et al., 2007; Yaniv et al., 2006).

Cellular lymphangiogenesis in the embryo

For some time, it has been known that the initiation of expression of the transcription factor Prospero-related homeobox domain 1 (PROX1) marks the initial steps of LEC emergence from approximately 9.5 days postcoitum (dpc) of mouse development. PROX1 is first expressed in a subpopulation of venous endothelial cells in a polarized manner in the dorsal wall of the CV (Wigle and Oliver, 1999). By 10.5 dpc, these cells can be observed delaminating from the wall of the CV. These initial LECs will form the primary lymphatic structures that include the LS.

Recent work using high-resolution imaging has described in more detail the cellular events that drive lymphatic vessel formation during mouse development (François et al., 2012; Hagerling et al., 2013; Yang et al., 2012). Using confocal and electron microscopy, Yang et al. has shown that LEC progenitors bud from the CV as an interconnected group of cells and that they can also arise from the intersomitic veins. Importantly, by examining adherens junctions during this process, it was found that the integrity of the cardinal vein is maintained by the presence of junctions between venous endothelial cells and LEC

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progenitors (Yang et al., 2012). A similar observation was made by Francois et al., who also observed LEC progenitors that delaminate as streams of cells from the CV. This second study additionally suggested that LEC progenitors are localized in discrete clusters arranged along the anteroposterior axis of the CV. These pre-lymphatic clusters (PLCs) are proposed to undergo progressive ballooning to generate primitive LS that initially contain blood cells (François et al., 2012). Finally a third study used ultramicroscopy to visualize early lymphangiogenesis in the embryo and suggested a number of significant changes to existing models. Hagerling et al. proposed that two populations of LECs arising from the CV contribute to the establishment of the first lymphatic structures. LECs emerging from the CV are seen as loosely attached networks consistent with the studies of Yang et al. and Francois et al., but they are observed to accumulate and condense close to the first lateral branch of the intersegmental vessels (ISV) to form a structure termed the peripheral longitudinal lymphatic vessel (PLLV), which subsequently gives rise to superficial lymphatic vessels that will probably contribute dermal lymphatics. At the same time, LECs located in closer proximity to the CV aggregate to form the primordial thoracic duct (pTD), which was suggested to be the structure previously defined as the LS (Hagerling et al., 2013). In addition to these observations, perhaps the most unexpected finding was that there is an additional source of LECs from a structure that is separate from the CV. This structure, dubbed the superficial venous plexus (sVP), appears to be a source of PROX1-positive LECs that is endothelial and likely venous in nature (Hagerling et al., 2013). This may suggest that multiple venous endothelial beds can give rise to LECs, a significant change to our way of thinking about the lymphatic vasculature as exclusively of CV origin.

It is well worthy of note that there remain differences between all of the models recently described. This is telling and suggests that our ability to visualize early lymphangiogenesis is limited in the mouse model. A model synthesizing the current view of how lymphangiogenesis occurs in the embryo is presented in Fig. 1.

In the zebrafish embryo, lymphangiogenesis can be directly visualized by live-imaging (Yaniv et al., 2006). This advantage has led to the appreciation that lymphangiogenesis occurs concurrently with the angiogenic sprouting of the venous ISVs (vISVs) from the posterior cardinal vein (PCV). Half of the venous sprouts connect to arterial intersegmental vessels (aISV) and the other half migrate more dorsally to the horizontal myoseptum, producing a pool of cells dubbed as parachordal lymphangioblasts (PLs) based on their anatomical location and developmental potential (Hogan et al., 2009a; Yaniv et al., 2006). Later in development, after an initial period within the myoseptum, PLs migrate dorsally or ventrally alongside the arterial ISVs (Bussmann et al., 2010; Cha et al., 2012), to form the intersegmental lymphatic vessels (ISLVs), dorsal longitudinal lymphatic vessel (DLLV) and the thoracic duct (TD) (reviewed in (Koltowska et al., 2013; van Impel and Schulte-Merker, 2014; van Impel et al., 2014). Recent work has characterized three other lymphatic networks in zebrafish, the facial lymphatics (FL), the lateral lymphatics and the intestinal lymphatics (Okuda et al., 2012). Interestingly, LEC-progenitors that contribute to the FL originate from a number of different blood vessel origins, together with the mouse studies of the sVP suggesting that there may be multiple ways to form LECs in the embryo. While the optical advantages of the zebrafish has led to many of the observations above, it is worth noting that the weakness here is the absence of well-defined markers of cell state in the zebrafish, it remains difficult to define specified and differentiated cell populations in this model (van Impel et al., 2014), in contrast to the mouse.

