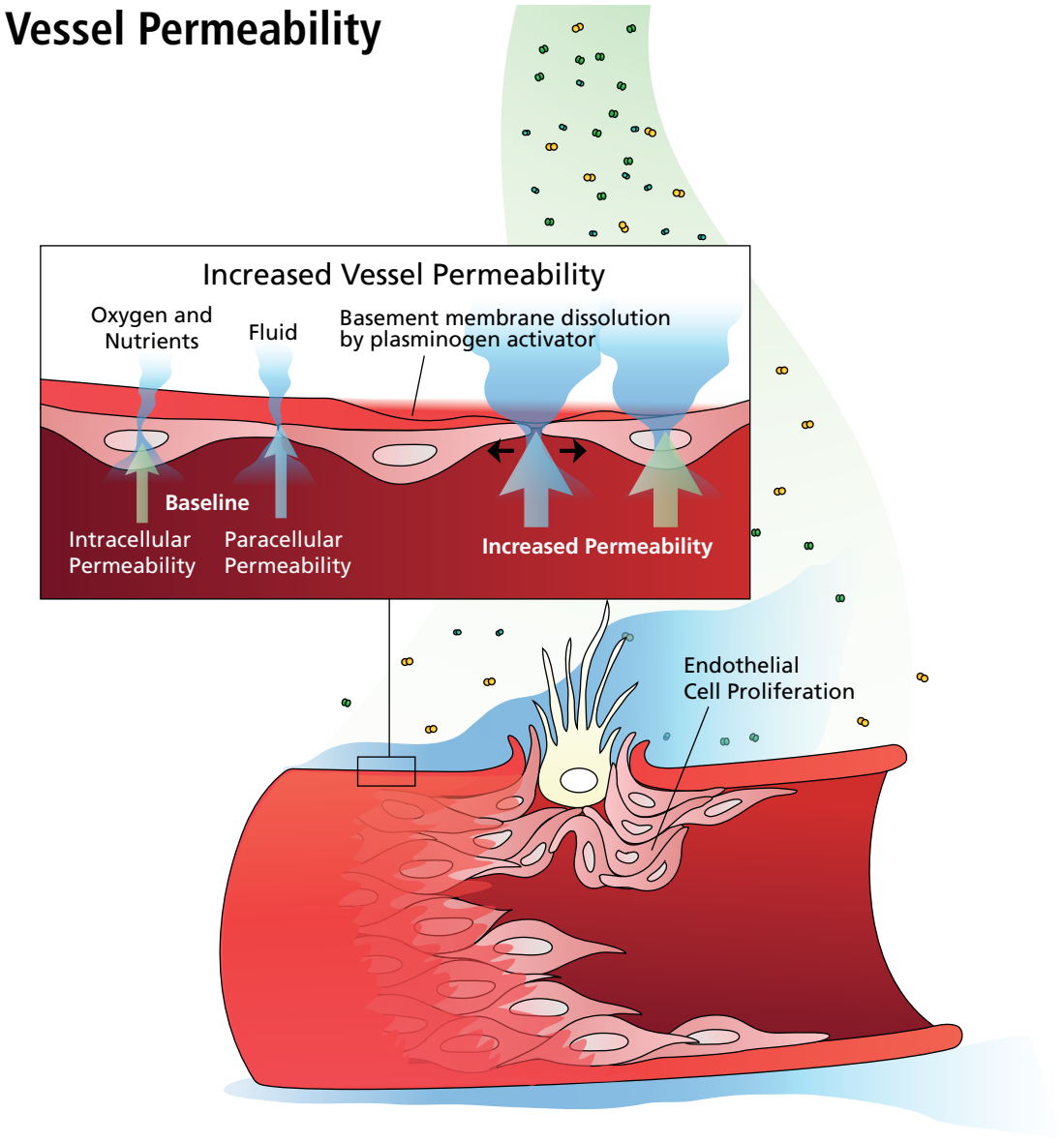
MODULE 4.3
VEGF and Vessel Permeability

The permeability of blood vessels must be dynamic and highly responsive to signals from the environment. Endothelial cells (ECs) 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 vascular endothelial growth factor (VEGF).[1] The effects of VEGF on vessel permeability are mediated primarily through VEGF receptor-2 (VEGFR-2). Binding of VEGF to VEGFR-2 leads to the receptor's phosphorylation. This results in the initiation of a series of signaling pathways including increased intracellular calcium, src activation, p42/p4MAPK and PI3 kinase pathway stimulation, Rho GTPase activation, and endothelial nitric oxide synthase (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 ECs results in phosphorylation, internalization, and disassembly of vascular endothelial - 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 TJ regulator zonula occludens-1 (ZO-1) and ubiquitin mediated endocytosis of other TJ components.[4]



These events lead to an overall decrease in the level of AJs and adherens proteins at the endothelial junctions, thus disrupting TJ 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 ECs 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 TJs between ECs by activating matrix metalloproteinases and phosphorylating both vascular EC cell cytoskeletal proteins and the junctional proteins, VEGF breaks down the blood-retinal barrier and increases capillary leakage into the intercellular matrix.[7]

References

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