My Findings

Ali Fele Paranj

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Contents

Chapter 4

Molecular Biology

Here in this chapter, I will be covering the basics of the relevant molecular biology concepts. This chapter will serve as a reference for the biological claims throughout the document, as well as the foundation for the review chapters of my thesis.

4.1 Molecular Mechanism of Angiogenesis

Blood vessels and the vascular structure are formed by the differentiation of the cells in the mesoderm layer during the embryo development (the layer which also give rise to blood cells, kidney, liver, connective tissue, etc.) **?**.

4.1.1 A Brief Anatomy of Vessels

Endothelial cells line all of the vessels. Blood vessels (like the arteries and the veins that are the largest vessels of the body) have a thick and tough wall of connective tissue with several layers of smooth muscles. The wall is lined by a very thin layer of endothelial cells (i.e. the endothelium) separated from the outer surrounding layers by basal lamina **?**. It is worth noting that the amount of connective tissue and smooth muscle depends on the diameter of the blood vessel as well as its function, **but the endothelial lining is always present**. In the finest branches of the vasculature (i.e. capillaries and sinusoids) the wall is just made up of endothelial cells and basal lamina. One of the major roles of the endothelial cells is to control to transport of material in an out of the bloodstream.

A study of embryo development reveals that the even larger vessels (like arteries and veins) start developing from smaller vessels that has only endothelial cells and basal lamina. The connective tissue, smooth muscles and pericytes are added later on, by the signaling from endothelial cells. In particular, the recruitment of pericytes are driven by PDGF (platelet driven growth factor) secreted by the endothelial cells.

