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REVIEW

Formation of cardiovascular tubes in invertebrates and vertebrates

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Abstract The cardiovascular system developed early in evolution and is pivotal for the transport of oxygen, nutrients, and waste products within the organism. It is composed of hollow tubular structures and has a high level of complexity in vertebrates. This complexity is, at least in part, due to the endothelial cell lining of vertebrate blood vessels. However, vascular lumen formation by endothelial cells is still controversially discussed. For example, it has been suggested that the lumen mainly forms via coalescence of large intracellular vacuoles generated by pinocytosis. Alternatively, it was proposed that the vascular lumen initiates extracellularly between adjacent apical endothelial cell surfaces. Here we discuss invertebrate and vertebrate cardiovascular lumen formation and highlight the possible modes of blood vessel formation. Finally, we point to the importance of a better understanding of vascular lumen formation for treating human pathologies, including cancer and coronary heart disease.

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Introduction

In all organisms, metabolic processes in most tissues rely on the supply of oxygen and nutrients as well as export of metabolic waste products. However, both solubility and diffusion rates of oxygen in aqueous solutions are so low that a cardiovascular system is needed for the growth and development of multilayered organisms (Fig. 1). For example, some invertebrates like Porifera and Cnidaria circulate oxygen and nutrients that are dissolved in external fluids in and out of a gastrovascular body cavity with the help of apical cilia and/or muscular movements (Fig. 1A, *a*). The evolution of more complex and often larger invertebrates like arthropods, mollusks, and annelids led to the formation of a transport system—the cardiovascular (circulatory) system—to deliver oxygen and nutrients to all cells located deep inside the organism (Fig. 1B, C) [1]. In mammals, the cardiovascular system is the first functional organ system to form during embryogenesis to ensure that the embryo grows and develops beyond a few millimeters in size (Fig. 1D).

Invertebrates, such as arthropods and mollusks, with the exception of cephalopods, have an open circulatory system (Fig. 1B), and the cardiovascular lumens are surrounded by the basal cell surfaces of cardioblasts (Fig. 1b) [2, 3]. Hemolymph, a type of extravascular fluid combining the properties of blood and interstitial fluid, is pumped from the heart through blood vessels into the open hemocoel, to provide the internal organs with its content.

