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Article

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PEER REVIEWED

Ocular Angiogenesis: The Science Behind the Symptoms

With a variety of factors contributing to neovascularization, many therapies are being developed.

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With most things in nature, a balance must be struck between two opposing forces, each necessary for a functional end product. Enormously complex interactions between production, degradation and reformation are necessary for any living organism. The eye, being one of the most complex and evolved organs, must also adhere to this delicate balance. Angiogenesis and antiangiogenesis are one of these many pairings that must achieve balance. In his groundbreaking 1971 article, Judah Folkman introduced the idea of a “diffusible message” released from solid tumor cells to invoke a robust capillary-sprouting response, more robust than ordinary wound healing or inflammation, to help support its cancerous growth. In the same light, Folkman introduced the concept of antiangiogenesis.[1]

A distinction between vasculogenesis and angiogenesis bears mention. Vasculogenesis is blood-vessel formation via endothelial progenitor cells and hemangioblast differentiation, while angiogenesis is the formation of new capillaries from pre-existing blood vessels. Angiogenesis requires endothelial cell migration, proliferation, survival, vessel maturation, vessel-wall remodeling and degradation of the extracellular matrix. It is a normal part not only of development but also of healing. Endothelial cell number is normally stable without significant proliferation, likely due to a balance between proangiogenic factors (ie, vascular endothelial growth factor) and antiangiogenic (angiostasis) factors (ie, pigment epithelium–derived factor). When there is an imbalance between these two, pathology ensues.

Ocular angiogenesis is a major cause of much ocular disease and blindness. It is a significant contributing factor in diabetic retinopathy, exudative AMD, corneal graft rejection, corneal neovascularization, retinopathy of prematurity, retinal vein occlusion, neovascular glaucoma and sickle cell retinopathy. In this article, different forms of ocular angiogenesis, their mediators and implications for treatment will be reviewed.

RETINAL AND CHOROIDAL NEOVASCULARIZATION

Proliferative diabetic retinopathy (**Figures 1-3**), RVO and sickle cell proliferative vitreoretinopathy are the most common forms of retinal neovascularization. Other causes include familial exudative vitreoretinopathy, sarcoidosis, pars planitis, radiation retinopathy, ocular ischemic syndrome and Eales disease. A combination of angiogenesis and vasculogenesis occurs during retinal neovascularization. Normally, minimal endothelial cell proliferation occurs in the retina.[2] "Hypoxia is believed to be the initial stimulus that causes an upregulation of growth factors, integrins and proteinases, which result in endothelial cell proliferation and migration."[3] Hypoxia upregulates VEGF mRNA in retinal endothelial cells, RPE cells, pericytes, Müller cells and ganglion cells.[4]

