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Review

Blood and lymphatic vascular tube formation in mouse

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ABSTRACT

The blood and lymphatic vasculatures are essential for nutrient delivery, gas exchange and fluid homeostasis in all tissues of higher vertebrates. They are composed of a hierarchical network of vessels, which are lined by vascular or lymphatic endothelial cells. For blood vascular lumen formation to occur, endothelial cell cords polarize creating apposing apical cell surfaces, which repulse each other and give rise to a small intercellular lumen. Following cell shape changes, the vascular lumen expands. Various junctional proteins, polarity complexes, extracellular matrix binding and actin remodelling molecules are required for blood vascular lumen formation. In contrast, little is known regarding the molecular mechanisms leading to lymphatic vascular tube formation. Current models agree that lymphatic vessels share a blood vessel origin, but they differ in identifying the mechanism by which a lymphatic lumen is formed. A ballooning mechanism was proposed, in which lymph sacs are connected via their lumen to the cardinal veins. Alternatively, a mechanism involving budding of streams of lymphatic endothelial cells from either the cardinal veins or both the cardinal veins and the intersomitic vessels, and subsequent assembly and lumenisation was recently described. Here, we discuss what is currently known about the molecular and cellular machinery that guides blood and lymphatic vascular tube formation in mouse.

Contents

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1. Introduction

Two vascular systems exist in mammals, namely the blood and lymphatic vasculatures. They are functionally linked to each other, and none of them is dispensable for higher vertebrates [1,2]. The blood vasculature is a closed circulatory system responsible for the transport of oxygen and nutrients, and for the removal of waste products from any given tissue (Fig. 1A, B). The arterial vascular network operates with a higher blood pressure than the venous vascular network. This causes plasma fluid to continuously leak from arterial capillaries into extracellular or interstitial spaces [3]. Since venous capillaries cannot absorb all interstitial plasma fluid, the organism requires the presence of the lymphatic vasculature to remove this remaining fluid from the interstitium (Fig. 1C, D). In addition, the lymphatic vasculature plays an essential role in immune cell trafficking and in uptake of dietary fatty acids [4].

The blood and lymphatic vasculatures are composed of a network of multicellular tubes with a central lumen. In this review, we introduce the tubular morphology of blood and lymphatic vessels, and summarize the key knowledge on the early development of both vasculatures. Furthermore, we outline current models that describe different mechanisms of lumen formation by blood and lymphatic endothelial cells.

2. Blood vasculature

2.1. Morphology of tubular blood vessels

The blood vasculature is composed of different types of blood vessels, including arteries, veins and capillaries. While blood is transported away from the heart by arteries and brought back by veins, capillaries connect these two types of vessels. Furthermore, capillaries are involved in the molecular exchange of gases, nutrients and other molecules between the blood vasculature and surrounding tissues. All blood vascular tubes are composed of vascular endothelial cells (ECs) surrounding a lumen. ECs are connected to each other via adherens and tight junctions, i.e. by cadherins and claudins [5]. In addition, they produce their own basement membrane and recruit perivascular muscle-like (mural) cells to the abluminal side of the blood vessels, where they stabilize the vessels and regulate blood flow [6].

Different types of blood vessels are composed of different tissue layers and mural cells (Fig. 1). Microvessels like capillaries, small arterioles and venules recruit pericytes, which are often embedded within the endothelial basement membrane (Fig. 1A) [6,7]. In contrast, large arteries and veins are composed of three tissue layers (Fig. 1B). The most inner layer (tunica intima) is composed of ECs and their vascular basement membrane. The second layer (tunica media) consists of vascular smooth muscle cells (vSMCs). Generally, veins exhibit less vSMCs than arteries because they experience a lower blood pressure than arteries. The most outer layer (tunica externa) mainly contains fibroblasts and collagen. In addition, different layers are separated by an elastic lamina [8,9].