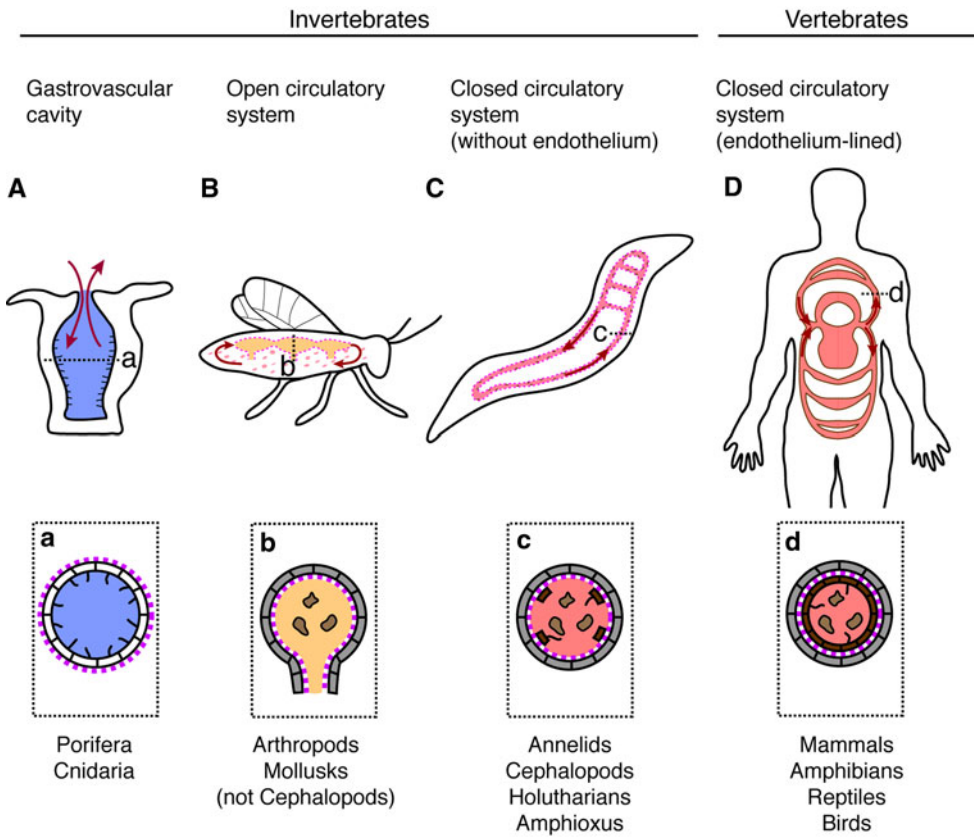

Fig. 1 Circulatory systems in multicellular organisms. Schematic drawings of representative multicellular organisms. *Black dotted lines* indicate the place of cross sections shown in the *boxes* below (*a–d*). **A** In Porifera and Cnidaria, external fluids are actively moved (*red arrow*) in and out of the gastrovascular cavity (*blue*) by apical cilia and/or contractive muscular movements. *a* Cilia on the apical cell surface of gastrodermal cells face the gastrovascular cavity, while the basement membrane (*purple*) faces away from the cavity lumen. The gastrovascular cavity contains no blood cells. **B** In arthropods and mollusks, with the exception of cephalopods, the heart pumps the hemolymph (*orange*) into the open hemocoel, from where it is retrieved back into the heart (*red arrows*). Organs are surrounded by the hemolymph. *b* The vascular lumen contains hemocytes (*light brown*) and is lined by the basement membrane (*purple*) of cardioblasts (*grey*). **C** In annelids, cephalopods, holothurians, and amphioxus, the blood (*red*) is located within blood vessels and is pumped by contractile myoepithelial cells. *Red arrows* indicate the direction of the blood flow. *c* The lumen of blood vessels is lined by the basement membrane (*purple*) of mesothelial cells (*grey*) and/or intestinal cells. Free hemocytes (*light brown*) locate inside the blood vessel lumen, while adherent hemocytes (*dark brown*) partially cover the luminal basement membrane. **D** In vertebrates, the circulatory system is closed. *Red arrows* indicate the direction of the blood flow. *d* The lumen contains blood cells (*light brown*) and is lined by the apical cell surface of endothelial cells (*dark brown*), which produce their own basement membrane (*purple*) and adhere to each other via junctions (not shown). Peripheral mural cells stabilize the blood vessels (*grey*)

In other invertebrates, such as cephalopods [4], holothurians [5], some annelids [6], and amphioxus [7], blood is localized in a closed circulatory system, meaning an anatomically defined compartment separated from the coelomic cavity (Fig. 1c). These blood vessels are simple channels surrounded by basal cell surfaces and extracellular matrix (ECM) of surrounding mesothelial cells and, in some cases, also intestinal cells that form the lining of several body cavities such as the pleura, peritoneum, pericardium and the intestine, respectively (Fig. 1c) [8, 9]. The vascular lumen contains plasma and blood cells involved in oxygen, nutrient and waste transport, immunity, and tissue remodeling [10].

In contrast, the closed vascular system of vertebrates is built by multicellular tubes with a central lumen [11], and is surrounded by the apical cell surface of endothelial cells (ECs) (Fig. 1d) [12]. The EC-lined blood vessels form a complex hierarchical network of arteries, veins, and capillaries [11, 13], and can be found in almost every tissue, with a few exceptions, such as cartilage or cornea. ECs produce their own basement membrane, which is involved in the recruitment of perivascular muscle-like (mural) cells to the outside of the EC-lined tubes (Fig. 1d) [14, 15]. These mural cells stabilize the blood vessels and regulate their blood flow [16].