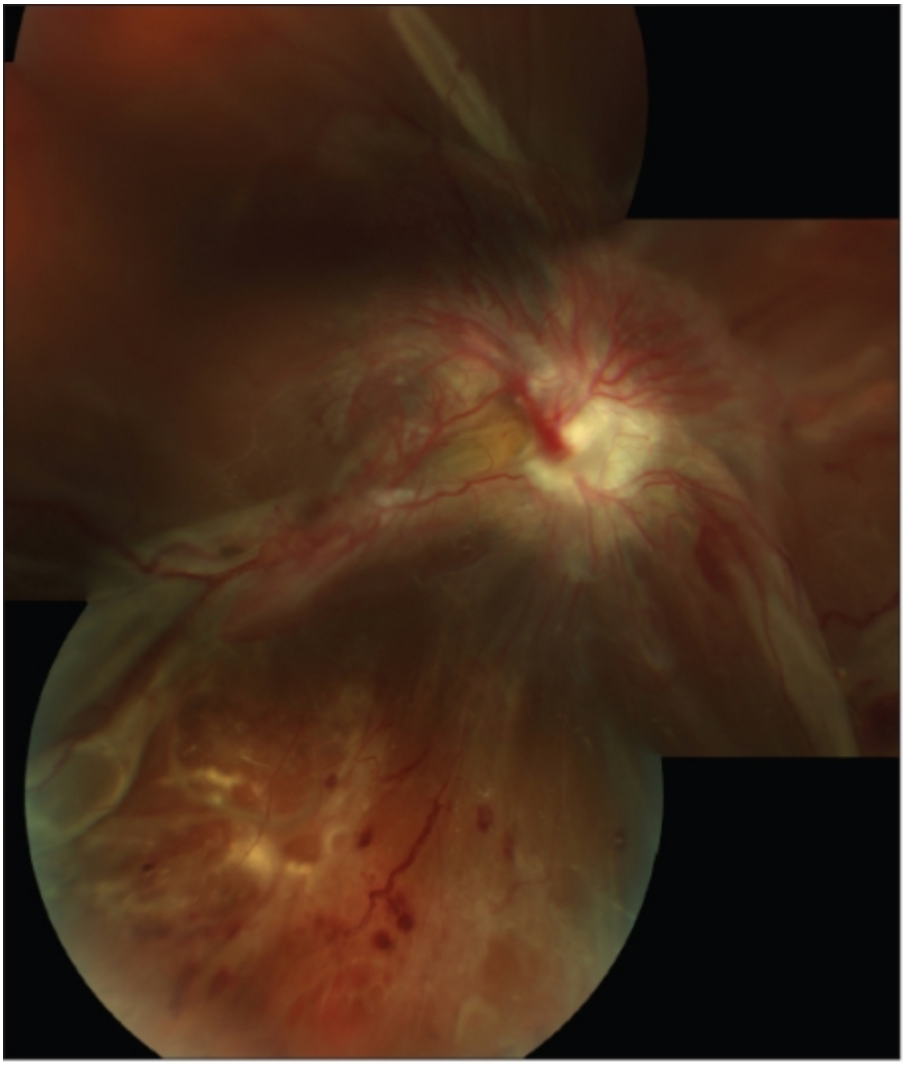
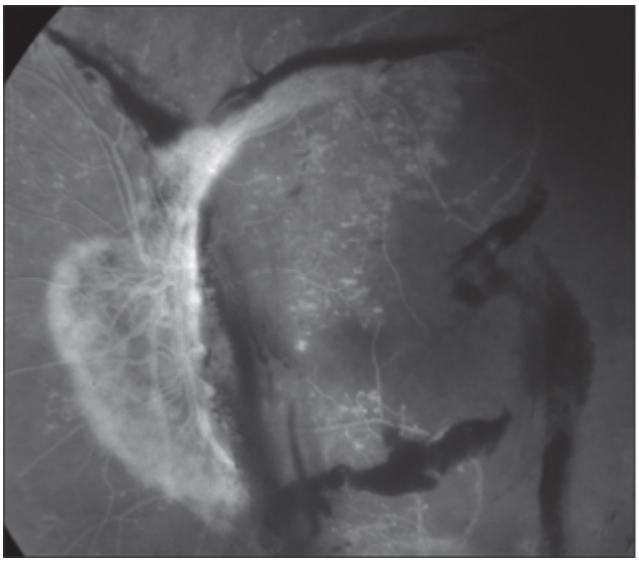
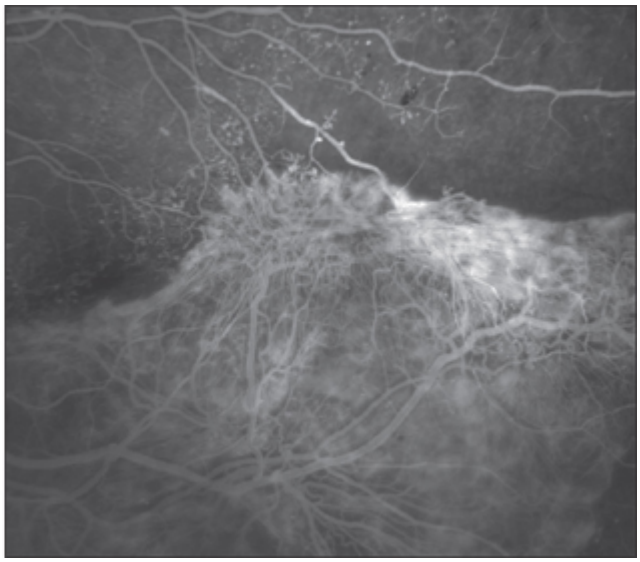