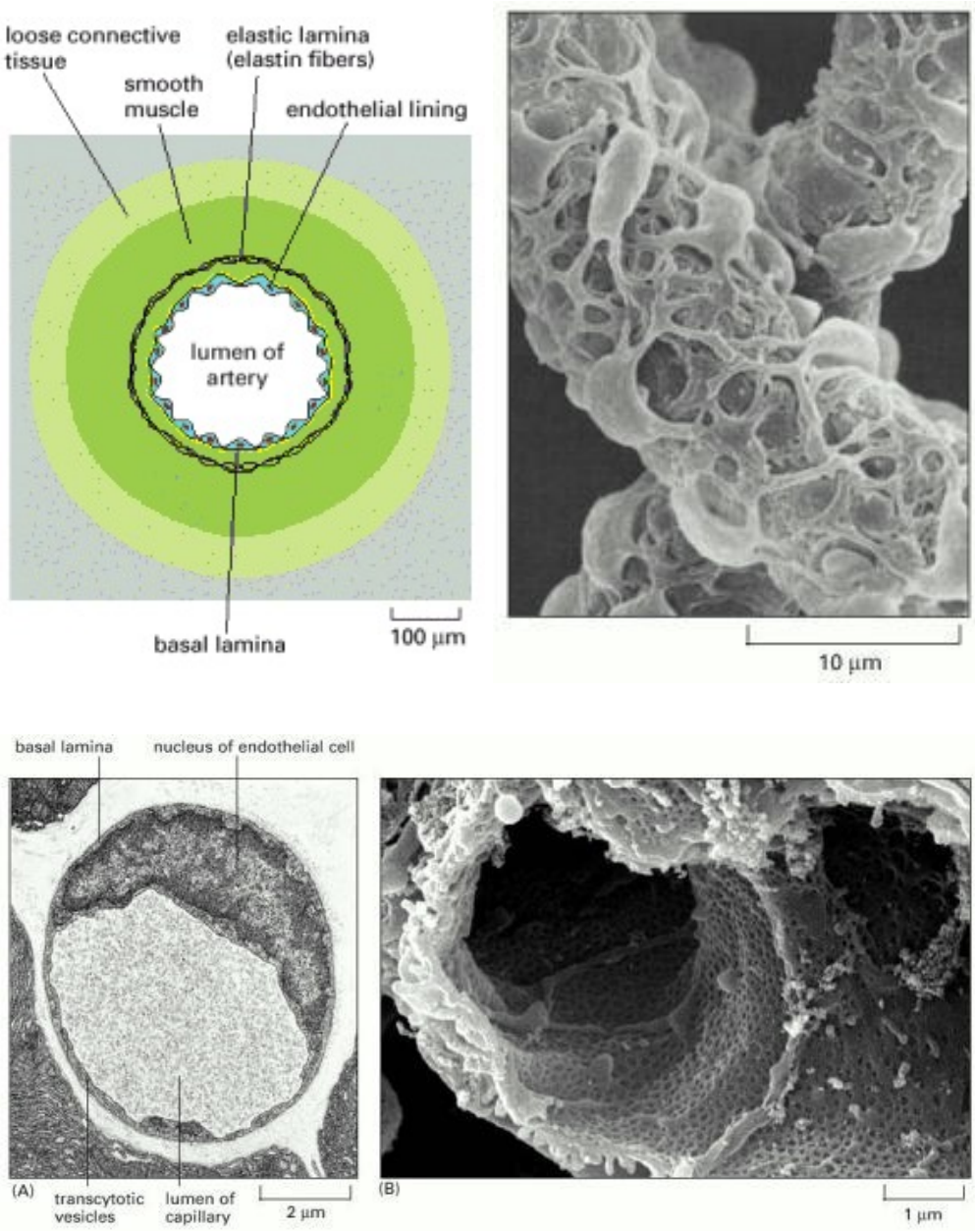

Figure 4.1.1: **Figure Top Left:** This figure shows the anatomy of a large vessel, like vein or arteries. Note that smaller vessels, like capillaries as well as sinusoids consists of only endothelial cells and basal lamina, except for some scattered pericytes wrapped around the walls (see figure Top Left). **Figure Top Right:** Electron micro graph showing small pericytes wrapped around small blood vessels. **Figure Bottom Left:** A capillary that its wall consists of only endothelial cell and basal lamina. **Figure Bottom Right:** Electron micro graph showing a cross section of small capillary in pancreas. All of the figures are from **?**

Also, the following figure summarizes the cross section of different types of vasculature.

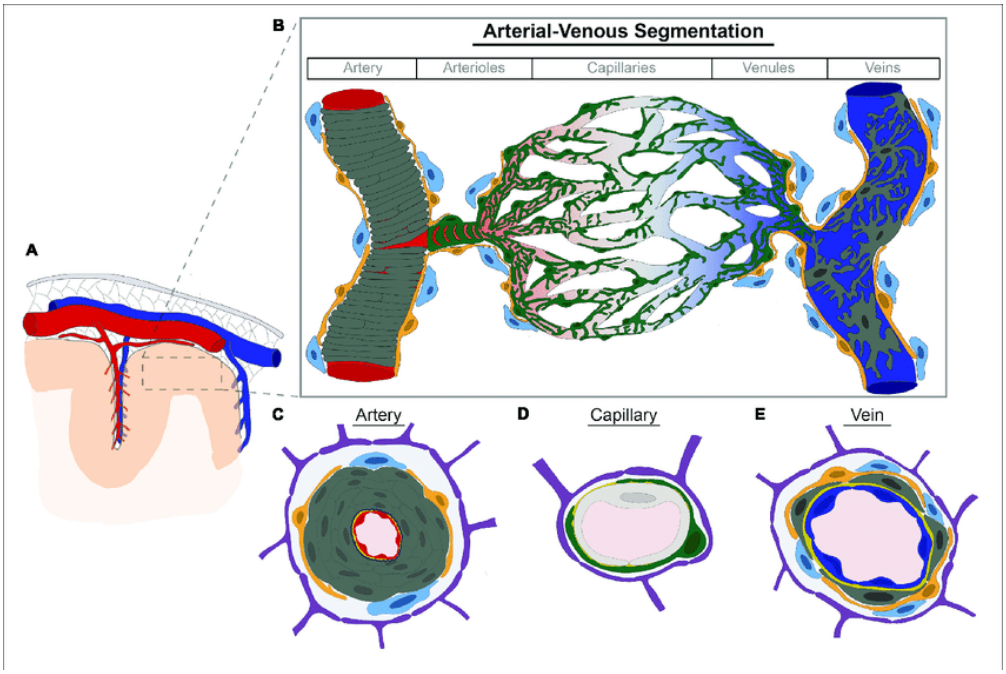

Figure 4.1.2: The cross section of vessels in the form of arteries, capillaries, and vein. Note the single lining of the endothelial cells for the capillary.