Blood vessel formation in invertebrates

Different mechanisms regulate vascular lumen formation in invertebrates. For example, during amphioxus development, a laminin-positive ECM separates the basal cell surfaces of endoderm and mesoderm along the anterior–posterior (A–P) axis [17, 18]. Blood cells are present in this ECM-filled space and may be involved in both depositing and finally clearing this ECM to form a patent vascular lumen [18]. This hypothesis of vascular lumen formation is in line with reports on ECM production by invertebrate hemocytes [19, 20], as well as the observed phagocytic activity of amphioxus hemocytes [21, 22].

According to a morphological analysis of the annelid *Sabellaria cementarium*, blood vessels form through separation of apposing basement membranes beneath mesothelial cell sheets [6]. De-adhesion progresses ventro-dorsally and is accompanied by the accumulation of blood in the space between the two mesothelial cell layers. Mechanistically, it is unlikely that osmotic pressure drives the formation of these lumens, as proposed for the zebrafish gut [23] or mouse blastocyst [24], since small gaps are found within the mesothelial cell layers. Therefore, the lumen is more likely to develop by cell–cell repulsion as proposed for the formation of the *Drosophila melanogaster* heart (see below) and/or the rising hydrostatic (blood) pressure.

During heart formation in *D. melanogaster*, cardioblasts originate from the lateral plate mesoderm and migrate towards the midline [25], a step regulated by the Robo-Slit pathway [26–28]. After mesenchymal-epithelial transition, cardioblasts form dorsal cell–cell contacts via *Drosophila* epithelial (DE)-cadherin, wrap around the developing lumen, and establish ventral junctional contacts [29]. Recently, two reports showed that the Robo-Slit pathway also controls cardiac cell shape change and prevents DE-cadherin-mediated junctional contacts at the luminal cell surfaces of the cardioblasts [30, 31]. Similar to other invertebrates, the luminal cell surface of cardioblasts displays a rather basal cell polarity, since apical markers are missing on the luminal side [30].

Advantages of endothelium-lined blood vessels

EC-lined blood vessels are modular and are involved in the secretion, protection, metabolism, and immunity of vertebrate tissues. Higher metabolic rates of tissues require greater cardiac output, thus resulting in a higher blood pressure, and the EC-lining of vertebrates helps to keep blood inside the vascular lumen. In addition, the apical endothelial cell surfaces facilitate blood flow by providing a smooth cell surface. The latter also inhibits platelet adhesion and blood clotting. In contrast, in the case of injury, the EC surface can become pro-thrombotic, thus enabling blood clotting.

ECs furthermore regulate the permeability of blood vessels as well as control the passage of immune cells from the blood into the surrounding tissues. Circumjacent signals induce the expression of homing factors on the luminal (apical) cell surface of ECs such as E- and P-selectin, intercellular cell adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 [32–35], to enable the transmigration of blood cells [36].

Mutual interaction between ECs and developing tissues also assist in tissue formation [37–41] as well as adaptation of blood vessel morphologies to the need of the surrounding tissue. For example, ECs in the brain are exposed to paracrine factors [42, 43], which induce ECs to form a blood–brain-barrier (BBB) [44] and to control the selective passage of molecules. In contrast, in other organs such as in endocrine glands, hepatic sinusoids, and kidney glomeruli, ECs are highly permeable. Permeability is regulated by the vascular endothelial growth factor-A (VEGF-A)—also known as vascular permeability factor (VPF) [45], which is expressed by pancreatic beta cells, hepatocytes, and renal glomerular epithelial cells, respectively [45–48]. Finally, perivascular mural cells can constrict and relax, thus controlling the lumen diameter of and blood flow through the EC-lined blood vessels.

Evolution of the endothelium-lined blood vessel system

The evolutionary origin of the vertebrate endothelium is unclear. One possibility is that EC-lined blood vessels of vertebrates are derived from invertebrate hemocytes or blood cells that formed intercellular contacts (Fig. 1c, d).