Transcriptional control of lymphatic endothelial cell specification

Prospero-related homeobox domain 1 (Prox1)

Prox1 is considered the master regulator of both specification and maintenance of the lymphatic endothelial cell phenotype. The first indication that lymphangiogenesis has begun is the specific expression of PROX1 in a restricted subpopulation of endothelial cells in the CV (Wigle et al., 2002). *Prox1*$^{-/-}$ embryos are completely devoid of lymphatic vessels and die between 14 and 15 dpc (Johnson et al., 2008; Wigle and Oliver, 1999). PROX1 activity is essential for the emergence of the LEC progenitors at the level of the CV (Yang et al., 2012). In addition, PROX1 is sufficient when overexpressed in cultured blood vascular endothelial cells, to induce the expression of lymphatic specific markers (podoplanin and VEGFR3) and is capable of suppressing 40% of blood endothelial cell-specific genes (Hong et al., 2002; Petrova et al., 2002). Furthermore, ectopic expression of *Prox1* under the control of *Tie1* promoter *in vivo* induces the expression of LEC markers in some blood vessels (Kim et al., 2010).

During zebrafish development, Prox1 also labels the lymphatic vasculature (Dunworth et al., 2014; van Impel et al., 2014; Yaniv et al., 2006). However, it has been recently shown that, in contrast to mammals, Prox1 is not necessary for the development of all lymphatic vessels but just a percentage of lymphatic vessels. *Prox1a/b* mutants show a reduction in lymphatic vessel development but still form up to 70% (in length) of the thoracic duct (TD). This study may suggest divergence

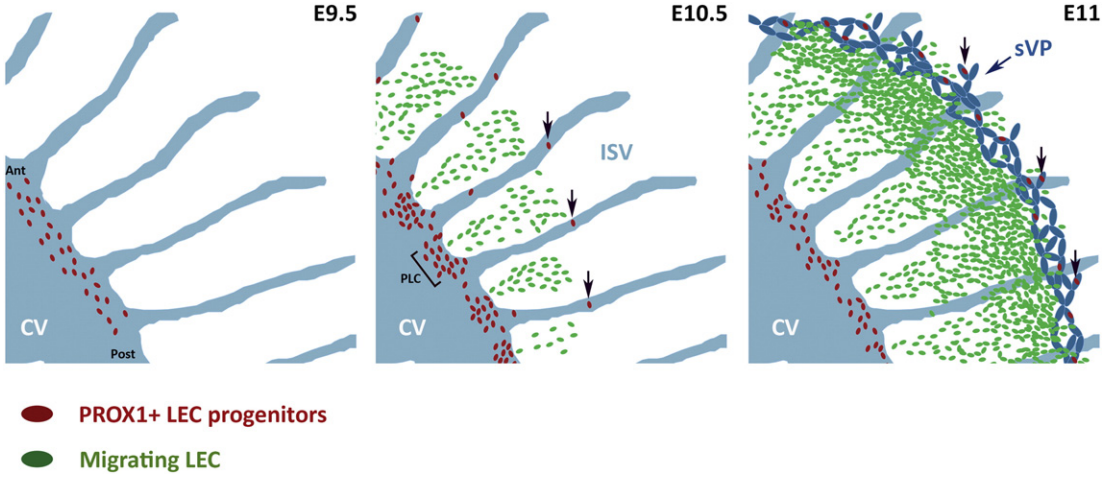

Fig. 1. LEC specification in embryonic veins during development. *(left panel)* During mouse embryonic development, LEC specification is marked at around 9.5 dpc with the induction of PROX1 expression in a subset of endothelial cells (red) in the dorsal wall of the cardinal vein (CV). *(middle panel)* At 10.5 dpc, LEC progenitors migrate out of the wall of the CV and acquire more lymphatic specific markers (NRP2, podoplanin) (green). LEC progenitors are localized in defined clusters arranged according to an anteroposterior axis along the CV (PLC). LEC specification is not restricted to the CV and also occurs at the level of intersegmental veins (vISV). *(right panel)* At around 11 dpc, migrating LECs (green) invade the surrounding environment to form the primary lymphatic structures. LEC progenitors (red) are detected in the superficial venous plexus (sVP) and probably contribute to the formation of the superficial lymphatic network.

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