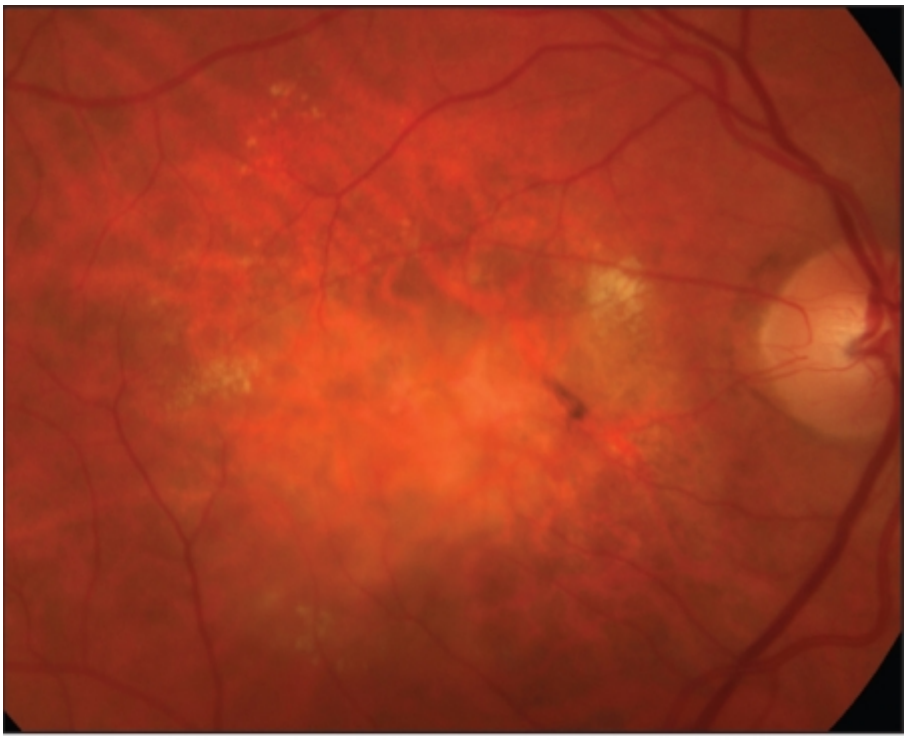
Figure 1. Severe proliferative diabetic retinopathy with trac-tional retinal detachment.

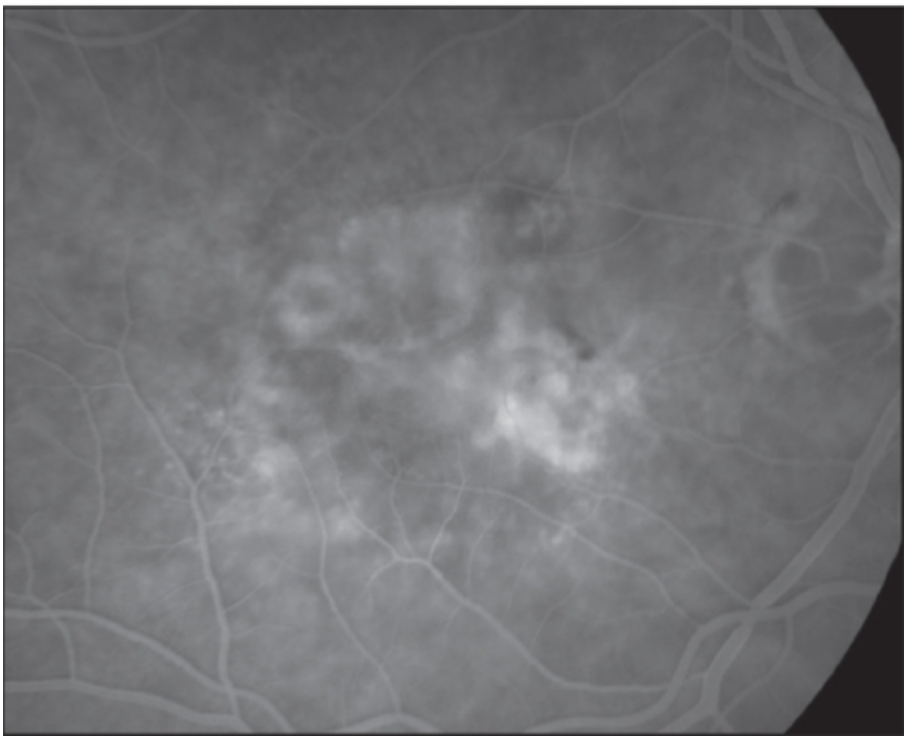



Figures 2 and 3. Early phase fluorescein angiography of leaking neovascular membranes and hemorrhage in patients with PDR.

Choroidal Neovascularization

Despite alterations in choroidal blood flow in AMD, it may not be enough to produce significant hypoxia to induce CNV.[3,5,6] Like retinal neovascularization, CNV is a combination of angiogenesis and vasculogenesis.[7] CNV is most commonly seen in wet AMD (**Figures 4 and 5**). Other common causes are high myopia, choroidal rupture, angioid streaks, ocular histoplasmosis syndrome, multifocal choroiditis, punctate inner choroidopathy and iatrogenic causes (intense laser photocoagulation). Wet AMD is the leading cause of severe vision loss in the elderly in the United States.[8] Oxidative damage and inflammation (and less so hypoxia) are thought to tip the pro- and antiangiogenic-factor balance in favor of angiogenesis.





Figures 4 and 5. Fundus photography and mid-phase fluorescein angiography of an active choroidal neovascular membrane in a patient with exudative age-related macular degeneration.