In support of this hypothesis, invertebrate hemocytes and vertebrate blood cells exhibit EC-like properties. For example, the hemocytes in annelids, hemichordates and amphioxus partially cover the luminal basement membrane (Fig. 1c) [7, 18, 49–51] and are sometimes called invertebrate-specific ECs [4, 5, 22, 52]. Furthermore, blood cells in *D. melanogaster* express receptors for platelet-derived growth factor (PDGF) and VEGF [53], i.e., PDGF/VEGF-like receptor (PVR), and are attracted by VEGF-like growth factors [54, 55]. In addition, hematopoietic progenitor cells respond to VEGF-A [56], and macrophages express the endothelial cell adhesion molecule CD31 [57] and form intercellular junctions upon activation [58]. Recently, macrophage-like cells were shown to display lymphatic endothelial cell markers and to incorporate into the wall of lymph vessels [59, 60].

Vice versa, vertebrate ECs possess several blood cell-like properties and can develop from hemangioblasts,

which are common precursors of ECs and hematopoietic cells [61–65]. Furthermore, some ECs give rise to blood cells [66–68], and ECs express hematopoietic stem cell markers such as CD34 and Podocalyxin [12, 69, 70].

Finally, one can speculate that mural cells arose from mesothelial cells during vertebrate evolution, since invertebrate mesothelial cells harbor properties of perivascular mural cells. For example, both coelomic myoepithelium in invertebrates and mural cells in vertebrates [pericytes and smooth muscle cells (SMCs)] are contractile [7, 71, 72]. In addition, during vertebrate embryonic development perivascular mural cells (SMCs) of coronary arteries arise from the epicardial mesothelium [73], and the mesothelium was shown to contribute to vascular SMCs in the gut and lung vasculature [74–76].

Blood vessel formation in vertebrates

Two processes describe vascular lumen formation in vertebrates: vasculogenesis and angiogenesis [77–79]. In the developing embryo, the dorsal aorta (DA) is the first blood vessel to form de novo via vasculogenesis [12, 79]. Endothelial precursor cells (angioblasts) migrate towards the endoderm, differentiate into ECs, and form the aortic primordium. In contrast, the formation of secondary blood vessels, such as intersomitic vessels (ISVs), is called angiogenesis, since these blood vessels form from pre-existing vessels, such as the DA [80, 81]. Recently, a third mode of vascular lumen formation has been described for the formation of the cardinal vein (CV), i.e., a subpopulation of aortic ECs sprouts ventrally from the DA primordium and connects with adjacent cells to form the CV primordium [82]. Strikingly, although these modes of vessel formation differ, the sequence of events that leads to lumenized vascular tubes is similar and consists of three basic steps: (1) formation of a multicellular EC cord, (2) formation of a central vascular lumen within this cord, and (3) initiation of blood flow through the vascular lumen [12, 82–84].

Endothelial vascular lumen formation

Historically, the endothelium-lined vascular lumen was suggested to form by two distinct ways: extracellularly via cord hollowing [85] or intracellularly via cell hollowing [86]. In the last decades, vascular lumen formation was suggested to exclusively occur via cell hollowing [83, 87, 88]. According to this model, each EC within an EC cord forms a large intracellular vacuole through fluid uptake, called pinocytosis. The vacuoles from adjacent ECs subsequently coalesce to form seamless vascular lumens, meaning that no junctions are found on cross sections [83]. This model was supported by in vivo time-lapse imaging of ISVs in zebrafish embryos [83], showing vacuole-like structures at the onset of vascular lumen formation. However, lumen formation in these vessels was subsequently re-investigated in zebrafish embryos and found not to develop from intracellular vacuoles, but instead to form extracellularly between adjacent ECs [84]. Therefore, to date, in vivo evidence for vascular lumen formation via intracellular vacuole coalescence is still missing.