4.1.2 Molecular Biology of Vascular Structure

New vessels in the adults originate as capillaries, which sprout from the existing small vessels. Endothelial cells on the arterial and venous side of the developing networks of vessels differ in their surface properties. In the embryo at least, the plasma membrane of the arterial cells contains trans membrane protein ephrine-B2, while the membrane of the venous cells contain the corresponding receptor protein Eph-B4, which is a receptor tyrosine kinase. These molecules mediate a signal delivered at sites of cell-cell contact, and they are essential for the development of a properly organized network of vessels. One suggestion is that they somehow define the rules for joining one piece of growing capillary tube to another **?**.

Observation 4.1.1 The difference in the surface properties of endothelial cells on the arterial and venous side of the developing networks of vessels control the rate an which one piece of growing capillary tube joins another. This becomes very interesting if we consider it along the observations in Köry u. a. (2024). They observed that the blunt-ended capillaries with small diameter are more susceptible for degradation after irradiation. And since the presence of blunt-ended vessels with small diameter increase the flow resistance of the network, pruning these branches "normalizes" the blood flow, hence increase the perfusion after irradiation.

Steps involved in angiogenesis

Individual endothelial cells responds to the signals produced by the organ that they invade. The signal is complex, but the main part of the signal is vascular endothelial growth factor (**VEGF**) (which is a distant relative of platelet driven growth factor (**PDGF**)). The control on the production of VEGF is through its mRNA stability and its rate of transcription. Under a low oxygen concentration, the intracellular concentration of an active form of gene regulatory protein called

hypoxia inducible factor 1 (HIF-1) increases. HIF-1 stimulates the transcription of VEGF gene (and the production of other genes that are needed when the oxygen supply is low). When the VEGF protein is secreted, it is then diffuses through the tissue and acts on nearby endothelial cells.

Endothelial cells that are to form a new capillary, grow out from the side of an existing capillary by forming long pseudopodia pioneering the formation of new capillary sprout that hallows out to form a tube. This process continues until the sprout encounters another capillary, where they merge. In the tumor micro environment, The growth rate of tumor increases abruptly as soon as the vessels reach it.

There are two general balancing forces acting on the angiogenesis

- Inhibitors:
  - endostatin
  - angiostatin
  - thrombospondin
- Angiogens
  - VEGF: Vascular Endothelial Growth Factors.
  - bFGF: Basic Fibroblast Growth Factor.
  - PDGF: Platelet Driven Growth Factor.

The Response of Endothelial Cells to VEGF

The response of endothelial cells to VEGF has four components. First, they produce proteases to digest through the basal lamina of the parent vessels. For the second step, they migrate towards the source of VEGF, and for the third step they proliferate. Finally, they form hallow tubes. It is worth mentioning that VEGF stimulates endothelial cells selectively, while other angiogens, like fibroblast growth factor stimulates other cell types as well. The following figure summarizes these steps.

Controlling Capillary Joining Process

In the following text from **?**, there is some vague hints about the mechanisms that are controlling capillary joining to each other

> Observations such as these reveal that endothelial cells that are to form a new capillary grow out from the side of an existing capillary or small venule by extending long pseudopodia, pioneering the formation of a capillary sprout that hollows out to form a tube (Figure 22-25). This process continues until the sprout encounters another capillary, with which it connects, allowing blood to circulate. Endothelial cells on the arterial and venous sides of the developing network of vessels differ in their surface properties, in the embryo at least: the plasma membranes of the arterial cells contain the transmembrane protein ephrin-B2 (see Chapter 15), while the membranes of the venous cells contain the corresponding receptor protein, Eph-B4, which is a receptor tyrosine kinase (discussed in Chapter 15). These molecules mediate a signal delivered at sites of cell-cell contact, and they are essential for the development of a properly organized network of vessels. One suggestion is that they somehow define the rules for joining one piece of growing capillary tube to another.

