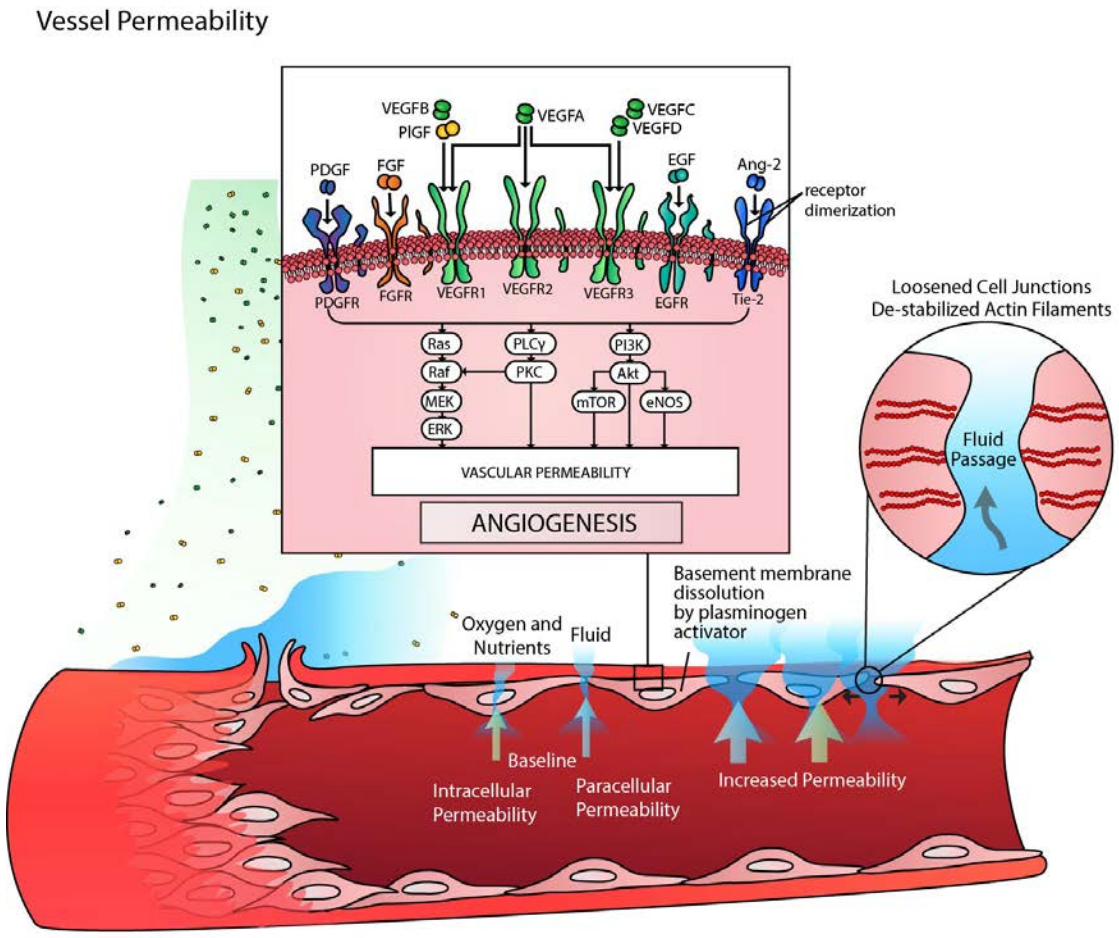
MODULE 4.3

VEGF and Vessel Permeability

The permeability of blood vessels must be dynamic and highly responsive to signals from the environment. Endothelial Cells function as a barrier and a selective filter between the blood and surrounding tissues. Passage through the endothelial barrier can occur either through cells (transcellular) or between them (paracellular). The control of vascular permeability involves complex processes that are mostly regulated by VEGF.[1] The effects of VEGF on vessel permeability are mediated primarily through VEGFR-2. Binding of VEGF to VEGFR2 leads to the receptor's phosphorylation. This results in the initiation of a series of signaling pathways including increased intracellular calcium, src activation, and stimulation of the p42/p4MAPK and the PI3 kinase pathways, RhoGTPase activation and eNOS signaling, as well as structural changes in ECs[1, 2] that eventually increase capillary leakage.

Tight junction (TJ) molecules maintain and regulate paracellular permeability, whereas adherens junction (AJ) molecules mediate cell-cell adhesion, cytoskeletal reorganization, and intracellular signaling.[3] VEGF-A promotes vascular permeability by disrupting both AJs and TJs. VEGF activation of Endothelial Cells results in phosphorylation, internalization and disassembly of VE-cadherin, the key component of AJs. Phosphorylation of other adherens junction components also modulates the affinity of adherens junction complex components for one another, thus affecting junctional stability. VEGF-induced activation of protein kinase C isoforms, particularly protein kinase C beta, stimulates phosphorylation of the tight junctional regulator Zona occludens-1 (ZO-1) and ubiquitin-mediated endocytosis of other TJ components.[4] These events lead to an overall decrease in the level of junctional and adherens proteins



at the endothelial junctions, thus disrupting tight junction assembly and junctional stability[1, 2, 5, 6] and resulting in transient opening of endothelial cell–cell contacts.

Other VEGF-induced structural changes include fenestration in endothelial cells and formation of vesicular vacuolar organelles (VVOs). VVOs are cytoplasmic vesicles and vacuoles that together form an organelle that traverses endothelial cytoplasm from lumen to albumen.[1, 2, 5] In addition to VVOs, transcellular permeability occurs also through caveolae (vesicles with high levels of caveolin-1) and transcellular channels.[1]

VEGF-induced capillary leakage plays a major role in ocular disease. By inducing fenestrations across cell bodies and dissolving the tight junctions between endothelial cells by activating matrix metalloproteinases and phosphorylating both vascular endothelial cell cytoskeletal proteins and the junctional proteins, VEGF breaks down the blood-retinal barrier and increase capillary leakage into the intercellular matrix.[7]

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