In contrast, several studies in both zebrafish and mouse argue for cord hollowing as a mechanism of vascular lumen formation [12, 82, 84, 89, 90]. In addition, a recent study suggests that EC-cords undergo junctional remodeling and cell-shape changes to create multicellular vascular tubes with a central “extracellular” vascular lumen (Fig. 2) [12].

Neither the cell hollowing model nor the cord hollowing model had been able to explain the underlying molecular mechanism of vascular lumen formation in vivo. However, a recent study uncovered parts of the molecular mechanism and identified the roles of vascular endothelial (VE)-cadherin and VEGF-A in vascular lumen formation in vivo [12]. More specifically, in non-lumenized EC cords (Fig. 2a), VE-cadherin is required for localizing the luminal plasma membrane to the endothelial cell–cell contact (Fig. 2b, green color), whereas VEGF-A is required to generate the physical force to separate the ECs from each other to form a multicellular vascular lumen (Fig. 2c) [12]. This described molecular mechanism was identified in the developing mouse aorta—the largest arterial blood vessel—in which two (Fig. 2a, c) or more (Fig. 2d, f) ECs can be found on cross sections at the onset of vascular lumen formation. A possible argument against the general applicability of this described mechanism could therefore be that it may not apply to lumen formation of smaller vessels, such as capillaries. This is because capillaries may also have only one junction, or even no junction, on cross sections.

However, based on elegant work on the tracheae of *D. melanogaster*, cord hollowing can still be considered as a possible mechanism for the formation of small vascular lumens with only one junction on cross sections (Fig. 3). More specifically, multicellular tracheal tubes were shown to remodel into unicellular tubes due to junctional rearrangements (Fig. 3a, d) [91]. Since vascular lumen formation is a dynamic process that also involves junctional remodeling [12, 84, 89, 92], it is possible that cord hollowing also accounts for the formation of most vascular lumens in vertebrates, including the lumens of capillaries.

Since fusogenic functions of endothelial plasma membranes have been described, e.g., during trans-cellular

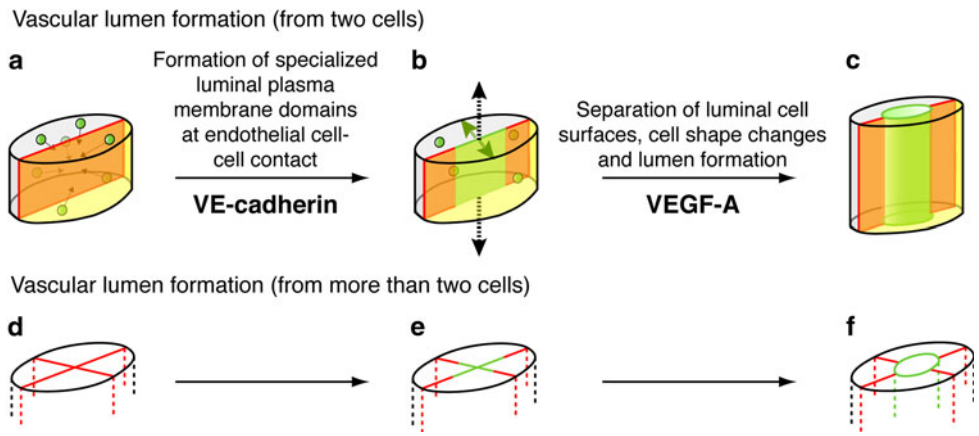

Fig. 2 Formation of multicellular blood vessels. The following scenario is based on observations made in the developing mouse aorta [12]. **a**, **d** Endothelial cells (*grey* and *yellow* in **a**–**c**) are joined by junctions (*red*) and harbor specific luminal or apical plasma membrane proteins in vesicles (*green* in **a**). **b**, **e** A specialized luminal plasma membrane forms (*green sheet*) that is flanked by junctions. This step is regulated by VE-cadherin. **c**, **f** Cell-shape changes result in separation of luminal or apical plasma membranes followed by formation of a vascular lumen (*green cylinder*). The endothelial cells elongate during this process of lumen formation. This step is regulated by VEGF-A

