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# Molecular pathogenesis of retinal and choroidal vascular diseases☆

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ABSTRACT

There are two major types of ocular neovascularization that affect the retina, retinal neovascularization (NV) and subretinal or choroidal NV. Retinal NV occurs in a group of diseases referred to as ischemic retinopathies in which damage to retinal vessels results in retinal ischemia. Most prevalent of these are diabetic retinopathy and retinal vein occlusions. Subretinal and choroidal NV occur in diseases of the outer retina and Bruch's membrane, the most prevalent of which is age-related macular degeneration. Numerous studies in mouse models have helped to elucidate the molecular pathogenesis underlying retinal, subretinal, and choroidal NV. There is considerable overlap because the precipitating event in each is stabilization of hypoxia inducible factor-1 (HIF-1) which leads to upregulation of several hypoxia-regulated gene products, including vascular endothelial growth factor (VEGF), angiopoietin 2, vascular endothelial-protein tyrosine phosphatase (VE-PTP), and several others. Stimulation of VEGF signaling and suppression of Tie2 by angiopoietin 2 and VE-PTP are critical for sprouting of retinal, subretinal, and choroidal NV, with perturbation of Bruch's membrane also needed for the latter. Additional HIF-1-regulated gene products cause further stimulation of the NV. It is difficult to model macular edema in animals and therefore proof-of-concept clinical trials were done and demonstrated that VEGF plays a central role and that suppression of Tie2 is also important. Neutralization of VEGF is currently the first line therapy for all of the above disease processes, but new treatments directed at some of the other molecular targets, particularly stabilization of Tie2, are likely to provide additional benefit for subretinal/choroidal NV and macular edema. In addition, the chronicity of these diseases as well as the implication of VEGF as a cause of retinal nonperfusion and progression of background diabetic retinopathy make sustained delivery approaches for VEGF antagonists a priority.



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## 1. Retinal blood supply

The retina is supplied by the retinal and choroidal vasculatures. The central retinal artery enters the eye through the optic nerve, branches on the surface of the nerve, and sends progressively branching arterioles along the surface of the retina to its anterior border. The surface arterioles send numerous penetrating branches to form the intermediate and deep capillary beds which supply the inner 2/3 of the retina. Retinal capillaries drain into retinal venules that retrace the path of the arterioles into progressively larger branch veins that enter the central retinal vein that exits the eye through the optic nerve. The endothelial cells of retinal vessels have tight junctions and specialized vesicular transport that limit efflux of plasma and its components into the interstitial space of the retina constituting the inner blood-retinal barrier. The outer 1/3 of the retina consisting of the outer nuclear layer containing photoreceptor cell bodies, photoreceptor inner segments, and photoreceptor outer segments is completely devoid of blood vessels (Fig. 1). Erythrocytes coursing through blood vessels contain hemoglobin which absorbs light and so the absence of blood vessels immediately anterior to photoreceptor outer segments is an important adaptation for visual function, but presents a unique challenge to the supply of oxygen and nutrients to photoreceptors. The challenge is heightened by the high metabolic activity of photoreceptors. The choroidal circulation surmounts this challenge because it has very high blood flow and forms the choriocapillaris, a dense plexus of fenestrated capillaries that allow plasma to bath the retinal pigmented epithelium (RPE) which contains apical tight junctions and specialized vesicular transport constituting the outer blood-retinal barrier.

## 2. Retinal and choroidal vascular diseases

The unique blood supply of the retina is an elegant solution to the challenges rendered by the need to eliminate blood vessels immediately anterior to photoreceptor outer segments, but is also the source of vulnerabilities. It requires a high flow vascular system in close proximity to the avascular outer retina ending in fenestrated capillaries allowing plasma free access to the RPE which has both epithelial and endothelial functions. The distance over which

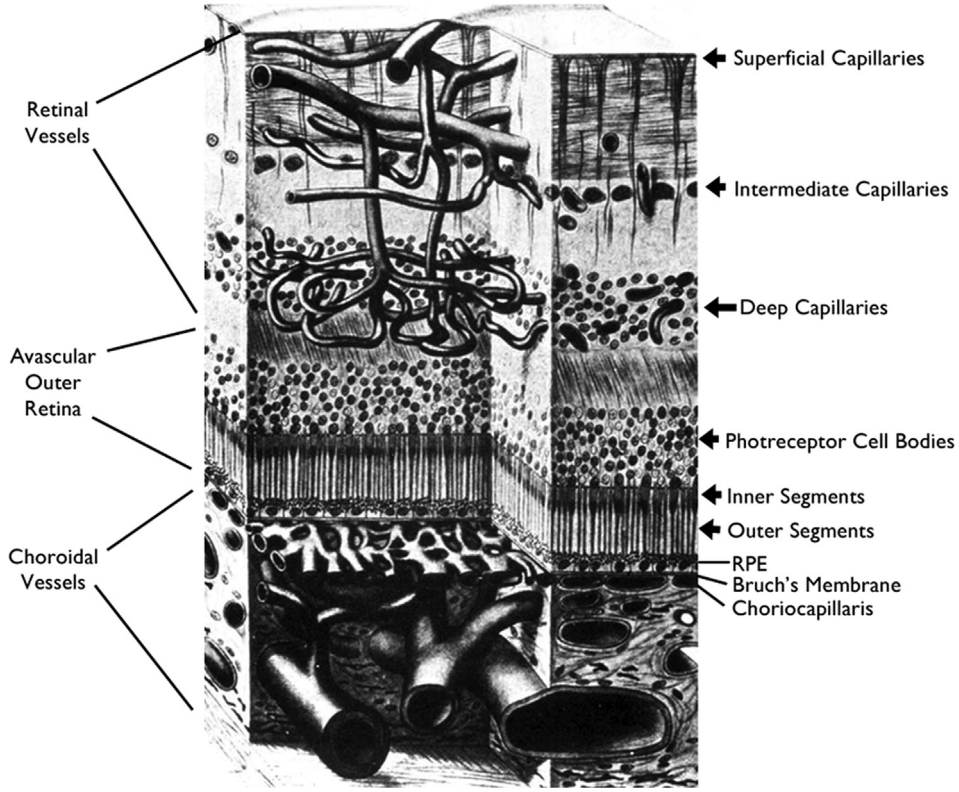


**Fig. 1.** Schematic showing the vascular supply of the retina. The retinal arteries branch to form the superficial capillary bed near the surface of the retina and send penetrating branches to form the intermediate and deep capillaries. Retinal vessels supply the inner two-thirds of the retina with oxygen and nutrients. The outer third of the retina which consists of photoreceptor outer and inner segments and cells bodies is avascular. It receives oxygen and nutrients from the choroidal circulation. Large choroidal vessels branch and become progressively smaller until they form the choriocapillaris which is fenestrated and allows plasma to pool along Bruch's membrane. The RPE, which has barrier characteristics prevents fluid from entering the outer retina but allows oxygen and nutrients to enter.