2.2. Early development of the blood vasculature

The blood vasculature is the first functional organ in the embryo, and is essential for embryonic development [10,11]. Two major ways of blood vessel formation have been described for mice: vasculogenesis and angiogenesis. Vasculogenesis describes de novo formation of a lumenised blood vessel from EC cords, while angiogenesis refers to the development of new blood vessels from pre-existing ones with already existing vascular lumens [12].

2.2.1. Vasculogenesis

The dorsal aorta is the first blood vessel formed via vasculogenesis [10,13]. At around embryonic day (E) 7.0, angioblasts start to migrate out of the mesoderm, differentiate into ECs, and form the aortic primordia [9,14,15]. The vascular endothelial growth factor receptor 2 (VEGFR2; also known in humans as Kdr and in mice as Flk1) regulates vasculogenesis, since its deficiency in mice impairs the formation of blood islands and vessels, and results in embryonic lethality [16,17]. At around E8.0 (1–2 somite (S) stage), clusters of ECs can be detected within the mouse embryo. By further reorganization, ECs form cords that are subsequently lumenised (at 3–5S stage), resulting in the formation of the paired dorsal aortae that are visible at each side of the notochord. By E8.25 (6–8S stage) lumen formation is complete, and the dorsal aortae become enlarged [10]. During later development, they fuse in the midline in order to form one single aorta [14]. From around E9.0 onwards the heart beats regularly and the development of other organs is initiated [11].

2.2.2. Angiogenesis

Following vasculogenesis, blood vessels undergo angiogenic remodelling and arterio-venous differentiation. Angiogenesis is initiated by pro-angiogenic signals like the vascular endothelial growth factor-A (VEGF-A), which is a VEGFR2 ligand secreted by hypoxic tissues during development, growth and disease [18]. In response to VEGF-A and other pro-angiogenic stimuli, cell–cell junctions are remodelled, vascular basement membrane is degraded, and certain ECs within a vessel are selected as 'tip cells' [3,18]. A tip cell is typically characterized by long filopodial extensions and guides the growth of the developing sprout. In contrast, neighbouring ECs, called 'stalk cells', follow the tip cell, proliferate, create a lumen, produce basement membrane and recruit pericytes [18,19]. Interestingly, the selection of tip and stalk cells is a dynamic process, as shown by a study in which ECs were observed competing for the tip cell position, and could dynamically replace this position [20]. The key molecular mechanism regulating the selection of tip and stalk cells is the Delta-like 4 (Dll4)/Notch signalling pathway, and is based on lateral inhibition [21–25]. A third cell type has been described for the most stable and mature ECs within the growing sprout, called 'phalanx cells', which are characterized by decreased migratory activity and proliferation rate [26].

Fully functional vessels are probably formed by anastomosis, which involves the fusion of the tips of two growing sprouts and the subsequent formation of a continuous vascular lumen [3,24]. Vascular endothelial cadherin (VE-Cadherin) is expressed on filopodial extensions of tip cells and was suggested to facilitate tip cell contacts [27]. Sprouting vessels undergo further maturation by depositing a basement membrane and recruiting mural cells, the latter via the upregulation of platelet-derived growth factor B (PDGFB) and transforming growth factor-β1 (TGFβ1) [7,18,28].

In the last years, our understanding of the molecular mechanisms underlying angiogenesis has benefited in a great manner from vascular model tissues like the mouse retina [29–31]. Additionally, computational modelling studies have contributed to better understand angiogenesis [32–34].

2.3. Formation of tubular blood vessels

The formation of functional blood vessels requires that a continuous lumen develops along the entire vessel to allow blood flow. Several studies performed in vivo (mouse and zebrafish) or in vitro have revealed different mechanisms of how a blood vessel might form [10,35–39]. All models share three common steps: the formation of a cord, the creation of a lumen, and the initiation of blood flow together with enlargement of the vessel. It is still controversial whether a lumen is formed by 'cell hollowing' or by 'cord hollowing', or both. In the first process, a new lumen emerges

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