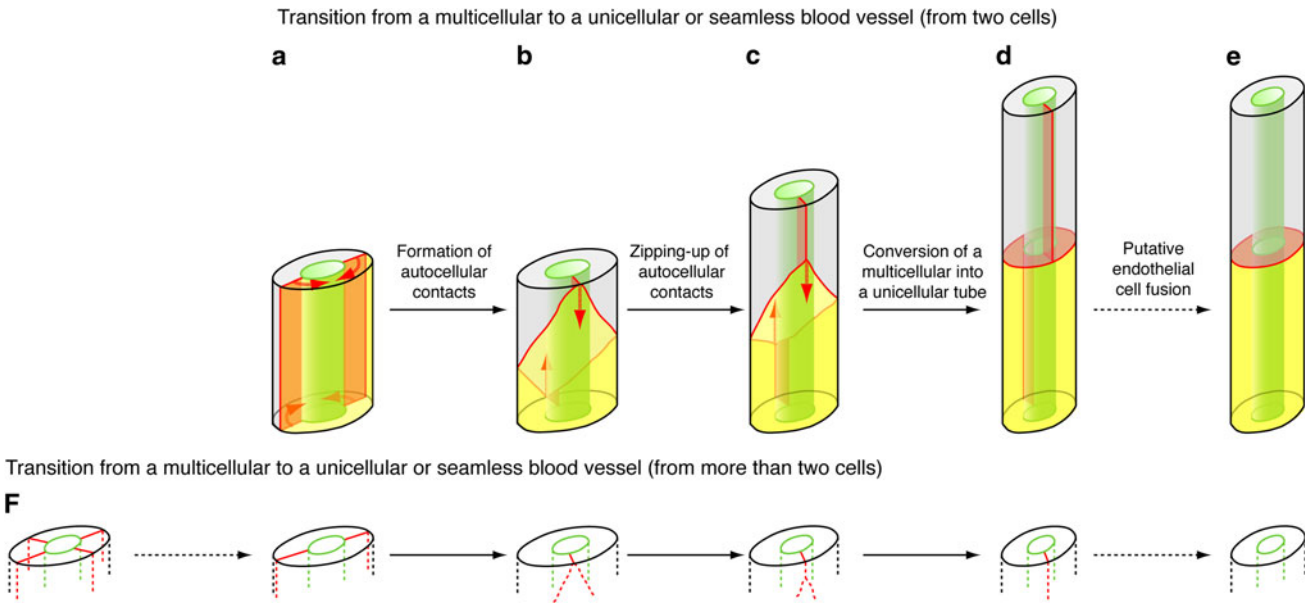

Fig. 3 Hypothetical transition of multicellular blood vessels into unicellular and seamless blood vessels. The following scenario is based on observations on tracheal development in *D. melanogaster* [91, 96] and pharynx development in *C. elegans* [97]. **a** A multicellular tube (consisting of a *grey* and a *yellow* cell in **a**–**e**) with a central lumen (*green cylinder*) is joined by lateral junctions (*red*). The cells reach around the lumen (*red arrows*). **b** Junctions meet at the opposite sides of the lumen, form autocellular contacts and start zipping-up in two directions (*red arrows*). **c** Autocellular contacts zip-up (*red arrows*) and replace intercellular with autocellular junctions. **d** Complete conversion of a multicellular tube into a unicellular tube. **e** Conversion of a unicellular into a seamless tube via autocellular fusion of the plasma membrane at the autocellular contact sites. **f** The same changes apply to a multicellular tube consisting of more than two cells to first form a bicellular and subsequently a unicellular or seamless tube

migration of leukocytes through ECs [93], it is even possible to speculate that a unicellular junction occasionally disappears if the EC fuses with itself at the junction site (Fig. 3d, e). However, the existence of seamless vessels in the in vivo situation was illustrated only a few times [94, 95]. It is therefore necessary to carefully analyze whether a vessel is seamless or not. Compared to blood vessels like the DA, the CV and ISVs, which have a distinct direction (i.e., anterioposterior for the aorta and the vein or dorsoventral for ISVs), capillaries are non-directional and curved. Thus, regions within a developing small blood vessel may, when sectioned and observed under the light or electron microscope, appear devoid of any intercellular junction, even though such a vessel is not seamless

(Fig. 4). Therefore, only consecutive sections along a large part of the vessel axis or a careful analysis of the junctions along the vessel in three dimensions can reveal whether a vessel is seamless, uni- or multicellular.