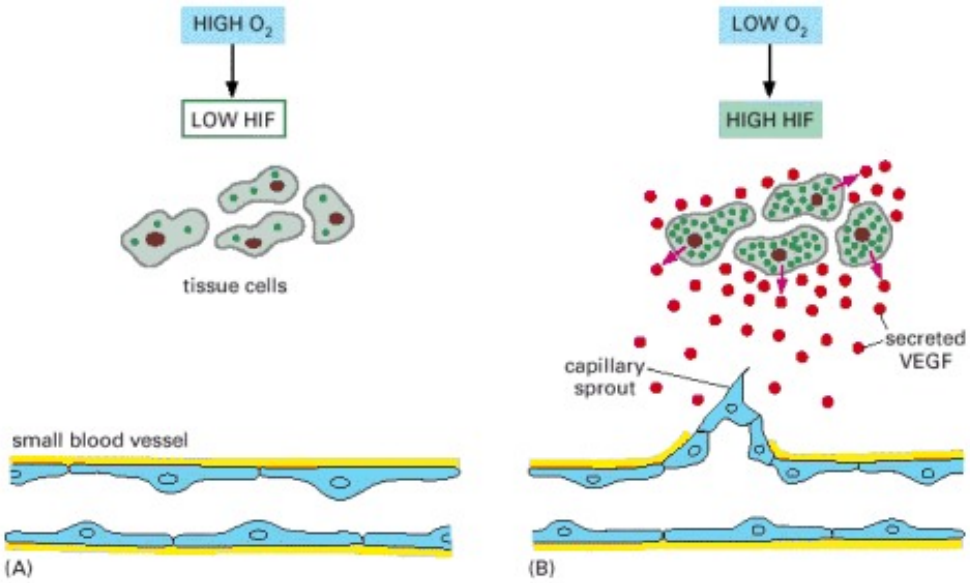

Figure 4.1.3: A summary of the response of the endothelial cells to VEGF. Under low oxygen concentration, the intracellular concentration of HIF-1 increases. This gene regulatory protein in turn increases the transcription of VEGF protein. Then VEGF diffuses through the tissue and stimulates the endothelial cells lining the vessels. Figure is from **?**.

Formation of tube structures by endothelial cells

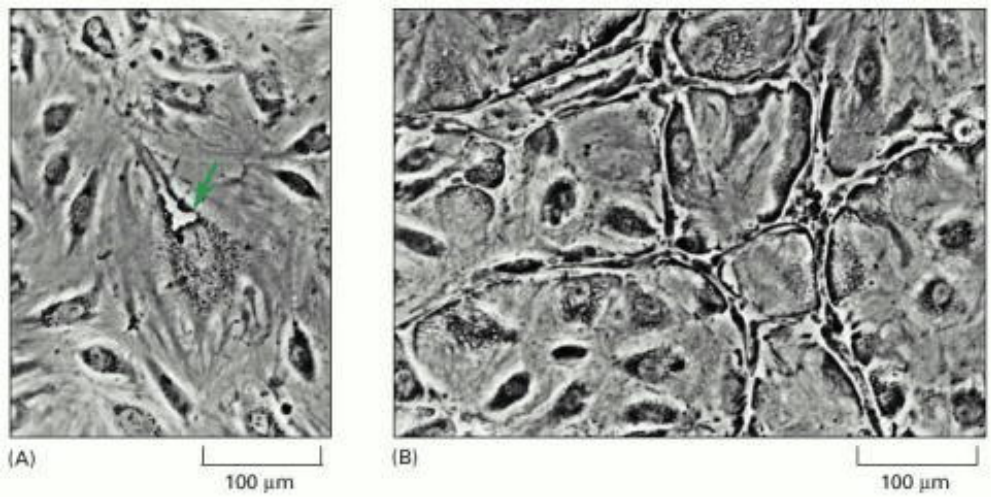

Figure 4.1.4: The endothelial cells, when supported by suitable growth medium and signals, start to form hallow structure, that do not contain any blood, and not fluid passes through them. This indicates that the no mechanical trigger (i.e. pressure) is required to form the hallow structure for the new vessels. Image from **?**.

It was one of my main concerns that what is the process in which a single lining of endothelial cells following a tip cell forms a hallow tube (i.e. vessel). The following text from **?** explains this clearly. This process has also been described in angiogenesisYoutube.

Experiments in culture show that endothelial cells in a medium containing suitable growth factors will spontaneously form capillary tubes, even if they are isolated from all other types of cells (Figure 22-26). The capillary tubes that develop do not contain blood, and nothing travels through them, indicating that blood flow and pressure are not required for the initiation of a new capillary network. Endothelial cells in culture spontaneously develop internal vacuoles that appear to join up from cell to cell, giving rise to a network of capillary tubes. These photographs show successive stages in the process.

