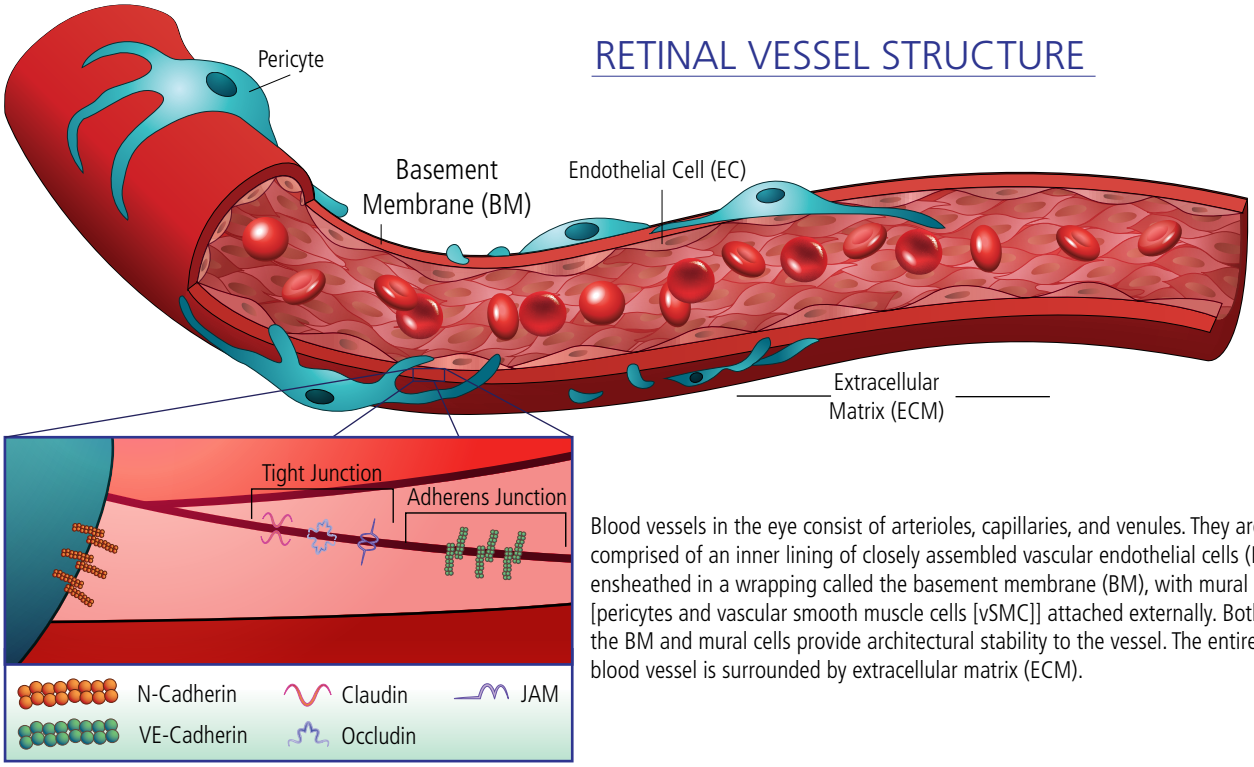
MODULE 4.1
Healthy Blood Vessels

Vascular health depends on complex intercellular communications that ensure the maintenance of healthy, quiescent blood vessels. Blood vessels differ in size and structure based on their function. However, the basic structure is similar: the innermost lining is made of tightly assembled vascular endothelial cells (ECs). These vessels, are covered by a “wrapping” called the basement membrane (BM), with mural cells (pericytes or vascular smooth muscle cells) attached externally. The BM and mural cells provide stability and control perfusion.[1] The entire blood vessel is surrounded by extracellular matrix (ECM). The ECM is composed mainly of collagens, laminins, fibronectin, heparin sulfate proteoglycans, and entactin.[2] This tight and multilayered structure prevents leakage and maintains a certain degree of structural flexibility. Importantly, ECs ensure the proper barrier function of the vessel. The regulation of cell-cell adhesion between the ECs and with their neighboring cells relies mostly on complexes of transmembrane adhesive proteins, including vascular endothelial (VE)-cadherin and neural (N-)cadherin at adherens junctions, as well as occludins and members of the claudin and junctional adhesion molecule (JAM) family at tight junctions.[3]