It is important to note that even if seamless vessels are found, based on careful consecutive EM sections or 3D light microscopic analyses of junctions, this finding will not prove intracellular vacuole coalescence as an underlying mechanism. Instead, seamless vessels could have formed via the mechanism described for the developing mouse aorta (Fig. 2) [12] and subsequently undergone junctional rearrangement and endothelial cell fusion (Fig. 3). This is even more likely because such events have already been described in vivo for the tracheae in *D. melanogaster* [91, 96] and pharynx in *C. elegans* [97] (applied to blood vessels in Fig. 3).

Endothelial cell polarity

Formation of an extracellular vascular lumen requires the establishment of endothelial cell polarity (Fig. 2) [12]. Similar to other tubular systems, such as MDCK cysts, cadherins, and integrins, possibly in combination with the phosphatase and tensin homolog PTEN, are required for the localization of apical plasma membrane molecules such as Podocalyxin/gp135 at the cell–cell contact. These apical proteins subsequently define the endothelial cell–cell contact as the place of vascular lumen formation [12, 98–101].

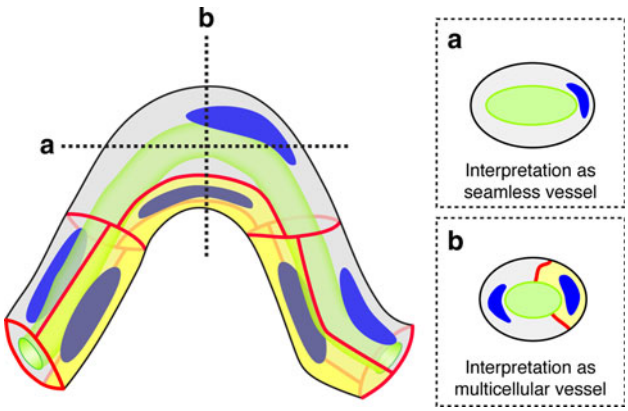

Fig. 4 Difficulties in interpretation of sections through blood vessels. A curved multicellular small blood vessel, e.g. capillary, indicating *a* and *b* places of hypothetical cross sections (*dotted lines*). Endothelial cells are shown in *grey* and *yellow*, the vascular lumen is shown in *green*, cell–cell junctions in *red* and nuclei in *blue*. *a* A cross section through the curved arch shows a blood vessel that appears devoid of intercellular junctions and is misinterpreted as seamless. *b* Different orientation of cross section through the same curved arch results in a correct interpretation of the blood vessel as multicellular

Vascular lumen expansion

Under physiological conditions in the adult, the vascular lumen diameter can be regulated through vasodilation and vasoconstriction, which is achieved by relaxation and constriction of perivascular SMCs. SMC-driven vasodilation can result in a short-term lumen expansion by a factor of ~2. During early embryogenesis, however, the lumen of the aorta is 5 µm in diameter [12] and increases until adulthood by a factor of ~200 in mice and ~5,000 in humans.

During embryogenesis, the lumen diameter is also regulated by mutual interaction between ECs and perivascular mural cells as blood vessels devoid of pericytes show irregular lumen diameters [102]. In the adult, hemodynamic stimuli caused by shear stress also induce lumen diameter expansion as seen for example during the growth of collateral arteries in arteriogenesis [103]. However, the embryonic aorta at early stages of lumen expansion lacks mural cells and blood flow [12, 104], showing that alternative mechanisms of vascular lumen expansion must be in place.

