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Anti-Angiogenic Therapy in Ophthalmology

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Preface

In 2006, intraocular anti-VEGF therapy for exudative age-related macular degeneration (AMD) was ranked among the top 10 breakthroughs of the year by Science Magazine. Since then, antiangiogenic therapy has broadened its impact from AMD treatment to various other diseases of the eye like macular oedema in diabetic retinopathy or retinal vein occlusion. In other areas, for example, retinopathy of prematurity (ROP), antiangiogenic therapy is just beginning to find its place and is currently being evaluated in clinical studies that weigh its benefit against potential risks. As a third category, there are indications like macular telangiectasia where antiangiogenic therapy has after initial hopeful use become to be seen as potentially unfavourable in the long run.

Due to the broad use of antiangiogenic therapies in these fundamentally different ocular diseases, it is crucial for the treating physician to understand both the underlying principles of angiogenic eye diseases and the available clinical data on therapies and outcome. This book therefore combines an overview over retinal vascular physiology with a detailed analysis of the available clinical data on antiangiogenic therapy in various ocular disorders. The authors are all experts in their respective fields and have achieved to combine concise but crucial pathophysiologic background information with detailed clinical data reflecting our current state of knowledge on antiangiogenic therapy in ophthalmology.

Freiburg, Germany — Andreas Stahl, MD

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Retinal Vascular Development

1

Jing Chen, Chi-Hsiu Liu, and Przemyslaw Sapieha

1.1 Anatomy of Blood Vessel Networks in the Eye

To aid in understanding retinal vascular development, we will first describe the origins of ocular blood vessels. The orbital vascular anatomy is highly complex in human. The ophthalmic artery, the first major branch of the internal carotid artery, is the main source of the arterial supply to the orbit and its derived arterial structures. It passes beneath the optic nerve and accompanies the nerve through the optic canal into the inner wall of the orbit. The central retinal artery, the first branch of the ophthalmic artery, pierces the optic nerve sheath inferiorly about 8–15 mm (in humans) behind the globe, and occupies a central position within the optic nerve when entering the retina. Other branches of ophthalmic artery, including the posterior ciliary arteries, serve the optic nerve head, choroid, ciliary body, and iris (Gray 2008; Paul Riordan-Eva 2011; Hayreh 2006).

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1.1.1 Retinal Vessels

The retina is one of the most structurally intricate and metabolically active tissues in the body. It receives its blood supply from two sources: (1) the central retinal artery and its three branched plexi, which supplies the inner two-thirds of the retina; and (2) the choriocapillaris (choriocapillary layer) adjacent to the Bruch's membrane which supplies the outer retina. The central retinal artery and its accompanying vein run along the inferior margin of the optic nerve sheath and enter the eye through the optic disk. The vessel branches then immediately bifurcate into the superior nasal and temporal, or the inferior nasal and temporal branches, each supplying a distinct quadrant of the retina. The branching pattern of the vessels is either dichotomous or at right angles to the original vessel (Gray 2008; Paul Riordan-Eva 2011; Netter 2006). Branches from the central retinal artery then dive into the retina towards photoreceptors forming a capillary plexus which provides nutrients to the inner retinal layers. The overall structure of retinal vessels is composed of three distinct capillary layers, one in the nerve fiber layer and the other two along each sides of the inner nuclear layer (Fig. 1.1).

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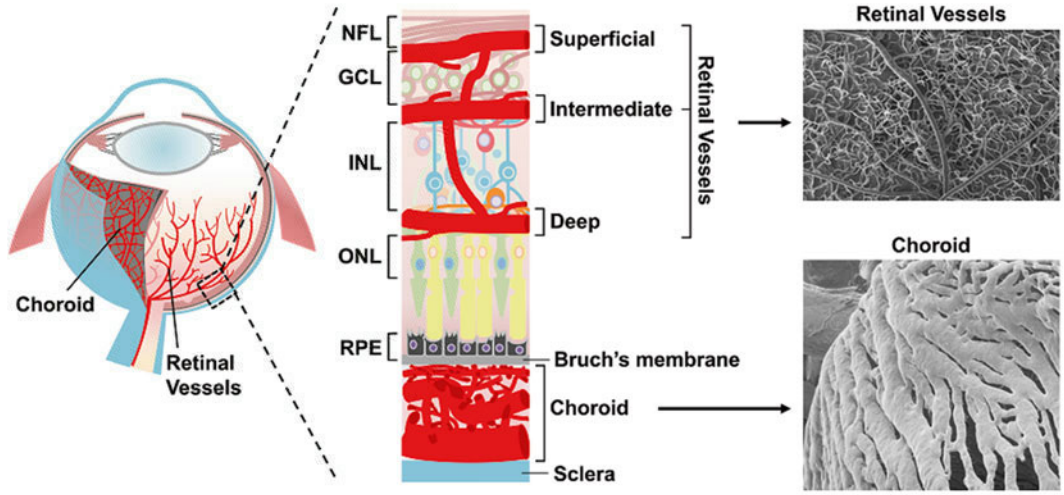