Blood vessel cells do not normally grow, and there is very little turnover of ECs in the healthy adult. Therefore, vessels are mostly inactive or quiescent.[1,4] Despite the label, maintaining quiescence is an active state: ECs and their surrounding environment must constantly balance multiple stimuli to prevent any changes in vessel structure. Endothelial cells’ quiescence is protected by the autocrine action of maintenance signals such as vascular endothelial growth factor (VEGF), Notch, angiopoietin-1 (ANG-1), and fibroblast growth factors (FGFs).[1] However, blood vessels must still retain flexibility and the ability to quickly respond to growth-stimulating signals. The transition of ECs from quiescence to active states is determined by the local balance between "on" and "off” factors.[5]

The VEGF family plays a major role in the maintenance of quiescent vasculature, in the induction and control of growth, and in remodeling and stabilization of vessels. The family includes placenta growth factor (PlGF) and VEGF-A, -B, -C, -D, and -E. Human VEGF-A comprises at least 5 different

Healthy Blood Vessels



Blood vessels in the eye consist of arterioles, capillaries, and venules. They are comprised of an inner lining of closely assembled vascular endothelial cells (EC) ensheathed in a wrapping called the basement membrane (BM), with mural cells [pericytes and vascular smooth muscle cells [vSMC]] attached externally. Both the BM and mural cells provide architectural stability to the vessel. The entire blood vessel is surrounded by extracellular matrix (ECM).

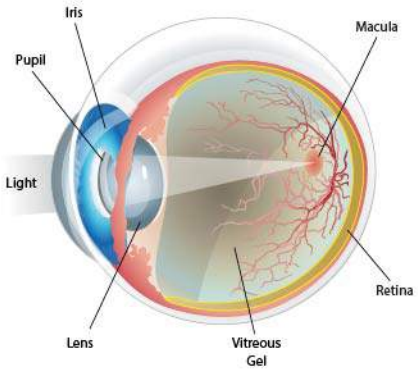
Cell-cell adhesion is crucial to maintain proper barrier function of the vessel; these cell-cell interactions are regulated by transmembrane adhesive proteins pictured above.

isoforms: VEGF110, VEGF121, VEGF165, VEGF189, and VEGF206.[6] VEGF receptor-1 (VEGFR-1 or FLT-1) and VEGF receptor-2 (VEGFR-1 or FLK-1) are activated by VEGF-A. VEGF-A stimulates angiogenesis and EC proliferation and migration, increases EC and vessel permeability, stimulates EC urokinase-type plasminogen activator/human plasminogen activator inhibitor type 1 (uPA/PAI-1) production, and inhibits EC apoptosis. VEGFR-2 is the main mediator of these effects of VEGF-A. VEGFR-1 possesses a higher affinity for VEGF than does VEGFR-2 and acts as a negative regulator and a "decoy" receptor of VEGFR-2. VEGFR-3 (FLT-4) binds to VEGF-C and VEGF-D. Additionally, two coreceptors for VEGF-A are neuropilin-1 (for VEGF165) and neuropilin−2 (for VEGF145 and 165). VEGF165, the most common isoform, is the most important for angiogenesis.[1,4,7]

VEGF and its receptors, VEGFR-1 and VEGFR-2, are constitutively expressed in normal vascularized intraocular tissues, including the conjunctiva, iris, retina, and choroid-retinal pigment epithelium (RPE) complex.[8] Within the posterior segment of the eye, VEGF is produced by retinal pigment epithelial cells, neurons, glial cells, endothelial cells, ganglion cells, Müller cells, and smooth muscle cells.

EYE ANATOMY

Blood vessel cells do not normally grow in the healthy adult; they are mostly inactive, or quiescent. Although healthy vessels are equipped with mechanisms to maintain quiescence, they also must retain the capability of rapid division in response to physiological stimuli.



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