4.2 Biological Assays to Study Angiogenesis

4.2.1 Corneal Micropocket Assay

This is one of the simple and reproducible assays to study angiogenesis in a eye. The process involves introducing growth factors in the eye ball of mouse, and then letting the vascular network to form. This is a video from JOVE explaining the details of the protocol (conealMicroPocketAssayJOVE)

4.3 Some Histology

In short, histology is the study of the animal tissue in the microscopic scale (which is also known as the microscopic anatomy or micro anatomy). Studying different types of animal tissue falls in the realm of histology.
There are four types of animal tissue

(i) Epithelium
- squamous: endothelial lining of the vascular structure is of this type.
- cuboidal
- columnar

(ii) Muscle tissue
- smooth muscle
- skeletal muscle
- cardiac muscle

(iii) Connective tissue
- cartilage
- bone
- blood
- lymph
- hemopoietic

(iv) Nervous tissue
- central nervous system
- peripheral nervous system

Among this list of the four basic types of the animal tissue, we will focus on the Epithelium.

4.3.1 Epithelium

Epithelium forms continuous sheets of cells that line internal surfaces and cover the external surfaces of the organs. A **basement membrane** separates an epithelium from the underlying connective tissue.

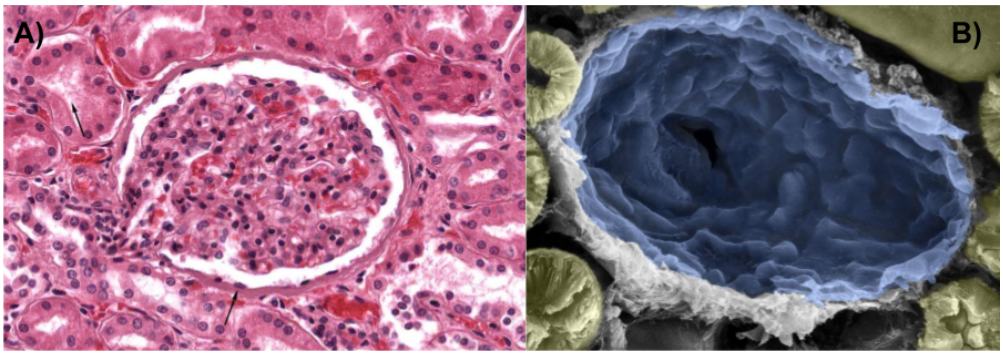

Figure 4.3.1: A) A microscopic image of renal corpuscle that contains a glomerulus (a tuft of capillaries) surrounded by Bowman's capsule. The interior of the capsule, is lined with a simple squamous epithelial that rests on a thick basement membrane. The only part of these cell visible is their nuclei bulging into the interior. B) Scanning electron microscope of renal corpuscle that its glomerulus is removed. The simple squamous epithelial can be seen in blue (borders of individual cells are not visible). Both images are from histologyguide.com.

Figure 4.3.2: A pathology image of bile duct (the large lumen at the center). There are many blood vessels in the surrounding connective tissue. Blood vessels are lined with simple squamous epithelial. The only par of these cells visible is their flatten nuclei. **Epithelium that lines blood vessels, heart, and lymphatic vessels is also known as endothelium.**