Fig. 1.1 A schematic illustration of the ocular vasculature. *Left*: A schematic cross-section through an eye showing the retinal vasculature lining the inner surface of the retina and the choroid vessels. *Right*: An enlarged cross-sectional illustration of the eye showing detailed structure of the retinal and choroidal vasculature. Three layers of retinal vessels are embedded among retinal neurons: the superficial retinal vasculature lies in the NFL; the intermediate and deep retinal vascular networks align along each sides of the INL. The choroidal vessels between RPE and sclera serve to supply blood to the outer portion of the retina. *GCL* ganglion cell layer, *INL* inner nuclear layer, *NFL* nerve fiber layer, *ONL* outer nuclear layer, *RPE* retinal pigment epithelium. Enlarged images on the *right* depict retinal and choroidal vascular cast from mouse eyes

Retinal vessels have a non-fenestrated endothelium forming the inner blood–retinal barrier. In addition, branches of the central retinal artery are terminal arteries that do not anastomose with each other (Gray 2008; Netter 2006). Contrary to the inner retinal layers, the photoreceptor layer is avascular without blood vessels from the central retinal artery. Thus, it relies on the choriocapillaris to supply oxygen and nutrient by diffusion from choroidal vessels.

1.1.2 Choroidal Vessels

The choroid, a thin highly vascular membrane, lies between the retina and the sclera and invests the posterior five-sixths of the globe in human. The choroid vessels originate from two groups of branches of the ophthalmic artery: (1) the short posterior ciliary arteries, which supply the posterior portion of choroid; (2) the long posterior ciliary arteries, which supply the anterior choroid, ciliary body, and iris. They are distinguished in three layers of choroidal vasculature: the innermost choriocapillaris, the intermediate Sattler's layer, and the outermost Haller's layer (Hartnett 2013). The more outer the vessels are located in the choroid, the bigger the size of their lumens. While the outermost choroidal layer is composed mainly of small arteries and veins, the innermost choriocapillaris is characterized by an exceedingly fine capillary plexus adjacent to the Bruch's membrane (Fig. 1.1) (Paul Riordan-Eva 2011; Ross and Pawlina 2005). In humans, the capillaries of the choriocapillaris are approximately 3–18 μm in diameter and oval shaped in the posterior eye, becoming gradually wider (approximately 6–36 μm in diameter) and longer (36–400 μm in length) as they move towards the equatorial region. The choriocapillaris is a sinusoidal vascular plexus with highly fenestrated endothelium, and as the site of the greatest blood flow in the body (Henkind et al. 1979), it provides 65–85 % of the blood volume in the eye. Through diffusion, it nourishes the cells in the outer portion of the retina (Bela et al. 2011), including the retinal pigment epithelium (RPE) and photoreceptors, as well as the fovea, which contains only photoreceptors for high acuity central vision and is devoid of other retinal neurons.

Interestingly, some mammalian species such as echidnas, guinea pigs, and rabbits lack retinal vasculature, with their oxygen and nutrient supply to the retina being solely provided by diffusion from the choriocapillaris. It appears that the thickness of the retina is directly related to their evolutionary vascularization state. These avascular retinas are typically thinner than the theoretical oxygen diffusion maximum of 143 μm, whereas vascularized retinas are approximately twice as thick, yet their avascular portion are still within the oxygen diffusion limit (Chase 1982; Buttery et al. 1991; Dreher et al. 1992).

1.1.3 Hyaloidal Vessels

The hyaloid vasculature is a transient embryonic vascular bed which develops during embryonic and fetal stages to provide blood supply to the developing eye. The hyaloid artery originates from the ophthalmic artery. It enters the embryonic fissure and extends through the vitreous to the lens. In the developing eye, the hyaloid vasculature plays an important role in many aspects. It supplies the inner part of the retina with oxygen and nutrients; it is also involved in the development and maturation of the lens and makes up the primary vitreous (Hartnett 2013; Fruttiger 2007). During human fetal development, the hyaloid vasculature is first seen at the fourth week of gestation and reaches its maximum prominence during the ninth week. During mid-gestation, the hyaloid vasculature regresses and the retinal vasculature contemporaneously develops. Regression of the hyaloid artery leaves a central extension from the optic disk to the posterior lens surface, called the hyaloid canal or Cloquet's canal (Hartnett 2013).

1.2 Development of Retinal Vasculature

Among the three vascular beds in the eye, the retinal vasculature is the most extensively studied. The development of the retinal vasculature has served as an excellent model for elucidating the mechanisms of vascular development, remodeling, and maturation. Studies on retinal vasculature over the past several decades have greatly expanded our understanding of the fundamental processes governing normal and pathologic vascularization including the relationship between hypoxia and vessel growth, as well as the contribution of neurovascular interaction in vascular homeostasis.

