MODULE 4.5
Summary

The vasculature in healthy adults is kept in a quiescent state while maintaining the capacity to quickly respond to a variety of signals from the vasculature microenvironment. The integrity and functionality of the vessels depend on a dynamic and tightly controlled network of signals between all the components which build the vessel: the endothelial cells (ECs) that line the innermost part of the vessel, the basement membrane (BM) that surrounds the EC layer, the pericytes that extend into and cover the BM, and the extracellular matrix (ECM) that surrounds the vessel unit as a whole. Under normal conditions, the ECs rarely proliferate, and blood vessels remain stable. The vascular endothelial growth factor (VEGF) family plays a major role in the maintenance of quiescent vasculature and in the induction and control of many of the physiologic activities of ECs. Of this family, VEGF-A and its receptor VEGFR-2 are the main mediators of angiogenesis.[1-3] They are both constitutively expressed in normal vascularized intraocular tissues.

The growth of new vessels begins after exposure to angiogenic stimuli. First, the vessel is destabilized by proteolytic degradation of the BM, detachment of pericytes from the vessel wall, and breakdown of contacts between ECs.[3-5] Selection of one of the ECs as a tip cell initiates sprouting.[6] The tip cell extends filopodia and migrates towards the angiogenic stimuli, leading the edge of the newly formed capillary, while its neighboring cells become stalk cells. Stalk cells divide to elongate the sprout and establish the lumen. When the edges of two sprout cells connect and their leading tip cells fuse, a new continuous tube is formed and blood starts to flow.[3,5,7] This process is accompanied by deposition of extracellular matrix (ECM) molecules, the recruitment of supporting pericytes and other cells, reduced EC proliferation,and increased formation of cell-cell junctions. The new vessels are formed as a dense tree-branch pattern. This net of vessels is then pruned back according to the tissue's needs. The remaining vessels mature as the ECs return to quiescence and establish their cell-cell contacts, and as the pericyte and ECM wrappings become tight again.[2-5]

Permeability of blood vessels is regulated by signals from the microenvironment. VEGF-A is one of the most potent inducers of vessel permeability. Binding of VEGF to VEGFR-2 activates a series of signaling pathways that lead to structural changes (cytoskeletal reorganization and junctional remodeling) in ECs and eventually increases capillary leakage.[8] VEGF affects the integrity and stability of both the tight and adherens junctions and induces fenestration and formation of vesicular vacuolar organelles (VVOs) in ECs.[8] VEGF-induced capillary leakage plays a major role in ocular disease, such as diabetic retinopathy (DR) and diabetic macular edema (DME), in which VEGF breaks down the blood–retinal barrier and increases capillary leakage into the intercellular matrix. Leakage and accumulation of fluids in the macula causes thickening and swelling of the macula and eventually can impair vision. DR is characterized by additional vascular abnormalities such as microaneurysms (MAs), intraretinal hemorrhages, hard exudates, macular edema, capillary occlusion, and neovascularization. In addition, leukostasis, reduced retinal perfusion, and retinal pericyte loss eventually leads to EC degeneration, microvascular destabilization, and perfusion alterations.[9]

References

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