4.4 Important Random Facts

- The over expression of ANG1 (angiopoeiting1) induces vascular remodeling that leads to the formation of vessels with a wider diameter (Augustin u. a. (2009)).
- TIE2-mediated EC activation controls the expression of endothelial apelin, which in turn acts in an autocrine manner on EC-expressed G-protein-coupled APJ receptors, the downstream signalling of which contributes to the control of vessel diameter (Augustin u. a. (2009); Kidoya u. a. (2008)).
- Differences in arterio-venous shear stress also control Ang–Tie signalling (Augustin u. a. (2009)).
- The quiescent EC phenotype is maintained by constitutive ANG1–TIE2 signalling. ANG1 clusters TIE2 junctionally at inter-endothelial cell junctions in trans to transduce survival signals. Differences in arterio-venous shear stress also control Ang–Tie signalling. During the transition from the quiescent to the activated phenotype, ECs liberate their endogenously stored pools of ANG2, and this antagonizes ANG1–TIE2 signalling to facilitate EC responsiveness to exogenous cytokines. As such, the absence or presence of stored ANG2 contributes to the control of the **adaptive plasticity of the vascular endothelium** (Augustin u. a. (2009)).
- Oscillatory flow has also been measured in humans and reported in Rodgers u. a. (1984) (Carr u. a. (2005)).
- Observed oscillation frequencies range up to 240 cycles per minute. High frequency oscillations (greater than 50 cycles per minute) have been attributed to either heart pulse or breathing rhythms. Lower frequency oscillations are thought to be caused by vasomotion. Observed frequencies of vasomotion have been reported to range from 2.7 to 32 cycles per minute.6,23 Recent analysis of RBC velocities and arteriole diameter dynamics by Parthimos et al. suggests, however, that low frequency oscillations may not be solely due to vasomotion. Their analysis demonstrates that two important measures (correlation dimension and Lyapunov exponent) of the RBC velocity oscillations depends on whether vasomotion is present or not. This indicates that something other than vasomotion is also driving the RBC velocity dynamics Carr u. a. (2005)
- The responses outlined above lead to continued vessel shrinking and eventually to pruning of vessels that are nonfunctional with respect to both convective and diffusive transport. Typically, such vessels have low shear stress and moderate or high oxygen levels and therefore receive a negative net growth stimulus, causing decrease in diameter Pries und Secomb (2014).
- The need for distribution of capillaries throughout the tissue implies the presence of both short and long flow pathways connecting the feeding arteriole to the draining venule Pries und Secomb (2014).
- If the shrinking of a given vessel leads neither to local hypoxia nor to increased wall shear stress, then it receives no increasing growth stimulus and continues to shrink, eventually being pruned Pries und Secomb (2014).
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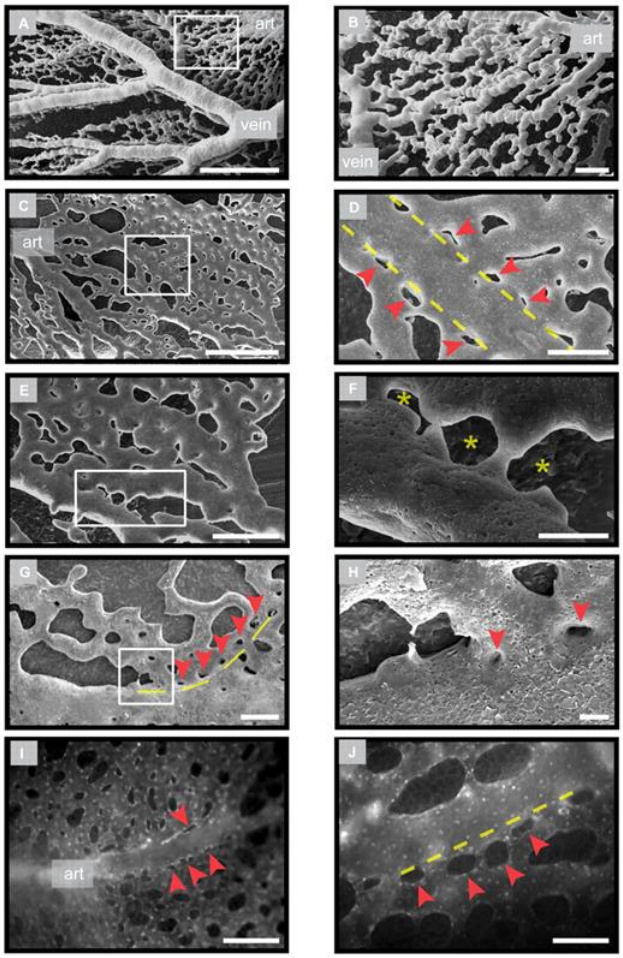

Figure 4.4.1: Splitting angiogenesis (intussusception) in ligation embryos. (A-H) Scanning electron micrographs of vascular corrosion casts of control (A,B) and ligation (C-H) chicken embryos. (A) Low magnification of the normal vasculature. The boxed region is shown at higher magnification in B. Splitting angiogenesis is not apparent. (C) Micrograph of ligation embryo showing extensive pillar formation. (D) Magnification of the boxed region in C, showing rows of pillars (red arrowheads) delineating the future arteriolar segment (dashed line). (E,F) Overview (E) and detail of the boxed area (F) showing fusion of pillars leading to segregation of the capillaries (asterisks). (G,H) Another example showing the advanced splitting by pillars (arrowheads); rows of pillars align (dashed line) and subsequent fusion will lead to separation of the feed vessel from the surrounding capillary plexus. (I,J) Fluorescent labeling of endothelial cells in vivo shows pillar formation (arrowheads) in distal arterioles and the connected capillary network. art, artery. Scale bars: 500 m in A,C; 200 m in E; 100 m in B,D,G; 50 m in F; 20 m in H; 30 m in I,J. Figure is from Buschmann u. a. (2010)

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