Importantly, EC proliferation directly affects lumen diameter and requires signaling via VEGF-A or other growth factors, such as Wnts [105, 106]. Interestingly, the soluble VEGF isoform VEGF-A_{120} generated vessels of larger diameter compared to VEGF-A_{188}. In contrast, VEGF-A_{164} generated intermediate vessel diameters [105]. However, other growth factors, such as Angiopoietin-2 (Ang2) and Apelin are also involved in EC proliferation and vascular lumen expansion [107–110]. Ang1 was shown to venous-specifically increase the blood vessel diameter by regulating EC proliferation [111, 112]. Furthermore, Notch-mediated signaling may regulate lumen diameter differentially in arteries and veins. For example, constitutively active Notch4 resulted in dilated brain capillaries and DA [113, 114], whereas the CV appeared underdeveloped. Moreover, inactivation of Notch1 resulted in smaller aortae and larger veins [114]. In contrast, inactivation of both Notch1 and Notch4 resulted in reduced or partially absent vascular lumens in both aortae and veins [115]. Finally, a recent study in zebrafish embryos showed that prior to blood flow, rapid luminal expansion of the CV coincided with the invasion of erythrocytes positioned ventral to the DA [82], suggesting that blood cells may also be involved in vascular lumen expansion.

Medical applications

The endothelium is involved in most human diseases. Despite substantial differences between the vertebrate and invertebrate vasculature, knowledge about the “primitive”

invertebrate blood vessels may also be important for understanding and treating human pathologies. For example, there are certain tubular structures in tumors that appear similar to the blood vessels formed in invertebrates [116]. Like in invertebrates, the lumen of these channels, possibly formed via "vasculogenic mimicry", are lined by basal cell surfaces (basement membranes) of the surrounding cells [117]. Although controversially discussed [118], these channels may contribute to the transport of plasma and nutrition to the tumor tissue [119].

The circulation of blood cells within a tumor is to a large extent enabled by EC-derived blood vessels [118]. Therefore, understanding the molecular mechanisms of vascular lumen formation in ECs is useful for identifying anti-angiogenic drugs in order to prevent blood cell-mediated oxygen transport to tumors in cancer patients. In this regard, it is noteworthy that in the absence of Delta-like ligand 4 (Dll4) the size of transplanted tumors was significantly decreased, because perfusion through the tumor vessels in Dll4-deficient mice was reduced [120]. Importantly, this appeared to be due to significantly smaller or missing vascular lumens [121–123]. However, although Dll4-mediated signaling has emerged as an attractive target for cancer therapy, chronic Dll4 blockade in mice and rats was shown to disrupt normal organ homeostasis and produced pathologies in multiple organs [124].

Collateral arteries are clinically relevant targets for drug-assisted lumen expansion in order to treat coronary heart disease. The growth of pre-existing blood vessels results in a lumen diameter increase of up to 20-fold [125]. Interestingly, in contrast to vasculogenesis and angiogenesis, arteriogenesis is induced independently of the presence of hypoxia [126–129]. Instead, increased fluid shear stress, usually caused by stenosis or occlusion of a major artery, activates expression of specific chemoattractant molecules in ECs. These cytokines include interleukin (IL) -1 and -6, the monocyte chemoattractant protein-1 (MCP-1) or macrophage inflammatory protein-1 (MIP-1) [130] and enhance the transmigration of monocytes/macrophages into deeper parts of the collateral vessel wall. The macrophages subsequently secrete proteases such as matrix metalloproteinases (MMPs) [131] or growth factors such as fibroblast growth factor-2 (FGF-2) and transforming growth factor beta 1 (TGF-β1) [132, 133] to induce proliferation of ECs and SMCs, thus resulting in the expansion of an arteriole into a large artery.

These examples of two common human diseases (cancer and coronary heart disease) illustrate our need to better understand vascular lumen formation at a molecular level in order to design appropriate drugs and therapies.

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