1.2.1 Angiogenesis Is the Dominant Process in Retinal Vascular Development

Blood vessels are generally composed of several distinct cell layers with a single layer of endothelial cells forming the lumen in the innermost part of the vessel. In large macrovessels such as aortae, the inner endothelial cell layer is covered by a central layer of mural cells/smooth muscle cells, and usually an external layer consisting of connective tissue lined with small vessels and nerves. In microvessels and capillaries, which constitute most of the retinal vessels, the endothelial cell layer is covered externally by a noncontiguous single layer of pericytes/mural cells, allowing close interaction of vascular endothelial cells with surrounding neurons, glia, and inflammatory cells to coordinate the process of vascular growth, remodeling, and repair.

The developmental vascularization process in the retina is mediated primarily via angiogenesis (Fruttiger 2002), similarly as some other tissues such as the kidney and the brain. In angiogenesis, vascular endothelial cells sprout and proliferate from preexisting blood vessels, usually venules, and develop into new vessels with fully functional lumen. During this process, local increases in growth factors destabilize a portion of the preexisting vessels, allowing the activation of pericytes and remodeling of extracellular matrix. Endothelial cell migration and proliferation subsequently occurs to form new vessels. Angiogenesis is also considered the dominant process governing new blood vessel growth during the wound healing process and in pathologic retinal vessel growth such as in tumors and retinopathies (Saint-Geniez and D'Amore 2004).

This mechanism of angiogenic development is in contrast with vasculogenesis where dispersed primitive vascular precursor cells or hemangioblasts cluster together and form into tube-like endothelial structures, in the absence of existing vessels. Vasculogenesis occurs during the embryonic development of the circulatory system and gives rise to the heart and the first primitive vascular plexus such as the yolk sac circulation. It was suggested that the very initial process of vascular development in the retina results from vasculogenesis from resident angioblasts (McLeod et al. 2006), then angiogenesis becomes dominant to form the rest of retinal vasculature. Yet with increasing evidences of circulating endothelial precursor cells from bone marrow modifying developing and injured retinal blood vessels (Grant et al. 2002; Sengupta et al. 2003; Dorrell et al. 2004), the precise distinction between angiogenesis and vasculogenesis is becoming blurry.

1.2.2 Temporal and Spatial Development of Three Layers of Retinal Vasculature

In humans, retinal vascularization starts in utero at about 16 weeks of gestational age and is completed at approximately 40 weeks of gestation, right before birth. Developmental retinal vascularization occurs concurrently as the hyaloid vessels regress. The retina is vascularized first in the most superficial (i.e., innermost) layer on the vitreous side, starting from the optic nerve head and then progressing centrifugally outwards towards the ora serrata, the peripheral edge of the retina. This superficial primary plexus reaches the nasal side of the ora serrata at about 36 weeks gestational age, and the temporal retina at approximately 40 weeks gestational age. As the superficial layer is nearing completion, retinal vessels dive into the retina to form first a deep and then an intermediate layer along with a well-organized network of inter-connecting vessels to complete three vascular layers: a superficial vascular layer which lies in the inner part of the nerve fiber layer, an intermediate layer in the inner plexiform layer, and a deep layer in the outer plexiform layer (Dorrell et al. 2002) (Fig. 1.1).

In other mammals such as primates and rodents, the conserved pattern of three retinal vascular layers forms over varying timescales (Gariano and Gardner 2005). In mice, one of the most studied model systems of retinal vascular development, the superficial vascular plexus starts to develop during the first week after birth, with radial growth as seen similarly in humans (Fig. 1.2). During the second week, angiogenic sprouts start to form from the superficial layer and grow perpendicular to the primary vascular plexus into the retina to create two deeper layers of capillary networks. A complete vascular system is formed by the end of three weeks after birth (Stahl et al. 2010a). Studies in the mouse retina have shed light on the cross talk among multiple cell types that function together to direct vascular growth in the retina, and identified the important roles of oxygen and oxygen-mediated growth factors in this process.

1.2.3 Oxygen and VEGF in Retinal Vascular Development

1.2.3.1 Lack of Oxygen Drives Blood Vessel Growth in the Eye

A hypothesized role of oxygen in retinal vascular development originates from early observations that capillaries grow more profusely near venules than around arteries (Michaelson 1948; Ashton 1966; Wise 1961). Observed retinal vascular patterns from some eye diseases also support this notion. In retinopathy of prematurity and diabetic retinopathy, an initial lack of retinal vessels with resulting retinal ischemia precedes pathologic vessel growth, supporting the idea of hypoxia as a critical stimulator of new blood vessel growth (Gariano and Gardner 2005). During development, as retinal neurons and glial cells differentiate and mature, their metabolic demands increase, creating a radial wave of hypothesized "physiologic hypoxia" that leads the development of new vessels from the center towards the periphery of the retina (Chan-Ling et al. 1995) (Fig. 1.2).