

# PREFACE

---

Angiogenesis is of fundamental importance in development, health, and disease. The study of angiogenesis in the eye, in particular, has increased exponentially in the last decade because retinal and choroidal neovascularization play an important role in the major blinding diseases of the industrialized world and represent an unprecedented economic burden on healthcare. It has now become an increasing challenge to manage the overwhelming bulk of information generated in the area of ocular angiogenesis. To meet the challenge, *Ocular Angiogenesis: Diseases, Mechanisms, and Therapeutics* assimilates the recent developments and summarizes the progress made in this field to date so that this information can be disseminated efficiently to the growing group of interested investigators, clinicians, and biotechnologists. Our intent is to foster new ideas, encourage discussion of the challenging concepts presented in the volume, increase our understanding of mechanisms that control this dynamic process, and translate the available information into targeted therapy.

Historically, the first use of the word “angiogenesis” can be traced back to 1787 when Hunter, a British surgeon, used it to describe the growth of blood vessels in the reindeer antler (1). A relationship between tumors and the blood supply was discussed as early as 1907 by Goldman, but the nature and significance of this relationship was not understood (2). Then, in 1935, Hertig (3) reported that angiogenesis occurred in the placenta of the Macaque monkey. Among the first references to angiogenesis in the eye were those of Mann, who, in 1928, developed the concept that retinal vessels originate by budding from the base of the fetal blood vessel of the eye and the 1941 report by Greene that the growth of tumors in the anterior chamber of the rabbit eye coincided with the growth of new blood vessels (neovascularization) (4,5). In 1948, Michaelson published a landmark paper describing the vasculature of the retina. He had developed a technique that allowed him to inject India ink into the arterial system to fill and blacken the retinal vasculature. Using this method, he was able to visualize blood vessels of the human fetal retina in flat mounts at various stages of development (6). From this study, he concluded that retinal capillaries sprout from new vessels that grew out from the region of the optic nerve and that they were more abundant near veins than arteries. He also reported that arteries have a zone around them, which is free of a capillary network. Based on these anatomical observations, Michaelson then made the astute comment that “... there is present in the developing retina a factor which affects the budding of new vessels.” He then suggested that this factor, which he named Factor X, was regulated by oxygen and was responsible for abnormal retinal vessel growth. Decades later, Factor X was identified as vascular endothelial growth factor (VEGF), possibly the most mitogenic endothelial growth factor isolated to date. Campbell expanded Michaelson’s studies and showed that the capillary-free zone around retinal arteries narrowed in animals in response to low-oxygen environments (7). We now know that Michaelson and Campbell were observing the effects of

hypoxia, which leads to increased expression of VEGF and subsequent neovascularization in the eye.

The field of modern angiogenesis, however, was founded in 1971 when Dr. Judah Folkman suggested that the progression of tumor cells is dependent on the growth of new blood vessels (8). In a striking test of this hypothesis, he showed that tumor fragments that were transplanted into the anterior chamber of rabbit eyes grew rapidly and increased in size when they attached to the blood vessel-rich iris, as compared with those that floated in the aqueous humor or attached to avascular regions.

In support of this theory, in 1975 Folkman isolated a factor from cartilage that could block vessel growth, a finding that initiated an explosion of molecular studies of angiogenesis (9). In 1984, the first soluble, endogenous angiogenesis-promoting molecule, fibroblast growth factor, was isolated by Shing, Klagsbrun, and colleagues (10). Shortly thereafter, in 1989, both Ferrara and Plouet identified VEGF as one of the most potent stimulators of blood vessel growth, although Dvorak had already isolated it in 1983 as vascular permeability factor (VPF) (11–13). These findings provided clear evidence that the growth of blood vessels is under the tight control of both positive and negative soluble endogenous regulators. Since then, the study of angiogenesis has burgeoned, and we have progressed to a stage where we know that angiogenesis is a complex process that involves a cascade of events regulated by at least 20 pro-angiogenic factors, more than 30 antiangiogenic factors, and several distinct cell types, as well as numerous receptors and signaling partners. During normal development, blood vessels grow in concert with the associated organs. In the adult, most vessels are quiescent. The growth of new blood vessels is important to a few adult processes, including those of the female reproductive system and those at wound sites, where vessels can be induced to grow rapidly and reconstitute capillary beds, indicating that they are highly dynamic structures capable of rapid and extensive remodeling.

The complexity of regulation of angiogenesis is an indication of how critical this process is to normal life and how catastrophic its disruption can be. In addition to the critical role of angiogenesis to tumor growth, neovascularization has been implicated as a major component of many diseases including psoriasis and arthritis. Lack of vessel growth is a serious problem in cardiovascular disease, in which heart muscle is starved for nutrition and oxygen. In general, however, it is the overgrowth of blood vessels that causes problems.