INFLAMMATION AND COMPLEMENT

In experimental models, a robust immune response is seen quickly after choroidal neovascular membrane (CNVM) is induced by laser. Within 72 hours, there is an influx of neutrophils, macrophages, natural killer cells, microglial cells and edema.[9] Macrophages are found near ruptured or thin areas in Bruch's membrane and have been isolated from CNVM removed via submacular surgery.[10] Activated macrophages secrete collagenase and elastase, which may erode Bruch's membrane, allowing for vascular mobilization. Recently, inhibition of vascular adhesion protein-1 decreased macrophage accumulation in CNV lesions and reduced CNV size[11] and expression

Drusen are likely the byproducts of RPE cells with some protein components, possibly arising from the choroid. It is still not truly known if drusen are epiphenomena of AMD, an active player in the inflammatory cascade, or a passive player via its physical barrier and disruption of transport across Bruch's membrane.[12] Shen was able to produce a CNV membrane by subretinal injection of Matrigel (BD Biosciences, Sparks, MD), a soluble basement membrane preparation mimicking drusen formation.[13] In the past decade, noting similarities between drusen found in AMD and drusen found in patients with membranoproliferative glomerulonephritis type 2, Hageman and colleagues formed the basis of complement system dysfunction and its role in CNVM formation.[14-16] Specifically, variants of complement factor H (CFH) and alterations in the alternative complement pathway have been genetically linked to AMD.[14-17] A myriad of targets of the complement sys tem exist and several phase 1 and 2 trials are ongoing. Potential agents work by either replacing a defective component (ie, CFH with the Y402H mutation) or by blocking a complement pathway (C3 and C5 inhibitors).[18]

VEGF

Vascular endothelial growth factor was initially named vascular permeability factor, as it originally was isolated in tumor ascites fluid from guinea pigs.[19] VEGF is 50,000 times more potent as a vasodilator than histamine.[20] It includes a family of growth factors — VEGF-A, VEGF-B, VEGF-C, VEGF-D and PlGF (placental growth factor). The major mediator of tumor angiogenesis is VEGF-A. Despite a very high affinity between VEGF and VEGF receptor 1 (VEGFR-1), most transduction occurs with VEGFR-2. VEGFR-1 may be a “decoy” receptor, preventing VEGF binding to VEGFR-2.[3,21] Thus, the interaction of VEGF and VEGFR-2 is crucial.

Vascular endothelial growth factor is expressed in most types of human cancers and is highly selective for endothelial cells.[10,22] As adapted from Hicklin, VEGF is involved in: (1) endothelial cell proliferation via activation of mitogen-activated protein kinases; (2) endothelial cell permeability via opening of endothelial fenestrations and cell junctions; (3) tumor-cell invasion via induction of metallo-proteinases (MMPs) and urokinase plasminogen activators (UPA), hence promoting extracellular matrix degradation; (4) migration through activation of FAK, p38 and nitric oxide; (5) survival of new endothelial cells by inhibiting apoptosis; and (6) activation and stabilization of the vascular network.[23]

Induction of VEGF results from hypoxia via hypoxia-inducible factor 1 (HIF-1), low pH, inflammatory cytokines (IL-6), growth factors (basic fibroblast growth factor), sex hormones (androgens and estrogens), chemokines, oncogene activation and decreased activity of tumor suppressor gene activity.[22,23] Numerous studies have shown increased aqueous and vitreous levels of VEGF and VEGFR-1 in a variety of ocular proliferative conditions.[24 31] Surgically removed CNVMs from AMD patients show increased VEGF expression in fibroblasts and RPE cells.[32 34]

But is VEGF itself sufficient enough to produce retinal and choroidal neovascularization? VEGF is found in the Bruch's membrane–choriocapillaris complex of normal healthy donor eyes.[10,35] Some animal models had difficulty producing both retinal and choroidal neovascularization. Ozaki implanted intravitreal, sustained-release VEGF pellets that induced retinal neovascularization in rabbits but not in primates.[36] Tolentino showed that intravitreal injections of VEGF in monkey eyes produced capillary nonperfusion and vessel dilation, but preretinal neovascularization in only the peripheral retina and not posterior pole.[37] Transgenic mice in which rhodopsin promoter was coupled to a VEGF gene, hence producing increased intraretinal VEGF, did form intraretinal and subretinal neovascularization. However, as Campochiaro has demonstrated, when increased VEGF levels are combined with photoreceptor degeneration, CNVM may form. Thus, healthy photoreceptors may somehow prevent the choriocapillaris from responding to elevated VEGF levels.[38,39]

Basic FGF

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