In the eye, pathological angiogenesis is a major contributing factor to many of the most prevalent and serious diseases. Wounds and infections of the cornea, as well as transplant rejection, involve a neovascular response. In the two most common blinding diseases of the retina, macular degeneration and diabetic retinopathy, degeneration and loss of vision are closely associated with neovascularization.

The cost of medical treatment, loss of income, and need for assistance in daily living combine to make the societal cost of pathological angiogenesis in the eye immense. Because these diseases can lead to severe loss of vision, their impact on the quality of life is also huge, thus increasing the urgency with which the causes and treatments of ocular angiogenic diseases are sought. As the chapters in this volume indicate, we have made tremendous strides over the last decade in understanding the pathogenesis and molecular mechanisms underlying many of the neovascular diseases of the eye.

The inhibition of blood vessel growth is now one of the fastest growing areas of research in ophthalmology. *Ocular Angiogenesis: Diseases, Mechanisms, and Thera-*

*peutics* offers a comprehensive review of what is currently known about angiogenesis and its role in blinding diseases as well as mechanisms leading to progressive vessel dysfunction. It identifies and assesses the most promising approaches with potential for commercial exploitation and discusses challenges encountered in developing therapeutics for ocular neovascular diseases. The volume features a wide spectrum of studies that will allow basic scientists to glean a better idea of the clinical features of pathological angiogenesis in the eye, and will provide ample opportunity for clinicians to draw from the current knowledge of molecular and environmental switches that govern vessel growth. What is equally exciting, and should be evident from the text, is the tremendous progress made in the development of new therapeutics and key areas of opportunities to combat neovascular eye diseases. The first Food and Drug Administration (FDA)-approved therapy for neovascular age-related macular degeneration was Visudyne® (Novartis), a photoactivated dye used in photodynamic therapy. By 1999, at least five antiangiogenic drugs were in clinical trials, and the number has greatly increased since then. One of these drugs, Macugen® (Pfizer), was approved for the treatment of macular degeneration in 2004. Thus, over the past decade of research, we have expanded human trials for ocular angiogenesis to include dozens of synthetic compounds, antibodies, cryptic peptides, and endogenous glycoproteins. These are starting to yield a few commercial products with proven efficacy in reducing the growth of blood vessels in the eye. Others remain promising approaches still in clinical development. We have come a long way in understanding neovascular growth in the eye and have identified several key promoters and inhibitors of the process. The challenges that lay ahead will be in development of early diagnoses of the diseases and of revolutionary, less-invasive methods of delivering antiangiogenic drugs into the eye.

***Joyce Tombran-Tink  
Colin J. Barnstable***

## REFERENCES

1. Hunter, J. Lectures on the Principles of Surgery. In: The Works of John Hunter, Palmer J., ed. London: Longmans, Rees, Orme, Brown, Green and Longman, 1837.
2. Goldman, E. The growth of malignant disease in man and the lower animals with special reference to the vascular system. *Lancet* 1907;2:1236–1240
3. Hertig AT. Angiogenesis in the early human chorion and in the primary placenta of the macaque monkey. Carnegie Institute of Washington Publication 459. *Contrib Embryol* 1935; p. 7.
4. Mann, I. The Development of the Human Eye. Cambridge, UK: Cambridge University Press, 1928.
5. Greene HSN. Heterologous transplantation of mammalian tumors: I. The transfer of rabbit tumors to alien species. *J Exp Med* 1941;73:461–474.
6. Michaelson IC. The mode of development of the vascular system of the retina, with some observations on its significance for certain retinal disease. *Trans Ophthalmol Soc UK* 1948;68:137–180.
7. Campbell, FW. The influence of a low atmospheric pressure on the development of the retinal vessels in the rat. *Trans Ophth Soc UK* 1951;71:287–300.
8. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971;285:1182–1186.
9. Brem H, Folkman J. Inhibition of tumor angiogenesis mediated by cartilage. *J Exp Med* 1975;141:427–439.
10. Shing Y, Folkman J, Sullivan R, Butterfield C, Murray J, Klagsbrun M. Heparin affinity: purification of a tumor-derived capillary endothelial cell growth factor. *Science* 1984;223:1296–1299.
11. Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochem Biophys Res Commun* 1989;161:851–858.
12. Plouet J, Schilling J, Gospodarowicz D. Isolation and characterization of a newly identified endothelial cell mitogen produced by AtT-20 cells. *EMBO J* 1989;8:3801–3806.
13. Senger DR., Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 1983;219:983–985.



<http://www.springer.com/978-1-58829-514-9>

Ocular Angiogenesis

Diseases, Mechanisms, and Therapeutics

Tombran-Tink, J.; Barnstable, C.J. (Eds.)

2006, XVI, 412 p., Hardcover

ISBN: 978-1-58829-514-9

A product of Humana Press